PHARMACOLOGICAL CUES, MORPHINE TOLERANCE, AND MORPHINE WITHDRAWAL

By

MARTA SOKOLOWSKA, B.SC.

A Thesis

Submitted to the School of Graduate Studies

In Partial Fulfillment of the Requirements

For the Degree

Doctor of Philosophy

McMaster University

PHARMACOLOGICAL CUES, MORPHINE TOLERANCE AND WITHDRAWAL

Rodzicom

z podziękowaniem

DOCTOR OF PHILOSOPHY (2004) McMaster University
(Psychology) Hamilton, Ontario

TITLE: Pharmacological Cues, Morphine Tolerance, and Morphine Withdrawal
AUTHOR: Marta Sokolowska, B. SC. (McMaster University)
SUPERVISOR: Professor Shepard Siegel
NUMBER OF PAGES: viii, 147

Abstract

Results of many studies have demonstrated an important contribution of Pavlovian conditioning to the phenomena of drug tolerance and withdrawal. Based on the conditioning analysis, cues paired with the drug administration conditionally elicit compensatory responses in anticipation of the subsequent drug-induced physiological disturbance. These conditional compensatory responses mediate tolerance development by counteracting the drug effect when the drug is administered in the presence of the drug predictive cues. Additionally, presentation of drug-predictive cues in the absence of the drug elicits the conditional responses, now unopposed by the drug effect. Such conditional responding, elicited by the usual pre-drug cues in the absence of the usual drug effect, constitutes withdrawal symptoms.

Most research evaluating the role of conditioning in drug effects have examined exteroceptive, environmental cues. Recently, however, there has been interest in the interoceptive, pharmacological cues. That is, within each drug administration, early drug onset cues (DOCs) may become associated with the later, larger drug effect (and mediate tolerance and withdrawal behaviors, much like exteroceptive cues). The present experiments examined the role of DOCs in morphine tolerance and withdrawal in rats. The first series of experiments (Chapter 2) concerned the role of DOCs in tolerance to the analgesic effect of morphine. Research described in Chapter 3 evaluated whether DOC pre-exposure attenuates acquisition of conditional compensatory responses, as would be expected on the basis of a conditioning analysis of tolerance. Research described in chapter 4 evaluated the role of exteroceptive cues and DOCs in the elicitation of withdrawal symptoms, using an acoustic startle measure of withdrawal. Research described in Chapter 5 evaluated DOC-elicited behavioral withdrawal symptoms, using procedures to assess whether such withdrawal behaviors represent an associative or sensitized response. The results of these studies have implications for a range of issues in drug tolerance, withdrawal, and the treatment of addition.

Acknowledgements

I am indebted to many people who have supported and assisted me during my years at McMaster. Foremost, I would like to thank my supervisor, Shepard Siegel, for his contribution in my development as a scientist, for his endless support, guidance and patience. Also, I would like to express my gratitude to my committee members, Loraine Allan and John Platt, for their insightful comments and assistance throughout the years.

I am grateful to the Siegel lab members who made my time at McMaster enjoyable. Thank you Barbara for your advice and friendship, Joe for your encouragement and support, Doreen for constantly believing in me, Mariyam for your help in running the startle project. Special thanks to Christine not only for your company but also for the hours and days you spend scoring my tapes.

Thank you to my friends who continually reminded me that I could do it, for the walks, talks, dinners, movies, coffees and cookies that made grad school fun and unforgettable.

I would like to thank my partner, Martin Dziasek, for his support and belief in me even if my goals seemed to me almost unattainable at times. Last but not least, I would like to express my gratitude to my parents, their unconditional love, encouragement, and sacrifice made it possible for me to accomplish my goals.

Thank you.

Table of Contents

List of Figures

Preface

This thesis contains previously published material. The experiments described in Chapter 2 have been reported as:

Sokolowska, M., Siegel, S., & Kim, J. A. (2002). Intra-administration associations: Conditional hyperalgesia elicited by morphine onset cues. *Journal of Experimental Psychology: Animal Behavioral Processes, 28,* 309-320.

The author of this thesis was primarily responsible for the design and execution of the experiments, the analysis of the results, and the preparation of the manuscript under the supervision of the second author. The third author was involved with designing of the experiments as well as data analysis.

Much of the material in the Introduction and General Discussion of the published manuscript has been eliminated here to avoid redundancies. Permission of the copyright holder has been obtained to reproduce this material here.

Chapter 1:
Introduction

Early observations of decreased drug effectiveness as a function of experience with the drug date back at least to the seventeenth century. In 1612 Jean Mousin, physician to the King of France, noted that occasionally individuals became gradually more sober as they continued to drink alcoholic beverages (see Kalant, 1998). Using contemporary terminology, this phenomenon is identified as acute drug tolerance.

Acute Drug Tolerance and Withdrawal

Acute tolerance refers to the decreasing effectiveness of a drug within the course of a single administration. For example, over the course of a single, gradual morphine infusion the analgesic effect of the drug diminishes (Tilson, Rech, & Stolman, 1973; Wei & Way, 1975). Likewise, the effectiveness of epinephrine, a hormone that increases blood pressure and heart rate, decreases over the course of a single, gradual infusion. (e.g., Bevan, 1983).

Researchers (e.g., Ramsey & Woods, 1997; Siegel & Allan, 1998) suggested that acute tolerance is an expression of both the drug induced pharmacological stimulation and adaptive compensatory responses that attenuate the drug-induced stimulation. That is, acute tolerance is a summation of both the primary drug effect and the secondary compensatory processes that counteract the drug effect. Another demonstration of compensatory responses may be seen following sudden termination of the drug delivery. Such cessation of the primary drug effect results in withdrawal responses. The withdrawal responses are an expression of the compensatory processes unopposed by the drug induced physiological disturbances. For instance, cessation of morphine delivery results in hyperalgesia, an increased sensitivity to pain (Tilson et al., 1973; Wei &Way, 1975). Hyperalgesia is opposite in effect to the analgesic effect of morphine.

Chronic Drug Tolerance and Withdrawal

Acute tolerance illustrates the effectiveness of a drug within a single administration, however both licit and illicit drugs typically are administered chronically. The drugs are administered as brief injections on repeated occasions, and the drug effect is measured following termination of each of the injections. It has been demonstrated that the effectiveness of many drugs decrease over the course of repeated presentations, a phenomenon termed chronic tolerance. For example, the sixth administration of morphine induces less analgesia then the first administration of the same morphine dose (e.g., Siegel, 1977).

Similarly to acute tolerance, chronic tolerance is mediated by compensatory responses. However, the compensatory responses are elicited not only by the drug effect, but also by cues that, in the past, have been associated with the drug effect. Furthermore, at some time following a series of drug administrations, if the drug no longer is administered, pharmacological aftereffects may be seen. These withdrawal symptoms, seen after a chronic administration, are termed chronic withdrawal symptoms. The contribution of learning to chronic tolerance and chronic withdrawal (generally referred to and hereafter termed tolerance and withdrawal, respectively) is integrated in a Pavlovian conditioning analysis of tolerance.

The Pavlovian Conditioning Paradigm

Pavlovian conditioning (otherwise termed classical, respondent, or Type I conditioning) is defined by a set of operations in which a neutral conditional stimulus (CS) is paired with a biologically significant unconditional stimulus (US). At the start of conditioning, the US reflexively (i.e., unconditionally) elicits some response, termed the unconditional response or unconditional reflex (UR). The UR is the response of the central nervous system to the US. As a result of CS-US pairings, the CS becomes associated with the US. The acquisition of this association is revealed by the emergence of a new response to the previously neutral CS. Because this new response is conditional on CS-US pairings, it is termed the conditional response or conditional reflex (CR).

Pavlovian Conditioning Interpretation of Drug Tolerance and Withdrawal

Results of many experiments indicate that Pavlovian conditioning plays an important role in the development of tolerance (Dworkin, 1993; Ramsay & Woods, 1997; Siegel, 1999; Siegel, Baptista, Kim, McDonald, & Weise-Kelly, 2000). According to the conditioning model, cues accompanying the primary drug effect function as CS. The direct effect of the drug constitutes the US. Prior to any learning, this pharmacological stimulation unconditionally elicits responses that compensate for the drug-induced disturbances. After some pairings of the pre-drug CS and pharmacological US, drug-compensatory responses are elicited as conditional responses. Such CRs that mimic the compensatory response unconditionally elicited by a drug have been termed conditional compensatory responses (CCRs; see Dworkin, 1993; Kim, Siegel, & Patenall, 1999). These CCRs attenuate the effect of the drug and contribute to tolerance. However, if the usual cues for drug administration are present but the drug is not delivered, these CCRs are fully expressed and are not modulated by the drug effect. In such circumstance, these CCRs are termed withdrawal symptoms (McDonald & Siegel, in press; Siegel, 1989; Siegel et al., 2000; Siegel & Allan, 1998).

Predictions Based on Pavlovian Conditioning Analysis of Tolerance

The extensive literature indicating that CCRs contribute to tolerance has recently been reviewed (Siegel et al., 2000; Siegel & Ramos, 2002). Briefly, consistent with the conditioning analysis, a variety of manipulations that attenuate the expression of conditional responding also attenuate the acquisition of tolerance. Thus, in common with other CRs, the expression of drug tolerance is disrupted by presenting a novel external stimulus ("external inhibition") or by altering the putative CS on each trial (i.e., changing the context of drug administration in an unpredictable manner). Partial reinforcement, CS preexposure (also termed latent inhibition), and inhibitory learning retard the acquisition of CRs and tolerance. Like other CRs, drug tolerance displays extinction (and spontaneous recovery following extinction), stimulus generalization, and a flattening of the generalization gradient as a result of extending the interval between acquisition and assessment. Tolerance also displays sensory preconditioning and a variety of compound

conditioning effects such as blocking and overshadowing. Post-trial events that affect memory consolidation similarly affect the rate of tolerance acquisition; thus, electroconvulsive shock or frontal cortical stimulation decrease the rate of acquisition of morphine tolerance, and glucose facilitates the rate of acquisition of morphine tolerance (Siegel et al., 2000; Siegel & Ramos, 2002).

Situational Specificity of Tolerance

The original phenomenon that inspired development of the conditioning model has been termed the "situational-specificity of tolerance" (Siegel, 1976). Situational-specificity of tolerance is readily demonstrated. An organism is administered a drug in a particular environment on a number of occasions – sufficient for tolerance to be apparent (i.e., the magnitude of the drug-elicited response is less than it was originally). If the drug is administered again, but in an environment that had not previously been paired with drug administration, tolerance is attenuated.

There have been many demonstrations of the situational-specificity of tolerance to a variety of drugs: caffeine, opiates, naloxone, ethanol, nicotine, pentobarbital, phencyclidine, immunoenhancing drugs, cholecystokinin, carisoprodol, haloperidol, and several benzodiazepines (see Siegel et al., 2000 and Siegel, Kim, & Sokolowska, 2003 for reviews). As an illustration of the situational specificity, Siegel (1975) demonstrated that rats repeatedly administered morphine in a distinctive environment and tested in the same distinctive environment displayed tolerance to the analgesic effect of the drug. However, rats repeatedly administered the same drug in home cage and tested in the distinctive environment displayed less tolerance to the drug than the subjects trained and tested in the distinctive environment.

Siegel (1975) demonstrated situational specificity of tolerance using a paradigm that involved explicit pairing of the drug administration cues with the drug effect. The phenomenon also may be demonstrated using a "naturalistic design," that exploits the subjects' extra-experimental conditioning histories. For example, McCusker and Brown (1990) provided one group of human subjects (beer-bar group) with an alcoholic drink (beer) in a setting designed to simulate a bar (a familiar form of alcohol in a

familiar setting associated with drinking). Another group (alcohol-office group) received the same amount of alcohol but mixed in carbonated water and consumed in an office setting (an unusual form of alcohol and setting). The impairment induced by the alcohol, as measured on cognitive and motor tasks, was greater in the subjects from the alcohol-office group than the beer-bar group.

The most dramatic manifestation of situational specificity concerns tolerance to the lethal effects of drugs. Siegel, Hinson, Krank, and McCully (1982) reported lower mortality rates in heroin-experienced rats administered a high dose of heroin in the presence of drug-associated cues than in the presence of alternative cues. Specifically, rats were repeatedly administered heroin in either an unfamiliar environment, the experimental room, or in a familiar environment, the colony room, throughout tolerance acquisition phase. At test, the subjects were presented with the drug in the context of cues associated with the drug (the experimental room for the rats trained in the experimental room or the colony room for the rats trained in the colony room) or in an environment not previously paired with the drug (the colony room for the rats trained in the experimental room or the experimental room for the rats trained in the colony room). The mortality rate was higher for the differently tested group than the similarly tested group. Subsequent research has demonstrated that altering the context of drug administration during tolerance testing also increases the lethality of pentobarbital (Vila, 1989) and ethanol (Melchior, 1990). There is evidence suggesting that alteration of the administration cues before final drug administration may be responsible for opiate overdoses experienced by addicts (Gutiérrez-Cebollada, de la Torre, Ortuño, Garcés, & Camí, 1994; Siegel, 1982) and by patients receiving opiates for pain relief (Siegel & Ellsworth, 1986; Siegel & Kim, 2000).

Cues for Drug Administration

Since tolerance expression is dependant on cues associated with the drug effect, it is important to identify these cues. Traditionally only the exteroceptive, environmental cues (e.g., sounds, illumination, ambient temperature) were studied as stimuli associated with the drug effect. However, several investigators (e.g., Grisel, Wiertelak, Watkins, &

Maier, 1994; Kim, et al., 1999, Siegel et al., 2000) have suggested that during drug administration other types of cues, such as interoceptive cues, are also available in addition to the environmental context. The interoceptive cues include stimuli incidental to self-administration of a drug (self-administration cues) and pharmacological changes induced by the initial effect of the administered drug (pharmacological cues).

Self-Administration Cues

Although typically humans self-administer the drugs that they use, most laboratory studies of addiction involve passive drug administration; the experimenter, not the subject, administers the drug. However, if drug delivery is contingent on a subject's response, interoceptive response-initiating (or response-produced) cues might be paired with the drug effect. Thus, the controllability and predictability of the drug delivery might serve as an additional cue, CS, facilitating tolerance development. Mello and Mendelson (1970) were the first to demonstrate the role of self-administration in drug tolerance and withdrawal. The researchers presented the subjects, who were alcoholics, with alcohol either when the subjects wished (free-choice phase), or on a schedule provided by the experimenters (programmed phase). The subjects ingested similar amounts of alcohol over similar time periods throughout both phases of the experiment. Subjects expressed greater tolerance to the effect of alcohol during the free-choice phase than during the programmed phase. Furthermore, subjects expressed more withdrawal effects following the free-choice than the programmed phase. Many subsequent experiments, with both humans and non-human animals, have demonstrated that a self-administered drug has a smaller effect (i.e., produces more tolerance) than passively administered drug (see Weise-Kelly & Siegel, 2001). This would be expected if self-administration cues act as CSs.

Pharmacological Cues

Traditionally drug effect is considered as an US. However, there is considerable evidence that a drug effect, when presented prior to administration of another drug or larger dose of the same drug, can function as a CS for the later delivered drug. Such CSs are referred to as pharmacological cues. Goddard (1999) emphasized that subjects can

associate stimuli, usually identified as a US, as a signal for delivery of another US. Thus stimuli, such as drug effect or shock, can function as both CSs and USs. Researchers have used various paradigms to examine the role of drug effect as a CS in drug tolerance and CCR expression. These paradigms include interdrug, intradrug, and intraadministration conditioning.

Interdrug conditioning. Interdrug conditioning involves repeated presentation of drug A prior to drug B, resulting in drug A acquiring CS properties. As an example Taukulis (1986) injected rats with atropine sulfate (a drug that, at the dose used in the experiment, did not affect body temperature), followed 30 min later, by injection of pentobarbital (a drug that induced substantial hypothermia). After repeated presentation of atropine sulfate and pentobarbital, tolerance to the hypothermic effect of the pentobarbital was observed only when administration of the barbiturate occurred after administration of atropine sulfate. If the pentobarbital injection was administered in the absence of the atropine signal, there was little evidence of tolerance to the barbiturate.

Intradrug conditioning. Intradrug conditioning is another technique used by researchers to examine the contribution of pharmacological cues to tolerance development and CCR expression. This conditioning procedure involves repeated presentation of a small dose of a drug followed by a larger dose of the same drug. The small drug dose acquires the CS properties and tolerance to the large dose of the drug is observed only if the small drug dose is presented prior to the large dose. The pairing of the same drug as a CS and a US should be particularly effective because associations form especially readily if the CS is similar to the UCS (see review by Mackintosh, 1983, pp. 213-214; Goddard, 1999).

Greely, Lê, Poulos & Cappell (1984) presented evidence demonstrating an intradrug association using a "paired-unpaired" design. During the tolerance development phase of their study, one group of rats (paired group) was repeatedly administered a low dose of ethanol (0.8 g/kg) followed 60 min later by a high dose of the same drug (2.5 g/kg). A second group (unpaired group) repeatedly received the same amounts of ethanol however, these injections were presented in an unpaired fashion. On

a tolerance test, following the tolerance development phase, the small ethanol dose was administered prior to the large ethanol dose for all rats. Paired group rats displayed greater tolerance to the hypothermic effect of the large ethanol dose than the unpaired group. Moreover, when the large dose was not preceded by the small dose, paired group rats failed to display their usual tolerance.

Additionally, some investigators demonstrated intradrug conditioning with morphine. Although the initial attempts to establish the intradrug conditioning with the opiate had been unsuccessful (Cepeda-Benito & Tiffany, 1993), more recently Cepeda-Benito and Short (1997) demonstrated such an association. In their research Cepada-Benito and Short repeatedly presented rats with small and large drug intraperitoneal injections (4 mg/kg and 12 mg/kg of morphine, respectively) in either a paired or an unpaired fashion. At test, tolerance to the analgesic effect of the drug was assessed following administration of the small morphine injection. Consistent with Greely et al. (1984), Cepeda-Benito and Short found that rats in the paired condition displayed greater tolerance to the analgesic effect of the large dose of morphine than did rats in the unpaired condition.

Intraadministration conditioning. Demonstrations of intradrug associations have important implications for the conditioning analysis of tolerance. A gradual increase in systemic drug accumulation is an inevitable consequence of most administration procedures. Thus, without explicit pairing, within a single drug administration, the initial early drug effect precedes the later, larger drug effect. The early drug effect (the drug onset cues, DOCs) can serve as a signal for the larger drug effect. Such an association, which forms within a single administration, has been termed an "intraadministration association" (Kim et al., 1999). Some investigators have suggested that intraadministration DOCs constitute an important component of the CS that elicits the drug CCRs that mediate tolerance (see Grisel et al., 1994; Kim et al., 1999; Siegel et al., 2000).

Pharmacological Cues and Withdrawal Symptoms

Based on the conditioning analysis, presentation of drug associated stimuli to subjects tolerant to the drug effect induces CCRs. When the CSs are present but the drug is not delivered, these CCRs are fully expressed and are not modulated by the drug effect. In such instance, these CCRs are termed withdrawal symptoms. A majority of drug withdrawal research examined the role of environmental CS in eliciting withdrawal symptoms (Kelsey, Aranow, & Matthews, 1990; McDonald and Siegel, 1998). However, withdrawal symptoms should be elicited not only by drug-associated environmental cues, but also by drug-associated pharmacological cues. DOC- elicited withdrawal symptoms have been examined by McDonald & Siegel (in press). During the drug exposure phase, the experimenters repeatedly injected rats from the experimental group with 50 mg/kg of morphine. On the test day, the subjects were administered 5 mg/kg of morphine, a small dose of the opiate designed as a replica of DOCs. In order to assess the withdrawal symptoms, the researchers measured morphine withdrawal behaviors. The animals from the experimental condition expressed a greater number of withdrawal symptoms than the control subjects. The control subjects were repeatedly injected with 50 mg/kg of morphine and tested with a saline injection.

Summary

The results of experiments from many laboratories suggest that tolerance may be mediated, in part, by associative mechanisms. Numerous studies demonstrated that, following a series of drug administrations, drug paired stimuli elicit CCRs. Furthermore, there are many parallels between tolerance and other conditional responses; various manipulations that attenuate tolerance acquisition similarly modulate the expression of conditional responding. Different types of drug-associated stimuli are identified including pharmacological cues. This thesis further assessed the contribution of a pharmacological CS to tolerance development and expression of withdrawal symptoms using intraadministration and intradrug conditioning.

Chapter 2:
Intraadministration Associations:
Conditional Hyperalgesia Elicited by Morphine Onset Cues

Experimental evaluations of the conditioning analysis of tolerance typically have manipulated exteroceptive signals for the drug. In addition to such exteroceptive stimuli, there are also interoceptive stimuli that are paired with a drug effect and thus may elicit CCRs that mediate tolerance. An example of such an interoceptive, pharmacological cue that has received considerable attention is the drug onset cue. That is, within each administration of a drug, early-drug onset cues (DOCs) may become associated with the later larger drug effect. Recently, Kim et al. (1999) demonstrated that such intraadministration associations contribute to tolerance to the analgesic effect of morphine. In the Kim et al. experiment, experimental-group rats were repeatedly intravenously infused with 5.0 mg/kg morphine during the initial tolerance development phase of the experiment. Infusions were gradual—each infusion was about 30 min in duration (hereinafter termed a long morphine infusion, LMor). When rats had displayed tolerance to the analgesic effect of the drug, they received a probe morphine (pMor) test trial. The pMor consisted of about the first 10% of the morphine infusion used during tolerance development, that is, 0.5 mg/kg morphine infused over a period of 3 min (hereinafter termed a 10% pMor), and was designed to reproduce the early effect of the tolerance development infusions. In these experimental-group rats, pMor elicited a CCR of hyperalgesia—extraordinary sensitivity to nociceptive stimulation.

Experiment 1

Although a 10% pMor was used in prior studies of intraadministration associations (Kim & Siegel, 2001; Kim et al., 1999), it is possible that the CCR elicited by this DOC would be even larger with a more salient probe. Obviously, there are many reasonable combinations of infusion rate and probe duration that may be evaluated. As a further complexity, because of the nature of an intraadministration association, the

putative CS (the DOC) is not, like most CSs, "neutral;" rather, it is a less intense version of the US. Thus, following tolerance acquisition with 5.0 mg/kg, a 1.0 mg/kg pMor may, by some measures, be a more effective signal than the 0.5 mg/kg morphine probe used in previous research. However, the expression of a morphine-compensatory CR elicited by the 1.0 mg/kg probe would be complicated because the greater conditional hyperalgesia (compared with 0.5 mg/kg) would be expressed in combination with a greater unconditional analgesia. The purpose of Experiment 1 was to investigate the effectiveness of several different pMor infusions.

Design

During the initial tolerance development phase of the experiment, rats received six LMor infusions—one every other day. They were then divided into four groups, and responsivity to nociceptive stimulation was determined for rats in each group following one of four different pMor infusions. One of the probe infusions consisted of physiological saline (0% pMor). The remaining probe infusions consisted of the same morphine solution that was used during tolerance development but differed with respect to the infusion duration. The 10% pMor was the same as the pMor used in previous research Kim & Siegel, 2001; Kim et al., 1999; 0.5 mg/kg infused in about 3 min). A smaller probe (5% pMor, i.e., 0.25 mg/kg infused in about 1.5 min) and a larger probe (20% pMor, i.e., 1.0 mg/kg infused in about 6 min) also were evaluated.

Method

Subjects and surgical preparation. The subjects were 28 experimentally naive, male, Sprague-Dawley derived rats (purchased from Charles River, Saint Constant, Montreal, Quebec, Canada), ranging from 350–450g at the start of the experiment. The rats were individually housed with ad lib. access to food and water throughout the experiment. They were handled daily for a week prior to surgery.

Between 10 and 15 days prior to the start of the experiment, intravenous catheters were implanted in the right jugular vein of each rat under general anesthetic (ketamine and xylazine cocktail), using a modified version of the technique of Brown and Breckenridge (1975). The tip of the catheter was implanted approximately 1 cm from the

heart. The catheters were assembled from 22-gauge hypodermic needles and 9.5 cm of silastic tubing (Dow Corning; 0.51-mm inner diameter and 0.94-mm outer diameter). The cannula was brought out to the skull and secured to the skull using dental acrylic. On the surgery day, 0.5 ml of Novo-Trimel (Novopharm, Toronto, Canada) was administered orally to each subject, followed by further administration of this antibiotic by addition of 4.5-ml to 500-ml water bottles in the home cage. Each catheter was flushed with a mixture of heparin and ampicillin (16.25 units/ml sodium heparin and 1.25 mg ampicillin) once daily during the recovery period (7–10 days).

Apparatus, drugs, infusion rates, and analgesia assessment. Drug administrations were conducted in chambers (30.4-cm long × 20.5-cm wide × 19.0 cm tall; Lehigh Valley Electronics (Beltsville, MD), constructed of clear Plexiglas with a grid floor and placed in a sound-attenuating cubicle. The rat's cannula was connected to a variable rate syringe infusion pump (Sage Model 341A) through flexible tubing (Tygon, Size 13, No. 6409), attached to a 0.025-micrometer micropore filter (Sartorium Filter, Sartorius, AG, Göttingen, Germany).

During tolerance-development sessions, 5.0 mg/ml morphine sulfate solution was delivered. Intravenous administrations were in a volume of 1 ml/kg and infused at a rate of 0.0166 ml/min. The infusion time varied between rats (24–34 min), depending on body weight, and was adjusted to deliver a dose of 5.0 mg/kg. The probe doses were delivered at the same rate of infusion as in the tolerance-acquisition and re-training sessions. The duration of probe infusion was also based on body weight adjusted to deliver 0.25, 0.5, and 1.0 mg/kg of morphine for 5%, 10%, and 20% probes, respectively. The 0% pMor infusion duration was constant (3 min) independent of the subject's weight.

Analgesia was measured with the tail-flick procedure (Fennessy & Lee, 1975). The tail of a lightly restrained rat was immersed 5 cm into a water bath (located in the same room as the infusion chambers). The latency for the rat to lift its tail out of the water (tail-flick latency, TFL) was noted. The water bath was maintained at 50 °C during the tolerance-development phase. During the test sessions the temperature was 48 °C to

increase the likelihood of observing a hyperalgesic response. Failure to respond within 30 s resulted in termination of tail immersion to prevent tissue damage.

Procedure

Tolerance development. All rats received six sessions of morphine administration, one session every other day. For each tolerance-development session, rats were transported, in their home cages, from the colony room to the room containing the infusion chambers. Prior to each session, each rat was weighed, and its cannula was flushed with 0.05 ml heparin solution (16.25 units/ml). The rat's cannula was then connected to the infusion pump, and the rat was placed in the infusion chamber. The rats were allowed free movement within the chamber while they were connected to the apparatus. Fifteen minutes after placement in the chamber, the morphine infusion started. Following the infusion, the subjects were detached from the apparatus, and 0.05 ml of a dextrose solution (3.3% dextrose and 0.3% sodium chloride) was injected into the cannula to help maintain patency between sessions. The animals were then returned to the infusion chamber. Thirty minutes post morphine infusion, tail-flick latency was assessed and the subjects were returned to home cages.

Probe tests. The rats were randomly assigned to one of the four test groups (n = 7), each group receiving a different test probe: 0% pMor (i.e., saline), 5% pMor, 10% pMor, or 20% pMor. Rats received four pMor tests, with two LMor infusions interpolated between tests. Each rat was administered the same pMor on each of the test sessions. During testing, as during tolerance development, rats participated in the experiment on alternate days. There was a 5-day interval between pMor tests. Rats received LMor infusions on the second and fourth days between each pMor test and were left undisturbed on the first, third, and fifth days between tests. Tail-flick latencies were recorded at 5, 15, 30, and 45 min following each pMor infusion.

Results and Discussion

Tolerance development. The mean (±1 *SEM*) TFLs following each tolerance-development LMor infusion for rats assigned to each pMor test group are shown in Figure 1.

Insert Figure 1 here

As can be seen in Figure 1, tolerance to the analgesic effect of morphine was apparent (i.e., TFLs decreased across tolerance-development sessions). As would be expected, the rats in the four groups, not yet subjected to differential treatment, displayed similar response latencies. These observations were confirmed by a mixed-design (one factor between and one factor within) analysis of variance (ANOVA) of the data summarized in Figure 1. The effect of sessions was statistically significant, $F(5, 120) = 29.99, p < .001$. Neither the effect of group nor the Group × Sessions interaction was statistically significant (Fs < 1).

Probe test. Rats assigned to each test group were treated identically on each of the four test sessions. Figure 2 displays the mean (±1 SEM) TFLs for each group at each post-pMor infusion test interval, collapsed across the four test sessions.

Insert Figure 2 here

As is apparent in Figure 2, the shortest response latencies were observed in the 10% pMor group.

A mixed-design (one factor between and one within) ANOVA of the data summarized in Figure 2 revealed a significant dose effect, $F(3, 24) = 9.62, p <.001$. Subsequent pairwise comparisons (Tukey's honestly significant difference [HSD]) indicated that rats in the 10% pMor group displayed shorter TFLs then did rats in each of the other groups (all ps < .03). None of the pairwise comparisons involving groups 0% pMor, 5% pMor, and 20% pMor were statistically significant.

The results of Experiment 1 indicated that rats with a history of LMor infusions display hyperalgesia in response to a 10% pMor, confirming the results of previous experiments (Kim & Siegel, 2001; Kim et al., 1999). This expression of hyperalgesia was interpreted as a CCR elicited by DOCs. In the earlier research, the choice of the first

10% of the LMor infusion as an effective DOC was arbitrary. The results of Experiment 1 indicate that it was a fortuitous choice.

Because the experiment was designed to assess the effectiveness of various proportions of the LMor infusion in eliciting conditional hyperalgesia, infusion duration and infused dose were necessarily confounded in the various pMor groups. Moreover, only a limited range of pMor values were evaluated; thus although the 10% pMor was a more effective DOC than was the smaller (5% pMor) or larger (20% pMor) pMor values, it is possible that another combination of morphine dose and/or infusion rate would be an even more effective DOC. Nevertheless, because the results of Experiment 1 indicated that a 10% pMor elicits greater hyperalgesia than the smaller or larger proportion of the LMor infusion evaluated in the experiment, this 10% pMor DOC was used in Experiment 2.

Experiment 2

The conditioning analysis of tolerance has generated a considerable amount of research. Many findings support the model, but some do not. For example, although there are numerous reports that the drug-experienced organism does not display tolerance in an environment not previously paired with drug administration (a nondrug environment), there are some reports to the contrary. That is, the animal with a history of drug administration may display about the same level of tolerance in the drug-paired environment as in an alternative environment (e.g., Griffiths & Goudie, 1986; Pinel & Puttaswamaiah, 1985; Sherman, 1979; Wolgin & Benson, 1991).

There are several reasons why tolerance, although associative, may be seen in a nondrug environment. For example, some drug-administration signals are common to the drug-paired and nondrug environments (e.g., handling, insertion of the hypodermic needle; see Dafters & Bach, 1985). Of special relevance to the present experiments are suggestions (e.g., Dworkin, 1993; Goudie, 1990; Kim et al., 1999; Siegel et al., 2000; Walter & Riccio, 1983) that tolerance may be seen in the nondrug environment, because the DOCs that enter into intraadministration associations are especially salient, and these DOCs overshadow (Kamin, 1969; Pavlov, 1927, pp. 142–143 and pp. 269–270)

simultaneously present environmental cues. Unlike typical exteroceptive CSs (which likely generalize to stimuli encountered outside the conditioning situation), DOCs are both novel and presented in a perfectly positively contingent manner with the subsequent drug effect. Also, there is evidence that CSs that are physically similar to the USs with which they are paired are especially salient (see review by Mackintosh, 1983, pp. 213–214), and the CS and US that are paired to form an intraadministration association are very similar indeed. Predrug cues can be characterized as compound stimuli with both environmental and interoceptive elements (exteroceptive cues and DOCs, respectively). Thus, tolerance seen in a nondrug environment may be mediated by CCRs elicited by highly salient DOCs that overshadow less salient environmental cues.

According to an intraadministration association interpretation of trans-environmental tolerance, tolerance should be displayed in the nondrug environment when the drug has been administered in a way that promotes the association between the early drug effect and the later, larger drug effect. In agreement with this prediction, Grisel, Wiertlak, Watkins, and Maier (1994) demonstrated that rats with a history of subcutaneous morphine administrations, but not rats with a history of intravenous drug administrations, display analgesic tolerance when they are assessed in a nondrug environment. Grisel et al. reasoned that the relatively more gradual onset of the subcutaneous opiate effect (compared with the intravenous opiate effect) resulted in an association between DOCs and the later, larger drug effect, and these pharmacological cues overshadowed simultaneously present environmental cues. However, as discussed by Grisel et al., the kinetics of morphine action after subcutaneous administration, rather than after intravenous administration, differ in a number of ways that might complicate interpretation of their findings.

Kim et al. (1999, Experiment 1) avoided the complications of comparing across different routes of administration by comparing two types of intravenous administration of the same dose of morphine: the slow rate of infusion used during the tolerance-development phase of Experiment 1 (LMor) or a rapid intravenous infusion occurring at over 100 times the speed of the LMor infusion (the more rapid infusion being termed

short morphine, SMor). Kim et al. found that tolerance to LMor, but not tolerance to SMor, was apparent in the nondrug environment. On the basis of an associative interpretation, DOCs served as a highly salient CS in the LMor condition (where they signaled a subsequent larger drug effect) but not in the SMor condition (because the maximum effect of the drug occurred so rapidly that it was not effectively signaled by a pharmacological cue). The purpose of Experiment 2 was to essentially replicate the design of the Kim et al. (Experiment 1) study, but to test animals with pMor in the presence of exteroceptive nondrug cues. It would be expected that pMor should elicit a CCR of hyperalgesia in rats that had acquired tolerance to LMor infusions but not in rats that had acquired tolerance to SMor infusions. On the basis of results of Experiment 1, a 10% pMor was used in this experiment to elicit a CCR.

The design of Experiment 2, like that of Kim et al. (1999, Experiment 1), used the "discriminative control of tolerance" procedure (Siegel, 1983). During the tolerance-development phase of Experiment 2, two groups of rats received 24 intravenous infusions—6 morphine infusions and 18 saline infusions. Each morphine infusion was preceded by a distinctive exteroceptive cue (CS+). Similarly, each saline infusion was preceded by another distinctive exteroceptive cue (CS–). The two morphine groups differed with respect to the rate of infusion, long or short (LMor and SMor, respectively). Two additional groups of rats also received 6 infusions in the presence of CS+ and 18 infusions in the presence of CS–, but the infused substance was always physiological saline. These two saline groups also differed with respect to infusion duration (either long or short saline infusions, LSal and SSal groups, respectively).

Method

Subjects, surgical preparation, and apparatus. The subjects were 30 experimentally naive rats of the same gender, strain, and age as those used in Experiment 1. All rats were implanted with chronic intravenous cannulae as described previously. The chamber and apparatus used for intravenous infusions were the same as those described previously. Each chamber was equipped with a houselight and speaker. The houselight was provided by a 15-W (nominal at 120 Volts A.C.) bulb (luminance was

approximately 225 cd/m^2). Flashing the houselight (3 flashes/s) constituted the CS+. A clicking sound (5 clicks/s) constituted the CS–. The clicks were generated by a Scientific Prototype, New York, NY, Model 4041J click generator, set at a nominal scale intensity volume of 2, which corresponded to a volume of approximately 6 dB SPL(C) above the ambient background of 73 dB SPL(C). The CS+ and CS– were the same at those used by Kim et al. (1999). The tail-flick assessment used in this experiment was the same as that used in Experiment 1. Eight rats were assigned to each of the morphine groups (LMor and SMor), and 7 rats were assigned to each of the saline groups (LSal and SSal).

Procedure

The experiment consisted of two phases: tolerance development and CCR test. The design of the experiment is summarized in Table 1.

Insert Table 1 here

Tolerance development. Rats received two trials on each of 12 days, with about 5 hr between trials. On even-numbered days, both trials consisted of presentations of CS–. On odd-numbered days, the first trial consisted of presentation of CS–, and the second trial consisted of presentation of CS+. For all rats, presentation of CS– was followed by saline infusion. For rats assigned to LMor and SMor groups, CS+ presentations were followed by infusion of morphine. For rats assigned to LSal and SSal groups, CS+ (like CS–) was followed by a saline infusion.

The concentration of the morphine solution for LMor, SMor, and pMor infusions was 5 mg/ml. As in Experiment 1, the LMor infusion rate was 0.0166 ml/min. The SMor infusion rate was 1.7 ml/min. For both infusions, the dose of morphine administered was 5.0 mg/kg, and the exact duration of the infusions depended on the weight of the rat. The mean duration of the LMor and SMor infusions was approximately 26 min and 15 s, respectively. As in Experiment 1, the pMor infusion consisted of the first 10% of the LMor infusion (i.e., 0.5 mg/kg infused at a rate of 0.0166 ml/min for duration of approximately 2.6 min).

On each tolerance-development session, a rat was placed in the chamber, its cannula was flushed with heparinized saline (as described in Experiment 1), and the cannula was connected to the syringe pump. The CS was then presented for 15 min. Coincidental with CS termination, the infusion started. Following completion of the infusion, the cannula connector was disconnected from the rat, the cannula was filled with a dextrose solution (as also described in Experiment 1), and the rat remained in the chamber for an additional 90 min before being returned to its home cage.

To minimize the possibility of tissue damage, morphine-induced analgesia was assessed following every second morphine infusion (i.e., following the first, third, and fifth infusion of the opiate, corresponding to Days 1, 5, and 9 of tolerance development). In addition, analgesia level following saline infusion was determined for rats in the two saline groups at the corresponding times. As was the case in the Kim et al. (1999) experiment, TFL (from 50 °C water) was assessed on three occasions following infusion: immediately after the infusion (0 min) and again at 45 and 90 min after the infusion. For the 0-min and 45-min determinations, the rat was briefly removed from the conditioning chamber for TFL assessment and then returned to the chamber. Following the 90-min determination of TFL, the rat was returned to its home cage.

CCR test. Following the tolerance-acquisition phase, all subjects were infused with pMor in the presence of the saline-associated exteroceptive cue (CS–). On the basis of the compound-CS analysis of pre-drug signal, the presentation of exteroceptive cue signaling saline administration (CS–) with the interoceptive pharmacological cue (the DOC) should induce a hyperalgesic response in LMor rats but not in SMor rats. Tail-flick latencies were assessed at 5, 15, 30, and 45 min post-pMor infusion. As was the case in Experiment 1 and in the Kim et al. (1999) study, the water temperature (which had been 50 °C for TFL determinations during tolerance development) was reduced to 48 °C during assessment of pMor-elicited hyperalgesia.

Results

Tolerance development. Analgesia was assessed at 0, 45, and 90 min following infusion on the first, third, and fifth tolerance-development sessions. The mean TFLs (±1 SEM) for each group for each post-infusion assessment are shown in Figure 3.

Insert Figure 3 here

The data summarized in Figure 3 were subjected to a mixed-design (one factor between and two factors within) ANOVA. The statistical analyses confirmed the trends apparent in the figure: (a) Group x Drug x Session interaction was significant [$F(12, 104) = 7.59, p < .001$]; (b) The two morphine-injected groups (that differed by infusion duration) displayed similar levels of responsivity to the thermal stimulation, as did the two saline-injected groups (Fs < 1); (c) morphine had an analgesic effect, that is, tail-flick latencies were longer for morphine- than for saline-injected rats (combined across infusion durations), $F(1, 28) = 330.87, p < .001$; (d) tolerance developed, that is, the Drug × Session interaction was significant, $F(2, 56) = 108.83, p < .001$, and the analgesic effect of morphine (but not saline) decreased from the first to the fifth tolerance-acquisition assessment, (unequal n HSD tests, $p < .001$ for morphine, $p > .3$ for saline).

CCR test. On the CCR test all rats were presented with CS– for 15 min prior to the 10% pMor infusion. The mean TFLs (±1 SEM) for each group for each post-infusion assessment are shown in Figure 4.

Insert Figure 4 here

As can be seen in Figure 4, LMor rats displayed more rapid TFLs than did rats in the other groups. A mixed-design (one factor between and one factor within) ANOVA of the data summarized in Figure 4 indicated a significant groups effect, $F(3, 26) = 11.30$, $p < .001$. Pairwise comparisons (unequal n HSD tests) indicated that the difference between LMor rats and rats assigned to each of the other groups was significant (all ps <

.04). None of the pairwise comparisons between SMor, SSal, and LSal groups were statistically significant (all *p*s > .40).

Discussion

Results of prior research demonstrated that LMor rats, but not SMor rats, displayed tolerance when the drug was administered following CS– (Kim et al., 1999). It was hypothesized that this tolerance was mediated by a CCR elicited by DOCs in LMor rats. The results of Experiment 2 demonstrated this hypothesized CCR. LMor rats, but not SMor rats, display hyperalgesia in response to 10% pMor (a pharmacological stimulus designed to duplicate DOCs).

The results of Experiment 2 further implicate intraadministration associations in tolerance. With such intraadministration associations, the CS and US are intrinsic parts of the same stimulus. This is in contrast with the typical Pavlovian conditioning situation in which the CS and US are two very different stimuli presented in different modalities (e.g., light and shock). Dworkin (1993) distinguished between these two types of conditioning situations. He applied the term *heteroreflexes* ("heterotopic conditioned reflexes") to the traditional, two-stimulus conditioning preparation, and distinguished heteroreflexes from *homoreflexes* ("homotopic conditioned reflexes"). In the case of homoreflexes, the CS and US are presented in the same modality and differ only in intensity. The type of learning studied in the present experiments, in which (within each administration) DOCs serve as cues for a later drug effect, is an example of a homoreflex.

As discussed by Dworkin (1993), "the heteroreflex makes for a clearer and more dramatic experimental demonstration. . . .Ultimately, however, homoreflexes may prove to be more basic and more ubiquitous" (p. 79). Although homoreflexes may be basic and ubiquitous, the experimental analysis of this type of conditioning presents special methodological challenges. The homoreflex CS is not, like the typical heteroreflex CS, "neutral"—rather, the homoreflex CS is a less intense version of the US. Little is known about the optimal way of evaluating conditional responding with this sort of CS. For example, in the case of homoreflexes (and in contrast with heteroreflexes) the CS is an inherent part of the US. As discussed by Dworkin, the traditional control procedures

used by learning researchers, which have been developed in heteroreflex studies, are not readily applicable to the study of homoreflexes (e.g., unpaired CS–US control groups). As suggested by Kim et al. (1999), "future research on homoreflexes in general, and intraadministration associations in particular, will have to develop control procedures suitable to this type of learning" (p. 502). Experiment 3 was conducted to evaluate CCRs elicited by DOCs using such a control procedure.

Experiment 3

It has been suggested that pMor duplicates DOCs that had previously signaled a larger effect of morphine and that pMor-elicited hyperalgesia is a CCR elicited by these DOCs. However, it is possible that this hyperalgesia represents a sensitized response, rather than a CR. For example, a small morphine dose (such as pMor) might elicit hyperactivity as a nonassociative, sensitized response in morphine-experienced rats (e.g., Powell & Holtzman, 2001), and the short response latencies seen in response to pMor on the tail-flick test may be secondary to this hyperactivity. The results of Experiment 2 suggest that the effects of pMor are indeed associative, as this small dose of the drug elicited hyperalgesia in LMor rats, but not in SMor rats. Prior to the test, rats in both groups received the same dose of the drug (5.0 mg/kg) equally often (six times) and at the same intervals (once every other day). However, it is conceivable that the protracted opiate effect resulting from the LMor administration procedure favored the development of sensitized responding more than did the rapid effect resulting from the SMor administration procedure. The purpose of Experiment 3 was to evaluate the ability of DOCs to elicit CCRs in a preparation not subject to an alternative nonassociative interpretation, such as sensitization.

On the basis of an intraadministration analysis, the putative CS (DOCs) and US (later, larger drug effect) are inevitably paired with each other. Experiment 3 used a procedure in which the pharmacological CSs and USs need not be presented in the order that is inevitably present in intraadministration association studies. To evaluate the role of sensitized responding in pharmacological cueing, Experiment 3 used an intradrug conditioning procedure, rather than the intraadministration procedure used in

Experiments 1 and 2. Siegel et al. (2000) distinguished the two types of pharmacological conditioning procedures. Intraadministration associations are hypothesized to inevitably form following certain types of drug administration and are assessed by presenting the small, early drug effect on a test trial. Intradrug associations are explicitly trained by administering a small dose of a drug prior to a larger dose of that same drug. There is evidence that, following such paired presentations of two doses of the same drug, the first, smaller dose serves as a cue for the later, larger dose (Cepeda-Benito & Short, 1997; Greeley, Lê, Poulos, & Cappell, 1984). For example, Greeley et al. (1984) used an intradrug conditioning procedure to demonstrate that a small dose of ethanol could serve as a CS for a larger dose of ethanol. Rats in one group (paired) were intraperitoneally injected with a low dose of ethanol (0.8 g/kg) 60 min prior to a high dose of ethanol (2.5 g/kg). Another group of rats (unpaired) received the low and high doses on an unpaired basis. When tested for the tolerance to the hypothermic effect of the high dose following the low dose, paired rats, but not unpaired rats, displayed tolerance. Moreover, if the high dose of ethanol was not preceded by the low dose, paired rats failed to display their usual tolerance. This tolerance, dependent on an ethanol–ethanol pairing, was apparently mediated by a thermic CCR; paired rats, but not unpaired rats, evidenced hyperthermia in response to the low dose of ethanol.

The procedure used in Experiment 3, with intravenous morphine, was similar to that used by Greeley et al. (1984) with intraperitoneal ethanol. During each day of the tolerance-development phase of Experiment 3, rats assigned to a forward-paired group received a brief intravenous infusion of a small dose of morphine (1.0 mg/kg) 10 min prior to a brief intravenous infusion of a large dose of the opiate (10.0 mg/kg). Rats assigned to a backward-paired group received the large dose 10 min prior to the small dose. Following tolerance development, the effect of 1.0 mg/kg intravenous morphine on TFL was assessed. If the small dose serves as a CS, it would be expected that forward-paired rats should display hyperalgesia on the test session. However, if this hyperalgesia results from sensitization to the drug, it would be expected that the equivalently drug-exposed backward-paired rats should also display hyperalgesia on the test session.

Method

Drugs and design. Depending on group assignment and phase of the experiment, rats received various intravenous infusions: a small dose of morphine (m; 1.0 mg/kg), a large dose of morphine (M; 10.0 mg/kg), or physiological saline. The saline infusions were volumetrically equated with either the m infusion or the M infusion (s and S, respectively). The parametric characteristics of the infusions used in Experiment 3 are summarized in Table 2.

Insert Table 2 here

The exact duration of all infusions depended on the weight of the rat but ranged from approximately 17 to 21 s.

The design of Experiment 3 is summarized in Table 3.

Insert Table 3 here

Rats were assigned to one of six independent groups. All rats received eight daily sessions during the tolerance-development phase of the experiment. During each tolerance-development session, rats received two intravenous infusions, with a 10-min interval between the infusions. Groups differed with respect to the content of each of the tolerance-development infusions—either m, M, or S, and the order in which the substances were infused. A CCR test session was conducted on the day following the last tolerance-development session. For this test session, rats received a single infusion, and TFL was assessed. Groups differed with respect to the substance infused on the CCR test session, m or s. The tolerance-development and training conditions are indicated by group abbreviations, thus rats in group mM–m were forward-paired experimental rats. These mM–m rats received m followed by M during each tolerance-development session and were tested with m on the CCR test session. Rats assigned to the Mm–m group were backward-paired experimental rats. These Mm–m rats were treated like mM–m rats,

except the order of the small and large doses was reversed during tolerance development. Control rats assigned to the Mm–s and mM–s groups were treated like rats assigned to the mM–m and Mm–m groups, respectively, during tolerance development, but they were infused with saline, rather than the opiate, on the CCR test session. Control rats assigned to the remaining two groups, mS–m and Sm–m, were tested with m on the test session but had no pretest experience with the large morphine dose. Rather, these rats received the small morphine dose either 10 min before (mS–m) or 10 min after (Sm–m) a saline infusion on each tolerance-development session.

Subjects, surgical preparation, and apparatus. Eighty-three experimentally naive rats of the same gender and strain as those used in Experiments 1 and 2 (weighing 275–375 g at the start of the experiment) were implanted with chronic intravenous cannulae. In Experiment 3 the cannula design was modified from that used in Experiments 1 and 2 such that the cannula exited from the rat's back (rather than the top of its head). The catheters used in Experiment 3 were assembled from a commercially available guide cannula assembly (Plastic One, Roanoke, VA; Model C313G). Twenty centimeters of silastic tubing (used for the cannula in Experiments 1 and 2) were attached to the guide cannula. Under general anesthetic the tip of the catheter was implanted into the right jugular vein, approximately 1 cm from the heart, and the cannula was brought out to the rat's back and secured between shoulder blades. Rats were randomly assigned to one of the six groups indicated in Table 3. The apparatus used for intravenous infusions and the assessment of TFL were the same as those described previously.

Procedure

Tolerance development. Prior to each tolerance-development session, the rat's cannula was flushed with heparinized saline, and at the end of the session, the cannula was filled with dextrose solution (as described in Experiment 1).

On each of the eight tolerance-development sessions, rats received two infusions, with the content of the infusions for rats assigned to each of the six groups indicated in Table 3. At the start of each tolerance-development session, the rat was placed in the infusion chamber with its cannula attached to the infusion pump. Fifteen minutes later,

rats were intravenously infused with either 1.0 mg/kg morphine (mM–m, Mm–s, and mS–m groups), 10.0 mg/kg morphine (Mm–m and Mm–s groups), or saline (Sm–m group). Ten minutes after the termination of the first infusion, each rat was infused with either 10.0 mg/kg morphine (mM–m and Mm–s groups), 1.0 mg/kg morphine (Mm–m, Mm–s, and Sm–m groups), or saline (mS–m group).

Following the second infusion, the rat was detached from the apparatus and was kept in the infusion chamber for 30 min. Thirty minutes after the second infusion, TFL (from 50 °C water) was assessed, and the rat was returned to its home cage.

CCR test. The CCR test was conducted on the day following the last tolerance-development session. Rats were infused either with 1.0 mg/kg morphine (mM–m, Mm–m, mS–m, and Sm–m groups) or saline (mM–s and Mm–s groups). Tail-flick latency (from 48 °C water) was measured at 15, 30, 45, and 75 min post-infusion. For the 15-min, 30-min, and 45-min determinations, the rate were briefly removed from the chambers for TFL assessment and then returned to the chambers. Following the 75-min determination of TFL, the rats were returned to their home cages.

Results

Tolerance development. The mean TFLs (±1 SEM) seen in all groups for each of the eight tolerance-development sessions are shown in Figure 5.

Insert Figure 5 here

Rats infused with a total of 11.0 mg/kg during each tolerance-development session (the four groups receiving m and M during each session, in whatever order) displayed substantial analgesia, compared with rats infused with only 1.0 mg/kg morphine (the two groups receiving m and S during each session, in whatever order). Moreover, rats infused with 11.0 mg/kg during each session displayed analgesic tolerance over the eight sessions.

A mixed-design (one factor between and one factor within) ANOVA of the data summarized in Figure 5 indicated a significant groups effect, $F(5, 77) = 43.66$, $p < .001$.

Tukey's unequal *n* HSD tests indicated that rats in all four groups infused both m and M on each session (mM–m, Mm–m, mM–s, and Mm–s groups) displayed longer TFLs than did rats in either group infused with m and S on each session (mS–m and Sm–m groups; all $ps < .001$).

The ANOVA also revealed a significant Groups × Sessions interaction, $F(35, 539) = 14.38$, $p < .001$. As may be seen in Figure 5, this interaction resulted because rats in the four groups infused with 11.0 mg/kg morphine on each tolerance-development session, but not rats infused with 1.0 mg/kg morphine on each session, displayed decreased TFLs across sessions. A mixed-design ANOVA of only the four groups infused both m and M on each session revealed a significant sessions effect, $F(7, 371) = 136$, $p < .001$. A similar analysis for the two groups infused with m and S on each tolerance-development session revealed no significant sessions effects, $F(7, 168) = 1.4$, $p = .20$.

CCR test. Two control groups were tested with m, differing only with respect to the order in which S and m were presented during tolerance development (mS–m and Sm–m groups). There was no appreciable difference in test session TFLs between these two groups, and for simplicity in data presentation, they are collapsed into a combined m-control group. Similarly, the two control groups tested with s that differed only with respect to the order in which M and m were presented during tolerance development (mM–s and Mm–s groups) were combined into an s-control group. The mean TFLs (±1 SEM) for the forward-paired experimental group (mM–m), the backward-paired experimental group (Mm–m), and the two combined control groups for each postinfusion assessment are shown in Figure 6.

Insert Figure 6 here

As can be seen in Figure 6, despite the fact that rats assigned to the mM–m and Mm–m groups were exposed to both the high and low morphine doses prior to the test, rats assigned to the mM–m group displayed shorter TFLs than did rats assigned to the

Mm–m group. A mixed-design (one factor between and one factor within) ANOVA of the data summarized in Figure 6 indicated a significant groups effect, $F(3, 79) = 8.00$, $p < .001$. Subsequent unequal n HSD tests indicated that, following m infusion, rats assigned to the mM–m group responded significantly more quickly on the CCR test than did rats assigned to the Mm–m group ($p < .001$). Moreover, mM–m rats responded significantly more rapidly than did rats assigned to control groups (all ps $\leq .05$). The control groups did not differ significantly from each other. Examination of Figure 6 indicates that the backward-paired (Mm–m) rats responded more slowly than did rats assigned to control groups, suggesting that the backward pairings resulted in an inhibitory association between the DOC and the later, larger drug effect (Siegel & Domjan, 1971, 1974); however, the differences between Mm–m rats and rats assigned to control groups did not attain conventional levels of statistical significance.

Discussion

The purpose of Experiment 3 was to evaluate whether m elicits hyperalgesia, conditional on that small dose having been a signal for M. The results indicated such conditional compensatory responding. Rats in a forward-paired experimental group received tolerance-development sessions in which 1.0 mg/kg morphine was intravenously administered 10 min prior to 10.0 mg/kg morphine. Rats in a backward-paired experimental group received the two doses of the opiate in the reverse order. When TFLs subsequently were assessed following 1.0 mg/kg morphine, forward-paired rats (mM–m group) responded more quickly than did backward-paired rats (Mm–m group), despite similar pretest exposure to morphine. In fact, mM–m group rats responded to m on the CCR test with shorter latencies than did (a) rats tested with m but with no prior exposure to M (mS–m and Sm–m groups) and (b) rats with prior exposure to both m and M but tested with s (Mm–s and mM–s groups). The results indicate that m elicited a CCR of hyperalgesia in mM–m rats.

The association that develops between a small dose of a drug administered prior to a larger dose of that same drug has been termed an intradrug association (Siegel et al., 2000). The results of the present experiment, demonstrating an intradrug association as

revealed by conditional compensatory responding in rats trained with intravenously infused morphine, are similar to results previously reported by Greeley et al. (1984) in rats trained with intraperitoneally injected ethanol. Greeley et al. reported that a CCR of hyperthermia was apparent in response to the smaller dose of ethanol that previously had signaled a larger dose of ethanol (and its hypothermic effect). Neither the results reported here nor the Greeley et al. results are readily explained by a nonassociative interpretation, such as drug sensitization. For example, in the present experiment both mM–m and Mm–m rats have the same pretest exposure to morphine—they should be equally sensitized to the effects of the opiate. The fact that mM–m rats but not Mm–m rats displayed hyperalgesia in response to m indicates that the order in which m and M are presented prior to the test determines whether m elicits hyperalgesia (as would be expected if an intradrug association formed during tolerance development). The results of Experiment 3 support the suggestion that the hyperalgesia seen in the response to the drug-onset cue in rats with a history of gradual morphine infusions (Experiments 1 and 2; Kim & Siegel, 2001; Kim et al., 1999) results from an intraadministration association, rather than drug sensitization.

General Discussion

According to a conditioning analysis, chronic drug tolerance results because cues present at the time of drug administration function as CSs and elicit CCRs that attenuate the effect of the drug. Several researchers have hypothesized that, within each drug administration, DOCs become associated with the later, larger drug effect and that these DOCs, in common with exteroceptive cues, are CSs that elicit CCRs (e.g., Goddard, 1999; King, Bouton, & Musty, 1987; Mackintosh, 1987; Tiffany, Petrie, Baker, & Dahl, 1983). Recently, Kim et al. (1999) provided evidence for such an intraadministration association. They demonstrated that following the development of analgesic tolerance acquired by repeated gradual intravenous infusions of morphine, rats respond with a CCR of hyperalgesia following a pMor infusion—an infusion consisting of only the initial 10% of the gradual morphine infusion used.

Kim et al. (1999) acknowledged that there was some arbitrariness in selecting as a DOC the first 10% of the longer morphine infusion used during tolerance development. That is, a pMor infusion of a different duration and/or dose may better capture the CS properties of the initial drug effect. However, in the case of an intraadministration association (as in the case of other homotopic CRs; see Dworkin, 1993) the fact that the CS is simply a weaker version of the US complicates analysis of effective CS characteristics. For example, increasing the intensity of the pMor cue (to increase its salience and thus its ability to conditionally elicit hyperalgesia) also increases its unconditional analgesic effect. Experiment 1 was designed to evaluate the effectiveness of various pMor infusions in eliciting conditional hyperalgesia. The concentration of morphine used in the pMor assessment was the same as that used during tolerance development, and various lengths (and thus doses) of pMor were evaluated: 5%, 10%, and 20% of the gradual infusion used during pretest tolerance-development sessions. The results of Experiment 1 indicated that the 10% pMor was more effective than the shorter or longer versions of the pharmacological CS, thus this 10% pMor was used in subsequent experiments.

Kim et al. (1999) reasoned that DOCs are more salient than simultaneously presented environmental cues; thus, if the drug is administered in a way that promotes the development of DOCs as signals for the later and larger drug effect, there may be little evidence of environmentally specific tolerance. Kim et al. developed two morphine administration procedures, both involving intravenous infusion of 5.0 mg/kg of the opioid that differed only in terms of infusion duration. The LMor infusion, but not the SMor infusion, should promote the development of intraadministration associations. As would be expected if DOCs overshadow environmental cues, Kim et al. found that morphine tolerance was seen when the drug was administered following a nondrug cue (CS–) when rats were trained and tested with LMor infusions but not when rats were trained and tested with SMor infusions. Experiment 2 was designed to assess whether the tolerance seen following LMor infusions (but not following SMor infusions) in the presence of CS– results because LMor-trained rats (but not SMor-trained rats) learn an

intraadministration association. In Experiment 2, following tolerance development, both LMor- and SMor-trained rats were infused with pMor following CS– presentation. Only LMor rats displayed conditional compensatory responding. Thus, the results of Experiment 2 confirm Kim et al.'s suggestion that tolerance seen in a nondrug environment is mediated by CCRs elicited by DOCs.

In Experiments 1 and 2, it was suggested that the pMor-elicited hyperalgesia seen in rats with a history of LMor administration is a CCR elicited by DOCs. However, it is possible that this pMor-elicited hypersensitivity to nociceptive stimulation is a manifestation of a nonassociative sensitized response, rather that an intraadministration association. Experiment 3 was designed to determine whether pMor-elicited hyperalgesia in morphine-experienced rats represents an unconditionally elicited sensitized response or a CCR. During the tolerance-development phase of Experiment 3, rats received an intravenous infusion of m (1.0 mg/kg) either before (forward) or after (backward) infusion of M (10.0 mg/kg). Following tolerance development, rats in the forward group displayed hyperalgesia in response to m. Inasmuch as both forward and backward rats had the same exposure to morphine during tolerance development, the hyperalgesia seen in forward rats likely represents an associative effect rather than a nonassociative effect.

Examination of the tolerance development data and CCR test data of Experiments 1-3 might suggest that the magnitude of conditional compensatory responding is modest, in comparison with the magnitude of tolerance that is hypothesized to be mediated by these CCRs. However, in these studies of intraadministration associations, the CCR is assessed on pMor test trials following LMor administrations (Experiments 1 and 2) or following a 1.0 mg/kg dose of morphine in rats that had previously received 1.0 mg/kg–10.0 mg/kg pairings of the drug (Experiment 3). These procedures correspond to the use of CS-alone test trials to assess conditioning that occurs following CS–US pairings. As noted by several investigators (e.g., Mackintosh, 1983, p. 210; Rescorla, 1980), the extent of conditioning evaluated on CS-alone test trials likely is underestimated because of generalization decrement resulting from the difference between training (CS followed by

US) and testing (CS alone) conditions. Furthermore, a distinctive feature of the intraadministration CS is that it unconditionally elicits a response that attenuates the expression of the CCR.

The results of Experiments 1–3 complement those presented in prior reports of intraadministration associations (Kim & Siegel, 2001; Kim et al., 1999) and intradrug associations (Cepeda-Benito & Short, 1997; Greeley et al., 1984). It is clear that a small dose of a drug can serve as a cue for a larger dose of that drug, and such associations form (even if there are no experimenter-presented pairings of pharmacological CS and US) if the drug-administration procedure results in a protracted period of drug effect—DOCs are ineluctable signals of the subsequent larger drug effect.

Chapter 3:
Latent Inhibition

As demonstrated in Experiment 3 of Chapter 2, a small morphine infusion can function as a pharmacological CS for a large dose of the opiate. That is, following repeated pairings of the small morphine infusion with the large morphine infusion, presentation of the small morphine infusion alone elicits a CCR of hyperalgesia. The research presented in Chapter 2, Experiment 3 provides support for the conditioning account of drug tolerance and CCR expression. However if conditioning contributes to tolerance it would be expected that CS manipulations known to affect the course of Pavlovian conditioning should similarly affect the course of tolerance development and CCR expression. An example of such manipulation is latent inhibition (for review see Siegel, 1989; Siegel at el., 2000).

Latent inhibition, otherwise known as a CS preexposure effect, is a manipulation that attenuates development of the CS-US associations. This manipulation involves repeated presentation of a CS prior to pairing of that CS with an US (Lubow, 1973; Lubow & Moore, 1959; Siegel, 1969). It has been demonstrated, with a variety of species and many conditioning preparations, that such preconditioning experience with the CS retards the acquisition of conditional responses (for review see Lubow, 1973).

Since latent inhibition is a well established Pavlovian conditioning phenomenon, it would be expected that if conditioning contributes to drug tolerance, latent inhibition should similarly retard CCR acquisition. Thus, subjects with extensive experience with drug administration cues (CS) prior to the pairing of these cues with the drug effect (US) should develop tolerance at lower rate than subjects with minimal exposure to these cues, even though the subjects with both extensive and minimal CS preexposure have the same history of drug administration. Such an effect of CS-preexposure has been established with respect to tolerance to the immunostimulatory effect of Poly:IC and the anorectic effect of cholecystokinin (see Siegel et al., 1999). Especially relevant to the present

experiment are reports that tolerance to the analgesic effect of morphine is retarded by the latent inhibition procedure (Siegel, 1977; Tiffany & Baker, 1981). The results of these experiments demonstrated that preconditioning exposure to environmental cues that subsequently signaled morphine retarded the development of morphine tolerance. For example, Siegel (1977) exposed rats to the drug administration cues either on 1 or 18 occasions prior to the tolerance development. The cues preexposure trials consisted of saline administration in the experimental room followed by hot plate test of analgesia. The tolerance development phase was conducted as the preexposure phase except the saline injections were replaced by morphine injections (5 mg/kg). Rats in the group that received 18 preexposures to the drug administration cues developed tolerance to the analgesic effect of morphine relatively slowly, compared to rats in the group that received only a single exposure to the drug administration cues.

If DOCs contribute to tolerance to the analgesic effect of morphine, preexposure to these pharmacological cues, like preexposure to drug-paired environmental cues, should retard the development of tolerance. This assumption was examined using intradrug association. That is, repeated presentation of a small morphine infusion prior to tolerance development (repeated presentation of the small followed by a large morphine infusion) should attenuate acquisition of morphine tolerance as compared to repeated presentation of saline infusions prior to tolerance development. The small morphine infusion following morphine preexposure should be less likely to acquire CS properties than the small morphine infusion following saline preexposure. Thus, presentation of the small morphine infusion after the tolerance acquisition should induce attenuated CCRs expression in morphine preexposed as compared to saline preexposed subjects.

Design

The experiment was conducted in three phases: preexposure, tolerance development, and CCR test. During the preexposure phase, all rats received two intravenous infusions per day (with an inter-infusion interval of approximately 4 h). For rats assigned to the m-preexposed group, one daily infusion consisted of a small dose of morphine (1 mg/kg), and the second daily infusion consisted of physiological saline. For

rats assigned to the s-preexposed group, both daily infusions consisted of physiological saline. The m-preexposed group was presented with both morphine and saline infusions in order to dissociate the pharmacological cues (the small morphine dose) from the environmental cues (a distinctive experimental room and an infusion procedure). The saline infusions provided additional exposure of the environmental cues without the pharmacological cues to further reduce the importance of the environmental cues.

The tolerance development phase was conducted as the tolerance development of the forward condition (mM-m) Experiment 3 of Chapter 2. That is, all subjects were presented with the small morphine infusion (1 mg/kg) followed in 10 minutes by the large morphine infusion (10 mg/kg). In order to examine tolerance acquisition to the analgesic effect of morphine, tail flick latency (TFL) was assessed 30 min post administration of the large morphine dose. On the CCR test session, all subjects were presented with the small morphine infusion and the TFL was examined 10, 15, 30, 45, and 75 min post infusion.

Method

Subjects and Surgical Preparation

The subjects were 16 experimentally naive, male Sprague-Dawley rats (Charles River, St. Constant, Quebec, Canada) ranging in weight from 275-325 g at the beginning of the experiment. The animals were individually housed with ad lib. access to food and water. The subjects were implanted with chronic intravenous cannulae as previously described in Chapter 2 Experiment 3.

Drugs, Infusion Rates, and Apparatus

As in Chapter 2, Experiment 3, the two substances infused were morphine sulfate solution (British Drug House) dissolved in physiological saline (5 mg/ml) and physiological saline. Depending on the phase of the experiment and group assignment, subjects were infused intravenously with the small morphine dose (m, 1 mg/kg), the saline infusion (s), volumetrically equivalent to the small opiate infusion, and the large morphine infusion (M, 10 mg/kg). The rate of drug administration was 0.28 and 2.8

ml/min for small and large infusions, respectively. The duration of the infusions was approximately 13-17 sec, depending on the weight of the subjects.

All infusions were administered using Med Associates variable rate infusion pumps operated by the Med Associates system and Med PC for Windows software (St. Albans, VT). The subjects were placed in Med Associates self-administration chambers, connected to the infusion pumps with a cannula connector (Plastic One, Roanoke, VA), and a 0.025-micrometer micropore filter (Sartorium Filter, Sartorius, AG, Göttingen, Germany).

As in Chapter 2, analgesia was assessed using tail-flick procedure. The tail of lightly restrained rat was immersed 5 cm into warm water bath. The latency of tail withdrawal was noted. The water temperature was 50 ^{0}C during the tolerance development phase and 48 ^{0}C during the CCR test phase. The water temperature was decreased for CCR testing in order to increase the likelihood of observing a hyperalgesic response.

Procedure

Preexposure. During each of the 14 preexposure days the subjects were presented with two trials, with about four hours between trials. For rats assigned to the m-preexposed group (n=8), one daily infusion consisted of the small dose of morphine, and the second consisted of saline (the order being randomly determined). For rats assigned to the s-preexposed group (n=8), both daily infusions consisted of saline.

Prior to each infusion session, subjects were transported to the experimental room, weighed, and their cannulae were flushed with heparin solution. They were connected to the infusion pumps, placed in the chambers, and left undisturbed for 15 minutes prior to the infusion. The m-preexposed rats were infused with either m or s and the s-preexposed rats were infused with s. Animals were then disconnected from the infusion pumps and remained in the apparatus for additional 40 minutes. The rats were then removed from the chambers, infused with a dextrose solution, and returned to their home cages.

Tolerance development. Following the preexposure phase, all rats received seven daily tolerance development sessions. On each session the rats from both groups were administered two morphine infusions, the small dose followed by the large dose, with 10 min between each infusion. Rats were transported to the experimental room, prepared for the session as previously described in the preexposure phase, placed in the chambers, and left undisturbed for 15 minutes. They were infused with the small morphine infusion followed in 10 minutes by the large morphine infusion. They were then disconnected from the pumps, infused with dextrose solution, and remained in the chambers for 30 minutes. As in Experiment 3 of Chapter 2, on each tolerance development day, 30 minutes following the second infusion the TFL was assessed in 50 ^{0}C water bath and the rats were returned to the home cages.

CCR test. On the day following the last tolerance development session the subjects were challenged with the small morphine infusion. The rats were transported to the experimental room, prepared as described in the preexposure phase, and connected to the infusion pumps in the chambers. They were left undisturbed for 15 minutes and then received the small morphine infusion. Following the small morphine infusion the rats were disconnected from the pumps and TFL (48 ^{0}C water bath) was assessed at 10, 15, 30, 45, and 75 min post infusion.

Results and Discussion

Tolerance Development

The mean (±1 *SEM*) TFLs following each tolerance development session for m-preexposed and s-preexposed groups are shown in Figure 7.

Inset Figure 7 here

As can be seen in Figure 7, tolerance to the analgesic effect of morphine was apparent (i.e., TFLs decreased across tolerance development sessions). The effect of sessions was statistically significant, $F(6, 84) = 37.75$, $p < .001$. Although there was a trend for m-preexposed rats to develop tolerance at a slower rate than s-preexposed rats,

neither the effect of groups, nor the Groups X Session interaction, was statistically significant, $F(1, 14) = 1.45, p > .24$, and $F(6, 84) = 1.42, p > .21$, respectively.

CCR Test

During the CCR test session all subjects were administered 1 mg/kg morphine. The mean (±1 *SEM*) TFLs for each group at each post-infusion test interval is displayed in Figure 8. As can be seen in the Figure 8, the m-preexposed group displayed shorter response latencies than the s-preexposed group.

Inset Figure 8 here

A mixed-design (one factor between and one factor within) ANOVA of the data summarized in Figure 8 revealed significant group effect $F(1, 14) = 4.99, p < .05$. Thus, the subjects presented with morphine prior to tolerance development (m-preexposed group) demonstrated significantly shorter response latency than the subjects presented with saline prior to the tolerance development phase. Additionally there was a significant time effect $F(2, 56) = 2.68, p < .05$, however the Group x Time interaction was not significant $F(4, 56) = 2.15$, $p > .08$

Even though the small morphine preexposure did not significantly attenuate acquisition of tolerance to the analgesic effect of morphine, the pharmacological cue preexposure attenuated the CCR expression. Based on the conditioning account of tolerance, acquisition of CS elicited CCR mediates tolerance development. However, besides conditioning other mechanisms might at least partially contribute to tolerance development. It could be hypothesized that although the pharmacological CS preexposure attenuated CCR acquisition (as demonstrated by the CCR test), the attenuation was not sufficient to significantly alter the tolerance acquisition. Previous research (Lubow, 1973; Siegel, 1969) demonstrated that increasing number of CS presentations prior to CS-US conditioning trials increased the latent inhibition effect. Thus further examination of pharmacological cues preexposure effect on tolerance development should include increased number of small morphine preexposure sessions.

Chapter 4:
CS-Elicited Morphine Withdrawal Assessed with Acoustic Startle Response

As discussed in Chapter 1, drug-experienced subjects display withdrawal responses when presented with drug associated cues but not administered the drug (e.g., Falls & Kelsey, 1989; McDonald & Siegel, in press). A number of indices of morphine withdrawal have been identified. These include hyperalgesia (e.g., Tilson, Rech, & Stolman, 1973), loss in body weight (e.g., Mansbach, Gold, & Harris, 1992), increased frequency of wet dog shakes (e.g., MacDonald & Siegel, in press), and genital licks (e.g., Falls & Kelsey, 1989). Research described in this chapter used another measure of morphine withdrawal, attenuated acoustic startle response (ASR).

Assessment of the attenuated ASR involves measurement of subjects' reflexive response to brief bursts of intense, auditory stimulation. The attenuated ASR as an index of withdrawal has many advantages; it is easily quantified and requires no training of subjects (Davis, Gendelman, Tischler, & Gendelman, 1982). It has been demonstrated that the magnitude of the startle response is altered during morphine withdrawal. For example, Mansbach et al. (1992) studied the attenuated ASR as a measure of naloxone-elicited morphine withdrawal. The researchers implanted rats with morphine pellets and repeatedly administered either naloxone or saline prior to the presentation of 122 dB acoustic startle stimuli. The rats administered naloxone decreased the magnitude of startle response as compared to the animals administered saline. Additionally, Kalinchev and Holtzman (2003) examined the attenuated ASR as an index of spontaneous morphine withdrawal. The investigators administered 105 dB acoustic stimuli to morphine experienced subjects following removal of the osmotic pumps delivering morphine. Such discontinuation of morphine delivery resulted in a decrease of the ASR. Thus naloxone-elicited and spontaneous morphine withdrawal induce an attenuation of the ASR.

Although attenuated startle response has been established as a measure of morphine withdrawal, the effect of CS elicited withdrawal on startle response has not

been evaluated. Experiment 1 was designed to evaluate the effectiveness of startle response as a measure of exteroceptive CS elicited withdrawal. In this study, a distinctive environment of drug administration was identified as the exteroceptive CS. In Experiment 2, the attenuated startle response was applied as a measure of withdrawal induced by a pharmacological CS using the intradrug association paradigm described in Chapter 2, Experiment 3.

Experiment 1

There are several demonstrations that withdrawal responses are elicited by drug-associated environmental cues. For example, Falls and Kelsey (1989) have illustrated the importance of the drug-paired environment in the display of morphine withdrawal symptoms. In the Falls and Kelsey experiment, "paired" rats were administered morphine in a distinctive environment of the experimental room and saline in an alternative environment (the colony room). "Unpaired" rats were administered saline in the distinctive environment and morphine in the alternative environment. On the test day, all subjects were administered saline in the distinctive environment. The researchers reported that the "paired" rats displayed more behavioral withdrawal responses than the "unpaired" rats. The present study evaluated the attenuated ASR as a measure of exteroceptive-CS elicited morphine withdrawal. That is, it was hypothesized that following saline presentation in the drug associated environment, the rats from the paired group would display attenuated ASR as compared to the rats from the unpaired condition.

Design

This experiment consisted of three phases: startle stimuli habituation, drug administration, and test. During the startle stimuli habituation phase all subjects were administered three, daily, startle stimuli sessions. Each startle stimuli session consisted of 60 tone presentations (10 kHz frequency, 20 msec duration) administered once per minute. The intensity of 30 of the tones was 105 dB sound pressure level C-weighting [SPL (C)] and the intensity of 30 of the tones was 115 dB SPL (C).

During the subsequent drug administration phase of the experiment, rats from the paired group were repeatedly intravenously infused with morphine in a distinctive

environment (an animal holder located in a startle apparatus chamber) and saline in an alternative environment (a home cage located in a colony room). The rats from the unpaired group were repeatedly infused with saline in the distinctive environment and morphine in the alternative environment. During this drug administration phase startle stimuli were not presented. On the test, all rats were infused with saline in the startle apparatus and the startle stimuli were again presented.

Method

Subjects and surgical preparation. The subjects were 32 experimentally naive, male, Sprague-Dawley rats (Charles River, St. Constant, Quebec, Canada) with weights ranging from 275-325g at the beginning of the experiment. The animals were individually housed with ad lib. access to food and water. The subjects were implanted with chronic intravenous cannulae as previously described (Chapter 2, Experiment 3).

Apparatus, drugs, and infusion rates. Drug administration sessions were conducted either in the clear plastic home cage (23 cm x 45 cm x 20 cm) or in the acoustic startle response system (Coulbourn Instruments, Allenton, PA). The acoustic startle response system consisted of an acoustically isolated test chamber with four startle platforms and four animal holders (each 11 cm x 18 cm x 10 cm). A multi-syringe Harvard Apparatus Compact Infusion Pump (Model No. 975; Harvard Apparatus Co., Mills, MA) was used to deliver either morphine or saline solution. The subjects were connected to the infusion pump through a cannula connector (Plastic One, Roanoke, VA), and a 0.025-micrometer micropore filter (Sartorium Filter, Sartorius, AG, Göttingen, Germany). Startle response data was recorded with Coulbourn Acoustic Startle System Software version 3.0.

The subjects were infused intravenously with physiological saline and morphine sulfate solution (British Drug House) dissolved in physiological saline. The morphine infusions delivered 15 mg/kg of morphine in a volume of 3 ml/kg and infused at a rate of 4.1 ml/min. The physiological saline infusions delivered 3 ml/kg of saline using the same infusion rate as the morphine infusion. The duration of the infusions was approximately 15-20 sec, depending on the weight of the subjects.

Acoustic startle stimuli. Sixty, 10 kHz, acoustic startle stimuli were presented during each startle stimuli habituation session and during the test. The startle stimuli consisted of thirty 105dB SPL (C) and thirty 115dB SPL (C), delivered once a minute for 60 min. The stimuli were presented randomly within three, 20-min blocks of ten 105dB SPL (C) and ten 115dB SPL (C) tones. Each tone was 20 msec in duration. The stimuli had rise and decay times of 0.1 msec. Subjects' responses to each stimulus presentation were recorded once every msec, for a period of 200 msec post stimulus presentation. The background noise was 60 dB SPL (C).

Procedure

Startle stimuli habituation. All subjects received three daily habituation sessions. Prior to each session, the rats were transported from the colony to the experimental room and weighed. Rats' cannulae were flushed with 0.1 ml of heparin solution, and the rats were placed in animal holders located in the startle chamber. The rats were left undisturbed for 5 min prior to the first stimulus presentation. The rats were presented with 60 startle stimuli, one per minute. After the last startle stimulus presentation the rats were removed from the holders, infused with dextrose solution, placed in the home cages, and returned to the colony.

Drug administration. For the drug administration phase, the subjects were divided randomly into two groups: paired (n = 16) and unpaired (n = 16). The subjects from the paired group were infused with morphine in the distinctive environment of the startle apparatus chamber and saline in the home cage. The subjects from the unpaired condition were administered morphine infusions in the home cage and saline infusions in the startle apparatus.

All rats received 12 daily infusion sessions, six morphine and six saline sessions. The morphine and saline sessions were delivered on alternate days. On the odd days all subjects were administered morphine and on the even days all subjects were administered saline.

The subjects assigned for the infusion in the apparatus were transported to the experimental room. After transport they were weighed, and their cannulae were infused

with heparin solution. The animals were connected to the infusion pump and they were placed in the animal holders located within the startle apparatus. The rats were left undisturbed for 5 min. Following the acclimatization time the animals were infused with either morphine or saline (paired and unpaired group, respectively). The rats were then detached from the infusion pump, and they remained in the startle apparatus for additional 60 min. The subjects then were removed from the startle apparatus, infused with dextrose solution, and transported in their home cages to the colony room.

On alternate days the animals were infused in the home cages located in the colony room. The subjects were weighed in the colony room and their cannulae were flushed with heparin solution. The rats were connected to the infusion pump and were returned to the home cages. For 5 min the animals were allowed free movement within the home cage while connected to the infusion pump. They were then infused with either saline or morphine infusion (paired and unpaired group, respectively). The animals were detached from the infusion pump, dextrose solution was injected into their cannulae, and the animals were returned to their home cages.

Test. During this phase all subjects were infused with saline in the startle apparatus. Two days after the last morphine administration the subjects were transported to the experimental room, connected to the infusion pump, and placed in the animal holders. Five min later the rats were infused with saline. The animals were disconnected from the infusion pump and startle stimuli were presented as in the startle stimuli habituation session.

Analysis

Throughout the startle stimuli habituation phase and the test phase, 60 stimuli were presented: thirty 105 dB SPL (C) and thirty 115 dB SPL (C). In order to decrease variability between the subjects, an ASR difference score was calculated. That is, the ASR on the third habituation session (baseline startle response) was subtracted from the ASR on the test. Since the initial period after acoustic stimulus presentation is considered as a measure of overall activity and not as a response to the stimulus, only the ASR difference score from 31 to 80 msec post stimuli presentation was analyzed (see

Kalinichev & Holtzman, 2003; Mucha & Fendt, 2001). The responses were evaluated separately for 105dB SPL (C) and 115dB SPL (C) stimuli.

Results and Discussion

The results of the test demonstrated that morphine withdrawal is expressed as a decrease in the acoustic startle response. That is, presentation of the environment associated with morphine (the paired group) results in a decrease of the ASR as compared to the presentation of the environment not associated with the drug (the unpaired group). For the paired and unpaired groups, the mean ASR difference score (±1 SEM) for 105 dB SPL (C) and 115 dB SPL (C) startle stimuli, are presented in Figure 9A and 9B, respectively.

Insert Figure 9 here

As can be seen in Figure 9, presentation of the startle stimuli resulted in attenuation of the startle response of the paired group as compared to the unpaired condition. The data summarized in Figures 9A and 9 B were subjected to a mixed-design (one factor between and two factors within) ANOVA. The statistical analysis confirmed the trends apparent in the figure: (a) the rats from the paired condition displayed lower ASR difference scores as compared to the rats from the unpaired condition $F(1, 30) = 5.94$, $p = .02$; (b) the ASR difference score (collapsed across groups) following presentation of the 105 dB SPL (C) stimuli was greater than following presentation of the 115dB SPL (C) stimuli $F(1, 30) = 6.54$, $p < .02$; (c) the Group x Time interaction was significant $F(48, 1440) = 9.45$, $p < .001$.

Previously researchers established that cues associated with morphine administration produce context specific withdrawal (Siegel, 1983; Falls & Kelsey, 1989; Kelsey, Aranow, & Matthews, 1990). Furthermore, cessation of morphine administration and presentation of naloxone or naltrexone to morphine-experienced subjects results in attenuation of the ASR (Kalinichev & Holtzman, 2003; Mansbach et al., 1992). The results of this experiment demonstrate that, in morphine-experience subjects, presentation

of the exteroceptive cues associated with the drug effect induces a decrease of the ASR as compared to presentation of the exteroceptive cues not associated with the drug effect. This finding suggests that the attenuation of ASR is a useful measure of associatively mediated morphine withdrawal.

Experiment 2

In Experiment 2 the attenuation of ASR was employed as a measure of pharmacological CS elicited morphine withdrawal using the intradrug association paradigm. As discussed in Chapter 1, presentation of a CS without administration of the drug (US) results in expression of a pharmacological CR characterized as withdrawal responses. The CRs that imitate the compensatory response unconditionally elicited by a drug are called CCRs. In Chapter 2, Experiment 3 using an intradrug association paradigm, the pharmacological CS (small morphine dose) elicited CCR was evaluated. Specifically, the rats from the mM-m group, trained with the small morphine infusion followed by the large morphine infusion, displayed hyperalgesia when presented with the small morphine infusion alone. Pain sensitivity expressed by the mM-m rats was significantly greater than pain sensitivity expressed by the Mm-m group, trained with the large followed by the small morphine infusion. The design of Experiment 2 was similar to the design of Chapter 2, Experiment 3 except the attenuation of ASR was assessed instead of pain sensitivity as a measure of morphine withdrawal.

Design

This experiment consisted of four phases: startle stimuli habituation, infusion habituation, drug administration, and test. During the startle stimuli habituation phase, the subjects were presented with the startle stimuli on three daily sessions as in the prior experiment. Subsequently, rats were assigned to one of four independent groups: mM-m, mM-s, Mm-m, and Mm-s. Throughout infusion habituation phase all subjects received daily two intravenous saline infusions, separated by a 10 min interval. The lower and upper case of the first and second letter of each group name indicates the volume of the first and second infusion. That is, the subjects from the mM-m and mM-s groups, received the small saline dose followed by the large saline dose, while the subjects from

Mm-m and Mm-s groups, received the large saline dose followed by the small saline dose. All rats were presented with two infusion habituation sessions followed by the drug administration phase. The drug administration phase was conducted as the infusion habituation phase except the saline infusions were replaced by the morphine infusions. That is, the mM-m and mM-s groups were infused with the small morphine followed in 10 min by the large morphine infusions while the Mm-m and Mm-s groups were infused with the large morphine followed in 10 min by the small morphine infusions. The rats were presented with eight drug administration sessions. After drug administration, the test was delivered. On the test all animals were administered the small infusion of either morphine or saline, as indicated by the third letter of the group name: morphine for rats in mM-m and Mm-m groups, and saline for rats in mM-s and Mm-s groups. After the test infusion the subjects were presented with the startle stimuli as in the startle stimuli habituation phase.

Method

Subjects and surgical preparation. Sixty experimentally naïve rats, of the same strain, gender, and weight as those used in the prior experiment were implanted with chronic intravenous cannulae as previously described.

Startle stimuli, drugs, and apparatus. The same acoustic startle stimuli were administered as in the prior experiment.

As in Chapter 2, Experiment 3, the subjects were administered morphine sulfate solution (5 mg/ml) or physiological saline. Based on the group assignment and phase of the experiment, the subjects were infused intravenously with the small dose of morphine (m, 1 mg/kg), the large dose of morphine (M, 10 mg/kg), or physiological saline. The saline infusions were volumetrically equated with either m infusion or M infusion (s and S, respectively). The infusion pump used was the same as described in the prior experiment. The substances were delivered at rates of 0.29 and 2.8 ml/min for the small and the large infusions. The exact duration of all infusions depended on the weight of the rats, but ranged from 13 to 18 sec. The startle apparatus used in this experiment was the same as described in the prior experiment.

Procedure

Startle stimuli habituation. During this phase, all subjects were presented with the startle stimuli on three daily sessions as previously described. The rats were placed in the animal holders located in the chamber of the startle apparatus and were left undisturbed for 5 min. The rats were administered 60 startle stimuli: thirty 105dB SPL (C) and thirty 115 dB SPL (C), 10 kHz, 20 msec in duration as previously described. Following the startle stimuli presentation the rats were removed from the animal holders, infused with dextrose solution, and returned to the animal colony.

Infusion habituation. At the beginning of the infusion habituation phase the rats were assigned to one of the four independent groups, mM-m (n = 16), mM-s (n = 16), Mm-m (n = 15), and Mm-s (n = 13).

Prior to each of the two daily infusion habituation sessions the subjects were transported to the experimental room, weighed, and their cannulae were flushed. They were connected to the infusion pump, placed in the animal holders, and left undisturbed for 5 min prior to the first saline infusion (s for mM-m and mM-s groups, and S for Mm-m and Mm-s groups). Ten minutes following the first infusion, the second saline infusion (S for groups previously infused with s and s for groups previously infused with S) was delivered. Animals were disconnected from the infusion pump and remained in the apparatus for additional 60 min. Subsequently they were removed from the holders, infused with dextrose solution, and returned to their home cages.

Drug administration. The subjects were presented with eight, daily drug administration sessions. This phase of the experiment was conducted as the infusion habituation phase except the saline infusions were replaced by the morphine infusions. The subjects were transported to the experimental room, weighed, infused with heparin solution, connected to the infusion pump, placed in animal holders, and left undisturbed for 5 min. The rats from the mM-m and mM-s groups received m followed by M infusion and the subjects from the Mm-m and Mm-s group received M followed by m infusion. The two infusions were separated by 10 min. After the second infusion the rats were disconnected from the pump and were left undisturbed in the apparatus for 60 min.

Then they were removed from the apparatus, infused with dextrose solution, and returned to the colony room.

Test. On the test the subjects were connected to the infusion pump and placed in the animal holders as previously described. They were left undisturbed for 5 minutes. Rats assigned to the mM-m and Mm-m groups were then infused with m, and rats assigned to the mM-s and Mm-s groups were infused with s. Following the infusion the animals were disconnected from the infusion pump and the startle stimuli were presented for 60 min, one per minute as during the startle stimuli habituation phase.

Results and Discussion

ASR difference scores were computed and analyzed as described in Experiment 1. The two control groups tested with saline differed only with respect to the order of morphine infusions during the drug administration phase (mM-s and Mm-s) and there was no appreciable difference in the ASR difference scores between these groups. Thus as in Chapter 2, Experiment 3, for simplicity of data presentation these groups were collapsed into a combined mor-train-sal-test group. The mean ASR difference score (±1 SEM) for the 105 dB SPL (C) and 115 dB SPL (C) startle stimuli, are presented in Figure 10A and Figure 10B, respectively.

Insert Figure 10 here

As is apparent in Figure 10, the rats assigned to the mM-m group displayed smaller ASR difference scores then did rats assigned to the Mm-m group and the control mor-train-sal-test group. However, the differences between these groups did not reach conventional statistical significance level. The observation was confirmed by statistical analysis as the data summarized in Figure 10 was subjected to a mixed design (one factor between and two factors within) ANOVA. The statistical analysis determined a non-significant group effect $F(2, 57) = 1.99$, $p > 0.14$ and Group x Time interaction, $F < 1$.

The results of Experiment 2 demonstrated that presentation of pharmacological CS, the small morphine dose (m), to subjects from the mM-m group, trained with the small followed by the large morphine infusion (M) did not significantly attenuate the acoustic startle response as compared to the control groups. These control groups included Mm-m group, subjects trained with M followed by m and tested with m and the mor-train-sal-test group, trained with m and M and tested with the small saline infusion. Previous examination of the intradrug association paradigm (Chapter 2, Experiment 3) demonstrated that presentation of the pharmacological cue to the mM-m subjects induced hyperalgesia, an expression of CCRs. Since environmental CS elicited morphine withdrawal attenuates ASR as demonstrated in Experiment 1, it was hypothesized that pharmacological CS elicited morphine withdrawal would have similar effect on ASR. Even though the attenuation of ASR expressed by the mM-m group did not reach conventional statistical level, the direction of the ASR differences between the mM-m group and the control groups were consistent with the initial hypotheses. Further investigation of attenuation of ASR as an index of the pharmacological CS elicited morphine withdrawal is necessary to evaluate the validity of the measure.

Chapter 5:
Pharmacological CS Elicited Morphine Withdrawal Behaviors

The research presented in Chapter 4 (Experiment 2) evaluated the contribution of intradrug associations to withdrawal symptoms using acoustic startle response as a measure of withdrawal. The results demonstrated that infusion of the small morphine dose to the subjects that had been repeatedly infused with the small followed by large morphine doses (mM-m) did not significantly attenuate the ASR. The present experiment further assessed the contribution of intradrug associations to withdrawal using a different withdrawal measure -- the frequency of expression of behaviors indicative of opiate withdrawal.

Researchers have examined a wide range of behavioral indices of morphine withdrawal in rats. These include ear wipes (e.g., MacRae & Siegel, 1997), genital licking (e.g., Falls & Kelsey, 1989), jumping (Kelsey, Aranow, & Mattews, 1990), mouth movements (e.g., McDonald & Siegel, in press), rearing (e.g., Alzarosa, Hartley, & Deffner-Rappold, 1994), and wet dog shakes (e.g., Wei, Loh, & Way, 1973). Although there are concerns about the validity of some of the measures (see McDonald and Siegel, 1998), two measures that have high inter-rater reliability are wet dog shakes (brief shaking of the head and body, presumably resulting from hypothermia) and genital licks (licking of the external genitalia, presumably reflecting spontaneous ejaculation) (Parker, Burton, McDonald, Kim, & Siegel, 2002).

The present experiment was designed to examine the contribution of intradrug association to expression of morphine withdrawal behaviors. Although previously such contribution has not been evaluated, the contribution of intraadministration associations to withdrawal has recently been studied (McDonald & Siegel, in press). The researchers repeatedly injected rats (intraperitoneally) with either large morphine dose (50 mg/kg), small morphine dose (5 mg/kg), or saline during the drug administration phase. On the test the subjects were injected with either the small morphine dose or saline. The small

morphine dose was selected to simulate the pharmacological cue for the group trained with the large morphine injections. The subjects trained with the large morphine dose and tested with the small morphine dose exhibited a higher frequency of wet dog shakes, genital licks, ear wipes, and mouth movements than the subjects from the other groups. The researchers interpreted the increase in frequency of these behaviors as evidence that the pharmacological CS conditionally elicited withdrawal symptoms.

Although McDonald and Siegel (in press) interpreted the morphine-elicited increase in expression of withdrawal behaviors as a CR, there are other possible interpretations of the results. Namely, "the small dose might elicit hyperactivity as a nonassociative, sensitized response in morphine experienced rats (e.g., Powell & Holtzman, 2001; Sokolowska et al., 2002), and behavioral displays apparent drug withdrawal symptoms might actually be behaviors secondary to this hyperactivity" (McDonald & Siegel, in press). In order to address the potential confound of sensitization of the morphine induced behaviors, McDonald and Siegel repeatedly administered the small morphine injection to subjects trained with the large morphine injection. Based on the sensitization account, repeated presentation of the small morphine dose was expected to increase the frequency of these behaviors. However based on the conditioning account, repeated presentation of the small morphine dose was expected to decrease the frequency of these behaviors (i.e., the CR should extinguish). As a result of the repeated presentation of the small morphine dose the frequency of the behaviors decreased, thus supporting the conditioning interpretation of the behaviors.

The research presented in Chapter 5 employed another technique to dissociate between the conditioning and sensitization explanation of the elicited behaviors. On the basis of an intraadministration analysis, the pharmacological CSs (DOCs) and US (later, larger drug effect) are inevitably paired with each other. That is within a single drug administration even if there is no explicit attempt to pair administration of a small drug dose with the subsequent administration of a larger drug dose, such pairing may occur. On the other hand, an intradrug paradigm applied in Chapter 5 involves administration of two separate drug infusions. That is the pharmacological CSs (small drug dose) does not

have to precede the USs (large drug dose). Based on the conditioning account of small drug dose elicited behaviors, these behaviors should be elicited only if during training the small drug dose is administered prior to the large drug dose. However based on the sensitization account, these behaviors should be elicited at the same frequency regardless of the order of the small and large drug infusions during training.

Design

This experiment consisted of three phases: habituation, drug administration, and test. Prior to the habituation phase the subjects were assigned to one of the eight independent groups: mM-m, mM-s, sS-m, sS-s, Mm-m, Mm-s, Ss-m, and Ss-s. During the habituation subjects were acclimatized to the environment of drug administration as well as the drug infusion procedure.

During each day of the drug administration phase, subjects were administered two infusions separated by a 10 min interval. Groups differed with a respect to the content of each of the drug infusions. These infusions consisted of either a small dose of morphine (m, 1 mg/kg), a large dose of morphine (M, 10 mg/kg) or saline. Saline infusions were volumetrically equated with either m or M infusion (s and S, respectively). The first and second letter of each group name indicates the substance and volume of the first and second infusion. Rats in groups mM-m, mM-s were infused with the m followed by M and rats in groups Mm-m and Mm-s were infused with M followed by m. The subjects from the sS-m, sS-s groups were infused with s followed by S and rats from the Ss-m, and Ss-s groups were infused with S followed by s.

On the test rats were presented with a small infusion of either morphine or saline as indicated by the third letter of the group name. That is, the rats from mM-m, sS-m, Mm-m, and Ss-m groups were infused with m, and the rats from mM-s, sS-s, Mm-s, and Ss-s groups were infused with s. Rats were videotaped all throughout the test session.

Subjects and Surgical Preparation

The subjects were 69 experimentally naive, male Sprague-Dawley rats (Charles River, St. Constant, Quebec, Canada) with weights ranging from 275-325g at the beginning of the experiment. The animals were individually housed with ad lib. access to

food and water. The subjects were implanted with chronic intravenous cannulae as described previously.

Drugs, Apparatus, and Scoring of Behavior

Depending on the group assignment and phase of the experiment, subjects were intravenously infused with the small dose of morphine (m, 1 mg/kg), the large dose of morphine (M, 10 mg/kg), or physiological saline. The concentration of the morphine solution was 5 mg/ml. Saline infusions were volumetrically equated with either m or M infusion (s and S, respectively). The substances were delivered at rates of 0.28 and 2.8 ml/min for the small and large infusions. The exact duration of all infusions depended on the weight of the rats, but ranged from 13 to 17 sec.

All infusions were administered using Med Associates variable rate infusion pumps operated by the Med Associates system and Med PC for Windows software (St. Albans, VT). The subjects were connected to the infusion pumps through cannula connectors (Plastic One, Roanoke, VA), and a 0.025-micrometer micropore filter (Sartorium Filter, Sartorius, AG, Göttingen, Germany).

The drug infusions were delivered in one of five identical, clear, acrylic chambers (30 cm x 30 cm x 30 cm) located in the experimental room. These observational chambers were supported on stands, and a mirror was mounted under the chamber at a 45° angle to allow observation of the rat from below. A digital video camera was used to videotape the subjects' behaviors during the test. Afterwards an impartial observer scored these behaviors using behavioral data collection software (The Observer, Noldus, Leesburg, VA). The observer was unaware of the rats' group assignments.

Procedure

Habituation. At the beginning of the habituation phase the rats were assigned to one of the eight independent groups, mM-m (n = 13), mM-s (n = 8), sS-m (n = 8), sS-s (n = 6), Mm-m (n = 11), Mm-s (n = 8), Ss-m (n = 8), and Ss-s (n = 7). The purpose of the habituation phase was to acclimatize rats to the infusion procedure, and only saline was infused during this phase of the experiment.

Prior to each of the four daily infusion habituation sessions subjects were transported to the experimental room, weighed, and their cannulae were flushed with heparin solution. They were connected to the infusion pumps, placed in the chambers, and left undisturbed for 15 min prior to the first saline infusion (s for mM-m, mM-s, sS-m, and sS-s groups and S for Mm-m, Mm-s, Ss-m, and Ss-s groups). Ten minutes after the first infusion, the second saline infusion was administered (S for groups initially infused with s and s for groups initially infused with S). Animals were disconnected from the infusion pumps and remained in the apparatus for additional 30 minutes. The rats were then removed from the chambers, infused with dextrose solution, and returned to their home cages.

Drug administration. During this phase eight, daily drug administration sessions were administered. This phase of the experiment was conducted as the habituation phase except the subjects from mM-m, mM-s, Mm-m, and Mm-s groups received the small and large morphine infusions instead of the small and large saline infusions. That is, the mM-m and mM-s groups were infused with m followed 10 min later by M and the Mm-m and Mm-s groups were infused with M followed 10 min later by m. The rats from sS-m, sS-s, Ss-m, and Ss-s groups were infused with the small and large saline dose as in the habituation phase. That is, the sS-m and sS-s groups were infused with s followed in 10 min by S and the Ss-m and Ss-s groups were infused with S followed in 10 min by s.

Test. During the test, the subjects were transported to the experimental room, weighed, and infused with heparin solution. They were connected to the infusion pumps, placed in the chambers, and left undisturbed for 15 minutes. The rats from the mM-m, sS-m, Mm-m, and Ss-m groups were infused with m and the rats from the mM-s, sS-s, Mm-s, and Ss-s groups were infused with s. Following the infusion the animals were disconnected from the infusion pumps and left uninterrupted for 30 minutes. The subjects were than removed from the chambers, infused with dextrose solution, and transported to the colony room. The rats were videotaped throughout the test session.

Analysis

For each subject the data was analyzed for the interval between 5 and 20 min post infusion. This interval was chosen as it represents the time period when the second infusion was scheduled during the drug administration phase. The behaviors scored were wet dog shakes (brief shaking of the head and body) and genital licks (licking of the external genitalia).

Results

The mM-s and Mm-s control groups were tested with s and differed only with respect to the order of m and M infusions that were delivered during the drug administration phase. There was no appreciable difference in expression of wet dog shakes and genital licks by these groups on the test and, for simplicity of data presentation (as in Chapter 2, Experiment 3,) they were collapsed into a combined mor-train-sal-test control group. Similarly sS-m and Ss-m control groups, tested with m and differing only with respect to the order of s and S infusions during the drug administration phase, were collapsed into a combined sal-train-mor-test control group. Likewise sS-s and Ss-s groups tested with s and differing with respect to the order of s and S infusions during the drug administration phase were collapsed into a combined sal-train-sal-test control group. The behavioral data collected for the forward paired mM-m group, backward paired Mm-m group and the three combined control groups are summarized in Figure 11.

Inset Figure 11 here

As is apparent in Figure 11, the mean frequency of wet dog shakes (Figure 11A) and genital licks (Figure 11B) varied between groups. That is, the small morphine infusion (1 mg/kg of morphine) elicited greater frequency of wet dog shakes and genital licks in mM-m rats than in Mm-m rats. Furthermore, mM-m subjects expressed more withdrawal behaviors than rats in the combined control groups. These observations were confirmed by a one-way ANOVA. There were significant differences among groups in

the mean frequency of wet dog shakes (Figure 11 A, $F(4,64) = 4.88$, $p<.002$) and genital licks (Figure 11B $F(4,64) = 3.51$, $p<.01$). Furthermore, pairwise comparisons (LSD) indicated that, for each of the indices of morphine withdrawal, the differences between group mM-m and each of the other groups were statistically significant (all $ps < .02$). None of the other pairwise comparisons were statistically significant.

Discussion

The results of this experiment demonstrated that infusion of a small dose of morphine elicits behavioral withdrawal symptoms if that small dose served as a signal for a large dose of the opiate. Specifically, mM-m group rats showed a greater frequency of wet dog shakes and genital licks than did subjects from the Mm-m group. Thus the order of the small and large morphine infusions during the drug administration phase was essential for the association between the small and large morphine infusion to be formed.

The results of the present experiment demonstrated that expression of the withdrawal behaviors is dependant on presentation of the pharmacological cue on the test. That is, the rats from mor-train-sal-test group, trained with m and M and tested with s, displayed lower mean frequency of the withdrawal behaviors than the rats from the mM-m group. Furthermore presentation of m on the test without prior morphine experience (sal-train-mor-test group) elicited lower frequency of the assessed behaviors compared to presentation of m on the test after training with m followed by M (mM-m group). The mean frequency of wet dog shakes and genital licks exhibited by the sal-train-sal-test group, trained and tested with saline, indicates the level of expression of those behaviors in naïve animals. The expression of the behaviors by the sal-train-sal-test group was significantly different from the mM-m group and not from the other groups. Thus the mean frequency of the behaviors displayed by the control groups was comparable to the mean frequency of the behaviors displayed by naïve rats.

The findings are not readily explained by a nonassociative interpretation, such as drug sensitization. Based on the sensitization analysis, mM-m and Mm-m groups should be equally sensitized to the effect of morphine as both groups were equally experienced with the opiate. However, the mM-m group displayed greater mean frequency of the

behavioral symptoms than the Mm-m group. It indicates that the order in which m and M were presented during the drug administration phase determined whether m elicited withdrawal behaviors on the test. These results suggest that the frequency of expression of wet dog shakes and genital licks seen in response to m in rats with the history of m followed by M infusions results from an intradrug association rather than drug sensitization.

The results of the present experiment support the associative interpretation of the findings of McDonald and Siegel (in press). McDonald and Siegel reported that presentation of 5 mg/kg morphine injection to subjects trained with 50 mg/kg morphine injections elicited behavioral withdrawal symptoms. The researchers concluded that the behavioral symptoms are an expression of the pharmacological CS elicited CR. However McDonald and Siegel acknowledged that due to the nature of the intraadministration paradigm, the early drug effect is unavoidably paired with the later larger drug effect. Thus presentation of the large drug effect prior to the small drug effect as a control was unfeasible. The present experiment, using intradrug association, demonstrated that presentation of the small morphine infusion to the rats from the mM-m group induced more behavioral symptoms than presentation of the small morphine infusion to the rats from Mm-m group. Thus, the present findings provide further support for the associative analysis of McDonald and Siegel findings.

Chapter 6:
General Discussion

As discussed in Chapter 1, there is extensive evidence, obtained with a variety of species and drugs, that Pavlovian conditioning plays an important role in the acquisition and expression of drug tolerance and withdrawal symptoms. That is, stimuli that are associated with the drug effect elicit conditional drug-compensatory responses, CCRs. The CCRs that are elicited by the drug-associated stimuli in the presence of the drug attenuate the drug effect; that is, they contribute to tolerance. Additionally, presentation of the usual drug-associated cues in the absence of the drug elicits the CCRs unopposed by the drug effect, and they are expressed as (so-called) withdrawal symptoms.

Pharmacological CS, Morphine Tolerance, and CCRs

Traditionally researchers interested in the associative basis of tolerance and withdrawal manipulated exteroceptive, environmental cues (e.g., audio/visual cues) for drug administration. However, recently internal, pharmacological cues (e.g., cues incidental to drug administration) have been shown to acquire control over the expression of drug tolerance and withdrawal. That is, under some circumstances the early drug effect (drug onset cues, DOCs) becomes associated with the later, larger drug effect. The parameters of the most effective DOCs in eliciting CCRs were examined using intraadministation association (Chapter 2, Experiment 1). The initial 10% of the gradual long morphine infusion (10% pMor) was determined as the more effective DOC than the smaller (5% pMor) or larger (20% pMor) versions of the pharmacological cue. That is, the 10% pMor was more effective than the other morphine probes in eliciting the CCR of hyperalgesia.

Since the 10% pMor was established as the effective DOC, the 10% pMor was used in subsequent experiments. The research presented in Chapter 2, Experiment 2 showed that only rats made tolerant to long, gradual morphine infusions, LMor, (but not following brief, rapid morphine infusions) expressed the CCR in the presence of the 10%

pMor and an environmental CS-. That is, DOCs overshadowed simultaneously present environmental cues. Tolerance expressed by rats administered LMor could be attributed to an intraadministration association. This finding, as well as findings of others (e.g., Kim et al., 1999; Kim & Siegel, 2000), suggests that tolerance seen in the absence of environmental cues previously presented with drug administrations is mediated by DOC elicited CCRs.

Although the hyperalgesia elicited by a 10% pMor was explained as a CCR elicited by the pharmacological CS (Chapter 2, Experiments 1 and 2), it is possible that this hyperalgesia is an expression of a nonassociative, sensitized response. The research presented in Chapter 2, Experiment 3 was designed to distinguish between the associative and nonassociative interpretations of the hyperalgesia elicited by the small morphine dose. Due to the nature of intraadministration association, the early, small drug effect is always presented prior to the later, larger drug effect. Therefore, presentation of the small and large drug effect independently is impossible. In comparison, the intradrug association involves an independent administration of small and large drug doses. That is, an investigator determines the order of administration of the drug doses. If a small morphine dose elicits hyperalgesia as a CCR, only rats in the forward condition, presented with the small morphine dose 10 min prior to the large morphine dose, should express hyperalgesia when presented with the small morphine dose on the test (mM-m group). The rats in the backward condition, presented with the large morphine dose 10 min prior to the small morphine dose, should not elicit hyperalgesia when presented with the small morphine dose on the test (Mm-m group). In contrast, on the basis of a sensitization interpretation of this apparent conditional hyperalgesia, the order of the infusions should be irrelevant as both groups would be treated with the same amount of the drug. The finding of the study presented in Chapter 2, Experiment 3 demonstrated that the small morphine dose elicited hyperalgesia only in rats from the forward condition. Thus, this hyperalgesia is an associative, rather than sensitized, response.

Pharmacological CS and Latent Inhibition

Based on the associative interpretation of drug tolerance, manipulations known to affect the course of Pavlovian conditioning should similarly affect the course of tolerance development. An example of such a Pavlovian conditioning manipulation is latent inhibition. Latent inhibition is a phenomenon seen when the to-be-conditioned stimulus is repeatedly presented prior to pairing it with the US. Such preconditioning exposure to the cues retards acquisition of the CS-US association (for review see Lubow, 1973). The study described in Chapter 3 demonstrated that repeated small-dose morphine infusions (m), prior to the pairing of this small infusion with a larger dose of the drug (M), resulted in an attenuated CCR expression. That is, following mM pairings, the magnitude of hyperalgesia elicited by m was less in these m-preexposed rats than in control rats that were preexposed to saline prior to mM pairings. Hence, the latent inhibition manipulation influenced pharmacological learning much as it influences more traditional learning preparations.

Although the expression of the m-elicited hyperalgesia differed between the morphine preexposed and saline preexposed groups, there was no significant difference in the rate of tolerance development between the groups. That is, the m-preexposure manipulation did not significantly retard the development of tolerance, although the difference was in the expected direction. Based on the previous research (e.g., Lubow, 1973; Siegel, 1969), the magnitude of latent inhibition is directly related to the number of CS preexposures, thus it is possible that more m-presentations prior to mM pairings would increase the magnitude of latent inhibition (as revealed by retarded tolerance acquisition).

Pharmacological CS and Morphine Withdrawal: Assessment of Attenuation of the Acoustic Startle Response

Based on the associative interpretation of morphine withdrawal symptoms, such symptoms are seen when the ususal drug is not presented following the usual pre-drug cues. One of the measures of morphine withdrawal is the attenuation of the acoustic startle response (ASR). Others (Mansbach et al., 1992; Kalinchev & Holtzman, 2003) demonstrated that the attenuation of the ASR is an index of spontaneous and naloxone

induced morphine withdrawal. However, the reduction of ASR as an index of CS elicited morphine withdrawal has not been examined.

Environmental CS elicited morphine withdrawal. There is a wealth of evidence demonstrating environmental CSs elicited morphine withdrawal (reviewed by Siegel & Ramos, 2002). Thus, the environmental CS was used for the initial examination of the effect of CS-elicited morphine withdrawal on the ASR. The research presented in Chapter 4, Experiment 1 indicated that the ASR was attenuated when morphine experienced rats were placed in the usual morphine administration environment but administered saline, rather than the opiate. Such attenuation of the ASR was not seen when morphine-experienced rats were tested in an environment not previously paired with the opiate.

Pharmacological CS elicited morphine withdrawal. Even though the environmental CS that had been paired with the drug elicited morphine withdrawal (assessed as the attenuation of the ASR), the pharmacological CS did not significantly modulate the ASR (Chapter 4, Experiment 2). However, it is important to note that in contrast to the environmental CS previously examined, the pharmacological CS (the small drug dose) is a weaker version of the US (the large morphine dose). Since the morphine withdrawal was assessed following administration of the small morphine dose, the administered morphine dose could unconditionally modulate the ASR. Further research of the attenuation of ASR as a measure of the pharmacological CS elicited morphine withdrawal is required. The future studies should examine various acoustic startle stimuli parameters, number and frequency of stimuli presentations to evaluate the uncommon measure of morphine withdrawal.

Pharmacological CS and Morphine Withdrawal: Assessment of Behavioral Withdrawal Symptoms

Another measure of morphine withdrawal is the frequency of expression of opiate withdrawal behaviors (e.g., Wei & Way, 1975; Falls & Kelsey, 1989; McDonald & Siegel, in press). Based on the associative analysis of withdrawal, it was expected that the pharmacological CS, the small morphine dose, would elicit an increased frequency of

wet dog shakes and genital licks in rats that received the small dose followed by the large dose on each acquisition session (mM-m rats), compared to rats that received the two doses in reverse order on each training session (Mm-m rats). However, based on sensitization, the small morphine dose should elicit a similar frequency of wet dog shakes and genital licks in the mM-m and Mm-m groups, as both groups were exposed to the same doses of morphine prior to test. The results of the experiment, presented in Chapter 5, demonstrated that the rats in the mM-m group expressed a higher frequency of withdrawal behaviors than did the rats in the Mm-m group, thus supporting the associative interpretation of the findings.

The research presented in Chapter 5 provides additional support for the associative interpretation of the findings of McDonald and Siegel (in press). Using the intraadministration association procedure, McDonald and Siegel demonstrated that rats injected with a small morphine dose after repeated injections with a large morphine dose expressed increased frequency of morphine withdrawal behaviors as compared to the control groups (e.g., rats injected with saline dose after repeated injections with the large morphine dose). However, the increased frequency of the behaviors observed following the small morphine dose injection could be attributed to sensitization. To substantiate the associative interpretation of the findings, McDonald and Siegel demonstrated that repeated presentation of the small morphine injection to the rats decreased the frequency of the withdrawal behaviors. That is, repeated presentation of the pharmacological CS extinguished the withdrawal behaviors. Based on sensitization, the repeated presentation of the small morphine dose should increase the frequency of the behaviors. The results of the experiment presented in Chapter 5 further corroborate the associative explanation of McDonald and Siegel's findings.

Implications

Recognition that intraadministration and intradrug associations contribute to drug effects not only has important implications for theories of tolerance and withdrawal but also for conditioning-based treatments of drug addiction. Since there is evidence that the conditional responses (CR) mediate tolerance and withdrawal distress, the extinction of

the CRs would eliminate drug tolerance and withdrawal. Some drug-addiction treatment protocols incorporate procedures to extinguish the association between predrug cues and the drug: "These treatments reflect a logical extension of classical conditioning theory. If addicts' responses to drug-related stimuli reflect CRs, then extinction of these CRs may be achieved through repeated unreinforced exposure to the CS" (Carter & Tiffany, 1999, p. 329). There are mixed reports of the efficacy of such cue-exposure treatments (see Drummond, Tiffany, Glautier, & Remington, 1995; Siegel & Ramos, 2002), but generally the results have been disappointing: "The value of these [cue-exposure] procedures in producing clinically meaningful reductions in substance use has been met with only modest success to date" (Carroll, 1999, p. 261). There are many reasons why cue-exposure treatments, as currently implemented, may have met with only limited success (Siegel & Ramos, 2002; Ramos, Siegel, & Bueno, 2002). Of special relevance to the results of the present experiment is Siegel and Ramos's observation that these treatments typically do not incorporate extinction of DOCs. As noted by Cepeda-Benito and Short (1997), "the inclusion of small drug doses during cue-exposure treatments may better reproduce the CSs responsible for craving" (p. 239). Indeed, some investigators have described successful cue-exposure treatment procedures for problem drinking that incorporate priming doses of alcohol (e.g., Sitharthan, Sitharthan, Hough, & Kavanagh, 1997; Dawe, Rees, Mattick, Sitharthan, & Heather, 2002).

References

Alzarosa, J. L., Hartley, N. E., & Deffner-Rappold, C. (1994). Context-specific morphine tolerance and withdrawal: The effects of interdose interval. *Psychobiology, 22,* 304-311.

Bevan, J. A. (1983). Symathomimetic drugs. In J. A. Bevan & J. H. Thompson (Eds.), *Essentials pf pharmacology* (3ed., pp. 166-180). Philadelphia: Harper& Raw.

Brown, R. J., & Breckenridge, C. B. (1975). A technique for long-term blood sampling or intravenous infusions in the freely moving rat. *Biochemical Medicine, 13,* 280–286.

Carroll, K. M. (1999). Behavioral and cognitive behavioral treatments. In B. McCrady & E. S. Epstein (Eds.), *Addictions: A comprehensive guidebook* (pp. 250–267). New York: Oxford University Press.

Cepeda-Benito, A., & Short, P. (1997). Morphine's interoceptive stimuli as cues for the development of associative morphine tolerance in the rat. *Psychobiology, 25,* 236–240.

Cepeda-Benito, A., & Tiffany, S. T. (1993). Morphine as a cue in associative tolerance to morphine's analgesic effects. *Pharmacology, Biochemistry, and Behavior, 46,* 149-152.

Childress, A. R., McLellan, A. T., & O'Brien, C. P. (1986). Abstinent opiate abusers exhibit conditioned craving, conditioning withdrawal and reductions in both through extinction. *British Journal of Addiction, 81,* 655–660.

Dafters, R., & Bach, L. (1985). Absence of environment-specificity in morphine tolerance acquired in nondistinctive environments: Habituation or stimulus overshadowing? *Psychopharmacology, 87,* 101–106.

Davis, M., Gendelman, D. S., Tischler, M. D., Gendelman, P. M. (1982). A primary acoustic startle circuit: lesion and stimulation studies. *Journal of Neuroscience* 2, 791-805.

Dawe, S., Rees, V.W., Mattick, R., Sitharthan, T., & Heather, N. (2002). Efficacy of moderation-oriented cue exposure for problem drinkers: A randomized controlled trial. *Journal of Consulting and Clinical Psychology, 70,* 1045-1050.

Drummond, D. C., Tiffany, S. T., Glautier, S., & Remington, B. (1995). Cue exposure in understanding and treating addictive behaviours. In D. C. Drummond, S. T. Tiffany, S. Glautier, & B. Remington (Eds.), *Addictive behaviour: Cue exposure theory and practice* (pp. 1–17). Chichester, England: Wiley.

Dworkin, D. G. (1993). *Learning and physiological regulation.* Chicago: University of Chicago Press.

Falls, W. A. & Kelsey, J. E. (1989). Procedures that produce context-specific tolerance to morphine in rats also produce context-specific withdrawal. *Behavioral Neuroscience, 103,* 842-849.

Fennessy, M. R., & Lee, J. R. (1975). The assessment of and the problems involved in the experimental evaluation of narcotic analgesics. In S. Ehrenpreis & A. Neidle (Eds.), *Methods in narcotics research* (pp. 73–99). New York: Marcel Dekker.

Goddard, M. J. (1999). The role of US signal value in contingency, drug conditioning, and learned helplessness. *Psychonomic Bulletin and Review, 6,* 412–423.

Goudie, A. J. (1990). Conditioned opponent processes in the development of tolerance to psychoactive drugs. *Progress in Neuro-Psychopharmacology and Biology Psychiatry, 14,* 675–688.

Greeley, J., Lê, D. A., Poulos, C. X., & Cappell, H. (1984). Alcohol is an effective cue in the conditional control of tolerance to alcohol. *Psychopharmacology, 83,* 159–162.

Griffiths, J. W., & Goudie, A. J. (1986). Analysis of the role of drug-predictive environmental stimuli in tolerance to the hypothermic effects of the benzodiazepine midazolam. *Psychopharmacology, 90,* 513–521.

Grisel, J. E., Wiertlak, E. P., Watkins, L. R., & Maier, S. F. (1994). Route of morphine administration modulates conditioned analgesic tolerance and hyperalgesia. *Pharmacology Biochemistry & Behavior, 49*, 1029–1035.

Gutiérrez-Cebollada. J., de la Torre, R., Ortuño, J., Garcés, M., & Camí, (1994). Psychotropic drug consumption and other factors associated with heroin overdose. *Drug and Alcohol Dependence, 35,* 169-174.

Kalant, H. (1998). Research on tolerance: What can we learn from history? *Alcohol: Clinical and Experimental Research, 22,* 67-76.

Kalinchev, M., & Holtzman, S. G. (2003) Changes in urination/defecation, auditory startle response, and startle-induced ultrasonic vocalizations in rats undergoing morphine withdrawal: Similarities and differences between acute and chronic dependence. *Journal of Pharmacology and Experimental Therapeutics, 304,* 603-609.

Kamin, L. J. (1969). Predictability, surprise, attention, and conditioning. In B. A. Campbell & R. M. Church (Eds.), *Punishment and aversive behavior* (pp. 279–296). New York: Appleton-Century-Crofts.

Kelsey, J. A., Aranow, J. S., & Matthews, R. T. (1990). Context-specific morphine withdrawal in rats: Duration and effects of clonidine. *Behavioral Neuroscience, 104,* 704-710.

Kim, J. A., & Siegel, S. (2001). The role of cholecystokinin in conditional compensatory responding and morphine tolerance in rats. *Behavioral Neuroscience, 115,* 704–709.

Kim, J. A., Siegel, S., & Patenall, V. R. A. (1999). Drug onset cues as signals: Intraadministration and tolerance. *Journal of Experimental Psychology: Animal Behavior Processes, 25,* 491–504.

King, D. A., Bouton, M. E., & Musty, R. E. (1987). Associative control of tolerance to the sedative effects of a short-acting benzodiazepine. *Behavioral Neuroscience, 101,* 104–114.

Lubow, R. E. (1973). Latent inhibition. *Psychological Bulletin, 79,* 398-407.

Lubow, R. E., & Moore, A. U. (1959). Latent inhibition: The effect of nonreinforced pre-exposure to the conditioned stimulus. *Journal of Comparative and Physiological Psychology, 52,* 415-419.

Mackintosh, N. J. (1983). *Conditioning and associative learning.* New York: Oxford University Press.

Mackintosh, N. J. (1987). Neurobiology, psychology, and habituation. *Behaviour Research and Therapy, 25,* 81–97.

MacRae, J. R., & Siegel, S. (1997). The role of self-administration in morphine withdrawal in rats. *Psychobiology, 25,* 77-82.

Mansbach, R. S., Gold, L. H., & Harris, L. S. (1992). The acoustic startle response as a measure of behavioral dependence in rats. *Psychopharmacology, 108,* 40-46.

McCusker C. J., & Brown, K. (1990). Alcohol-predictive cues enhance tolerance to and precipitate "craving" for alcohol in social drinkers. *Journal of Studies on Alcohol, 51,* 494-499.

McDonald R. V., & Siegel S. (in press). Intra-administration associations and withdrawal symptoms: Morphine-elicited morphine withdrawal. *Experimental and Clinical Psychopharmacology.*

McDonald, R. V., & Siegel, S. (1998). Environmental control of morphine withdrawal: Context specificity or stimulus novelty? *Psychobiology, 26,* 53-56.

Melchior, C. L. (1990) Conditioned tolerance provides protection against ethanol lethality. *Pharmacology, Biochemistry and Behavior, 37,* 205-206.

Mello N. K. & Mendelson J. H. (1970). Experimentally induced intoxication in alcoholics: A comparison between programmed and spontaneous drinking. *Journal of Pharmacology and Experimental Therapeutics, 173,* 101-116.

Parker, L. A., Burton, P., McDonald, R. V., Kim, J. A., & Siegel, S. (2002). Ibogaine interferes with motivational and somatic effects of naloxone-precipitated withdrawal from acutely administered morphine. *Progress in Neuro-Psychopharmacology and Biological Psychiatry, 26,* 293-297.

Pavlov, I. P. (1927). *Conditioned reflexes* (G. V. Anrep, Trans.). London: Oxford University Press.

Pinel, J. P., & Puttaswamaiah, S. (1985). Tolerance to alcohol's anticonvulsant effect is not under Pavlovian control. *Pharmacology Biochemistry & Behavior, 23,* 959–964.

Powell K. R., & Holtzman S. G. (2001). Parametric evaluation of the development of sensitization to the effects of morphine on locomotor activity. *Drug and Alcohol Dependence, 62,* 83–90.

Ramsay, D. S., & Woods, S. C. (1997). Biological consequences of drug administration: Implications fro acute and chronic tolerance. *Psychological Review, 104,* 170-193.

Rescorla, R. A. (1980). Simultaneous and successive associations in sensory preconditioning. *Journal of Experimental Psychology: Animal Behavior Processes, 6*, 207–216.

Sherman, J. E. (1979). The effects of conditioning and novelty on the analgesic and pyretic responses to morphine. *Learning and Motivation, 10,* 383–418.

Siegel, S. (1969). Effect of CS habituation on eyelid conditioning. *Journal of Comparative and Physiological Psychology, 68,* 245-248.

Siegel, S. (1975). Evidence from rats that morphine tolerance is a learned response. *Journal of Comparative and Psychological Psychology, 89,* 498-506.

Siegel, S. (1976). Morphine analgesic tolerance: Its situation specificity supports a Pavlovian conditioning model. *Science, 193*, 323-325.

Siegel, S. (1977). Morphine tolerance acquisition as an associative process. *Journal of Experimental Psychology: Animal Behavior Processes, 3,* 1-13.

Siegel, S. (1978). Replay to Hayes and Mayer's Technical Comment ("Morphine tolerance: Is there evidence for a conditioning model?"). *Science, 200*, 344-345.

Siegel, S. (1983). Classical conditioning, drug tolerance, and drug dependence. In Y. Israel, F. B. Glaser, H. Kalant, R. E. Popham, W. Schmidt, & R. G. Smart (Eds.), *Research advances in alcohol and drug problems* (Vol. 7, pp. 207–246). New York: Plenum.

Siegel, S. (1989). Pharmacological conditioning and drug effects. In A. J. Goudie & M. Emmett-Oglesby (Eds.), Psychoactive Drugs, (pp115-180). Clfton, NJ: Humana.

Siegel, S. (1999). Drug anticipation and drug addiction: The 1998 H. David Archibald lectures. *Addiction, 94,* 1113–1124.

Siegel, S. (2001). Pavlovian conditioning and drug overdose: When tolerance fails. *Addiction Research and Theory, 9*, 503–513.

Siegel, S., & Allan, L. G. (1998). Learning and homeostasis: Drug addiction and McCollough effect. *Psychological Bulletin, 124,* 230-239.

Siegel, S., Baptista, M., Kim, J. A., McDonald, R., & Weise-Kelly, L. (2000). Pavlovian psychopharmacology: The associative basis of tolerance. *Experimental and Clinical Psychopharmacology, 8,* 276–293.

Siegel, S., & Domjan, M. (1971). Backward conditioning as an inhibitory procedure. *Learning and Motivation, 2,* 1–11.

Siegel, S., & Domjan, M. (1974). The inhibitory effects of backward conditioning as a function of the number of backward pairings. *Bulletin of the Psychonomic Society, 4,* 122–124.

Siegel, S., & Ellsworth, D. W., (1986). Pavlovian conditioning and death from apparent overdose of medically prescribed morphine: A case report. *Bulletin of the Psychonomic Society, 24,* 278-280.

Siegel, S., Hinson, R. E., Krank, M. D., & McCully, J. (1982, April 23). Heroine overdose death: Contribution of drug-associated environmental cues. *Science, 216,* 436-437.

Siegel, S., & Kim, J. A. (2000). Absence of cross-tolerance and the situational specificity of tolerance. *Palliative Medicine, 14,* 75–77.

Siegel, S., Kim, J.A., & Sokolowska, M. (2003). Coffeine and Coffee Tolerance. *Circulation, 108,* e38

Siegel, S., & Ramos, B. C. (2002). Applying laboratory research: Drug anticipation and the treatment of drug addiction. *Experimental and Clinical Psychopharmacology, 10,* 162-183.

Siegel, S., Ramos, B. M. C., & Bueno, J. L. O. (2002). Occasion setting and drug tolerance. *Integrative Physiological and Behavioral Science, 37*, 165-177.

Sitharthan, T., Sitharthan, G., Hough, M. J., & Kavanagh, D. J. (1997). Cue exposure in moderation drinking: A comparison with cognitive-behavior therapy. *Journal of Consulting and Clinical Psychology, 65,* 878–882.

Sokolowska, M., Siegel, S., & Kim, J.A. (2002). Intraadministration Associations: Conditional Hyperalgesia Elicited by Morphine Onset Cues. *Journal of Experimental Psychology: Animal Behavior Processes 28,* 309-320.

Taukulis, H. K. (1986). Conditional hyperthermia in response to atropine associated with a hypothermic drug. *Psychopharmacology, 90,* 327-331.

Tiffany, S. T., & Baker, T. B. (1981). Morphine tolerance in rats: Congruence with a Pavlovian paradigm. *Journal of Comparative and Physiological Psychology, 95,* 747-762.

Tiffany, S. T., Petrie, E. C., Baker, T. B., & Dahl, J. (1983). Conditioned morphine tolerance in the rat: Absence of conditional compensatory response and cross-tolerance with stress. *Behavioral Neuroscience, 97,* 335–353.

Tilson, H. A., Rech, R. H., & Stolman, S. (1973). Hyperalgesia during withdrawal as a means of measuring the degree of dependence in morphine dependant rats. Psychopharmacologia, 28, 287-300.

Vila, C. J. (1989). Death by pentobarbital overdose mediated by Pavlovian conditioning. *Pharmacology Biochemistry and Behavior, 32,* 365-366.

Walter, T. A., & Riccio, D. C. (1983). Overshadowing effects in the stimulus control of morphine analgesic tolerance. *Behavioral Neuroscience, 97,* 658–662.

Wei, E., & Way, E. L. (1975). Application of the pellet implantation technique fro the assessment of tolerance and physical dependence in the rodent. In S. Ehrenpreis & A. Neidle (Eds.), Methods in Narcotics Research (pp. 243-259). New York: Marcel Dekker.

Wei, E. , Loh, H. H., Way, E. L. (1973). Quantitative aspects of precipitated abstinence in morphine dependent animals. *Journal of Pharmacology and Experimental Therapeutics,* 225, 391-398.

Weise-Kelly, L., & Siegel, S. (2001). Self-administration cues as signals: Drug self-administration and tolerance. *Journal of Experimental Psychology: Animal Behavior Processes, 27,* 125–136.

Wolgin, D. L., & Benson, H. D. (1991). Role of associative and nonassociative mechanisms in tolerance to morphine "anorexia." *Pharmacology Biochemistry & Behavior, 39,* 279–286.

Table 1

Design of Experiment 2

Phase of Experiment		
Tolerance Development		
Odd days[b]	Even days[c]	CCR test[a] (Day 13)
Morphine groups		
CS- → LSal and CS+ → LMor	CS- → LSal CS- → LSal	CS- → pMor
CS- → SSal and CS+ → SMor	CS- → SSal CS- → SSal	CS- → pMor
Saline groups		
CS- → LSal and CS+ → LSal	CS- → LSal CS- → LSal	CS- → pMor
CS- → SSal and CS+ → SSal	CS- → SSal CS- → SSal	CS- → pMor

Note. CS = conditional stimulus. CCR = conditional compensatory responses.

[a] Rats were infused with the first 10% of the long morphine (LMor) infusion (probe morphine [pMor]) following CS- presentation.

[b] Subjects in morphine groups were presented with CS+ (a flashing light) prior to either long or short morphine infusion (LMor and SMor, respectively). And CS- (a clinking sound) prior to physiological saline administration delivered in the same rates as morphine. Rats in saline groups received infusions of physiological saline via either the long or short delivery rate (LSal and SSal, respectively) following both CS+ and CS- presentations.

[c] Rats were administered physiological saline at either the long (LMor and LSal) or short (SMor and SSal) infusion rate proceeded by CS-.

Table 2

Infusions Used in Experiment 3

Infused substance	Morphine concentration (mg/ml)	Infusion rate (ml/min)	Volume of infusion (ml/kg)	Morphine dose (mg/kg)
M	5	2.70	2.0	10
m	5	0.24	0.2	1
S	0	2.70	2.0	0
s	0	0.24	0.2	0

Note. M = large morphine dose; m = small morphine dose; S = large saline dose; s = small saline dose.

Table 3

Design of Experiment 3

Group	Tolerance Development [a]	CCR test	*n*
mM-m	morphine (1mg/kg) → Morphine (10 mg/kg)	morphine (1mg/kg)	14
Mm-m	Morphine (10mg/kg) → morphine (1 mg/kg)	morphine (1mg/kg)	14
mM-s	morphine (1mg/kg) → Morphine (10 mg/kg)	saline	14
Mm-s	Morphine (10mg/kg) → morphine (1 mg/kg)	saline	15
mS-m	morphine (1mg/kg) → Saline	morphine (1mg/kg)	13
Sm-m	Saline → morphine (1 mg/kg)	morphine (1mg/kg)	13

Note. m = small morphine dose; M = large morphine dose; s = small saline dose; S = large saline dose; CCR conditional compensatory responses.

[a] There was a 10-min interval between the two infusions on each tolerance development session.

Figure Captions

Figure 1. Mean tail-flick latencies (±1 SEM) following each morphine infusion for rats assigned to each probe morphine (pMor) test group during the tolerance-development phase (Chapter 2 Experiment 1).

Figure 2. Mean tail-flick latencies (±1 SEM) for each group at each post-probe morphine (pMor) infusion test interval during the probe test (Chapter 2 Experiment 1).

Figure 3. Mean tail-flick latencies (± 1 SEM) during the tolerance-development phase (Chapter 2 Experiment 2). Rats were administered 5.0 mg/kg morphine as either a long or a short intravenous infusion (LMor and SMor groups, respectively) or were administered physiological saline at the long or short infusion duration (LSal and SSal, respectively). Tail-flick latencies were determined at 0, 45, and 90 min following the first (A), third (B), or fifth (C) tolerance-development session.

Figure 4. Mean tail-flick latencies (±1 SEM) for each group for each postinfusion assessment during the CCR test (Chapter 2 Experiment 2). SMor = short intravenous morphine infusion; LMor = long intravenous morphine infusion; LSal = long intravenous physiological saline; SSal = short intravenous physiological saline.

Figure 5. Mean tail-flick latencies (±1 SEM) for each group during the tolerance-development phase (Chapter 2 Experiment 3). The first two letters of the group designation indicate the sequence of two infusions that occurred on each tolerance development session (m = 1 mg/kg morphine, M = 10 mg/kg morphine, S = 2 ml/kg physiological saline), and the third letter indicates the substance infused on the conditional compensatory response test session (m = 1 mg/kg morphine, s = 0.2 ml/kg physiological saline).

Figure 6. Mean tail-flick latencies (±1 SEM) for each postinfusion assessment for the CCR test (Chapter 2 Experiment 3) for the forward-paired experimental group (mM–m, trained with 1 mg/kg morphine followed by 10 mg/kg morphine, and tested with 1 mg/kg morphine), the backward-paired experimental group (Mm–m, trained with 10 mg/kg morphine followed by 1 mg/kg morphine, and tested with 1 mg/kg morphine), and the two combined control groups (s-test control are groups tested with saline following either mM or Mm training; m-test control are groups tested with 1 mg/kg morphine following mS or Sm training).

Figure 7. Mean tail-flick latencies (±1 SEM) after two morphine infusions (the small morphine infusion, 1 mg/kg, followed in 10 minutes by the large morphine infusion, 10 mg/kg) for rats assigned to each preexposure group during the tolerance-development phase (Chapter 3).

Figure 8. Mean tail-flick latencies (±1 SEM) for each group following the small morphine infusion (1 mg/kg) during the CCR test (Chapter 3).

Figure 9. Mean acoustic startle response (ASR) difference scores (±1 SEM) for each group following saline infusion during the test (Chapter 4, Experiment 1). (A) the ASR difference score following presentation of 105dB SPL(C) tones (B) the ASR difference score following presentation of 115dB SPL(C) tones.

Figure 10. Mean acoustic startle response (ASR) difference scores (±1 SEM) for each group following the small morphine infusion (1 mg/kg) to rats from the mM-m and Mm-m groups and following the small saline infusion to rats from the mM-s and Mm-s groups during the test (Chapter 4, Experiment 2). (A) the ASR difference score following presentation of 105dB SPL(C) tones (B) the ASR difference score following presentation of 115dB SPL(C) tones.

Figure 11. Mean frequency (± 1 SEM) of wet dog shakes (A) and genital licks (B) for the forward-paired experimental group (mM–m, trained with 1 mg/kg morphine followed by 10 mg/kg morphine, and tested with 1 mg/kg morphine), the backward-paired experimental group (Mm–m, trained with 10 mg/kg morphine followed by 1 mg/kg morphine, and tested with 1 mg/kg morphine), and the three combined control groups (mor-train-sal-test are groups tested with saline following either mM or Mm training; sal-train-mor-test are groups tested with 1 mg/kg morphine following sS or Ss training; sal-train-sal-test are groups tested with saline following sS or Ss training) (Chapter 5).

Figure 1

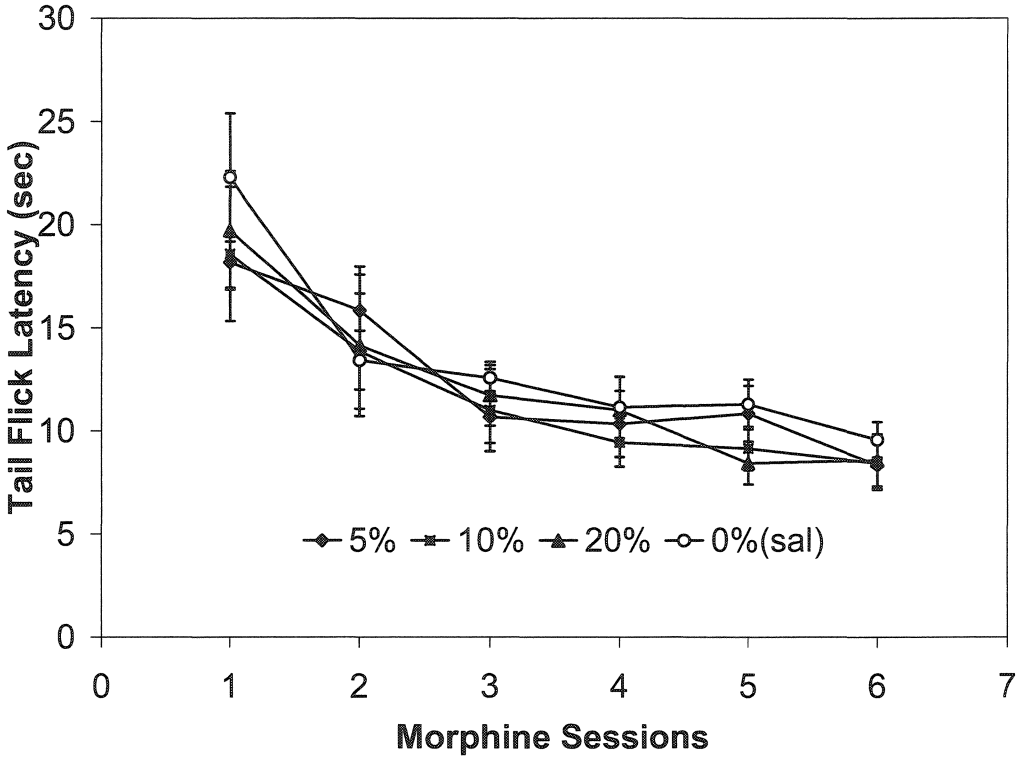

30
25
20
15
10
5
0
Tail Flick Latency (sec)
0
1
2
3
4
5
6
7
Morphine Sessions
5%
10%
20%
0%(sal)

Figure 2

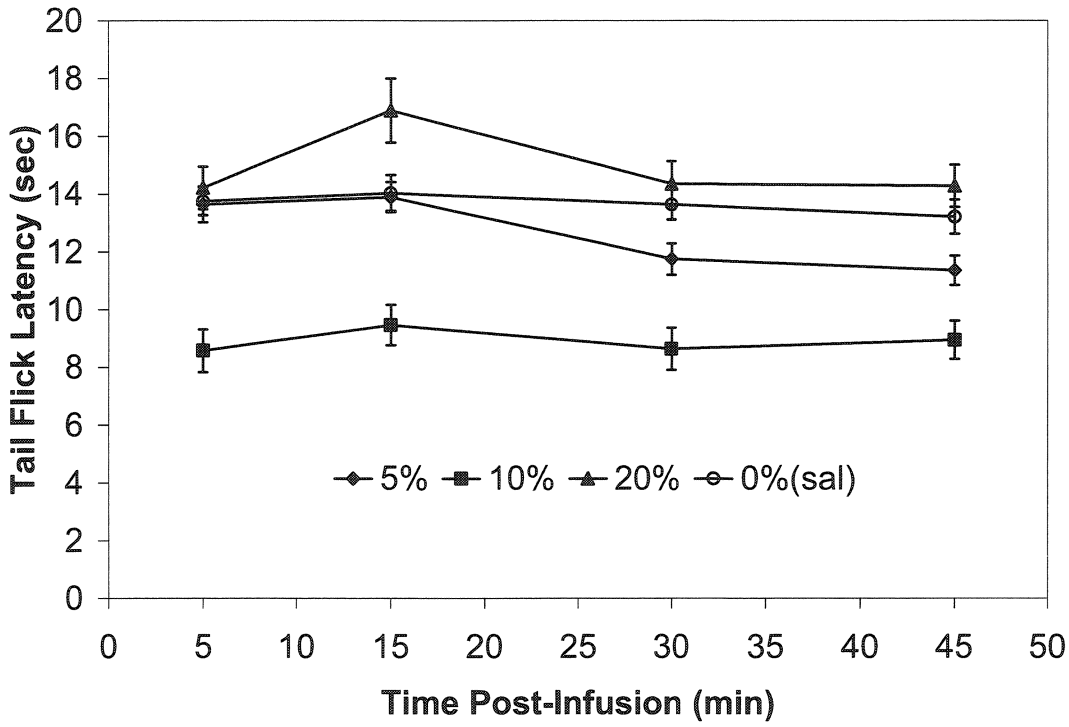

Tail Flick Latency (sec)
20
18
16
14
12
10
8
6
4
2
0
0
5
10
15
20
25
30
35
40
45
50
Time Post-Infusion (min)
5%
10%
20%
0%(sal)

Figure 3

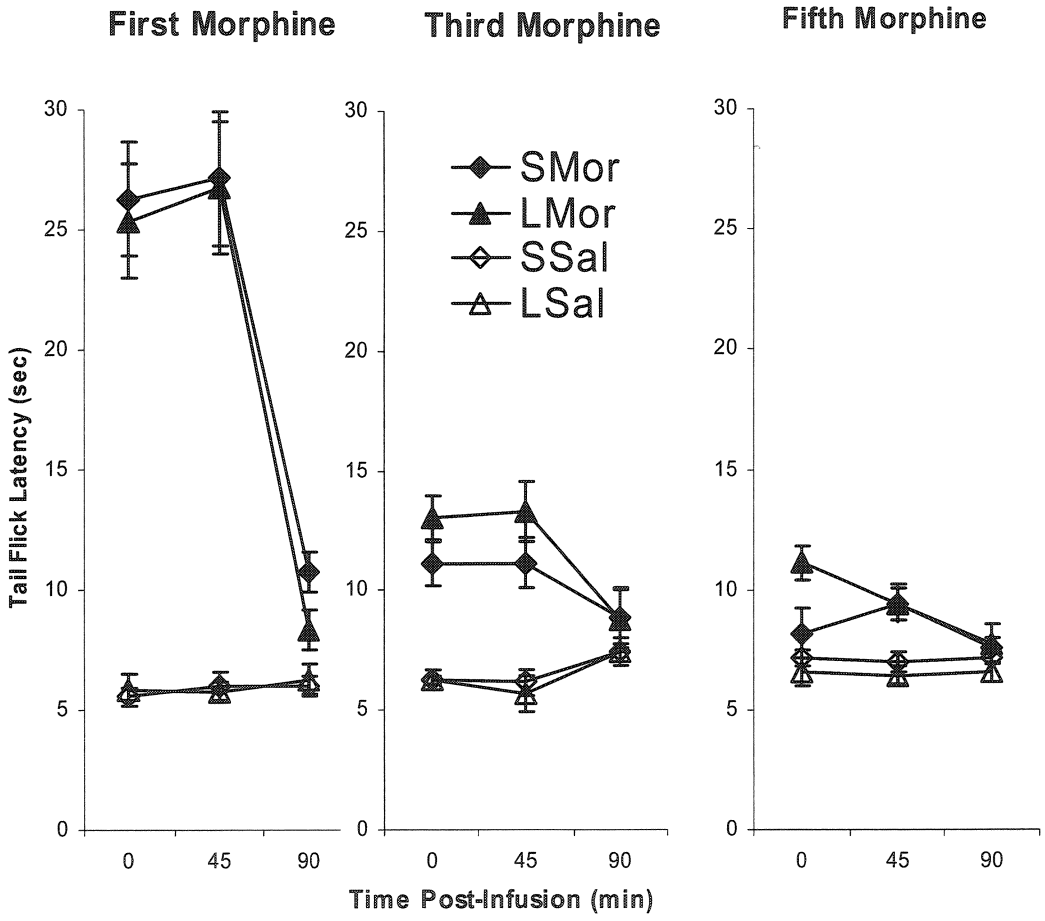

First Morphine
Third Morphine
Fifth Morphine
SMor
LMor
SSal
LSal
Tail Flick Latency (sec)
Time Post-Infusion (min)
0
5
10
15
20
25
30
0
45
90

Figure 4

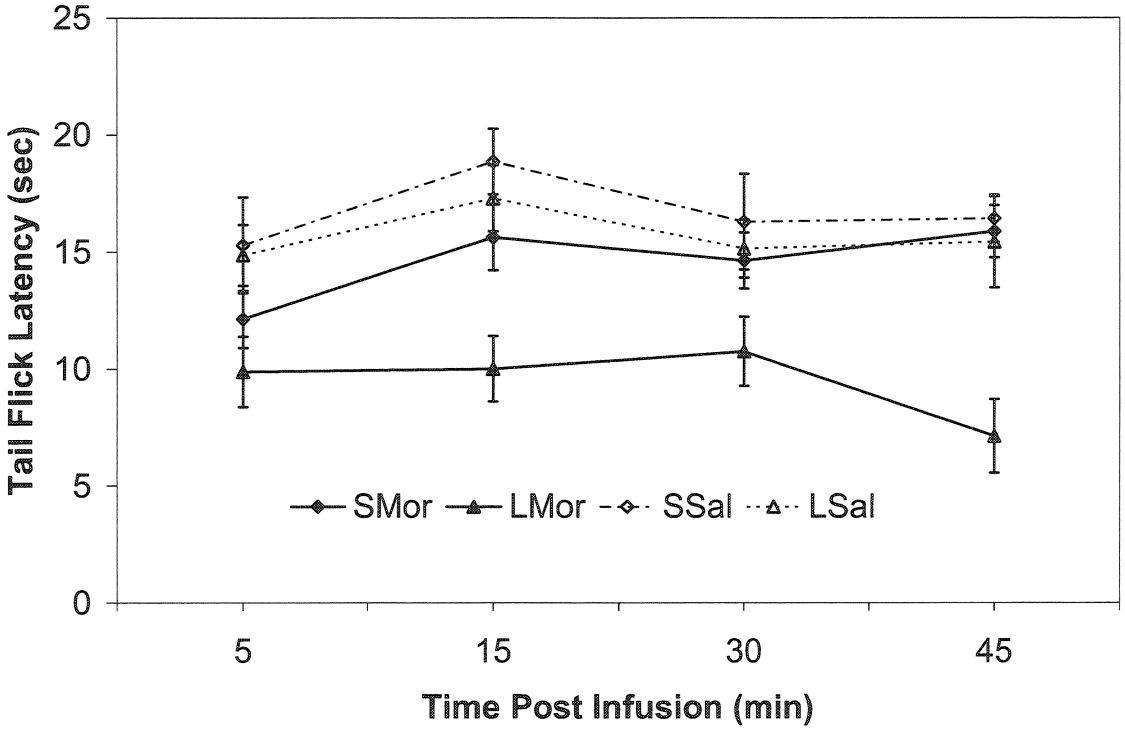

25
20
15
10
5
0
Tail Flick Latency (sec)
SMor
LMor
SSal
LSal
5
15
30
45
Time Post Infusion (min)

Figure 5

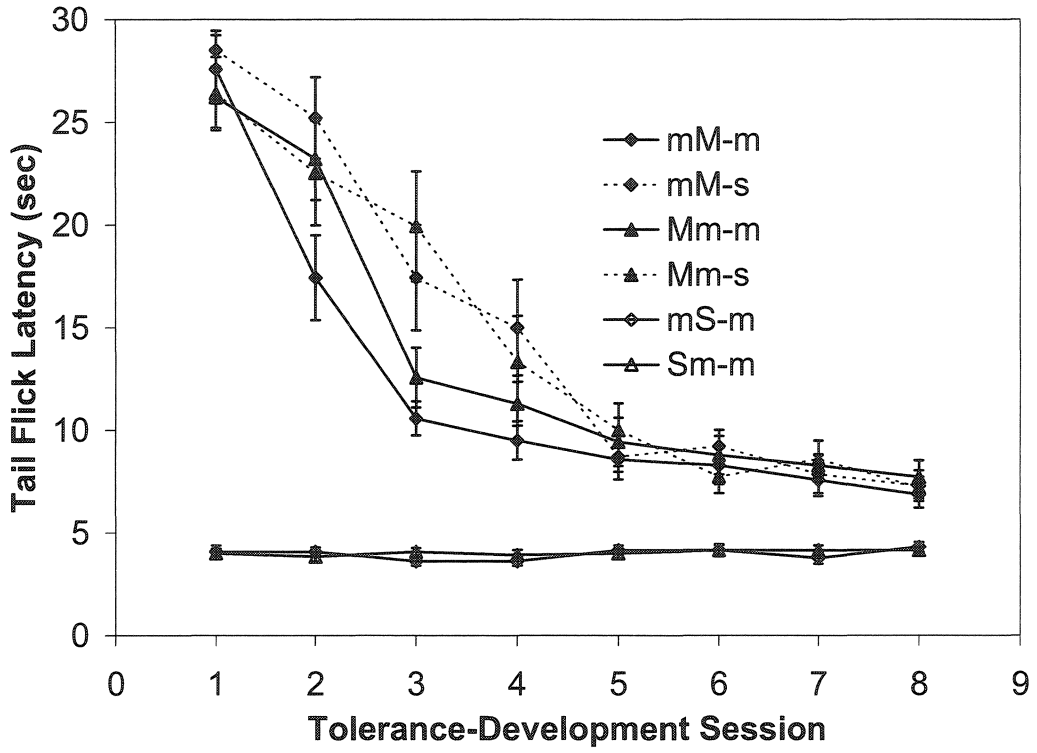

30
25
20
15
10
5
0
Tail Flick Latency (sec)
0
1
2
3
4
5
6
7
8
9
Tolerance-Development Session
mM-m
mM-s
Mm-m
Mm-s
mS-m
Sm-m

Figure 6

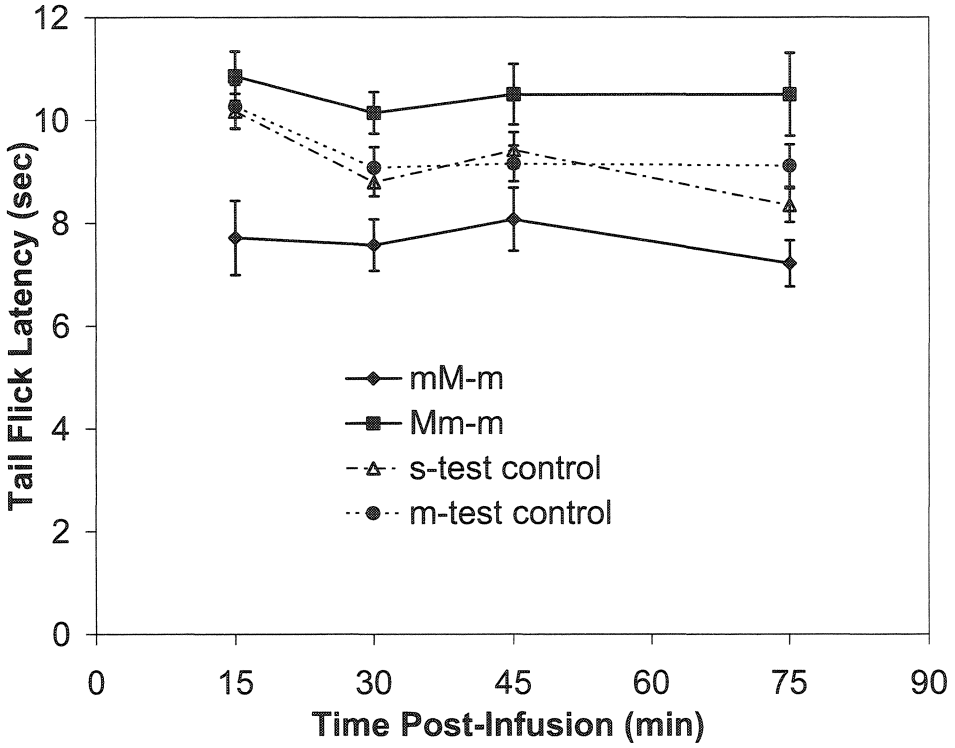

12
10
8
6
4
2
0
Tail Flick Latency (sec)
0
15
30
45
60
75
90
Time Post-Infusion (min)
mM-m
Mm-m
s-test control
m-test control

Figure 7

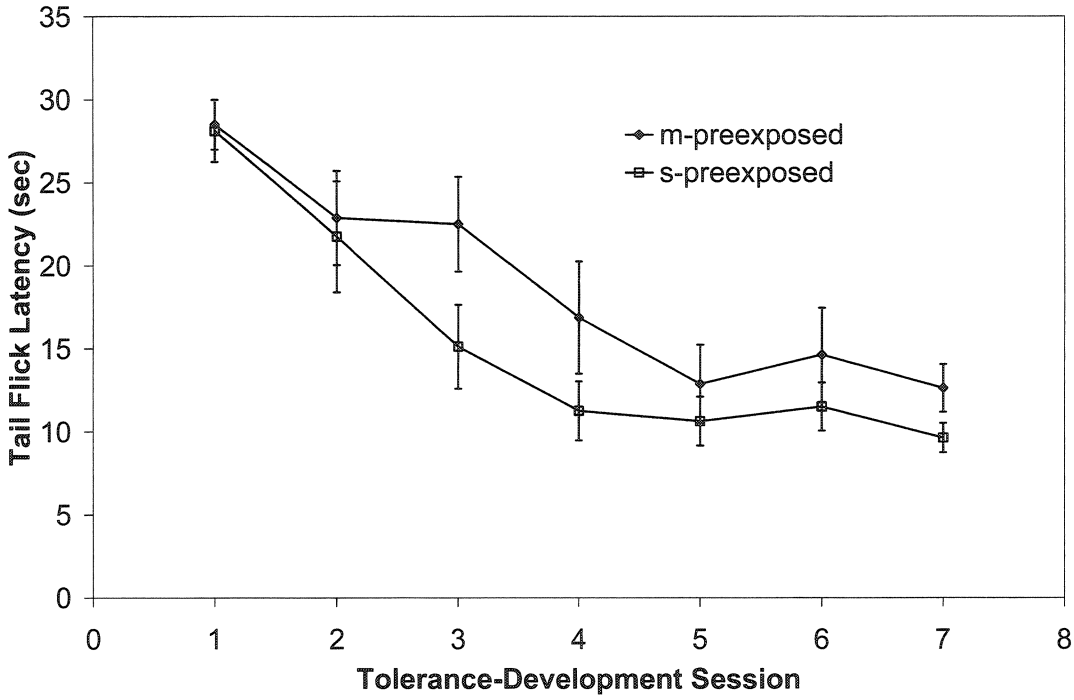

35
30
25
20
15
10
5
0
Tail Flick Latency (sec)
0
1
2
3
4
5
6
7
8
Tolerance-Development Session
m-preexposed
s-preexposed

Figure 8

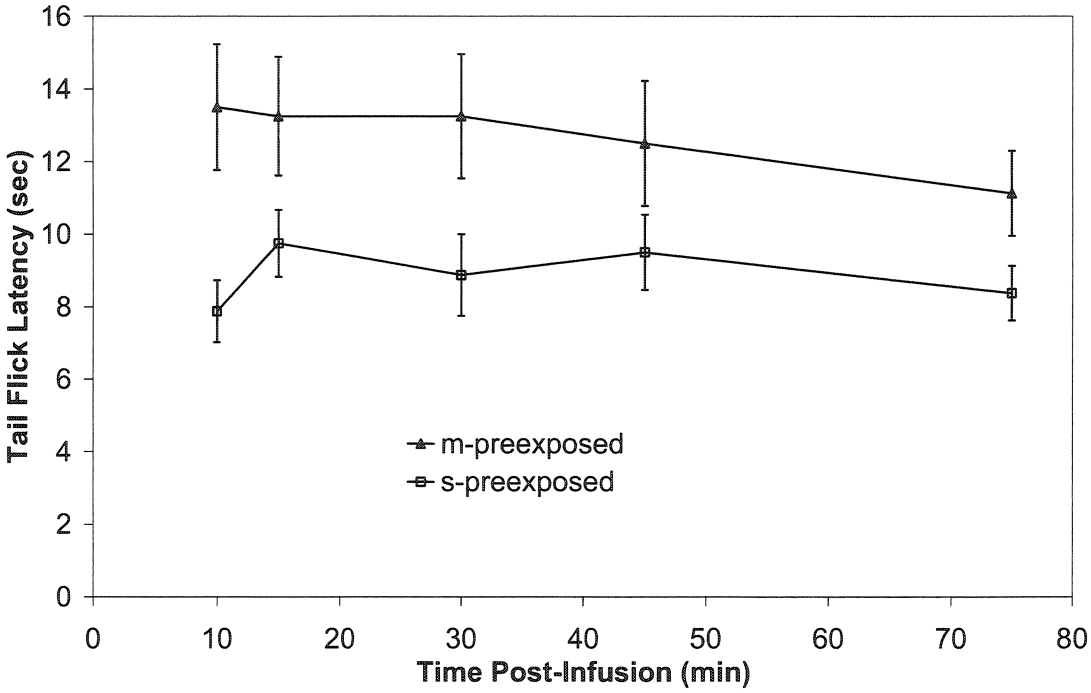
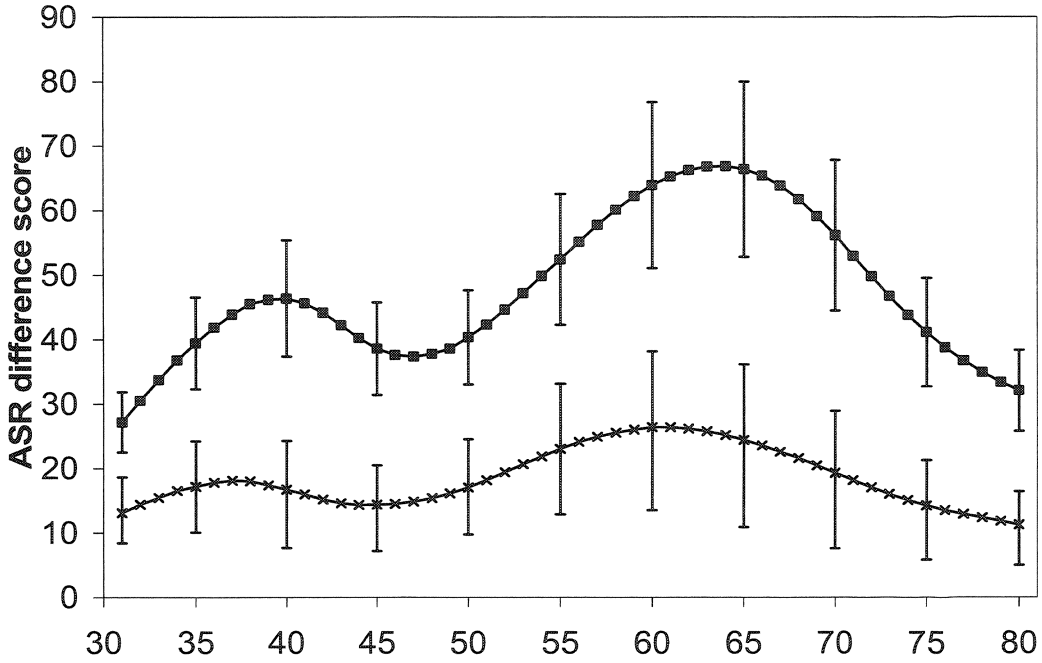

16
14
12
10
8
6
4
2
0
Tail Flick Latency (sec)
0
10
20
30
40
50
60
70
80
Time Post-Infusion (min)
m-preexposed
s-preexposed

Figure 9

A


ASR difference score
90
80
70
60
50
40
30
20
10
0
30
35
40
45
50
55
60
65
70
75
80

B

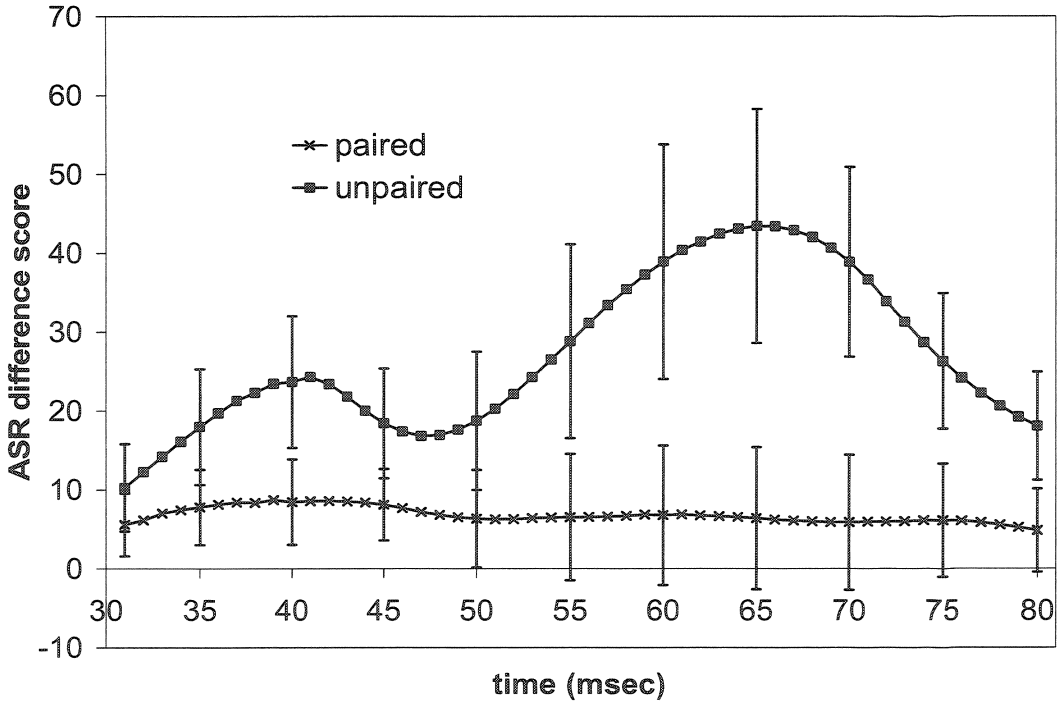
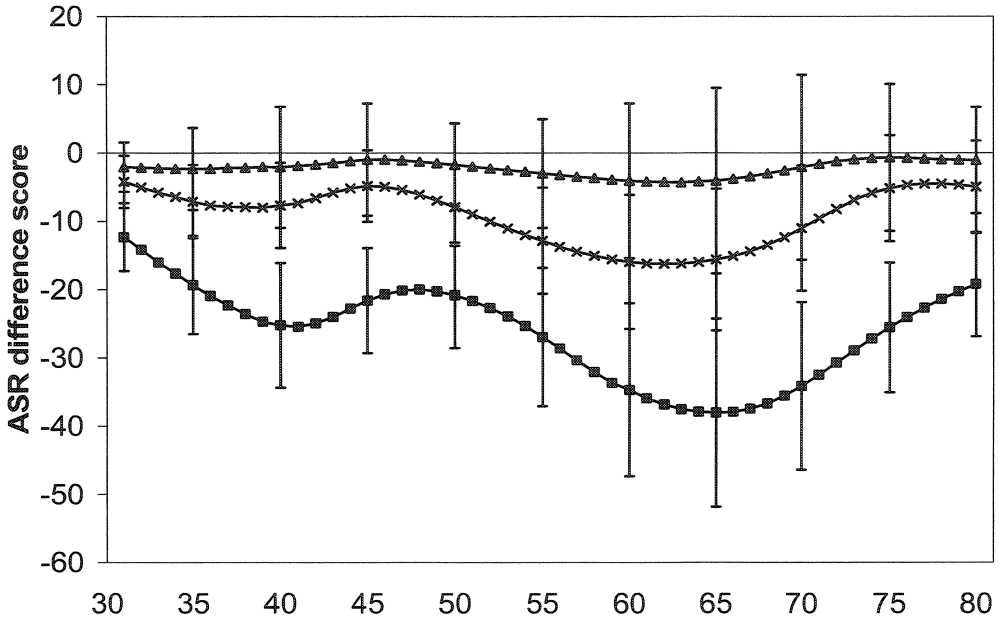

paired
unpaired
ASR difference score
70
60
50
40
30
20
10
0
-10
30
35
40
45
50
55
60
65
70
75
80
time (msec)

Figure 10
A


20
10
0
-10
-20
-30
-40
-50
-60
ASR difference score
30
35
40
45
50
55
60
65
70
75
80

B

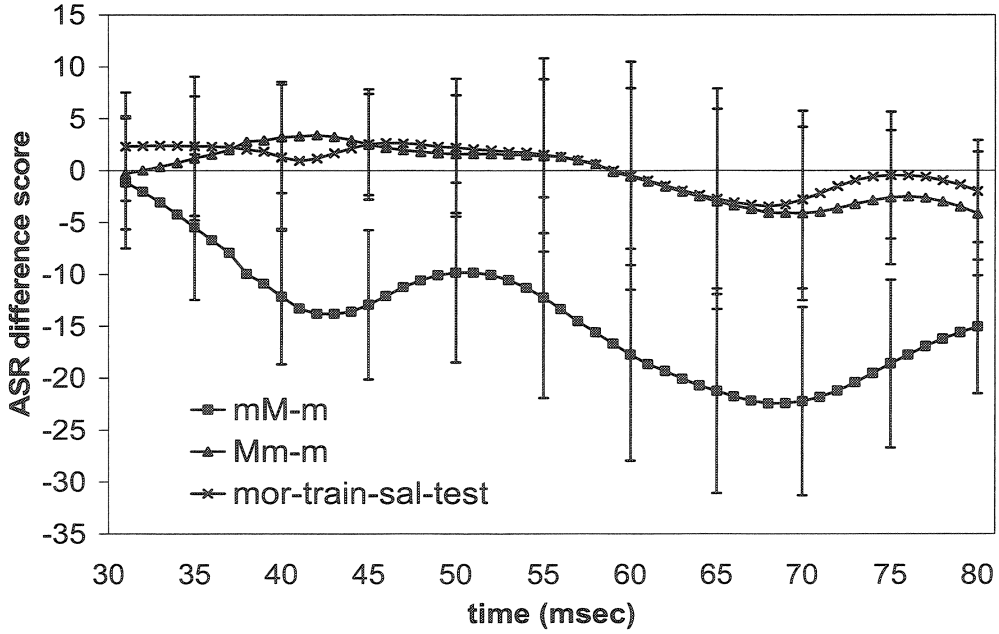
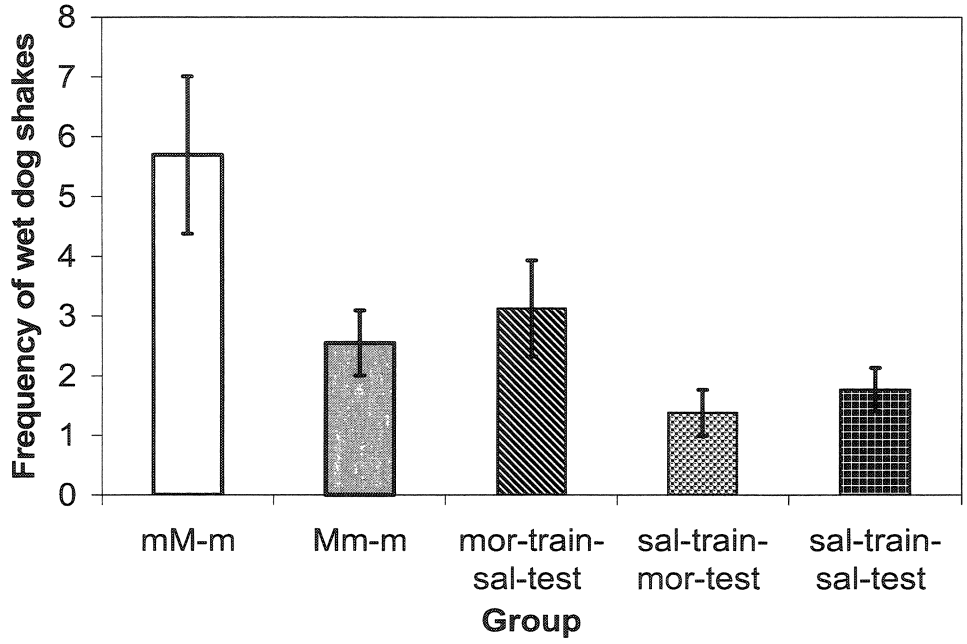
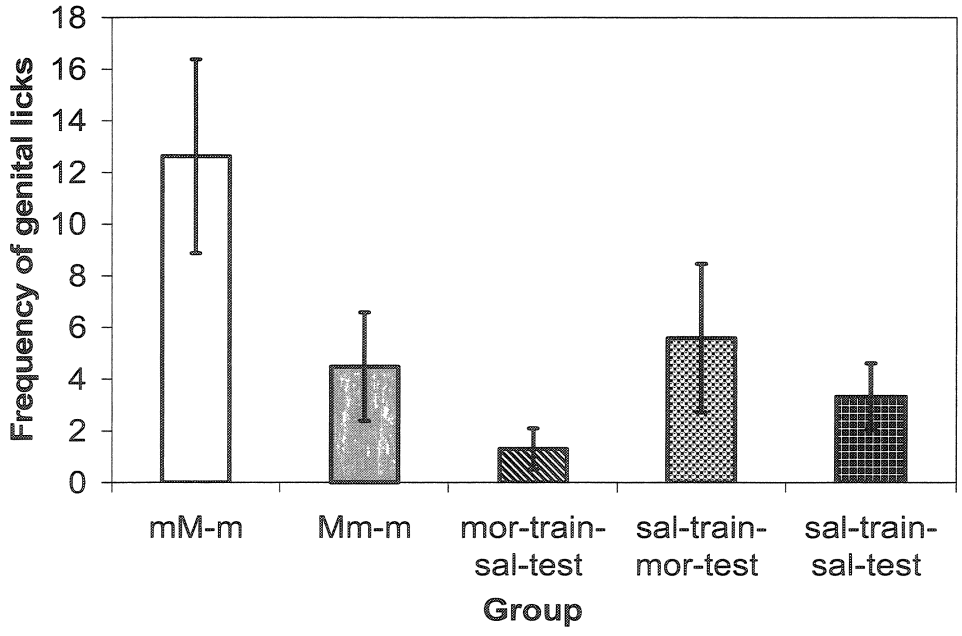

15
10
5
0
-5
-10
-15
-20
-25
-30
-35
ASR difference score
mM-m
Mm-m
mor-train-sal-test
30
35
40
45
50
55
60
65
70
75
80
time (msec)

Figure 11
A


Frequency of wet dog shakes
0
1
2
3
4
5
6
7
8
mM-m
Mm-m
mor-train-sal-test
sal-train-mor-test
sal-train-sal-test
Group

B


Frequency of genital licks
0
2
4
6
8
10
12
14
16
18
mM-m
Mm-m
mor-train-sal-test
sal-train-mor-test
sal-train-sal-test
Group

Appendix A

Chapter 2 Experiment 1
Tolerance Development

Group	Subject	Tolerance-Development Session					
		1	2	3	4	5	6
5%pMor	M2	14	11	13	12	11	8
5%pMor	S6	17	12	5	4	9	3
5%pMor	S12	24	24	11	14	17	13
5%pMor	S17	16	10	12	9	7	7
5%pMor	F4	20	18	15	16	13	11
5%pMor	F7	18	20	8	7	8	8
5%pMor	F18	20	10	12	13	14	9
10%pMor	M4	30	16	14	7	6	9
10%pMor	S7	10	9	8	8	11	6
10%pMor	S13	13	16	10	7	6	4
10%pMor	F2	24	8	6	10	10	11
10% pMor	F8	14	10	11	11	10	11
10% pMor	F15	9	8	6	7	7	5
10% pMor	F17	30	30	22	16	14	13
20% pMor	M11	18	30	10	15	7	6
20% pMor	S4	10	9	9	11	8	8
20% pMor	S19	30	9	13	9	7	7
20% pMor	E7	30	24	20	18	11	14
20% pMor	F1	16	11	10	5	10	6
20% pMor	F13	15	10	9	9	11	9
20% pMor	F19	19	6	11	10	5	10
0% pMor	M7	18	16	10	8	11	8
0% pMor	S21	30	13	12	17	15	9
0% pMor	S5	20	20	13	14	11	8
0% pMor	S9	16	13	12	12	12	10
0% pMor	F5	30	10	15	12	14	13
0% pMor	F11	12	11	11	7	8	9
0% pMor	F5	30	11	15	8	8	10

Chapter 2, Experiment 1
CCR Test

Group	Subject	Test	Time post-infusion (min)			
			5	15	30	45
5% pMor	M2	1	24	12	12	14
5% pMor	S12	1	15	16	12	11
5% pMor	S17	1	11	16	15	11
5% pMor	S6	1	12	12	11	13
5% pMor	F4	1	11	20	20	8
5% pMor	F7	1	11	14	4	14
5% pMor	F17	1	14	13	13	8
5% pMor	M2	2	14	21	9	10
5% pMor	S12	2	12	15	15	13
5% pMor	S17	2	12	14	14	11
5% pMor	S6	2	15	11	12	11
5% pMor	F4	2	14	12	13	18
5% pMor	F7	2	10	13	14	13
5% pMor	F17	2	11	15	11	13
5% pMor	M2	3	20	12	10	15
5% pMor	S12	3	16	17	11	5
5% pMor	S17	3	14	15	15	15
5% pMor	S6	3	12	15	10	11
5% pMor	F4	3	14	17	13	13
5% pMor	F7	3	11	11	13	8
5% pMor	F17	3	16	14	11	11
5% pMor	M2	4	18	16	10	9
5% pMor	S12	4	16	12	9	13
5% pMor	S17	4	12	11	12	11
5% pMor	S6	4	12	12	12	10
5% pMor	F4	4	10	9	8	9
5% pMor	F7	4	9	13	9	11
5% pMor	F17	4	16	11	11	9

Chapter 2, Experiment 1
CCR Test

Group	Subject	Test	Time post-infusion (min)			
			5	15	30	45
10% pMor	M4	1	8	12	18	6
10% pMor	S13	1	11	15	16	19
10% pMor	S7	1	7	10	6	9
10% pMor	F2	1	20	19	13	14
10% pMor	F8	1	12	11	10	10
10% pMor	F15	1	6	10	7	7
10% pMor	F16	1	8	10	8	6
10% pMor	M4	2	8	13	2	10
10% pMor	S13	2	17	15	13	14
10% pMor	S7	2	6	6	6	10
10% pMor	F2	2	15	15	14	11
10% pMor	F8	2	5	5	7	6
10% pMor	F15	2	3	6	5	7
10% pMor	F16	2	8	1	10	10
10% pMor	M4	3	7	11	1	14
10% pMor	S13	3	8	9	11	4
10% pMor	S7	3	7	8	8	6
10% pMor	F2	3	16	13	13	10
10% pMor	F8	3	9	8	7	6
10% pMor	F15	3	6	7	6	4
10% pMor	F16	3	8	11	9	10
10% pMor	M4	4	5	6	6	9
10% pMor	S13	4	7	7	11	13
10% pMor	S7	4	9	7	8	8
10% pMor	F2	4	10	12	10	14
10% pMor	F8	4	9	10	10	7
10% pMor	F15	4	7	8	9	8
10% pMor	F16	4	6	9	6	7

Chapter 2, Experiment 1
CCR Test

Group	Subject	Test	Time post-infusion (min)			
			5	15	30	45
20% pMor	M11	1	12	14	13	14
20% pMor	S19	1	18	20	14	13
20% pMor	S4	1	13	17	14	13
20% pMor	E7	1	19	27	20	22
20% pMor	F1	1	23	27	30	14
20% pMor	F13	1	11	15	13	13
20% pMor	F19	1	10	12	15	12
20% pMor	M11	2	20	23	7	28
20% pMor	S19	2	14	16	12	13
20% pMor	S4	2	11	18	16	14
20% pMor	E7	2	12	21	19	13
20% pMor	F1	2	16	27	16	17
20% pMor	F13	2	11	14	13	13
20% pMor	F19	2	9	12	12	11
20% pMor	M11	3	17	8	13	17
20% pMor	S19	3	15	15	15	16
20% pMor	S4	3	16	16	14	14
20% pMor	E7	3	19	22	14	18
20% pMor	F1	3	16	19	18	19
20% pMor	F13	3	13	14	10	12
20% pMor	F19	3	6	10	12	10
20% pMor	M11	4	9	11	16	12
20% pMor	S19	4	16	15	15	15
20% pMor	S4	4	12	9	9	11
20% pMor	E7	4	18	16	12	10
20% pMor	F1	4	16	30	14	12
20% pMor	F13	4	15	13	14	13
20% pMor	F19	4	11	12	12	11

Chapter 2, Experiment 1
CCR Test

Group	Subject	Test	Time post-infusion (min)			
			5	15	30	45
0% pMor	M7	1	10	19	18	17
0% pMor	S21	1	17	14	15	13
0% pMor	S5	1	15	12	21	10
0% pMor	S9	1	14	16	12	16
0% pMor	E10	1	16	15	13	13
0% pMor	F5	1	20	26	16	8
0% pMor	F11	1	12	12	9	13
0% pMor	M7	2	14	15	15	16
0% pMor	S21	2	19	12	11	20
0% pMor	S5	2	11	15	13	8
0% pMor	S9	2	14	15	7	11
0% pMor	E10	2	12	10	12	16
0% pMor	F5	2	14	14	16	15
0% pMor	F11	2	13	13	12	13
0% pMor	M7	3	17	15	17	17
0% pMor	S21	3	14	15	15	15
0% pMor	S5	3	16	12	12	14
0% pMor	S9	3	14	15	15	14
0% pMor	E10	3	11	12	13	13
0% pMor	F5	3	15	13	14	10
0% pMor	F11	3	11	13	11	9
0% pMor	M7	4	13	8	16	13
0% pMor	S21	4	15	11	14	11
0% pMor	S5	4	10	12	14	9
0% pMor	S9	4	12	12	12	11
0% pMor	E10	4	12	17	13	17
0% pMor	F5	4	13	17	15	17
0% pMor	F11	4	11	13	11	11

Chapter 2 Experiment 2
Tolerance Development

Group	Subject	Tolerance-Development Session								
		Day 1			Day 3			Day 5		
		0'	45'	90'	0'	45'	90'	0'	45'	90'
SMor	M1	30	30	30	8	16	9	8	11	9
SMor	M4	30	30	14	8	9	6	10	11	9
SMor	M11	30	13	11	15	9	7	6	9	4
SMor	B6	30	30	13	10	13	10	8	12	10
SMor	B7	15	30	11	13	15	7	7	8	8
SMor	C6	30	30	7	12	9	15	8	8	8
SMor	C8	24	30	9	8	10	8	7	8	6
SMor	D5	25	27	10	12	13	9	11	10	8
LMor	M6	25	20	9	10	8	10	10	8	8
LMor	M7	22	30	7	9	10	5	15	9	6
LMor	M8	21	30	9	12	11	8	13	13	8
LMor	B2	30	30	10	16	17	8	13	8	8
LMor	B3	22	30	5	13	18	4	14	10	8
LMor	C1	30	30	8	15	13	9	7	6	7
LMor	C2	29	18	7	16	16	16	10	11	10
LMor	C3	24	26	12	13	13	10	7	10	7
SSal	M13	6	7	4	6	4	7	8	9	8
SSal	B9	4	4	7	5	5	6	6	6	6
SSal	B10	5	4	6	7	7	8	8	7	8
SSal	C9	7	6	5	7	7	9	8	7	7
SSal	C10	6	8	7	8	8	8	7	8	7
SSal	D3	6	7	6	5	7	7	7	6	7
SSal	D4	5	6	7	6	5	7	6	6	7
LSal	M10	5	5	6	6	2	5	6	6	5
LSal	M12	4	5	4	6	7	7	4	5	8
LSal	B4	7	6	8	6	5	6	8	7	6
LSal	B5	8	6	8	7	8	9	6	6	6
LSal	C5	8	8	8	7	5	8	6	6	6
LSal	D1	5	5	5	6	6	8	8	8	7
LSal	D2	4	5	5	6	7	9	8	7	8

Chapter 2 Experiment 2
CCR Test

Group	Subject	Time Post-Infusion (min)				
		5	15	30	45	75
SMor	M1	10	12	11	13	14
SMor	M4	14	16	20	19	10
SMor	M11	16	21	17	21	19
SMor	B6	8	15	14	16	13
SMor	B7	10	12	14	13	15
SMor	C6	17	21	17	17	13
SMor	C8	10	12	11	14	11
SMor	D5	12	16	13	14	15
LMor	M6	12	11	13	4	6
LMor	M7	14	8	18	17	15
LMor	M8	10	8	12	6	7
LMor	B2	13	16	12	4	11
LMor	B3	14	16	12	10	11
LMor	C1	7	8	7	4	6
LMor	C2	2	7	5	6	10
LMor	C3	7	6	7	6	8
SSal	M13	7	20	23	18	19
SSal	B8	14	15	14	14	18
SSal	B9	15	18	7	12	16
SSal	C9	21	22	17	18	22
SSal	C10	20	23	17	20	18
SSal	D3	10	13	14	17	20
SSal	D4	20	21	22	16	12
LSal	M10	15	15	14	17	10
LSal	M12	11	12	12	11	7
LSal	B4	21	22	20	11	13
LSal	B5	16	19	18	18	18
LSal	C5	11	14	11	11	11
LSal	D1	16	21	14	25	18
LSal	D2	14	18	17	15	15

Chapter 2 Experiment 3
Tolerance Development

Group	Subject#	Tolerance-Development Session							
		1	2	3	4	5	6	7	8
mM-m	1a	30	12	5	5	4	7	6	7
mM-m	2a	30	12	10	8	12	8	8	10
mM-m	3a	15	17	15	12	13	13	11	9
mM-m	5a	30	14	10	6	8	2	11	8
mM-m	6a	30	16	11	7	9	6	6	6
mM-m	14a	30	30	14	12	9	12	6	5
mM-m	15a	30	16	9	14	8	9	9	7
mM-m	16a	30	23	14	16	9	15	11	10
mM-m	5b	30	13	7	6	7	6	3	4
mM-m	6b	11	30	14	8	8	11	12	11
mM-m	3d	30	9	9	6	7	6	3	4
mM-m	5d	30	8	10	11	10	7	6	5
mM-m	2e	30	30	7	13	7	6	6	6
mM-m	18f	30	14	13	9	9	8	8	4
mM-s	7b	23	13	30	8	8	8	7	6
mM-s	8b	30	30	14	30	18	16	15	7
mM-s	10b	30	27	9	12	4	10	10	10
mM-s	6c	30	30	30	30	5	6	8	7
mM-s	7c	30	30	25	30	10	10	5	6
mM-s	8c	30	30	11	11	8	7	6	6
mM-s	9c	30	30	30	13	4	6	8	7
mM-s	10c	28	15	16	11	4	13	4	5
mM-s	11c	30	30	7	16	11	9	8	8
mM-s	1d	30	30	13	13	9	7	5	6
mM-s	2d	18	13	4	3	6	11	6	6
mM-s	4d	30	30	16	10	11	7	8	5
mM-s	1e	30	15	9	8	9	7	5	7
mM-s	17f	30	30	30	15	15	12	15	16
Mm-m	7a	24	11	8	8	5	8	7	5
Mm-m	8a	30	30	15	7	8	16	11	11
Mm-m	9a	30	30	13	13	11	12	11	10
Mm-m	10a	30	16	8	8	3	6	8	4
Mm-m	11a	30	30	11	10	9	5	8	6
Mm-m	12a	30	30	13	20	20	6	6	14
Mm-m	13a	15	17	11	15	11	11	9	8
Mm-m	3b	30	30	30	8	11	11	10	9
Mm-m	4b	30	22	13	9	9	9	8	6

Chapter 2 Experiment 3
Tolerance Development

Group	Subject#	Tolerance-Development Session							
		1	2	3	4	5	6	7	8
Mm-m	13c	20	13	8	11	6	6	6	6
Mm-m	7d	20	20	12	18	16	14	12	12
Mm-m	10d	30	30	10	11	6	7	7	6
Mm-m	5e	18	30	11	12	8	6	7	6
Mm-m	20f	30	16	13	8	9	6	6	5
Mm-s	1b	30	30	30	18	6	6	10	7
Mm-s	2b	30	30	30	5	12	12	12	9
Mm-s	9b	10	4	4	5	4	4	4	4
Mm-s	1c	18	16	10	12	10	8	8	7
Mm-s	2c	13	8	9	9	7	5	4	4
Mm-s	3c	30	15	30	30	22	15	13	7
Mm-s	4c	30	30	7	5	6	6	6	7
Mm-s	12c	25	12	16	14	15	11	11	10
Mm-s	14c	30	30	30	17	10	5	8	6
Mm-s	6d	30	30	25	18	12	9	11	10
Mm-s	8d	30	13	6	3	4	5	4	4
Mm-s	9d	30	30	30	7	5	5	4	7
Mm-s	3e	30	30	30	30	15	8	10	8
Mm-s	4e	30	30	24	19	14	9	14	9
Mm-s	19f	30	30	18	8	8	8	10	9
mS-m	6e	5	4	4	4	5	5	4	5
mS-m	7e	5	5	4	3	4	5	5	5
mS-m	8e	5	3	3	3	4	5	3	4
mS-m	9e	4	4	3	4	4	3	4	4
mS-m	10e	5	4	4	4	4	5	5	5
mS-m	6f	4	4	3	4	4	3	3	5
mS-m	7f	2	4	3	3	5	3	2	4
mS-m	8f	5	5	4	3	4	4	5	4
mS-m	9f	3	4	4	3	5	3	4	4
mS-m	10f	4	5	4	5	4	5	4	5
mS-m	14f	2	3	2	3	2	3	2	2
mS-m	15f	5	5	4	3	5	4	4	4
mS-m	16f	4	3	5	5	4	6	4	5
Sm-m	11e	3	3	4	4	3	4	4	4
Sm-m	12e	5	4	4	5	5	4	3	4
Sm-m	13e	5	4	4	4	5	6	5	5
Sm-m	14e	3	3	3	3	3	3	4	4

Chapter 2 Experiment 3
Tolerance Development

Group	Subject#	Tolerance-Development Session							
		1	2	3	4	5	6	7	8
Sm-m	15e	4	4	4	3	4	4	4	4
Sm-m	1f	4	5	3	4	4	3	3	3
Sm-m	2f	4	5	5	4	5	5	5	4
Sm-m	3f	5	5	5	6	4	5	5	5
Sm-m	4f	4	3	4	4	5	5	5	5
Sm-m	5f	3	4	4	4	4	4	3	4
Sm-m	11f	3	4	4	3	3	4	5	3
Sm-m	12f	4	2	4	3	3	3	4	4
Sm-m	13f	5	4	5	4	4	4	4	5

Chapter 2 Experiment 3
CCR Test

Group	Subject #	Time Post-Infusion (min)			
		15	30	45	75
mM-m	1a	8	8	10	6
mM-m	2a	9	7	6	7
mM-m	3a	8	9	12	9
mM-m	5a	6	7	8	3
mM-m	6a	7	6	7	7
mM-m	14a	5	10	8	9
mM-m	15a	7	10	11	9
mM-m	16a	15	10	11	8
mM-m	5b	7	9	9	8
mM-m	6b	10	4	4	5
mM-m	3d	8	6	8	7
mM-m	5d	4	6	6	8
mM-m	2e	5	6	6	7
mM-m	18f	9	8	7	8
Mm-m	7b	11	12	11	10
Mm-m	8b	13	10	12	11
Mm-m	10b	15	12	13	12
Mm-m	6c	10	9	9	7
Mm-m	7c	9	12	15	16
Mm-m	8c	10	11	8	8
Mm-m	9c	12	11	12	12
Mm-m	10c	8	8	13	8
Mm-m	11c	9	9	10	8
Mm-m	1d	11	10	9	10
Mm-m	2d	11	11	9	17
Mm-m	4d	12	11	10	11
Mm-m	1e	10	8	8	9
Mm-m	17f	11	8	8	8
mM-s	7a	11	9	10	8
mM-s	8a	11	10	12	10
mM-s	9a	12	10	14	9
mM-s	10a	9	8	8	8
mM-s	11a	14	10	12	9
mM-s	12a	11	9	12	9
mM-s	13a	9	7	10	10
mM-s	3b	7	10	10	11
mM-s	4b	9	8	7	9

Chapter 2 Experiment 3
CCR Test

Group	Subject #	Time Post-Infusion (min)			
		15	30	45	75
mM-s	13c	11	9	12	9
mM-s	7d	9	8	8	7
mM-s	10d	9	7	9	9
mM-s	5e	13	9	9	10
mM-s	20f	8	7	6	4
Mm-s	1b	9	8	10	7
Mm-s	2b	7	7	10	8
Mm-s	9b	11	9	9	9
Mm-s	1c	9	9	8	9
Mm-s	2c	12	11	9	10
Mm-s	3c	12	9	9	7
Mm-s	4c	11	11	9	5
Mm-s	12c	10	8	10	9
Mm-s	14c	10	8	8	6
Mm-s	6d	12	12	10	9
Mm-s	8d	9	7	8	6
Mm-s	9d	7	7	7	7
Mm-s	3e	13	11	11	12
Mm-s	4e	9	7	6	7
Mm-s	19f	11	10	10	9
mS-m	6e	9	7	9	8
mS-m	7e	10	8	8	8
mS-m	8e	10	9	9	8
mS-m	9e	10	10	9	10
mS-m	10e	10	9	8	10
mS-m	6f	11	9	9	8
mS-m	7f	7	6	6	6
mS-m	8f	12	14	10	6
mS-m	9f	8	9	8	9
mS-m	10f	9	8	9	9
mS-m	14f	6	8	8	7
mS-m	15f	11	12	10	12
mS-m	16f	17	14	13	15
Sm-m	11e	9	7	7	7
Sm-m	12e	10	9	9	9
Sm-m	13e	13	11	12	12

Chapter 2 Experiment 3
CCR Test

Group	Subject #	Time Post-Infusion (min)			
		15	30	45	75
Sm-m	14e	9	7	7	10
Sm-m	15e	11	8	10	7
Sm-m	1f	11	8	9	10
Sm-m	2f	11	8	9	9
Sm-m	3f	11	11	10	10
Sm-m	4f	9	10	12	10
Sm-m	5f	13	9	12	9
Sm-m	11f	10	10	10	11
Sm-m	12f	8	7	6	6
Sm-m	13f	12	8	9	11

Chapter 3,
Tolerance Development

Group	Subject	Days of morphine administration						
		1	2	3	4	5	6	7
m-preexposed	M1	30	30	30	30	14	16	17
m-preexposed	M2	30	30	15	10	10	10	11
m-preexposed	M3	30	21	17	12	11	5	7
m-preexposed	M4	30	30	30	24	22	22	19
m-preexposed	M5	18	16	15	13	12	11	12
m-preexposed	M7	30	30	30	30	23	30	15
m-preexposed	M8	30	12	13	9	7	9	9
m-preexposed	M9	30	14	30	7	4	14	11
s-preexposed	S1	30	19	14	8	13	11	10
s-preexposed	S2	30	30	20	12	7	12	14
s-preexposed	S3	30	30	23	17	16	14	10
s-preexposed	S4	30	25	18	14	14	16	10
s-preexposed	S6	30	30	23	18	12	15	10
s-preexposed	S7	30	24	11	10	11	12	10
s-preexposed	S8	30	11	9	8	9	9	8
s-preexposed	S9	15	5	3	3	3	3	5

Chapter 3
CCR Test

Group	Subject	Time Post-Infusion (min)				
		10	15	30	45	75
m-preexposed	M1	19	21	19	15	13
m-preexposed	M2	12	12	12	12	12
m-preexposed	M3	10	11	10	9	8
m-preexposed	M4	11	10	13	10	12
m-preexposed	M5	13	13	15	15	15
m-preexposed	M7	11	13	12	11	10
m-preexposed	M8	9	7	5	6	5
m-preexposed	M9	23	19	20	22	14
s-preexposed	S1	10	12	13	14	10
s-preexposed	S2	9	7	8	8	9
s-preexposed	S3	5	9	7	8	6
s-preexposed	S4	11	14	14	13	10
s-preexposed	S6	9	10	7	10	9
s-preexposed	S7	7	9	10	10	11
s-preexposed	S8	8	11	7	8	7
s-preexposed	S9	4	6	5	5	5

Chapter 4 Experiment 1
Test, 105 dB SPL (C)

Group	Subject	Time Post Startle Stimuli Presentation (msec)						
		31	32	33	34	35	36	37
paired	2a	5.46	5.30	5.46	5.43	4.88	4.56	3.97
paired	5a	-36.03	-38.47	-40.90	-42.79	-44.69	-46.07	-47.50
paired	9a	67.56	70.75	70.35	71.88	71.64	70.15	67.09
paired	10a	4.01	3.07	1.88	0.63	-0.31	-1.86	-2.81
paired	16a	-1.68	-1.53	-1.39	-1.11	-0.83	-0.50	0.02
paired	19a	11.22	12.39	13.62	14.54	15.23	15.98	16.58
paired	20a	3.93	4.92	6.00	6.96	6.24	6.29	5.72
paired	21a	14.48	15.89	17.30	18.33	17.58	18.26	18.37
paired	3b	23.82	25.73	27.42	28.97	30.30	31.43	32.00
paired	6b	21.50	23.23	24.99	26.36	27.78	29.10	30.04
paired	10b	-5.05	-5.95	-6.76	-7.52	-8.18	-8.72	-9.47
paired	11b	-3.97	-4.47	-4.99	-5.45	-5.83	-6.23	-6.44
paired	12b	16.09	17.07	17.97	18.67	19.06	19.36	19.30
paired	13b	29.31	33.67	37.99	42.04	46.09	49.76	52.62
paired	16b	24.36	29.03	33.33	37.89	42.00	45.73	49.07
paired	17b	34.30	39.58	44.63	49.46	53.97	57.86	61.31
unpaired	3a	33.48	36.03	38.29	40.45	40.81	42.53	43.36
unpaired	11a	13.44	14.72	15.62	16.52	17.30	17.66	17.94
unpaired	12a	36.59	40.09	43.24	45.99	48.01	49.49	50.08
unpaired	13a	44.15	48.86	53.40	57.52	61.03	64.02	66.29
unpaired	18a	20.51	22.87	24.83	26.74	28.04	28.88	29.23
unpaired	1b	27.36	32.20	37.01	42.10	46.98	51.83	56.23
unpaired	2b	28.72	31.91	35.21	38.35	41.27	44.32	47.15
unpaired	4b	12.69	14.94	17.21	19.49	21.81	23.80	25.50
unpaired	5b	53.27	61.72	70.17	78.15	86.05	93.60	100.90
unpaired	8b	68.04	76.54	84.60	92.02	98.58	104.51	109.16
unpaired	9b	44.28	51.46	58.37	65.42	72.00	78.12	83.65
unpaired	14b	12.64	13.21	13.86	14.34	14.37	13.96	13.49
unpaired	15b	14.70	15.87	17.08	17.85	18.64	19.41	20.15
unpaired	18b	8.15	9.49	10.88	12.11	13.34	14.40	15.27
unpaired	19b	20.72	22.77	24.74	26.42	27.98	28.84	29.38
unpaired	23b	-3.88	-4.28	-4.63	-4.92	-5.34	-5.43	-5.69

Chapter 4 Experiment 1
Test, 105 dB SPL (C)

Group	Subject	Time Post Startle Stimuli Presentation (msec)						
		38	39	40	41	42	43	44
paired	2a	3.52	2.40	1.18	0.13	-0.70	-0.67	-0.47
paired	5a	-48.87	-49.64	-50.31	-49.32	-48.70	-47.20	-44.89
paired	9a	62.66	57.26	51.94	48.47	46.35	45.93	47.05
paired	10a	-4.22	-5.35	-5.76	-5.43	-3.73	-1.10	1.57
paired	16a	0.52	1.30	2.18	5.67	6.79	7.90	8.84
paired	19a	17.03	16.95	16.75	16.50	15.83	15.23	14.37
paired	20a	4.53	1.16	-0.92	-3.33	-5.56	-6.15	-5.39
paired	21a	17.81	16.87	15.79	14.62	14.18	13.53	13.09
paired	3b	32.28	32.10	31.41	30.23	28.53	26.50	24.59
paired	6b	30.99	31.05	30.64	28.46	26.66	25.17	24.17
paired	10b	-10.02	-10.37	-10.28	-9.74	-8.62	-7.21	-6.12
paired	11b	-6.61	-6.58	-6.39	-5.93	-5.38	-4.61	-3.90
paired	12b	18.85	16.66	15.64	14.56	13.90	13.33	13.52
paired	13b	54.45	54.97	54.88	53.28	50.33	46.88	43.53
paired	16b	51.70	53.60	54.49	54.67	52.75	48.90	44.66
paired	17b	64.01	65.67	65.97	63.25	60.26	57.38	54.63
unpaired	3a	43.49	42.52	41.44	36.90	36.18	36.01	34.99
unpaired	11a	17.68	16.96	15.59	14.03	12.41	11.36	11.19
unpaired	12a	49.85	48.61	46.55	43.71	41.10	39.09	38.54
unpaired	13a	67.50	67.89	67.06	64.94	61.36	56.92	52.66
unpaired	18a	28.80	27.74	25.99	28.77	27.36	26.36	25.97
unpaired	1b	60.58	62.10	64.28	65.34	65.20	63.15	59.91
unpaired	2b	50.61	52.49	54.27	55.31	55.47	53.83	50.26
unpaired	4b	27.24	28.16	28.76	28.93	28.62	27.97	27.12
unpaired	5b	107.88	114.12	116.48	118.77	118.10	113.97	107.19
unpaired	8b	112.97	113.78	111.35	105.24	97.26	89.24	84.47
unpaired	9b	88.27	92.32	95.28	95.41	93.24	88.70	83.97
unpaired	14b	12.55	11.33	13.30	12.75	13.22	14.15	15.20
unpaired	15b	20.64	21.25	21.82	21.50	21.06	19.58	17.34
unpaired	18b	16.01	16.30	16.65	16.60	16.27	15.65	15.02
unpaired	19b	29.65	29.07	27.80	25.93	23.75	22.40	21.75
unpaired	23b	-5.87	-5.95	-4.66	-4.29	-3.78	-3.00	-1.95

Chapter 4 Experiment 1
Test, 105 dB SPL (C)

Group	Subject	Time Post Startle Stimuli Presentation (msec)						
		45	46	47	48	49	50	51
paired	2a	0.40	1.36	2.52	3.66	4.93	6.35	7.73
paired	5a	-42.99	-42.88	-43.85	-46.18	-49.00	-52.15	-55.47
paired	9a	49.33	52.74	56.95	61.49	66.21	70.99	75.45
paired	10a	3.17	3.66	2.73	1.21	-0.52	-2.16	-3.64
paired	16a	8.94	8.13	6.74	5.24	3.37	1.49	-0.35
paired	19a	13.96	13.71	13.64	13.80	14.04	14.55	15.34
paired	20a	-4.08	-2.56	-1.20	0.24	1.64	3.59	5.92
paired	21a	13.14	13.51	14.07	15.08	16.31	17.83	19.67
paired	3b	23.44	22.99	23.55	24.44	26.16	28.02	30.30
paired	6b	23.89	23.70	24.30	25.15	26.43	27.75	29.45
paired	10b	-5.43	-5.12	-5.17	-5.62	-6.39	-7.31	-8.38
paired	11b	-3.24	-3.09	-3.34	-3.51	-4.06	-4.84	-5.55
paired	12b	13.97	14.88	16.16	17.65	19.03	20.33	21.78
paired	13b	40.94	38.82	37.66	37.61	38.68	40.68	43.28
paired	16b	40.95	38.42	37.45	38.03	39.84	42.62	46.38
paired	17b	53.43	53.67	55.18	57.84	61.18	64.97	69.22
unpaired	3a	33.99	33.38	33.14	33.28	33.63	38.13	38.97
unpaired	11a	11.75	13.47	15.77	17.96	20.00	21.85	24.23
unpaired	12a	39.04	40.61	43.01	46.11	49.78	53.60	57.83
unpaired	13a	50.03	49.58	50.75	53.37	56.90	61.41	66.17
unpaired	18a	26.13	26.91	27.92	29.36	30.98	32.72	34.79
unpaired	1b	55.42	50.73	46.27	42.82	40.68	40.05	40.81
unpaired	2b	46.08	42.49	39.37	37.18	35.22	33.71	32.62
unpaired	4b	26.07	24.77	23.81	23.56	23.53	24.23	24.93
unpaired	5b	100.44	94.93	91.65	90.09	87.64	88.35	90.23
unpaired	8b	82.66	83.89	87.44	93.06	98.44	106.47	114.77
unpaired	9b	78.93	74.43	71.14	69.45	69.48	71.17	74.32
unpaired	14b	15.71	15.84	15.77	15.79	15.80	15.84	15.58
unpaired	15b	15.59	14.16	13.28	13.02	13.61	14.39	15.41
unpaired	18b	14.45	13.88	13.62	13.45	13.62	14.05	14.78
unpaired	19b	22.14	23.08	24.75	26.64	29.07	31.61	34.42
unpaired	23b	-1.08	-0.55	-0.52	-0.93	-1.45	-2.23	-3.05

Chapter 4 Experiment 1
Test, 105 dB SPL (C)

Group	Subject	Time Post Startle Stimuli Presentation (msec)						
		52	53	54	55	56	57	58
paired	2a	9.16	10.58	11.96	13.25	14.39	15.30	15.90
paired	5a	-58.81	-61.97	-65.01	-67.67	-69.38	-71.80	-73.94
paired	9a	79.52	83.27	85.99	88.32	89.73	90.52	90.74
paired	10a	-5.36	-7.14	-8.88	-10.28	-11.76	-13.13	-14.36
paired	16a	-2.09	-3.51	-4.75	-5.69	-6.23	-6.82	-6.81
paired	19a	16.27	17.37	18.57	19.73	20.73	21.79	22.93
paired	20a	8.38	10.88	13.01	14.95	16.37	16.97	16.69
paired	21a	21.06	22.48	23.58	24.63	25.45	25.73	25.77
paired	3b	32.67	35.40	38.14	40.94	43.60	46.06	48.61
paired	6b	31.42	33.25	35.43	37.41	39.23	41.09	42.67
paired	10b	-9.54	-10.80	-11.96	-13.11	-14.08	-15.14	-15.92
paired	11b	-6.57	-7.61	-8.74	-9.79	-10.75	-11.73	-12.65
paired	12b	22.94	24.18	25.04	25.87	26.43	26.82	27.04
paired	13b	46.53	50.42	54.32	58.49	62.38	66.22	69.66
paired	16b	50.88	55.79	60.61	65.78	70.56	75.10	78.90
paired	17b	73.78	78.00	82.26	85.91	89.01	91.65	93.81
unpaired	3a	40.22	41.52	42.82	43.95	44.94	45.73	46.15
unpaired	11a	25.38	26.48	27.56	28.60	29.41	30.14	30.40
unpaired	12a	62.03	66.25	70.07	73.61	76.59	79.07	80.88
unpaired	13a	71.03	76.18	80.94	85.62	89.94	93.89	97.27
unpaired	18a	36.52	38.51	40.19	41.95	43.51	44.50	45.55
unpaired	1b	42.76	45.72	49.53	53.93	58.59	63.52	68.50
unpaired	2b	32.45	32.94	33.89	35.24	37.36	39.76	42.47
unpaired	4b	26.35	27.96	29.69	31.60	33.24	34.97	36.65
unpaired	5b	93.40	97.56	102.66	105.32	112.09	118.81	125.53
unpaired	8b	123.61	132.60	141.46	150.03	157.86	164.68	170.46
unpaired	9b	78.86	84.62	91.01	98.07	105.46	112.92	120.04
unpaired	14b	15.45	15.20	14.88	14.60	14.29	13.96	13.74
unpaired	15b	16.61	17.64	18.70	19.72	20.59	21.39	22.26
unpaired	18b	15.75	16.80	18.05	19.44	20.74	22.28	23.60
unpaired	19b	37.16	39.67	42.43	44.77	46.86	48.61	50.16
unpaired	23b	-3.93	-5.24	-6.45	-7.84	-9.22	-10.54	-11.80

Chapter 4 Experiment 1
Test, 105 dB SPL (C)

Group	Subject	Time Post Startle Stimuli Presentation (msec)						
		59	60	61	62	63	64	65
paired	2a	16.62	16.55	16.55	16.25	15.87	15.36	14.86
paired	5a	-75.88	-77.67	-79.31	-80.60	-81.70	-82.37	-82.55
paired	9a	90.16	88.98	87.14	84.71	81.72	78.50	74.74
paired	10a	-15.25	-16.04	-16.41	-16.66	-16.42	-15.96	-15.28
paired	16a	-6.50	-6.27	-5.59	-4.51	-3.53	-2.64	-1.34
paired	19a	23.81	24.13	24.92	25.36	25.53	25.71	25.85
paired	20a	16.10	18.54	16.55	14.35	11.96	9.19	6.48
paired	21a	25.78	25.52	25.17	24.69	24.08	23.41	22.61
paired	3b	50.82	52.70	54.30	55.54	56.31	56.64	56.65
paired	6b	44.06	45.04	45.95	46.40	46.70	46.64	46.37
paired	10b	-16.97	-17.87	-18.45	-19.16	-19.70	-19.98	-20.17
paired	11b	-13.35	-14.08	-14.79	-15.08	-15.20	-14.86	-14.46
paired	12b	26.93	26.68	26.15	25.59	24.58	23.67	22.53
paired	13b	72.46	74.72	76.53	77.36	77.70	77.29	76.09
paired	16b	82.16	84.83	86.61	87.51	87.76	87.43	86.33
paired	17b	95.56	96.61	97.09	97.43	96.57	94.95	92.58
unpaired	3a	46.35	46.44	44.92	44.75	44.37	43.45	42.04
unpaired	11a	30.31	29.74	28.67	27.24	25.39	23.23	20.66
unpaired	12a	82.14	82.64	82.65	81.78	80.30	78.37	75.61
unpaired	13a	100.27	102.67	104.39	105.48	105.72	105.49	104.40
unpaired	18a	46.06	46.32	46.19	45.55	44.61	43.44	41.95
unpaired	1b	73.39	77.88	82.01	85.85	89.01	91.59	93.52
unpaired	2b	45.37	48.38	51.46	54.51	57.49	60.32	63.02
unpaired	4b	37.89	39.14	40.02	40.92	41.41	41.70	41.72
unpaired	5b	131.93	138.24	144.24	149.60	154.25	157.85	160.59
unpaired	8b	174.89	177.77	179.09	178.64	176.78	173.18	167.84
unpaired	9b	126.77	132.45	137.58	141.54	144.41	145.87	146.37
unpaired	14b	13.52	13.21	13.12	12.97	12.83	12.53	12.50
unpaired	15b	23.54	24.54	25.83	26.94	28.30	29.48	30.63
unpaired	18b	24.91	26.02	27.09	27.87	28.50	29.02	29.10
unpaired	19b	50.98	51.61	51.74	51.44	50.57	49.49	47.79
unpaired	23b	-13.10	-14.19	-14.69	-15.01	-15.36	-15.30	-15.17

Chapter 4 Experiment 1
Test, 105 dB SPL (C)

Group	Subject	Time Post Startle Stimuli Presentation (msec)						
		66	67	68	69	70	71	72
paired	2a	14.16	13.64	13.08	12.33	11.41	10.52	9.38
paired	5a	-82.15	-81.24	-80.03	-78.05	-75.97	-73.63	-71.02
paired	9a	70.78	66.96	63.19	59.67	56.77	53.79	50.32
paired	10a	-14.25	-13.11	-11.65	-10.02	-8.32	-6.59	-5.29
paired	16a	-0.22	1.03	2.20	3.47	4.64	6.00	6.99
paired	19a	25.66	25.44	25.19	24.82	24.18	23.57	22.71
paired	20a	3.81	1.13	-1.42	-3.69	-5.98	-7.88	-8.83
paired	21a	21.66	20.92	20.36	19.55	19.02	18.54	17.78
paired	3b	56.04	55.21	54.14	52.64	50.69	48.74	46.51
paired	6b	45.84	45.12	44.34	43.19	41.72	40.34	38.52
paired	10b	-20.16	-19.96	-18.99	-17.90	-16.43	-14.28	-12.16
paired	11b	-13.81	-12.80	-11.43	-10.18	-8.47	-6.90	-5.35
paired	12b	21.33	20.20	19.03	18.11	17.33	16.58	16.21
paired	13b	74.64	72.02	68.68	64.59	59.94	55.32	50.69
paired	16b	84.60	82.00	78.74	74.40	69.19	63.48	57.38
paired	17b	89.26	85.32	80.30	74.67	68.67	63.36	59.04
unpaired	3a	40.27	37.92	35.44	32.71	30.55	28.87	27.24
unpaired	11a	18.06	15.51	12.85	10.29	7.97	5.64	3.95
unpaired	12a	72.36	68.65	64.61	60.32	55.97	51.96	48.48
unpaired	13a	102.42	99.75	96.30	92.27	87.29	81.57	75.71
unpaired	18a	39.94	37.82	35.23	32.52	29.91	27.50	25.65
unpaired	1b	94.78	95.23	94.78	93.16	90.52	86.96	82.55
unpaired	2b	65.32	67.17	69.01	70.09	70.74	71.04	70.47
unpaired	4b	41.57	41.17	40.39	39.42	38.06	36.81	35.22
unpaired	5b	161.84	161.78	159.92	156.20	150.35	143.40	135.52
unpaired	8b	160.71	151.65	140.90	129.03	116.85	105.16	95.00
unpaired	9b	145.31	143.02	139.53	134.47	128.13	121.15	114.13
unpaired	14b	12.19	11.71	11.01	10.54	10.17	9.73	9.45
unpaired	15b	31.41	32.20	32.88	32.66	32.32	31.12	29.16
unpaired	18b	29.09	28.97	28.47	27.84	27.08	26.00	25.08
unpaired	19b	45.61	43.01	40.05	36.90	33.92	31.24	29.24
unpaired	23b	-14.61	-14.30	-13.36	-12.75	-11.71	-10.94	-9.99

Chapter 4 Experiment 1
Test, 105 dB SPL (C)

Group	Subject	Time Post Startle Stimuli Presentation (msec)						
		73	74	75	76	77	78	79
paired	2a	8.27	7.20	6.65	6.57	6.79	7.10	7.94
paired	5a	-68.37	-65.53	-62.16	-58.58	-54.78	-50.51	-46.64
paired	9a	46.67	42.77	38.54	34.64	30.87	27.21	23.68
paired	10a	-4.46	-4.01	-4.09	-4.37	-4.88	-5.78	-6.79
paired	16a	7.88	8.66	9.11	9.28	8.71	8.01	7.11
paired	19a	21.55	20.47	19.47	18.51	17.43	16.63	15.79
paired	20a	-9.23	-8.73	-7.85	-6.48	-5.07	-3.54	-2.22
paired	21a	17.16	16.70	16.22	15.54	14.76	14.08	13.10
paired	3b	43.99	41.35	38.57	35.94	33.77	31.95	30.89
paired	6b	36.49	34.26	32.42	31.03	29.91	29.22	28.95
paired	10b	-9.96	-7.99	-6.39	-5.29	-4.54	-3.99	-3.91
paired	11b	-3.83	-2.56	-1.55	-0.97	-0.56	-0.47	-0.61
paired	12b	16.20	16.33	16.56	16.72	16.87	17.00	16.89
paired	13b	47.06	44.09	41.59	39.75	38.13	36.89	35.85
paired	16b	51.29	45.52	40.11	35.15	31.08	27.84	24.88
paired	17b	55.62	53.07	51.03	49.25	47.79	46.19	44.18
unpaired	3a	25.44	23.46	21.68	19.65	18.01	16.46	15.26
unpaired	11a	2.44	1.42	1.00	1.12	1.34	1.80	2.45
unpaired	12a	45.84	43.66	42.14	41.21	40.47	40.07	39.98
unpaired	13a	69.33	63.35	57.61	52.35	47.90	44.35	41.72
unpaired	18a	24.24	22.94	22.42	21.93	21.99	22.07	22.48
unpaired	1b	77.45	72.02	66.41	61.20	56.22	51.68	47.84
unpaired	2b	69.17	66.72	63.06	58.54	53.09	47.15	41.32
unpaired	4b	33.67	32.11	30.53	28.88	27.56	26.25	25.34
unpaired	5b	126.90	118.39	110.43	103.65	97.47	92.28	87.58
unpaired	8b	86.44	79.70	74.43	70.13	66.76	64.01	61.78
unpaired	9b	107.61	101.36	95.59	90.93	86.87	83.46	80.62
unpaired	14b	9.12	8.86	8.44	8.14	7.76	7.19	6.61
unpaired	15b	26.87	24.51	22.64	21.05	19.75	18.76	17.94
unpaired	18b	23.90	22.66	21.46	20.39	19.49	18.58	17.70
unpaired	19b	27.94	27.21	27.05	27.15	27.61	28.18	28.99
unpaired	23b	-8.85	-7.88	-6.83	-5.85	-4.94	-4.13	-3.55

Chapter 4 Experiment 1
Test, 115 dB SPL (C)

Group	Subject	Time Post Startle Stimuli Presentation (msec)						
		31	32	33	34	35	36	37
paired	2a	18.79	20.33	21.84	23.19	24.30	25.11	25.38
paired	5a	-35.75	-36.89	-38.03	-38.85	-39.62	-40.30	-40.77
paired	9a	17.10	17.41	17.54	17.02	16.14	14.85	13.33
paired	10a	-7.99	-10.08	-12.41	-14.68	-16.69	-18.49	-19.95
paired	16a	-2.93	-0.74	1.36	3.42	5.66	8.18	11.03
paired	19a	21.71	21.74	21.55	21.38	21.38	21.17	21.41
paired	20a	20.42	22.22	24.18	25.94	27.45	28.25	28.56
paired	21a	25.91	28.79	31.56	34.31	36.58	38.41	39.91
paired	3b	8.58	9.15	9.68	9.94	9.95	9.71	9.28
paired	6b	5.12	6.32	7.73	8.95	10.06	10.91	11.71
paired	10b	16.81	17.08	17.03	16.82	16.43	15.73	14.67
paired	11b	9.39	10.14	10.88	11.31	11.54	11.59	11.40
paired	12b	4.92	3.68	2.14	0.36	-1.32	-3.03	-4.75
paired	13b	7.02	10.18	13.51	16.77	19.31	22.43	25.26
paired	16b	-11.30	-12.79	-13.87	-14.36	-14.15	-12.27	-10.12
paired	17b	-9.06	-8.65	-2.91	-2.73	-2.66	-2.47	-2.11
unpaired	3a	11.21	14.43	18.18	21.39	24.18	26.67	28.61
unpaired	11a	43.87	46.28	48.11	49.56	50.50	50.93	50.95
unpaired	12a	50.21	55.73	61.13	65.90	70.41	74.14	76.95
unpaired	13a	9.07	11.27	13.14	15.10	16.88	18.46	19.69
unpaired	18a	43.92	47.57	50.70	53.68	55.96	58.06	59.83
unpaired	1b	-5.16	-3.29	-1.48	1.19	4.33	7.21	9.12
unpaired	2b	-2.80	-1.81	-0.82	0.26	1.43	2.48	3.57
unpaired	4b	-5.72	-6.37	-7.09	-7.65	-7.93	-8.53	-8.91
unpaired	5b	-2.07	1.76	5.48	9.45	13.56	15.08	20.59
unpaired	8b	14.63	20.24	25.93	31.55	37.54	43.44	49.42
unpaired	9b	25.72	30.83	35.87	40.65	45.36	49.65	53.86
unpaired	14b	-4.20	-4.29	-4.25	-3.95	-3.76	-0.10	0.05
unpaired	15b	-27.93	-31.12	-34.08	-36.82	-39.09	-40.78	-41.91
unpaired	18b	9.92	11.29	12.52	13.73	14.88	15.99	16.83
unpaired	19b	18.74	20.39	21.99	23.46	24.64	25.66	26.14
unpaired	23b	-15.38	-16.97	-18.58	-20.26	-21.58	-23.03	-24.70

Chapter 4 Experiment 1
Test, 115 dB SPL (C)

Group	Subject	Time Post Startle Stimuli Presentation (msec)						
		38	39	40	41	42	43	44
paired	2a	25.38	24.74	23.56	21.83	19.65	17.74	16.01
paired	5a	-43.41	-43.18	-43.23	-41.40	-40.06	-38.37	-37.17
paired	9a	11.28	10.95	9.36	8.88	10.18	12.05	13.65
paired	10a	-20.36	-20.64	-24.61	-23.45	-21.89	-19.56	-17.20
paired	16a	14.08	17.58	19.79	23.91	27.10	28.45	26.97
paired	19a	21.17	21.07	22.65	22.05	20.76	19.45	19.30
paired	20a	28.13	27.12	25.25	24.09	22.34	20.89	20.71
paired	21a	40.69	40.91	40.61	40.62	39.51	38.28	37.25
paired	3b	12.23	11.50	9.94	9.36	7.85	6.12	4.64
paired	6b	12.36	13.03	13.55	15.43	15.54	14.78	13.65
paired	10b	13.06	11.60	10.89	7.93	8.12	9.23	11.12
paired	11b	10.99	10.30	9.35	7.14	6.18	5.14	4.49
paired	12b	-4.60	-6.32	-7.77	-9.15	-9.89	-9.45	-7.83
paired	13b	27.60	31.84	35.64	34.98	35.14	33.74	31.43
paired	16b	-13.30	-9.67	-8.46	-3.79	-0.60	0.45	-0.30
paired	17b	-1.85	-1.67	-1.65	-1.76	-2.52	-3.02	-3.16
unpaired	3a	30.32	31.84	21.37	20.14	18.14	14.52	9.81
unpaired	11a	50.64	49.72	46.67	49.48	47.28	46.69	47.33
unpaired	12a	78.72	79.23	78.28	76.18	72.95	69.87	67.91
unpaired	13a	16.13	16.61	17.09	17.42	16.79	15.97	15.08
unpaired	18a	60.94	59.88	58.91	56.60	52.99	49.38	45.91
unpaired	1b	13.03	16.23	19.21	24.81	26.39	26.26	24.34
unpaired	2b	5.03	6.47	8.36	10.36	12.43	13.56	13.22
unpaired	4b	-9.39	-10.05	-10.58	-8.94	-9.20	-9.17	-8.37
unpaired	5b	22.14	28.30	34.33	38.35	37.66	30.77	21.38
unpaired	8b	54.87	58.81	58.74	54.23	46.55	38.79	33.81
unpaired	9b	57.67	62.81	67.93	69.57	70.30	69.58	67.38
unpaired	14b	0.74	1.82	3.14	4.63	5.69	6.44	5.99
unpaired	15b	-42.20	-41.71	-40.30	-38.89	-36.04	-33.37	-30.94
unpaired	18b	17.30	17.30	17.15	17.29	16.17	14.63	12.92
unpaired	19b	26.28	24.35	25.71	25.41	23.76	22.02	20.83
unpaired	23b	-25.80	-26.73	-27.49	-27.82	-27.69	-27.34	-26.60

Chapter 4 Experiment 1
Test, 115 dB SPL (C)

Group	Subject	Time Post Startle Stimuli Presentation (msec)						
		45	46	47	48	49	50	51
paired	2a	15.10	14.70	14.93	15.58	16.60	17.83	19.52
paired	5a	-37.31	-39.57	-44.27	-49.50	-54.52	-59.31	-63.19
paired	9a	14.40	14.73	14.53	13.89	12.82	11.53	9.95
paired	10a	-14.90	-13.79	-14.17	-15.95	-18.68	-22.35	-26.17
paired	16a	22.43	15.86	8.37	2.54	-1.46	-3.47	-3.85
paired	19a	20.15	22.37	25.59	28.83	31.92	34.61	36.45
paired	20a	21.69	23.35	26.37	30.08	34.10	38.04	41.65
paired	21a	36.55	36.27	36.11	36.09	36.74	37.50	38.21
paired	3b	3.68	3.30	3.28	3.90	5.16	7.31	9.70
paired	6b	12.08	10.64	9.42	8.21	7.08	6.23	5.64
paired	10b	13.49	15.66	17.75	19.34	20.50	21.13	21.84
paired	11b	3.97	3.58	3.09	2.81	2.92	3.47	4.08
paired	12b	-5.66	-3.16	-1.46	-0.30	-0.46	-1.70	-4.23
paired	13b	28.64	26.01	24.35	23.59	23.64	24.42	25.68
paired	16b	-2.12	-4.89	-7.46	-9.29	-10.93	-11.92	-12.19
paired	17b	-2.79	-2.36	-1.54	-1.08	-1.35	-2.21	-3.28
unpaired	3a	5.28	1.84	-0.99	-2.80	-3.94	-4.09	-3.26
unpaired	11a	49.61	53.38	58.46	64.42	71.08	78.61	86.04
unpaired	12a	67.01	67.18	68.25	70.18	72.87	76.43	80.54
unpaired	13a	14.61	14.54	14.71	16.03	18.09	20.10	22.29
unpaired	18a	43.06	41.91	42.60	45.27	49.08	54.22	59.97
unpaired	1b	21.33	17.09	12.27	7.92	4.22	1.50	-0.22
unpaired	2b	11.35	8.55	5.74	3.09	0.94	-0.72	-2.14
unpaired	4b	-6.94	-5.59	-5.30	-5.62	-6.73	-8.24	-10.08
unpaired	5b	12.97	7.08	3.97	4.29	7.22	11.94	17.70
unpaired	8b	31.57	31.78	34.38	38.09	43.14	48.75	55.07
unpaired	9b	64.10	61.27	58.71	57.23	56.87	56.94	57.39
unpaired	14b	4.25	1.98	-0.87	-4.06	-7.76	-11.61	-14.91
unpaired	15b	-29.71	-29.63	-30.88	-33.01	-35.80	-39.04	-42.35
unpaired	18b	11.63	10.92	10.87	11.37	12.26	13.45	14.84
unpaired	19b	19.97	19.80	20.07	20.74	21.74	23.02	24.59
unpaired	23b	-25.50	-24.32	-23.18	-22.24	-21.70	-21.38	-21.26

Chapter 4 Experiment 1
Test, 115 dB SPL (C)

Group	Subject	Time Post Startle Stimuli Presentation (msec)						
		52	53	54	55	56	57	58
paired	2a	21.47	23.70	26.02	28.52	30.95	33.42	35.76
paired	5a	-66.76	-69.82	-72.44	-74.11	-75.46	-76.10	-76.25
paired	9a	8.20	6.39	4.60	2.78	0.87	-0.98	-2.67
paired	10a	-29.78	-33.14	-36.44	-39.30	-41.92	-44.27	-46.30
paired	16a	-3.07	-0.93	1.76	5.15	7.66	11.51	15.88
paired	19a	37.62	38.00	37.81	36.37	35.75	34.73	35.49
paired	20a	44.71	47.13	48.95	49.73	49.78	49.00	45.63
paired	21a	38.93	39.69	39.98	40.16	40.33	40.56	40.56
paired	3b	12.36	14.64	16.46	17.75	18.76	19.33	19.52
paired	6b	5.16	4.72	4.23	3.84	3.34	2.94	2.45
paired	10b	22.72	23.64	24.86	26.04	27.19	27.97	28.54
paired	11b	5.02	6.37	7.49	9.08	10.38	11.84	13.01
paired	12b	-7.10	-10.31	-13.55	-16.86	-19.77	-22.96	-25.57
paired	13b	27.48	29.76	32.41	35.17	37.89	40.68	43.40
paired	16b	-12.74	-12.81	-12.89	-12.99	-13.08	-12.55	-11.46
paired	17b	-3.89	-4.89	-5.98	-7.28	-8.44	-9.86	-11.27
unpaired	3a	-1.86	0.32	2.90	5.75	8.42	10.90	13.27
unpaired	11a	93.34	100.38	106.84	112.53	117.56	121.95	125.13
unpaired	12a	85.24	90.07	94.92	99.81	104.57	108.94	112.70
unpaired	13a	24.67	27.02	29.43	31.78	34.09	36.20	38.19
unpaired	18a	66.39	72.94	79.39	85.35	91.10	96.56	101.28
unpaired	1b	-0.95	-0.91	-0.20	1.30	3.17	5.44	8.00
unpaired	2b	-3.06	-3.71	-4.10	-4.30	-4.50	-4.41	-4.47
unpaired	4b	-11.59	-13.08	-14.13	-15.23	-16.10	-16.75	-17.16
unpaired	5b	23.68	29.80	35.87	42.01	48.01	55.70	60.53
unpaired	8b	61.64	68.74	75.80	82.91	89.88	96.58	102.66
unpaired	9b	58.55	60.49	63.09	66.36	69.91	73.72	77.60
unpaired	14b	-17.74	-20.04	-21.97	-23.29	-24.13	-25.69	-25.56
unpaired	15b	-45.73	-48.44	-50.99	-53.20	-55.14	-56.87	-58.15
unpaired	18b	16.45	18.08	19.83	21.62	23.20	24.81	26.22
unpaired	19b	26.08	27.90	29.39	31.18	32.89	34.32	35.75
unpaired	23b	-21.36	-21.60	-22.16	-23.34	-25.00	-27.23	-29.73

Chapter 4 Experiment 1
Test, 115 dB SPL (C)

Group	Subject	Time Post Startle Stimuli Presentation (msec)						
		59	60	61	62	63	64	65
paired	2a	37.74	39.43	40.81	41.86	42.33	42.88	43.01
paired	5a	-73.77	-73.91	-73.69	-73.37	-73.33	-73.45	-73.34
paired	9a	-4.21	-6.15	-7.42	-8.58	-9.39	-9.86	-9.95
paired	10a	-48.47	-49.55	-49.72	-49.79	-49.27	-48.20	-46.60
paired	16a	20.55	25.52	30.59	35.97	41.20	46.26	50.84
paired	19a	34.42	32.94	31.47	29.60	27.74	25.87	24.06
paired	20a	43.49	40.97	38.16	34.66	31.08	27.16	22.94
paired	21a	40.30	40.24	40.26	39.50	39.22	38.56	38.03
paired	3b	19.55	19.13	18.55	16.71	15.82	14.65	13.30
paired	6b	2.10	1.76	1.88	1.99	2.35	3.12	3.85
paired	10b	28.83	28.76	28.13	26.96	25.31	23.39	21.12
paired	11b	14.17	15.04	15.65	16.77	17.31	18.00	18.25
paired	12b	-27.98	-29.91	-31.47	-32.50	-33.26	-33.58	-33.46
paired	13b	45.88	48.03	49.88	51.28	52.34	53.11	53.31
paired	16b	-10.74	-9.77	-7.97	-6.13	-4.32	-2.32	-0.10
paired	17b	-12.81	-14.38	-15.86	-17.40	-19.26	-21.02	-23.10
unpaired	3a	15.49	17.38	19.58	21.60	24.60	27.06	29.58
unpaired	11a	127.50	128.91	128.22	125.60	123.53	119.81	114.93
unpaired	12a	115.93	118.45	119.97	120.62	120.24	119.05	116.82
unpaired	13a	40.64	42.35	43.81	44.79	45.27	45.30	44.81
unpaired	18a	105.45	108.96	111.89	114.18	115.70	116.42	116.40
unpaired	1b	10.84	13.80	17.05	19.98	23.33	26.67	29.61
unpaired	2b	-4.48	-4.27	-4.04	-3.57	-2.66	-1.51	-0.02
unpaired	4b	-17.46	-17.54	-17.64	-17.54	-17.17	-16.87	-16.53
unpaired	5b	65.04	69.50	75.56	79.47	82.82	86.01	88.74
unpaired	8b	107.85	112.23	115.47	118.03	119.46	119.60	118.32
unpaired	9b	81.44	84.89	88.12	90.84	93.10	94.78	95.88
unpaired	14b	-25.43	-24.76	-23.49	-21.89	-19.70	-17.32	-14.16
unpaired	15b	-58.82	-59.08	-58.87	-58.19	-56.97	-55.18	-52.92
unpaired	18b	27.51	28.66	29.49	29.98	30.45	30.53	30.47
unpaired	19b	36.81	37.76	38.39	38.88	38.83	38.64	38.02
unpaired	23b	-32.34	-34.95	-37.52	-39.81	-41.76	-43.68	-45.27

Chapter 4 Experiment 1
Test, 115 dB SPL (C)

Group	Subject	Time Post Startle Stimuli Presentation (msec)						
		66	67	68	69	70	71	72
paired	2a	42.93	42.58	42.11	41.16	40.18	38.71	36.86
paired	5a	-73.43	-73.31	-72.76	-71.99	-70.96	-69.37	-67.81
paired	9a	-9.66	-8.86	-7.38	-5.67	-3.54	-1.27	0.83
paired	10a	-44.22	-41.23	-37.43	-33.25	-28.73	-23.86	-19.10
paired	16a	55.11	58.92	62.16	65.05	67.29	68.76	69.32
paired	19a	22.07	20.30	18.38	16.64	14.94	13.29	11.84
paired	20a	18.62	14.26	9.53	5.01	0.80	-3.31	-6.99
paired	21a	37.01	35.91	34.53	32.82	31.39	29.93	28.56
paired	3b	11.69	9.95	7.94	5.74	3.62	1.59	-0.43
paired	6b	4.71	5.59	6.58	7.56	8.45	9.43	10.29
paired	10b	18.68	16.28	14.05	12.31	10.91	10.23	9.83
paired	11b	18.54	18.62	18.66	18.51	18.25	17.73	17.08
paired	12b	-32.84	-31.78	-30.28	-28.28	-25.85	-23.01	-19.72
paired	13b	52.96	52.53	51.81	50.62	48.99	46.99	44.32
paired	16b	2.21	4.83	7.27	9.57	11.89	13.83	14.91
paired	17b	-25.31	-27.54	-29.75	-32.00	-33.81	-34.91	-34.94
unpaired	3a	31.71	32.56	32.85	32.01	30.64	28.32	21.85
unpaired	11a	109.04	102.04	94.54	86.56	78.98	71.78	65.24
unpaired	12a	113.63	109.50	104.71	99.30	93.88	88.18	82.62
unpaired	13a	43.82	42.80	41.60	40.26	38.54	36.62	34.11
unpaired	18a	115.47	113.52	110.91	107.48	103.24	98.29	92.75
unpaired	1b	32.26	34.51	36.22	37.17	37.49	36.69	34.91
unpaired	2b	1.54	3.50	5.54	7.51	9.61	11.74	13.67
unpaired	4b	-15.70	-14.86	-13.91	-12.47	-11.19	-9.73	-8.04
unpaired	5b	91.50	93.55	95.08	95.04	92.43	87.39	80.45
unpaired	8b	114.80	109.78	102.91	94.53	85.24	75.74	66.93
unpaired	9b	96.24	95.83	94.53	92.32	89.22	85.45	81.24
unpaired	14b	-10.79	-6.92	-2.96	0.98	4.63	7.22	8.99
unpaired	15b	-50.00	-46.99	-43.53	-39.94	-36.54	-33.33	-30.30
unpaired	18b	29.89	29.46	28.40	27.23	25.70	24.06	22.13
unpaired	19b	37.26	35.82	34.09	31.93	29.70	27.28	24.96
unpaired	23b	-46.75	-47.81	-48.68	-49.29	-49.65	-49.58	-49.40

Chapter 4 Experiment 1
Test, 115 dB SPL (C)

Group	Subject	Time Post Startle Stimuli Presentation (msec)						
		73	74	75	76	77	78	79
paired	2a	34.66	32.11	29.41	26.55	23.72	21.45	19.37
paired	5a	-65.75	-63.81	-61.93	-59.75	-57.31	-54.52	-51.61
paired	9a	2.85	4.21	5.12	5.02	4.33	2.96	1.09
paired	10a	-14.51	-10.36	-7.30	-5.33	-4.47	-4.45	-5.02
paired	16a	69.08	67.99	65.90	62.81	58.91	54.40	49.98
paired	19a	11.00	10.77	11.25	12.18	13.45	14.61	16.38
paired	20a	-9.99	-12.25	-13.42	-13.66	-13.14	-12.04	-10.75
paired	21a	27.34	26.50	25.94	25.32	24.90	24.58	24.09
paired	3b	-2.35	-4.23	-5.78	-7.32	-8.43	-9.42	-10.13
paired	6b	11.02	11.56	11.42	10.62	9.06	7.00	4.76
paired	10b	10.25	11.11	12.39	13.88	15.48	16.96	18.30
paired	11b	16.07	14.97	13.75	12.36	10.67	8.92	6.94
paired	12b	-16.72	-13.54	-10.54	-7.72	-5.68	-3.98	-2.86
paired	13b	41.47	38.72	35.78	33.08	30.41	27.94	25.73
paired	16b	15.13	14.54	13.65	12.82	12.38	11.92	11.67
paired	17b	-33.55	-30.99	-27.69	-24.27	-20.89	-17.63	-14.37
unpaired	3a	17.76	13.27	9.36	5.70	2.20	-0.79	-3.28
unpaired	11a	59.44	54.49	50.50	47.65	45.61	44.25	43.31
unpaired	12a	77.82	73.67	70.11	67.26	64.93	63.12	61.74
unpaired	13a	31.31	28.86	26.82	25.17	23.36	22.13	20.91
unpaired	18a	86.67	80.13	73.87	67.84	62.45	57.44	52.86
unpaired	1b	32.29	29.65	26.70	23.87	21.05	18.56	16.37
unpaired	2b	15.59	17.11	17.70	16.89	14.91	12.02	8.80
unpaired	4b	-5.97	-4.38	-2.95	-1.91	-0.93	-0.21	0.34
unpaired	5b	72.62	64.93	57.89	51.13	45.40	41.13	37.58
unpaired	8b	59.10	52.00	46.08	40.68	36.24	32.49	29.33
unpaired	9b	77.48	74.12	71.25	69.08	67.11	65.53	64.06
unpaired	14b	9.77	9.53	8.85	7.99	6.70	5.71	4.64
unpaired	15b	-28.06	-26.31	-24.77	-23.46	-22.06	-21.16	-19.94
unpaired	18b	20.21	18.39	16.39	15.06	13.98	13.29	12.74
unpaired	19b	22.92	21.21	19.65	18.38	17.46	16.67	16.26
unpaired	23b	-48.64	-47.70	-46.36	-44.58	-42.67	-40.43	-38.23

Chapter 4 Experiment 2
Test, 105 dB SPL (C)

Group	Subj	Time Post Startle Stimuli Presentation (msec)						
		31	32	33	34	35	36	37
mM-m	1	28.46	29.81	31.16	32.27	33.11	33.90	34.24
mM-m	2	-6.29	-6.44	-6.44	-5.93	-4.93	-3.41	-1.86
mM-m	9	-28.89	-31.70	-34.13	-36.30	-37.86	-38.87	-39.23
mM-m	11	-25.05	-28.67	-32.94	-37.41	-41.93	-46.67	-51.48
mM-m	17	-11.70	-12.89	-14.15	-15.19	-16.10	-17.24	-18.21
mM-m	20	-9.06	-9.54	-10.09	-10.55	-10.89	-11.18	-11.31
mM-m	26	6.98	8.66	10.24	11.72	12.90	13.68	14.40
mM-m	6	11.84	11.96	12.17	12.06	12.03	11.85	11.42
mM-m	15	-42.89	-46.46	-49.60	-52.68	-55.42	-57.87	-60.15
mM-m	16	-0.79	-0.86	-1.14	-1.20	-1.25	-1.22	-1.03
mM-m	22	-32.46	-35.91	-38.87	-41.58	-43.50	-44.98	-45.69
mM-m	24	-20.43	-21.61	-22.77	-23.77	-24.77	-25.94	-26.80
mM-m	25	5.30	5.62	5.61	5.76	5.62	5.29	5.18
mM-m	26	-44.06	-52.97	-62.16	-68.81	-77.56	-85.58	-92.86
mM-m	32	-16.21	-19.50	-22.90	-25.82	-29.20	-32.65	-36.03
mM-m	40	-11.81	-16.11	-20.76	-25.22	-29.60	-33.94	-37.83
Mm-m	6	9.74	12.16	14.85	17.80	20.48	23.39	26.03
Mm-m	13	-7.79	-8.19	-8.38	-8.55	-8.30	-8.22	-7.67
Mm-m	15	-10.12	-10.95	-11.73	-12.50	-13.19	-13.73	-14.01
Mm-m	16	23.66	31.53	40.27	49.16	58.43	67.85	76.76
Mm-m	24	11.73	13.10	14.19	15.14	15.81	16.13	16.11
Mm-m	4	11.84	11.96	12.17	12.06	12.03	11.85	11.42
Mm-m	10	1.76	1.90	2.00	1.93	2.12	2.17	2.23
Mm-m	11	-0.79	-0.86	-1.14	-1.20	-1.25	-1.22	-1.03
Mm-m	12	-32.46	-35.91	-38.87	-41.58	-43.50	-44.98	-45.69
Mm-m	18	-20.43	-21.61	-22.77	-23.77	-24.77	-25.94	-26.80
Mm-m	35	-4.66	-6.44	-8.53	-10.60	-12.96	-15.43	-18.20
Mm-m	37	-5.15	-5.58	-6.30	-6.72	-7.49	-8.03	-8.66
Mm-m	41	7.36	5.61	3.72	1.20	-1.32	-4.28	-6.25
Mm-m	43	-8.66	-10.49	-12.52	-14.46	-16.45	-18.37	-19.80
Mm-m	45	-7.20	-8.82	-10.74	-12.69	-14.45	-16.10	-17.49

Chapter 4 Experiment 2
Test, 105 dB SPL (C)

Group	Subj	Time Post Startle Stimuli Presentation (msec)						
		38	39	40	41	42	43	44
mM-m	1a	33.98	33.35	34.62	32.75	31.12	29.46	28.04
mM-m	2a	0.12	1.27	0.99	-0.46	-3.52	-6.60	-9.59
mM-m	9a	-40.72	-39.42	-37.89	-36.68	-35.73	-35.41	-35.62
mM-m	11a	-55.86	-60.24	-64.28	-68.15	-71.49	-73.61	-74.64
mM-m	17a	-18.41	-19.06	-17.59	-17.63	-17.22	-16.15	-14.17
mM-m	20a	-11.44	-11.64	-11.77	-13.03	-12.48	-11.59	-10.60
mM-m	26a	14.57	14.64	14.63	14.77	14.63	13.54	12.26
mM-m	6b	10.96	10.35	9.52	8.45	7.60	7.23	7.06
mM-m	15b	-61.74	-62.54	-62.47	-61.17	-58.82	-55.60	-51.98
mM-m	16b	-1.38	-1.14	-2.45	-2.51	-2.52	-2.86	-3.21
mM-m	22b	-45.57	-44.42	-42.94	-40.26	-37.35	-35.13	-33.98
mM-m	24b	-27.23	-27.24	-29.18	-27.96	-26.63	-24.99	-23.08
mM-m	25b	4.74	4.42	4.27	4.38	4.51	4.92	5.34
mM-m	26b	-98.55	-106.70	-109.53	-110.38	-108.03	-102.59	-95.32
mM-m	32b	-39.35	-42.17	-42.80	-41.44	-38.12	-34.22	-30.08
mM-m	40b	-41.55	-44.77	-47.03	-47.66	-45.14	-40.43	-34.99
Mm-m	6a	28.31	30.13	31.17	30.78	28.72	25.34	21.72
Mm-m	13a	-8.41	-7.57	-6.46	-5.97	-5.82	-6.23	-6.65
Mm-m	15a	-14.13	-13.74	-12.87	-11.49	-9.44	-8.06	-7.49
Mm-m	16a	85.49	93.63	100.70	106.77	110.88	111.86	108.19
Mm-m	24a	15.66	15.07	16.66	15.97	15.57	15.38	15.78
Mm-m	4b	10.96	10.35	9.52	8.45	7.60	7.23	7.06
Mm-m	10b	2.32	2.39	2.50	2.40	2.57	2.51	2.57
Mm-m	11b	-1.38	-1.14	-2.45	-2.51	-2.52	-2.86	-3.21
Mm-m	12b	-45.57	-44.42	-42.94	-40.26	-37.35	-35.13	-33.98
Mm-m	18b	-27.23	-27.24	-29.18	-27.96	-26.63	-24.99	-23.08
Mm-m	35b	-20.27	-23.08	-25.90	-28.36	-30.16	-30.68	-29.71
Mm-m	37b	-7.41	-7.90	-8.28	-8.56	-9.09	-9.51	-9.64
Mm-m	41b	-9.98	-14.15	-18.49	-21.97	-24.53	-23.94	-19.94
Mm-m	43b	-21.77	-23.14	-24.47	-25.15	-25.19	-24.38	-23.10
Mm-m	45b	-18.98	-20.07	-20.90	-20.87	-20.28	-18.77	-16.73

Chapter 4 Experiment 2
Test, 105 dB SPL (C)

Group	Subj	Time Post Startle Stimuli Presentation (msec)						
		45	46	47	48	49	50	51
mM-m	1a	27.45	27.83	28.71	29.88	31.40	33.16	35.03
mM-m	2a	-12.58	-15.19	-17.61	-19.67	-21.41	-22.62	-23.47
mM-m	9a	-36.38	-37.34	-38.68	-40.44	-42.87	-45.58	-48.37
mM-m	11a	-74.39	-73.09	-70.65	-66.73	-62.72	-58.58	-54.72
mM-m	17a	-12.05	-10.39	-9.46	-9.01	-9.17	-9.66	-10.43
mM-m	20a	-9.45	-8.54	-7.76	-7.04	-6.41	-6.12	-5.82
mM-m	26a	11.60	11.45	11.95	13.02	14.41	15.93	17.81
mM-m	6b	7.19	7.34	7.64	7.96	8.10	8.22	8.40
mM-m	15b	-49.25	-47.92	-47.93	-48.94	-51.27	-53.78	-57.06
mM-m	16b	-3.54	-3.80	-4.03	-4.16	-4.10	-4.19	-4.23
mM-m	22b	-33.51	-34.01	-35.34	-37.17	-39.52	-42.21	-45.24
mM-m	24b	-21.81	-21.37	-21.45	-21.95	-22.71	-23.60	-24.72
mM-m	25b	5.82	6.39	6.91	7.66	8.19	8.76	9.14
mM-m	26b	-88.46	-82.72	-79.60	-79.20	-81.13	-84.84	-90.06
mM-m	32b	-26.27	-23.10	-20.84	-19.22	-18.61	-18.51	-19.18
mM-m	40b	-30.02	-26.74	-24.93	-25.11	-26.84	-29.96	-33.86
Mm-m	6a	18.57	16.12	14.73	14.18	14.58	16.01	18.06
Mm-m	13a	-7.40	-8.40	-9.41	-10.26	-11.17	-12.04	-13.08
Mm-m	15a	-7.51	-8.31	-9.39	-10.98	-12.40	-13.87	-15.21
Mm-m	16a	100.38	90.78	81.13	72.30	65.70	61.82	60.36
Mm-m	24a	16.15	16.79	17.51	18.50	19.59	20.69	21.81
Mm-m	4b	7.19	7.34	7.64	7.96	8.10	8.22	8.40
Mm-m	10b	2.53	2.43	2.44	2.46	2.46	2.68	2.94
Mm-m	11b	-3.54	-3.80	-4.03	-4.16	-4.10	-4.19	-4.23
Mm-m	12b	-33.51	-34.01	-35.34	-37.17	-39.52	-42.21	-45.24
Mm-m	18b	-21.81	-21.37	-21.45	-21.95	-22.71	-23.60	-24.72
Mm-m	35b	-27.04	-23.47	-19.84	-15.76	-11.53	-7.82	-5.30
Mm-m	37b	-9.23	-8.44	-7.21	-6.69	-6.48	-6.87	-7.60
Mm-m	41b	-12.96	-7.27	-3.20	-0.11	1.56	2.07	1.81
Mm-m	43b	-21.31	-19.49	-17.93	-16.66	-15.95	-15.59	-15.83
Mm-m	45b	-15.03	-13.43	-12.10	-11.05	-10.88	-11.24	-12.18

Chapter 4 Experiment 2
Test, 105 dB SPL (C)

Group	Subj	Time Post Startle Stimuli Presentation (msec)						
		52	53	54	55	56	57	58
mM-m	1a	36.73	38.40	40.08	41.69	43.03	44.45	45.54
mM-m	2a	-23.76	-23.37	-22.41	-21.19	-19.30	-17.02	-14.52
mM-m	9a	-51.43	-54.24	-57.00	-59.48	-61.48	-63.12	-64.82
mM-m	11a	-50.83	-48.50	-48.90	-51.58	-55.90	-61.60	-68.18
mM-m	17a	-11.49	-12.74	-14.28	-15.79	-17.45	-19.12	-20.79
mM-m	20a	-5.86	-6.04	-6.19	-6.60	-7.09	-7.69	-8.34
mM-m	26a	19.78	21.75	23.69	25.27	26.90	28.34	29.40
mM-m	6b	8.30	8.28	8.22	8.04	7.91	7.51	7.54
mM-m	15b	-60.82	-64.97	-69.10	-73.63	-78.14	-82.57	-86.86
mM-m	16b	-3.94	-4.03	-3.78	-3.61	-3.31	-3.04	-2.74
mM-m	22b	-48.14	-51.02	-53.85	-56.23	-58.33	-60.03	-61.22
mM-m	24b	-26.05	-27.65	-29.50	-31.53	-33.74	-36.26	-38.65
mM-m	25b	9.64	10.11	10.52	10.84	10.99	11.21	11.19
mM-m	26b	-96.09	-102.37	-108.77	-115.27	-121.43	-127.51	-133.36
mM-m	32b	-20.33	-21.97	-23.94	-25.99	-28.61	-31.52	-34.31
mM-m	40b	-38.86	-44.20	-50.12	-56.19	-62.19	-67.89	-73.25
Mm-m	6a	20.80	24.13	27.68	31.53	35.24	38.90	42.18
Mm-m	13a	-14.04	-14.97	-15.79	-16.41	-17.20	-17.78	-18.22
Mm-m	15a	-16.62	-17.92	-19.03	-20.29	-21.28	-22.01	-22.59
Mm-m	16a	61.13	64.13	69.28	75.78	83.31	91.78	100.80
Mm-m	24a	22.83	23.95	24.96	25.80	26.42	27.03	27.26
Mm-m	4b	8.30	8.28	8.22	8.04	7.91	7.51	7.54
Mm-m	10b	3.44	4.15	5.05	6.41	7.70	9.01	10.43
Mm-m	11b	-3.94	-4.03	-3.78	-3.61	-3.31	-3.04	-2.74
Mm-m	12b	-48.14	-51.02	-53.85	-56.23	-58.33	-60.03	-61.22
Mm-m	18b	-26.05	-27.65	-29.50	-31.53	-33.74	-36.26	-38.65
Mm-m	35b	-3.76	-3.24	-3.46	-4.45	-6.00	-7.96	-10.30
Mm-m	37b	-8.56	-9.69	-11.11	-12.61	-14.05	-15.63	-17.19
Mm-m	41b	0.56	-1.36	-4.07	-7.38	-11.14	-15.10	-19.28
Mm-m	43b	-16.46	-17.54	-18.98	-20.70	-22.65	-24.74	-26.90
Mm-m	45b	-13.47	-15.12	-17.06	-19.26	-21.74	-24.19	-26.54

Chapter 4 Experiment 2
Test, 105 dB SPL (C)

Group	Subj	Time Post Startle Stimuli Presentation (msec)						
		59	60	61	62	63	64	65
mM-m	1a	46.34	46.91	47.24	47.13	46.65	45.79	44.81
mM-m	2a	-11.54	-8.35	-5.13	-1.80	1.33	4.19	6.48
mM-m	9a	-65.21	-65.14	-64.42	-63.24	-61.50	-59.23	-56.48
mM-m	11a	-75.00	-81.48	-87.53	-92.98	-97.90	-101.95	-105.40
mM-m	17a	-22.31	-24.15	-25.15	-26.94	-28.30	-29.60	-30.81
mM-m	20a	-9.20	-9.83	-10.94	-11.67	-12.71	-13.78	-14.70
mM-m	26a	30.29	30.93	31.22	31.47	31.25	30.81	30.07
mM-m	6b	7.17	7.10	7.02	6.97	6.90	7.12	7.18
mM-m	15b	-90.78	-94.16	-97.14	-99.40	-100.84	-101.61	-101.61
mM-m	16b	-2.49	-2.20	-2.09	-1.72	-1.49	-1.16	-0.77
mM-m	22b	-61.78	-62.04	-61.51	-60.59	-59.46	-57.71	-55.69
mM-m	24b	-41.01	-43.16	-45.19	-46.87	-48.22	-49.03	-49.74
mM-m	25b	11.27	11.15	10.94	10.61	10.16	9.71	9.09
mM-m	26b	-139.09	-142.53	-147.17	-150.70	-153.59	-155.47	-156.15
mM-m	32b	-37.32	-36.41	-39.43	-42.11	-44.24	-45.95	-46.90
mM-m	40b	-78.00	-81.79	-85.24	-87.38	-88.67	-88.95	-88.42
Mm-m	6a	45.05	47.66	49.87	51.46	52.73	53.43	53.33
Mm-m	13a	-18.61	-18.83	-19.05	-19.00	-18.98	-18.65	-18.16
Mm-m	15a	-22.91	-23.04	-22.99	-22.61	-22.13	-21.24	-20.37
Mm-m	16a	109.57	118.20	126.41	133.93	140.71	146.60	151.51
Mm-m	24a	27.51	27.28	26.98	26.53	25.51	24.61	23.41
Mm-m	4b	7.17	7.10	7.02	6.97	6.90	7.12	7.18
Mm-m	10b	11.80	12.98	14.14	15.23	16.12	17.15	18.12
Mm-m	11b	-2.49	-2.20	-2.09	-1.72	-1.49	-1.16	-0.77
Mm-m	12b	-61.78	-62.04	-61.51	-60.59	-59.46	-57.71	-55.69
Mm-m	18b	-41.01	-43.16	-45.19	-46.87	-48.22	-49.03	-49.74
Mm-m	35b	-12.88	-15.54	-18.31	-21.02	-23.80	-26.64	-29.26
Mm-m	37b	-18.87	-20.42	-21.84	-23.11	-24.29	-25.10	-25.72
Mm-m	41b	-23.51	-27.30	-30.86	-34.03	-36.64	-38.61	-39.93
Mm-m	43b	-29.18	-31.15	-33.08	-34.95	-36.34	-37.54	-38.46
Mm-m	45b	-28.79	-30.79	-32.58	-34.06	-35.33	-36.08	-36.68

Chapter 4 Experiment 2
Test, 105 dB SPL (C)

Group	Subj	Time Post Startle Stimuli Presentation (msec)						
		66	67	68	69	70	71	72
mM-m	1a	43.31	41.52	39.52	37.27	34.92	32.43	30.08
mM-m	2a	7.63	8.02	7.67	7.03	5.88	4.37	3.00
mM-m	9a	-53.58	-50.56	-48.01	-45.67	-43.79	-42.36	-41.11
mM-m	11a	-108.39	-110.69	-112.50	-113.79	-114.20	-113.66	-112.14
mM-m	17a	-31.81	-32.63	-33.26	-33.59	-33.57	-33.27	-32.34
mM-m	20a	-15.53	-15.96	-15.86	-15.05	-13.71	-11.64	-9.73
mM-m	26a	28.93	27.49	25.92	24.37	22.84	21.39	20.17
mM-m	6b	7.32	7.59	7.81	8.07	8.47	8.74	9.23
mM-m	15b	-100.87	-99.54	-97.52	-94.83	-91.71	-87.83	-83.57
mM-m	16b	-0.47	-0.26	-0.03	0.15	-0.09	-0.39	-0.73
mM-m	22b	-53.29	-50.57	-47.75	-45.00	-42.49	-39.83	-37.55
mM-m	24b	-49.56	-48.63	-47.20	-45.16	-42.55	-39.43	-36.18
mM-m	25b	8.35	7.78	7.13	6.73	6.46	6.30	6.39
mM-m	26b	-155.49	-153.37	-149.50	-143.87	-136.57	-127.50	-117.89
mM-m	32b	-47.12	-46.31	-44.83	-42.57	-39.63	-36.59	-33.70
mM-m	40b	-86.56	-83.37	-78.68	-72.78	-66.40	-60.58	-55.44
Mm-m	6a	52.54	51.07	49.12	45.93	42.04	37.93	33.68
Mm-m	13a	-17.50	-16.59	-15.58	-14.49	-13.22	-12.27	-11.63
Mm-m	15a	-19.33	-17.84	-16.00	-13.94	-11.82	-9.78	-8.07
Mm-m	16a	155.75	158.81	161.00	161.80	161.24	158.98	154.65
Mm-m	24a	21.98	20.45	18.86	17.62	16.44	15.47	14.67
Mm-m	4b	7.32	7.59	7.81	8.07	8.47	8.74	9.23
Mm-m	10b	19.12	19.96	20.80	21.30	21.85	22.12	21.86
Mm-m	11b	-0.47	-0.26	-0.03	0.15	-0.09	-0.39	-0.73
Mm-m	12b	-53.29	-50.57	-47.75	-45.00	-42.49	-39.83	-37.55
Mm-m	18b	-49.56	-48.63	-47.20	-45.16	-42.55	-39.43	-36.18
Mm-m	35b	-31.54	-33.62	-35.59	-37.11	-38.34	-39.00	-39.25
Mm-m	37b	-26.10	-26.07	-26.09	-25.97	-25.74	-25.64	-24.87
Mm-m	41b	-40.64	-40.71	-40.24	-39.31	-37.67	-35.20	-32.36
Mm-m	43b	-38.96	-39.06	-38.67	-37.97	-36.92	-35.36	-33.63
Mm-m	45b	-36.63	-36.19	-35.48	-34.43	-32.82	-30.60	-28.28

Chapter 4 Experiment 2
Test, 105 dB SPL (C)

Group	Subject	Time Post Startle Stimuli Presentation						
		73	74	75	76	77	78	79
mM-m	1a	28.12	26.2	24.76	23.64	22.85	22.24	21.67
mM-m	2a	1.68	0.8	0.32	0.02	0.03	0.53	1.32
mM-m	9a	-40.37	-39.68	-39.09	-38.68	-38.1	-37.66	-37.04
mM-m	11a	-109.56	-105.8	-100.9	-95.2	-89.04	-82.42	-75.29
mM-m	17a	-30.55	-28.32	-25.81	-23.02	-20.43	-17.53	-15.38
mM-m	20a	-7.49	-5.53	-3.61	-2.02	-0.45	0.82	1.72
mM-m	26a	19.23	18.73	18.48	18.23	18.24	18.25	18.25
mM-m	6b	9.56	9.57	9.03	8.14	7.04	5.79	4.68
mM-m	15b	-79.15	-74.39	-69.89	-66.29	-63.54	-61.38	-59.84
mM-m	16b	-1.34	-1.8	-1.99	-2.24	-2.54	-2.51	-2.62
mM-m	22b	-35.42	-33.44	-31.58	-29.82	-28.2	-26.54	-24.95
mM-m	24b	-32.9	-29.85	-27.38	-25.22	-23.71	-22.53	-21.65
mM-m	25b	6.47	6.57	6.69	6.93	7.14	7.47	7.58
mM-m	26b	-108.99	-101.32	-94.98	-89.66	-85.25	-81.63	-79.14
mM-m	32b	-30.82	-27.98	-25.3	-22.99	-20.67	-18.8	-17.19
mM-m	40b	-51.72	-49.18	-47.63	-46.8	-46.63	-46.76	-47.04
Mm-m	6a	29.69	26.32	23.29	20.77	18.55	16.74	15.25
Mm-m	13a	-11.53	-11.67	-12.28	-13.02	-14.05	-15.13	-16.51
Mm-m	15a	-6.76	-5.61	-5.09	-4.75	-4.89	-5.21	-5.62
Mm-m	16a	148.37	140.7	132.43	123.78	115.55	107.9	100.98
Mm-m	24a	14.13	13.9	13.73	13.61	13.82	14	14.14
Mm-m	4b	9.56	9.57	9.03	8.14	7.04	5.79	4.68
Mm-m	10b	21.41	20.55	19.58	18.45	17.49	16.79	16.71
Mm-m	11b	-1.34	-1.8	-1.99	-2.24	-2.54	-2.51	-2.62
Mm-m	12b	-35.42	-33.44	-31.58	-29.82	-28.2	-26.54	-24.95
Mm-m	18b	-32.9	-29.85	-27.38	-25.22	-23.71	-22.53	-21.65
Mm-m	35b	-38.83	-37.64	-35.76	-33.13	-30.38	-27.42	-23.99
Mm-m	37b	-23.93	-22.93	-21.77	-20.71	-19.82	-18.98	-18.28
Mm-m	41b	-29.4	-26.42	-23.71	-21.41	-19.52	-17.84	-16.47
Mm-m	43b	-31.57	-29.52	-27.57	-25.71	-24.15	-22.78	-21.45
Mm-m	45b	-25.76	-23.41	-21.2	-19.39	-17.92	-16.58	-15.65

Chapter 4 Experiment 2
Test, 105 dB SPL (C)

Group	Subject	Time Post Startle Stimuli Presentation						
		31	32	33	34	35	36	37
mM-s	4a	-20.63	-22.71	-24.62	-25.98	-27.02	-27.72	-27.80
mM-s	10a	-16.11	-17.71	-19.03	-20.29	-21.24	-21.94	-22.31
mM-s	12a	-1.73	-2.28	-2.79	-3.24	-3.76	-4.59	-5.24
mM-s	18a	5.47	7.35	9.23	11.24	13.31	15.38	17.33
mM-s	19a	-44.57	-49.27	-53.56	-56.97	-59.65	-61.23	-61.77
mM-s	27a	-9.26	-9.65	-9.82	-9.82	-9.78	-9.57	-7.84
mM-s	28a	42.65	47.34	51.73	55.78	59.54	63.00	66.55
mM-s	5b	2.19	2.04	2.03	1.95	1.79	1.69	1.72
mM-s	8b	0.31	0.24	0.27	0.38	0.34	0.50	0.42
mM-s	13b	0.78	0.66	0.54	0.73	0.62	0.45	0.55
mM-s	14b	1.76	1.90	2.00	1.93	2.12	2.17	2.23
mM-s	21b	-0.47	-0.56	-0.44	-0.58	-0.48	-0.38	-0.48
mM-s	33b	-18.42	-20.86	-23.16	-23.26	-25.44	-27.04	-28.11
mM-s	36b	14.63	14.83	15.11	14.55	13.84	12.74	10.96
mM-s	39b	-26.17	-30.45	-34.69	-39.00	-42.74	-46.30	-48.20
mM-s	42b	-3.28	-4.65	-6.34	-8.21	-10.09	-12.27	-10.88
Mm-s	8a	47.29	51.01	54.45	57.84	60.89	63.60	66.27
Mm-s	22a	-40.30	-42.23	-43.95	-45.16	-46.17	-46.41	-46.14
Mm-s	23a	13.63	14.16	14.40	14.43	14.09	13.39	12.38
Mm-s	1b	2.19	2.04	2.03	1.95	1.79	1.69	1.72
Mm-s	2b	0.31	0.24	0.27	0.38	0.34	0.50	0.42
Mm-s	3b	0.78	0.66	0.54	0.73	0.62	0.45	0.55
Mm-s	9b	5.86	6.30	6.63	7.36	8.01	8.64	9.37
Mm-s	17b	-0.47	-0.56	-0.44	-0.58	-0.48	-0.38	-0.48
Mm-s	19b	0.66	0.76	0.64	0.66	0.70	0.65	0.66
Mm-s	20b	1.14	0.99	0.99	0.94	1.05	0.98	0.96
Mm-s	38b	-32.63	-37.86	-43.10	-48.08	-53.19	-57.40	-61.07
Mm-s	44b	-12.95	-15.38	-17.55	-19.77	-21.73	-23.56	-24.99
Mm-s	46b	-35.29	-42.41	-49.43	-56.53	-63.40	-69.70	-75.41

Chapter 4 Experiment 2
Test, 105 dB SPL (C)

Group	Subject	Time Post Startle Stimuli Presentation (msec)						
		38	39	40	41	42	43	44
mM-s	4a	-27.29	-26.04	-23.97	-21.84	-20.20	-20.12	-21.32
mM-s	10a	-21.41	-20.79	-17.99	-16.74	-16.02	-15.62	-15.44
mM-s	12a	-4.46	-5.20	-5.61	-5.59	-5.47	-5.12	-4.77
mM-s	18a	19.16	20.75	21.49	16.66	15.30	13.19	11.01
mM-s	19a	-60.64	-58.34	-54.74	-53.41	-49.44	-46.78	-46.17
mM-s	27a	-7.10	-6.20	-5.12	-4.77	-4.86	-5.39	-6.24
mM-s	28a	70.18	73.60	76.95	80.28	83.21	84.84	84.72
mM-s	5b	1.66	1.71	1.71	1.77	1.78	1.77	1.86
mM-s	8b	0.47	0.43	0.52	0.44	0.53	0.64	0.69
mM-s	13b	0.40	0.37	0.28	0.14	0.21	0.19	0.04
mM-s	14b	2.32	2.39	2.50	2.40	2.57	2.51	2.57
mM-s	21b	-0.37	-0.40	-0.28	-0.11	-0.18	-0.08	-0.06
mM-s	33b	-28.60	-29.81	-29.38	-28.71	-27.40	-25.90	-24.85
mM-s	36b	12.30	10.00	7.80	5.90	5.44	6.86	9.14
mM-s	39b	-50.60	-52.60	-53.59	-52.34	-50.47	-46.96	-42.72
mM-s	42b	-13.78	-16.92	-19.73	-20.88	-21.91	-20.82	-17.77
Mm-s	8a	68.09	69.21	69.39	68.01	65.67	62.02	57.72
Mm-s	22a	-44.72	-42.48	-38.99	-34.54	-30.16	-27.25	-27.01
Mm-s	23a	11.23	9.56	7.90	6.62	6.60	7.81	9.26
Mm-s	1b	1.66	1.71	1.71	1.77	1.78	1.77	1.86
Mm-s	2b	0.47	0.43	0.52	0.44	0.53	0.64	0.69
Mm-s	3b	0.40	0.37	0.28	0.14	0.21	0.19	0.04
Mm-s	9b	10.14	10.82	11.71	12.61	13.37	14.39	14.96
Mm-s	17b	-0.37	-0.40	-0.28	-0.11	-0.18	-0.08	-0.06
Mm-s	19b	0.69	0.58	0.55	0.47	0.43	0.24	0.17
Mm-s	20b	0.85	1.09	1.04	1.16	1.16	1.27	1.36
Mm-s	38b	-63.77	-65.43	-65.72	-64.89	-62.67	-60.11	-57.20
Mm-s	44b	-26.10	-26.79	-27.14	-26.44	-25.08	-23.19	-21.26
Mm-s	46b	-80.27	-83.61	-84.43	-82.00	-76.57	-69.18	-61.24

Chapter 4 Experiment 2
Test, 105 dB SPL (C)

Group	Subject	Time Post Startle Stimuli Presentation (msec)						
		45	46	47	48	49	50	51
mM-s	4a	-23.54	-26.25	-29.20	-31.87	-34.11	-36.09	-38.15
mM-s	10a	-15.57	-16.01	-16.76	-17.95	-19.53	-21.06	-23.05
mM-s	12a	-4.14	-3.18	-2.23	-1.47	-0.81	-0.23	-0.18
mM-s	18a	9.18	8.17	8.05	8.61	9.75	11.08	13.15
mM-s	19a	-47.57	-50.40	-54.39	-59.38	-64.86	-70.87	-76.93
mM-s	27a	-7.35	-8.55	-9.65	-10.73	-11.70	-12.61	-13.32
mM-s	28a	82.33	77.72	72.28	67.11	62.11	57.49	54.27
mM-s	5b	1.98	2.16	2.22	2.44	2.37	2.45	2.27
mM-s	8b	0.59	0.69	0.72	0.76	0.57	0.56	0.47
mM-s	13b	0.01	-0.13	-0.26	-0.34	-0.69	-1.01	-1.41
mM-s	14b	2.53	2.43	2.44	2.46	2.46	2.68	2.94
mM-s	21b	-0.07	0.04	0.20	0.43	1.10	2.05	3.41
mM-s	33b	-24.03	-24.26	-25.13	-26.56	-28.65	-31.03	-33.55
mM-s	36b	11.82	14.52	17.12	19.66	21.57	23.25	24.38
mM-s	39b	-38.48	-36.79	-37.12	-39.10	-42.40	-46.52	-51.17
mM-s	42b	-14.15	-10.99	-8.38	-6.72	-5.68	-5.28	-5.58
Mm-s	8a	54.05	51.90	51.42	51.83	53.70	56.28	59.55
Mm-s	22a	-28.95	-32.52	-37.17	-42.29	-47.41	-52.74	-58.01
Mm-s	23a	10.99	12.68	14.22	15.83	17.29	18.56	19.77
Mm-s	1b	1.98	2.16	2.22	2.44	2.37	2.45	2.27
Mm-s	2b	0.59	0.69	0.72	0.76	0.57	0.56	0.47
Mm-s	3b	0.01	-0.13	-0.26	-0.34	-0.69	-1.01	-1.41
Mm-s	9b	14.91	14.06	12.38	10.46	9.01	7.53	6.50
Mm-s	17b	-0.07	0.04	0.20	0.43	1.10	2.05	3.41
Mm-s	19b	0.06	0.09	-0.04	-0.11	-0.14	-0.10	-0.01
Mm-s	20b	1.41	1.48	1.80	1.66	1.63	1.36	0.54
Mm-s	38b	-55.08	-54.45	-55.37	-57.15	-59.45	-62.23	-65.87
Mm-s	44b	-19.56	-18.77	-18.78	-19.22	-20.51	-22.11	-23.98
Mm-s	46b	-54.62	-50.33	-48.57	-49.05	-51.44	-55.46	-60.42

Chapter 4 Experiment 2
Test, 105 dB SPL (C)

Group	Subject	Time Post Startle Stimuli Presentation (msec)						
		52	53	54	55	56	57	58
mM-s	4a	-40.33	-42.14	-44.00	-45.39	-46.56	-47.45	-47.83
mM-s	10a	-25.03	-26.77	-28.71	-30.38	-32.04	-33.37	-34.52
mM-s	12a	-0.39	-0.86	-1.47	-2.48	-3.68	-5.06	-6.26
mM-s	18a	15.51	17.98	20.64	23.49	26.46	29.38	31.99
mM-s	19a	-83.05	-89.16	-95.10	-100.38	-104.97	-108.91	-111.79
mM-s	27a	-13.79	-14.28	-14.37	-14.61	-14.33	-13.95	-14.08
mM-s	28a	52.67	52.96	54.95	58.31	62.73	67.96	73.82
mM-s	5b	1.98	1.65	1.01	0.23	-0.71	-1.89	-3.29
mM-s	8b	0.10	-0.08	-0.58	-1.12	-1.85	-2.85	-3.68
mM-s	13b	-1.88	-2.42	-2.98	-3.52	-4.06	-4.71	-5.20
mM-s	14b	3.44	4.15	5.05	6.41	7.70	9.01	10.43
mM-s	21b	5.37	7.57	9.97	12.61	15.19	17.67	20.14
mM-s	33b	-36.12	-38.60	-40.93	-42.39	-44.16	-45.95	-47.27
mM-s	36b	24.90	25.30	25.15	24.57	23.73	22.32	20.66
mM-s	39b	-56.08	-61.14	-65.81	-70.15	-73.98	-77.35	-80.50
mM-s	42b	-6.24	-7.34	-8.89	-10.59	-12.66	-14.64	-16.86
Mm-s	8a	63.54	68.27	73.08	78.39	83.92	89.53	95.32
Mm-s	22a	-63.43	-68.24	-73.21	-77.78	-81.85	-85.52	-88.56
Mm-s	23a	20.77	21.56	22.14	22.44	22.51	22.23	21.98
Mm-s	1b	1.98	1.65	1.01	0.23	-0.71	-1.89	-3.29
Mm-s	2b	0.10	-0.08	-0.58	-1.12	-1.85	-2.85	-3.68
Mm-s	3b	-1.88	-2.42	-2.98	-3.52	-4.06	-4.71	-5.20
Mm-s	9b	5.78	5.18	4.59	4.50	4.68	4.93	5.30
Mm-s	17b	5.37	7.57	9.97	12.61	15.19	17.67	20.14
Mm-s	19b	0.06	0.34	0.78	1.24	1.71	2.28	2.91
Mm-s	20b	-0.75	-2.63	-5.06	-8.00	-11.49	-15.25	-19.38
Mm-s	38b	-70.52	-75.70	-81.09	-86.42	-91.77	-96.61	-100.96
Mm-s	44b	-26.21	-28.43	-30.94	-33.37	-35.73	-37.84	-39.72
Mm-s	46b	-66.37	-73.09	-79.85	-86.52	-95.70	-101.88	-107.48

Chapter 4 Experiment 2
Test, 105 dB SPL (C)

Group	Subj	Time Post Startle Stimuli Presentation (msec)						
		59	60	61	62	63	64	65
mM-s	4a	-47.76	-47.50	-46.64	-45.37	-43.97	-42.06	-39.88
mM-s	10a	-35.17	-35.58	-35.48	-35.43	-34.81	-34.10	-33.01
mM-s	12a	-7.73	-9.34	-10.77	-12.24	-13.53	-14.92	-16.03
mM-s	18a	34.62	37.25	39.19	40.97	42.26	43.19	43.73
mM-s	19a	-113.99	-114.74	-114.50	-113.07	-110.65	-107.26	-102.83
mM-s	27a	-13.43	-12.63	-11.45	-10.67	-9.61	-8.61	-7.68
mM-s	28a	79.78	86.09	92.04	97.93	103.51	108.87	113.61
mM-s	5b	-4.69	-6.43	-8.19	-9.97	-11.86	-13.69	-15.64
mM-s	8b	-4.77	-5.87	-7.12	-8.31	-9.53	-10.80	-11.94
mM-s	13b	-5.79	-6.34	-6.98	-7.56	-8.16	-8.58	-8.90
mM-s	14b	11.80	12.98	14.14	15.23	16.12	17.15	18.12
mM-s	21b	22.25	24.01	25.70	26.88	27.60	27.73	27.30
mM-s	33b	-48.25	-49.31	-49.66	-49.39	-48.73	-47.66	-46.24
mM-s	36b	18.57	16.29	13.89	11.45	8.77	6.20	3.53
mM-s	39b	-83.41	-85.94	-88.62	-90.52	-92.15	-93.17	-93.37
mM-s	42b	-19.14	-21.36	-23.75	-25.69	-27.84	-29.57	-30.96
Mm-s	8a	100.43	105.37	109.65	113.03	115.70	117.56	118.44
Mm-s	22a	-90.90	-92.55	-93.07	-92.84	-91.65	-89.84	-87.36
Mm-s	23a	21.32	20.50	19.41	18.30	16.81	15.26	13.43
Mm-s	1b	-4.69	-6.43	-8.19	-9.97	-11.86	-13.69	-15.64
Mm-s	2b	-4.77	-5.87	-7.12	-8.31	-9.53	-10.80	-11.94
Mm-s	3b	-5.79	-6.34	-6.98	-7.56	-8.16	-8.58	-8.90
Mm-s	9b	5.99	6.48	7.48	8.59	10.02	11.35	12.84
Mm-s	17b	22.25	24.01	25.70	26.88	27.60	27.73	27.30
Mm-s	19b	3.54	4.36	5.17	6.17	7.19	8.29	9.39
Mm-s	20b	-23.48	-27.56	-31.51	-35.14	-38.49	-41.13	-43.36
Mm-s	38b	-104.52	-107.48	-109.24	-109.84	-109.32	-107.62	-104.87
Mm-s	44b	-41.14	-42.28	-42.88	-42.98	-42.71	-41.90	-40.62
Mm-s	46b	-112.19	-116.16	-119.36	-121.52	-122.82	-122.72	-121.65

Chapter 4 Experiment 2
Test, 105 dB SPL (C)

Group	Subj	Time Post Startle Stimuli Presentation (msec)						
		66	67	68	69	70	71	72
mM-s	4a	-37.66	-35.47	-32.73	-30.31	-28.19	-26.36	-24.91
mM-s	10a	-31.62	-29.87	-28.17	-26.62	-24.98	-23.57	-22.19
mM-s	12a	-16.85	-17.31	-17.28	-16.86	-16.45	-15.83	-15.45
mM-s	18a	43.34	42.64	41.03	38.52	35.28	31.85	28.33
mM-s	19a	-97.59	-91.68	-85.09	-78.53	-72.60	-67.87	-64.07
mM-s	27a	-7.17	-6.86	-7.01	-7.48	-8.10	-8.94	-9.59
mM-s	28a	118.31	122.49	126.46	129.88	132.96	135.49	137.15
mM-s	5b	-17.42	-18.91	-20.48	-21.46	-22.06	-22.16	-21.13
mM-s	8b	-12.94	-13.85	-14.49	-15.01	-15.45	-15.27	-14.85
mM-s	13b	-9.16	-9.23	-9.13	-9.28	-9.22	-9.28	-9.59
mM-s	14b	19.12	19.96	20.80	21.30	21.85	22.12	21.86
mM-s	21b	26.15	24.17	22.16	20.08	19.28	20.37	22.15
mM-s	33b	-44.56	-42.57	-40.42	-37.84	-35.31	-33.13	-30.85
mM-s	36b	1.10	-1.34	-3.20	-4.33	-4.64	-4.13	-3.19
mM-s	39b	-92.45	-90.41	-87.00	-82.35	-76.61	-70.73	-65.39
mM-s	42b	-31.95	-32.43	-32.52	-32.01	-31.14	-29.55	-27.30
Mm-s	8a	118.37	117.48	115.85	113.33	110.21	106.29	101.77
Mm-s	22a	-84.17	-80.26	-76.02	-71.34	-65.91	-60.69	-55.40
Mm-s	23a	11.36	9.53	8.34	7.72	7.83	8.45	9.26
Mm-s	1b	-17.42	-18.91	-20.48	-21.46	-22.06	-22.16	-21.13
Mm-s	2b	-12.94	-13.85	-14.49	-15.01	-15.45	-15.27	-14.85
Mm-s	3b	-9.16	-9.23	-9.13	-9.28	-9.22	-9.28	-9.59
Mm-s	9b	14.28	15.80	17.32	18.79	20.17	21.13	22.04
Mm-s	17b	26.15	24.17	22.16	20.08	19.28	20.37	22.15
Mm-s	19b	10.47	11.39	13.29	14.09	14.49	14.28	13.60
Mm-s	20b	-44.94	-45.35	-45.02	-43.41	-40.87	-37.76	-34.56
Mm-s	38b	-101.05	-96.39	-91.30	-85.74	-80.27	-75.16	-70.55
Mm-s	44b	-38.74	-36.60	-34.13	-31.28	-28.64	-26.39	-24.55
Mm-s	46b	-119.08	-115.15	-109.47	-101.96	-93.76	-85.24	-77.55

Chapter 4 Experiment 2
Test, 105 dB SPL (C)

Group	Subj	Time Post Startle Stimuli Presentation (msec)						
		73	74	75	76	77	78	79
mM-s	4a	-23.33	-22.01	-20.84	-19.97	-18.95	-18.00	-17.23
mM-s	10a	-20.77	-19.65	-18.89	-18.31	-17.69	-17.63	-17.43
mM-s	12a	-14.77	-14.44	-14.21	-13.74	-13.24	-12.82	-12.34
mM-s	18a	25.39	22.60	20.05	18.09	16.49	15.36	14.54
mM-s	19a	-61.47	-59.89	-59.20	-59.18	-59.73	-60.12	-60.87
mM-s	27a	-10.32	-10.68	-11.07	-11.25	-11.09	-10.98	-10.78
mM-s	28a	137.73	137.37	135.40	131.71	126.66	120.23	112.93
mM-s	5b	-19.16	-17.04	-15.14	-13.97	-13.45	-13.70	-14.54
mM-s	8b	-14.09	-13.16	-12.07	-11.19	-10.63	-10.40	-10.71
mM-s	13b	-9.87	-9.98	-10.01	-9.88	-9.65	-9.28	-9.07
mM-s	14b	21.41	20.55	19.58	18.45	17.49	16.79	16.71
mM-s	21b	24.61	27.09	29.76	32.43	35.14	37.66	39.84
mM-s	33b	-28.99	-27.48	-26.28	-25.23	-24.32	-23.60	-22.97
mM-s	36b	-1.97	-0.75	0.43	1.42	2.15	2.81	3.31
mM-s	39b	-60.71	-56.79	-53.70	-51.12	-48.82	-46.88	-45.04
mM-s	42b	-24.69	-21.58	-19.10	-16.70	-14.47	-12.34	-10.21
Mm-s	8a	97.07	91.89	87.04	82.57	78.95	75.71	73.20
Mm-s	22a	-50.34	-45.70	-42.29	-39.81	-38.75	-39.03	-40.01
Mm-s	23a	10.59	11.60	12.50	13.30	13.87	14.24	14.59
Mm-s	1b	-19.16	-17.04	-15.14	-13.97	-13.45	-13.70	-14.54
Mm-s	2b	-14.09	-13.16	-12.07	-11.19	-10.63	-10.40	-10.71
Mm-s	3b	-9.87	-9.98	-10.01	-9.88	-9.65	-9.28	-9.07
Mm-s	9b	22.59	22.53	21.68	20.79	18.93	17.19	15.24
Mm-s	17b	24.61	27.09	29.76	32.43	35.14	37.66	39.84
Mm-s	19b	12.17	10.88	9.49	8.18	6.94	6.38	6.17
Mm-s	20b	-32.91	-32.46	-33.43	-35.59	-38.38	-41.98	-45.76
Mm-s	38b	-66.53	-63.03	-60.11	-57.57	-55.56	-53.54	-51.62
Mm-s	44b	-23.17	-22.27	-21.76	-21.54	-21.77	-21.88	-22.03
Mm-s	46b	-70.75	-65.04	-60.33	-56.10	-53.17	-50.11	-47.57

Chapter 4 Experiment 2
Test, 115 dB SPL (C)

Group	Subject	Time Post Startle Stimuli Presentation (msec)						
		31	32	33	34	35	36	37
mM-m	1a	7.38	7.95	8.52	9.18	9.69	10.12	10.27
mM-m	2a	-36.12	-37.17	-37.62	-36.62	-34.56	-30.82	-25.99
mM-m	9a	-21.86	-23.20	-24.39	-25.24	-25.85	-26.02	-25.67
mM-m	11a	-8.32	-8.49	-9.79	-12.54	-16.69	-22.15	-28.18
mM-m	17a	15.13	15.59	16.14	16.20	16.24	16.14	15.61
mM-m	20a	14.29	15.40	16.23	16.76	17.13	17.15	16.81
mM-m	26a	19.52	22.50	25.17	27.65	29.72	31.64	33.02
mM-m	6b	-26.43	-29.45	-32.23	-35.18	-37.49	-39.67	-41.38
mM-m	15b	-20.54	-23.20	-25.61	-27.94	-30.11	-32.23	-34.10
mM-m	16b	-24.30	-27.68	-30.76	-33.55	-36.18	-38.19	-39.67
mM-m	22b	-29.33	-32.68	-35.78	-38.53	-40.86	-42.94	-44.11
mM-m	24b	12.05	13.14	13.72	13.90	13.43	12.21	10.50
mM-m	25b	-16.78	-18.63	-20.31	-21.90	-22.95	-23.66	-23.94
mM-m	26b	56.38	55.66	53.80	51.11	47.67	43.57	38.92
mM-m	32b	16.43	15.75	14.71	13.53	11.94	10.11	7.86
mM-m	40b	24.49	22.00	19.06	15.48	11.74	7.62	3.35
Mm-m	6a	-18.67	-17.76	-16.11	-14.26	-11.84	-9.13	-5.93
Mm-m	13a	-43.49	-45.81	-47.97	-49.44	-50.12	-50.18	-49.27
Mm-m	15a	6.25	6.53	6.43	6.21	5.39	4.48	2.91
Mm-m	16a	-24.91	-22.51	-19.33	-15.83	-11.51	-6.97	-1.61
Mm-m	24a	4.18	4.83	5.31	5.74	6.09	6.23	6.21
Mm-m	4b	4.52	4.49	4.40	4.40	4.35	4.39	4.38
Mm-m	10b	0.80	0.86	0.85	0.68	0.67	0.63	0.68
Mm-m	11b	-1.56	-1.74	-1.95	-2.13	-2.19	-2.38	-2.58
Mm-m	12b	-0.90	-0.68	-0.81	-0.67	-0.68	-0.70	-0.60
Mm-m	18b	3.71	3.70	3.64	3.73	3.78	3.70	3.78
Mm-m	35b	32.19	34.19	36.05	37.59	38.88	39.83	40.28
Mm-m	37b	5.89	5.81	5.77	5.72	5.65	5.40	5.03
Mm-m	41b	43.11	46.23	49.04	51.10	52.66	53.43	53.63
Mm-m	43b	-9.13	-10.51	-11.86	-13.27	-14.58	-15.96	-17.15
Mm-m	45b	-6.45	-7.33	-7.98	-8.48	-9.01	-9.76	-10.23

Chapter 4 Experiment 2
Test, 115 dB SPL (C)

Group	Subject	Time Post Startle Stimuli Presentation (msec)						
		38	39	40	41	42	43	44
mM-m	1a	9.62	9.39	8.84	9.20	8.56	7.99	8.25
mM-m	2a	-24.57	-19.64	-17.25	-17.63	-20.50	-24.67	-29.67
mM-m	9a	-24.87	-23.64	-21.88	-19.85	-18.15	-17.16	-17.07
mM-m	11a	-35.79	-43.54	-52.33	-63.16	-72.00	-80.39	-87.69
mM-m	17a	15.26	14.37	13.19	11.37	9.59	7.90	6.66
mM-m	20a	15.67	14.45	12.99	11.17	10.24	10.36	11.51
mM-m	26a	34.04	34.55	32.79	29.60	26.94	23.63	20.23
mM-m	6b	-42.56	-42.89	-41.67	-40.40	-38.14	-35.32	-32.50
mM-m	15b	-35.35	-34.62	-34.90	-34.30	-33.31	-31.24	-29.47
mM-m	16b	-42.07	-40.61	-40.25	-38.71	-36.37	-33.06	-29.54
mM-m	22b	-44.84	-44.60	-44.89	-43.49	-41.40	-38.97	-36.98
mM-m	24b	8.41	6.40	4.78	3.20	3.95	5.86	7.59
mM-m	25b	-23.58	-22.81	-21.46	-19.73	-18.11	-17.48	-17.76
mM-m	26b	30.40	24.62	18.22	12.77	9.46	9.07	9.70
mM-m	32b	5.34	3.32	2.80	3.44	4.63	6.14	6.77
mM-m	40b	-4.36	-9.04	-13.15	-15.94	-16.15	-13.19	-7.38
Mm-m	6a	1.83	5.70	9.63	10.00	11.09	10.01	7.11
Mm-m	13a	-47.38	-44.79	-41.63	-38.44	-35.93	-35.71	-36.60
Mm-m	15a	1.49	-0.88	-3.42	-5.68	-7.17	-7.69	-7.05
Mm-m	16a	7.51	13.49	20.92	28.30	35.34	38.95	39.06
Mm-m	24a	5.92	5.46	4.98	6.05	5.69	5.35	5.17
Mm-m	4b	4.39	4.58	4.66	4.84	4.94	5.05	5.13
Mm-m	10b	0.58	0.63	0.60	0.54	0.61	0.55	0.57
Mm-m	11b	-2.55	-2.69	-2.76	-2.77	-2.72	-2.73	-2.71
Mm-m	12b	-0.58	-0.61	-0.65	-0.57	-0.57	-0.71	-0.74
Mm-m	18b	3.69	3.68	3.73	3.57	3.63	3.70	3.73
Mm-m	35b	40.17	36.98	35.21	33.29	31.14	29.19	27.38
Mm-m	37b	4.51	2.99	1.02	-0.68	-2.53	-4.60	-5.95
Mm-m	41b	51.33	49.06	45.70	41.47	37.34	34.71	33.72
Mm-m	43b	-18.15	-19.14	-19.31	-19.96	-19.86	-18.85	-17.61
Mm-m	45b	-10.81	-11.03	-10.86	-10.60	-9.78	-8.48	-7.16

Chapter 4 Experiment 2
Test, 115 dB SPL (C)

Group	Subject	Time Post Startle Stimuli Presentation (msec)						
		45	46	47	48	49	50	51
mM-m	1a	8.89	9.92	11.02	11.85	12.62	13.02	13.30
mM-m	2a	-35.21	-40.83	-46.31	-51.50	-56.22	-60.14	-63.11
mM-m	9a	-18.19	-19.74	-21.47	-23.58	-25.77	-27.70	-29.99
mM-m	11a	-92.69	-95.42	-95.35	-92.23	-85.41	-77.00	-68.05
mM-m	17a	6.65	7.94	10.62	13.64	16.50	18.98	20.96
mM-m	20a	13.20	15.52	18.02	20.60	23.20	25.63	28.00
mM-m	26a	17.22	15.56	15.17	16.14	18.20	21.09	24.53
mM-m	6b	-30.00	-28.15	-27.65	-28.58	-30.60	-33.48	-37.09
mM-m	15b	-27.08	-25.25	-24.30	-24.02	-24.63	-25.98	-27.79
mM-m	16b	-26.40	-24.77	-24.97	-26.70	-29.72	-33.83	-38.20
mM-m	22b	-35.57	-34.54	-34.54	-35.06	-36.19	-37.93	-39.80
mM-m	24b	9.46	11.04	12.42	13.81	14.98	15.98	16.94
mM-m	25b	-18.67	-19.97	-21.78	-23.92	-26.48	-28.88	-31.47
mM-m	26b	13.51	19.03	26.28	32.67	37.64	41.08	42.91
mM-m	32b	8.74	10.50	12.22	13.44	14.32	14.87	14.88
mM-m	40b	-0.61	5.71	10.78	14.09	16.25	17.18	16.89
Mm-m	6a	3.65	-0.04	-3.16	-6.15	-8.56	-10.14	-11.18
Mm-m	13a	-38.64	-41.00	-43.97	-47.17	-50.55	-53.99	-56.23
Mm-m	15a	-4.84	-2.21	1.15	4.40	7.15	9.46	11.26
Mm-m	16a	35.57	31.17	26.40	21.36	16.95	13.40	10.98
Mm-m	24a	4.81	4.77	4.70	4.95	5.10	5.56	5.88
Mm-m	4b	5.28	5.46	5.37	5.29	4.86	3.96	2.57
Mm-m	10b	0.57	0.58	0.50	0.63	0.59	0.65	0.66
Mm-m	11b	-2.70	-2.66	-2.57	-2.71	-2.75	-3.02	-3.51
Mm-m	12b	-0.71	-0.78	-0.95	-1.04	-1.25	-1.56	-2.33
Mm-m	18b	3.67	3.76	3.73	3.72	3.84	3.92	3.99
Mm-m	35b	26.05	25.56	25.61	25.82	26.36	27.05	28.29
Mm-m	37b	-7.34	-7.77	-7.68	-7.44	-6.64	-5.41	-4.09
Mm-m	41b	34.52	36.31	39.04	42.60	46.46	50.22	54.19
Mm-m	43b	-15.80	-14.09	-12.62	-11.25	-10.23	-9.62	-9.53
Mm-m	45b	-6.49	-6.16	-6.17	-6.16	-6.42	-6.65	-7.06

Chapter 4 Experiment 2
Test, 115 dB SPL (C)

Group	Subject	Time Post Startle Stimuli Presentation (msec)						
		52	53	54	55	56	57	58
mM-m	1a	13.38	13.40	13.09	13.12	12.44	11.96	11.28
mM-m	2a	-64.62	-64.88	-63.98	-61.91	-58.79	-54.55	-49.14
mM-m	9a	-31.96	-33.79	-35.41	-36.74	-37.90	-38.71	-39.01
mM-m	11a	-59.33	-52.30	-47.57	-45.43	-45.57	-47.18	-49.64
mM-m	17a	22.55	23.54	24.20	24.32	24.24	23.63	23.03
mM-m	20a	30.09	31.94	33.42	34.65	35.42	35.76	35.81
mM-m	26a	28.30	32.66	36.98	41.35	45.43	49.22	53.06
mM-m	6b	-41.23	-45.94	-50.73	-55.76	-60.54	-65.36	-69.65
mM-m	15b	-30.33	-33.30	-36.53	-39.93	-43.29	-46.39	-49.35
mM-m	16b	-43.00	-47.42	-51.40	-55.17	-58.29	-60.98	-63.08
mM-m	22b	-42.04	-44.59	-46.98	-49.46	-51.67	-53.61	-55.08
mM-m	24b	17.41	17.61	17.29	16.29	14.92	12.88	10.60
mM-m	25b	-33.96	-36.31	-38.45	-40.22	-41.64	-42.60	-42.97
mM-m	26b	43.78	43.25	41.77	39.84	37.32	34.70	31.56
mM-m	32b	14.65	14.08	13.03	11.80	10.52	9.07	7.42
mM-m	40b	15.61	13.40	10.69	7.46	3.93	-0.24	-4.26
Mm-m	6a	-11.32	-10.76	-9.49	-7.88	-5.63	-3.22	-0.84
Mm-m	13a	-60.00	-63.57	-66.57	-69.08	-71.08	-72.74	-73.96
Mm-m	15a	12.75	13.85	14.27	14.27	13.67	12.38	10.53
Mm-m	16a	9.33	8.92	9.18	10.06	11.54	13.46	15.43
Mm-m	24a	6.26	6.66	6.99	7.22	7.25	7.31	7.09
Mm-m	4b	0.81	-1.61	-4.53	-7.67	-9.60	-13.37	-16.91
Mm-m	10b	0.75	0.84	0.88	1.08	1.15	1.03	1.10
Mm-m	11b	-4.10	-4.98	-6.15	-7.74	-9.50	-11.82	-14.47
Mm-m	12b	-3.42	-5.02	-7.05	-9.57	-12.36	-15.54	-18.84
Mm-m	18b	4.06	4.36	4.83	5.30	6.10	6.93	8.17
Mm-m	35b	29.91	31.80	33.75	35.75	37.72	39.33	40.76
Mm-m	37b	-2.24	-0.63	0.83	2.21	3.25	4.08	4.74
Mm-m	41b	58.47	61.80	65.05	67.97	70.09	71.71	72.83
Mm-m	43b	-9.84	-10.38	-11.21	-12.06	-12.93	-14.04	-15.17
Mm-m	45b	-7.46	-8.00	-8.50	-9.01	-9.57	-10.20	-10.71

Chapter 4 Experiment 2
Test, 115 dB SPL (C)

Group	Subject	Time Post Startle Stimuli Presentation (msec)						
		59	60	61	62	63	64	65
mM-m	1a	10.51	9.73	8.81	7.97	7.07	5.93	4.92
mM-m	2a	-42.04	-35.84	-28.88	-21.62	-14.17	-7.13	-1.00
mM-m	9a	-39.21	-39.14	-38.55	-37.80	-36.92	-35.73	-34.13
mM-m	11a	-53.18	-56.89	-60.74	-62.93	-67.72	-72.64	-77.84
mM-m	17a	21.83	20.76	19.28	17.80	16.03	14.19	12.39
mM-m	20a	35.27	34.47	33.18	31.72	29.73	27.60	25.27
mM-m	26a	56.12	58.66	60.72	62.19	63.03	62.77	62.14
mM-m	6b	-73.87	-77.33	-80.21	-82.27	-83.70	-84.39	-84.32
mM-m	15b	-51.60	-53.48	-54.63	-55.19	-55.40	-55.10	-54.46
mM-m	16b	-64.34	-64.90	-64.80	-64.17	-62.71	-60.71	-58.05
mM-m	22b	-56.11	-56.89	-57.15	-56.85	-56.15	-55.06	-53.54
mM-m	24b	7.57	4.67	1.74	-1.31	-4.28	-6.74	-8.82
mM-m	25b	-43.00	-42.57	-41.46	-40.11	-38.27	-36.07	-33.60
mM-m	26b	27.80	24.05	19.65	14.79	9.35	3.72	-2.31
mM-m	32b	5.74	3.83	2.04	0.35	-1.17	-2.59	-3.75
mM-m	40b	-8.36	-12.76	-17.11	-21.45	-25.43	-29.45	-32.65
Mm-m	6a	1.30	3.89	6.27	8.63	10.75	13.00	14.78
Mm-m	13a	-74.28	-74.06	-73.15	-71.83	-69.81	-67.14	-64.52
Mm-m	15a	8.34	5.68	2.80	-0.45	-3.73	-7.15	-10.44
Mm-m	16a	13.25	16.41	19.93	23.64	27.44	31.46	35.51
Mm-m	24a	6.70	6.43	5.98	5.57	4.94	4.37	3.64
Mm-m	4b	-20.28	-23.38	-26.43	-29.45	-32.23	-35.18	-37.49
Mm-m	10b	0.90	0.46	0.16	-0.24	-0.58	-1.10	-1.41
Mm-m	11b	-17.53	-20.87	-24.30	-27.68	-30.76	-33.55	-36.18
Mm-m	12b	-22.31	-25.92	-29.33	-32.68	-35.78	-38.53	-40.86
Mm-m	18b	9.28	10.81	12.05	13.14	13.72	13.90	13.43
Mm-m	35b	41.80	42.70	43.57	43.95	44.30	44.45	44.52
Mm-m	37b	5.01	5.08	4.83	4.42	3.73	3.18	2.23
Mm-m	41b	73.24	73.00	72.10	70.74	68.72	66.19	63.12
Mm-m	43b	-16.34	-17.44	-18.42	-19.30	-20.15	-20.85	-21.19
Mm-m	45b	-11.17	-11.40	-11.67	-11.54	-11.32	-10.74	-10.14

Chapter 4 Experiment 2
Test, 115 dB SPL (C)

Group	Subject	Time Post Startle Stimuli Presentation (msec)						
		66	67	68	69	70	71	72
mM-m	1a	3.96	2.96	2.05	1.17	0.63	0.08	-0.47
mM-m	2a	3.90	7.23	9.13	10.23	10.57	10.35	9.79
mM-m	9a	-32.42	-30.69	-28.86	-27.05	-25.62	-24.68	-23.93
mM-m	11a	-83.59	-89.36	-95.04	-100.50	-105.76	-110.18	-113.77
mM-m	17a	10.38	8.30	6.37	4.43	2.49	0.88	-0.30
mM-m	20a	22.74	20.35	18.26	16.43	14.93	14.24	14.06
mM-m	26a	60.53	58.26	55.29	51.53	47.08	42.44	37.78
mM-m	6b	-83.57	-82.18	-79.97	-77.11	-73.70	-69.65	-65.07
mM-m	15b	-53.38	-52.00	-50.17	-48.08	-45.48	-42.66	-39.64
mM-m	16b	-54.83	-51.23	-47.18	-43.19	-38.90	-34.66	-30.55
mM-m	22b	-51.79	-50.02	-48.42	-46.34	-44.49	-42.27	-40.23
mM-m	24b	-10.75	-12.03	-12.91	-12.85	-12.54	-11.71	-10.13
mM-m	25b	-31.07	-28.62	-26.52	-24.91	-23.88	-23.41	-23.22
mM-m	26b	-8.21	-13.81	-18.60	-21.82	-23.49	-24.16	-23.81
mM-m	32b	-4.72	-5.62	-6.10	-6.49	-6.51	-6.59	-6.44
mM-m	40b	-35.30	-36.42	-36.04	-33.95	-30.89	-27.10	-23.59
Mm-m	6a	16.30	17.30	17.39	16.44	14.76	12.94	11.38
Mm-m	13a	-61.05	-57.49	-53.54	-49.61	-45.88	-42.69	-40.28
Mm-m	15a	-13.48	-16.29	-18.51	-19.67	-20.29	-19.94	-19.20
Mm-m	16a	39.58	43.48	47.07	49.60	50.88	50.82	49.21
Mm-m	24a	3.24	2.93	2.60	2.38	2.18	1.95	1.94
Mm-m	4b	-39.67	-41.38	-42.56	-42.89	-41.67	-40.40	-38.14
Mm-m	10b	-1.64	-1.66	-2.23	-2.16	-2.14	-2.06	-1.90
Mm-m	11b	-38.19	-39.67	-42.07	-40.61	-40.25	-38.71	-36.37
Mm-m	12b	-42.94	-44.11	-44.84	-44.60	-44.89	-43.49	-41.40
Mm-m	18b	12.21	10.50	8.41	6.40	4.78	3.20	3.95
Mm-m	35b	44.33	44.27	44.29	44.25	44.32	44.22	43.60
Mm-m	37b	1.21	-0.08	-1.38	-2.82	-4.40	-5.68	-6.94
Mm-m	41b	59.53	55.31	51.01	46.81	43.00	40.12	37.53
Mm-m	43b	-21.15	-20.93	-20.41	-19.49	-18.46	-17.28	-15.82
Mm-m	45b	-9.03	-7.82	-6.52	-5.34	-3.83	-2.77	-2.30

Chapter 4 Experiment 2
Test, 115 dB SPL (C)

Group	Subj	Time Post Startle Stimuli Presentation (msec)						
		73	74	75	76	77	78	79
mM-m	1a	-0.78	-0.96	-0.67	0.12	1.27	2.52	3.63
mM-m	2a	9.41	8.84	8.62	8.40	8.58	8.76	9.21
mM-m	9a	-23.49	-23.14	-22.83	-22.48	-21.97	-21.58	-21.11
mM-m	11a	-115.91	-116.53	-115.57	-112.78	-108.56	-102.82	-95.86
mM-m	17a	-0.82	-0.63	0.14	1.20	2.48	3.72	4.86
mM-m	20a	14.12	14.49	15.03	15.32	15.88	16.48	17.06
mM-m	26a	33.44	29.62	26.15	23.36	21.10	19.18	17.35
mM-m	6b	-60.26	-55.00	-49.80	-45.58	-41.65	-38.53	-36.15
mM-m	15b	-36.26	-33.15	-30.66	-29.18	-28.67	-28.88	-29.26
mM-m	16b	-26.85	-23.81	-21.60	-20.16	-19.34	-18.81	-18.22
mM-m	22b	-37.63	-35.22	-32.84	-30.09	-27.60	-25.26	-22.89
mM-m	24b	-8.49	-6.93	-6.44	-6.37	-7.11	-8.14	-9.54
mM-m	25b	-23.53	-24.01	-24.77	-25.67	-26.43	-27.34	-27.97
mM-m	26b	-23.02	-21.73	-20.13	-18.86	-18.20	-18.51	-19.44
mM-m	32b	-6.02	-5.45	-4.62	-3.82	-2.62	-1.55	-0.57
mM-m	40b	-20.68	-18.68	-17.66	-17.47	-18.03	-18.96	-20.63
Mm-m	6a	9.98	9.20	8.69	8.66	8.84	9.41	10.01
Mm-m	13a	-38.71	-37.28	-36.40	-35.77	-35.35	-35.23	-35.01
Mm-m	15a	-18.04	-16.44	-14.67	-12.83	-11.10	-9.61	-8.21
Mm-m	16a	45.87	41.63	36.97	32.70	28.96	26.10	23.95
Mm-m	24a	1.81	1.63	1.29	0.87	0.46	0.15	-0.42
Mm-m	4b	-35.32	-32.50	-30.00	-28.15	-27.65	-28.58	-30.60
Mm-m	10b	-1.97	-2.48	-2.51	-2.89	-2.93	-3.09	-3.02
Mm-m	11b	-33.06	-29.54	-26.40	-24.77	-24.97	-26.70	-29.72
Mm-m	12b	-38.97	-36.98	-35.57	-34.54	-34.54	-35.06	-36.19
Mm-m	18b	5.86	7.59	9.46	11.04	12.42	13.81	14.98
Mm-m	35b	42.88	41.54	40.31	38.69	36.82	34.49	32.23
Mm-m	37b	-7.72	-8.51	-9.03	-9.62	-9.92	-10.20	-10.04
Mm-m	41b	35.48	34.13	32.84	31.76	30.81	29.91	29.02
Mm-m	43b	-14.18	-12.49	-10.91	-9.41	-8.02	-6.59	-5.30
Mm-m	45b	-2.41	-2.56	-2.93	-3.10	-3.44	-3.69	-3.88

Chapter 4 Experiment 2
Test, 115 dB SPL (C)

Group	Subj	Time Post Startle Stimuli Presentation (msec)						
		31	32	33	34	35	36	37
mM-s	4a	-22.55	-23.69	-24.26	-24.06	-23.27	-21.77	-19.64
mM-s	10a	37.58	42.79	47.99	52.76	57.41	61.48	64.87
mM-s	12a	14.06	15.23	16.30	16.88	17.08	16.54	15.49
mM-s	18a	46.39	51.77	56.76	61.11	64.71	67.48	69.31
mM-s	19a	-85.19	-93.84	-101.75	-108.66	-114.41	-118.74	-121.65
mM-s	27a	-27.79	-27.99	-27.91	-27.30	-26.07	-24.16	-21.63
mM-s	28a	-8.59	-6.95	-5.55	-4.33	-3.11	-1.98	-0.27
mM-s	5b	-0.39	-0.43	-0.45	-0.43	-0.53	-0.44	-0.50
mM-s	8b	0.49	0.48	0.37	0.25	0.16	0.03	0.05
mM-s	13b	1.35	1.31	1.30	1.26	1.14	1.34	1.14
mM-s	14b	0.80	0.86	0.85	0.68	0.67	0.63	0.68
mM-s	21b	1.16	1.00	1.08	1.02	1.06	1.00	1.06
mM-s	33b	26.84	28.88	30.83	32.43	33.65	34.31	34.20
mM-s	36b	28.14	29.55	30.47	30.81	30.86	30.05	28.64
mM-s	39b	31.27	31.80	31.93	31.46	30.55	29.21	28.12
mM-s	42b	35.92	38.15	40.36	42.20	43.73	44.67	45.27
Mm-s	8a	49.64	53.57	56.99	60.19	63.12	65.84	67.87
Mm-s	22a	-38.67	-40.43	-41.69	-43.00	-43.62	-43.63	-43.18
Mm-s	23a	-22.48	-25.41	-28.02	-30.49	-32.64	-34.65	-35.96
Mm-s	1b	-0.39	-0.43	-0.45	-0.43	-0.53	-0.44	-0.50
Mm-s	2b	0.49	0.48	0.37	0.25	0.16	0.03	0.05
Mm-s	3b	1.35	1.31	1.30	1.26	1.14	1.34	1.14
Mm-s	9b	4.30	4.73	5.33	5.49	5.94	6.52	7.32
Mm-s	17b	1.16	1.00	1.08	1.02	1.06	1.00	1.06
Mm-s	19b	0.53	0.49	0.50	0.39	0.40	0.48	0.52
Mm-s	20b	0.38	0.28	0.27	0.29	0.23	0.09	0.06
Mm-s	38b	-31.76	-37.02	-41.85	-46.12	-50.07	-53.46	-56.43
Mm-s	44b	-2.00	-2.87	-3.57	-4.19	-4.67	-5.16	-5.38
Mm-s	46b	24.83	23.47	21.18	18.02	13.92	8.99	3.29

Chapter 4 Experiment 2
Test, 115 dB SPL (C)

Group	Subj	Time Post Startle Stimuli Presentation (msec)						
		38	39	40	41	42	43	44
mM-s	4a	-17.29	-14.10	-10.64	-6.49	-2.97	-0.51	0.06
mM-s	10a	67.96	69.96	71.18	66.19	64.46	60.68	55.96
mM-s	12a	14.66	12.53	10.19	8.14	7.08	6.66	7.01
mM-s	18a	69.81	69.19	67.32	64.24	60.21	56.33	53.73
mM-s	19a	-126.38	-125.31	-121.84	-116.17	-108.31	-99.43	-91.73
mM-s	27a	-18.43	-14.62	-16.32	-15.04	-13.18	-12.51	-12.83
mM-s	28a	5.08	7.73	10.79	11.82	16.67	21.51	25.10
mM-s	5b	-0.57	-0.58	-0.58	-0.66	-0.75	-0.60	-0.66
mM-s	8b	-0.09	-0.19	-0.29	-0.13	-0.30	-0.35	-0.48
mM-s	13b	1.15	1.04	1.10	1.05	1.10	0.94	0.95
mM-s	14b	0.58	0.63	0.60	0.54	0.61	0.55	0.57
mM-s	21b	1.08	1.03	0.96	0.97	0.96	0.98	1.01
mM-s	33b	32.85	31.38	29.00	26.13	24.49	24.37	23.46
mM-s	36b	26.35	22.01	16.90	12.81	10.13	9.63	11.24
mM-s	39b	25.41	22.37	18.61	14.40	10.63	8.62	9.16
mM-s	42b	43.75	42.63	40.66	38.49	36.44	35.53	34.97
Mm-s	8a	69.04	69.24	68.18	65.77	62.13	57.45	53.32
Mm-s	22a	-41.37	-38.72	-35.26	-30.51	-26.24	-21.73	-18.83
Mm-s	23a	-37.03	-37.18	-36.77	-35.31	-33.49	-30.83	-29.33
Mm-s	1b	-0.57	-0.58	-0.58	-0.66	-0.75	-0.60	-0.66
Mm-s	2b	-0.09	-0.19	-0.29	-0.13	-0.30	-0.35	-0.48
Mm-s	3b	1.15	1.04	1.10	1.05	1.10	0.94	0.95
Mm-s	9b	6.44	7.06	7.63	8.01	8.71	9.28	9.77
Mm-s	17b	1.08	1.03	0.96	0.97	0.96	0.98	1.01
Mm-s	19b	0.46	0.57	0.54	0.54	0.53	0.42	0.57
Mm-s	20b	0.23	0.08	0.14	0.06	0.08	0.15	0.01
Mm-s	38b	-58.77	-60.84	-66.68	-65.58	-63.11	-59.30	-55.89
Mm-s	44b	-5.62	-5.61	-4.52	-4.18	-3.68	-3.45	-3.60
Mm-s	46b	-2.74	-9.09	-15.54	-19.85	-19.90	-16.90	-12.25

Chapter 4 Experiment 2
Test, 115 dB SPL (C)

Group	Subj	Time Post Startle Stimuli Presentation (msec)						
		45	46	47	48	49	50	51
mM-s	4a	-0.99	-3.76	-7.99	-13.65	-20.08	-25.63	-30.34
mM-s	10a	51.35	48.06	46.77	47.06	49.08	52.82	57.65
mM-s	12a	8.96	10.90	13.53	16.66	20.54	24.09	27.25
mM-s	18a	52.51	52.69	54.34	57.33	61.35	66.17	71.33
mM-s	19a	-87.80	-86.98	-88.90	-92.97	-98.98	-106.85	-115.97
mM-s	27a	-14.07	-15.95	-18.47	-20.90	-22.88	-24.19	-25.03
mM-s	28a	26.52	25.43	21.62	16.12	10.01	3.64	-1.80
mM-s	5b	-0.65	-0.94	-1.00	-1.24	-1.58	-2.03	-2.63
mM-s	8b	-0.40	-0.46	-0.60	-0.56	-0.50	-0.51	-0.61
mM-s	13b	0.86	0.89	0.77	0.74	0.68	0.66	0.64
mM-s	14b	0.57	0.58	0.50	0.63	0.59	0.65	0.66
mM-s	21b	1.03	1.08	1.14	2.44	2.70	3.54	3.63
mM-s	33b	25.14	26.98	29.14	31.19	33.00	35.05	37.52
mM-s	36b	13.91	17.22	21.05	24.77	28.79	32.93	36.79
mM-s	39b	12.35	17.29	22.72	27.82	32.08	35.76	38.92
mM-s	42b	35.00	35.04	34.95	35.13	35.93	37.46	39.41
Mm-s	8a	50.00	48.51	48.62	49.71	51.85	54.84	59.31
Mm-s	22a	-18.95	-21.53	-26.60	-33.03	-39.59	-45.70	-51.01
Mm-s	23a	-28.72	-29.12	-30.09	-31.55	-33.12	-34.88	-37.04
Mm-s	1b	-0.65	-0.94	-1.00	-1.24	-1.58	-2.03	-2.63
Mm-s	2b	-0.40	-0.46	-0.60	-0.56	-0.50	-0.51	-0.61
Mm-s	3b	0.86	0.89	0.77	0.74	0.68	0.66	0.64
Mm-s	9b	10.15	10.30	10.42	9.78	8.98	7.99	7.17
Mm-s	17b	1.03	1.08	1.14	2.44	2.70	3.54	3.63
Mm-s	19b	0.42	0.20	-0.16	0.70	0.17	1.81	0.80
Mm-s	20b	0.04	0.13	0.17	0.19	0.16	0.16	-0.29
Mm-s	38b	-54.50	-55.09	-56.52	-58.52	-60.74	-63.14	-65.44
Mm-s	44b	-3.51	-3.69	-3.82	-4.16	-4.28	-4.53	-4.71
Mm-s	46b	-6.78	-1.33	3.81	7.91	10.70	12.29	12.76

Chapter 4 Experiment 2
Test, 115 dB SPL (C)

Group	Subj	Time Post Startle Stimuli Presentation (msec)						
		52	53	54	55	56	57	58
mM-s	4a	-34.26	-37.37	-39.64	-41.22	-42.18	-42.22	-41.39
mM-s	10a	63.27	69.10	75.04	80.94	86.50	91.60	96.30
mM-s	12a	29.68	31.59	32.83	33.39	33.36	32.78	31.48
mM-s	18a	76.74	82.28	87.71	92.69	97.38	101.56	105.06
mM-s	19a	-125.88	-136.48	-146.78	-157.00	-166.24	-174.45	-181.45
mM-s	27a	-25.34	-24.83	-23.73	-22.13	-19.82	-17.06	-13.73
mM-s	28a	-6.32	-10.02	-12.98	-15.05	-16.34	-16.73	-16.86
mM-s	5b	-3.22	-4.13	-5.03	-6.11	-6.28	-7.50	-8.85
mM-s	8b	-0.81	-1.20	-1.50	-2.10	-2.75	-3.66	-5.04
mM-s	13b	0.61	0.46	0.22	-0.04	-0.40	-0.75	-1.16
mM-s	14b	0.75	0.84	0.88	1.08	1.15	1.03	1.10
mM-s	21b	3.85	4.04	4.22	4.13	3.61	3.08	2.26
mM-s	33b	39.79	41.93	43.94	45.60	47.00	47.66	48.13
mM-s	36b	40.30	43.52	46.27	48.26	49.66	50.28	50.44
mM-s	39b	41.45	43.16	44.44	44.98	45.27	44.82	44.31
mM-s	42b	41.71	43.89	46.24	48.16	49.88	51.32	52.33
Mm-s	8a	63.57	68.45	73.85	79.56	85.30	90.78	96.01
Mm-s	22a	-55.47	-59.28	-62.90	-66.03	-69.34	-72.32	-74.84
Mm-s	23a	-39.72	-42.63	-45.83	-49.07	-52.26	-55.17	-57.93
Mm-s	1b	-3.22	-4.13	-5.03	-6.11	-6.28	-7.50	-8.85
Mm-s	2b	-0.81	-1.20	-1.50	-2.10	-2.75	-3.66	-5.04
Mm-s	3b	0.61	0.46	0.22	-0.04	-0.40	-0.75	-1.16
Mm-s	9b	6.49	6.36	6.66	6.68	6.90	7.59	7.30
Mm-s	17b	3.85	4.04	4.22	4.13	3.61	3.08	2.26
Mm-s	19b	-0.39	-1.66	-1.72	-3.57	-5.63	-7.90	-10.26
Mm-s	20b	-0.86	-1.77	-3.04	-4.52	-6.43	-8.35	-10.59
Mm-s	38b	-67.57	-69.28	-70.41	-71.77	-72.73	-73.20	-73.23
Mm-s	44b	-4.98	-5.12	-5.26	-5.34	-5.57	-5.61	-5.74
Mm-s	46b	12.47	10.95	8.96	6.41	3.34	-0.19	-4.14

Chapter 4 Experiment 2
Test, 115 dB SPL (C)

Group	Subj	Time Post Startle Stimuli Presentation (msec)						
		59	60	61	62	63	64	65
mM-s	4a	-40.14	-38.09	-35.47	-32.40	-28.80	-24.80	-20.83
mM-s	10a	100.03	102.90	104.96	105.91	106.12	105.61	104.08
mM-s	12a	29.72	27.46	24.88	22.09	18.88	15.68	12.26
mM-s	18a	107.42	109.25	110.09	110.03	108.89	107.05	104.06
mM-s	19a	-186.63	-190.68	-192.67	-193.36	-192.45	-189.96	-186.06
mM-s	27a	-10.05	-6.12	-1.94	2.41	6.69	11.11	15.04
mM-s	28a	-19.13	-18.32	-17.26	-15.83	-14.54	-12.98	-10.77
mM-s	5b	-10.13	-11.40	-12.60	-13.58	-14.54	-15.06	-15.27
mM-s	8b	-6.62	-8.57	-10.59	-12.87	-15.22	-17.75	-20.18
mM-s	13b	-1.78	-2.24	-2.58	-3.09	-3.32	-3.63	-3.78
mM-s	14b	0.90	0.46	0.16	-0.24	-0.58	-1.10	-1.41
mM-s	21b	1.33	0.45	-0.59	-1.55	-2.57	-3.65	-4.76
mM-s	33b	48.18	47.50	46.43	45.14	43.03	40.49	37.43
mM-s	36b	49.69	48.42	46.63	44.21	41.62	38.47	35.08
mM-s	39b	43.16	41.70	39.92	37.57	34.78	31.49	28.13
mM-s	42b	52.72	52.88	52.45	51.78	50.73	49.80	48.62
Mm-s	8a	100.46	104.43	107.51	109.65	111.04	111.45	110.94
Mm-s	22a	-77.14	-78.50	-79.07	-79.02	-77.80	-75.79	-73.00
Mm-s	23a	-60.30	-62.30	-63.90	-64.99	-65.62	-65.77	-65.56
Mm-s	1b	-10.13	-11.40	-12.60	-13.58	-14.54	-15.06	-15.27
Mm-s	2b	-6.62	-8.57	-10.59	-12.87	-15.22	-17.75	-20.18
Mm-s	3b	-1.78	-2.24	-2.58	-3.09	-3.32	-3.63	-3.78
Mm-s	9b	8.00	8.55	9.37	9.73	10.65	11.33	12.16
Mm-s	17b	1.33	0.45	-0.59	-1.55	-2.57	-3.65	-4.76
Mm-s	19b	-12.56	-14.86	-16.98	-19.09	-20.87	-22.36	-23.30
Mm-s	20b	-12.82	-15.03	-17.00	-19.13	-21.11	-23.16	-25.01
Mm-s	38b	-72.95	-72.04	-70.37	-68.40	-65.94	-62.82	-59.37
Mm-s	44b	-5.86	-5.84	-5.97	-5.90	-5.64	-5.29	-4.79
Mm-s	46b	-8.15	-12.26	-16.46	-20.31	-23.80	-26.65	-29.01

Chapter 4 Experiment 2
Test, 115 dB SPL (C)

Group	Subj	Time Post Startle Stimuli Presentation (msec)						
		66	67	68	69	70	71	72
mM-s	4a	-16.66	-12.53	-8.49	-4.52	-1.10	1.95	4.39
mM-s	10a	101.73	98.62	94.81	90.58	85.94	80.70	75.03
mM-s	12a	9.01	6.07	3.53	1.28	-0.06	-1.14	-1.56
mM-s	18a	100.22	95.59	89.98	83.63	76.61	69.87	63.24
mM-s	19a	-180.77	-174.05	-166.18	-157.33	-147.67	-137.34	-126.87
mM-s	27a	18.77	21.83	23.94	24.84	24.59	23.45	21.66
mM-s	28a	-8.42	-5.73	-2.72	0.37	3.67	6.97	10.38
mM-s	5b	-15.25	-14.93	-14.25	-13.27	-11.67	-10.54	-9.64
mM-s	8b	-22.43	-24.64	-26.35	-27.80	-28.80	-29.81	-30.23
mM-s	13b	-3.84	-3.71	-3.96	-3.58	-2.99	-2.46	-2.05
mM-s	14b	-1.64	-1.66	-2.23	-2.16	-2.14	-2.06	-1.90
mM-s	21b	-6.14	-7.43	-8.76	-9.43	-8.81	-7.15	-4.94
mM-s	33b	34.11	30.26	26.37	23.08	20.85	19.76	19.62
mM-s	36b	31.60	27.95	24.28	21.20	19.01	17.74	17.23
mM-s	39b	24.29	20.66	16.82	13.48	11.03	9.37	8.72
mM-s	42b	47.04	45.32	43.66	42.08	40.33	38.77	37.25
Mm-s	8a	109.85	108.06	105.58	102.68	99.21	95.24	90.76
Mm-s	22a	-69.36	-65.18	-60.53	-55.58	-50.42	-45.18	-40.00
Mm-s	23a	-64.69	-63.40	-61.55	-58.88	-55.18	-50.69	-46.19
Mm-s	1b	-15.25	-14.93	-14.25	-13.27	-11.67	-10.54	-9.64
Mm-s	2b	-22.43	-24.64	-26.35	-27.80	-28.80	-29.81	-30.23
Mm-s	3b	-3.84	-3.71	-3.96	-3.58	-2.99	-2.46	-2.05
Mm-s	9b	13.07	13.89	14.67	15.56	16.28	17.34	18.25
Mm-s	17b	-6.14	-7.43	-8.76	-9.43	-8.81	-7.15	-4.94
Mm-s	19b	-23.80	-23.74	-23.08	-22.02	-20.48	-18.70	-17.32
Mm-s	20b	-27.02	-28.69	-29.93	-27.94	-27.37	-26.34	-24.80
Mm-s	38b	-55.68	-51.54	-47.38	-42.83	-38.31	-33.88	-30.24
Mm-s	44b	-4.21	-3.75	-3.14	-2.56	-2.03	-2.08	-2.29
Mm-s	46b	-30.91	-32.10	-32.29	-31.42	-29.62	-27.49	-25.31

Chapter 4 Experiment 2
Test, 115 dB SPL (C)

Group	Subj	Time Post Startle Stimuli Presentation (msec)						
		73	74	75	76	77	78	79
mM-s	4a	6.33	6.89	6.68	5.59	4.19	2.27	0.69
mM-s	10a	68.92	63.10	57.96	53.36	49.12	45.51	42.32
mM-s	12a	-1.61	-1.29	-0.78	-0.25	0.29	0.72	1.25
mM-s	18a	57.21	52.02	47.65	43.71	40.21	37.08	34.28
mM-s	19a	-117.33	-108.86	-102.01	-96.03	-91.12	-86.75	-83.18
mM-s	27a	19.34	16.77	14.19	11.50	8.87	6.40	4.04
mM-s	28a	13.61	16.46	18.89	20.51	21.27	20.97	19.49
mM-s	5b	-9.56	-10.26	-11.46	-13.37	-15.51	-17.95	-20.57
mM-s	8b	-30.17	-29.63	-28.73	-27.41	-25.58	-23.56	-21.54
mM-s	13b	-1.79	-1.63	-2.40	-2.76	-3.29	-3.89	-4.42
mM-s	14b	-1.97	-2.48	-2.51	-2.89	-2.93	-3.09	-3.02
mM-s	21b	-2.73	-0.74	1.14	2.42	3.21	3.57	3.54
mM-s	33b	19.71	20.22	20.66	21.13	21.43	21.47	21.69
mM-s	36b	17.27	17.34	17.38	17.42	17.42	17.10	16.92
mM-s	39b	8.91	9.72	10.83	12.25	13.85	15.92	18.06
mM-s	42b	35.78	34.17	32.23	30.09	28.14	26.02	24.28
Mm-s	8a	85.81	80.72	75.69	71.22	67.15	63.78	60.87
Mm-s	22a	-35.11	-30.84	-27.38	-24.88	-23.11	-22.32	-22.25
Mm-s	23a	-42.20	-39.08	-36.49	-34.58	-33.01	-31.72	-30.69
Mm-s	1b	-9.56	-10.26	-11.46	-13.37	-15.51	-17.95	-20.57
Mm-s	2b	-30.17	-29.63	-28.73	-27.41	-25.58	-23.56	-21.54
Mm-s	3b	-1.79	-1.63	-2.40	-2.76	-3.29	-3.89	-4.42
Mm-s	9b	18.92	19.64	20.35	20.91	21.30	20.59	20.16
Mm-s	17b	-2.73	-0.74	1.14	2.42	3.21	3.57	3.54
Mm-s	19b	-16.57	-16.92	-17.37	-17.80	-18.74	-20.18	-22.15
Mm-s	20b	-23.40	-22.38	-21.59	-21.15	-20.65	-20.68	-20.77
Mm-s	38b	-26.96	-24.59	-22.82	-21.34	-20.21	-19.21	-18.50
Mm-s	44b	-2.37	-2.52	-2.86	-2.99	-3.13	-3.43	-3.35
Mm-s	46b	-22.86	-20.73	-18.97	-17.35	-15.71	-14.68	-13.72

Chapter 5: Test

Group	Subject #	Wet Dog Shakes	Genital Licks
mM-m	1a	12	38.9
mM-m	2a	4	10.8
mM-m	3a	10	41.8
mM-m	4a	3	4.2
mM-m	5a	4	15.5
mM-m	6c	6	3.1
mM-m	7c	0	19.9
mM-m	8c	4	6.8
mM-m	9c	2	1
mM-m	10c	2	2.3
mM-m	19c	11	0
mM-m	20c	15	1.7
mM-m	30c	1	18.2
Mm-m	6a	5	17.5
Mm-m	7a	2	0
Mm-m	8a	2	0
Mm-m	9a	4	0
Mm-m	10a	3	9
Mm-m	1c	2	0
Mm-m	2c	6	0
Mm-m	3c	1	16.8
Mm-m	5c	2	6
Mm-m	24c	1	0
Mm-m	25c	0	0
mM-s	4b	8	0
mM-s	5b	9	0
mM-s	17c	7	0
mM-s	18c	1	7.5
mM-s	27c	3	0
mM-s	29c	1	0
mM-s	31c	0	0
mM-s	2d	3	3.8
Mm-s	9b	3	0
Mm-s	10b	0	0
Mm-s	12c	0	0
Mm-s	13c	6	9.5
Mm-s	14c	7	0
Mm-s	15c	0	0
Mm-s	22c	0	0

Chapter 5: Test

Group	Subject#	Wet Dog Shakes	Genital Licks
Mm-s	23c	2	0
sS-m	1b	1	16.2
sS-m	2b	2	0
sS-m	3b	0	0
sS-m	16c	2	11
sS-m	28c	0	0
sS-m	1d	3	32
sS-m	3d	0	0
sS-m	5d	2	0
Ss-m	6b	5	1.2
Ss-m	7b	3	0
Ss-m	8b	0	0
Ss-m	11c	1	0
Ss-m	21c	0	0
Ss-m	7d	0	0
Ss-m	9d	0	0
Ss-m	18d	3	19.5
sS-s	4d	2	0
sS-s	11d	1	7.1
sS-s	12d	3	1.5
sS-s	13d	2	0
sS-s	14d	0	4.6
sS-s	15d	0	0
Ss-s	6d	3	2.6
Ss-s	8d	2	15.8
Ss-s	10d	2	6.7
Ss-s	16d	0	0
Ss-s	17d	4	0
Ss-s	19d	1	0
Ss-s	20d	3	5