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Examination Of The Rewarding Effects Of Nicotine And The Negative Effects Of Withdrawal In A Rodent Model Of Diabetes

Joseph Allan Pipkin
University of Texas at El Paso, jpipkin264@yahoo.com

EXAMINATION OF THE REWARDING EFFECTS OF NICOTINE AND THE NEGATIVE EFFECTS OF WITHDRAWAL IN A RODENT MODEL OF DIABETES

JOSEPH ALLAN PIPKIN

Doctoral Program in Psychology

APPROVED:

_____
Laura E. O'Dell, Ph.D., Chair

_____
Edward Castañeda, Ph.D.

_____
Katherine Serafine, Ph.D.

_____
Arshad Khan, Ph.D.

_____
Luis Carcoba, M.D., Ph.D.

_____
Charles Ambler, Ph.D.
Dean of the Graduate School

Dedicated to my family Susan Pipkin, Allan Pipkin, Mae Jimenez, Sharon Hagerty, Richard J. Jimenez, Marissa Pipkin, Katie Pipkin, Jamie Pipkin, and my beautiful wife Jennifer Pipkin and our amazing children, Noah, Caleb, and Elijah Pipkin.

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by

Joseph A. Pipkin, M.A.

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Abstract

Introduction: The present study utilized a rodent model of diabetes to examine the rewarding effects of nicotine as well as negative affective states and physical signs of withdrawal from this drug. **Methods:** Separate groups of rats received systemic administration of vehicle or streptozotocin (STZ), which destroys the insulin-producing beta cells in the pancreas and elevates plasma glucose levels. Place conditioning procedures were utilized to compare the rewarding effects of various doses of nicotine (conditioned place preference; CPP) and the aversive effects of nicotine withdrawal (conditioned place aversion; CPA) in vehicle- and STZ-treated rats. CPA and physical signs of withdrawal were compared following administration of the nicotine receptor antagonist mecamylamine to precipitate withdrawal in rats that had received nicotine exposure for 7-14 days. Control rats received a sham surgical procedure. A subsequent study compared anxiety-like behavior produced by nicotine withdrawal in vehicle- and STZ-treated rats. Anxiety-like behavior was assessed using the elevated plus maze (EPM) and light-dark transfer (LDT) tests. **Results:** STZ-treated rats displayed CPP across a wider dose range of nicotine and a larger magnitude of CPA produced by withdrawal as compared to controls. STZ-treated rats also displayed significantly higher levels of physical signs of withdrawal as compared to controls. STZ-treated rats also displayed higher levels of anxiety-like behavior produced by nicotine withdrawal on both the EPM and LDT tests. **Conclusion**: Our findings suggest that both nicotine reward and withdrawal from this drug are enhanced in a rodent model of diabetes. Our findings imply that the strong behavioral effects of nicotine promote tobacco use in persons with metabolic disorders, such as diabetes.

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Chapter 1: Introduction

1.1 Tobacco use is a public health and economic concern

In the United States, tobacco use is the leading contributing factor to preventable disease and death (Centers for Disease Control & Prevention [CDC], 2016). Approximately 440,000 people in the United States and 4 million people worldwide die each year from tobacco-related illnesses (Giovino, 2002). For example, long-term tobacco use leads to negative health consequences such as lung cancer, cardiovascular disease, and emphysema (D'Alessandro et al., 2012; Hecht, 2012; Milara & Cortijo, 2012). Tobacco use is also an economic burden, as each year the cost associated with tobacco use exceeds 300 billion dollars (CDC, 2016). Given the magnitude of problems associated with tobacco use, more research is needed to understand the various factors that promote smoking behavior in certain sub-populations that are more vulnerable to smoking, including persons with metabolic disorders, such as diabetes.

1.2 Tobacco use in persons with diabetes

Epidemiological studies have revealed that individuals with metabolic disorders, such as diabetes are more likely to engage in tobacco use and have a harder time quitting smoking (Gill et al., 2005). Moreover, the recent decline in smoking rates has been shown to be lower in persons with diabetes (Fan et al., 2013). Clinical reports further suggest that persons with diabetes report that they are less likely to quit smoking as compared to non-diabetic persons (Solberg et al., 2004). Persons with diabetes also display reduced awareness of smoking cessation approaches, and they generally consider smoking interventions to be unsafe (Gill et al., 2005).

Persons with diabetes that smoke display higher rates of negative affect, stress, and depression-like symptoms as compared to diabetic persons that do not smoke (Tonstad et al.,

2009). These studies suggest that persons with diabetes may have a greater pre-disposition to smoke as a tool to cope with mental health issues. There are an array of other factors that might also promote tobacco use in persons with diabetes, such as control of appetite, weight gain, and pain management. Although persons with diabetes appear to be more vulnerable to tobacco use, the factors that promote tobacco use in this sub-population are presently unclear. Thus, this dissertation will examine the behavioral effects of nicotine in a rodent model of diabetes.

1.3 Nicotine modulates tobacco use

Of the 4,800+ chemicals that are found in tobacco products, nicotine has been shown to be the primary habit forming compound (Stolerman, & Jarvis, 1995). In humans, nicotine administration induces feelings of euphoria, alertness, and relaxation (Heishman et al., 2010; Hukkanen et al., 2005; Le Foll & Goldberg, 2006; 2009; NIDA, 2009). In animals, nicotine is readily self-administered by humans, dogs, rodents, and primates (Caille, 2012; Corrigall, 1999; Harvey et al., 2004; Katner et al., 2004; Le Foll et al., 2007; Le Foll & Goldberg, 2006; 2009; Risner et al., 1983). In the early stages of nicotine addiction, tobacco use is largely motivated by experiencing the positive rewarding effects of nicotine. However, following chronic tobacco use, smoking abstinence elicits a withdrawal syndrome that consists of both physical and affective states, such as intense craving, anxiety, and depression. Indeed, the emergence of these physical and affective states produced by nicotine withdrawal has been closely associated with the development of nicotine dependence and relapse behavior (Hughes, 2007; Piper et al., 2011; Ríos-Bedoya et al., 2008; West et al., 2006). Thus, both the positive rewarding effects of nicotine and avoiding the negative consequences of withdrawal both play a role in continued tobacco use and relapse behavior. Understanding both nicotine reward and the aversive effects of withdrawal from this drug are important to consider when assessing vulnerability to tobacco use. Therefore,

the present dissertation studies include an examination of both nicotine reward and withdrawal from this drug in a rodent model of diabetes.

1.4 Nicotine dependence in rodents

Nicotine dependence can be induced in rodents via chronic administration of nicotine via a subcutaneously implanted osmotic pump (Malin & Goyarzu, 2009). The pump is filled with nicotine and is then surgically implanted subcutaneously under the rodents back. The nicotine is delivered via osmosis at a constant rate in a dose range of 3-9 mg/kg/per day (Hamilton et al., 2010; 2009; Kolokotroni et al., 2012; Malin et al., 2001; 2009; O'Dell et al., 2006; 2007). Previous work in our laboratory has revealed that nicotine must be delivered for at least 7 days in order to induce nicotine dependence, as evidenced by the emergence of physical signs of withdrawal following pump removal (spontaneous withdrawal) or administration of a nACHr antagonist, such as mecamylamine (precipitated withdrawal). Both spontaneous and precipitated nicotine withdrawal elicits physical signs and negative affective states. The physical signs of withdrawal include writhes, gasps, shakes, tremors, teeth chattering, chewing, and ptosis (Hamilton et al., 2009; 2010; Malin et al., 1992; Malin & Goyarzu, 2009; Skjei & Markou, 2003). The negative affective states of withdrawal can be assessed using place-conditioning procedures, where animals avoid a compartment paired previously with nicotine withdrawal (Bruijnzeel, 2012; O'Dell & Khroyan, 2009). Negative affective states produced by nicotine withdrawal have been assessed in behavioral procedures that measure anxiety-like behavior, as described below.

Previous studies have revealed that the physical signs and negative affective states produced by nicotine withdrawal are distinctly mediated. Specifically, previous studies have shown that the physical signs of nicotine withdrawal are mediated via central and peripheral

nicotinic acetylcholine receptors (nAChRs), whereas affective states produced by withdrawal are mediated via central nervous systems nAChRs (De Biasi & Dani, 2011; Watkins et al., 2000). Moreover, work in our laboratory has shown that adolescent rats display fewer physical signs and affective states as compared to adults experiencing nicotine withdrawal (O'Dell et al., 2006; 2007). Also, pre-clinical reports have shown that female rats display greater negative affective states, but similar physical signs of nicotine withdrawal as compared to males (Carcoba et al., 2016). These group differences suggest that the physical and affective states produced by nicotine withdrawal are distinctly mediated. Therefore, this dissertation will assess physical signs and affective states produced by nicotine withdrawal in a rodent model of diabetes.

1.5 Place conditioning in rodents

Place conditioning is a behavioral approach that utilizes Pavlovian principles to assess the motivational effects of nicotine (Tzschentke, 1998). This paradigm employs a conditioning apparatus that consists of 2 distinct compartments that differ in sensory modalities for visual stimuli (stripped versus solid walls), tactile cues (smooth versus serrated floors), and odors (pine versus cedar bedding). The chamber is separated by a solid removable door that can be replaced with another door that has an opening in it that allows the rat to pass freely between the 2 sides of the chamber. This dissertation employs a biased design, whereby rats are pre-tested for their initial preference for either side of the conditioning chamber. During conditioning, the rats are given an injection of nicotine and are confined to their initially non-preferred compartment (i.e., the side they spent less than 50% of their time in during the pre-test). On intervening days, the rats are given an injection of saline and are confined to the alternate compartment. During conditioning, the rats form an association between the environmental cues (conditioned stimuli; CS) and the affective states produced by nicotine (unconditioned stimuli; US). Following

conditioning, the rats are given free access to both compartments simultaneously in the absence of drug. The rewarding effects of nicotine are evident as a positive shift in preference behavior for the environment paired with nicotine (i.e., conditioned place preference; CPP). However, the aversive effects of high doses of nicotine can also be observed as a negative shift in preference behavior (conditioned place aversion; CPA). Thus, an important advantage of the place conditioning procedure is that it has the ability to assess both the positive rewarding effects of nicotine as well as negative affective states produced by high doses of this drug. Indeed, previous studies have revealed that doses of nicotine within a dose range of 0.2-0.6 mg/kg produce CPP, whereas nicotine doses within a range of 0.8-1.2 mg/kg produce CPA in adult male rats (Le Foll & Goldberg, 2005; Torres et al., 2009).

Place conditioning procedures can also be used to measure aversive effects induced by nicotine withdrawal. In these studies, animals first receive chronic nicotine exposure via osmotic pumps for 5-7 days. During conditioning, the animal receives a nicotinic receptor antagonist (such as mecamylamine) to precipitate withdrawal and is confined to one side of the apparatus. On alternating days they receive saline in the other compartment. In this procedure, the rat receives mecamylamine in their initially preferred side, such that a negative shift in preference indicates a CPA. It has been well established, that following conditioning, nicotine-dependent adult rats reliably display a CPA for the compartment where they experienced nicotine withdrawal (O'Dell et al., 2007; Suzuki et al., 1996). In CPA studies, the negative affective state produced by withdrawal serves as the US and the environmental cues serve as the CS. Previous studies have revealed that nicotine withdrawal produces CPA in a linear manner, with higher doses of mecamylamine producing a larger magnitude of aversion in adult male rats (O'Dell et al., 2007).

1.6 Anxiety-like behavior in rodents

The elevated plus maze (EPM) is a well-established procedure for assessing anxiety-like behavior in rodents (Bertoglio & Carobrez, 2002; Crawley, 2007; Pello & File, 1986; Rodgers & Dalvi, 1997; Rodgers et al., 1997). The apparatus consists of a 4-arm maze that is elevated 2 feet from the floor. Typically, enclosed walls surround 2 of the arms and the other 2 arms are on unprotected open platforms (Bourin et al., 2007). During EPM testing, time spent in the open, center, and closed arms are recorded (Walf & Frye, 2007). This behavioral test takes advantage of a rodent's natural tendency to explore novel environments and to avoid elevated and open areas. This test places the animal in an approach/avoidance conflict that induces the release of stress markers in rodents (Holmes et al., 2003). An animal that experiences anxiety will spend more time in the closed versus open arms as compared to a control rat that is relatively less stressed (Overstreet, 2012).

The light-dark transfer (LDT) procedure is another behavioral test that assesses anxiety-like behavior in rodents. The LDT apparatus consists of a protected and dark compartment and an unprotected and well-lit compartment. During LDT testing, time spent in the light versus dark areas of the apparatus, transitions between compartments, and total entries into each side are recorded (Bailey & Crawley, 2009). A stressed animal will spend more time in the dark side of the apparatus as compared to a control rat that is presumably less stressed. The LDT and EPM procedures are similar in that they both place the animal in an approach/avoidance situation. This dissertation will employ both EPM and LDT tests in order to provide converging lines of evidence with regard to our assessments of anxiety-like behavior produced by nicotine withdrawal. These tests are an important addition to our experimental design, given that the CPA procedure does not provide explicit information about the nature of the aversive state produced

with nicotine withdrawal.

Previous research has shown that animals experiencing nicotine withdrawal display an increase in anxiety-like behavior (Bruijnzeel et al., 2012; O'Dell, 2009). For example, both precipitated and spontaneous nicotine withdrawal produces an increase in time spent in the closed arm of the EPM relative to control rats (Chae et al., 2007; Irvine et al., 2001; Jonkman et al., 2008; Tejeda et al., 2012; Wilmouth & Spear, 2006). Nicotine withdrawal has also been shown to produce an increase in time spent in the dark side of the LDT apparatus as compared to control rats (Jonkman et al., 2005; Stoker et al., 2008). These reports suggest that nicotine withdrawal produces an increase in anxiety-like behavior that can be assessed using both EPM and LDT procedures.

1.7 Rodent models of diabetes

Diabetes is a complex disease that can be studied using an array of animal models. The underlying characteristic of Type 1 diabetes is a lack of insulin production from the pancreas. Various approaches have been used to study Type 1 diabetes, including genetic, viral, or chemical induction of a diabetic state. One of the most common approaches in diabetes research involves chemical induction of hypoinsulinemia via administration of streptozotocin (STZ). This compound has a similar structure to glucose, and as a result, is taken up via glucose (Type 2) transporters that are highly concentrated on insulin-producing beta cells in the pancreas. Once inside the cell, STZ causes DNA alkylation and activation of PARP-1, which depletes NAD+ and produces cell death (Sandler & Swenne, 1983). Since STZ is toxic to these cells, it produces a profound decrease in insulin (hypoinsulinemia) and a concomitant increase in blood glucose (hyperglycemia). This compound is a widely used and reliable method for studying diabetes in rodents (Artinano & Castro, 2009; Lee et al., 2010).

The underlying characteristic of Type 2 diabetes is insulin resistance that also results in elevated blood glucose levels. Various types of approaches are used to study Type 2 diabetes, involving selective breeding or consumption of a high-fat diet (HFD) regimen. Chronic administration of a HFD regimen produces obesity, hyperinsulinemia, and hyperglycemia (Baladi et al., 2011; Winzell & Ahren, 2004; Woods et al., 2003). The percentage of fat content and the length of the regimen are important factors that influence the development of insulin resistance. The standard HFD regimen consists of >30% fat content with a regimen that lasts 4-20 weeks to establish insulin resistance (Baladi et al., 2011; Buettner et al., 2007).

Although there are several different approaches to induce a diabetic state in rodents, this dissertation will employ the STZ model for the following reasons. First, the STZ model provides a rapid induction of hypoinsulinemia that is well characterized in our laboratory. Second, the present dissertation studies will extend previous work in our laboratory showing that STZ-treated rats display greater nicotine self-administration as compared to vehicle controls (O'Dell et al., 2014). This study suggests that the rewarding effects of nicotine are enhanced in rodent models involving a disruption in insulin signaling. However, it remains unclear whether STZ administration would produce an enhancement in the aversive effects of high doses of nicotine and/or negative affective states or physical signs produced by nicotine withdrawal.

1.8 Dissertation aims and hypotheses

This dissertation will utilize place-conditioning procedures to compare both the rewarding effects of nicotine (CPP) and the aversive effects of nicotine withdrawal (CPA) in vehicle- and STZ-treated rats. Previous studies have focused primarily on the rewarding effects of nicotine. Since place-conditioning procedures assess both rewarding properties and aversive states in the same experimental procedure, this dissertation expands previous work by comparing

both nicotine reward and withdrawal in a rodent model of diabetes. In addition, the application of place conditioning procedures allows for concomitant assessment of the physical signs of withdrawal during conditioning in the CPA study. This dissertation also expands previous work by comparing anxiety-like behavior produced by nicotine withdrawal in a rodent model of diabetes.

This dissertation is organized into 2 Specific Aims that compare the rewarding effects of nicotine (Aim 1) and the negative effects of nicotine withdrawal (Aim 2) in vehicle- and STZ-treated rats. Aim 1 examined place-conditioning produced by various doses of nicotine in vehicle- and STZ-treated rats. Aim 2 utilized CPA procedures to compare the aversive effects of nicotine withdrawal in vehicle- and STZ-treated rats. CPA and physical signs were examined in nicotine-dependent rats following administration of the nicotine receptor antagonist mecamylamine to precipitate withdrawal. Aim 2 also utilized EPM and LDT procedures to compare anxiety-like behavior produced by nicotine withdrawal in vehicle- and STZ-treated rats.

A schematic of the hypothesized results for Aim 1 and Aim 2

Aim 1: To characterize the rewarding effects of nicotine in a rodent model of diabetes.		
Behavioral changes produced by the rewarding effects of nicotine in healthy and STZ-treated rats	**Vehicle** 	**STZ** 
Aim 2: To characterize the aversive effects of nicotine withdrawal in a rodent model of diabetes.		
Behavioral changes produced by the aversive effects of nicotine withdrawal in healthy and STZ-treated rats	**Vehicle** 	**STZ** 

Our hypotheses for Aims 1 and 2 are shown in the diagram to the right. The goal of Aim 1 was to characterize place-conditioning produced by nicotine in a rodent model of diabetes. Our hypothesis was that STZ-treated rats will display greater rewarding effects of nicotine as compared to controls. Our hypothesis was based on previous studies in our laboratory showing that STZ-treated rats display higher levels of nicotine self-administration as compared to vehicle controls (O'Dell et al., 2014). The goal of Aim 2 was to characterize the

aversive effects of nicotine withdrawal in a rodent model of diabetes. Our hypothesis was that STZ-treated rats would display greater aversive effects of nicotine withdrawal as compared to vehicle controls. To our knowledge, there are no pre-clinical reports that have compared the negative affective states produced by nicotine withdrawal in a rodent model of diabetes. Therefore, our hypothesis is based largely on clinical studies that have revealed that individuals with diabetes display higher levels of anxiety and depression, and they also have a harder time quitting smoking (Eliasson et al., 1997; Fan et al., 2013; Haire-Joshu et al., 1994; Spangler et al., 2001).

Chapter 2: Methods

2.1 Subjects

Male Wistar rats were obtained from an out-bred stock of animals (Envigo, Inc., Indianapolis, IN). Each experimental group consisted of rats from distinct litters that were housed in a humidity- and temperature-controlled (22°C) vivarium on a 12-hr light/dark cycle (lights off at 8:30 am and on at 8:30 pm). The rats were group-housed with 2-3 same sex littermates. All of our procedures were approved by our Institutional Animal Care and Use Committee.

2.2 Overall design

This dissertation consisted of 3 studies that were conducted in separate cohorts of rats. The objectives of Aim 1 were examined in Study 1, and the objectives of Aim 2 were examined in Studies 2 and 3. Specifically, Study 1 compared place-conditioning produced by nicotine using CPP procedures in vehicle- and STZ-treated rats. Study 2 compared the aversive effects of nicotine withdrawal using CPA procedures in vehicle- and STZ-treated rats. The physical signs of withdrawal were also assessed on the last 2 days of conditioning following saline and mecamylamine administration. An additional group of STZ-treated rats that did not receive nicotine exposure were conditioned in the CPA procedure in order to examine the effects of mecamylamine alone in STZ-treated rats. Study 3 compared anxiety-like behavior produced by nicotine withdrawal in vehicle- and STZ-treated rats.

In each study, the rats first received vehicle (citrate buffer) or STZ (45 mg/kg; expressed as salt) administration. Fresh solutions of STZ were prepared for each cohort, and the drug was administered within 15 min of preparation. Glucose levels were monitored every other day after STZ administration. A small sample of blood was expressed on a test strip that was inserted into

a glucometer that is appropriate for rodent blood plasma (AlphaTRAK, Abbott Laboratories, Inc.). STZ increased glucose levels within approximately 3-5 days after STZ administration within a range of approximately 250-550 mg/dL. Animals that displayed average glucose levels higher than 550 mg/dL were eliminated from our analysis. Vehicle-treated rats displayed glucose levels in a range of approximately 120-160 mg/dL. The rats were conditioned and tested approximately 2 weeks after vehicle or STZ administration.

2.3 Place conditioning procedures

Our conditioning chambers consisted of 2 distinct compartments of equal proportions (76 × 24 × 30 cm) that were separated by a removable solid partition. There were 1-way mirrors on the front walls to allow for behavioral observations. One compartment had black walls with pine bedding beneath a smooth Plexiglas® floor with small holes. The other compartment had black and white stripped walls with a mixture of pine bedding and blue paper chips beneath a textured Plexiglas® floor with small holes. Both compartments were equally illuminated, and there was continuous white noise (0-20 kHz) in the room to minimize any disturbances from outside the test area.

This dissertation employed a biased procedure that consisted of 3 phases: an initial pre-test, 8 conditioning days, and a final post-test. The conditioning phase consisted of 4 drug pairings and 4 saline pairings. In order to test for preference behavior, the solid partition that separated the compartments was removed and replaced with a partition that had an opening in the center (8 × 8 cm high). The rats were allowed to shuttle freely between the compartments for 15 min. Rats that displayed an initial preference of greater than 65% were eliminated from the study. Five days after the initial preference test, the 8-day conditioning phase of the study was initiated using 30-min sessions. The day after the last conditioning session, the rats were re-

tested for shifts in preference behavior for 15 min. In each study, the order of drug treatment was counterbalanced within treatment groups such that some rats received drug on the first day of conditioning and the other half of rats received drug on the second day of conditioning.

Study 1 compared CPP produced by various doses of nicotine in vehicle- and STZ-treated rats. During conditioning, separate groups of rats received either saline (n=7 vehicle; n=5 STZ) or various doses of nicotine (0.1 [n=6 vehicle; n=6 STZ], 0.2 [n=11 vehicle; n=9 STZ], 0.4 [n=9 vehicle; n=12 STZ], or 0.8 [n=8 vehicle; n=6 STZ] mg/kg). Immediately following the injection, the rats were placed into their initially non-preferred side for 30 min. (-)Nicotine-hydrogen tartrate (Sigma Aldrich, Inc.) was dissolved in 0.9% sterile saline and administered subcutaneously in a volume of 1 ml/kg (expressed as base). The range of nicotine doses was selected based on previous research in our laboratory employing CPP procedures with adult rats (Torres et al., 2008).

Study 2 compared CPA produced by nicotine withdrawal in vehicle- and STZ-treated rats. Twelve days after vehicle or STZ administration, the rats were anesthetized (1-3% isoflurane) and surgically prepared with an osmotic pump (Alzet model 2ML2, Durect Corporation, Inc.) that delivered nicotine (3.2 mg/kg/expressed as base) for 14 days. An additional group of STZ-treated rats were given a sham surgery and did not receive nicotine exposure in order to examine the effects of mecamylamine alone in STZ-treated rats. The concentration of nicotine in the pump was adjusted based on the animals' weight on the day of surgery. Two days after surgery, the rats were tested for their initial preference behavior. Five days later, separate groups of nicotine-exposed rats received subcutaneous administration of either saline (n=14 vehicle; n=8 STZ) or various doses of mecamylamine (0.75 [n=13 vehicle; n=5 STZ], 1.5 [n=14 vehicle; n=8 STZ], or 3.0 [n=12 vehicle; n=7 STZ] mg/kg/expressed as

salt) to precipitate withdrawal in their initially preferred side. The STZ-treated rats that did not receive nicotine pumps were conditioned with the highest doses of mecamylamine (1.5 [n=7 STZ] or 3.0 [n=7 STZ] mg/kg). (-)Mecamylamine hydrochloride (Sigma Aldrich, Inc.) was dissolved in sterile 0.9% saline solution and administered in a volume of 1 ml/kg. The range of mecamylamine doses was chosen based on previous studies showing that these doses precipitate physical signs and negative affective states during nicotine withdrawal in healthy adult rats (O'Dell et al., 2006; 2007).

The physical signs of withdrawal were compared on the last 2 days of conditioning following saline or mecamylamine administration. Somatic signs were recorded by an observer that was blind to the animals' treatment condition. The frequency of occurrence of the following signs was recorded for 10 min: eye blinks, body shakes, gasps, yawns, headshakes, ptosis, and teeth chattering. Multiple successive counts of any sign required a distinct pause between episodes. If present continuously, ptosis was counted only once.

2.4 Anxiety-like behavior assessments

Study 3 compared anxiety-like behavior produced by nicotine withdrawal using EPM and LDT procedures. The EPM apparatus consists of 4 arms (10 × 50 cm) that are elevated to a height of 50 cm above the ground. The closed arm of the EPM has 20 cm high walls around it and the open arms do not have walls to enclose the open arm platform. The LDT apparatus consists of a Plexiglas® box that is separated into a light side (25 × 25 × 35cm) and a smaller but connected dark side (25 × 25 × 23 cm) with an opening (10 × 10 cm) in the center that allows the rat to move freely between both sides.

Fourteen-days after vehicle or STZ administration, the rats were implanted with osmotic pumps that delivered nicotine for 14 days, as described above. Anxiety-like behavior produced

by nicotine withdrawal was compared following 7 days of nicotine exposure using EPM procedures and again following 14 days of nicotine exposure using LDT procedures. During each test, separate groups of vehicle- or STZ-treated rats received subcutaneous administration of either saline (n=15 vehicle; n=9 STZ) or the 1.5 mg/kg (n=9 vehicle; n=9 STZ) or 3.0 mg/kg (n=9 vehicle; n=9 STZ) dose of mecamylamine. For the EPM test, the rats were first acclimated to the testing room in a rectangular Plexiglas® cage for 10 min, and then they received saline or mecamylamine administration. Ten min later, they were placed in the center of the EPM apparatus facing the open arm. Time spent in the closed versus open arms was recorded for 5 min. For the LDT test, the rats were re-acclimated to the testing room in a rectangular Plexiglas® cage for 10 min, and then received saline or mecamylamine administration. Ten min later, they were placed into the dark side of the LDT apparatus. Time spent in the light versus dark side of the apparatus was recorded for 5 min. Both the EPM and LDT test chambers were located in the middle of their respective testing rooms beneath a red light. Each apparatus was thoroughly cleaned with 70% ethanol and then water between each test.

2.5 Statistical approach

With regard to dependent variables, pre- and post-test scores were compared to assess shifts in time spent in initially non-preferred side following nicotine administration (Study 1) or in the initially preferred side following mecamylamine administration (Study 2). CPP was operationally defined as a significant increase in time spent on the initially non-preferred side after conditioning, whereas CPA was defined as a decrease in time spent on the initially preferred compartment after conditioning. Mean total signs of withdrawal were compared following saline versus mecamylamine administration in nicotine-exposed and nicotine-naïve rats. Time spent in the open versus closed arm of the EPM apparatus and light versus dark side

of the LDT apparatus (Study 3) were compared in vehicle- and STZ-treated rats. Anxiety-like behavior was operationally defined as a significant increase in time spent in the closed arm of the EPM or the dark side of the LDT as compared to controls. Blood glucose levels were compared across groups after the post-test in Study 1 and 2. Average glucose levels were compared across treatment groups during the EPM and LDT tests in Study 3.

With regard to our statistical approach, the place conditioning data were analyzed using a mixed-measures ANOVA with day as a within subject factor (pre- versus post-test) and dose of nicotine or mecamylamine, state (vehicle versus STZ or nicotine exposed versus naïve) as between subject factors. A trend analyses was used to assess the curvature of the CPP dose-response curve and the linearity of CPA with increasing doses of mecamylamine. The physical signs of withdrawal were analyzed using day as a within-subjects factor (saline versus mecamylamine) and dose (mecamylamine) and state (vehicle or STZ) as between subject factors. For the additional group of STZ-treated rats that did not receive nicotine exposure, these data were analyzed using day as within-subjects factor (saline versus mecamylamine) and dose (mecamylamine) and state (nicotine exposed versus naïve) as between subject factors. For anxiety-like behavior, the data were analyzed using 2-way ANOVA with dose of mecamylamine and state (vehicle or STZ) as between subject factors. Subsequent planned comparisons were assessed between groups using a Bonferonni correction factor that reduced our p value to an appropriate level based upon the number of comparisons that were made in each figure. Glucose levels were compared using 2-way ANOVA with dose (nicotine or mecamylamine) and state (vehicle or STZ) as between subject factors.

Chapter 3: Results

3.1 CPP

Figure 1 reflects CPP produced by nicotine in vehicle- and STZ-treated rats from Study 1. Although our CPP curves did appear to be an inverted U-shape, our quadratic trend analysis did not reach statistical significance (p=0.94). A subsequent ANOVA analysis revealed a significant interaction between day and state [F(1,69) = 4.7, $p\leq0.05$], with STZ-treated rats displaying a larger upward shift in time spent in their initially non-preferred side as compared to vehicle-treated controls. Indeed, a significant increase in time spent in the initially non-preferred compartment was observed in vehicle-treated rats that received the 0.2 mg/kg dose and STZ-treated rats that received the 0.2 and 0.4 mg/kg dose of nicotine (*$p\leq0.01$).

3.2 CPA

Figure 2 reflects CPA produced by nicotine withdrawal in vehicle- and STZ-treated rats from Study 2. Our linear trend analysis revealed that nicotine withdrawal produced CPA that increased across mecamylamine doses in a linear manner in both treatment groups ($p\leq0.05$). Our subsequent ANOVA analysis revealed a significant interaction between day and dose [F(3,73) = 3.1, $p\leq0.05$], indicating that higher doses of mecamylamine produced a larger magnitude CPA. Indeed, a significant decrease in time spent in the initially preferred compartment was observed in vehicle-treated rats that received the 3.0 mg/kg dose and STZ-treated rats that received the 1.5 and 3.0 mg/kg dose of mecamylamine (*$p\leq0.01$). A separate control group of STZ-treated rats were included that did not receive nicotine exposure (data not shown). In the absence of nicotine, mecamylamine did not produce a decrease in time spent in the initially preferred compartment (1.5 mg/kg dose of mecamylamine pre-test value $\overline{x}$=506.6±16.7 and post-test value $\overline{x}$=476.0±45.0; 3.0 mg/kg dose of mecamylamine pre-test value $\overline{x}$=529.0±16.0 and post-test

value $\overline{x}$=526.8±55.1). These data show that the effects of mecamylamine in STZ-treated rats are uniquely exacerbated in nicotine-dependent rats.

3.3 Physical signs

Figure 3 reflects the total physical signs of withdrawal (top panel) and individual counts of body shakes (bottom panel) in vehicle- and STZ-treated rats from Study 2. Our analyses revealed a significant interaction of day, state, and dose [$F(3,68) = 3.7$, $p \leq 0.05$], indicating that the physical signs of withdrawal were dose-dependently increased in STZ- versus vehicle-treated rats. Specifically, a significant increase in physical signs was observed in vehicle-treated rats following administration of the 1.5 and 3.0 mg/kg dose of mecamylamine and STZ-treated rats that received the 1.5 and 3.0 mg/kg dose of mecamylamine (*$p \leq 0.01$). Importantly, the magnitude of this effect was larger in STZ-treated rats that received the 3.0 mg/kg dose as compared to vehicle-treated controls (†$p \leq 0.01$).

Our analyses of body shakes revealed a significant interaction of day, state, and dose [$F(3,68) = 2.9$, $p \leq 0.05$], indicating that body shakes were dose-dependently higher in STZ- versus vehicle-treated rats during withdrawal. Specifically, a significant increase in body shakes was observed in STZ-treated rats that received the 3.0 dose of mecamylamine (*$p \leq 0.01$), and the magnitude of this effect was larger in STZ- versus vehicle-treated controls (†$p \leq 0.01$).

A separate control group of STZ-treated rats were included that did not receive nicotine exposure (data not shown). Our analysis revealed that in the absence of nicotine, there was no difference in the total physical signs of withdrawal following saline (1.5 mg/kg treatment group $\overline{x}$=4.3±0.6; 3.0 mg/kg treatment group $\overline{x}$=5.1±1.7) or mecamylamine (1.5 mg/kg dose of mecamylamine, $\overline{x}$=4.9±1.1; 3.0 mg/kg dose of mecamylamine, $\overline{x}$=3.6±0.9) administration during the last 2 days of conditioning. These data show that the effects of mecamylamine in STZ-treated

rats are uniquely exacerbated in rats that received nicotine exposure.

3.4 EPM

Figure 4 reflects the percent time spent in the closed arms of the EPM. Our trend analysis revealed that nicotine withdrawal increased time spent in the closed arms in a linear manner with increasing doses of mecamylamine in STZ-treated rats (linear trend; $p \leq 0.05$). Subsequent analyses revealed a significant interaction of state and dose [$F(2,54) = 7.5$, $p \leq 0.05$], indicating that STZ- treated rats displayed a dose-dependent increase in time spent in the closed arms of the EPM. Indeed, a significant increase in time spent in the closed arms was observed in vehicle-treated rats that received the 3.0 mg/kg dose and STZ-treated rats that received the 1.5 and 3.0 mg/kg dose of mecamylamine as compared to their respective saline controls ($*p \leq 0.02$). Importantly, the magnitude of this effect was larger in STZ-treated rats that received the 1.5 mg/kg dose of mecamylamine as compared to vehicle-treated controls ($\dagger p \leq 0.02$).

3.5 LDT

Figure 5 reflects the percent time spent in the dark area of the LDT. Our trend analysis revealed that the mecamylamine elicited a linear increase in time spent in the dark area with increasing doses of mecamylamine ($p \leq 0.05$). Subsequent analyses revealed a main effect of dose [$F(2,54) = 10.6$, $p \leq 0.05$], indicating that mecamylamine produced an increase in time spent in the closed area of the LDT. Although we did not observe an overall interaction, subsequent planned comparisons revealed a significant increase in time spent in the closed area of the LDT in vehicle-treated rats that received the 3.0 mg/kg dose and STZ-treated rats that received the 1.5 and 3.0 mg/kg dose of mecamylamine ($*p \leq 0.02$). The magnitude of this effect was larger in STZ-treated rats that received the 1.5 mg/kg dose as compared to their respective vehicle-treated controls ($\dagger p \leq 0.02$).

3.6 Glucose levels

Table 1 reflects glucose values during the post-test days in Study 1 and 2 and the average levels following the EPM and LDT tests in Study 3. Overall, STZ produced a significant increase in glucose levels that was similar across treatment conditions in each study. For Study 1 and 2, our analyses revealed a main effect of state, with STZ-treated rats displaying higher glucose levels as compared to vehicle-treated controls regardless of their nicotine dose in Study 1 [$F(1,69) = 761.5$, $p \leq 0.01$] or mecamylamine treatment in Study 2 [$F(1,73) = 931.2$, $p \leq 0.01$]. For Study 3, our analyses also revealed a main effect of state, with STZ-treated rats displaying higher glucose levels as compared to vehicle-treated rats during the EPM and LDT tests [$F(1,54) = 799.4$, $p \leq 0.01$].

Table 1. Plasma glucose values (mg/dL)

Study 1: Nicotine doses (mg/kg)	**Vehicle**	**STZ**
0	152.0 ± 9.3	459.8 ± 28.0*
0.1	118.3 ± 3.4	466.1 ± 39.2*
0.2	142.9 ± 10.0	494.2 ± 31.1*
0.4	124.8 ± 5.6	480.3 ± 13.3*
0.8	121.1 ± 7.2	482.0 ± 25.4*
Study 2: Mecamylamine doses (mg/kg)		
0	137.5 ± 5.5	468.3 ± 17.8*
0.75	155.5 ± 7.1	495.2 ± 16.1*
1.5	159.2 ± 6.4	445.1 ± 21.2*
3.0	151.0 ± 7.3	334.4 ± 29.8*
Study 3: Mecamylamine doses (mg/kg)		
0	132.0 ± 3.1	451.6 ± 32.6*
1.5	126.1 ± 3.8	460.9 ± 16.0*
3.0	142.3 ± 5.0	513.1 ± 12.8*

The asterisks (*) denote a significant difference between vehicle- and STZ-treated rats ($p \leq 0.01$).

Chapter 4: Discussion

4.1 Summary

The major findings of this report is that STZ-treated rats experience greater rewarding effects of nicotine and aversive effects of withdrawal as compared to vehicle-treated controls. CPP was observed across a wider range of doses of nicotine in STZ- versus vehicle-treated rats. CPA produced by nicotine withdrawal was observed at a lower dose in STZ- versus vehicle-treated rats. Also, the physical signs of withdrawal were greater in STZ- versus vehicle-treated rats. Lastly, the explicit nature of the aversive effects of nicotine withdrawal are likely related to an increase in anxiety-like behavior in STZ-treated rats. Together, our results suggest that diabetes enhances both the rewarding effects of nicotine and negative affective states and physical signs produced by nicotine withdrawal.

4.2 STZ-treated rats experience strong rewarding effects of nicotine

Our results revealed that nicotine produced CPP in a pattern and dose range consistent with previous work from our laboratory and others (Fudala et al., 1985; Janhunen et al., 2005; Le Foll & Goldberg, 2005; Torres et al., 2009). Importantly, CPP produced by nicotine was observed across a wider range of doses in STZ- versus vehicle-treated rats. This finding suggests that the rewarding effects of nicotine are enhanced in a rodent model of diabetes. Consistent with the latter suggestion, previous work in our laboratory demonstrated that STZ-treated rats display higher levels of nicotine intake in an extended self-administration procedure as compared to vehicle-treated controls (O'Dell et al., 2014). Also, previous studies revealed that rats that were fed a HFD regimen and were insulin-resistant displayed CPP at a dose of nicotine that did not produce this effect in rats that were not insulin resistant (Richardson et al., 2014). Both our IVSA and CPP data provide converging lines of evidence that the rewarding effects of nicotine are

enhanced in an animal model of diabetes. It is important to note that one report revealed that mice placed on a HFD regimen did not display nicotine CPP (Blendy et al., 2005). However, one possibility that might explain the discrepancy between the Richardson and Blendy et al. studies is that the mice in the Blendy study were not insulin resistant. The discrepancy in the CPP data may also be related to differences in nicotine metabolism between rats and mice and/or different doses of nicotine and routes of administration that were used. Together, the results from this dissertation and previous reports suggest that diabetes enhances the rewarding effects of nicotine via a disruption in insulin signaling.

4.3 STZ-treated rats display strong aversive effects of withdrawal

Our results revealed that STZ-treated rats display greater aversive effects of nicotine withdrawal as compared to controls using CPA procedures. Furthermore, increasing doses of mecamylamine elicited a larger magnitude of CPA, which is consistent with previous results from our laboratory and others (O'Dell et al., 2007; Shram et al., 2008). Importantly, CPA was observed across a wider range of doses and at a lower dose of mecamylamine in STZ- versus vehicle-treated rats. These data suggest that STZ-treated rats are more sensitive to the aversive effects of nicotine withdrawal. To our knowledge, the aversive effects of nicotine withdrawal have not been investigated in an animal model of diabetes. Thus, our findings provide a novel contribution to the literature regarding nicotine withdrawal in diabetic rats.

4.4 STZ-treated rats display intense physical signs of withdrawal

Another finding of this dissertation is that the physical signs of withdrawal were greater in STZ- versus vehicle-treated rats. As previously mentioned, nicotine withdrawal produces both physical signs and negative affective states that contribute to continued tobacco use and relapse behavior. Previous review papers have suggested that negative affective states produced by

withdrawal play a larger role in continued use and relapse to smoking as compared to the physical symptoms produced by nicotine withdrawal (Koob et al., 1993; Markou et al., 1998). However, a comparison of the magnitude of our group differences between affective tests of withdrawal versus physical signs, revealed that the largest effects observed in STZ-treated rats was in our assessment of the physical signs of withdrawal. These data suggest that persons with diabetes may experience intense physical symptoms during nicotine withdrawal that may promote tobacco use in this population. Indeed, there are significant negative health complications associated with diabetes, such as neuropathic pain (Holt et al., 2010) that may exacerbate the use of tobacco to cope with pain and other peripheral neuropathies. Thus, the intense physical effects of nicotine withdrawal might explain why diabetic persons have a harder time quitting smoking in comparison to persons that use tobacco but are not diabetic.

4.5 STZ-treated rats experience greater anxiety-like behavior during nicotine withdrawal

Our EPM and LDT results revealed that nicotine withdrawal produced an increase in anxiety-like behavior that was larger in STZ- versus vehicle-treated rats. When the EPM test was conducted after 7 days of nicotine exposure, our results revealed that withdrawal produced an increase in anxiety-like behavior that was larger in STZ- versus vehicle-treated rats. These data suggest that STZ-treated rats display anxiety-like behavior at an earlier time point of nicotine dependence as compared to vehicle-treated rats. Notably, our largest group differences were at the intermediate dose of mecamylamine. One possible explanation for this outcome is that STZ-treated rats that received high doses of mecamylamine may have experienced physical stress or motor impairments that may have influenced our behavioral assessments. In summary, the EPM and LDT provide a deeper understanding of our CPA results because they suggest that the increase in the negative affective states observed in STZ-treated rats is related to an enhancement

of anxiety-like states. Thus, our results suggest that diabetes enhances the negative affective states produced by nicotine withdrawal.

4.6 Potential mechanisms and future directions

There are several mechanisms that might modulate the strong behavioral effects of nicotine withdrawal in STZ-treated rats. One likely candidate is dopamine transmission in the mesolimbic pathway, which originates in the ventral tegmental area and terminates in the nucleus accumbens (NAcc; Deveto & Flore, 2006; Koob & Kreek, 2007; Wanat et al., 2009). Previous work has shown nicotine withdrawal produces a decrease in dopamine release in the NAcc in healthy adult rats (Natividad et al., 2010; Zhang et al., 2012). A recent study in our laboratory demonstrated that STZ-treated rats display lower basal dopamine levels in the NAcc (O'Dell et al., 2014). Thus, the possibility exists that the decreases in NAcc dopamine levels that modulate nicotine withdrawal are exacerbated in STZ-treated rats that already display suppressed basal dopamine transmission. Future studies are needed to examine whether reduced dopamine levels promote the aversive effects of withdrawal in rats that display a disruption in insulin signaling. Indeed, we recently hypothesized that enhanced tobacco use in persons with diabetes is likely mediated via a suppression of dopamine signaling in the mesolimbic pathway (O'Dell & Nazarian, 2016). Or hypothesis was based largely on recent theories suggesting that deficits in the brain dopamine system weaken inhibitory control of excessive pleasure seeking that result in an increased sensitivity to drugs of abuse (George et al., 2011; Melis, Spiga, & Diana, 2005). Future studies are needed to examine whether compulsive tobacco use in persons with diabetes is related to overcompensation for a reward deficiency syndrome that is rooted in suppressed dopamine neurotransmission. Ongoing work in our laboratory is examining whether insulin replacement normalizes the strong rewarding effects of nicotine in rodent models of diabetes.

4.7 Clinical implications

There are several clinical implications from this dissertation. First, our results suggest that persons with diabetes experience intense rewarding effects of nicotine and heightened sensitivity to nicotine withdrawal during smoking abstinence. Thus, the strong rewarding effects of nicotine likely promote the initiation and continued use of tobacco in persons with diabetes. Also, clinical reports have shown individuals with diabetes display low tobacco cessation rates and a diminished readiness to quit smoking (Fan et al., 2013; Solberg et al., 2004). They also display high levels of negative affect, depression, and stress compared to non-diabetic smokers (Haire-Joshu et al., 1994; Spangler et al., 2001). Thus, intense aversive states of nicotine withdrawal might promote smoking behavior during the maintenance and abstinence phases of tobacco dependence in persons with diabetes. Lastly, diabetes may produce dopamine deficits that are self-medicated with substances that increase dopamine, such as nicotine in tobacco products. As a result, treatment strategies that normalize dopamine transmission may be effective for smoking cessation in persons with diabetes. Future studies are needed to elucidate the underlying mechanisms by which diabetes promotes nicotine reward and withdrawal in order to develop more effective smoking cessation medications for this vulnerable population.

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Torres, O.V., Natividad, L.A., Tejeda, H.A., Van Weelden, S.A., & O'Dell, L.E. (2009). Female rats display dose-dependent differences to the rewarding and aversive effects of nicotine in an age-, hormone-, and sex-dependent manner. *Psychopharmacology* (Berl), 206:303–312.

Torres, O.V., Tejeda, H.A., Natividad, L.A., & O'Dell, L.E. (2008). Enhanced vulnerability to the rewarding effects of nicotine during the adolescent period of development. *Pharmacology Biochemistry and Behavior*, 90:658–663.

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Figure 1.

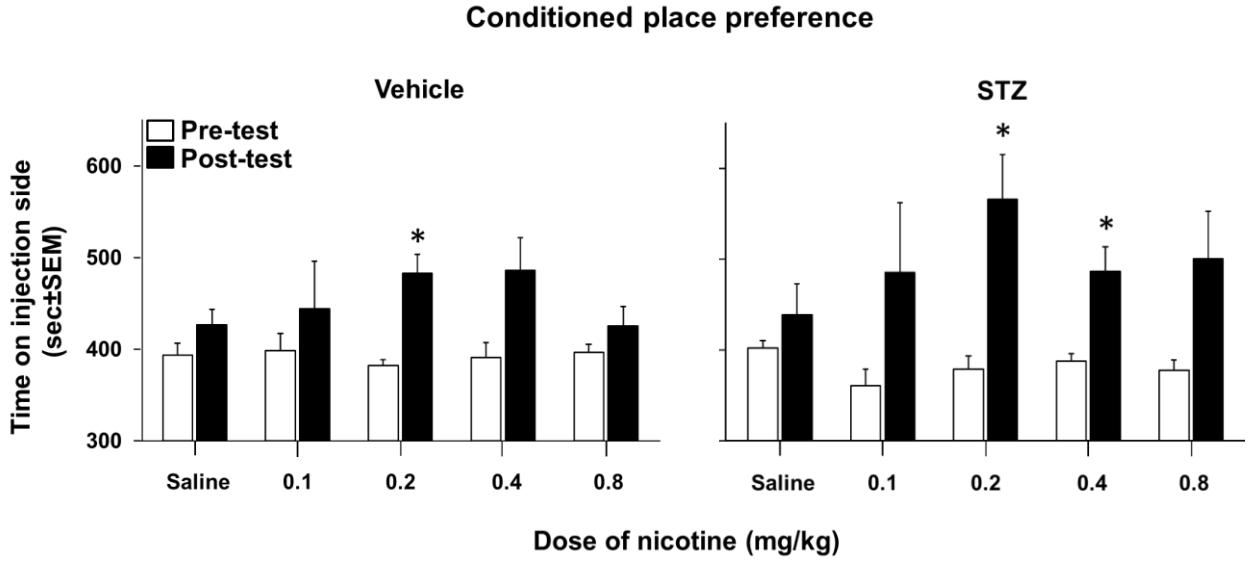

Figure 1 depicts vehicle- and STZ-treated rats that were conditioned with various doses of nicotine in Study 1. The panel reflects time spent (±SEM) in the initially non-preferred compartment before (pre-test) and after conditioning (post-test). The asterisks (*) denote a significant difference between pre- versus post-test scores ($p \leq 0.01$).

Figure 2.

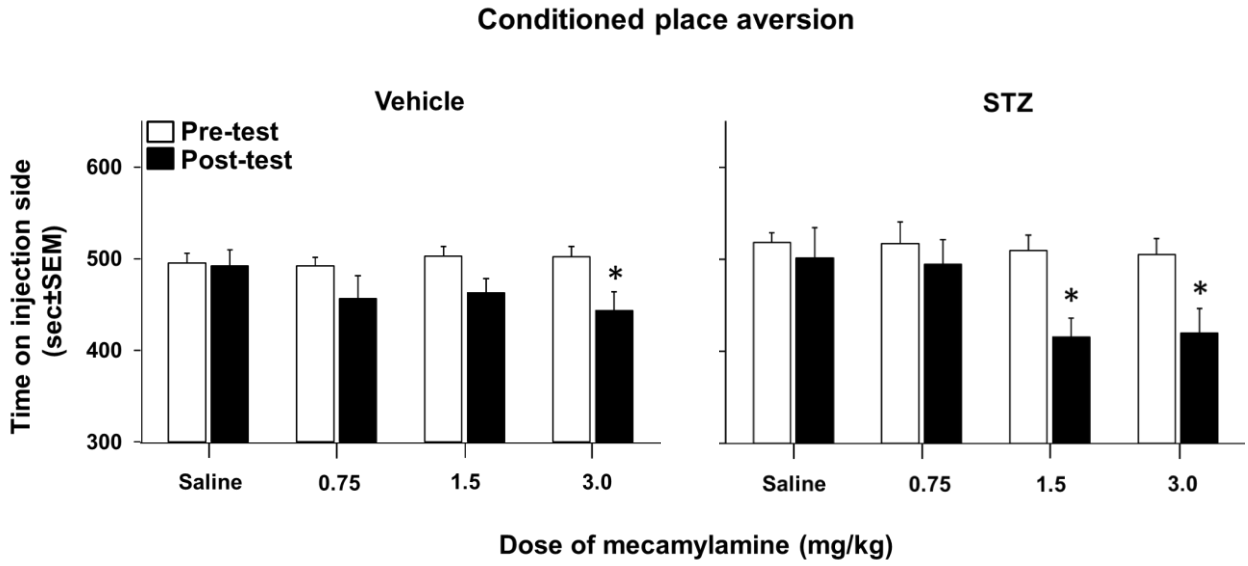

Figure 2 depicts vehicle- and STZ-treated rats that were conditioned various doses of mecamylamine in Study 2. The panel reflects time spent (±SEM) in the initially preferred compartment before (pre-test) and after conditioning (post-test). The asterisks (*) denote a significant difference between pre- versus post-test scores ($p \leq 0.01$).

Figure 3.

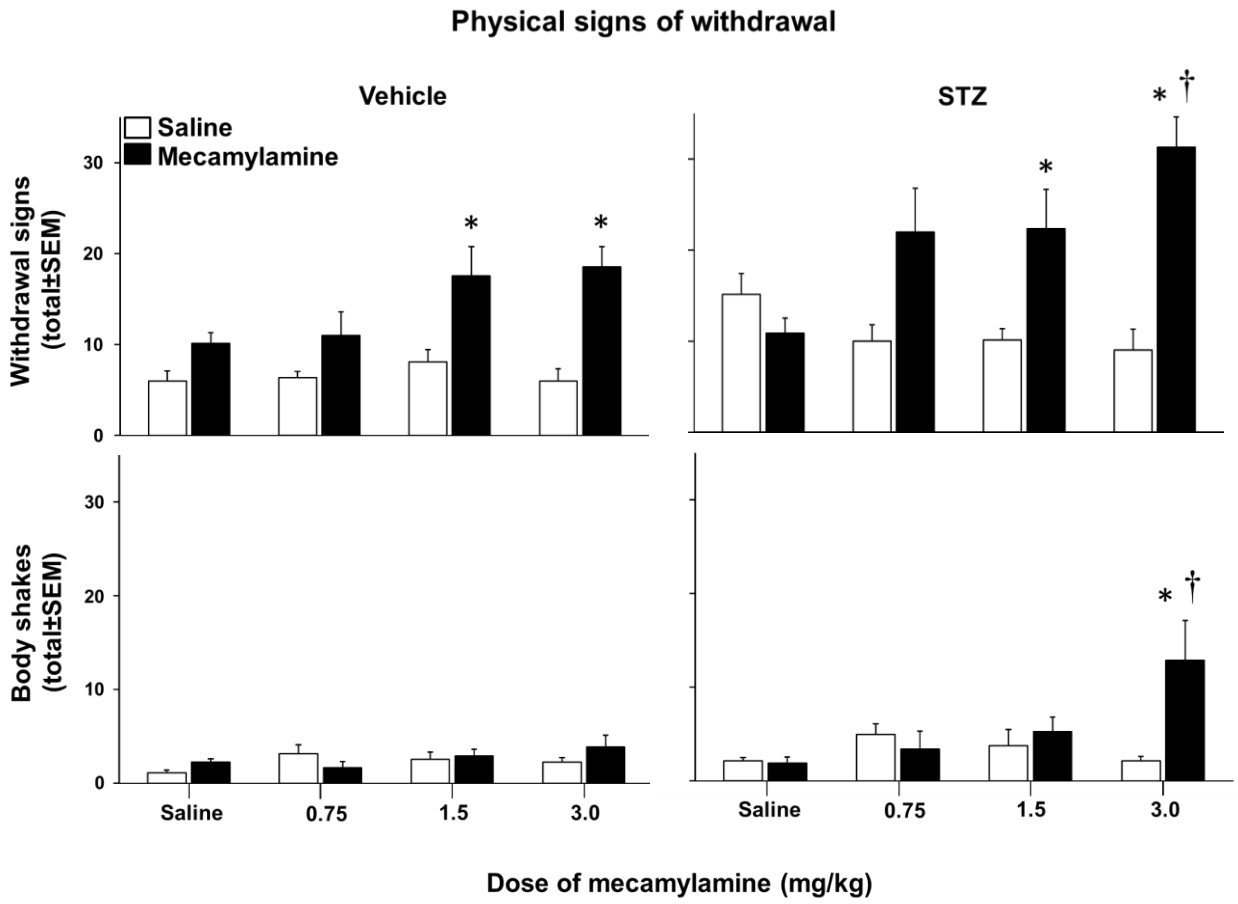

Figure 3 depicts mean total physical signs of withdrawal (top panel) (±SEM) and body shakes (bottom panel) following saline and mecamylamine administration on the last 2 days of conditioning in Study 2. The asterisks (*) denote a significant difference between saline and mecamylamine and daggers (†) denote a difference between vehicle- and STZ-treated rats ($p \leq 0.01$).

Figure 4.

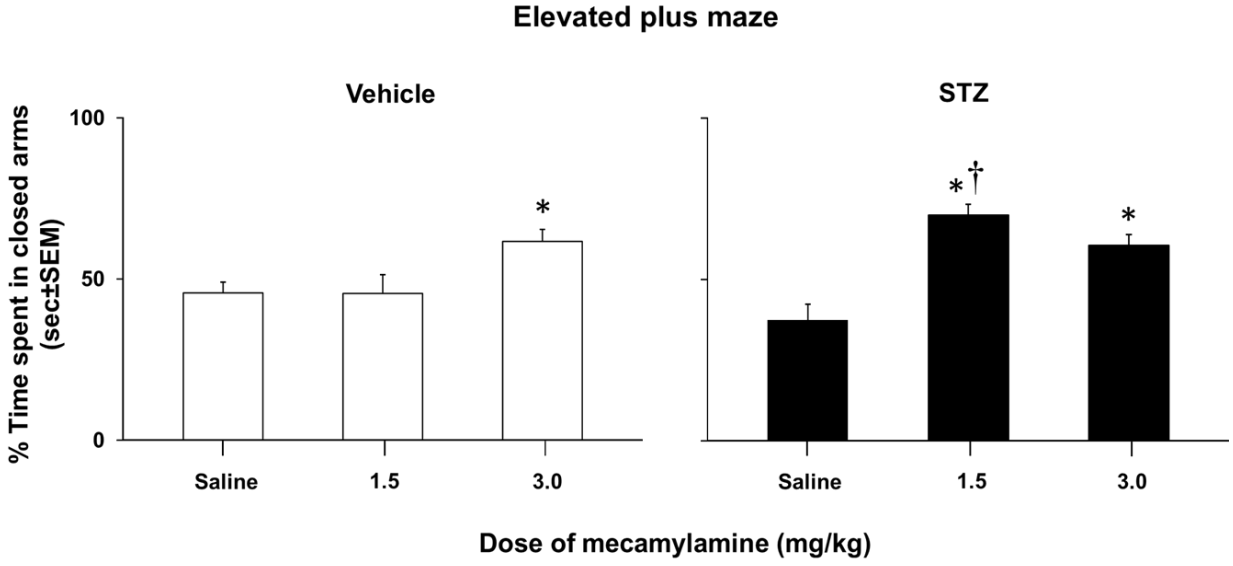

Figure 4 depicts mean percent time spent in the closed arm of the EPM (±SEM) following saline and mecamylamine administration in Study 3. The asterisks (*) denote a significant difference from saline controls and daggers (†) denote a difference between vehicle- and STZ-treated rats ($p \leq 0.02$).

Figure 5.

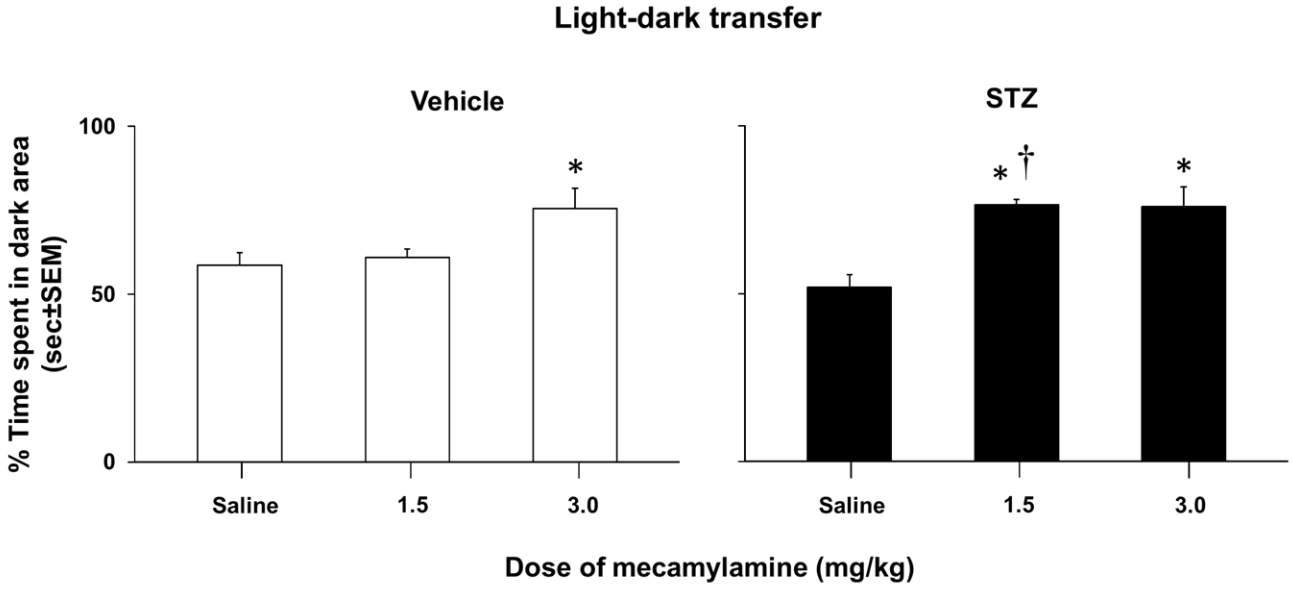

Figure 5 depicts mean percent time spent in the dark area of the LDT (±SEM) following saline and mecamylamine administration in Study 3. The asterisks (*) denote a significant difference from saline controls and daggers (†) denote a difference between vehicle- and STZ-treated rats ($p \leq 0.02$).

Curriculum Vitae

Joseph Allan Pipkin was born to Allan Lee Pipkin and Susan Pipkin in Woodland, California on September 24th, 1982. He graduated from Southwest High School in the Spring semester of 2000. He entered Imperial Valley College in the Summer semester of 2006 and immediately became interested in psychology and alcohol and drug studies. He received his Associate of Arts and Associate of Science degrees in the Summer of 2008. Thereafter, Joseph received his Bachelor of Arts in Psychology from San Diego State University in the Spring semester of 2010, with departmental honors. During his last year as an undergraduate student Joseph became interested in understanding the neuroscience of addiction. After he graduated from San Diego State University he began his graduate career at California State University, San Bernardino under the supervision of Dr. Cynthia Crawford. Her laboratory combines behavioral, biochemical and molecular techniques to study the mechanisms that mediate drug addiction. Joseph received his Master's degree in Experimental Psychology in the Fall semester of 2013. Joseph continued to follow his research interests and entered the Social, Cognition, and Neuroscience doctoral program at UTEP in the Fall of 2012 under the direct supervision of Dr. Laura E. O'Dell. Her laboratory also combines behavioral, biochemical and molecular techniques to study the mechanisms that mediate nicotine addiction in vulnerable populations, such as adolescents, females, and persons with diabetes. Joseph has published 2 first- author papers, and is co-author on 10 publications. He is also first- author on a book chapter. During his graduate career he presented 38 poster abstracts and 5 oral presentations at scientific conferences. While pursuing his degree, Joseph was also a primary instructor for 2 courses including Introduction to Psychology and Experimental Psychology.

Permanent address: 670 Lenrey Ave.
El Centro, California 92243

CURRICULUM VITAE

Joseph Allan Pipkin

Contact Information
The University of Texas at El Paso, 500 West University Avenue, Department of Psychology, El Paso, TX 79902; Tel. (760) 222-7480; E-mail: japipkin@miners.utep.edu

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Education

Ph.D., Social, Cognitive, & Neuroscience (*Prospectus Approved*) In progress
The University of Texas at El Paso, El Paso, TX.

M.A., Experimental Psychology (*Biological Psychology*) 2013
California State University, San Bernardino, San Bernardino, CA.

B.A., Psychology, San Diego State University, San Diego, CA. 2010

A.S., Alcohol and Drug Studies & A.A., Psychology 2008
(distinction in both majors), Imperial Valley College, Imperial, CA.

Credentials

Certified Addictions Treatment Counselor License
2009 (**CATC III**; Cert. # 091971), California Association for Alcohol/Drug Educators
Imperial Valley College, Imperial, CA.

Publications

1. Flores, R.J., **Pipkin, J.A.,** Uribe, K.P., Perez, A., & O'Dell, L.E. (2016). Estradiol promotes the rewarding effects of nicotine in female rats. *Behavioural Brain Research,* 307: 258-263.

2. Carcoba, L.M., Torres, O.V., **Pipkin., J.A.,** Ontiveros, T., & O'Dell, L.E. (2016). Insight into the Potential Factors That Promote Tobacco Use in Vulnerable Populations. Invited review for the journal *Current Addiction Reports,* 3: 27-36.

3. Godfrey, J., Castro, N., Olney, J.J., Dudley, J., **Pipkin, J.A.,** Jeanguenin, L., Walls, S.M., Herr, D.R., Harris, G.L., & Brasser, S.M. (2015). Chronic Voluntary Ethanol Consumption Induces Favorable Ceramide Profiles in Selectively Bred Alcohol-Preferring (P) Rats. *PLoS ONE*, 10:e0139012

4. Darcy, C.E., Luevano, J., **Pipkin, J.A.,** Castaneda, E., Gosselink, K., O'Dell, L.E., & Miranda, M. (2015). Extended access to methamphetamine self-administration up-regulates dopamine transporter levels 72 hours after withdrawal in rats. *Behavioural Brain Research*, 296: 125-128.

5. Horn-Amodeo, L.R., Greenfield, V.Y., Rios, V., **Pipkin, J.A.,** Johnson, J.D., Wang, L., and Crawford, C.A. (2015). Effects of repeated paroxetine and fluoxetine treatment on affective behavior and BDNF levels of male and female adolescent rats. *Psychopharmacology,* 232:3515-3528

6. O'Dell, L. E., Torres, O.V., Ferree, P.L., **Pipkin, J.A.,** and Carcoba, L.M. (2015). Nicotine withdrawal increases stress-associated genes in the nucleus accumbens of female rats in a hormone-dependent manner. *Nicotine & Tobacco Research*, 17: 422-430.

7. McDougall, S.A., **Pipkin, J.A.,** Der-Ghazarian, T., Cortez, A.M., Gutierrez, A., Lee, R.J., Carbajal, S.M., and Crawford, C.A. (2014). Age-Dependent Differences in the Strength and Persistence of Psychostimulant-Induced Conditioned Activity in Rats: Effects of a Single Environment-Cocaine Pairing. *Behavioural Pharmacology*, 25:695-704.

8. **Pipkin, J.A.,** Kaplan, G.J., Plant, C.P., Eaton, S.E., Gil, S.M., Zavala, A.R., & Crawford, C.A. (2014). Nicotine exposure beginning in adolescence and continuing into adulthood enhances the acquisition of methamphetamine self-administration, but not methamphetamine-primed reinstatement in male rats. *Drug and Alcohol Dependence*, 142:341-344

9. Richardson, J.R., **Pipkin, J.A.,** O'Dell, L.E., and Nazarian, A. (2014). Enhanced nicotine reward in a diet-induced model of insulin resistance in rats. *Drug and Alcohol Dependence*, 140: 205-207.

10. Carcoba, L.M., Orfilia, J.R., Natividad, L.A., Torres, O.V., **Pipkin, J.A.,** Ferree, P.L., Casteneda, E., Moss, D.E., & O'Dell, L.E. (2014). Cholinergic transmission during nicotine withdrawal is influenced by age and pre-exposure to nicotine: Implications for teenage smoking. *Developmental Neuroscience*, 36: 347-355.

11. O'Dell, L.E., Natividad, L., **Pipkin, J.A.,** Roman, F., Torres, I., Juardo, J., Torres, O.V., Friedman, T.C., Tenayuca, J.M., and Nazarian, A. (2014). Enhanced nicotine self-administration and suppressed dopaminergic systems in a rat model of diabetes. *Addiction Biology*, 19: 1006-1019.

12. **Pipkin, J.A.,** Valentine, J., Greenfield, V.Y., Rios, V., & Butt, A.E. (2011). Cholinergic modulation of reinforcement effects in a reinstatement model of drug relapse using sucrose reward. *California State University, San Bernardino, Psychology Student Research Journal, 1*(2), 30-34.

Book Chapters

1. **Pipkin, J.A.,** Ontiveros, T., Carcoba, L.M., and L.E. O'Dell. Enhanced tobacco use vulnerability in adolescents, females, and persons with diabetes. Invited chapter for a

book entitled, "Negative Affective States and Cognitive Impairments in Nicotine Dependence."

Manuscripts Submitted

1. **Pipkin, J.A.,** Hinojosa, C., Flores, R.J., Carcoba, L.M., Ibarra, M., Francis, W., Nazarian, A., & O'Dell, L.E. (2016). Both nicotine reward and withdrawal are enhanced in a rodent model of diabetes. Submitted October 5th, 2016 to *Psychopharmacology.*

Awards & Honors

Early Career Spotlight presented in El Faro, February 2014
a newsletter of the National Hispanic Science Network.

Master's Thesis Highlight presented by the
Society for Neuroscience Hot Topics Issue. November 2013

PSI CHI Regional Research Award April 2012
Awarded at the Annual Convention of the Western Psychological Association

Graduated *Magna Cum Laude* - San Diego State University (3.79 GPA)
with distinction in major (3.93 GPA) May 2010

San Diego State University-IVC
Faculty Outstanding Graduate Student Award May 2010
This award is only given to one student, based on both high GPA and extracurricular activity involvement.

PHI KAPPA PHI Honor Society, inducted April 2010

Deans list—San Diego State University Fall 2008 – Spring 2010

Golden Key International Honour Society, inducted November 2009

EOPS Academic Achievement Award
Imperial Valley College May 2008

Alcohol and Drug Studies Award-Student of the year
Imperial Valley College June 2007

Professional Research Experience

Graduate Research Assistant 2012 - Present
The University of Texas at El Paso
Department of Psychology
Supervisor: Laura E. O'Dell, Ph.D.

Projects: My projects involve the underlying behavioral, neurobiological, and neurochemical mechanisms of nicotine exposure and withdrawal, across: age groups and sex differences. I am also investigating the behavioral, neurobiological, and neurochemical mechanisms that mediate enhanced vulnerability to tobacco abuse using an animal model of diabetes.

Primary skills include: Training graduate and undergraduate research assistants, coordination and management of project meetings, literature searches, statistical analyses, and in charge of the animal colony.

Overall Lab techniques: Experienced with Coulbourn Instruments, Graphic State, SPSS, SoftMax Pro, Med-Associates, and Truscan.

Behavioral Skills Acquired: Conditioned Place Preference, Conditioned Place Aversion, Open-field, Light/Dark box.

Molecular/Neurochemical Skills Acquired: RT-PCR, High-Performance Liquid Chromatography, *in vivo* microdialysis, Enzyme-linked immunoabsorbent assay (ELISA – AChE assay).

Surgical Techniques Acquired: Proficient in a number of surgical techniques including jugular vein catheterization using subsequent back mounts of cannulae. Osmotic pump implantation. Ovariectomies (OVX). Removal of the: nucleus accumbens, hypothalamus, amygdala, hippocampus.

Graduate Research Assistant 2010 - 2012
California State University, San Bernardino
Developmental Neuropharmacology and Psychophysiology Laboratory
Supervisors: Cynthia Crawford, Ph.D. & Sanders McDougall, Ph.D.

Projects: Investigated early methylphenidate exposure on adult cocaine self-administration, effects on body temperature and In Vivo microdialysis measuring dopamine release. Also, studied the effects of effects of one-trial cocaine-induced conditioned activity in young and adult rats. Looked at D1 and D2 agonists in the Ventral Lateral Striatum on locomotor activity and stereotypy. Examined differences between fluoxetine and paroxetine during adolescent periods. And early nicotine exposure on methamphetamine acquisition, extinction, and reinstatement.

Behavioral Skills Acquired: Acquired skills in a number of behavioral techniques including subcutaneous and intraperitoneal injection of drugs, intracranial drug administration (cocaine/methamphetamine/nicotine, etc.). Drug self-administration/reinstatement, locomotor activity, elevated plus maze, sucrose water preference, sucrose-reinforced bar pressing (hand shaping), body temperature, unbiased stereology, tail flick, and hot plate. Operation of stereotaxic device, maintenance of microinjection equipment (e.g., microinfusion syringes, syringe pumps, injectors), operant chamber maintenance.

Molecular/Neurochemical Skills Acquired: In Vivo microdialysis, Immunohistochemistry (c-Fos assay).

Surgical Techniques Acquired: Proficient in a number of surgical techniques including jugular vein catheterization using subsequent head and back mounts of cannulae, as well as stereotaxic surgery with small and adult animals (intracranial cannulation) focusing on mesocorticolimbic structures (Ventral Lateral Striatum, Dorsal Striatum, Ventral Tegmental Area, Nucleus Accumbens, Ventricles). In Vivo Microdialysis probe implantation, cardiac perfusions, brain extraction—specific regions (striatum, PFC, hippocampus).

Graduate Research Assistant 2010 - 2011
California State University, San Bernardino
Neuropharmacology, Learning and Memory Laboratory
Supervisor: Allen Butt, Ph.D.

Project head on investigating sucrose-seeking behavior with Nucleus Basalis Magnocellularis 192 IgG-saporin lesions on Long-Evans rats. Investigated differences between groups with and without lesions on environmental associations on sucrose preference. Performed animal surgical procedures (e.g., Basal Forebrain), stereotaxic techniques, operant chamber maintenance, intraperitoneal and subcutaneous injections.

Surgical Skills Acquired: Stereotaxic 192 IgG-saporin lesions.

Undergraduate Research Assistant 2008 - 2010
San Diego State University - Imperial Valley Campus
Wellness in College and Community Studies (Clinical Psychology Laboratory)
Supervisor: Elizabeth Cordero, Ph.D.

Conducted experiments and managed data for studies of body image among Latino/a and Latino/a Americans. Served as co-recorder for focus groups in the evaluation of Project Juntos, a program designed to promote healthy marriage among Latino/a and Latino/a Americans.

Undergraduate Research Assistant 2009 - 2010
San Diego State University
Neuroscience Laboratory
Supervisor: Susan Brasser, Ph.D.

Investigated the effects of chronic ethanol exposure on lipid composition of biological tissues in selectively-bred alcohol-preferring (P) rats. Duties involved animal care, operant chamber maintenance, ethanol preparation, data organization and analysis.

Undergraduate Research Assistant 2009 Spring - 2009 Fall
San Diego State University - Imperial Valley Campus
Social Psychology Laboratory
Supervisor: Donna Castañeda, Ph.D.

Worked on a longitudinal study investigating the relationship between marital satisfaction and mental health among Mexican-American and European-American couples. Conducted telephone interviews of newlywed couples, computer data entry with SPSS, clerical duties (e.g., maintaining addresses, telephone numbers, and scheduling appointments).

Clinical Experience

Fresh Start Outreach Community Services 2010 - 2011
Supervisor: Richard Hernandez

I was Director of alcohol and drug services, head group facilitator, mentor, and in charge of training future group facilitators. Duties included: Community services, alcohol/drug awareness in schools, helping expunge misdemeanor and felony records, mentoring at-risk youth, gang deaffiliation, domestic violence, anger management groups, (youth and adults) and help convicted felons find employment in San Bernardino and Los Angeles counties.

Students for Political Awareness 2006 - 2010
Supervisor: Gaylla Finell, M.A., Instructor of Political Science

Worked with veterans, helped get them health care and housing. Volunteered at Calipatria State Penitentiary with inmates on the Level 4 yard (serving life-sentences) in 23-hour lockdown and helped criminal veterans deliver requested packages.

Food and clothing delivery every Thanksgiving and Christmas to Salvation Mountain fed homeless individuals and was in charge of food handling and oversaw food preparation. I have been interviewed on television, explaining the importance of the program on KYMA Channel 11, Yuma, Arizona and El Centro, California, which aired November 26th and 27th, 2009.

Desert Behavioral Specialties, LLC August 2006 - June 2009
El Centro, California
Supervisor: John Agee, M.A., C.A.T.C.

Forensic Programs Manager and group facilitator. Worked with individuals with alcohol and drug problems. Conducted family counseling. One-on-one counseling with parents. Public speaking to high schools and community college. Community counseling during San Diego Fires, October, 2007. Transitional living for convicted felons and employment. Managed legal documents for Proposition 36 and PC 1000.

Graduated clients who met criteria and completed program. Attended court representing our clients' enrollment verification. Oversaw drug testing and validity testing of urine specimen. Worked with methadone clinic, helping clients' transition from the 21-day detoxification program to drug court or aftercare. Probationary compliance. Finalized the closure of clinic on June 1st, 2009.

Poster Presentations

1. Ibarra, M., **Pipkin, J.A.,** Martinez, R.D., Ontiveros, T., & O'Dell, L.E. (2016). *Diabetic rats display intense negative affective states during nicotine withdrawal.* The University of Texas at El Paso COURI Symposium, El Paso, TX.

2. Hinojosa, C.A., **Pipkin, J.A.,** & O'Dell, L.E. (2016). *Characterization of nicotine reward and withdrawal in diabetic rats.* CUR. Posters on the hill, Washington, D.C.

3. Flores, R.J., **Pipkin, J.A.,** Perez, A., Uribe, K., and O'Dell, L.E. (2016). *The ovarian hormone estradiol promotes the rewarding effects of nicotine in female rats*. Behavior, Biology, & Chemistry Conference, San Antonio, TX.

4. Hinojosa, C., **Pipkin, J.A.,** Edwards, V., & O'Dell, L.E. (2015). *Characterization of nicotine withdrawal in diabetic rats.* The University of Texas at El Paso COURI Symposium, El Paso, TX.

5. Castaneda, K., **Pipkin, J.A.,** Perez, A., Walker, E., Khan, A., Miranda, M., O'Dell, L.E., Roychowdhury, S. (2015). *Alteration of Gβγ-Cytoskeletal Mediated Pathway during Nicotine Addiction.* The University of Texas at El Paso COURI Symposium, El Paso, TX.

6. Flores, R.J., Perez, A., **Pipkin, J.A.,** Tejeda, C., & O'Dell, L.E. (2015). *B-Estradiol modulates the rewarding effects of nicotine in female rats.* The University of Texas at El Paso COURI Symposium, El Paso, TX.

7. Ibarra, M., **Pipkin, J.A.,** Garcia-Hernandez, R.E., Loveless, K.W., Edwards, V., Martinez, R.D., and O'Dell, L.E. (2015). *Negative affective states produced by nicotine withdrawal are observed in diabetic rats*. The University of Texas at El Paso COURI Symposium, El Paso, TX.

8. Loveless, K.W., **Pipkin, J.A.,** Garcia-Hernandez, R.E., Ibarra, M., O'Dell, L.E. (2015). *Insulin Modulates the Enhanced Rewarding Effects of Nicotine in Diabetic Versus Control Rats.* The University of Texas at El Paso COURI Symposium, El Paso, TX.

9. Garcia-Hernandez, R.E., **Pipkin, J.A.,** Hinojosa, C.A., Ibarra, M., Edwards, V., Loveless, K.W., & O'Dell. L.E. (2015). *Diabetic rats display enhanced rewarding effects of nicotine and aversive effects of withdrawal from this drug*. The University of Texas at El Paso COURI Symposium, El Paso, TX.

10. Ontiveros, T., **Pipkin, J.A.,** O'Dell, L.E. (2015). *Enhanced Tobacco use in Vulnerable Populations. The* University of Texas at El Paso COURI Symposium, El Paso, TX.

11. Valle, I., **Pipkin, J.A.,** Tejeda, C., Edwards, V., Hinojosa, C., Perez, A., Withrow, E., Woldemariam, S., Carcoba, L.M., & O'Dell, L.E. (2014). *Activation of stress systems in the nucleus accumbens (NAcc) enhances anxiety-like behavior produced by nicotine*

withdrawal to a larger extent in female versus male rats. The University of Texas at El Paso COURI Symposium, El Paso, TX.

12. Woldemariam, S., **Pipkin, J.A.,** Hinojosa, C., Edwards, V., Perez, A., Tejeda, C., Valle, I., Withrow, E., Carcoba, L.M., & O'Dell, L.E. (2014). *The rewarding effects of nicotine are enhanced in female rats in an estradiol-dependent manner.* The University of Texas at El Paso COURI Symposium, El Paso, TX.

13. Withrow, E., **Pipkin, J.A.,** Carcoba, L.M., Hinojosa, C., Chris Tejeda, C., Edwards, V., Perez, A., Woldemariam, S., Valle, I., & O'Dell, L.E. (2014). *Insulin normalizes the enhanced rewarding effects of nicotine in self-administration but not nicotine-induced conditioned place preference in diabetic rats.* The University of Texas at El Paso COURI Symposium, El Paso, TX.

14. **Pipkin, J.A.,** Richardson, J.R., Steele, Z.D., Hinojosa, C., Tejeda, C., Flores, R., Ferree, P.L.,Carcoba, L.A., Nazarian, A. & O'Dell, L.E. (2014). *The rewarding effects of nicotine are enhanced and the aversive effects of withdrawal are similar in hypoinsulinemic rats.* American Diabetes Association Conference, San Francisco, CA.

15. **Pipkin, J.A.,** Steele, Z.D., Hinojosa, C., Tejeda, C., Flores, R., Ferree, P.L., Carcoba, L.A., & O'Dell, L.E. (2014). *The rewarding effects of nicotine are enhanced and the aversive effects of withdrawal are similar in hypoinsulinemic rats.* Vulnerability Issues in Drug Abuse Conference, El Paso, TX.

16. Steele, Z.D., Tejeda, C.H., **Pipkin, J.A.,** Hinojosa, C. A., & O'Dell, L.E. (2014). *Activation of stress systems in the nucleus accumbens promote anxiety-like behavior produced by nicotine withdrawal in female rats.* Behavior, Biology, & Chemistry Conference, San Antonio, TX.

17. **Pipkin, J.A.,** Steele, Z.D., Hinojosa, C., Tejeda, C., Flores, R., Ferree, P.L., Carcoba, L.A., & O'Dell, L.E. (2014). *The rewarding effects of nicotine are enhanced and the aversive effects of withdrawal are similar in hypoinsulinemic rats.* Behavior, Biology, & Chemistry Conference, San Antonio, TX.

18. Carcoba, L.M, Orfila, J. E., Natividad, L. A., Torres, O.V., **Pipkin, J.A.,** Ferree, P.L., Castañeda, E., Moss D. & O'Dell, L. E. (2014). *Cholinergic transmission during nicotine withdrawal is influenced by age and pre-exposure to nicotine: Implications for teenage smoking.* Behavior, Biology, & Chemistry Conference, San Antonio, TX.

19. Godfrey, J., Olney, J.J., Castro, N., Dudley, J., **Pipkin, J.A.,** Jeanguenin, L., Herr, D.R., Walls, S.M., Harris, G.L., & Brasser, S.M. (2014). *Chronic Voluntary Ethanol Intake induces favorable Membrane Lipid Profiles in Selectively Bred Alcohol-Preferring (P) Rats.* Research Society on Alcoholism, Bellevue, WA.

20. Flores, R., **Pipkin, J.A.,** Hinojosa, C., Tejeda, C., & O'Dell, L.E. (2013). *The Role of Insulin in Modulating the Rewarding Effects of Nicotine in an Animal Model of Diabetes.* Annual Biomedical Research Conference for Minority Students, Nashville, TN.

21. **Pipkin, J.A.,** Hinjojosa, C., Tejeda, C., Carcoba, L.M., Ferree, P.L., Steele, Z.D., Nazarian, A., & O'Dell, L.E. (2013). *Enhanced Rewarding Effects of Nicotine in a Rodent Model of Diabetes.* MCA Biomedical Research Symposium, El Paso, TX.

22. Tejeda, C., **Pipkin, J.A.,** Flores, R., Hinojosa, C., & O'Dell, L.E. (2013). *Activation of stress systems in the nucleus accumbens (NAcc) enhances anxiety-like behavior produced by nicotine withdrawal in female versus male rats.* The University of Texas at El Paso COURI Symposium, El Paso, TX.

23. Flores, R., **Pipkin, J.A.,** Hinojosa, C., Tejeda, C., & O'Dell, L.E. (2013). *The effects of insulin on nicotine self-administration in an animal model of diabetes.* The University of Texas at El Paso COURI Symposium, El Paso, TX.

24. Hinojosa, C., **Pipkin, J.A.,** Tejeda, C., Flores, R., & O'Dell, L.E. (2013). *Enhanced rewarding effects of nicotine as assessed by place preference procedures in a rodent model of diabetes.* The University of Texas at El Paso COURI Symposium, El Paso, TX.

25. **Pipkin, J.A.,** Hinjojosa, C., Tejeda, C., Carcoba, L.M., Ferree, P.L., Steele, Z.D., Nazarian, A., O'Dell, L.E. (2013). *Enhanced Rewarding Effects of Nicotine in Diabetic Rats.* Society for Neuroscience, San Diego, CA.

26. **Pipkin, J.A.,** Kaplan, G., Pullaro, A., Abdulla, Z., Zavala, A.R., & Crawford, C.A. (2013). *Adolescent and adult nicotine exposure on the acquisition of methamphetamine self-administration and the reinstatement of extinguished methamphetamine-seeking in male rats.* Society for Neuroscience, San Diego, CA.

27. McDougall, S.A., **Pipkin, J.A.,** Der-Ghazarian, T., Cortez, A.M., Gutierrez, A., Lee, R.J., Carbajal, S.M., Shaddox, J.L., & Crawford, C.A. (2013). *Age-dependent differences in the persistence of cocaine-induced conditioned activity in adult and young rats: regional differences in Fos immunoreactivity.* International Behavioral Neuroscience Society, Dublin, Ireland.

28. **Pipkin, J.A.,** Juardo, J.A., Torres, I., Torres, O.V., Carcoba, L.M., & O'Dell, L.E. (2013). *Enhanced rewarding effects of nicotine as assessed by place preference procedures.* American Diabetes Association Conference, Chicago, IL.

29. **Pipkin, J.A.,** Juardo, J.A., Carcoba, L.M., Torres, O.V., & O'Dell, L.E. (2013). *The rewarding effects of nicotine are observed in diabetic rats as assessed by conditioned place preference procedures.* Behavior, Biology, & Chemistry Conference, San Antonio, TX.

30. Varela, F.A., Rios, V., Gutierrez, A., **Pipkin, J.A.,** Crowley, D., Johnson, J., & McDougall, S.A. (October, 2012). *D1 and D2 receptor stimulation in the ventrolateral striatum (VLS) of preweanling rats: impact on locomotor activity and stereotypy.* Society for Neuroscience, New Orleans, LA.

31. **Pipkin, J.A.,** Johnson, J.D., Wang, L., Motley, L.S., & Crawford, C.A. (October, 2012). *Time-dependent behavioral effects of chronic paroxetine and fluoxetine exposure in adolescent rats.* Society for Neuroscience, New Orleans, LA.

32. Valentine, J.M., Britt, C.E., Herbert, M.S., Der-Ghazarian, T., Varela, F.A., Kozanian, O.O., Whittenburg, K.L., **Pipkin, J.A.,** Johnson, J.D., Humphrey, D.E., & Crawford, C.A. (October, 2012). *Early methylphenidate exposure alters kappa opioid receptor mediated antinociception and body temperature.* Society for Neuroscience, New Orleans, LA.

33. **Pipkin, J.A.,** Kaplan, G., Pullaro, A., Abdulla, Z., Rios, V., Shin, C., Zavala, A.R., & Crawford, C.A. (September, 2012). *Juvenile methylphenidate enhances cocaine self-administration and escalation in adult rats*. National Hispanic Science Network on Drug Abuse, San Diego, CA.

34. Shin, C., **Pipkin, J.A.,** Kozanian, O., Rios, V., Kaplan, G., Pullaro, A., Abdulla, Z., Crawford, C.A., & Zavala, A.R. (April, 2012). *Juvenile methylphenidate enhances cocaine self-administration and escalation in adult rats.* Western Psychological Association, San Francisco, CA.

35. **Pipkin, J.A.,** Kozanian, O., Rios, V., Herbert, M.S., Horn, L.A., Mohd-Yusof, A., Palmer, A.G., Farley, C.M., Zavala, A.R., & Crawford, C.A. (November, 2011). *Cue- and cocaine-induced reinstatement of extinguished cocaine-seeking in methylphenidate pretreated rats.* National Institute on Drug Abuse Mini Convention, Washington, D.C.

36. Der-Ghazarian, T., **Pipkin, J.A.,** Gutierrez, A., Carbajal, S.M., Cortez, A.M., Crawford, C.A., & McDougall, S.A. (November, 2011). *Persistence of one-trial cocaine-induced conditioned activity in young and adult rats.* Society for Neuroscience, Washington, D.C.

37. Horn, L.R., Greenfield, V.Y., Johnson, J.D., **Pipkin, J.A.,** Rios, V., & Crawford, C.A. (November, 2011). *Behavioral and neurochemical effects of chronic paroxetine and fluoxetine exposure in adolescent rats.* Society for Neuroscience, Washington, D.C.

38. **Pipkin, J.A.,** Greenfield, V.Y., Rios, V., Butt, A., & Valentine, J. (June, 2011). *Cholinergic modulation of reinforcement effects in a reinstatement model of drug relapse using sucrose reward.* College on Problems of Drug Dependence conference, Hollywood, Fl.

39. **Pipkin, J.A.,** Anglin, S., Rodriguez, I., Rodriguez, J., & Castañeda, D. (March, 2011). *Acculturation, acculturative stress, and academic achievement among Latino/a college students.* San Diego State University Student Research Symposium, San Diego, CA.

40. Cordero, E. D., Lara, D., **Pipkin, J. A.,** & Ramos, A. (August, 2010). *Project Juntos, machismo, and caballerismo among Mexicans and Mexican-Americans.* American Psychological Association, San Diego, CA.

41. Olney, J.J., Castro, N., Dudley, J., **Pipkin, J.A.,** Herr, D.R., Walls, S.M., Harris, G.L., & Brasser, S.M. (June, 2010). *Microstructural characteristics of oral alcohol consumption in selectively bred ethanol-preferring (P) rats given intermittent access to 20% ethanol.* Research Society on Alcoholism, San Antonio, TX.

42. **Pipkin, J.A.,** & Cordero, E.D. (April, 2010). *Body image and alcohol use in Mexican-American college students.* Western Psychological Association, Cancun, México.

43. **Pipkin, J.A.,** & Cordero, E.D. (March, 2010). *Body image and alcohol use in Mexican-American college students.* San Diego State University Student Research Symposium, San Diego, CA.

44. Rios, P., Patel, A., **Pipkin, J.A.,** Hidalgo, L., & Castañeda, D. (May, 2009). *Actor and partner effects of anxiety and depression on marital satisfaction: The case of Mexican American newlywed couples.* The ninth annual Stanford Undergraduate Psychology Conference, Palo Alto, CA.

45. Galvez, J.A., Villalobos, L., Merino, M., Ramos, A.M., **Pipkin, J.A.,** Monge, E., Villafana, S., Pinedo, J.G., Sesma., J., & Cordero, E.D. (April, 2009). *Adoption of the thin-ideal and body image in Latinas.* Western Psychological Association, Portland, OR.

Oral Presentations

1. *Enhanced Rewarding Effects of Nicotine in Diabetic Rats.* Presented October 10th, 2013 at the National Hispanic Science Network on Drug Abuse, Bethesda, MD.

2. *Adolescent and adult nicotine exposure on the acquisition of methamphetamine self-administration and the reinstatement of extinguished methamphetamine-seeking in male rats.* Presented October 9th, 2013 at the National Hispanic Science Network on Drug Abuse, Bethesda, MD.

3. *Enhanced Rewarding Effects of Nicotine as assessed by place preference procedures.* Presented June 24th, 2013 at the American Diabetes Association Conference, Chicago, IL.

4. *Adoption of the thin-ideal and body image in Latinas.* San Diego State University Student Presented February 28th, 2009 at the San Diego State University Research Symposium, San Diego, CA. ***Winner of the 2009 SDSU-IV Dean's Award***

Invited Oral Presentations

1. *Insulin normalizes the rewarding effects of nicotine in diabetic rats.* National Hispanic Science Network on Drug Abuse, El Paso, TX, 2014.

2. *Behavioral and neurochemical effects of chronic paroxetine and fluoxetine exposure in adolescent rats.* National Hispanic Science Network on Drug Abuse, San Diego, CA, 2012.

3. *The importance of pre-clinical research on addiction biology*. California Association for Alcohol/Drug Educators, Primm Valley, Nevada, 2011.

4. *The physiological effects of alcohol and drugs*. Imperial Valley College, Imperial, California, 2010.

5. *The enneagram and the different personality types.* Presenter at the XIII Bi-National Conference on Education Mexicali, Baja California, México 2009.

Teaching Experience

Graduate Teaching Associate
The University of Texas at El Paso August 2015 - December 2015
Department of Psychology
Supervisor: Jennifer Enolouoden, Ph.D.

Taught Psychology-1301: Introduction to Psychology. I helped design and presented lectures for all class sessions, proctored exams, held office hours, graded papers and tests.

Graduate Teaching Associate
California State University, San Bernardino January 2012 - March 2012
Department of Psychology
Supervisor: Yuchin Chien, Ph.D.

Taught Psychology-311 (LAB): Introduction to Psychological Research Methods Class. Designed and presented lectures for all class sessions, proctored exams, held office hours, graded papers and tests, supervised psychology experiments for undergraduate students.

Graduate Teaching Assistant
California State University, San Bernardino January 2011- June 2011
Department of Psychology
Supervisor: Allison Kaufman, Ph.D.

Assisted with instruction of class and conducted lectures, specifically for *Biological Psychology* and *Drugs & Behavior*. Taught classes on Psychopharmacology and Drug Prevention and relapse.

Undergraduate Teaching Assistant

San Diego State University, Department of Psychology January 2010 - May 2010
Supervisor: Krista L. Byrd, M.A.

Graded weekly assignments, exam administration, tutoring, and assisted with lecture for Social Psychology. 4 hours weekly.

Professional Organizations

Psi Chi – The International Honor Society in Psychology	2011 - Present
National Hispanic Science Network on Drug Abuse	2011 - Present
Society for Neuroscience	2010 - Present
PHI KAPPA PHI Honor Society	2010 - Present
Research Society on Alcoholism	2010 - Present
Golden Key International Honour Society	2009 - Present
APA—Student Affiliate	2008 - Present
California Association for Alcohol/Drug Educators	2007 - Present

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Other Professional Activities

Fundraising Chair, General Experimental Psychology Club 2010 - 2011
Advisor: Bob Ricco, Ph.D.

- Help promote knowledge about doctoral programs and careers in psychology.
- Help serve as a social and educational forum for undergraduates and graduates.

President, Psychology Club 2008 - 2010
Advisors: Donna Castañeda, Ph.D. & Elizabeth D. Cordero, Ph.D.

- Re-activated club after two-year hiatus.
- Organized various activities and workshops in the field of psychology.
- Coordinated fundraisers for students to attend the WPA 2010. Fundraised over 3,000 dollars, plus 6,000-dollar SDSU research travel grant recipients.
- Peer Advising about graduate school

Protégé of the Faculty-Student Mentoring Program
San Diego State University-Imperial Valley Campus 2008 - 2010
Advisor: Elizabeth D. Cordero, Ph.D.

- Involved in research and promoted the essentials of research.
- Had research mentor, specifically to help learn how to write a manuscript.

American Sign Language Club Fall 2008 - Winter 2008
Advisor: Charles Mason, Instructor of American Sign Language

- Helped interpret for deaf children.
- Fundraising for deaf children to go on field trips.

References

1. Laura O'Dell, Ph.D., (Doctoral Advisor), Associate Professor, Department of Psychology, The University of Texas at El Paso, El Paso TX 79902. Voice: 915.747.6557; E-mail: lodell@utep.edu

2. Edward Castañeda, Ph.D., (Doctoral Co-Advisor), Professor, Department of Psychology, The University of Texas at El Paso, El Paso TX 79902. Voice: 915.747.6558; E-mail: ecastaneda9@utep.edu

3. Cynthia Crawford, Ph.D., (Masters Advisor), Professor, Department of Psychology, California State University, San Bernardino, CA 92407-2318. Voice: 909.537.7416; E-mail: ccrawfor@csusb.edu

4. Sanders McDougall, Ph.D., (Masters Co-Advisor), Professor, Department of Psychology, California State University, San Bernardino, CA 92407-2318. Voice: 909.537.5581; E-mail: smcdouga@csusb.edu