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Nicotine and Alcohol Interactions

Charles C. J. Frye
Utah State University

NICOTINE AND ALCOHOL INTERACTIONS

by

Charles C.J. Frye

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Approved:

_____	_____
Amy Odum, Ph.D. Major Professor	Christopher Warren, Ph.D. Committee Member
_____	_____
Gregory Madden, Ph.D. Committee Member	Kerry Jordan, Ph.D. Committee Member
_____	_____
Erin Bobeck, Ph.D. Committee Member	Janis L. Boettinger, Ph.D. Acting Vice Provost for Graduate Studies

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ABSTRACT

Alcohol and Nicotine Interactions

by

Charles C.J. Frye, Doctor of Philosophy

Utah State University, 2020

Major Professor: Dr. Amy L. Odum
Department: Psychology

Alcohol and nicotine are the two most commonly abused drugs in the United States and are often used in combination. The focus of this dissertation was to investigate the relation between the rewarding properties of these drugs. Chapter I describes the rewarding properties of alcohol and nicotine and describes commonalities between the drugs. Chapter II, Chapter III, and Experiment 1 of Chapter IV explore how exposure to nicotine influences various aspects of alcohol value. Chapter II describes a study that investigated how exposure to nicotine affects resurgence of alcohol seeking in rats. We hypothesized, but did not find, that nicotine would increase resurgence of alcohol seeking. In Chapter III we assessed how exposure to nicotine and nicotine + MAOI affects progressive ratio breakpoint for alcohol in rats. We hypothesized that nicotine would increase breakpoint, but that nicotine + MAOI would increase breakpoint to a greater degree than nicotine alone. Nicotine did increase breakpoint for alcohol, but nicotine + MAOI *reduced* progressive ratio breakpoint below saline levels. In Experiment I of Chapter IV, we examined how the hypothetical opportunity to smoke tobacco cigarettes affects demand for hypothetical alcoholic beverages in human participants. We

hypothesized that indices of alcohol demand would be affected by whether participants could smoke, but we did not find any evidence to support this hypothesis. In Experiment 2 of Chapter IV, we investigated how the hypothetical opportunity to drink alcoholic beverages affects demand for hypothetical tobacco cigarettes. We hypothesized that indices of tobacco cigarette demand would be affected by whether participants could not drink alcohol. One aspect of demand (Maximum Expenditure; O_{max}) was higher in the non-drinking condition. Finally, in Experiment 3 of Chapter IV, we investigated the economic relation between alcoholic beverages and tobacco cigarettes. We hypothesized that tobacco cigarettes and alcoholic beverages would be complementary goods, but found that the goods were independent of one another, contrary to epidemiological and unpublished laboratory data. Together, this series of studies highlights how nicotine exposure affects alcohol-related behavior and points to potential limitations of hypothetical purchase tasks.

(205 pages)

PUBLIC ABSTRACT

Alcohol and Nicotine Interactions

Charles C.J. Frye

Charles C.J. Frye, a graduate student in the Behavior Analysis program at Utah State University, completed this dissertation as part of the requirements of the degree of Doctor of Philosophy in Psychology.

Alcohol and Nicotine are the two most commonly abused drugs in the United States, often used at the same time. The goal of the dissertation was to more fully understand how exposure to one drug alters motivation for the other. In Chapter I, we investigated how exposure to nicotine affects relapse for alcohol in rats. Nicotine did not affect relapse for alcohol, possibly due to the method of nicotine delivery used. In Chapter II, we investigated how exposure to nicotine and nicotine combined with MAOI (a drug commonly used as an antidepressant and found in tobacco cigarettes) affects motivation for alcohol in rats. We found that nicotine increased motivation for alcohol, but nicotine combined with MAOI reduced motivation for alcohol. Chapter IV consisted of 3 experiments using hypothetical purchase tasks with human participants. In Experiment 1, we assessed how the hypothetical opportunity to smoke cigarettes at a concert influenced purchasing of hypothetical alcohol. We found that having the opportunity to smoke did not alter purchasing alcohol. In Experiment 2, we assessed the opposite relation: how the hypothetical opportunity to drink alcoholic beverages at a concert altered purchasing of hypothetical tobacco cigarettes. We found that the Maximum Expenditure was greater when participants were told that they could not drink alcohol at the concert. Lastly, in Experiment 3, we assessed how consumption of alcohol and cigarettes was affected by manipulating the price of one of the drugs. Specifically, we assessed how purchasing of tobacco cigarettes changed (despite a constant price) when we increased the cost of alcoholic beverages. We also assessed how the purchasing of alcoholic beverages changed (despite a constant price) when we increased the price of tobacco cigarettes. We found that tobacco cigarette purchasing was independent of alcohol beverage price and alcoholic beverage purchasing was independent of tobacco cigarette price. Each study in this dissertation produced surprising results and has the potential to stimulate new research questions.

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Charles C.J. Frye

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ABBREVIATION LIST

α - Elasticity parameter

APT – Alcohol Purchase Task

AUD – Alcohol Use Disorder

AUDIT – Alcohol Use Disorder Identification Task

BP – Break Point

CPT – Cigarette Purchase Task

FTND – Fagerstrom Test for Nicotine Dependence

HPT – Hypothetical Purchase Task

IA2BC – Intermittent Access Two-Bottle Choice

ICC – Intraclass Correlation

ICCPPT – Income Compensated Cross-Price Purchase Task

MAOI – Manoamine Oxidase Inhibition (Inhibitor)

MLM – Multilevel Modeling (Model)

nAChR – nicotinic Acetylcholine Receptor

O_{max} – Maximum Expenditure

P_{max} – The point of Unit Elasticity

PR – Progressive Ratio

Q_0 – Intensity of Demand

VR – Variable Ratio

CHAPTER I

INTRODUCTION

Alcohol and tobacco are the two most commonly used drugs in the United States (Fryar et al., 2006). In 2016-2017, over 50% percent of Americans reported being current consumers of alcohol (Center for Behavioral Health Statistics and Quality, 2019), making alcohol the most commonly used drug in the U.S. Alcohol abuse is responsible for an average of 88,000 deaths per year and represents a significant economic burden (i.e., $220 billion each year; Esser et al., 2014). Tobacco use is the leading cause of preventable death (e.g., Smith et al., 2014) and is the second most commonly abused drug in the U.S. (Fryar et al., 2006). There are many pieces of evidence that suggest alcohol and nicotine use are related.

Alcohol and tobacco use are often comorbid. Between 80 to 95% of alcoholics are tobacco cigarette users, and alcoholism is 10 times more likely in smokers compared to non-smokers (DiFranza & Guerrera, 1990). Selective breeding for high alcohol preference in mice simultaneously increases sensitivity to nicotine's reinforcing effects (Hauser et al., 2014). The rewarding properties of alcohol and nicotine are mediated by the mesolimbic dopamine system (e.g., Soderpalm, Ericson, Olausson, Blomqvist, & Engel, 2000) and there is evidence of cross-tolerance to the effects of these drugs (e.g., de Fiebre & Collins, 1993). Despite clear evidence that alcohol and tobacco use are related, relatively little research has directly examined how exposure to one substance influences the value of the other substance.

The Properties of Nicotine

Tobacco use has a long history in human culture and continues to be used despite negative health consequences. Humans began cultivating tobacco between 3000-5000

BC. Tobacco has been used for a variety of purposes (e.g., medicinally, religious ceremonies, fertility, etc.) and is administered in a variety of ways (e.g., chewing, eating, smoking, drinking, sniffing, eye drops, enemas; Musk & de Klerk, 2003). The route of administration that is most prevalent for tobacco use is smoking (e.g., cigars, pipe, cigarettes, etc.). Since the rise in tobacco cigarette use, much research has been dedicated to the deleterious health effects of smoking. Many diseases have been linked to smoking tobacco cigarettes (e.g., heart disease, stroke, numerous types of cancer, and several other diseases; see Bartal, 2001). Despite the link between smoking and these health consequences, people still regularly engage in this behavior.

There are multiple reasons that people may use nicotine (see Garcia-Rivas & Deroche-Gamonet, 2018 for an in-depth discussion of this issue). Numerous well-documented factors are associated with initiation of nicotine use (e.g., psychosocial, familial, genetic, and neurobiological; McKay, 1999; Munafo et al., 2004; Garcia-Rivas & Deroche-Gamonet, 2018). Once nicotine use is initiated, it produces dependence at a higher rate than any other drug of abuse (Markou, 2008).

The properties of nicotine are complex. According to the dual-reinforcement model of nicotine action, nicotine has two distinct effects: primary reinforcing effects and reward-enhancing effects (Caggiula et al., 2008). The primary reinforcing effects of nicotine are due to its action on the central nervous system, where it acts as a stimulant. Nicotine increases alertness and alters mood. As a primary reinforcer, nicotine is relatively weak (e.g., Chaudhri et al., 2007). The reward-enhancing effects of nicotine are much more pronounced. Nicotine increases the value of other stimuli in animals (e.g., Caggiula et al., 2001; 2002; Chaudhri et al., 2007) and in humans (e.g., Attwood et al.,

2009; Perkins & Karelitz, 2013; Perkins, Karelitz, & Boldry, 2017). We argue that nicotine may augment the reinforcing value of drugs of abuse (e.g., the value of alcohol) through these reward-enhancing properties and thus, make initial exposure to other drugs of abuse more rewarding. This rewarding drug experience may then augment the probability and/or intensity of repeated use of the other drug of abuse, addiction to the other drug of abuse, and/or the probability (or intensity) of relapse following successful cessation of using the other drug.

The Properties of Alcohol

Alcohol has been used throughout human history and continues to be used despite negative health consequences. Archaeological evidence suggests that fermentation of grains (for beer) and grapes (for wine) dates back approximately 20,000 years (Guidot & Mehta, 2014). Alcoholic beverages contain ethanol, a psychoactive drug. The effects of ethanol progress along a biphasic time-course with initial feelings of relaxation, euphoria, and reduced inhibition that transition to exhaustion, depression, headache and, in the case of high doses, loss of motor coordination, vomiting, and loss of consciousness (Nagoshi & Wilson, 1989).

Most people who drink alcoholic beverages are able to moderate their use; however, some people develop alcohol use disorder (AUD), which is associated with a variety of problems. Grant et al. (2015) found that, in a large representative sample, 13.9% of people met the criteria for AUD in the previous year and 29.1% of people met the criteria for AUD at some point in their life. Alcohol use disorder is a chronic and relapsing condition that negatively affects interpersonal relationships, decision making, and neurological function (Cox et al., 2018). Twenty-five chronic diseases are completely

due to alcohol consumption and alcohol use contributes to the risk of developing a variety of other diseases (e.g., a variety of cancers, cardiovascular diseases, digestive diseases, and numerous others; Shield, Parry, & Rehm, 2014).

The Relation Between Alcohol and Nicotine Use

Alcohol and tobacco use are highly correlated. Smokers are more likely to consume alcohol (Grant, 1998) and meet the criteria for AUD (Harrison & McKee, 2011). Adult daily smokers have a three-fold greater risk for developing AUD and hazardous drinking (McKee et al., 2007); these numbers are even more severe for adolescents who smoke daily (seven-fold increase in hazardous drinking and four-fold increase in AUD; Harrison, Desai, & McKee, 2008). Adolescents tend to mature out of drinking heavily, but adolescent smokers are slower to do so than adolescent non-smokers (Karlamangla et al., 2006). Diseases typically associated with tobacco use are a leading cause of death in alcoholics (Hurt et al., 1996) and risk of mortality is greater when alcohol and tobacco are conjointly used (Rosengren et al., 1988).

Nicotinic acetylcholine receptors (nAChRs) are a mechanism that is central to both nicotine and alcohol use. Activation and desensitization of nAChRs is the mechanism that allows nicotine to exert its action throughout the central nervous system (Picciotto et al., 1998). Nicotine's rewarding and sensitizing effects (Corrigall et al., 1992) and alcohol's rewarding effects (Gonzales & Weiss, 1998) are both thought to be mediated by dopamine release in the nucleus accumbens and ventral tegmental area. Nicotine receptor binding is facilitated by chronic alcohol exposure (Yoshida et al., 1982) and cross-tolerance has been observed across the two drugs (e.g., de Fiebre & Collins, 1993). Mecamylamine (a nicotinic antagonist) blocks typical dopamine release caused by

alcohol administration in the nucleus accumbens (Tizabi et al., 2002) and alcohol consumption and preference are dampened by mecamylamine (Le et al, 2000). Alcohol use acts as a conditioned cue for tobacco use, and the alternative is true as well (see Burton & Tiffany, 1997). Clearly, nicotine and alcohol reward systems are linked, likely and at least in part, through the nAChR system.

Goal of Dissertation

The overarching goal of the dissertation was to elucidate how alcohol and nicotine interact on a behavioral level. Thus, we designed experiments to assess investigate some of these relations. The first three experiments of the dissertation (covered in Chapter 2, Chapter 3, and the Experiment 1 of Chapter 4) focus on how nicotine exposure impacts some aspect of alcohol value. The fourth experiment (Experiment 2 of Chapter 4) focuses on how alcohol exposure impacts demand for nicotine. Finally, the fifth experiment (Experiment 3 of Chapter 4) examines how alcohol and nicotine value interact economically.

In Chapter 2 (Frye, Rung, Nall, Galizio, Haynes, & Odum, 2018) we assessed whether exposure to nicotine increases the probability and/or intensity of relapse for alcohol seeking in rats. In this experiment, we were interested in how the reward-enhancing effects of nicotine would impact both initial responding for alcohol and relapse for alcohol seeking following a period of abstinence. We hypothesized that the reward-enhancing effects of alcohol would augment both initial responding for alcohol and relapse for alcohol seeking in rats.

In Chapter 3 (Frye, Galizio, Haynes, DeHart, & Odum, 2019), we assessed whether nicotine and nicotine + tranylcypromine increases the value of alcohol on

progressive ratio schedules in rats. Prior research had shown that nicotine increases progressive ratio breakpoint for alcohol (Leão et al., 2015). In this study, we planned to replicate this finding and extend it to novel treatment of nicotine combined with tranylcypromine. The reason we were interested in tranylcypromine is due to separate literature that has reliably found that tranylcypromine pretreatment drastically increases nicotine self-administration. We thought that if tranylcypromine is increasing the value of nicotine and nicotine is increasing the value of alcohol then tranylcypromine combined with nicotine may augment the value of alcohol to greater extent than nicotine alone. Thus, we hypothesized that nicotine would increase the value of alcohol and nicotine + tranylcypromine would increase the value of alcohol to greater extent.

The final three experiments of the dissertation are contained in Chapter 4. The experiments in Chapter 4 were designed to investigate interactions of nicotine and alcohol use. These experiments were conducted with human participants instead of rats due to the limitations in current models of non-human nicotine and alcohol self-administration (e.g., catheter patency, mortality, etc.). In the first experiment in Chapter 4, we assessed how the opportunity to smoke tobacco cigarettes influences demand for alcohol on an Alcohol Purchase Task (APT). Thus, both of the experiments in Chapters 2 and 3 and the first experiment in Chapter 4 all focus on how exposure to nicotine influences some aspect of alcohol self-administration. The second experiment in Chapter 4, however, examined the opposite relation: how the opportunity to consume alcoholic beverages influences demand for tobacco cigarettes using a Cigarette Purchase Task (CPT). Finally, in the third and final experiment of Chapter 4, we assessed Cross-Price

Elasticity for alcohol and tobacco cigarettes to understand the economic relation between the two drugs.

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CHAPTER II

CONTINUOUS NICOTINE EXPOSURE DOES NOT AFFECT RESURGENCE OF ALCOHOL SEEKING IN RATS

Abstract

Alcohol is the most commonly used drug in the United States and alcohol abuse can lead to alcohol use disorder. Alcohol use disorder is a persistent condition and relapse rates following successful remission are high. Many factors have been associated with relapse for alcohol use disorder, but identification of these factors has not been well translated into preventative utility. One potentially important factor, concurrent nicotine use, has not been well investigated as a causal factor in relapse for alcohol use disorder. Nicotine increases the value of other stimuli in the environment and may increase the value of alcohol. If nicotine increases the value of alcohol, then nicotine use during and after treatment may make relapse more probable. In the current study, we investigated the effect of continuous nicotine exposure (using osmotic minipumps to deliver nicotine or saline, depending on group, at a constant rate for 28 days) on resurgence of alcohol seeking in rats. Resurgence is a type of relapse preparation that consists of three phases: Baseline, Alternative Reinforcement, and Resurgence Testing. During Baseline, target responses produced a dipper of alcohol. During Alternative Reinforcement, target responses were extinguished and responses on a chain produced a chocolate pellet. During Resurgence Testing, responses on the chain were also extinguished and a return to responding on the target lever was indicative of resurgence. Multilevel modeling was used to analyze the effect of nicotine on resurgence. Both the nicotine and saline group showed resurgence of alcohol seeking, but there was no difference in the degree of resurgence across groups. Future directions could involve testing alternative drug delivery techniques.

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Frye, C. C., Rung, J. M., Nall, R. W., Galizio, A., Haynes, J. M., & Odum, A. L. (2018). Continuous nicotine exposure does not affect resurgence of alcohol seeking in rats. *PloS one*, *13*(8).

Introduction

Alcohol is the most commonly used drug in the United States [1]. Alcohol is a depressant and is rewarding due to its disinhibiting and euphoria-producing effects. Due to the high reinforcing efficacy of alcohol, some people are unable to moderate the frequency and/or intensity of their drinking and develop alcohol use disorder (AUD). AUD has a negative effect on a person's ability to thrive in society and is associated with long-term health detriments. Alcohol is responsible for an average of 88,000 deaths per year and the effects of alcohol use cost the United States $220 billion each year [2]. A recent study, using a large representative sample, found that 13.9% of individuals met the criteria for AUD in the last year and 29.1% of individuals met the criteria for AUD at some point in their life [3]; these numbers indicate a significant increase over the past decade [4].

The rate of relapse for AUD following remission is high [5], but the reasons for high rates of relapse are not well-understood. Relapse for AUD, following successful treatment, has been linked to a variety of social and biological markers, but these findings have not been well translated into preventative utility. Indeed, most people relapse at least once before successfully overcoming the disorder [6]. One under-investigated factor for the high rates of relapse in people who are in remission for AUD is concurrent nicotine use.

Tobacco cigarette consumption is still a leading cause of preventable death in the United States [7] and electronic cigarette use is on the rise. Nicotine is the constituent in tobacco cigarettes that is believed to be responsible for the high rates of addiction. Dependence is more common with nicotine than with any other substance [8]. Although

tobacco cigarette consumption has declined in recent years, alternative forms of nicotine delivery have increased [1,9]. The majority of past research on nicotine use has focused on the deleterious health effects of tobacco cigarette consumption. Whereas much is known about the effects of tobacco cigarettes on health, relatively little is known about the behavioral effects of nicotine consumption alone.

Nicotine is a complex drug of abuse. According to the dual reinforcement model of nicotine action [10], nicotine consumption has both primary reinforcing effects and reward-enhancing effects. As a primary reinforcer nicotine is relatively weak [11], but is a much stronger reinforcer if it is accompanied by other stimuli. Nicotine increases the value of these stimuli through its reward-enhancing properties and increases the behavior that produces them. Furthermore, nicotine ingestion has been shown to increase the value of other stimuli in the environment that are unrelated to nicotine delivery. For example, nicotine increases the value of food [12], contingent light presentations [13], sucrose [14], attractiveness to facial cues [14], reported happiness while watching films categorized as “happy films” [15], and sensory rewards such as music [16]. It has been argued that the reward-enhancing properties of nicotine are, at least partially, responsible for the prevalence of its use [8,14].

Nicotine abuse is often comorbid with alcohol abuse and may facilitate relapse for AUD symptoms. Approximately 80-95% of people with alcoholism smoke tobacco cigarettes [17]. Selective breeding for high alcohol preference in mice simultaneously increases sensitivity to nicotine’s reinforcing effects [18]. In rats, exposure to nicotine increases alcohol consumption [19]. The increase in alcohol consumption under the influence of nicotine could be the result of nicotine increasing the value of alcohol and its

corresponding effects. The increase in the value of alcohol – through nicotine's reward-enhancing properties – may lead to higher rates of relapse for those undergoing treatment for alcoholism if they continue to use nicotine during and after treatment. Human clinical observations support this assertion. Female smokers who undergo treatment for alcoholism have higher cravings for alcohol than their non-smoking counterparts [20]. Daily smoking abstinence is associated with lower alcohol consumption, lower urges to drink, greater alcohol abstinence self-efficacy, and perceived self-control demands [21]. Furthermore, smoking during abstinence for alcohol, when people are in treatment for AUD, is associated with an increase in the frequency of urges to drink [22,23]. In physiological studies, nicotine has been found to increase salivary cortisol levels, which are associated with relapse [24] and promote sustained $GABA_A$ receptor levels, which are associated with craving for alcohol [25]. The reward-enhancing properties of nicotine could be (at least partially) responsible for the high rates of relapse seen in those with AUD, due to the high rate of concurrent nicotine use in this population. The causal relation of nicotine exposure to relapse for alcohol seeking is difficult to study, however, in human populations.

Animal models of relapse provide a methodology for assessing the effect of nicotine on relapse for alcohol seeking. There are several ways to model relapse in the laboratory (e.g., spontaneous recovery, reinstatement, renewal, resurgence, etc.) [26]. Each of these methodologies share the same overarching research strategy. For example, each relapse preparation consists of Phase 1: acquisition of target responding (e.g., responding on a lever to earn a drug), Phase 2: the cessation/reduction of target responding (e.g., no longer responding on the lever that is associated with drug), and

Phase 3: a relapse test (e.g., some manipulation occurs to assess whether target responding recurs). However, the strategies employed during Phase 2 and Phase 3 set the relapse methodologies apart. The key features of resurgence, one type of relapse methodology, offer promise as a human analogue of relapse [27].

The resurgence paradigm models acquisition (e.g., of drug use or another problem behavior), cessation (through alternative reinforcement that is incompatible with the problem behavior), and relapse (through removal of alternative reinforcement) of problem behavior [28]. In animal models, these processes are modeled by making a reward (e.g., a drug) available for responding on a target manipulandum (e.g., lever) during a baseline phase. Once responding is established and the subject reliably earns rewards, target responses are placed on extinction and responses to an alternative manipulandum (e.g., a chain) produce an alternative reward. Finally, once responding on the target manipulandum has stabilized in the presence of the alternative manipulandum and its associated reward, responses on the alternative manipulandum are also placed on extinction and a return to the target manipulandum is indicative of relapse (in this case, resurgence).

Resurgence is an especially attractive model of relapse because it adequately captures the process of problem behavior acquisition, treatment, and potentially relapse (upon treatment termination) in the real world [28]. For example, a person acquires drug-taking when they encounter the reinforcing effects of the drug and begin using the drug regularly. In severe cases, the person cannot moderate use of the drug and must receive help from a treatment facility. Inside the treatment facility, drugs are no longer available and we can bring them in contact with alternative sources of reinforcement (e.g., social

reinforcement, hobbies, etc.). Finally, when they check out of the treatment facility, those alternative sources of reinforcement are no longer available, and they may return to using drugs (i.e., they may experience resurgence of drug taking). Thus, this methodology captures the key features of acquisition, treatment, and relapse for severe problem behavior [27]. Despite the attractive features of resurgence as an analogue to severe human problem behavior, it is not as widely used as other relapse techniques (e.g., reinstatement).

To assess the role of nicotine in relapse for AUD symptomology, we conducted an experiment assessing the effect of continuous nicotine exposure on resurgence for alcohol seeking in rats. First, rats acquired alcohol consumption in their home cage. Next, the rats responded on levers to earn alcohol rewards in an operant chamber. Then, we conducted surgery on each subject to implant an osmotic minipump that delivered saline or nicotine (depending on the group) at a constant rate for 28 days. Osmotic minipumps were chosen over pre-session drug injections because injections can cause stress [29], which itself can induce relapse in rats [30]. Finally, all subjects experienced a typical resurgence task to model what humans experience in the clinic: a drug-taking phase (Baseline), a treatment phase (Alternative Reinforcement), and a relapse phase (Resurgence Testing). We hypothesized that both groups would show relapse (increased responses on the lever that was associated with alcohol rewards, the target lever) during resurgence testing, but the nicotine group would relapse to a greater extent.

Method

Subjects

Twelve experimentally naïve male Long Evans rats, aged 71-90 days, were obtained from Charles River Laboratories. Following Pretraining (see below), rats were assigned to one of two groups: Sal (saline; $n = 6$) or Nic (nicotine; $n = 6$), such that groups were matched based on dose of self-administered alcohol during pretraining. Rats were maintained at 100% of their free-feeding body weight through post-session supplemental feeding throughout the experiment. Rats were fed LabDiet® rat chow and had continuous access to water in their home cages. Rats were individually housed in a temperature-controlled colony room with a 12:12 hour light/dark cycle. Sessions were conducted every day at approximately the same time each day during the light cycle. The current study was approved by the Utah State University Institutional Animal Care and Use Committee.

Materials

Apparatus. Four standard Coulbourn operant chambers (Coulbourn Instruments) enclosed in light- and sound-attenuating cubicles were used for this experiment. Each operant chamber was equipped with two fixed levers on the front panel. The lever designated as the target response (i.e., left or right) was counterbalanced across rats. Each lever had a green, red, and yellow LED light above the lever. A receptacle was located in the middle of the front panel and equipped with a light. A pellet dispenser above the receptacle delivered 45-mg dustless precision chocolate pellets into the receptacle. Chocolate pellets were obtained from Bio-Serv®. There was also a dipper located under the receptacle that could be raised to provide 0.1 mL of liquid solution. Each chamber had a houselight located on the ceiling of the front panel to provide general illumination.

Drugs. Distilled water and 95% ethanol were used to make a 20% ethanol solution that was self-administered orally in the home cage during the two-bottle choice procedure and in the operant chamber. During surgery, osmotic mini-pumps were filled with 2 mL of drug solution. The drug solution used for the Sal group was 0.9% sterile saline solution. The drug solution for the Nic group was made using nicotine hydrogen tartrate salt (MP Biomedicals, LLC.) dissolved in 0.9% sterile saline solution. Nicotine was delivered at approximately 3 mg/kg/day [12].

Procedure

Two-bottle choice. An intermittent-access two-bottle choice procedure was used to establish ethanol consumption [31]. Rats were given access to a bottle containing 20% ethanol solution 3 days per week (i.e., Monday, Wednesday, Friday, or Tuesday, Thursday, Saturday) in their home cages. Water was freely available in another bottle during ethanol sessions and ethanol-free sessions. This phase lasted for 8 weeks (24 sessions) and all subjects consumed a dose of alcohol that was above the criterion dose (> 0.3 g/kg) [31] by the end of this phase.

Pretraining. Following the two-bottle choice procedure, rats began daily sessions in the operant chambers. Session initiation consisted of illumination of the houselight and the target lever stimulus light. Rats initially responded on the target lever according to a fixed ratio (FR) schedule of reinforcement. Reinforcer deliveries consisted of access to a single dipper (.1 mL) of 20% alcohol. The dipper remained in the raised position for 10 s, during which a light in the dipper aperture was illuminated. If a photobeam, directly in front of the dipper, was broken, the alcohol reward was considered “consumed”. On the first day of pretraining, alcohol was available on an FR 1 schedule (each response

produced an alcohol reward). Each day, the dose of alcohol consumed was calculated and, if the subject consumed a dose above the criterion dose (>0.3 g/kg), then the ratio schedule was increased on the following day. After a subject consumed a dose above the criterion dose on an FR 4 schedule of reinforcement, subsequent sessions were conducted with a variable ratio (VR) schedule (modified from Fleschler & Hoffman's [32] constant probability distribution), in which the number of required responses varied around an average value. Rats first responded on a VR 4, and the average ratio schedule increased by 2 on subsequent days if the dosing criterion was met. Throughout Pretraining, there were no programmed consequences for presses to the inactive lever, and the chain (alternative reinforcement manipulandum) was not available.

After subjects consumed a dose of alcohol above the criterion at a VR 10 schedule of reinforcement, they were assigned to a group (Sal or Nic; matched on pre-training alcohol consumption) and surgery was conducted (see below). Throughout the experiment, all sessions terminated after 60 min.

Surgery. Osmotic minipumps (model 2ML4; Alzet, Cupertino, CA), dispensing 60 µl of solution/day at a constant rate for 28 days (i.e., 3.0 mg/kg/day), were used for nicotine administration. Prior to implantation, pumps were filled with a liquid solution. For half of the subjects, nicotine solution (3.0 mg/kg free base per day) was used and for the other half of the subjects, saline alone was used. Rats were anesthetized with isoflurane and pumps were inserted into a subcutaneous pocket in the rat's dorsal thoracic area via a small incision [33]. Rats were allowed two days to recover from surgery during which twice-daily injections of an NSAID analgesic (Flunixin Meglumine, 1.1 mg/kg, subcutaneous) and an antibiotic (Gentamicin, 2.0 mg/kg, intraperitoneal) were

administered. Following recovery from surgery rats began alcohol self-administration (i.e., Baseline).

Baseline. During Baseline, a VR 10 schedule of reinforcement was in place on the target lever, and reinforcer deliveries consisted of access to a single dipper (0.1 mL) of 20% ethanol solution for 10 s. During reinforcer deliveries, the LED lights above the lever extinguished and the light in the dipper aperture was illuminated. There were no programmed consequences for presses to the inactive lever, and the chain (alternative reinforcement manipulandum) was not available.

Alternative Reinforcement. Following Baseline, rats responded on the chain to earn access to chocolate pellets. A VR 4 schedule of reinforcement was in effect for 10 days. During the first two sessions of the phase, the first 10 reinforcers were available on an FR 1 to facilitate acquisition of chain pulling [34]. Reinforcer deliveries consisted of a single chocolate pellet. Following a pellet delivery the LED lights above the lever were extinguished and the light in the pellet/dipper aperture was illuminated for 10 s. There were no programmed consequences for presses to the target or inactive levers.

Resurgence Testing. Following the Alternative phase, rats completed three sessions in which all reinforcement was suspended. There were no programmed consequences for responses to the levers or the chain.

Data Analysis

To first establish that the two-bottle choice procedure was successful in inducing consumption of alcohol, a linear mixed-effects model was conducted, using the lme4 package [35] in *R* [36]. For this analysis, the percentage of alcohol consumed (i.e., the amount of alcohol consumed divided by the total amount of liquid consumed) per day

was the dependent variable and session was the sole independent variable. A random intercept of subject (rat) and random slope (session) were included because they were found to significantly improve the model. The significance of the predictor was evaluated using a Wald test via the car package [37], and the necessity of additional random effects was evaluated using likelihood ratio tests.

Next, the effects of nicotine on target responding were assessed across phases. To account for any individual differences in response rate, we calculated the proportion of baseline responding for each session during the subsequent phases. To calculate the proportion of baseline responding, the response rate (target responses / min) during each session of Alternative Reinforcement and Resurgence Testing was divided by the response rate during the last session of Baseline. If responding did not change from Baseline, the proportion of baseline responding would be equal to 1. If responding increased or decreased from Baseline, the proportion of baseline responding would be greater than or less than 1, respectively. Proportion of baseline responding was used as the dependent measure for the analyses that follow.

The effects of nicotine on target responding were analyzed across phases using linear mixed-effects modeling in *R* [36] using the lme4 package [35]. The initial model tested included Session, Phase, Group, and all of their interactions as predictors of target responding. This initial model included a random intercept of subject (rat) and no a-priori random slope effects. A three-way interaction between these variables was anticipated because the contingencies for target responding changed across phases, behavior subsequently shifted to conform to these new contingencies across sessions (more or less rapidly, depending on the phase), and thereafter, any effect of nicotine would most likely

further moderate these differences. Significance of predictors and necessity of random effects were assessed as described above. Specific comparisons of target responding across phases and groups were conducted using the lsmeans package [38]. To clarify the nature of the three-way interaction, follow-up models were conducted within each experimental phase, including predictors of Group, Session, and their interaction. The random effects structure for these follow-up models was the same as that for the final model (see Results below).

Finally, we conducted two additional analyses to assess any additional relations in the data. First, we assessed the latency to the first target lever press during the first session of Resurgence Testing as a function of group membership with a Mann Whitney *U* test. Then, we assessed the correlation between alcohol consumption during the two-bottle choice procedure and the degree of resurgence observed by conducting a Spearman correlation on average g/kg consumed during the final week (i.e., 3 sessions) of two-bottle choice and degree of resurgence on the first day of resurgence testing (number of target responses on the first day of Resurgence Testing – number of target responses on the last day of Alternative Reinforcement).

Results

The two-bottle choice procedure produced escalation of alcohol intake across the 24 sessions using this procedure. Figure 2-1 shows session-by-session percent alcohol consumption during the two-bottle choice procedure. The increase in percent alcohol consumption was confirmed via a significant fixed effect of session on percent of alcohol consumption χ_2 (1) = 24.43, $p < .0001$, such that percent of alcohol consumption increased as duration of exposure increased ($B = 1.64$, $SE = 0.33$). On the first day of

exposure, rats overall showed a relatively low percentage of alcohol consumption (31%, *SE* = 6.5), which subsequently increased to 49% (*SE* = 4.70) and 69% (*SE* = 5.50) in sessions 12 and 24, respectively. Although the percent of alcohol consumption overall increased with session, there were individual differences in the extent to which alcohol consumption changed across sessions (random slope of session; χ_2 (2) = 30.61, p < .0001).

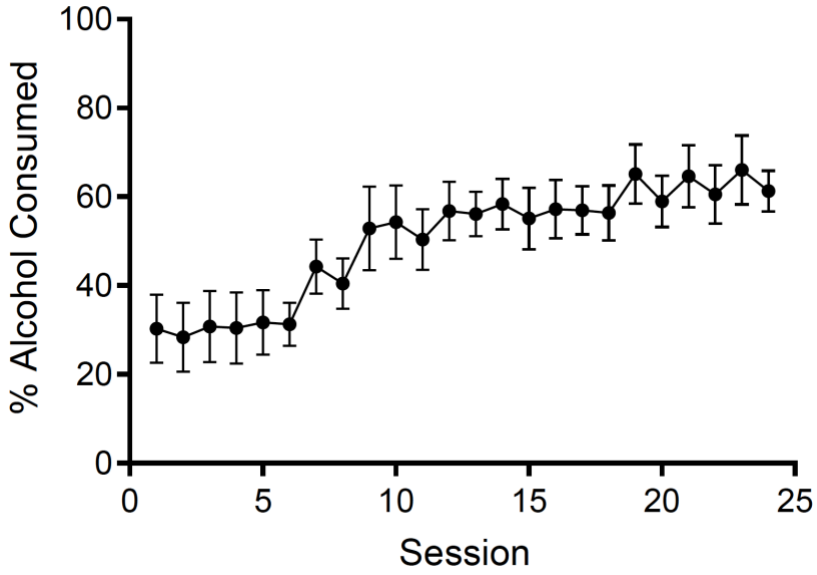

Fig 2-1. Percentage of alcohol consumed (i.e., ml of 20% alcohol / (ml of water + ml of 20% alcohol) averaged across all subjects for each session of the two-bottle choice procedure. Error bars represent standard error of the mean.

Figure 2-2 depicts the average number of responses on the target lever (red data path) and alternative reinforcement chain (blue data path) as a function of session for the Sal (open circles) and Nic (closed circles) groups, across each phase of the experiment. The average number of target responses per session was relatively high for both groups during Baseline (when responses on this lever produced alcohol), decreased during Alternative Reinforcement (when responses on this lever no longer produced alcohol and

responses on a chain produced chocolate pellets), and increased during Resurgence Testing (when responses to both manipulanda were placed on extinction). Responding on the chain increased during Alternative Reinforcement (when responses on the chain produced chocolate pellets) and decreased during Resurgence Testing (when responses on the chain no longer produced chocolate pellets) at similar rates for both groups.

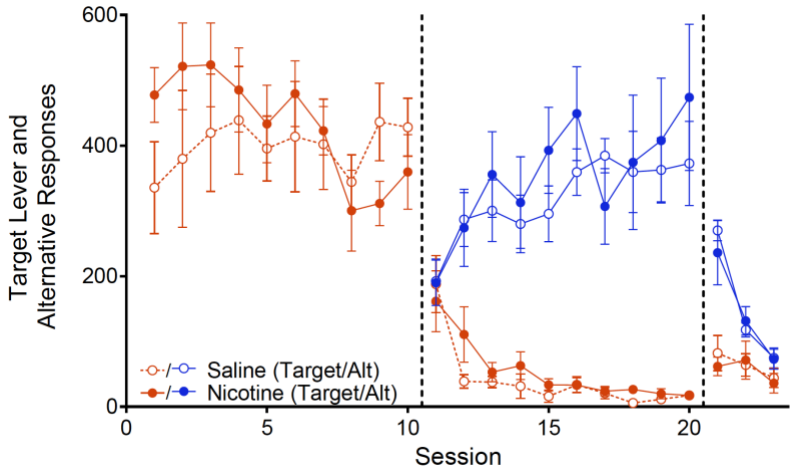

Fig 2-2. Average Target (red data paths) and Alternative (blue data paths) manipulanda responses plotted as a function of session across phases. Filled circles represent data for the Nicotine group and open circles represent data for the Saline group. Error bars represent standard error of the mean.

The number of inactive lever responses per session did not significantly increase for either group from the last session of Alternative Reinforcement (Nic: M = 12.17, SEM = 7.37; Sal: M = 11.17, SEM = 3.89) to the first session of Resurgence Testing (Nic: M = 20.67, SEM = 9.47; Sal: M = 10.00, SEM = 2.91). A 2 X 2 (Session X Group) mixed-model ANOVA performed on inactive lever responses between the last session of Phase 2 and the first session of Phase 3 revealed non-significant main effects of session $F(1,10) = .618$, $p = .45$, $\eta_{p2} = .058$ and group $F(1,10) = .012$, $p = .526$, $\eta_{p2} = .041$ and a non-significant Session X Group interaction $F(1,10) = 1.073$, $p = .325$, $\eta_{p2} = .097$. Thus, inactive lever responding did not increase when alternative reinforcement was removed,

indicating that responding during Phase 3 was directed at the target lever, rather than the product of a general increase in responding induced by extinction of the alternative response.

The final linear mixed-effects model (referred to as "main model" henceforth for simplicity) included the addition of a random slope effect of session, which significantly improved the model, χ_2 (2) = 10.59, p = .005. Responding shifted systematically as a function of session and phase. This result is evident in the main model (see Table 2-1) by significant main effects of Session (χ_2 [1] = 15.03, p < .001) and Phase (χ_2 [2] = 958.45, p < .001). The number of lever presses per session for the Sal and Nic groups, however, was not significantly different throughout the experiment. This result is illustrated by the lack of a main effect of Group (χ_2 [1] = 1.86, p = .17). The interaction between Session, Group, and Phase was significant (χ_2 [2] = 9.75, p = .008), however, which required follow-up analyses to understand. Thus, the main model was used to evaluate differences in responding across phases, but group differences and trends of responding within each phase are determined from follow-up models.

Fixed Effects	**β**	**S.E.**
Intercept	328.03	25.47
Session	-22.96	4.96
Saline	92.05	36.02
Alternative Reinforcement	-333.27	31.76
Resurgence	-258.75	41.49
Session x Saline	27.58	7.01
Session x Alternative Reinforcement	9.74	5.95
Session x Resurgence	10.13	27.35
Saline x Alternative Reinforcement	-98.58	44.92
Saline x Resurgence	-78.57	58.68
Session x Saline x Alternative Reinforcement	-25.88	8.41
Session x Saline x Resurgence	-33.83	38.67
Random Effects	**Variance**	**S.D.**

Subject (Intercept)	864.40	29.40
Session	41.30	6.43
Residual	8761.70	93.60

Table 2-1. Multilevel model results from the full final model.

During baseline, the two groups showed different trends in the number of responses per session across sessions (see Figure 2-1). The Nic group showed a downward trend in the number of target responses across Baseline sessions relative to the Sal group. This finding is evident in the follow-up model of responding in baseline (see Table 2-2) where a significant Session X Group interaction (χ^2 [1] = 6.28, p = .01) was observed. Despite this difference in the trend of responding for alcohol, there were no differences in the number of responses per session between groups in any given session (all ps > .13).

Fixed Effects	**β**	**S.E.**
Intercept	328.03	44.64
Session	-22.96	7.78
Saline	92.05	63.13
Session x Saline	27.58	11.00

Random Effects	**Variance**	**S.D.**
Subject (Intercept)	8495.10	92.17
Session	241.60	15.54
Residual	10014.90	100.07

Table 2-2. Follow-up model for Baseline Phase.

From Baseline to Alternative Reinforcement, the main model showed a significant decrease in target responding across both groups (t [254] = 17.03, p < .001). Figure 2-1 shows that target responding decreased substantially from the end of Baseline to the beginning of Alternative Reinforcement for both groups. Within the Alternative

Reinforcement phase, target responding decreased across sessions in both groups to a similar extent. This effect is evident in the Alternative Reinforcement follow-up model (see Table 2-3), which shows a significant main effect of Session (χ_2 [1] = 53.73 p < .001), but no significant main effect of Group (χ_2 [1] = 1.44, p = .223) nor a Session X Group interaction (χ_2 [1] = 0.25, p = .61).

Fixed Effects	**β**	**S.E.**
Intercept	-5.24	13.01
Session	-13.22	3.74
Saline	-6.53	18.39
Session x Saline	1.70	5.28
Random Effects	**Variance**	**S.D.**
Subject (Intercept)	203.70	14.27
Session	55.30	7.44
Residual	2348.30	48.46

Table 2-3. Follow-up model for Alternative Reinforcement Phase.

From Alternative Reinforcement to Resurgence Testing, target responding increased for both groups to a similar extent (see Figure 2-3). Results from the main model showed a significant increase in target responding across both groups (t [254] = -2.88, p = .004); however, there was no difference between groups in target responding on the first day of Resurgence testing (t [150] = -0.26, p = .80). These results are depicted in the first data point of the last phase in Figure 2-2. To further highlight this finding, Figure 2-3 depicts the proportion of baseline target responses as a function of session, for the last three days of Alternative Reinforcement and the three days of Resurgence Testing for the Sal (open circles) and Nic (closed circles) groups. There was an increase in proportion of baseline responding from the last day of Alternative Reinforcement to the first day of

Resurgence Testing in both groups, but the increase was similar for both groups (i.e., there was no group difference in the degree of resurgence).

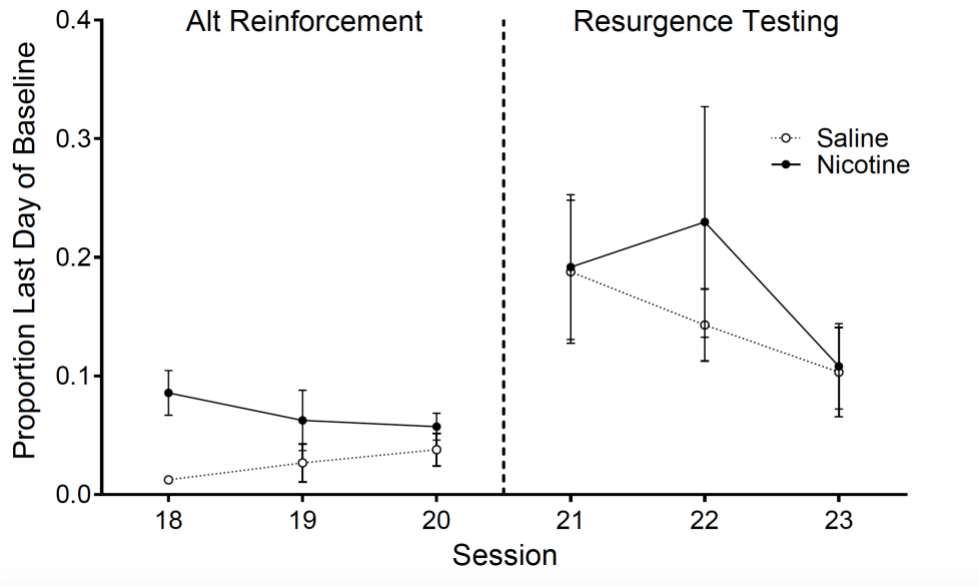

Fig 2-3. Average proportion of Baseline Target (alcohol) lever responses plotted as a function of session for the Nicotine and Saline groups. Data are plotted for the last three days of the Alternative Reinforcement Phase (left) and the three days of Resurgence Testing (right). Filled circles represent data for the Nicotine group and open circles represent data for the Saline group. Error bars represent standard error of the mean.

The two follow-up analyses also yielded no significant results. All rats responded on the chain at the beginning of the first session of Resurgence Testing. However, there was no group difference in the latency to the first response emitted (Nic: *Mdn* = 2.67 mins.; Sal: *Mdn* = 2.01 mins.) on the target lever during the first session of resurgence testing, $U = 17.00$, $p = .937$. There was also no correlation between the degree of resurgence (i.e., the number of target responses on the first day of Resurgence – the number of target responses on the last day of Alternative Reinforcement) and average consumption of alcohol for the last three days of the two-bottle choice procedure, $r_s(10) = .378$, $p = .227$.

Discussion

The results clearly illustrate that resurgence of alcohol seeking occurred in both the Nic and Sal groups. That is, in both groups, there was a significant increase in the number of target responses on the first day of Resurgence Testing relative to the number of target responses on the last day of Alternative Reinforcement. The findings for both groups in this experiment replicate the few prior studies that have shown resurgence of alcohol seeking [34,39].

This study is the first to investigate the effect of nicotine on resurgence of alcohol seeking. We did not find any evidence to support our hypothesis that nicotine augments relapse for alcohol seeking. There were no group differences observed across the entire study. Both groups responded on the target lever for alcohol to a similar degree during Baseline, both groups decreased responses on the target lever to a similar degree during Alternative Reinforcement, and both groups increased responses on the target lever during Resurgence Testing to a similar degree.

The results of the current study suggest that nicotine administration does not influence resurgence for alcohol seeking, but it is also possible that that the methodology employed hindered our ability to detect an effect of nicotine on resurgence of alcohol seeking. Osmotic minipumps have been used extensively to investigate the effects of chronic drug exposure. They are a useful tool that overcomes many challenges that are encountered with other drug delivery techniques (e.g., stress, conditioned drug effects from regular injections, costly equipment, lengthy training of staff, etc.). Osmotic minipumps have been used successfully to investigate the relation between continuous nicotine exposure and alcohol self-administration [40].

However, Brynildsen et al. [41] argue that continuous nicotine delivery, via osmotic minipumps, may not adequately model human nicotine intake. Human smokers (and "vapers") have an intermittent pattern of nicotine intake throughout the day and prolonged withdrawal throughout the night. Brynildsen et al. argue that this pattern of intake allows nicotinic acetylcholine receptors to return to a fully active state between smoking episodes [42]. The intermittency of nicotine exposure in human smokers is thought to be critical to the addictive nature of the drug and may also play an important role in the reward-enhancing effects attributed to the drug. By using a continuous nicotine delivery method in the current study, the reward-enhancement of alcohol by nicotine may have been affected, as the reward-enhancing properties of nicotine are mediated by these receptors as well [43].

The decreasing trend in target responding for the Nic group during Baseline (as opposed to stable responding for Sal group during this phase; see Figure 1) may be indicative of desensitization of nicotinic acetylcholine receptors. The initial elevation in target lever responding for the Nic group relative to the Sal group suggests that nicotine may have made alcohol more reinforcing, but this effect waned across sessions to the point that the Nic group actually responded for alcohol slightly less than the saline group by the end of this phase. This decreasing trend in target responses may be the product of nicotinic acetylcholine receptor desensitization and directly related to our decision to use continuous delivery of nicotine as opposed to intermittent delivery of nicotine. Future research should investigate the effect of intermittent nicotine exposure on resurgence of alcohol seeking to assess whether or not the same results are observed.

In summary, we investigated the effect of continuous nicotine exposure on resurgence of alcohol seeking. We predicted and found resurgence of alcohol seeking in both the Nic and Sal groups. We further predicted, however, that nicotine would augment resurgence of alcohol seeking relative to a saline control group. We found no evidence to support this latter hypothesis. However, this null result may be due to the continuous drug delivery method that was chosen, and different results may be observed if nicotine administration was conducted intermittently as opposed to continuously.

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CHAPTER III

THE EFFECT OF NICOTINE AND NICOTINE + MAOI ON THE VALUE OF ALCOHOL: A SHORT REPORT

Abstract

Alcohol is the most commonly abused drug in the United States and many people suffer from Alcohol Use Disorder. Many factors are associated with Alcohol Use Disorder, but the causal role of comorbid nicotine use has not been extensively considered. Nicotine has reward-enhancing properties and may increase the value of alcohol. Monoamine oxidase inhibition increases nicotine self-administration and may increase the reward-enhancing effects of nicotine. We assessed the effect of nicotine and nicotine in combination with a commonly used monoamine oxidase inhibitor (tranylcypromine) on the value of alcohol using a progressive ratio schedule of reinforcement in rats. Nicotine administration increased the breakpoint for alcohol, but nicotine in combination with tranylcypromine decreased the breakpoint for alcohol. The current study adds to previous research showing that nicotine increases the value of alcohol. This finding has important implications for the etiology of addiction, due to the comorbidity of smoking with many drugs of abuse. The finding that nicotine in combination with tranylcypromine reduces the value of alcohol warrants further investigation.

Reference:

Frye, C. C., Galizio, A., Haynes, J. M., DeHart, W. B., & Odum, A. L. (2019). The effect of nicotine and nicotine+ monoamine oxidase inhibitor on the value of alcohol. *Behavioural Pharmacology*, *30*(4), 363-369.

Keywords: Nicotine, Alcohol, Monoamine Oxidase Inhibitor, Self Administration,

Substance Abuse

Introduction

Alcohol is the most commonly abused drug in the United States (Johnston et al., 2013). In 2014, over fifty percent of Americans (12 and older) reported being current drinkers of alcohol (Center for Behavioral Health Statistics and Quality, 2015). Excessive alcohol consumption is responsible for an average of 88,000 deaths and costs the United States over $220 billion each year (Esser et al., 2014). The majority of adult Americans drink alcohol regularly (Centers for Disease Control and Prevention, 2015), but the frequency and intensity of drinking varies dramatically across individuals (e.g., Ward et al., 2015).

Most people who drink are able to moderate their use, but a minority of individuals are unable to moderate use and develop an alcohol use disorder (AUD). The Diagnostic and Statistical Manual of Mental Disorders (DSM-5) outlines the criteria for diagnosis of AUD, which consists of at least 2 symptoms out of a possible 11 (e.g., more than once wanted to cut down or stop drinking but couldn't). A recent study, using a representative sample, found that 13.9% and 29.1% of people have met the criteria for AUD in the previous year or at some point in their life, respectively (Grant et al., 2015). AUD is a chronic illness characterized by problematic drinking patterns, which has drastic detrimental effects on quality of life (Dawson et al., 2009).

Of the many factors that contribute to AUD, nicotine use is under investigated. The heritability of AUD is high (see Verhulst, Neale, and Kendler, 2015 for a meta-analysis on the topic), and several genes (susceptibility factors and protective factors) have been linked to the disease (see Foroud & Phillips, 2012 for a review). Many environmental factors, such as psychosocial risk factors (e.g., Donovan, 2004), personality (e.g., Gratzer et al., 2004), parental substance use (e.g., Jacob et al., 2003), peer influences (Fergusson et al., 2002), and psychiatric disorders (e.g., Kessler et al.,

1997), have also been associated with AUD. One robust risk factor for the development of AUD – that has received surprising little attention – is nicotine use. Between 80 to 95% of alcoholics are tobacco cigarette users (Patten et al., 1996). Daily smoking abstinence is associated with lower alcohol consumption, lower urge to drink, greater alcohol abstinence self-efficacy, and perceived self-control demands (Cooney et al., 2015). Smoking during abstinence, when people are in treatment for alcohol and cigarette dependence, is associated with an increase in the frequency of urges to drink (Cooney et al., 2007; Cooney et al., 2003). Smoking status in adults with remitted AUD is associated with the likelihood of alcohol abuse and dependence 3 years later (Weinberger et al., 2015). These epidemiological associations suggest that the causal role of nicotine in the development of AUD warrants investigation.

Nicotine is a complex drug of abuse. According to the dual-reinforcement model of nicotine action, nicotine has two distinct reinforcing effects upon ingestion: primary reinforcing effects and reward-enhancing effects (Caggiula et al., 2009). The primary reinforcing effects of nicotine are due to its action on the central nervous system, where it acts as a stimulant, increasing alertness and altering mood. As a primary reinforcer, nicotine is relatively weak (e.g., Chaudhri et al., 2007). The reward-enhancing effects of nicotine are much more pronounced. Nicotine increases the value of other stimuli in animals (e.g., Caggiula et al., 2001; 2002; Chaudhri et al., 2007; Donny et al., 2003; Palmatier et al., 2006) and in humans (e.g., Attwood et al., 2009; Dawkins et al., 2007; Perkins and Karelitz, 2013). The reward-enhancing effects of nicotine may cause an increase in the value of other drugs of abuse such as alcohol. If nicotine increases the

value of alcohol, then it may increase acquisition and maintenance of alcohol drinking, making AUD more likely.

The reinforcing efficacy of nicotine is augmented by monoamine oxidase inhibitors (MAOIs). Monoamine oxidase is involved in the breakdown of many organic compounds, including the neurotransmitters serotonin and dopamine. Smokers show a 40% reduction in levels of MAO relative to non-smoking controls (Fowler et al., 1996). A large body of literature indicates that MAOI drastically increases self-administration of nicotine (e.g., Guillem et al, 2005; Smith et al., 2015; Villégier, Lotfipour, McQuown, Belluzzi, & Leslie, 2007). Recent research suggests that MAOIs increase the primary and reward-enhancing effects of low dose nicotine (e.g., Smith et al., 2016). If MAOI augments the reward-enhancing effects of nicotine, then it may increase nicotine's influence on the value of other stimuli, such as alcohol.

In the current study, we investigated the effect of nicotine and nicotine + MAOI on the value of alcohol using a Progressive Ratio (PR) schedule of reinforcement. First, we trained rats to consume 20% alcohol in their home cage. We then trained the rats to respond on levers for 20% alcohol in operant chambers. Next, we implemented a PR schedule to assess the value of alcohol for each subject. In PR schedules of reinforcement, the response requirement increases after each reinforcer delivery (see Hodos & Kalman, 1963). The dependent measure, "Breakpoint", reflects the response requirement at which subjects stopped earning reinforcers. Breakpoint thus serves as a measure of a reinforcer's value. Finally, we assessed the change in Breakpoint during drug administration (saline, nicotine, or nicotine + MAOI, depending upon group assignment). Our hypotheses were two-fold: We expected nicotine to increase the value

of alcohol (i.e., Breakpoint) and nicotine + MAOI to increase the value of alcohol (i.e., Breakpoint) to greater extent than nicotine alone.

Method

Subjects

Fifteen experimentally naïve male Long Evans rats, aged 71-90 days, were obtained from Charles River Laboratories. After completing Baseline (see below), rats were randomly assigned to a Sal group (saline; $n = 5$), Nic group (nicotine alone; $n = 5$), and Nic + MAOI group (nicotine with tranylcypromine; $n = 5$). Groups were matched in terms of alcohol consumption in Baseline. Rats were provided ad libitum access to food and water during the intermittent access two-bottle choice procedure (IA2BC; see below) and were reduced to 80% of their free-feeding weight prior to the Baseline Phase. Rats were fed LabDiet® rat chow and had continuous access to water in their home cages throughout all phases of the experiment. Rats were individually housed in a temperature-controlled colony room with a 12:12 hour light/dark cycle. Sessions were conducted every day at approximately the same time each day during the light cycle. All procedures were approved by the Institutional Animal Care and Use Committee at Utah State University.

Materials

Apparatus. Four standard operant chambers (Coulbourn Inc.) enclosed in light- and sound-attenuating cubicles were used for all experimental sessions. Each chamber was equipped with two fixed levers (one active and one inactive) on the front wall. Each lever had a green, red, and yellow LED light above each lever. A food and liquid receptacle was located in the middle of the front panel and equipped with a light and

photosensor beam for detecting head-entries. There was a dipper located under the receptacle that could be raised to provide 0.1 mL of liquid solution. Each chamber had a houselight located on the top modular panel of the center back wall to provide general illumination.

Drugs. Distilled water and 95% ethanol were mixed to make a 20% ethanol solution, which was consumed orally in the home cage during IA2BC and in the operant chamber during all other experimental sessions. For pre-session drug injections, the drug solution used for the Sal group was 0.9% sterile saline solution. The drug solution for the Nic group was made using nicotine hydrogen tartrate salt, dissolved in 0.9% sterile saline solution. Nicotine was administered in doses of 0.2 mg/kg (free base; pH unadjusted). The drug solution for the Nic + MAOI group was made using nicotine hydrogen tartrate salt and tranylcypromine, dissolved in 0.9% sterile saline solution. Tranylcypromine is a commonly used non-selective MAOI. This solution was administered in doses of 0.2 mg/kg nicotine (free base; pH unadjusted) and 1.0 mg/kg tranylcypromine. Saline, nicotine, and nicotine with tranylcypromine solutions were administered subcutaneously five minutes prior to experimental sessions. All drugs were obtained from MP Biomedicals, LLC.

Procedure

Intermittent Access Two-Bottle Choice Procedure. IA2BC began within two weeks of the rats' arrival in the laboratory. This procedure was based on that used by Simms and colleagues (2008). During IA2BC, rats were given continuous access to food and water. Three days per week (half of the subjects received alcohol on Monday, Wednesday, and Friday and the other half received alcohol on Tuesday, Thursday, and

Saturday), rats were given access to 20% ethanol for 24 hours, starting at the beginning of the dark cycle. IA2BC was conducted for 8 weeks.

Baseline. Following IA2BC, each rat responded on a PR schedule on one lever (the active lever) for 10 sessions. The other lever (the inactive lever) was not associated with any programmed consequences but served as a measure of non-specific activity. Active lever assignment to left or right was counterbalanced across rats. Reward deliveries consisted of access to a single dipper (0.1 mL) of 20% ethanol raised for 10 s. If the photosensor beam was broken while the dipper was raised, the reward was considered "consumed" and 0.1 mL was added to the solution consumption measure for the session. In a PR schedule, the ratio of responses to rewards is increased with each successive reward delivery. The increase in ratio requirement is known as "step size". We used a non-fixed step size. Specifically, the ratio requirements occurred in the following order: 1, 1, 2, 2, 3, 3, 4, 4, 5, 6, 7, 8, 9, 10, 12, 14, 16, 18, 20, 25, 30, 35, etc. Sessions ended after 5 mins with no recorded responses or one hour, whichever occurred first. Rats were assigned to groups following Baseline to match for alcohol consumption. All subjects earned access to 0.3 g/kg alcohol or greater (Simms et al., 2008) during Baseline.

Drug Administration. Following Baseline, subjects completed 5 sessions of Drug Administration. These sessions were identical to Baseline, except that rats received a subcutaneous injection 5 mins before the session. Rats in the Sal group received saline alone, rats in the Nic group received nicotine (0.2mg/kg free base) suspended in a saline base, and rats in the Nic + MAOI group received nicotine (0.2 mg/kg free base) and tranylcypromine (1.0 mg/kg) in a saline base.

Data Analysis

Multilevel modeling (e.g., mixed modeling, hierarchical linear modeling; MLM) was used to analyze the change in responding for alcohol as a function of session, drug phase, and group. Multilevel modeling was selected over techniques such as repeated measures ANOVA for two important reasons. First, MLM allows us to quantify the contribution of individual subject variability in explaining the dependent variable (i.e., random effects; Gelman, 2006) whereas ANOVA compresses variability into group statistics. Random intercepts (individual subject variability in the first data point) and random slopes (individual subject variability in the degree of change in the dependent variable over time) can both be included to quantify individual subject variability. This allowed us to analyze the change in responding for alcohol before and after drug administration while permitting the degree of individual subject responding (both during baseline and during drug administration) to vary. Second, MLM allows us include all data and compare changes between Baseline and Drug Administration without central tendency serving as the main datum. Additionally, pairwise comparisons were conducted to compare the change in responding for alcohol between baseline and drug administration for each group using a false discovery rate adjustment for multiple comparisons. All statistical and visual analyses were conducted in R (R Core Team, 2017) using the lmer (Bates, Maechler, Bolker, & Walker 2015), and lsmeans (Lenth, 2016) packages.

The final model was selected because it accounted for the largest percentage of variability in the data (76%) while removing fixed and random effects that did not improve the model fit. The final model included a random intercept for subject (40% of variability) and a random slope for drug phase (baseline versus drug administration; 36%

of variability; see Table 1). The large random slope indicates that the degree of change in alcohol consumption between baseline and drug administration varied considerably between subjects. All analyses of the effects of nicotine or nicotine + MAOI were made in comparison to saline.

Results

Figure 1 depicts the mean and individual subject breakpoints for the Sal (Panel A), Nic (Panel B), and Nic + MAOI (Panel C) group along with the fit for the MLM with 95% confidence intervals. Table 1 shows the results of the MLM including the coefficients and respective 95% confidence intervals for each fixed effect. The breakpoint for alcohol was higher for the Nic group than for the Sal group during Drug Administration (significant interaction of drug phase and Nic). The breakpoint for alcohol did not differ between the Nic + MAOI group compared to the Sal group during Drug Administration (no significant interaction of drug phase and Nic + MAOI). Panel D depicts pairwise comparisons across phases for each of the three groups (Sal, Nic, and Nic + MAOI). For within-group pairwise comparisons across phase, administration of nicotine increased breakpoint (t = 2.407, p < .05), administration of nicotine + MAOI decreased breakpoint (t = -2.938, p < .05), and administration of saline did not change breakpoint (t = 1.187, p = 0.336) relative to Baseline.

Finally, to assess whether non-specific activity generated by nicotine or nicotine + MAOI influenced the results, we conducted a 2 (Phase) by 3 (Group) ANOVA on inactive lever responses. We found no main effect of Group (F(2,12) = .063, p =0.939) or Phase (F(1,12) = .567, p =0.466) and no significant interaction (F(2,12) = 2.547, p

=0.120). Thus, we concluded that the results on breakpoint for alcohol were not likely due to general locomotor activity effects induced by the drugs.

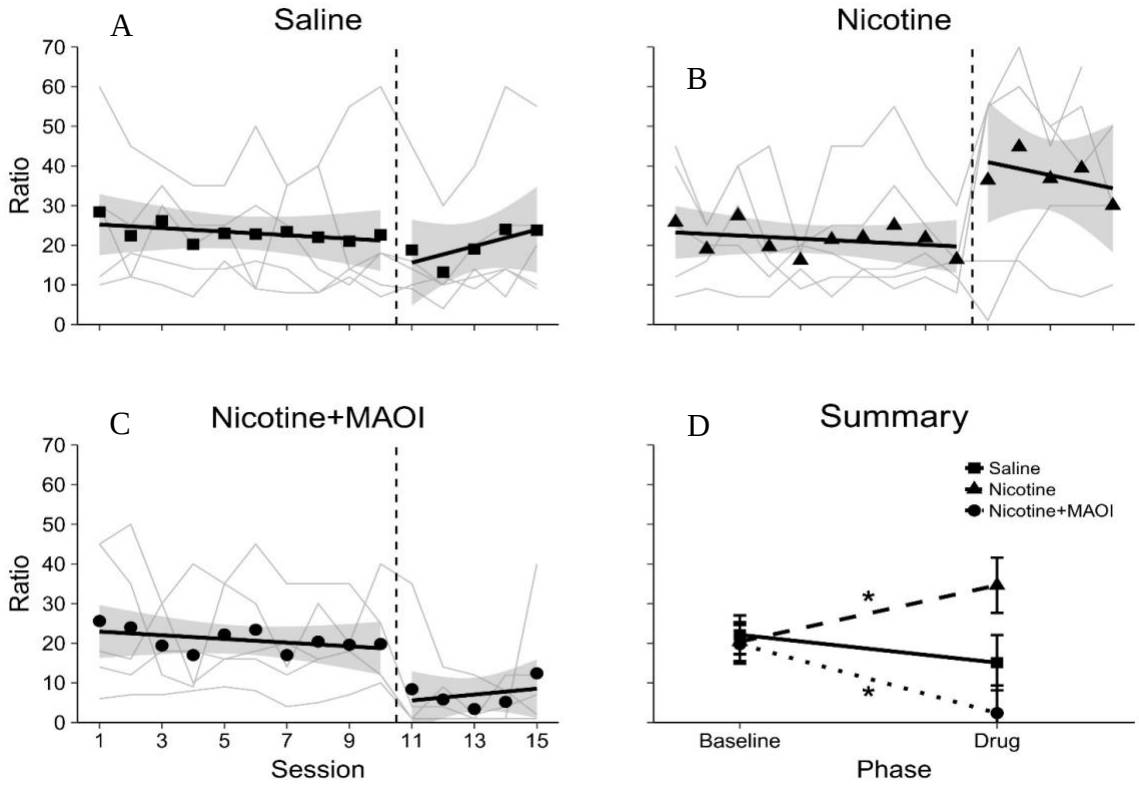

Figure 3-1. Top Left (A), Top Right (B), and Bottom Left Panel (C): Breakpoints for individual subjects (gray lines) with model fit (black line) to mean breakpoints for the Saline, Nicotine, and Nicotine + MAOI groups, respectively. Gray shading highlights the 95% confidence interval of the model fit. The dotted line indicates the phase change from baseline to drug administration. Bottom Right Panel (D): Within-group pairwise comparisons across phases. * indicates significant change from baseline to drug administration.

Table 1

Multilevel model results

Fixed Effects	β	S.E.	Conf. Int.	
Intercept	25.589***	5.021	15.157	36.021
Session	-0.434	0.228	-0.884	0.014
Drug Phase	-17.962	9.901	-37.501	1.576
Nicotine Group	-1.740	6.875	-16.125	12.645
Nicotine+MAOI Group	-2.360	6.875	-16.745	12.025
Drug Phase x Session	1.368*	0.694	0.001	2.734
Drug Phase x Nicotine	21.260***	6.919	6.783	35.737
Drug Phase x Nicotine+MAOI	-10.360	6.919	-24.837	4.117

Random Effects	Variance	S.D.
Subject (Intercept)	111.732	10.570
Drug Phase	100.375	10.018
Residual	64.378	8.023

Table 3-1. Table of MLM results including both fixed and random effects. * $p < .05$, ** $p < .01$, *** $p < .001$.

Discussion

The current study shows that nicotine increases the value of alcohol and nicotine + MAOI decreases the value of alcohol. Pairwise comparisons indicate that nicotine produced an increase in breakpoint relative to baseline, saline produced no change in breakpoint relative to baseline, and nicotine + MAOI produced a reduction in breakpoint relative to baseline. These findings were consistent with our first hypothesis that nicotine administration would increase the breakpoint for alcohol due to the reward-enhancing effects of nicotine. However, our results did not support our second hypothesis, that nicotine + MAOI administration would increase the breakpoint for alcohol to a greater extent than nicotine alone. This hypothesis was based on previous findings that MAOI

administration increases nicotine self-administration (e.g., Smith et al., 2015). Because MAOI increases nicotine self-administration, we expected MAOI to enhance the reward-enhancing properties of nicotine and thus, increase nicotine's augmentation of the value of alcohol. However, the present results contradicted this hypothesis; nicotine + MAOI decreased the breakpoint for alcohol. In fact, subjects rarely responded for alcohol when under the conjoint influence of nicotine and MAOI.

The MLM showed that breakpoints for the Nic group were different from the Sal group during Drug Administration (i.e., there was a significant interaction between phase and the Nic group), but that breakpoints were not different between the Sal group and the Nic + MAOI group (i.e., there was a non-significant interaction between phase and the Nic + MAOI group). The possible reason that breakpoints were not different between the Nic + MAOI and the Sal group is two-fold: 1) The breakpoints for the Sal group decreased slightly during Drug Administration (though non-significantly) and 2) The breakpoints for the Nic + MAOI group dropped to near-zero levels (i.e., subjects in the Nic + MAOI group rarely responded during Drug Administration), indicating a potential floor effect. Thus, we believe that the within-group pairwise comparisons demonstrating differences between phases within each group are a better representation of how the drugs affected behavior.

Results from the inactive lever suggest that the non-specific activity effects of the drug did not affect the results in the current study. We found no significant differences in inactive lever responding across phases. The Group X Phase interaction for the ANOVA run on the inactive lever was near significance, but this result was largely driven by a reduction in responding on the inactive lever during drug administration in the NIC +

MAOI group (Baseline M = 0.52 response per min., Drug M = 0.15 responses per min.). We did not specifically measure locomotor activity under the influence NIC + MAOI in the current study, however prior research suggests that doses of tranylcypromine, similar to the dose used in the current study, does not affect locomotor behavior (Guillem et al., 2005; Villegier et al., 2003). Furthermore, higher doses of tranylcypromine enhance locomotor behavior, rather than reduce it. Thus, we conclude that the psychomotor effects of the drugs did not substantially influence the current findings.

The current study clearly shows that nicotine increases the value of a drug of abuse (in this case, alcohol). This finding, with Long Evans rats, is in-line with prior research in humans (e.g., Barrett, Tichauer, Leyton, & Pihl, 2006) and Wistar rats (e.g., Leão et al., 2015), suggesting that this is a robust phenomenon with theoretical and applied implications. Nicotine consumption may facilitate acquisition and maintenance of responding for alcohol and other drugs. Smoking is an associated comorbidity for most drugs of abuse, and quitting smoking predicts success for cessation of taking other drugs (e.g., Lemon, Friedmann, & Stein, 2003). With the rise in electronic cigarette use affecting all age groups (see Chapman & Wu, 2014), new populations of individuals are being exposed to nicotine (especially young people; e.g., Dobbs, Hammig, & Sudduth, 2016; Dockrell et al., 2013) – populations that may not have otherwise been exposed to nicotine. Thus, although electronic cigarettes are promoted as a “safer” alternative (e.g., Caponnetto et al., 2013) to tobacco cigarette smoking, they could alter the probability of drug acquisition and make addiction or dependence more likely.

There are at least two potential explanations for the above findings regarding the combined effect of nicotine and MAOI reducing the value of alcohol. First, MAOI may

reduce the motivation for drinking alcohol, and thus override the reward-enhancing effects of nicotine. There is some precedence for this interpretation. Although the effect of MAOI on alcohol drinking has not been well investigated, there is at least one report of MAOI decreasing alcohol consumption. Sanders, Collins, Peterson, and Fish (1977) found that two out of three different types of MAOI reduced voluntary alcohol consumption in mice. They argued that the mechanism for this effect on alcohol consumption was due to increased acetaldehyde levels, rather than MAO inhibition. Specifically, all three types of MAOI affected MAO levels similarly, but only the two MAOIs that greatly increased acetaldehyde levels led to decreased alcohol consumption. Tranylcypromine (the MAOI used in our study) has only been linked to a small elevation in acetaldehyde levels (Dembiec, MacNamee, & Cohen, 1976). However, the potential for tranylcypromine to directly reduce the motivation to consume ethanol cannot be ruled out. Another possible explanation is that MAOI enhanced the reinforcing properties of nicotine to such an extent that animals no longer sought further stimulation that would be provided by ethanol. The conjoint effect of MAOI and nicotine on responding for another reward or drug has not been investigated, but the combination of the effects of these two drugs could synergize to the point that stimulation produced by a third drug is no longer reinforcing.

The effect of nicotine + MAOI on alcohol value is surprising given that smoking tobacco cigarettes inhibits MAO, but many tobacco cigarette smokers drink alcohol regularly. In the current study, we administered an acute dose of tranylcypromine that presumably produced inhibition of MAO. However, acute doses of tranylcypromine have also been shown to have off-target effects such as short-term serotonin release that occurs

prior to the longer-term MAO inhibition (e.g., Villegier et al., 2011). It is possible that this short-term serotonin release, as opposed to MAO inhibition, is responsible for the effects observed in the current study. Treatments that increase serotonin levels also decrease alcohol drinking (e.g., Gill, Amit, & Koe, 1988; McBride, Murphy, Lumeng, & Li, 1990). Future research could investigate whether tranylcypromine has this effect on alcohol value through MAO inhibition or these off-target effects (e.g., by having a group that receives tranylcypromine 23 hours prior to the session and one that receives the drug immediately prior to the session).

In conclusion, we have shown that nicotine increases the value of alcohol and nicotine + MAOI decreases the value of alcohol. It is not clear whether the augmentation of the value of alcohol by nicotine is a general effect that would generalize to other drugs of abuse. Future research should address this issue. The reason that nicotine + MAOI decreased the value of alcohol is also not clear. Future research should investigate the effect of MAOI alone on alcohol drinking to assess whether this effect is the product of the combined effect of nicotine and MAOI or the result of MAOI alone. Future research could also compare the effect of nicotine + MAOI on self-administration of other drugs of abuse, as there is some evidence of tranylcypromine (the MAOI used in the current study) augmenting the reward-enhancing effects of low-dose nicotine (see Smith et al., 2016).

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CHAPTER IV

INVESTIGATING NICOTINE AND ALCOHOL INTERACTIONS VIA PURCHASE TASKS

Abstract

Alcohol and tobacco are the two most commonly used drugs in the United States. Despite these drugs being commonly co-abused, relatively few studies have investigated how exposure to one drug influences demand for the other drug in humans. In Experiment 1, we investigated how the hypothetical opportunity to smoke tobacco cigarettes affected demand for alcoholic beverages. In Experiment 2, we investigated how the hypothetical opportunity to drink alcoholic beverages affected demand for tobacco cigarettes. In Experiment 3, we investigated the economic relationship between tobacco cigarettes and alcoholic beverages by assessing cross-price elasticity of the drugs to classify them as substitutes, complements, or independent goods. All three experiments utilized hypothetical purchase tasks and data were collected with Amazon Mechanical Turk©. In Experiment 1, there was no difference in any of the demand indices for alcoholic beverages across the smoking and non-smoking contexts. In Experiment 2, one index of demand (Maximum Expenditure; Q_0) for tobacco cigarettes was different across the drinking and non-drinking contexts, but it was higher in the non-drinking context than in the drinking context, which was opposite of our prediction. In Experiment 3, we found that the vast majority of participants treated alcoholic beverages and tobacco cigarettes as independent goods. There is robust evidence that exposure to nicotine increases the value of alcohol in preclinical studies and this finding has been replicated in human laboratory studies. There is also evidence that alcohol increases the value of nicotine in preclinical and human laboratory studies. The fact that there was no evidence to support these findings in Experiment 1 and Experiment 2 suggests that people may be unable to accurately gage how they would behave under the imagined influence of a drug. This finding could point to a larger limitation of using hypothetical purchase tasks to answer fundamental behavioral pharmacology questions. The findings of Experiment 3 were also contrary to the findings of laboratory and epidemiological studies, but consistent with the only other hypothetical purchase task to explore a similar question.

Introduction

Alcohol and tobacco are the two most commonly used drugs in the US (Center for Behavioral Health Statistics and Quality, 2019). Alcohol is a depressant and is rewarding due to its disinhibitory- and euphoria-producing effects. The active ingredient in tobacco, nicotine, is a stimulant, but its reinforcing properties are largely due to its reward-enhancing effects (i.e., nicotine is reinforcing because it increases the value of other stimuli; Caggiula et al., 2008). Nicotine and alcohol co-abuse is prevalent, but the relation between nicotine use and alcohol use is not well understood. Human clinical work suggests that smokers in treatment for alcoholism have more cravings than non-smokers and that smoking during alcohol abstinence increases the urge to drink (Hitschfeld et al., 2015; Cooney et al., 2015). Daily smoking abstinence is associated with lower alcohol consumption and cravings for alcohol (Cooney et al., 2003, 2007). Physiological states that are associated with smoking (e.g., elevated cortisol and elevated GABAA receptor levels) have been linked to relapse and craving for alcohol (Cosgrove et al., 2014; Gilbertson, Frye, & Nixon, 2010). Likewise, using alcohol has been shown to increase cravings for cigarettes (Sayette et al., 2005). Understanding how exposure to one of these drugs influences behavior in regard to the other drug will allow us to treat the use and co-abuse of these drugs more effectively.

In a recent study, we showed that nicotine increases progressive ratio breakpoint for alcohol reinforcement in Long-Evans Hooded rats (Frye, Galizio, Haynes, DeHart, & Odum, 2018). In progressive ratio schedules, the ratio of responses to rewards increases with each successive reward delivery until the ratio reaches a point at which no more rewards are earned (Hodos, 1965). The ratio at which no more rewards are earned is

termed the “breakpoint,” which served as the dependent measure in our study. Rats were divided into 3 groups (Control, Nicotine, or Nicotine + tranylcypromine) based on baseline alcohol self-administration levels such that there was not a difference across groups in terms of degree of alcohol self-administration on a progressive ratio schedule. Following the baseline phase, all subjects received a presession injection prior to self-administering alcohol on the same progressive ratio schedule during the drug phase. Subjects that received nicotine in their presession injection increased their responding and consumption relative to their own performance during baseline and had elevated responding during the drug phase relative to the other two groups.

Progressive ratio breakpoint may not be the best measure of reinforcer value, however. The results of Frye et al. (2019) replicated and extended previous experiments that showed that nicotine increases progressive ratio breakpoint for alcohol (e.g., Barrett, Tichauer, Leyton & Pihl, 2006; Leao et al., 2015), but this measure has limitations. Hursh and Silberberg (2008) point out several problems with progressive ratio breakpoint as a measure of reinforcer value. These problems include the fact that breakpoint is a discontinuous measure that provides no information about responding on ratios prior to the breakpoint, breakpoint tends to vary with manipulations of step-size (the size of the successive changes in the ratio progression), and breakpoint can be influenced by the amount of time that is required to pass without a response for the session to terminate (i.e., the duration that defines the terminal ratio). Hursh and Silberberg proposed economic demand as an alternative measure of reinforcer value that overcomes these problems.

Economic demand can be assessed by manipulating the unit price of a good and measuring consumption across a range of unit prices (see Hursh, 1980). In animal models, this unit price manipulation typically consists of an adjusting work requirement (e.g., the number of lever presses or the number of nose pokes) required to earn one unit of the reward (e.g., a food pellet or cocaine infusion) and assessing the number of rewards earned (consumption) at each work requirement (price). When consumption is plotted as a function of price in log-log coordinates, a demand curve is constructed. A demand curve is a useful tool to understand the elasticity of a particular good. Elasticity refers to the rate at which consumption declines with increases in price. The concept of elasticity provides a means for evaluating the abuse liability of a drug and an evaluation tool for assessing the potential for other compounds to mitigate the likelihood of abuse of a particular drug. Hursh and Silberberg (2008) proposed and tested a quantitative model that could be fit to a demand curve (Equation 4-1):

$$log_{10}Q = log_{10}Q_0 + k(e^{-\alpha \bullet Q_0 \bullet P} - 1) \quad (4\text{-}1)$$

where Q is the quantity consumed, Q_0 is consumption at zero price, k is a constant that specifies the range of the data in log units, α represents the inverse of the essential value of a good and determines the rate of decline in relative consumption as a function of increases in price (i.e., elasticity), and P represents the price of a good. Equation 4-1 is referred to as the exponential demand equation.

This quantitative methodology allows for several important empirical and derived measures related to reinforcer value. Intensity (represented as Q_0 in Equation 4-1) is the number of rewards consumed when the reward is available at its minimal price. Breakpoint, which was the dependent measure used in Frye et al. (2018) and other

experiments using progressive ratio schedules, is the price at which no rewards are earned and has the same meaning and interpretation in economic demand methodology. P_{max} is the point of unit elasticity on the demand curve. Thus, P_{max} represents the point on the demand curve where the reward transitions from inelastic demand to elastic demand (i.e., slope of -1). O_{max} is the point of maximum expenditure, or the maximum amount of work expended to earn the rewards. Finally, an important measure of reinforcer value is the essential value of a good (represented by $1/\alpha$ in Equation 4-1). The essential value of a good represents the rate of change in elasticity with increases in price (i.e., the rate of change of the slope of the demand curve).

Consumer demand methodology has provided insights in the field of behavioral pharmacology. In animal models, economic concepts have proven useful as an assessment of abuse liability of various drugs, the degree to which compounds reduce demand for a drug (i.e., identification of pharmacotherapeutics), and how demand for one drug of abuse is affected by the presence of other concurrently available drugs (i.e., cross-price elasticity between drugs; see Hursh, Galuska, Winger, & Woods, 2005). However, with human subjects, the use of this methodology for evaluation of drug abuse liability, compounds that reduce demand for drugs of abuse, and evaluation of potential substitutes for drugs of abuse has been limited due to logistical and ethical considerations (see Jacobs & Bickel, 1999).

Hypothetical purchase tasks provide a time and cost-efficient means of assessing reinforcer value in humans. The first hypothetical purchase task questionnaire was developed by Jacobs and Bickel (1999; though see Petry & Bickel, 1998 for a similar approach using ‘play money’ during a structured interview). In this study, opioid-

dependent outpatients were asked questions about how many cigarettes and bags of heroin (both alone and when concurrently available) they would purchase across a range of prices. The authors concluded that hypothetical purchase tasks provide a supplemental or, in instances where the laboratory assessments are difficult or impossible to conduct, alternative means of assessing reinforcer value for drugs of abuse.

Alcohol Purchase Tasks

The first hypothetical purchase task to assess alcohol purchasing was conducted by Murphy and Mackillop (2006). Murphy and Mackillop modified the hypothetical purchase task methodology that was employed by Jacobs and Bickel (1999) to assess alcohol demand. Participants stated the number of alcoholic drinks they would consume at a range of prices. The authors assessed the relation between alcohol demand indices and clinical symptomology (from alcohol-related questionnaires). They found significant correlations between demand indices (Intensity and O_{max}) and important alcohol-related clinical markers (number of drinks per week, number of heavy drinking episodes per week, and score on the Rutgers Alcohol Problem Inventory), providing the first evidence for the clinical utility of Alcohol Purchase Tasks (APTs).

Since Murphy and Mackillop (2006), several studies have been conducted to further assess the validity of APTs. Alcohol demand tends to correlate highly with self-report measures of drinking intensity and frequency. For example, Kiselica, Webber and Bornovalova (2016) conducted a meta-analysis that included 16 studies using an APT. The meta-analysis assessed the construct validity of APTs by estimating the effect size for correlations between demand indices and an alcohol-related outcome. They found a significant effect size for the relation between all demand indices assessed (i.e., Intensity,

Breakpoint, Omax, Pmax, and Elasticity) and all alcohol outcomes (i.e., alcohol consumption, binge/heavy drinking, alcohol problems, and alcohol use disorder symptomology). Mackillop and Murphy (2007) and Murphy et al. (2015) investigated the predictive utility of APTs for outcomes following a brief intervention. Both studies found that performance on an APT predicted alcohol consumption patterns following the intervention. The authors argued that these data suggest that APTs may be useful as a diagnostic tool for predicting clinical responses to alcohol interventions.

Several studies have assessed the reliability of APTs. Amlung et al. (2012) and Amlung and Mackillop (2015) compared responding on a hypothetical APT and an APT where one of the participants' responses would be actually received and consumed. Both studies found a high correspondence between the hypothetical APT and the potentially-real reward APT, suggesting that performance on hypothetical APTs reflects actual alcohol purchasing behavior. Amlung and Mackillop (2012) assessed the internal consistency of the APT by comparing performance on a version of the APT where the price increased in a systematic fashion across trials versus a version of the APT where the price order was randomly determined across trials. Although there were slight differences across APT versions (statistically significant differences were found at 5 out of the 25 prices at which alcohol purchasing was assessed), there was remarkable consistency across the two versions of the task, and the authors concluded that APTs have high internal reliability. Murphy, Mackillop, Skidmore, and Pederson (2009) and Acuff and Murphy (2017) assessed the stability of APT measures over a two-week and one-month time period, respectively. Both studies found good correspondence across the two time periods. Murphy and colleagues found large correlations across demand indices and no

significant differences across the time points. Acuff and Murphy found moderate correspondence between demand indices across the two time points and concluded that demand was especially stable in individuals that reported consistent drinking behavior across the duration of the study.

To date, relatively few studies have assessed the effect of an experimental manipulation on demand indices on APTs. Most studies employing an APT assess correlates of elevated demand for alcohol (e.g., symptoms of depression and PTSD; see Murphy et al., 2013) or group differences (e.g., smokers versus non-smokers; see Yurasek et al., 2013) in alcohol demand. However, the effect of some experimental manipulations on demand for alcohol have been examined using an APT. For example, several studies have found that hypothetical next-day responsibilities decrease demand for alcohol (e.g., Gentile et al., 2012; Gilbert et al., 2014; Murphy et al., 2014; Skidmore & Murphy, 2011). A few studies have found that induced stress and/or craving increase alcohol demand using an APT (e.g., Amlung & Mackillop, 2014; Owens, Ray, & Mackillop, 2015). Kaplan and Reed (2018) found that hypothetical happy hour drink specials increase alcohol demand using an APT. Kaplan et al. (2017) found that longer hypothetical drinking durations produce higher alcohol demand using an APT. Amlung et al. (2015) assessed the effect of a brief laboratory alcohol challenge (i.e., one group consumed alcohol before completing the APT) on demand for alcohol using an APT and found that demand increased during the ascending limb of alcohol intoxication and decreased thereafter. Finally, Teeters and Murphy (2015) found that telling participants to imagine that they would have to drive home after a drinking episode reduced demand for alcohol. Many of these studies used hypothetical manipulations to alter demand for

alcohol. However, no study has assessed the effect of hypothetical exposure to another drug on demand for alcohol.

In Experiment 1, we assessed the impact of hypothetical tobacco cigarette availability on alcohol demand using an APT. We expected to find elevated demand for alcohol when participants were told they would be able to smoke during the alcohol purchasing scenario, relative to when participants were told that they would not be able to smoke during the alcohol purchasing scenario.

Experiment 1

Experiment 1 examined how the opportunity to smoke tobacco cigarettes during a drinking episode influences purchases for alcoholic beverages. A large body of literature indicates that exposure to nicotine increases the value of alcohol in humans (e.g., Barrett, Tichauer, Leyton & Pihl, 2006) and non-human animals (e.g., Leao et al., 2015), but this finding has not been extended to hypothetical purchase tasks using economic demand indices. Extending this literature to a more sophisticated measure of reinforcer value, as well as to hypothetical rewards, could further validate the use of alcohol purchase tasks. Participants engaged in two APTs: one APT was completed in a hypothetical context in which participants were told that they *were not* permitted to smoke tobacco cigarettes and the other APT was completed in a hypothetical context where participants were told that they *were* permitted to smoke tobacco cigarettes freely. The key research question was, "Does the hypothetical opportunity to smoke tobacco cigarettes increase demand for hypothetical alcoholic beverages?"

Method

Participants

Participants were recruited and screened for eligibility online with Amazon Mechanical Turk (MTurk) until one hundred eligible participants were identified. Studies conducted on MTurk have obtained similar results to studies conducted in the laboratory (e.g., Crump, McDonnell, & Gureckis, 2013) and the use of crowdsourcing is an especially useful tool for addiction science research and behavioral economic research (see Strickland & Stoops, 2019; Zvorsky et al., 2019 for discussion). A screener (see Appendix A) was used to assess participant eligibility for the study. Participants were at least 21 years old, and reported the following: at least one heavy drinking episode in the past 30 days (4 drinks in one sitting for women and 5 for men), daily smoking of 10 or more tobacco cigarettes per day, smoking tobacco cigarettes for at least 3 months, and smoking tobacco cigarettes each day the past week. The study was only viewable by MTurk workers who had a 95% or better approval rating, had completed at least 100 studies, and self-identified as a smoker. Participants were paid $2.00 upon completion of the study (approximately 15 minutes). No names, IP addresses, or any other identifying information was recorded by the software (Qualtrics; Provo, Utah, USA). All procedures were approved by the Utah State Institutional Review Board prior to beginning data collection.

A total of 77 participants passed all data screening (see below). The sample was predominately Male, White/Caucasian, and reported some college or a bachelor's degree for education. The average AUDIT score for the sample would be classified as harmful

or hazardous drinking and the average FTND score for the sample would be classified as moderate nicotine dependence (see Table 4-1 for additional details).

Table 4-1.

Demographic Characteristics (N = 77)

Gender	Male = 55 Female = 22
Race/Ethnicity	White/Caucasian = 53 Asian = 9 African American = 10 Native American = 2 Combination of multiple options = 3
Income	M = $36,545 (SD = $20,827)
Discretionary Income	M = $12,945 (SD = $11,834)
Education	High School = 12 Some College = 26 Bachelor's Degree = 30 Graduate Degree = 9
AUDIT Score	M = 14.77 (SD = 8.01)
FTND Score	M = 5.65 (SD = 1.87)

Demographic characteristics for sample in Experiment 1.

Materials/Procedure

Prior to engaging in the APT, each participant provided demographic information (Appendix B) and completed The Alcohol Use Disorder Identification Test (AUDIT; Saunders et al., 1993; Appendix C) and the Fagerstrom Test for Nicotine Dependence (FTND; Heatherton, Kozlowski, Frecker, & Fagerstrom, 1991; Appendix D) in counterbalanced order. The AUDIT is a 10-item questionnaire that assesses how people behave in regard to alcohol and the consequences that they encounter from alcohol-related behavior. The FTND is a 6-item questionnaire that is a widely used quantitative assessment of physical dependence on nicotine.

Participants then completed two APTs in counterbalanced order. They were instructed to answer the hypothetical questions on the APTs as if they were actually going to receive the alcoholic beverages. At the beginning of each APT, participants read a vignette (Appendix E and Appendix F; modified from Kaplan et al., 2018) that explained the hypothetical context in which they were making choices about alcoholic beverages. Participants were then asked multiple choice questions (also in Appendix E and Appendix F) to assess comprehension of the hypothetical context. Any participants that failed to answer all multiple-choice questions correctly in their first two attempts were permitted to complete the experiment, but their data were removed from the analyses. In both conditions, participants were told that they were going to a concert with friends for the entire evening at a local park and would be permitted to purchase alcoholic

beverages while they were at the venue. The hypothetical contexts were identical, except that in one condition (The Non-Smoking Context) participants were told that they were not allowed to smoke or use any alternative forms of nicotine during the concert, and the other condition (The Smoking Context) participants were told that they *were* permitted to bring their own cigarettes with them to the concert and smoke as much as they would like throughout the concert. In the APTs, participants stated the number of alcoholic beverages they would purchase from vendors at the concert at the following prices per drink: $0.00, $0.10, $0.50, $1.50, $3.00, $5.00, $8.00, $15.00, $30.00, and $60.00 (see Kaplan et al., 2018). Immediately following the $60.00 price question, participants were once again asked how many alcoholic beverages they would purchase at $0.10. This final question was used as an attention check, to assess whether participants were tracking the changing prices. Data from any participant that did not increase consumption from the $60.00 question to the final $0.10 question were eliminated from analyses.

Data Analyses

Prior to conducting any data analyses, data were screened for systematicity. Reports of zero consumption were also replaced with an arbitrarily low value (0.01; see Murphy et al., 2013) so that Equation 4-1 (restated below for convenience) could be fit to those data. For identification of outliers, distributions of alcohol consumption at each price were analyzed after conducting a z-transformation on the data. Any alcohol consumption data point with a z-score greater than or equal to 3.29 (Tabachnick & Fidell, 2001) was considered an outlier and these data were recoded as one unit higher than the greatest nonoutlying value (see Kaplan, Gilroy, Reed, Koffarnus, & Hursh, 2018). Non-systematic data were evaluated according to the Stein et al. (2015) quantitative criteria for

data exclusion, which include identification of data trend, bounce, reversals from zero, and delta Q. Trend refers to the expectation of a global reduction in responding (i.e., a non-negligible reduction in consumption from first to last price) and violations of this expectation were identified by calculating the log-unit reduction in consumption from the first to the last price. Data from any participant with less than a 0.025 log-unit reduction in consumption per log-unit range in price were considered to have an insufficient trend. Bounce refers to local increases in consumption following increases in price and is identified by calculating the number of "jumps" (i.e., increases in consumption compared to the amount of consumption at the previous price) that exceed 25% of consumption at the lowest price (free). If there was more than one "jump" in the data for a participant, the data failed the bounce criterion. Reversal from zero refer to an increase in purchasing at a higher price following a report of no purchasing at a lower price and is formally identified by assessing any increase in consumption following a report of no consumption at two consecutive prices. Finally, Delta Q refers to zero consumption at the lowest price and is formally identified as zero consumption at the free price. All data from participants which did not meet any of the criteria were not included in analyses.

$$log_{10}Q = log_{10}Q_0 + k(e^{-\alpha \bullet Q_0 \bullet P} - 1) \quad (4\text{-}1)$$

Each of the preceding data cleaning methods were conducted in R with the beezdemand package (Kaplan et al., 2018).

Once data screening was complete, we obtained empirical and derived demand measures. Intensity (Q_0), breakpoint (BP_1), Maximum Expenditure (O_{max}), and Unit Elasticity (P_{max}) were empirically derived for each participant. Q_0 was recorded as the reported number of drinks consumed at zero price. BP_1 was recorded as the price

following the first report of zero consumption. If a participant reported purchasing and consuming drinks at all prices assessed, we recorded BP_1 as \$60.00, the highest price at which alcohol consumption was assessed. P_{max} was the price at which the maximum expenditure occurred. O_{max} was the maximum amount of money spent on alcoholic beverages. Finally, Equation 4-1 was fit to the data to obtain derived measures (k & α). K was fit globally to data from all participants, in both conditions, and was held constant for both group and individual analyses (i.e., the same k-value was used for all model fits). α, however, was fit locally and was free to vary for each participant (in individual analyses) and across groups (in group analyses). The reason for the different methods of fitting these parameters is due to the fact that α-values cannot be compared across data sets that were fit with different k-values (see Kaplan, Gilroy, Reed, Koffarnus & Hursh, 2018).

Once all empirical and derived measures were obtained, multilevel modeling was used to find the best predictive linear model for each of the empirical measures and α. In total, five longitudinal multilevel models (MLMs) were constructed: Q_0, BP_1, P_{max}, O_{max}, and α. Multilevel modelin5g was selected over more typical techniques such as repeated measures ANOVA, because MLM allows us to quantify the contribution of individual subject variability in explaining the dependent variable (i.e., random effects; Gelman, 2006) whereas ANOVA compresses variability into group statistics. Random intercepts (individual participant variability in the first data point) and random slopes (individual participant variability in the degree of change in the dependent variable across condition) can be included to quantify individual subject variability.

We used a bottom-up approach for model construction with each MLM (see Parker & Vannest, 2012). Each initial model was an intercept-only model, allowing only

the y-intercept to vary (i.e., no predictors were included in the model). Next, each subsequent candidate model consisted of the addition of a single fixed effect (i.e., predictor variable). Once all significant fixed effects were identified, subsequent candidate models included the addition of a candidate random effect (i.e., a variable that explains individual subject variability in the y-intercept). Random slopes were not able to be investigated with the methodology employed (i.e., because there were only two time-points, the smoking condition and the non-smoking condition, there were not enough time points to estimate random slope parameters in addition to random intercepts). Fixed effects and random intercepts that did not provide a significant increase in proportion of variance accounted for were not included in the final model, with the exception of "condition", which was the predictor of primary theoretical importance and served as the longitudinal component of the model. The candidate models were then compared using the Akaike Information Criterion (AIC; Akaike, 1974). AIC is a measure that assesses the relative quality of model (i.e., goodness of fit) while punishing for model complexity. The candidate model with the lowest AIC score was considered the best model.

Results

Of the 100 participants tested, data from twenty-three participants were eliminated from all analyses. Fifteen participants were eliminated from analyses for missing at least one multiple-choice question about the vignette more than one time. Two participants were eliminated for failing the bounce criterion. Six participants were eliminated for failing the Delta Q criterion. Additionally, six participants failed to increase consumption for the final $0.10 question (i.e., the attention check), but all of those participants that did so had already been eliminated from analyses for failing one of

the other criteria. No participant that passed the other criteria was eliminated for failing the attention check. After removal of the twenty-three participants that failed one of these criteria, seventy-seven participants remained and were included in the following analyses.

Mean Consumption

Figure 4-1 depicts mean alcohol purchasing as a function of price for both conditions. In general, mean alcohol purchasing decreased as price increased. Mean alcohol purchasing was not differentiated across conditions. The parameters that were free to vary (*k* was free to vary but held constant for both conditions and α was free to vary independently for each condition) and derived from the mean purchasing data (Q_0, O_{max}, and P_{max}) are show in Table 4-2. Equation 4-1 fit the data well with relatively high R^2 values for both conditions (see Figure 4-1).

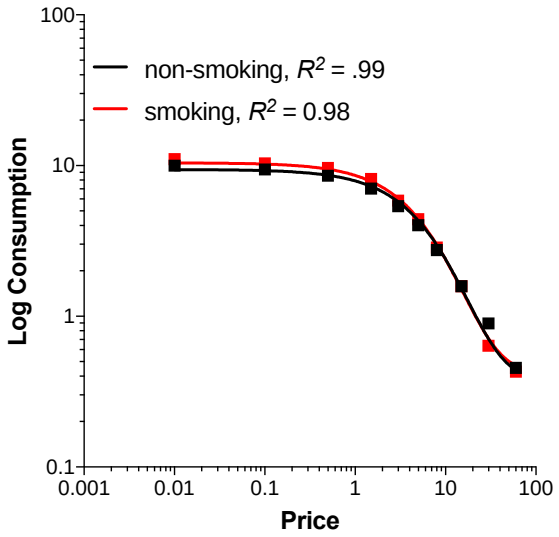

Fig. 4-1. Mean alcohol purchasing plotted as a function of price for the smoking (red squares) and non-smoking (black squares) condition. Data paths represents nonlinear regression model fits to Equation 4-1 for the smoking (red data path) and non-smoking (black data path) condition. Fitted parameters are presented in the legend.

Table 4-2
Free and Derived Parameters (Group)

Parameter	Non-Smoking	Smoking
α	0.0089	0.0091
k	1.09	1.09
Q_0	8.28	9.33
O_{max}	22.09	21.51
P_{max}	8.86	7.66

Free and derived parameters from fitting Equation 4-1to mean purchasing data.

Individual Participants

Figure 4-2 illustrates each of the mean derived parameters and mean α from individual participant analyses, as a function of condition. The value for *k* was held constant for all individuals, across both conditions. The parameters are undifferentiated across conditions (see Table 4-3).

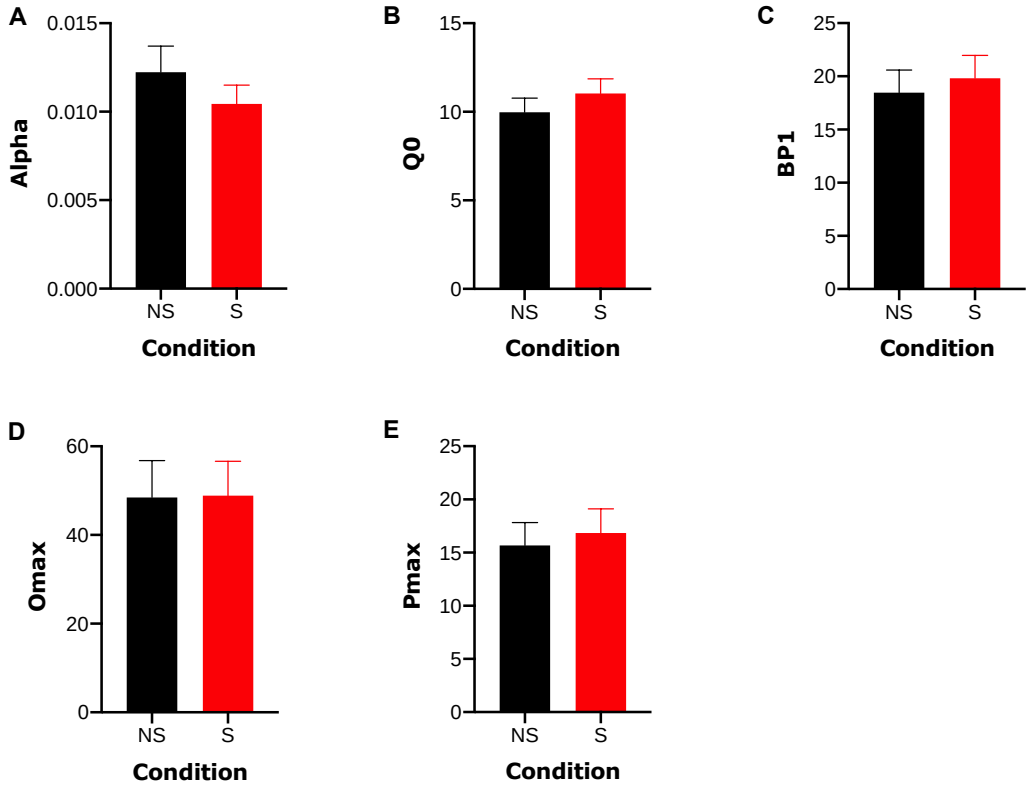

Fig. 4-2. Average parameter values for α, Q_0, BP_1, O_{max}, and P_{max}, from individual participant data. Black bars represent the non-smoking condition and red bars represent the smoking condition. Error bars represent standard error of the mean.

Table 4-3
Free and Derived Parameters (Individual)

Parameter	Non-Smoking	Smoking	P-Value
α	0.0122 (0.0015)	0.0104 (0.0010)	0.197
k	1.09	1.09	N/A
Q_0	9.97 (0.80)	11.03 (0.83)	0.066
O_{max}	48.49 (8.35)	48.88 (7.81)	0.950
P_{max}	15.68 (2.17)	16.84 (2.28)	0.456
BP_1	18.46 (2.15)	19.83 (2.15)	0.356

Mean (standard error of the mean) free and derived parameters from fitting Equation 4-1 to individual participant alcohol purchasing data. P-value is for matched-sample *t*-test. The *k* parameter was held constant for all participants in both conditions.

Intraclass Correlation

The first step in constructing the multilevel models that are presented below was to assess the intraclass correlation (ICC) for each parameter. Intraclass correlation refers to the correlation of observations within a cluster (i.e., ICC provides a quantitative measure of the degree of dependency across scores, ranging from 0 to 1; see Park & Lake, 2005). For the purposes of the current experiment, ICC provides the correlation of individual participants' scores in the smoking condition to their scores in the non-smoking condition. The higher the ICC, the more one would benefit from using a multi-level model and the more useful random effects are for the dataset. There is no clear-cut rule for how large of an ICC is large enough to justify a multilevel model, but generally any ICC higher than 0.1 is large enough to justify using a multilevel model (Aguinis, Gottfredson, & Culpepper, 2013). Each parameter had a relatively high ICC (see Table 4-4), suggesting that multilevel modeling was an appropriate analysis for these data and that use of a random intercept drastically improved the models.

Table 4-4
Intraclass Correlations

Parameter	Intraclass Correlation
α	0.509
Q_0	0.751
O_{max}	0.694

$\mathbf{P_{max}}$	0.752
$\mathbf{BP_1}$	0.763

Intraclass correlations for each parameter used in multilevel models.

Multilevel Modeling

α

Income was a significant fixed effect and Participant was used as a random intercept in the best fitting model for α (the slope of the demand curve). The final multilevel model included Condition and Income as fixed effects and participant as a random intercept (see Table 4-5). Condition was not a significant predictor but was included in the final model due to its theoretical relevance and the fact that Condition was the repeated measures factor in this experiment. Condition was also included in all of the final models reported below, regardless of whether it was a significant predictor. Income was a significant predictor of α, and the addition of income significantly improved the model (χ_2 [1] = 7.66, $p < .01$). The coefficient for Income was negative; thus, for every unit increase in Income, there was a 0.0000014 decrease in α. Smokers who made relatively more money in this population were more persistent in their purchasing of alcoholic beverages when the price of alcoholic beverages increased.

Table 4-5.
MLM Results for α

Fixed Effects	**β**	**S.E.**
Intercept	0.0174222	0.0022189

Condition	-.0.0017418	0.0012599
Income	-0.0000014**	0.0000005
Random Effects	**Variance**	**S.D.**
Participant (Intercept)	0.0000544	0.0073756
Residual	0.0000605	0.0077782

Multilevel model results for α.
*p < .05, **p < .01, ***p < .001

Q_0

AUDIT score and Discretionary Income were significant fixed effects and Participant was used as a random intercept in the best fitting model for Q_0 (Intensity of Demand). The final multilevel model included Condition, AUDIT score, and Discretionary Income as fixed effects and Participant as a random intercept (see Table 4-6). Condition was not a significant predictor of Q_0. Thus, Q_0 was undifferentiated across the smoking and non-smoking conditions. AUDIT score was a significant predictor of Q_0, and the addition of AUDIT score significantly improved the model (χ^2 [1] = 12.81, p < .001). The coefficient for AUDIT score was positive; thus, for every unit increase in AUDIT score there was a 0.38 increase in Q_0. Discretionary Income was also a significant predictor of Q_0 and the addition of Discretionary Income significantly improved the model (χ^2 [1] = 4.04, p = .044). The coefficient for Discretionary Income was negative; thus, for every unit increase in Discretionary Income there was a 0.00012 decrease in Q_0. Thus, individuals who had a relatively high AUDIT score (i.e., reported experiencing more problems with alcohol) or had a relatively low Discretionary Income tended to have a higher Q_0 (i.e., Intensity of Demand) for alcohol.

Table 4-6.
MLM Results for Q_0

Fixed Effects	**β**	**S.E.**
Intercept	6.65	1.61
Condition	1.05	0.56
AUDIT Score	0.38***	0.08
Discretionary Income	-0.00012*	0.00006
Random Effects	**Variance**	**S.D.**
Participant (Intercept)	29.16	5.40
Residual	12.05	3.47

Multilevel model results for Q_0.
*p < .05, **p < .01, ***p < .001

O_{max}

AUDIT score and Discretionary Income were significant fixed effects and Participant was used as a random intercept in the best fitting model for O_{max} (Maximum Expenditure). The final multilevel model included Condition, AUDIT score, and Discretionary Income as fixed effects and Participant as a random intercept (see Table 4-7). Condition was not a significant predictor of O_{max}. In other words, O_{max} was not different across the smoking and non-smoking conditions. AUDIT score was a significant predictor of O_{max}, and the addition of AUDIT score significantly improved the model (χ^2 [1] = 4.69, p = .03). The coefficient for AUDIT score was positive; thus, for every unit increase in AUDIT score there was a 1.90 increase in O_{max}. Discretionary Income was also a significant predictor of O_{max} and the addition of Discretionary Income significantly improved the model (χ^2 [1] = 5.67, p = .017). The coefficient for Discretionary Income

was positive; thus, for every unit increase in Discretionary Income there was a 0.00141 increase in O_{max}. Thus, individuals with a relatively higher AUDIT score or relatively higher Discretionary Income tended to have a higher O_{max} (i.e., Maximum Expenditure) for alcohol.

Table 4-7.
MLM Results for O_{max}

Fixed Effects	**β**	**S.E.**
Intercept	2.18	6.38
Condition	0.39	6.27
AUDIT Score	1.90*	0.86
Discretionary Income	0.00141*	0.00058
Random Effects	**Variance**	**S.D.**
Participant (Intercept)	2862	53.50
Residual	1515	38.92

Multilevel model results for O_{max}.
*p < .05, **p < .01, ***p < .001

P_{max}

AUDIT score and Discretionary Income were significant fixed effects and Participant was used as a random intercept in the best fitting model for P_{max} (the price at which maximum expenditure occurred). The final multilevel model included Condition, AUDIT score, and Discretionary Income as fixed effects and Participant as a random intercept (see Table 4-8). Condition was not a significant predictor of P_{max}. That is, P_{max} was not different in the smoking and non-smoking conditions. AUDIT score was a significant predictor of P_{max}, and the addition of AUDIT score significantly improved the

model (χ_2 [1] = 11.153, $p < .001$). The coefficient for AUDIT score was positive; thus, for every unit increase in AUDIT score, there was a 0.81 increase in P_{max}. Discretionary Income was also a significant predictor of P_{max} and the addition of Discretionary Income significantly improved the model (χ_2 [1] = 4.94, $p = .026$). The coefficient for Discretionary Income was positive; thus, for every unit increase in Discretionary Income there was a 0.00035 increase in P_{max}. Thus, similar to what was found with Q_0 and O_{max}, the only factors that predicted P_{max} (i.e., the price at which maximum expenditure occurred) were AUDIT score and Discretionary Income. Individuals with relatively high AUDIT scores or relatively high Discretionary Income tended to have higher P_{max} for alcohol.

Table 4-8.
MLM Results for P_{max}

Fixed Effects	**β**	**S.E.**
Intercept	3.48	6.38
Condition	1.17	6.27
AUDIT Score	0.81***	0.86
Discretionary Income	0.00035*	0.00016
Random Effects	**Variance**	**S.D.**
Participant (Intercept)	217	14.73
Residual	92	9.59

Multilevel model results for P_{max}.
*$p < .05$, **p < .01, ***p < .001

BP_1

AUDIT score and Discretionary Income were significant fixed effects and Participant was used as a random intercept in the best fitting model for BP_1 (Break Point). The final multilevel model included Condition, AUDIT score, and Discretionary Income as fixed effects and participant as a random intercept (see Table 4-9). Condition was not a significant predictor of BP_1. Thus, there was no difference between BP_1 in the smoking versus non-smoking conditions. AUDIT score was a significant predictor of BP_1, and the addition of AUDIT score significantly improved the model (χ_2 [1] = 11.288, $p < .001$). The coefficient for AUDIT score was positive; thus, for every unit increase in AUDIT score there was a 0.79 increase in BP_1. Discretionary Income was also a significant predictor of BP_1 and the addition of Discretionary Income significantly improved the model (χ_2 [1] = 4.71, $p = .029$). The coefficient for Discretionary Income was positive; thus, for every unit increase in Discretionary Income there was a 0.00033 increase in BP_1. Thus, as in the previous 3 models, the only factors that predicted BP_1 (i.e., Break Point) were AUDIT score and Discretionary Income. Individuals who had a relatively high AUDIT score or relatively high Discretionary Income tended to have higher a BP_1 for alcohol.

Table 4-9.
MLM Results for BP_1

Fixed Effects	**β**	**S.E.**
Intercept	2.41	4.27
Condition	1.37	1.46
AUDIT Score	0.79***	0.22
Discretionary Income	0.00033*	0.00015

Random Effects	Variance	S.D.
Participant (Intercept)	207	14.39
Residual	82	9.05

Multilevel model results for BP_1.
*p < .05, **p < .01, ***p < .001

Discussion

The current experiment assessed hypothetical alcohol purchasing in two contexts, one where smoking tobacco cigarettes was permitted and one where smoking tobacco cigarettes was forbidden. We hypothesized that demand indices for alcoholic beverages would be affected by smoking context. Specifically, we hypothesized that all demand indices would be significantly greater in the smoking condition than in the non-smoking condition, with the exception of α, which we expected to be greater in the non-smoking condition than in the smoking condition. The results of the current study are all in the predicted direction, but not none of them reach statistical significance. It could be argued that we would find the hypothesized results if we had included more participants in the sample; however, it is important to point out how small the effect sizes are in the current experiment. In order to find statistical mean differences in smoking context with the current effect sizes (see Figure 4-2), we would need the following *ns* for each parameter (effect size in parentheses): α: n = 26,946 (0.017), Q_0: n= 187 (0.215), O_{max}: n = 3,502 (0.047), P_{max}: n = 287 (0.166), BP_1: n = 224 (0.188). Thus, it is possible that we would have found statistically significant results with additional participants, but the effects themselves are so small as to not be meaningful. Condition (smoking vs non-smoking

context) was not a significant predictor for any of the five demand indices examined in the experiment. Thus, none of the demand indices were significantly different across smoking contexts. In the current study, we did not find support for the hypothesis that that hypothetical nicotine exposure (via tobacco cigarettes) increases demand for hypothetical alcoholic beverages, despite robust evidence that nicotine exposure increases responding for alcohol in laboratory studies with rodents and humans (see above discussion).

Overall, the data were orderly. Even though the major hypothesis was not supported in this experiment, Equation 4-1 fit the data well and each measure of demand had at least one significant predictor. AUDIT score (a measure of severity of alcohol-related problems a person encounters) and Discretionary Income were both significant predictors in 4 out of the 5 demand indices, and Income was a significant predictor of one of the demand indices. Several studies have found AUDIT score to be related to these demand indices for alcohol in hypothetical purchase tasks (e.g., Gray & Mackillop, 2014). As price increased, consumption decreased, as would be expected by consumer choice theory.

Data from the current study had a similar correlational structure to data from previous studies using an APT. Mackillop et al. (2009) found that the indices of alcohol demand cluster into two factors, amplitude and persistence. Amplitude consists of Q_0 and persistence consists of α, BP, and P_{max}, while O_{max} partially loads onto both factors. The current data support this finding. Figure 4-3 is a correlation matrix for these demand indices in the current experiment. The figure clearly shows that α, BP, and P_{max} are highly correlated and Q_0 is not correlated with these measures. In fact, the measure that

Q_0 correlates with the most is O_{max}, and O_{max} is also correlated with the other three measures. Thus, data in the current study had a similar correlational structure to what Mackillop et al. found.

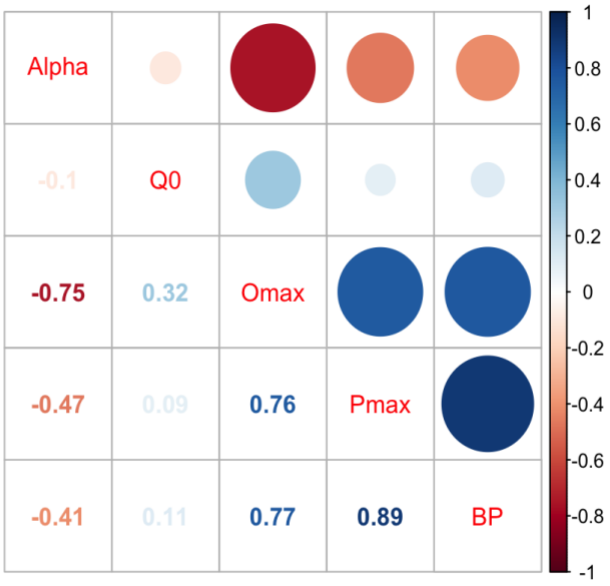

Fig. 4-3. A correlation matrix for demand indices in the current experiment.

The current data should be interpreted with a sense of caution. It is possible that smoking cigarettes has no impact on a person's demand for alcoholic beverages. However, it is also possible that hypothetical purchase tasks are not sensitive enough to detect the effect that nicotine exposure has on demand for alcoholic beverages, or that people are not capable of reporting how the opportunity to smoke would actually affect their alcohol beverage purchasing. Many studies have found APTs to provide reliable and valid measures of alcohol demand, using hypothetical money and hypothetical alcoholic beverages. Studies have also shown that purchasing of real vs. hypothetical alcoholic beverages is comparable (e.g., Amlung et al., 2012), but no study has assessed the effect of a *hypothetical drug* on purchasing of real or hypothetical

alcoholic beverages. We thought that an adding an additional layer of hypothetical imagining to the situation would was feasible (i.e., imagining a situation in which you are allowed to smoke vs. a situation in which you are not allowed to smoke, in addition to imagining purchasing alcoholic beverages). Perhaps, however, the hypothetical nature of the drug exposure (i.e., being permitted to smoke) did not impact behavior in the same way that actually being permitted to smoke during the purchasing episode would.

A recent study asked a similar question with rats. Barrett et al. (2020) found that nicotine affected intensity of demand (Q_0) for alcohol in both sexes of rats at high doses but affected elasticity of demand only in females across a range of doses. Gender was not a significant predictor for any of the demand indices in the current study and we did not find any difference in either of these demand indices across the smoking and non-smoking context. The difference in the findings of the current study and the findings of Barrett et al. may be due to methodological differences (real vs. hypothetical rewards or real vs. hypothetical drug exposure), species differences (rats vs. humans), or another variable (e.g., effort vs. money being expended).

Future research will need to tease these possibilities apart as an increasing number of behavioral pharmacology studies are utilizing hypothetical purchase tasks to answer fundamental questions. Understanding the limits of these tasks' usefulness in answering research questions of this sort must be more fully examined.

Experiment 2

Hypothetical purchase tasks have also been adapted for assessing purchasing of other commodities, such as cigarettes. The first hypothetical purchase task ever conducted assessed cigarette purchasing (Jacobs & Bickel, 1999), but the results were

replicated and extended by Mackillop et al. (2008). Mackillop et al. took a similar approach to assessing the validity of a cigarette purchase task (CPT) as Murphy and Mackillop (2006) took with validating APTs. Participants stated the number of cigarettes they would purchase and consume at a range of prices. The authors assessed the relation between cigarette demand indices and clinical symptomology (from The Fagerstrom Test of Nicotine Dependence; Heatherton, Kozlowski, Frecker, & Fagerstrom, 1991). Specifically, the authors found a difference in demand indices (Intensity and Omax) between participants with minimal nicotine dependence and mild to moderate nicotine dependence, providing the first evidence for the clinical utility of CPTs.

Since the Mackillop et al. (2008) study, several studies have been conducted to further assess the validity of CPTs. Several studies indicate that CPTs have high construct validity. For example, several experiments have shown that demand indices on a CPT are associated with nicotine dependence (e.g., Murphy et al., 2011; Few et al., 2012; Chase, Mackillop, & Hogarth, 2013; Mackillop et al, 2015; O'Connor et al., 2016; Secades-Villa et al., 2018), higher rates of smoking (e.g., Murphy et al., 2011; Few et al., 2012; Mackillop et al., 2015; Secades-Villa et al., 2018), and motivation/intention to quit smoking (e.g., Murphy et al., 2011; O'Connor et al., 2016). Studies also indicate that CPTs have high predictive validity. For example, Mackillop et al. (2015) provide initial evidence of the predictive validity of CPTs by showing that baseline demand indices predicted abstinence from smoking during treatment in the absence of contingent vouchers. Secades-Villa, Pericot-Valverde, and Weidberg (2016) provided additional support for the predictive validity of CPTs by showing that demand indices predict smoking cessation among treatment-seeking smokers.

Only a few studies have been conducted to assess the reliability of CPTs. Similar to the method employed for comparing real versus hypothetical rewards on APTs (described above), Wilson, Franck, Koffarnus, and Bickel (2015) assessed performance on CPTs when the rewards from the questionnaire were hypothetical, potentially-real, or actually real. Although demand indices were statistically different on the hypothetical version of the task compared to the potentially and actually real versions, performance was highly correlated across all versions and the authors cite methodological differences that may explain these differences. Few, Acker, Murphy, and Mackillop (2012) assessed the test-retest reliability of a CPT with a 1-week interval between the assessments. They found statistically significant correlations across all demand indices (*rs* = .76-.99) and no statistically significant differences across the two time-points, illustrating that CPTs have good temporal stability over this time frame. Despite the paucity of studies examining the reliability of CPTs, the similarity of CPTs to APTs, as well as the demonstrated reliability of APTs, suggests that CPTs are reliable. More studies are needed to empirically verify this, however.

Relatively few studies have assessed the effect of an experimental manipulation on demand indices from a CPT. However, the effects of some manipulations on demand indices from a CPT have been examined. For example, Smith et al. (2017) showed that smoking cigarettes with a reduced nicotine content for a 6-week experimental period, reduced demand indices on a CPT. Similarly, Higgins et al. (2018) found that smoking reduced-nicotine cigarettes just prior to completing a CPT reduced demand indices relative to smoking cigarettes with higher nicotine concentrations prior to completing a CPT. Murphy et al. (2017) assessed the effect of varenicline (a pharmacotherapy for

nicotine) and nicotine replacement therapy on demand for cigarettes and found that both reduced demand indices on a CPT (see McClure et al., 2013 for similar results with varenicline only). Weidberg et al. (2018) showed that smokers who receive contingency management show decreases in intensity on a CPT and cotinine and nicotine levels (and reduction in each during treatment) were positively related to cigarette demand. These studies have been beneficial in terms of elucidating some of the factors that affect cigarette demand, but no study has examined the effect of hypothetical drug exposure on cigarette demand.

Experiment 2 examined the effect of hypothetical alcoholic beverage availability on tobacco cigarette demand. Several experiments have demonstrated that alcohol exposure in a laboratory increases responding for nicotine in rats (Le et al., 2010) and humans (e.g., Barrett, Campbell, Rocah, Stewart, & Darredeau, 2013), but this finding has not been extended to hypothetical purchase tasks and economic demand indices. Extending this literature to a more sophisticated measure of reinforcer value, and with hypothetical rewards and drug exposure, provides a benefit to the literature and would potentially further validate the use of cigarette purchase tasks. Participants completed two CPTs: one CPT was completed in a hypothetical context where participants were told that they are not permitted to drink alcoholic beverages and the other CPT was completed in a hypothetical context where participants were told that they are permitted to drink alcoholic beverages. The key research question was, “Does the hypothetical opportunity to drink alcoholic beverages increase demand for hypothetical tobacco cigarettes?”

Method

Participants

Participants were recruited and screened for eligibility online with Amazon Mechanical Turk (Mturk) until one hundred eligible participants were identified. The same screener and inclusion criteria that were used in Experiment 1 were used in Experiment 2 (see Appendix A). No names, IP addresses, or any other identifying information was recorded by the software (Qualtrics; Provo, Utah, USA). All procedures were approved by the Utah State Institutional Review Board prior the beginning of data collection. Participants were paid $2.00 for completing the task.

A total of 81 participants passed all data screening (see below). The sample was predominately Male, White/Caucasian, and reported some college or a bachelor's degree for education. The average AUDIT score for the sample would be classified as harmful or hazardous drinking and the average FTND score for the sample would be classified as moderate nicotine dependence (see Table 4-10 for additional details).

Table 4-10.

Demographic Characteristics (N = 81)

Gender	Male = 59
	Female = 22
Race/Ethnicity	White/Caucasian = 59
	Asian = 11
	African American = 4
	Native American = 4

	Combination of multiple options = 3
Income	M = $36,003 (SEM = $2,055)
Discretionary Income	M = $16,205 (SEM = $1,594)
Education	High School = 13 Some College = 32 Bachelor's Degree = 25 Graduate Degree = 11
AUDIT Score	M = 13.85 (SEM = 0.91)
FTND Score	M = 5.45 (SEM = 0.20)

Demographic characteristics for sample in Experiment 2.

Materials/Procedure

Participants completed two CPTs in counterbalanced order. Prior to engaging in the CPTs, each participant provided demographic information (see Appendix B) and completed the AUDIT (Appendix C) and the FTND (Appendix D), as in Experiment 1. For the CPTs, participants were instructed to answer the hypothetical questions on the CPTs as if they were going to receive the tobacco cigarettes. At the beginning of each CPT, participants read a vignette (Appendix G & H; modified from Kaplan et al., 2018) that explained the hypothetical context in which they were making choices about tobacco cigarettes. Participants were then asked multiple choice questions (also in Appendix G &

H) to assess comprehension of the hypothetical context. Any participant that failed to answer all multiple-choice questions correctly within their first two attempts were permitted to complete the experiment and receive payment but were removed from all data analyses. In both conditions, participants were told that they were going to a concert with friends for the entire evening at a local park and would be permitted to purchase tobacco cigarettes while they were at the venue. The hypothetical contexts were identical, except that in one condition (The Non-Drinking Context) participants were told that they were not allowed to drink alcoholic beverages during the concert, and the other condition (The Drinking Context) participants were told that they *were* permitted to bring their own alcoholic beverages with them to the concert and drink as much as they would like throughout the concert. In the CPTs, participants stated the number of tobacco cigarettes they would purchase from vendors at the concert at the following prices: $0.00, $0.05, $0.10, $0.25, $0.50, $1.00, $3.00, $10.00, $30.00, and $60.00. Immediately following the $60.00 price question, participants were once again asked how many tobacco cigarettes they would purchase at $0.10. This final question was used as an attention check, to assess whether participants were tracking the changing prices. Any participant that did not increase consumption from the $60.00 question to the final $0.10 question was eliminated from analyses.

Data Analysis

Data were screened, and demand indices were generated in the same manner as Experiment 1. Zero-consumption was replaced with an arbitrarily low value, outliers were recoded as one unit higher than the greatest nonoutlying value, and data were subjected to the Stein et al. (2015) quantitative criteria for data exclusion, as in

Experiment 1. Intensity (Q_0), breakpoint (BP_0), O_{max}, and P_{max} were empirically derived for each participant, as described in Experiment 1. Equation 4-1 was fit to data in order to obtain derived measures (*k* and α). *k* was fit globally to data from all participants, in both conditions, and was held constant for both group and individual analyses (i.e., the same *k*-value was used for all model fits). Alpha was fit locally and was free to vary for each participant (in individual analyses) and for each group (in group analyses).

Once all empirical and derived measures were obtained, multilevel modeling was used to find the best predictive linear model for each of the empirical measures and α. In total, five longitudinal multilevel models (MLMs) were constructed: Q_0, BP_0, P_{max}, O_{max}, and α. The same MLM approach described in Experiment 1 was used in Experiment 2.

Results

Nineteen participants were eliminated from all analyses. Fifteen participants were eliminated from analyses for failing one of the quizzes twice. Two participants were eliminated for failing the bounce criterion. One participant was eliminated for failing the Delta Q criterion. Additionally, eight participants failed the "attention check", but seven of those participants that failed the attention check had already been eliminated from analyses for failing one of the other criteria. Thus, only one participant was eliminated solely for failing the attention check. After removal of the nineteen participants that failed one of these criteria, eighty-one participants remained and were included in the following analyses.

Mean Consumption

Figure 4-4 depicts mean tobacco cigarette purchasing as a function of price for both conditions. In general, mean tobacco cigarette purchasing decreased as price increased.

Mean tobacco cigarette purchasing was not differentiated across conditions. The parameters that were free to vary (*k* was free to vary, but held constant for both contexts and α was free to vary independently for each condition) and derived from mean purchasing (Q_0, O_{max}, and P_{max}) are show in Table 4-11. Equation 4-1 fit the data well, with relatively high R^2 values for both conditions (see Figure 4-11).

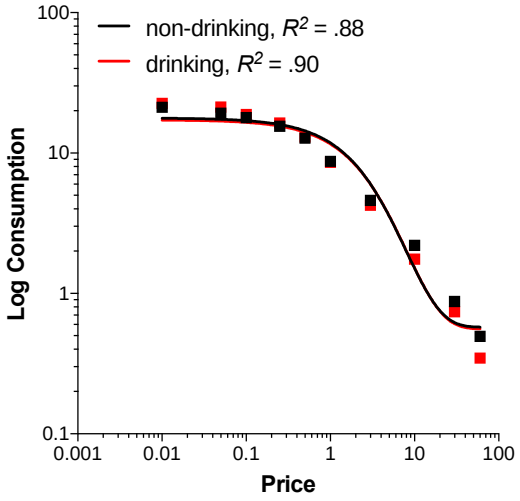

Figure 4-4. Mean cigarette purchasing plotted as a function of price for the drinking (red squares) and non-drinking (black squares) contexts. Data paths represents nonlinear regression model fits to Equation 4-1 for the drinking (red data path) and non-drinking (black data path) contexts. Fitted parameters (*k* and α) are presented in the legend.

Table 4-11
Free and Derived Parameters (Group)

Parameter	Non-Drinking	Drinking
α	0.0022	0.0018
k	2.22	2.22
Q_0	13.80	15.08
O_{max}	44.13	36.28

P_{max}	9.99	7.52

Free and derived parameters from fitting Equation 4-1to mean purchasing data.

Individual Participants

Figure 4-5 illustrates each of the mean derived parameters and mean α from individual participant analyses, as a function of condition. The value for *k* was held constant for all individuals, in both conditions. O_{max} was the only parameter that was significantly different across conditions. None of the other parameters were significantly different across conditions (see Table 4-12).

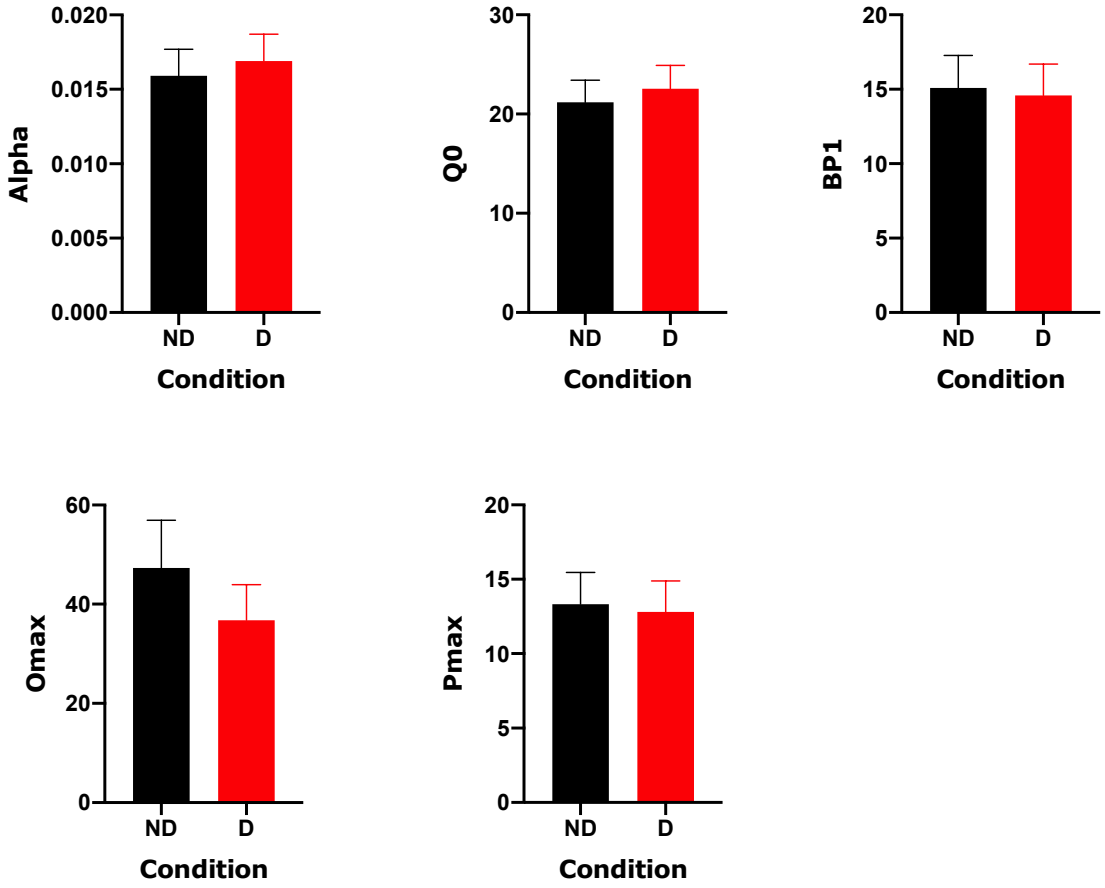

Figure 4-5. Average parameter values for α, Q_0, BP_1, O_{max}, and P_{max}, from individual participant data. Error bars represent standard error of the mean.

Table 4-12
Free and Derived Parameters (Individual)

Parameter	Non-Drinking	Drinking	P-Value
α	0.0159 (0.0017)	0.0169 (0.0018)	0.499
k	2.22	2.22	N/A
Q_0	21.19 (2.25)	22.57 (2.37)	0.117
O_{max}	47.35 (9.64)	36.78 (7.16)	0.010*
P_{max}	13.33 (2.14)	12.81 (2.10)	0.716
BP_1	15.09 (2.20)	14.58 (2.12)	0.361

Mean (standard error of the mean) free and derived parameters from fitting Equation 4-1 to individual participant cigarette purchasing data. P-value is for matched-sample *t*-test. The *k* parameter was held constant for all participants in both conditions.

Intraclass Correlation

As in Experiment 1, the first step in constructing the multilevel models that are presented below, was to assess the intraclass correlation (ICC) for each parameter. Intraclass correlation provides the correlation of individual participants' scores in the drinking context to their scores in the non-drinking context. The higher the ICC, the more one would benefit from using a multi-level model and the more useful random effects are for the dataset. Each parameter had a relatively high ICC score (see Table 4-13), suggesting that multilevel modeling is an appropriate analysis for these data and use of a random intercept drastically improved the models.

Table 4-13

Parameter	Intraclass Correlation
α	0.666
Q_0	0.926
O_{max}	0.879
P_{max}	0.771
BP_1	0.791

Intraclass correlations for each parameter that used in multilevel models.

Multilevel Modeling

α

Income and AUDIT score were significant fixed effects and Participant was used as a random intercept in the best fitting model for α. The final multilevel model included Condition, Income, and AUDIT score as fixed effects and participant as a random intercept (see Table 4-14). Condition was not a significant predictor but was included in the model due to its theoretical relevance and the fact that condition was the repeated measures factor in this experiment. Condition was included as a fixed effect in all subsequent models, regardless of whether it was a significant predictor or not. AUDIT score was a significant predictor of α, and the addition of AUDIT score significantly improved the model (χ^2 [1] = 4.65, p = .03). The coefficient for AUDIT score was negative; thus, for every unit increase in AUDIT score there was a 0.00047 decrease in α. Individuals who had relatively more problems with alcohol also tended to have a smaller α (i.e., show more persistence to increasing alcohol prices). Income was also a significant predictor of α, and the addition of income significantly improved the model (χ^2 [1] = 6.63, p = .01). The coefficient for income was negative; thus, for every unit increase in income there was a 0.00000021 decrease in α. Smokers who made relatively more money in this population tended to be more persistent in their purchasing of cigarettes when the price of cigarettes increased.

Table 4-14.
MLM Results for α

Fixed Effects	**β**	**S.E.**
Intercept	0.0300058	0.0043817
Condition	0.0009946	0.0014534
AUDIT	-0.0004672*	0.0001853
Income	-0.00000021**	0.0000008
Random Effects	**Variance**	**S.D.**
Participant (Intercept)	0.0001393	0.0118025
Residual	0.0000845	0.0091923

Multilevel model results for α.
*p < .05, **p < .01, ***p < .001

Q_0

FTND score was a significant fixed effect and Participant was used as a random intercept in the best fitting model for Q_0. The final multilevel model included Condition and FTND score as fixed effects and Participant as a random intercept (see Table 4-15). Condition was not a significant predictor of Q_0. That is, there was no difference in Q_0 across the drinking and non-drinking condition. FTND score was the only significant predictor of Q_0, and the addition of FTND score significantly improved the model (χ^2 [1] = 9.29, p < .01). The coefficient for FTND score was positive; thus, for every unit increase in FTND score there was a 3.79 increase in Q_0. Thus, individuals who had a relatively high FTND score (i.e, experience more dependence on nicotine) tended to have a higher Q_0 (i.e., Intensity of Demand) for Cigarettes.

Table 4-15.
MLM Results for Q_0

Fixed Effects	**β**	**S.E.**
Intercept	0.50	6.94
Condition	1.38	0.87
FTND Score	3.79**	1.21
Random Effects	**Variance**	**S.D.**
Participant (Intercept)	346.85	18.62
Residual	30.48	5.52

Multilevel model results for Q_0.
*p < .05, **p < .01, ***p < .001

O_{max}

Condition, FTND score, AUDIT score and Age were significant fixed effects and Participant was used as a random intercept in the best fitting model for O_{max}. The final multilevel model included Condition, FTND Score, AUDIT Score, and Age as fixed effects and Participant ID as a random intercept (see Table 4-16). Condition was a significant predictor and the addition of Condition significantly improved the model (χ^2 [1] = 6.70, p < .01). The coefficient for Condition was negative; thus, moving from the non-drinking context to the drinking context led to a 10.56 reduction in O_{max}. In other words, O_{max} (i.e., maximum expenditure) was significantly higher in the non-drinking condition than in the drinking condition. FTND score was a significant predictor of O_{max}, and the addition of FTND score significantly improved the model (χ^2 [1] = 10.44, p < .01). The coefficient for FTND score was positive; thus, for every unit increase in FTND score there was a 12.89 increase in O_{max}. AUDIT score was a significant predictor of

O_{max}, and the addition of AUDIT score significantly improved the model (χ_2 [1] = 8.79, p < .01). The coefficient for AUDIT score was positive; thus, for every unit increase in AUDIT score there was a 2.31 increase in O_{max}. Finally, Age was also a significant predictor of O_{max}, and the addition of Age significantly improved the model (χ_2 [1] = 4.99, p = .03). The coefficient for Age was negative; thus, for every unit increase in Age there was a 1.90 decrease in O_{max}. Those individuals who had a relatively high FTND score (i.e., show higher dependence on nicotine), high AUDIT score (i.e., encounter more alcohol-related problems), or were relatively young tended to have a relatively high O_{max} for tobacco cigarettes and all individuals tended to have a higher O_{max} in the non-drinking condition than in the drinking condition .

Table 4-16.
MLM Results for O_{max}

Fixed Effects	**β**	**S.E.**
Intercept	10.69	37.24
Condition	-10.56**	3.99
FTND Score	12.89**	4.18
AUDIT Score	2.31*	0.92
Age	-1.90*	0.84
Random Effects	**Variance**	**S.D.**
Participant (Intercept)	3659	60.49
Residual	646	25.42

Multilevel model results for O_{max}.
*p < .05, **p < .01, ***p < .001

P_{max}

FTND score, AUDIT score, and Age were significant fixed effects and Participant was used as a random intercept in the best fitting model for P_{max}. The final multilevel model included Condition, FTND score, AUDIT score and Age as fixed effects and participant as a random intercept (see Table 4-17). Condition was not a significant predictor P_{max}. Thus, drinking context did not have an effect on P_{max}. FTND score was a significant predictor of P_{max}, and the addition of FTND score significantly improved the model (χ_2 [1] = 11.07, $p < .001$). The coefficient for FTND score was positive; thus, for every unit increase in FTND score there was a 3.29 unit increase in P_{max}. AUDIT score was a significant predictor of P_{max} and the addition of AUDIT score significantly improved the model (χ_2 [1] = 10.31, $p < .01$). The coefficient for AUDIT score was positive; thus, for every unit increase in AUDIT score there was a 0.56 increase in P_{max}. Finally, Age was also a significant predictor of P_{max} and the addition of Age significantly improved the model (χ_2 [1] = 9.85, $p < .01$). The coefficient for Age was negative; thus, for every unit increase in Age there was a 0.63 decrease in P_{max}. Thus, while Condition did not significantly predict P_{max} (the price at which maximum expenditure occurred), people with relatively high AUDIT scores, high FTND scores, and relatively young people tended to have a relatively high P_{max} for tobacco cigarettes.

Table 4-17.
MLM Results for P_{max}

Fixed Effects	**β**	**S.E.**
Intercept	9.25	8.65
Condition	-0.52	1.43

FTND Score	3.29***	0.97
AUDIT Score	0.56**	0.21
Age	-0.63**	0.19
Random Effects	**Variance**	**S.D.**
Participant (Intercept)	173	13.15
Residual	82	9.06

Multilevel model results for P_{max}.
*p < .05, **p < .01, ***p < .001

BP_1

FTND score, AUDIT score, Age, and Discretionary Income were significant fixed effects and Participant was used as a random intercept in the best fitting model for BP_1. The final multilevel model included Condition, FTND score, AUDIT score, Age, and Discretionary Income as fixed effects and participant as a random intercept (see Table 4-18). Condition was not a significant predictor of BP_1. In other words, BP_1 was not affected by drinking context. FTND score was a significant predictor of BP_1, and the addition of FTND score significantly improved the model (χ_2 [1] = 11.355, p < .001). The coefficient for FTND score was positive; thus, for every unit increase in FTND score there was a 3.26 increase in BP_1. AUDIT score was a significant predictor of BP_1, and the addition of AUDIT score significantly improved the model (χ_2 [1] = 15.658, p < .001). The coefficient for AUDIT score was positive; thus, for every unit increase in AUDIT score there was a 0.63 increase in BP_1. Age was also a significant predictor of BP_1, and the addition of Age significantly improved the model (χ_2 [1] = 8.48, p < .01). The coefficient for Age was negative; thus, for every unit increase in Age there was a 0.56

decrease in BP_1. Finally, Discretionary Income was also a significant predictor of BP_1 and the addition of Discretionary Income significantly improved the model (χ_2 [1] = 8.48, p < .01). The coefficient for Discretionary Income was positive; thus, for every unit increase in Discretionary Income, there was a small increase in BP_1. Individuals who had a relatively high FTND score, relatively high AUDIT score, were relatively young, or had relatively higher Discretionary Income tended to have a higher BP_1 for tobacco cigarettes.

Table 4-18.
MLM Results for BP_1

Fixed Effects	β	**S.E.**
Intercept	6.23	8.27
Condition	-0.50	1.39
FTND Score	3.26***	0.96
AUDIT Score	0.63**	0.21
Age	-0.56**	0.0027
Discretionary Income	0.000099**	0.000036
Random Effects	**Variance**	**S.D.**
Participant (Intercept)	156	12.49
Residual	78	8.83

Multilevel model results for BP_1.
*p < .05, **p < .01, ***p < .001

Discussion

The current experiment assessed hypothetical tobacco cigarette purchasing in two contexts, one where drinking alcoholic beverages was permitted and one where drinking alcoholic beverages was forbidden. We hypothesized that demand indices for tobacco cigarettes would be affected by drinking context. Specifically, we predicted that all demand indices would be greater in the drinking context than in the non-drinking context, with the exception of α (i.e., the elasticity parameter), which we predicted to be greater in the non-drinking context than in the drinking context. The current study provides no evidence to support this hypothesis. Condition (smoking vs non-smoking context) was only a significant predictor for one of the five demand indices examined in the experiment (O_{max}; Maximum Expenditure) and this effect was in the opposite direction of what we predicted (O_{max} was higher in the non-drinking context than in the drinking context). Despite robust evidence that alcohol exposure increases responding for nicotine or cigarettes in rodents and humans (see above discussion), the current study found the opposite: alcohol availability led to a lower O_{max} than when alcohol was not available. Participants spent more on tobacco cigarettes when they were not allowed to drink alcoholic beverages. It could be argued that we would have found statistically significant results for the other parameters with additional participants. However, to find statistical mean differences in drinking context with the current effect sizes (see Figure 4-11), we would need the following *ns* for each parameter (effect size in parentheses): α: n = 2,044 (0.062), Q_0: n= 1751 (0.067), P_{max}: n = 10,014 (0.028), BP_1: n = 11,613 (0.026). Thus, it is possible we would have found statistically significant results if we had added more participants to the study, but the effects themselves are so small as to not be meaningful.

Overall, the data were orderly. Equation 4-1 fit the data well and each measure of demand had at least one significant predictor. AUDIT score (a measure of the severity of alcohol-related problems a person encounters) and FTND score (a measure of the degree of nicotine dependence for a person) were significant predictors in 4 out of the 5 demand indices, Age was a significant predictor for 3 of the demand indices, and Condition (Drinking versus Non-Drinking Context) and Discretionary Income were each a significant predictor for one index of demand. Several studies have found FTND score to be related to these demand indices (e.g., Few, Acker, Murphy, & Mackillop, 2012). As price increased, consumption decreased, as would be expected by consumer choice theory.

Data from the current study had a similar correlational structure as data from previous studies using a CPT. Bidwell et al. (2012) found that the indices of cigarette demand cluster into two factors, amplitude and persistence, like the way indices cluster for alcohol demand. Amplitude consists of Q_0 and persistence consists of α, BP, and P_{max}, while O_{max} partially loads onto both factors. The current data support this finding. Figure 4-6 is a correlation matrix for these demand indices in the current experiment. The figure clearly shows that α, BP, and P_{max} are highly correlated and Q_0 is not correlated with these measures. In fact, the measure that Q_0 correlates with the most is O_{max}, and O_{max} is also correlated with the other three measures. Thus data in the current study seemed to have a similar correlational structure as found by Bidwell et al..

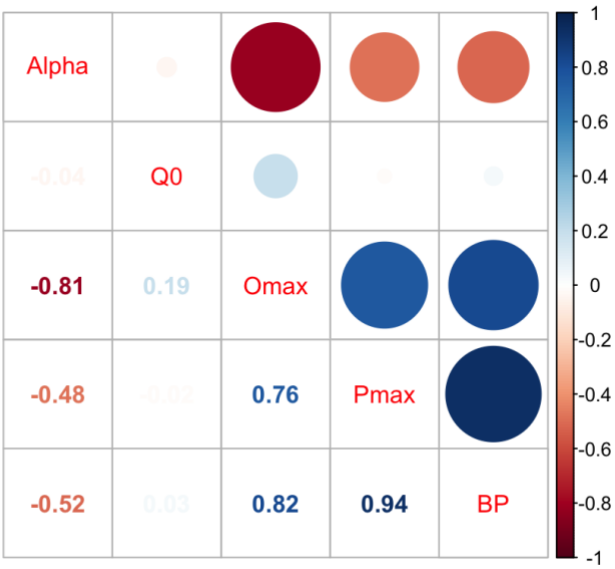

Fig. 4-6. A correlation matrix for demand indices in the current experiment.

These data should be interpreted with a sense of caution. The current experiment shows that being forbidden to drink alcoholic beverages increases maximum expenditure for tobacco cigarettes relative to being allowed to drink alcoholic beverages, but does not affect other indices of demand. It is possible that the opportunity to drink alcoholic beverages (or being forbidden to do so) has no impact on other indices of demand for tobacco cigarettes. However, it is also possible that either hypothetical purchase tasks are not sensitive enough to detect the effect that alcoholic beverage exposure has on demand for tobacco cigarettes or, alternatively, people may not be capable of reporting how the opportunity to drink would actually affect their tobacco cigarette purchasing. Many studies have shown that hypothetical CPTs provide a valid and reliable measure of cigarette demand, but no study has assessed the effect of a hypothetical drug availability on purchasing of real or hypothetical tobacco cigarettes. It is possible that this additional

layer of hypothetical imagining may not have been possible for participants. Future research will need to tease these possibilities apart.

Experiment 3

Economic demand methodology can be used to understand the relation between purchasing of alcoholic beverages and tobacco cigarettes. To assess the economic relation between goods, changes in consumption of concurrently available goods are evaluated when the price of one good (Good A) is systematically manipulated while the price of another good (Good B) remains constant (see Green & Freed, 1993). If consumption of Good B increases as a result of increasing the price of Good A, then Good B is considered a substitutable good to Good A (e.g., Coke and Pepsi). However, if consumption of Good B decreases as a result of increasing the price of Good A, then Good B is considered a complimentary good to Good A (e.g., chips and salsa). Finally, if consumption of Good B is unaffected by increasing the price of Good A, then the goods are considered to have an independent relation (e.g., candy bars and screwdrivers). This evaluative concept of assessing the changes in consumption of a constant-priced good while the price of a concurrently available good systematically changes is termed cross-price elasticity and can be used to assess the economic relation between alcoholic beverages and tobacco cigarettes.

When assessing cross-price elasticity, it is important to disentangle price effects and income effects. When the price of one good increases, while the price of another good remains constant, the increasing-priced good now costs a higher proportion of a person's income than the constant-priced good does. Thus, any changes in consumption of the two goods may be due to the differential amount of a person's income that the

increasing-priced good now accounts for, or changes in consumption could be due solely to the changing price of the increasing-priced good. These two possible explanations are difficult to disentangle. One way to disentangle these explanations is to compensate a person's income when increasing the price of the increasing-priced good, such that the same bundle of the two goods can be purchased after increasing the price of the increasing-priced good and that bundle will account for the same proportion of a person's income as it did in the previous bundle. This way of manipulating price is called an income-compensated price change and allows us to rule out income effects as an explanation for changes in consumption when altering the prices of goods, isolating price-changes as the sole determinant for changes in consumption (Kagel, Battalio, & Green, 1995).

Few cross-price elasticity studies have been conducted using hypothetical purchase tasks and additional evidence is needed to understand how the price of alcoholic beverages and tobacco cigarettes influence consumption of each drug. Recent research has begun to evaluate the substitutability of alternatives to tobacco cigarettes using hypothetical purchase tasks (e.g., Johnson, Johnson, Rass, & Pacek, 2017; O'Conner et al., 2014; Snider, Cummings, & Bickel, 2017) and Roma, Hursh, and Hudja (2016) discuss the utility of using hypothetical purchase tasks to assess the economic relation between a variety of everyday goods. However, only one cross-price elasticity study has been conducted to evaluate the economic relation between alcohol and nicotine using a hypothetical purchase task. Petry (2001) assessed the substitutability of cocaine, Valium, heroin, marijuana, and cigarettes for alcohol. Only cocaine was considered a substitute for alcohol; purchasing of the other drugs was independent of alcohol price. However, the

participants recruited in this study were not required to be cigarette smokers, they just needed to have sampled at least three other drugs (the study investigated substitutability in polydrug users). Petry also did not assess the substitutability of alcohol for cigarettes. There is a report of unpublished data evaluating the relation between alcohol and cigarette puffs in a laboratory assessment cited in Hursh and Roma (2016; see their Figure 9), but this study shows a complimentary relation between the drugs. Epidemiological data also suggests a complimentary relation between alcohol and cigarettes (e.g., Decker & Schwartz, 2000). Clearly, an assessment of the cross-price elasticity of alcohol and tobacco cigarettes with a hypothetical purchase task would fill a gap in the literature.

Experiment 3 examined the economic relation between alcoholic beverages and tobacco cigarettes while controlling for income effects by using income-compensated price manipulations. Participants engaged in an Income-Compensated Cross-Price Purchase Task (ICCPPT). In the initial condition, alcoholic beverages and mini-packs of tobacco cigarettes were the same price, with no ceiling on income. Subsequent conditions consisted of income-compensated price changes to either mini-packs of tobacco cigarettes or alcoholic beverages, while holding the other commodity at the initial price. The maximum amount of mini-packs of tobacco cigarettes and alcoholic beverages that could be purchased was always set to the amount that was purchased in the original condition, such that the original bundle was always available to the participant. The key research question was, “Are alcoholic beverages and tobacco cigarettes substitutable, complementary, or independent goods?”

Method

Participants

Participants were recruited and screened for eligibility online with Amazon Mechanical Turk (MTurk) until one hundred eligible participants were identified. The same screener that was used in Experiment 1 and 2 was used for assessing eligibility in the current study (see Appendix A). No names, IP addresses, or any other identifying information was recorded by the software (Qualtrics; Provo, Utah, USA). All procedures were approved by the Utah State Institutional Review Board prior the beginning of data collection. Participants were paid $2.00 for completing the task.

A total of 75 participants passed all data screening (see below). The sample was predominately Male, White/Caucasian, and reported some college or a bachelor's degree for education. The average AUDIT score for the sample would be classified as harmful or hazardous drinking and the average FTND score for the sample would be classified as moderate nicotine dependence (see Table 4-19 for additional details).

Table 4-19.

Demographic Characteristics (N = 75)

Gender	Male = 54 Female = 21
Race/Ethnicity	White/Caucasian = 55 Asian = 8 African American = 6 Combination of multiple options = 6
Income	M = $48,932

	(SEM = $3,863)
Discretionary Income	M = $13,880 (SEM = $1,311)
Education	High School = 10 Some College = 27 Bachelor's Degree = 29 Graduate Degree = 9
AUDIT Score	M = 12.84 (SEM = 0.97)
FTND Score	M = 7.28 (SEM = 0.19)

Demographic characteristics for sample in Experiment 3.

Material/Procedure

Participants completed several surveys prior to the ICCPPT (see Figure 4-7 for an overview of the experimental conditions). Prior to engaging in the ICCPPT, participants provided demographic information (see Appendix B) and completed the AUDIT (see Appendix C) and the FTND (see Appendix D), as in the previous experiments. Participants were instructed to answer the hypothetical questions as if they were actually receiving the alcoholic beverages and mini-packs of tobacco cigarettes. At the beginning of the ICCPPT, participants read a vignette (see Appendix I) that explained the hypothetical context and took a multiple-choice quiz to ensure comprehension of the context. Briefly, participants were told to imagine that they had won an all-inclusive day trip that takes place on a boat that is docked on a local body of water and contains a

variety of indoor and outdoor recreational activities. Participants were told that they would be allowed to drink alcoholic beverages and smoke tobacco cigarettes that were provided to them while they engaged in recreational activities on the boat. Participants then read a second vignette (see Appendix J) that explained how to acquire tickets (tickets could be exchanged for mini-packs of tobacco cigarettes or alcoholic beverages on the boat) and took a multiple-choice quiz to ensure comprehension of the ticket acquisition process. Participants were told that they would have no other access to alcohol or cigarettes (and no alternative forms of nicotine) other than what they purchase with tickets. Participants were told that, in order to access tickets, they would have to expend five minutes of their recreational time to walk to a ticket machine and acquire an electronic ticket (on a card that was supplied to them). Specifically, participants were told that ticket dispensers would only dispense one ticket to a participant's card at a time and they could not acquire consecutive tickets from the same machine (i.e., after acquiring a ticket from a ticket dispenser, they would have to walk to another ticket dispenser to get their next ticket). Thus, participants were told to imagine that each ticket would take precisely five minutes to acquire. Any participant that failed either the context quiz or the ticket quiz more than one time was permitted to complete the study and earn the $2.00 payment, but their data were not included in data analysis. After completing the vignettes and quizzes, participants began the ICCPPT.

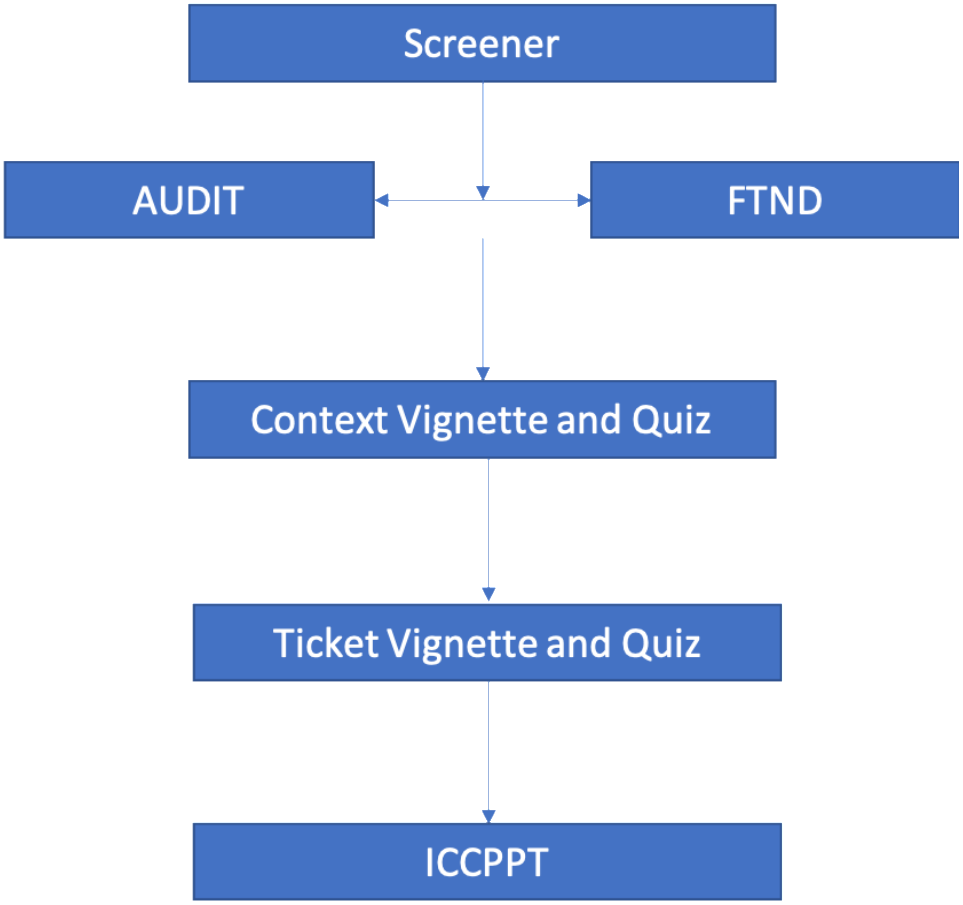

Figure 4-7. A flow chart of the Experimental conditions. First participants completed a screener that assessed participant eligibility. Then participants completed the AUDIT and FTND in a counterbalanced fashion. Next, participants read the context vignette and completed a multiple-choice quiz. Participants then read the ticket vignette and completed another multiple-choice quiz. Finally, participants completed an Income-Compensated Cross-Price Purchase Task.

In the first condition of the ICCPPT, participants were asked how many alcoholic beverages and mini-packs of tobacco cigarettes (2 cigarettes per mini-pack) they would purchase and consume if each beverage and mini-pack cost 1 ticket each. There were no limitations on how many tickets participants could acquire and spend in this initial condition. Following the initial condition, there were four income-compensated price manipulations. Alcoholic beverages served as the increasing-priced good in two of the income-compensated price manipulations and mini-packs of tobacco cigarettes were the

constant-priced good in these conditions. Alcoholic beverages were increased to 2 tickets per drink and then were increased again to 4 tickets per drink in the next condition (mini-packs of tobacco cigarettes were 1 ticket per drink in both of these conditions). Mini-packs of tobacco cigarettes served as the increasing-priced good in the other two income-compensated price. Mini-packs of tobacco cigarettes were increased to 2 tickets per mini-pack and then and were increased again to 4 tickets per mini-pack in the next condition (alcoholic beverages were 1 ticket per drink in both of these conditions). The order of the price manipulated conditions for alcoholic beverages and mini-packs of tobacco cigarettes was counterbalanced (see Figure 4-8 for details about the possible orders of conditions), but both alcoholic beverage price manipulations occurred in sequence, as did both mini-pack of tobacco cigarette price manipulations. The number of tickets that could be acquired and spent on alcoholic beverages and mini-packs of tobacco cigarettes was not capped in the initial condition but was capped in the price-manipulated conditions. The maximum number of tickets that could be spent in these price-manipulated conditions was based on the number of tickets that participants reported they would acquire and spend in the initial condition, such that the bundle (i.e., number of alcoholic beverages and mini-packs of tobacco cigarettes) purchased in the initial condition could always be purchased and consumed in the price-manipulated conditions. For an example of the maximum number of tickets in each condition for a participant that spent 5 tickets on alcoholic beverages and 10 tickets on tobacco cigarettes in the first condition (and the algorithm employed to reach the max tickets in each condition) see Table 4-20.

Figure 4-8. A list of the possible orders of experience for the initial and price-manipulated conditions. Conditions 2-5 had a cap on the total number of tickets that could be acquired and spent (see text for details). Half of the participants experienced Order A and the other half of the participants experienced Order B.

Table 4-20.

Max Ticket Algorithm and Example

Condition	Algorithm for Max Tickets	Max Tickets Example
Alcohol 1 Cigarettes 2	X + (Y*2) = Z	5 + (10*2) = 25
Alcohol 1 Cigarettes 4	X + (Y*4) = Z’	5 + (10*4) = 45
Alcohol 2 Cigarettes 1	(X*2) + Y = Z’’	(5*2) + 10 = 20

Alcohol 4 Cigarettes 1	(X*4) + Y = Z’’’	(5*4) + 10 = 30

Algorithm and example for calculating the maximum amount of tickets per condition. X in the algorithm (5 in the example) was the reported number of tickets that the participant said they would spend on alcoholic beverages in the initial condition. Y in the algorithm (10 in the example) was the reported number of tickets that the participant said they would spend on min-packs of tobacco cigarettes in the initial condition. There was no max on how many tickets could be used in the initial condition. In the initial condition, there was no maximum number of tickets, however the number of tickets that participants spent on alcoholic beverages and mini-packs of cigarettes were recorded (X and Y respectively for the algorithm and 5 and 10 respectively for the example) in this condition. These responses were then used to calculate the maximum number of tickets that could be used in each of the other conditions (Z, Z’, Z’’, and Z’’’ for the algorithm and 25, 45, 20, and 30 for the example).

Data Analysis

Prior to analyses data were subjected to screening. First, any participant that failed either the context quiz or the ticket quiz more than one time was eliminated from data analysis. A total of 12 participants were eliminated for failing one of the quizzes more than one time. Second, any participant that stated that they would purchase two or fewer alcoholic beverages *and* two or fewer mini packs of tobacco cigarettes, in the initial condition, was eliminated from data analysis due to an inability to asses changes in consumption in subsequent conditions. A total of 12 participants were eliminated due to this criterion. Lastly, any participant that spent greater than 60% of their leisure time collecting tickets was eliminated from data analysis because those participants would have exceeded 100% of their leisure time if they consumed the same bundle in each condition of the experiment. One participant was eliminated due to this criterion. Thus, a total of 25 participants were eliminated from data analysis and all analyses include only the 75 participants that passed the above criteria.

The primary data used in all analyses consisted of cross-price elasticity scores for each participant in each price-manipulated condition. Cross-price elasticity is the percent change in consumption of the static-priced good divided by the percent change in the price of the increasing-priced good (Madden, Smethells, Ewan, & Hursh, 2007). The initial condition served as the reference condition for all of the cross-price elasticity scores in the price-manipulated conditions. With cross-price elasticity, a negative value indicates that the goods are compliments, a positive value indicates a that the goods are substitutes, and a value of zero indicates that the goods are independent (Madden et al., 2007). Histograms were constructed to assess the distribution of cross-price elasticity scores in each condition. Next, because cross-price elasticity scores were predominately zero, we recoded the cross-price elasticity data into a binary format, where a cross-price elasticity of 0 was coded as 0 and any non-zero cross-price elasticity score was coded as 1. Putting cross-price elasticity data into binary format allowed us to assess whether a score of zero was statistically more probable than any non-zero score, using logistic regression. We performed a logistic regression analysis to assess the relative probability of having a cross-price elasticity of zero versus a non-zero cross-price elasticity score in each condition (see Fletcher, Mackenzie & Villouta, 2005 for a discussion of this data analytic strategy). Lastly, we included predictors in the model to assess whether any variables predicted a cross-price elasticity score of zero.

Results

Consumption of the static-priced good did not change systematically as the price of the increasing-priced good increased. Figure 4-9 shows mean consumption of alcoholic beverages and tobacco cigarettes in each of the five conditions (the initial

condition is shown in the leftmost column of each panel). In Panel A, alcohol is the increasing-priced good and consumption of alcohol decreased as price increased. Consumption of cigarettes was relatively stable across increasing alcohol prices. In Panel B, cigarettes are the increasing-priced good and consumption of cigarettes decreased as price increased. Consumption of alcohol was relatively stable across increasing cigarette prices.

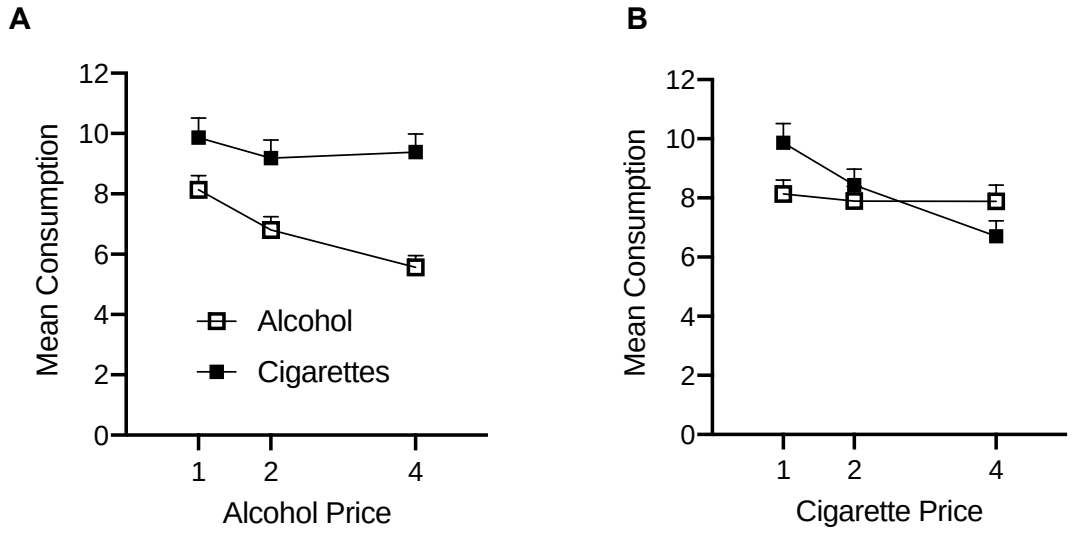

Fig. 4-9. Mean (SEM) alcohol and cigarette consumption are plotted as a function of Alcohol Price (Panel A) and Cigarette Price (Panel B). The price of mini-packs of cigarettes was always 1-ticket in Panel A and the price of alcohol was always 1-ticket in Panel B.

Zero was the predominant cross-price elasticity score across all four conditions. Figure 4-10 shows the frequency of cross-price elasticity scores for each condition. A negative cross-price elasticity score indicates that the goods are compliments, a positive score indicates that the goods are substitutes, and a score of zero indicates that the goods are independent of one another. For the vast majority of participants, in each condition,

the goods were independent of one another (i.e., a cross-price elasticity score of zero was predominant). See Appendix K for individual participant data.

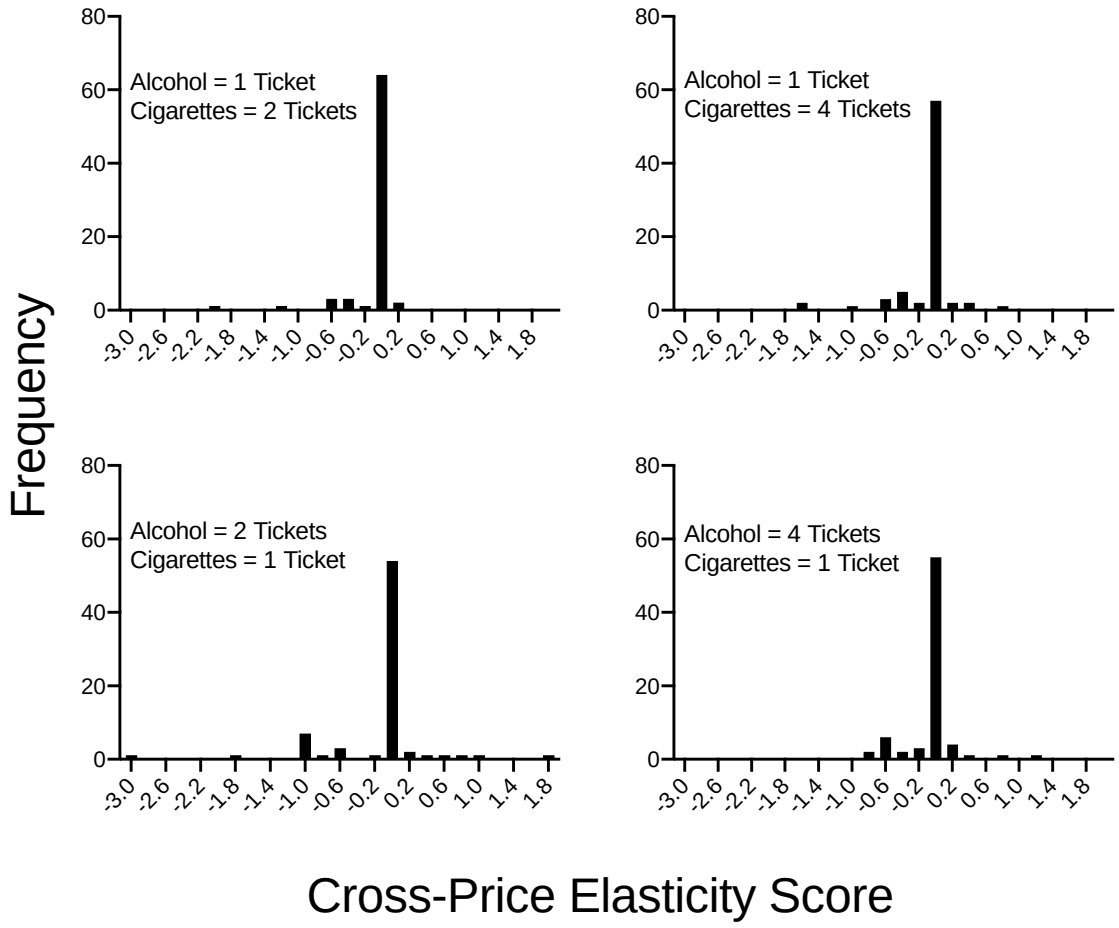

Fig. 4-10. Histograms showing the frequency of cross-price elasticity scores for each condition: Alcohol 1 Ticket, Cigarettes 2 Tickets (A), Alcohol 1 Ticket, Cigarettes 4 Tickets (B), Alcohol 2 Tickets, Cigarettes 1 Ticket. (C), and Alcohol 4 Tickets, Cigarettes 1 Ticket (D). Note individually scaled axes.

The intercept-only logistic regression models indicated that a cross-price elasticity score of zero was significantly more likely than a non-zero score. The intercept coefficients in Tables 4-21, 4-22, 4-23, and 4-24 are all negative and significant. Because cross-price elasticity scores of zero were coded as 0 and cross price elasticity scores that

were non-zero were coded as 1, the negative coefficients for intercept in these tables indicate that it was significantly more likely to get a score of zero than to get a non-zero score in each condition. These intercept coefficients are presented in logit form, but the logit can be converted to calculate the probability of getting a cross-price elasticity of zero, which is presented in the "Prob. of Zero" section of Tables 4-21 - 4-24.

Table 4-21.

Alcohol 1 Ticket Cigarettes 2 Tickets

(Intercept)	-1.76 ***
	(0.33)
AIC	64.53
BIC	66.85
Log Likelihood	-31.27
Deviance	62.53
Num. obs.	75
Prob. Of Zero	85%

*** p < 0.001, ** p < 0.01, * p < 0.05
Output from the intercept-only logistic regression for the condition where Alcohol cost 1 Ticket and Cigarettes cost 2 Tickets.

Table 4-22.

Alcohol 1 Ticket Cigarettes 4 Tickets

(Intercept)	-1.15 ***
	(0.27)
AIC	84.66
BIC	86.98
Log Likelihood	-41.33
Deviance	82.66
Num. obs.	75
Prob. Of Zero	76%

*** p < 0.001, ** p < 0.01, * p < 0.05
Output from the intercept-only logistic regression for the condition where Alcohol cost 1 Ticket and Cigarettes cost 4 Tickets.

Table 4-23.

Alcohol 2 Tickets	Cigarettes 1 Ticket
(Intercept)	-0.94 ***
	(0.26)
AIC	90.94
BIC	93.26
Log Likelihood	-44.47
Deviance	88.94
Num. obs.	75
Prob. Of Zero	72%

*** p < 0.001, ** p < 0.01, * p < 0.05
Output from the intercept-only logistic regression for the condition where Alcohol cost 2 Ticket and Cigarettes cost 1 Tickets.

Table 4-24.

Alcohol 4 Tickets	Cigarettes 1 Ticket
(Intercept)	-0.94 ***
	(0.26)
AIC	90.94
BIC	93.26
Log Likelihood	-44.47
Deviance	88.94
Num. obs.	75
Prob. Of Zero	72%

*** p < 0.001, ** p < 0.01, * p < 0.05
Output from the intercept-only logistic regression for the condition where Alcohol cost 1 Ticket and Cigarettes cost 4 Tickets.

We then added predictors to the intercept-only logistic regression models to assess whether any of these variables predicted whether participants had a zero cross-price elasticity score in any condition. Predictors were added to the logistic regression models using a step-wise approach (see Fletcher, Mackenzie, & Villouta, 2005). The predictors that were investigated were as follows: AUDIT score, FTND score, Gender, Income, Discretionary Income, Education, and Ethnicity. None of these variables significantly predicted whether someone would have a cross-price elasticity score of zero in any condition. The addition of these variables also did not significantly improve the models.

Discussion

The vast majority of participants treated alcohol and cigarettes as independent goods. As can be seen in both the histograms (see Figure 4-9) and individual participant data (see Appendix K), participants did not alter their consumption of the static-priced good as a function of increasing the price of the other good (i.e., most participants had a cross-price elasticity score of 0) in any condition. The logistic regression models show that it was much more likely to get a cross-price elasticity score of zero than any non-zero cross-price elasticity score. None of the investigated predictors significantly predicted a cross-price elasticity score of zero, a finding that is likely due to the limited variability (i.e., the vast majority of participants had a cross-price elasticity score of zero, making it difficult to predict that score).

The finding that alcohol and cigarettes are independent goods replicates the only previous study that has been conducted using a hypothetical purchase task (Petry, 2001) but disagrees with epidemiological data. Petry (2001) used a hypothetical purchase task

to assess whether cigarettes (among other drugs) would substitute for alcohol. Petry found that cigarette purchasing was independent of alcohol price, a finding replicated in the current study. The current study extended this finding by showing that alcohol purchasing is also independent of cigarette price. The question remains, however, whether this finding is due to the methodology employed (i.e., it is possible that this finding is a result of using hypothetical purchase tasks and would not be replicated in a laboratory study with real rewards, or in the natural environment). An unpublished laboratory study using cigarette puffs and alcoholic beverages found a complimentary relation between alcohol and cigarettes (see Hursh & Roma, 2016; their Figure 9). There is a dearth of epidemiological data regarding this issue, but the limited data available agree with the findings of the laboratory study cited in Hursh and Roma, suggesting a complimentary relation between alcohol and cigarettes (e.g., Decker & Schwartz, 2000).

General Discussion

In Experiment 1, we examined how the opportunity to smoke tobacco cigarettes influences demand indices for alcoholic beverages using an APT. APT data were orderly and were well fit by Equation 4-1. In the current study, alcohol demand indices had a correlational structure that was consistent with a study that examined the latent structure of these alcohol demand indices (e.g., Mackillop et al., 2009). Mackillop et al. found that these variables load onto two factors, amplitude (Q_0) and persistence (P_{max}, BP, and α). These variables were highly correlated in the current study as well. We also found Audit Score and Discretionary Income to be important predictors (i.e., fixed effects) for 4 of the demand indices (Q_0, O_{max}, P_{max}, and BP_1) and Income to be an important predictor for α. AUDIT score has been shown to be correlated with these demand indices on APTs in

previous studies (e.g., Gray & Mackillop, 2014; Amlung et al., 2013). Despite robust evidence that nicotine increases the value of alcohol in laboratory studies with real exposure to the drugs (e.g., Leão et al., 2015), we did not find any evidence that demand indices were different across the smoking and non-smoking condition in Experiment 1 with hypothetical drug exposure and hypothetical alcoholic beverage purchasing.

In Experiment 2, we examined how the opportunity to drink alcoholic beverages influences demand indices for tobacco cigarettes using a CPT. CPT data were orderly and were well fit by Equation 4-1. Cigarette demand indices had a correlational structure that was consistent with the results of a prior study. Bidwell et al. (2012) found that these variables load onto two factors, amplitude (Q_0) and persistence (P_{max}, BP, and α). These variables were highly correlated in the current study as well. We found Audit Score, FTND score, Income, Discretionary Income, and Age to be important predictors (i.e., fixed effects) in the multilevel models that were constructed to predict the various cigarette demand indices. Several other studies have also found FTND score to be related to demand indices on CPTs (e.g., Few, Acker, Murphy, & Mackillop, 2012). We also found that drinking context (i.e., Condition) significantly predicted Maximum Expenditure in that O_{max} was reliably different across the non-drinking and drinking context. To our surprise, however, O_{max} was higher in the non-drinking context than in the drinking context. This finding, with hypothetical alcohol exposure and hypothetical cigarette purchasing, is in the opposite direction of our hypothesis and in the opposite direction of a laboratory study that has shown that real exposure to alcohol increases responding for real cigarettes (e.g., Barrett, Campbell, Rocah, Stewart, & Darredeau, 2013). All other demand indices were unaffected by drinking context.

In Experiment 3, we examined the economic relation between alcohol and nicotine using a cross-price purchase task. Most participants treated the drugs as independent goods. We found that it was more probable for a participant to treat the drugs as completely independent goods than it was for participants to treat the drugs as either complementary goods or substitutable goods. This finding is at odds with the only laboratory experiment (unpublished) to investigate this effect (see Hursh & Roma, 2016; see Figure 9) and epidemiological data (e.g., Decker & Schwartz, 2000), but is in agreement with the findings of the only published study to investigate this relation using a hypothetical purchase task (see Petry, 2001).

The current experiments produced novel findings and point to potential limitations of using hypothetical purchase tasks. Experiment 1 is the first study to assess differences in hypothetical alcohol purchasing across a hypothetical smoking and non-smoking context. We found that smoking context did not affect alcohol demand indices. This result is surprising, because nicotine exposure increases alcohol self-administration in laboratory studies. Experiment 2 is the first study to assess differences in hypothetical tobacco cigarette purchasing across a hypothetical drinking and non-drinking context. We found that only one index of demand (O_{max}) was affected by drinking context, and the effect was in the opposite direction of our hypothesis. Similar to Experiment 1, the results of Experiment 2 are also surprising, because alcohol exposure increases smoking in laboratory studies. Whether this finding is due to a limitation of hypothetical purchase tasks, or due to the fact that the drug exposure was hypothetical, is something that will need to be answered by future research. It may simply be too difficult for people to predict how exposure to a drug will influence their motivation for another drug. Or, in a

broader since, layering a hypothetical context on top of a hypothetical task may be too taxing for participants.

Experiment 3 is the first study designed to explicitly assess the bidirectional cross-price elasticity of alcohol and cigarettes using a hypothetical purchase task. The results replicate and extend the results from the only other study to partially address this issue (Petry, 2001). However, the results of both Petry (2001) and the current study are at odds with epidemiological data (e.g., Decker & Schwartz, 2000) and the results of an unpublished laboratory study (see Hursh & Roma, 2016; their Figure 9). Future research should aim to understand this discrepancy.

Future research in this domain should attempt to bring participants into closer contact with the contingencies (i.e., smoking or drinking context), perhaps through some sort of manipulation that mirrors approaches used in episodic future thinking manipulations. Episodic future thinking is a technique that facilitates participants' imagining how decisions made now impact their future experiences and has been used to reduce impulsivity (Peters & Buchel, 2010), but these techniques are broadly applicable. For example, *episodic specificity induction* consists of a detailed interview that promotes retrieval of specific details of past experiences to bring participants into contact with details surrounding those experiences (Schacter, Benoit, & Szpunar, 2017). Using this technique in the current study could remind participants what it is like to be under the influence of nicotine or alcohol while having the opportunity to consume the other drug and may bring their behavior more under the control of the contextual manipulation. Perhaps, behavior on an APT or CPT will be more comparable to laboratory experiments

if combined with episodic specificity induction or some other episodic thinking technique.

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CHAPTER V

GENERAL DISCUSSION

The most commonly abused drugs in the United States are alcohol and nicotine. These drugs are commonly co-abused. People who smoke are more likely to have problems with alcohol (e.g., McKee et al., 2007) and chronic alcohol exposure facilitates nicotine receptor binding (e.g., Yoshida et al., 1982). Exposure to nicotine increases alcohol consumption in non-human preclinical studies (Burns & Proctor, 2013) and human laboratory studies (e.g., Barrett, Tichauer, Leyton, & Pihl, 2006) and exposure to alcohol increases nicotine consumption in non-human preclinical studies (Le et al., 2010) and in human laboratory studies (e.g., Barrett, Campbell, Rocah, Steward, & Darredeau, 2013).

The studies described in Chapters II, III, and the first Experiment of Chapter IV examined how nicotine exposure affects aspects of alcohol value. In Chapter II, we assessed how continuous nicotine exposure affects resurgence of alcohol seeking in rats in a laboratory study. We found that both the Nicotine and Saline group demonstrated resurgence of alcohol seeking, but we did not find any difference in the degree of resurgence across the two groups. In Chapter III, we assessed how nicotine and nicotine + tranylcypromine affects progressive ratio breakpoint for alcohol in a laboratory study with rats. We found that nicotine increased progressive ratio breakpoint for alcohol, a finding that replicates what has been found in other non-human laboratory studies (e.g., Leao et al., 2015) and human laboratory studies (e.g., Barrett, Tichauer, Leyton, & Pihl, 2006). However, to our surprise, we found that nicotine + tranylcypromine decreased progressive ratio breakpoint for alcohol, relative to saline levels. In Experiment 1 of

Chapter IV, we assessed how the hypothetical opportunity to smoke tobacco cigarettes affects demand for hypothetical alcoholic beverages in humans. We hypothesized that alcohol demand indices would be more extreme in the Smoking condition than in the Non-Smoking condition. Despite data being orderly and in accord with prior studies, we found no difference in alcohol demand indices between the smoking and non-smoking condition.

The study described in Experiment 2 of Chapter IV focused on the opposite relation of the first three experiments, how exposure to hypothetical alcohol affects demand for hypothetical tobacco cigarettes. We hypothesized that cigarette demand indices would be more extreme in the Drinking condition than in the Non-Drinking condition. We found that one of the five demand indices examined (O_{max}; Maximum Expenditure) was differentiated across the drinking and non-drinking condition. However, this finding was in the opposite direction than what we predicted (O_{max} was higher in the Non-Drinking than Drinking context). Despite data being orderly and in accord with prior studies, we found no difference between the Drinking and Non-Drinking condition in the other four demand indices examined.

The study described in Experiment 3 of Chapter IV focused on the how consumption of hypothetical alcoholic beverages changes when the price of hypothetical tobacco cigarettes in increased and how consumption of hypothetical tobacco cigarettes changes when the price of hypothetical alcoholic beverages is increased. To our surprise, consumption of alcoholic beverages was not affected by increasing the price of mini-packs of tobacco cigarettes and consumption of mini-packs of tobacco cigarettes was not affected by increasing the price of alcoholic beverages (i.e., the most common cross-price

elasticity score was zero). This finding is at odds with epidemiological data (e.g., Decker & Schwartz, 2000) and the only laboratory study conducted on the issue (see an unpublished study described in Hursh & Roman, 2016, Figure 9), but is in agreement with the only study that has been conducted using a similar methodology to the current experiment (Petry, 2001).

Together, this set of experiments has examined several different ways that alcohol and nicotine exposure affect behavior. The results of each study invoke new questions. In Chapter II, we argued that the methodology employed (i.e., the use of continuous nicotine delivery) may have affected the results, due to desensitization of nicotinic acetylcholine receptors. In Chapter III, we speculated that nicotine + tranylcypromine may decrease alcohol value through short-term off-target effects associated with acute tranylcypromine exposure, such as increased serotonin production. In Experiment 1 of Chapter IV, we concluded that it may not be possible for humans to accurately imagine how exposure to a drug (i.e., nicotine) would impact decisions about other drugs (i.e., alcohol). In Experiment 2 of Chapter IV, we were surprised to find that alcoholic beverage availability only affected one index of demand for tobacco cigarettes (O_{max}) and not the others. It is not clear why this index of demand would be affected in the opposite direction than we would predict. Finally, in Experiment 3 of Chapter IV, we noted that there is a seeming disparity between cross-price elasticity scores for alcohol and cigarettes in epidemiological and laboratory studies versus hypothetical purchasing task studies. Future research will need to examine the cause of this disparity.

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Appendix A. SCREENER FOR PARTICITPANT RECRUITMENT

1. How old are you (open-ended, with only numerical responses permitted)?

2. What is your Gender?
    a. Male
    b. Female

3. **Do you drink alcoholic beverages at least occasionally?**
    a. Yes
    b. No

4. **In the past 30 days, what is the greatest number of drinks you have consumed in a single sitting?**
    a. 0
    b. 1 – 3
    c. 4 (minimum criterion for females)
    d. 5 or more (criterion for males)

5. Do you drink coffee or tea daily?
    a. Yes
    b. No

6. What time do you tend to wake up in the morning?
    a. Before 5 AM
    b. Between 5 and 7 AM
    c. Between 7 and 9 AM
    d. After 9 AM

7. **How long have you smoked tobacco cigarettes?**
    a. I do not smoke tobacco cigarettes
    b. Less than one month
    c. Less than three months
    d. More than three months

8. **Have you smoked tobacco cigarettes each day in the past week?**
    a. Yes
    b. No

9. **How many tobacco cigarettes do you smoke in a day?**
    a. I do not smoke tobacco cigarettes
    b. Less than five
    c. Less than ten
    d. More than ten

10. How many meals do you tend to eat in a day?
    a. 1
    b. 2
    c. 3
    d. More than 3

***Bolded questions are questions that determine participant inclusion. Participants must choose the bolded answer on these questions to be eligible to participate in the study. In addition to the screener, participants will be filtered using MTurk filters, where only participants that are 21 years or older and have a 95% approval rating will be able to see the study on the website.

Appendix B. DEMOGRAPHIC QUESTIONS

1. What ethnicity do you identify with (select all that apply)?
    a. White/Caucasian
    b. African American
    c. Asian
    d. Hispanic/Latinx
    e. Native American
    f. Pacific Islander
    g. Prefer not to answer
    h. Other (Please specify in the textbox)

2. What is your annual income (please state in whole dollars, no decimal points)?

3. What is your annual discretionary income (i.e., the amount you have left over, after paying all your bills and expenses)?

4. What is the highest level of education that you have completed?
    a. Did not finish high school
    b. High School
    c. Some college
    d. Bachelor's degree
    e. Graduate degree

Appendix C. ALCOHOL USE DISORDERS IDENTIFICATION TEST

1. How often do you have a drink containing alcohol?

    a. Never
    b. Monthly or less
    c. 2-4 time a month
    d. 2-3 times a week
    e. 4 or more times a week

2. How many standard drinks containing alcohol do you have on a typical day when drinking?
    a. 1 or 2
    b. 3 or 4
    c. 5 or 6
    d. 7 or 8
    e. 9 or more

3. How often do you have six or more drinks on one occasion?
    a. Never
    b. Less than monthly
    c. Monthly
    d. Weekly
    e. Daily or almost daily

4. During the past year, how often have you found that you were not able to stop drinking once you had started?
    a. Never
    b. Less than monthly
    c. Monthly
    d. Weekly
    e. Daily or almost daily

5. During the past year, how often have you failed to do what was normally expected of you because of drinking?
    a. Never
    b. Less than monthly
    c. Monthly
    d. Weekly
    e. Daily or almost daily

6. During the past year, how often have you needed a drink in the morning to get yourself going after a heavy drinking session?
    a. Never
    b. Less than monthly

c. Monthly
d. Weekly
e. Daily or almost daily

7. During the past year, how often have you had a feeling of guilt or remorse after drinking?
    a. Never
    b. Less than monthly
    c. Monthly
    d. Weekly
    e. Daily or almost daily

8. During the past year, have you been unable to remember what happened the night before because you had been drinking?
    a. Never
    b. Less than monthly
    c. Monthly
    d. Weekly
    e. Daily or almost daily

9. Have you or someone else been injured as a result of your drinking?
    a. No
    b. Yes, but not in the past year
    c. Yes, during the past year

10. Has a relative or friend, doctor or health worker been concerned about your drinking or suggested you cut down?
    a. No
    b. Yes, but not in the past year
    c. Yes, during the past year

*Scoring the AUDIT
Scores for each question range from 0 to 4, with the first response for each question (eg never) scoring 0, the second (eg less than monthly) scoring 1, the third (eg monthly) scoring 2, the fourth (eg weekly) scoring 3, and the last response (eg. Daily or almost daily) scoring 4. For questions 9 and 10, which only have three responses, the scoring is 0, 2 and 4 (from left to right). A score of 8 or more is associated with harmful or hazardous drinking, a score of 13 or more in women, and 15 or more in men, is likely to indicate alcohol dependence.

Appendix D. Fagerstrom TEST FOR NICOTINE DEPENDENCE

1. How soon after waking do you smoke your first cigarette?
    a. Within 5 minutes (3)
    b. 5-30 minutes (2)
    c. 31-60 minutes (1)
    d. More than 60 minutes (0)

2. Do you find it difficult to refrain from smoking in places where it is forbidden? E.g. church, library, etc.
    a. Yes (1)
    b. No (0)

3. Which cigarette would you hate to give up?
    a. The first in the morning (1)
    b. Any other (0)

4. How many cigarettes per day do you smoke?
    a. 10 or less (0)
    b. 11-20 (1)
    c. 21-30 (2)
    d. 31 or more (3)

5. Do you smoke more frequently in the morning?
    a. Yes (1)
    b. No (0)

6. Do you smoke even if you are sick in bed most of the day?
    a. Yes (1)
    b. No (0)

*Scores (a sum of the scores marked in parentheses by the options) of 1-2 = low dependence, 3-4 = low to moderate dependence, 5-7 = moderate dependence, and 8+ = high dependence.

Appendix E. NON-SMOKING APT VIGNETTE AND QUIZ

In the questionnaire that follows, we would like you to pretend to purchase and consume alcoholic beverages during an 8-hour period. The alcoholic beverages that you will be purchasing in the questions that follow are a standard size beer (12 oz.), a glass of wine (5 oz.), one shot of hard liquor/distilled spirits (1.5 oz.), or a mixed drink containing one shot of liquor/distilled spirits (1.5 oz.).

Imagine that you are going to an outdoor concert at a local park with friends, for the entire evening (from 5 pm until 1 am). The weather is ideal. Imagine that you do not have any obligations the next day (i.e., no work or classes).

Once you enter the venue, you are not permitted to exit and re-enter. Pretend that you will not be able to bring your own alcoholic beverages with you to this event; you will only be able to consume the alcoholic beverages that you purchase from the vendors at this event. You must consume all of the alcoholic beverages that you purchase during the 8-hour period. You will also not be permitted to share the alcoholic beverages that you purchase with anyone else and no one will share with you.

The alcoholic beverages you purchase are for your consumption only and must be consumed during the 8-hour period (no stockpiling for later). Pretend that you did not drink any alcohol or use any drugs before arriving, that you will not drink any alcohol or use any drugs after you leave to go home, and pretend that transportation is provided to you (i.e., you will not be driving home afterwards).

We also want you to imagine that **the park does not permit smoking or the use of any other form of nicotine**. Thus, you will be completely nicotine-free throughout the duration of the concert (i.e., no cigarettes, no e-cigarette use, no nicotine gum/lozenges, etc.). Please respond to these questions honestly, as if you were actually in this situation.

1. How long are you going to be at the concert?
    a. 1 hour
    b. 3 hours
    c. 5 hours
    d. 8 hours

2. Will you be permitted to smoke cigarettes during the 8-hour period you are at the concert?
    a. Yes
    b. No

3. Will you be permitted to use any alternative forms of nicotine during the 8-hour period you are at the concert?

a. Yes
b. No

4. Will you have access to any alcohol other than what you are purchasing at the concert?
    a. Yes
    b. No

5. Are you allowed to bring drinks home with you or give any drinks away at the concert?
    a. Yes
    b. No

Appendix F. SMOKING APT VIGNETTE AND QUIZ

In the questionnaire that follows, we would like you to pretend to purchase and consume alcoholic beverages during an 8-hour period. The alcoholic beverages that you will be purchasing in the questions that follow are a standard size beer (12 oz.), a glass of wine (5 oz.), one shot of hard liquor/distilled spirits (1.5 oz.), or a mixed drink containing one shot of liquor/distilled spirits (1.5 oz.).

Imagine that you are going to an outdoor concert at a local park with friends, for the entire evening (from 5 pm until 1 am). The weather is ideal. Imagine that you do not have any obligations the next day (i.e., no work or classes).

Once you enter the venue, you are not permitted to exit and re-enter. Pretend that you will not be able to bring your own alcoholic beverages with you to this event; you will only be able to consume the alcoholic beverages that you purchase from the vendors at this event. You must consume all of the alcoholic beverages that you purchase during the 8-hour period. You will also not be permitted to share the alcoholic beverages that you purchase with anyone else and no one will share with you.

The alcoholic beverages you purchase are for your consumption only and must be consumed during the 8-hour period (no stockpiling for later). Pretend that you did not drink any alcohol or use any drugs before arriving, that you will not drink any alcohol or use any drugs after you leave to go home, and pretend that transportation is provided to you (i.e., you will not be driving home afterwards).

We also want you to imagine that **the park permits smoking** . Thus, you will be able to bring your own cigarettes with you and smoke as much as you would like during the concert. You will not have access to any alternative forms of nicotine. Please respond to these questions honestly, as if you were actually in this situation.

1. How long are you going to be at the concert?
    a. 1 hour
    b. 3 hours
    c. 5 hours
    d. 8 hours

2. Will you be permitted to smoke cigarettes during the 8-hour period you are at the concert?
    a. Yes
    b. No

3. Will you be permitted to use any alternative forms of nicotine during the 8-hour period you are at the concert?

a. Yes
b. No

4. Will you have access to any alcohol other than what you are purchasing at the concert?
    a. Yes
    b. No

5. Are you allowed to bring drinks home with you or give any drinks away at the concert?
    a. Yes
    b. No

Appendix G. NON-DRINKING CPT VIGNETTE AND QUIZ

In the questionnaire that follows, we would like you to pretend to purchase and consume tobacco cigarettes during an 8-hour period. The tobacco cigarettes that you are purchasing are standard cigarettes and you should imagine that they are your favorite brand.

Imagine that you are going to an outdoor concert at a local park with friends, for the entire evening (from 5 pm until 1 am). The weather is ideal. Imagine that you do not have any obligations the next day (i.e., no work or classes).

Once you enter the venue, you are not permitted to exit and re-enter. Pretend that you will not be able to bring your own tobacco cigarettes with you to this event; you will only be able to consume the tobacco cigarettes that you purchase from the vendors at this event. You must consume all of the tobacco cigarettes that you purchase during the 8-hour period. You will also not be permitted to share the tobacco cigarettes that you purchase with anyone else and no one will share with you.

The tobacco cigarettes that you purchase are for your consumption only and must be consumed during the 8-hour period (no stockpiling for later). Pretend that you did not drink any alcohol or use any drugs before arriving, that you will not drink any alcohol or use any drugs after you leave to go home, and pretend that transportation is provided to you (i.e., you will not be driving home afterwards).

We also want you to imagine that **the park does not permit alcoholic beverages**. Thus, you will not have any alcohol in your system throughout the duration of the concert. The park also does not permit the use of any alternative forms of nicotine (i.e., no e-cigarette use, no nicotine gum/lozenges, no chewing tobacco etc.). Please respond to these questions honestly, as if you were actually in this situation.

1. How long are you going to be at the concert?
    a. 1 hour
    b. 3 hours
    c. 5 hours
    d. 8 hours

2. Will you be permitted to drink alcoholic beverages during the 8-hour period you are at the concert?
    a. Yes
    b. No

3. Will you be permitted to use any alternative forms of nicotine during the 8-hour period you are at the concert?
    a. Yes
    b. No

4. Will you have access to any alcohol other than what you are purchasing at the concert?
    a. Yes
    b. No

5. Are you allowed to bring drinks home with you or give any drinks away at the concert?
    a. Yes
    b. No

Appendix H. DRINKING CPT VIGNETTE AND QUIZ

In the questionnaire that follows, we would like you to pretend to purchase and consume tobacco cigarettes during an 8-hour period. The tobacco cigarettes that you are purchasing are standard cigarettes and you should imagine that they are your favorite brand.

Imagine that you are going to an outdoor concert at a local park with friends, for the entire evening (from 5 pm until 1 am). The weather is ideal. Imagine that you do not have any obligations the next day (i.e., no work or classes).

Once you enter the venue, you are not permitted to exit and re-enter. Pretend that you will not be able to bring your own tobacco cigarettes with you to this event; you will only be able to consume the tobacco cigarettes that you purchase from the vendors at this event. You must consume all of the tobacco cigarettes that you purchase during the 8-hour period. You will also not be permitted to share the tobacco cigarettes that you purchase with anyone else and no one will share with you.

The tobacco cigarettes that you purchase are for your consumption only and must be consumed during the 8-hour period (no stockpiling for later). Pretend that you did not drink any alcohol or use any drugs before arriving, that you will not drink any alcohol or use any drugs after you leave to go home, and pretend that transportation is provided to you (i.e., you will not be driving home afterwards).

We also want you to imagine that **the park permits alcoholic beverages**. Thus, you will be allowed to bring your own alcoholic beverages with you to the event and drink as much as you want during the concert, while you are purchasing cigarettes from the vendors. The park does not permit the use of any alternative forms of nicotine (i.e., no e-cigarette use, no nicotine gum/lozenges, no chewing tobacco etc.). Please respond to these questions honestly, as if you were actually in this situation.

1. How long are you going to be at the concert?
    a. 1 hour
    b. 3 hours
    c. 5 hours
    d. 8 hours

2. Will you be permitted to drink alcoholic beverages during the 8-hour period you are at the concert?
    a. Yes
    b. No

3. Will you be permitted to use any alternative forms of nicotine during the 8-hour period you are at the concert?
    a. Yes
    b. No

4. Will you have access to any alcohol other than what you are purchasing at the concert?
    a. Yes
    b. No

5. Are you allowed to bring drinks home with you or give any drinks away at the concert?
    a. Yes
    b. No

Appendix I. ICCPPT CONTEXT VIGNETTE AND QUIZ

Imagine that you have won an all-expenses paid day trip for yourself and 3 guests. The day trip will begin at 8 AM and last until midnight. The event will occur on a stationary boat that is docked on a local body of water. The boat is large and has a variety of recreational activities to engage in while you are on board.

Imagine that the boat has all of your favorite recreational activities, both indoor and outdoor (e.g., bowling, swimming, volleyball, arcade games, movies, etc.). All recreational activities are completely free and you should pretend like there are no lines or delays for engaging in the recreational activities.

We also want you to imagine that you are not allowed to bring any alcohol or cigarettes with you onto the boat. You are also not allowed to bring any alternative forms of nicotine with you onto the boat (e.g., no electronic cigarettes, nicotine gum/lozenges, chewing tobacco, etc.). Alcoholic beverages (standard size beer, glass of wine, shot of liquor, or mixed drink with a shot of liquor in it) and cigarettes will be provided to you once you are on the boat, free of charge. You are allowed to drink alcoholic beverages and smoke freely throughout the boat, including while you are engaged in the recreational activities. We will describe how you get access to alcoholic beverages and cigarettes on the next page.

We want you to imagine that the alcoholic beverages and cigarettes that you receive on the boat is for your consumption only (you won't share your drinks or cigarettes with anyone else), must be consumed before you leave the boat (no stockpiling for later), and you have no obligations the following day. Please also imagine that you did not have any drugs or alcohol before boarding the boat and you will not have any drugs or alcohol after leaving the boat, at the end of the day. We will provide transportation to and from the boat for you, so you do not need to worry about driving under the influence of alcohol.

1. How long will you be at the event?
    a. 8 AM to 8 PM
    b. 4 PM to midnight
    c. 6 PM to 10 PM
    d. 8 AM to midnight

2. Will you be able to bring any alcoholic beverages or tobacco cigarettes with you onto the boat?
    a. Yes
    b. No

3. Are you allowed to give any alcoholic beverages or tobacco cigarettes away or take any home with you?
    a. Yes

b. No

4. Will transportation to and from the boat be provided to you?
   a. Yes
   b. No

5. Are you allowed to use any alternative forms of nicotine, other than cigarettes (e-cigs, nicotine gum/lozenge, chewing tobacco, etc.)?
   a. Yes
   b. No

Appendix J. ICCPPT TICKET VIGNETTE AND QUIZ

Read the description of how to acquire alcoholic beverages and tobacco cigarettes while you are on the boat below:

In order to receive alcoholic beverages and tobacco cigarettes while you are on the boat, you must acquire tickets. Tickets are awarded electronically and do not cost any money. We will give you an electronic card when you check in and you can load the card with tickets by inserting the card into a ticket dispenser on the boat. Ticket dispensers will only load one ticket onto your card at a time. You must visit a different ticket dispenser before returning to a previously used ticket dispenser. In other words, you cannot receive consecutive tickets from the same ticket dispenser.

Ticket dispensers are located throughout the boat. Assume that it will take you five minutes to travel from any recreational activity to a ticket dispenser and back to the recreational activity (2.5 minutes each way). It will also take you five minutes to travel from one ticket dispenser to another ticket dispenser. You should assume that each ticket you acquire will cost you five minutes of recreational activity. Servers will be walking around the boat and you will be able to use the tickets on your card to acquire alcoholic beverages and tobacco cigarettes from the servers, who will bring them to you. Assume that the servers do not accept tips.

In the questionnaire that follows, we will ask you about how many alcoholic beverages and mini packs of tobacco cigarettes you will acquire and consume throughout your duration on the boat. The mini packs of tobacco cigarettes contain 2 cigarettes. Sometimes alcoholic beverages and mini packs of tobacco cigarettes will cost the same number of tickets and sometimes they will cost a different number of tickets. Sometimes we will limit the number of tickets that you are allowed to use and sometimes we will allow you to use as many tickets as you would like. Please read the descriptions of each question carefully and answer as if you were actually in this situation.

1. What can you use tickets for while on the boat?
    - **a. Alcoholic beverages and tobacco cigarettes**
    - b. Alcoholic beverages only
    - c. Tobacco cigarettes only
    - d. None of these

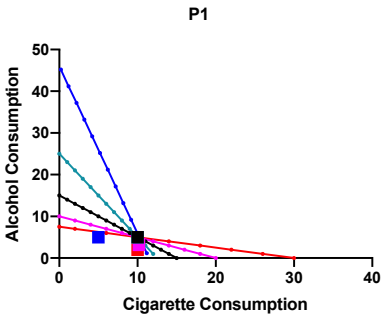
2. How much time will it take to acquire each ticket?
    - a. 2 minutes
    - **b. 5 minutes**
    - c. 10 minutes
    - d. 30 minutes

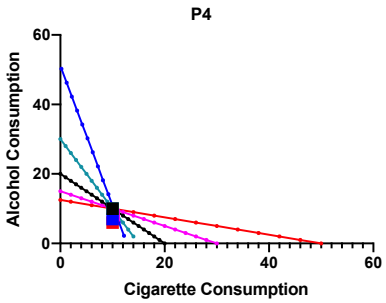
3. Are you able to get more than one ticket from a ticket dispenser in a single trip?
    - a. Yes

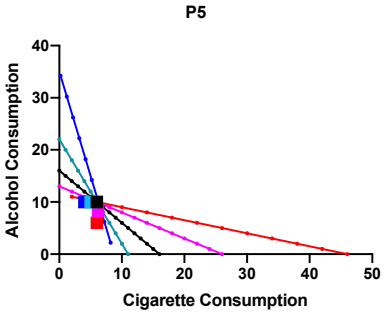
b. No

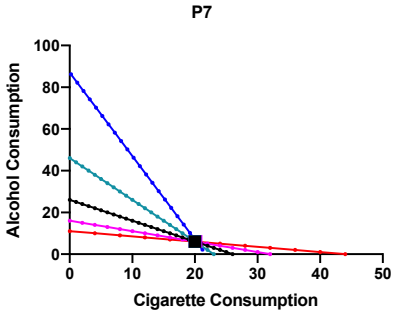
4. How many cigarettes are in each mini pack?
    a. 1
    b. 2
    c. 5
    d. 10

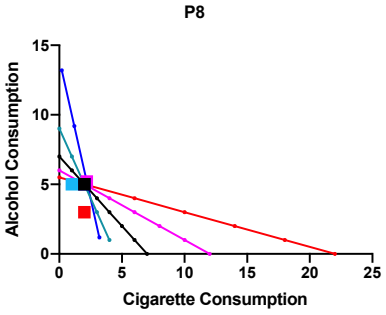
Appendix K. INDIVIDUAL SUBJECT DATA FOR EXPERIMENT 3

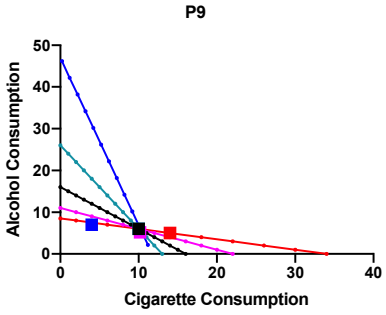


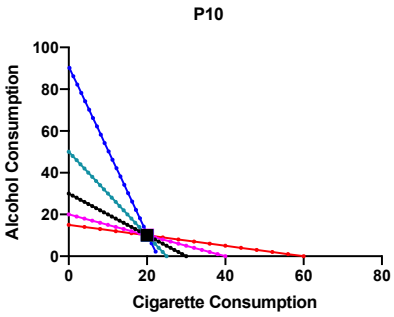


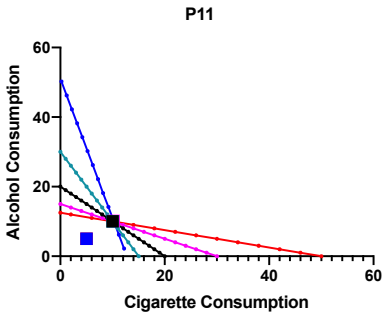


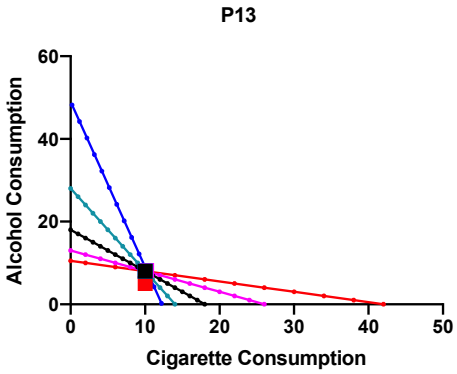








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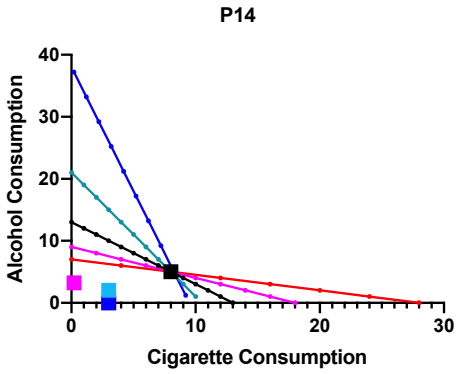
Cigarette Consumption
0
20
40
60
0
10
20
30
40
50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Cigarette Consumption
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10
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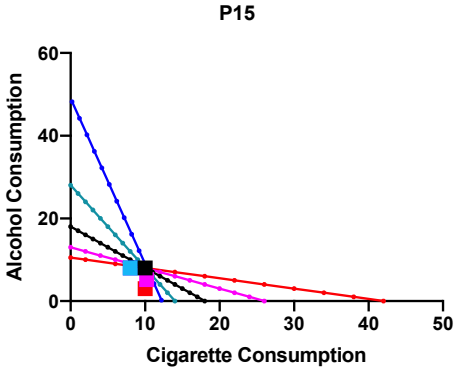
30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Cigarette Consumption
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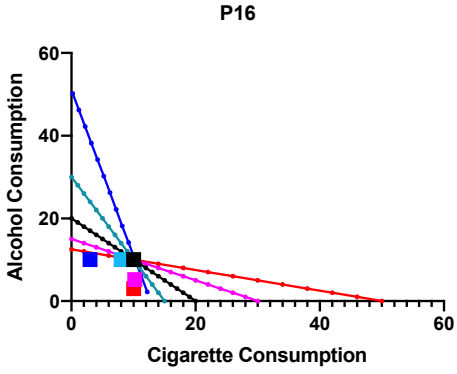
20
40
60
0
10
20
30
40
50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Cigarette Consumption
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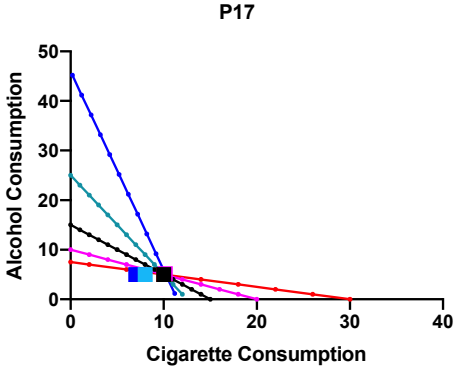
0
20
40
60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Cigarette Consumption
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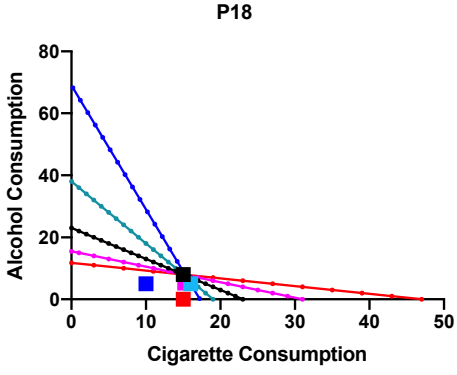
10
20
30
40
50
0
10
20
30
40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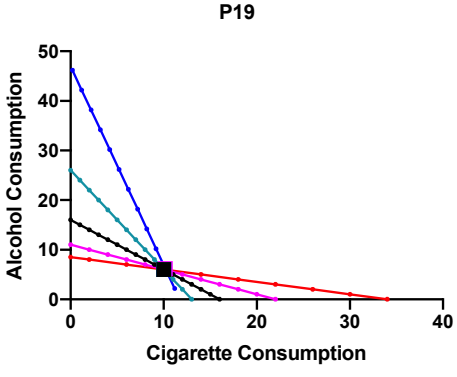
Alcohol Consumption
Cigarette Consumption
0
20
40
60
80
0
10
20
30
40
50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Cigarette Consumption
0
10
20
30
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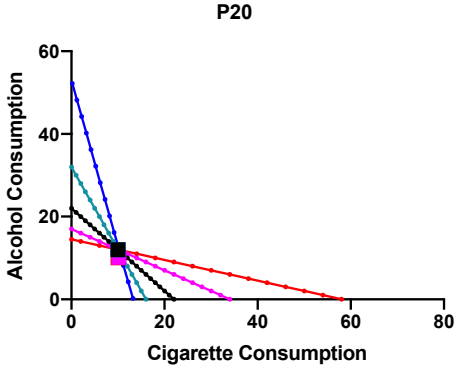
0
10
20
30
40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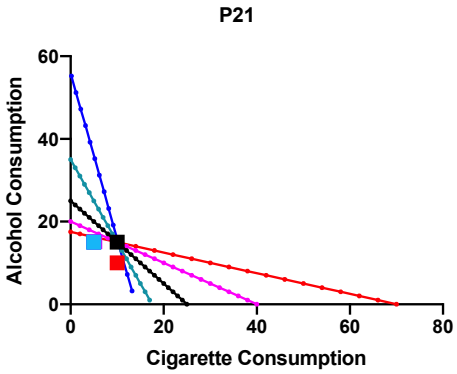
Alcohol Consumption
Cigarette Consumption
0
20
40
60
0
20
40
60
80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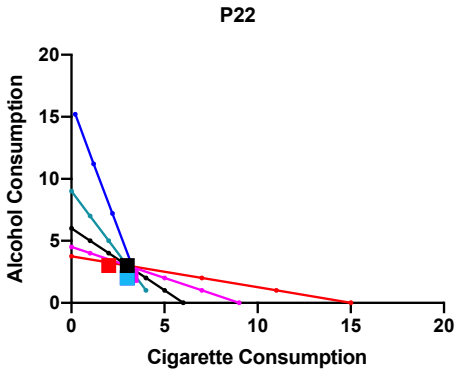
Alcohol Consumption
Cigarette Consumption
0
20
40
60
80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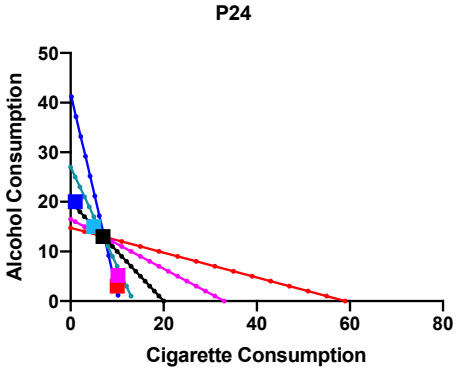
Alcohol Consumption
Cigarette Consumption
0
5
10
15
20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Cigarette Consumption
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10
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30
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50
60
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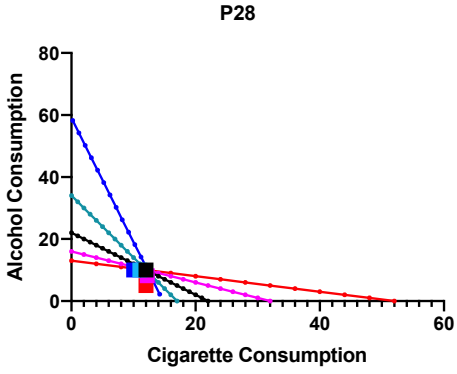
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Alcohol Consumption
Cigarette Consumption
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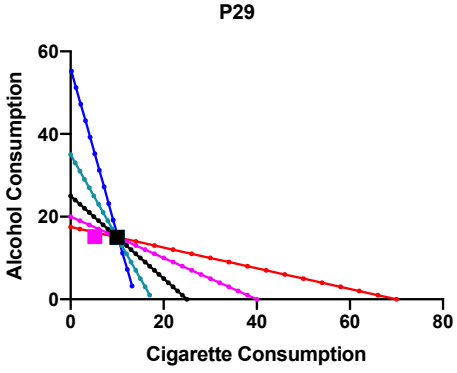
20
40
60
80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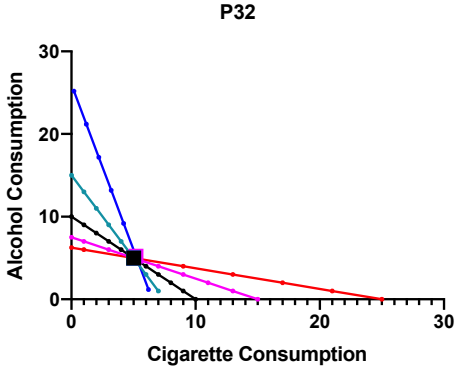
Alcohol Consumption
Cigarette Consumption
0
20
40
60
80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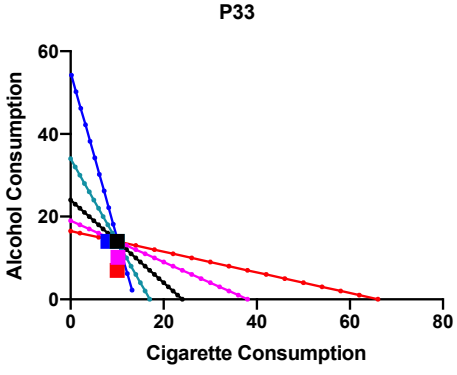
Alcohol Consumption
Cigarette Consumption
0
10
20
30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Cigarette Consumption
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20
40
60
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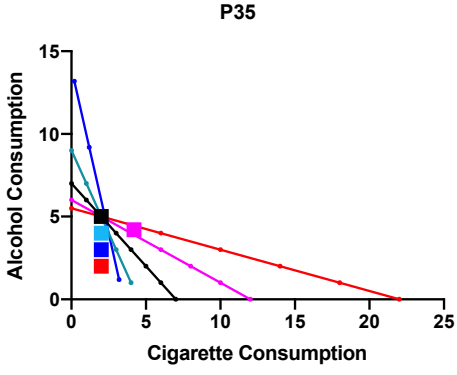
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Cigarette Consumption
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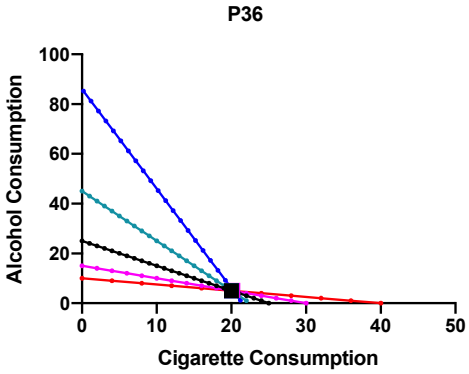
5
10
15
20
25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Cigarette Consumption
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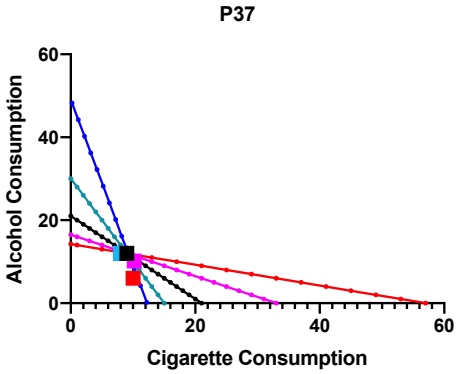
40
60
80
100
0
10
20
30
40
50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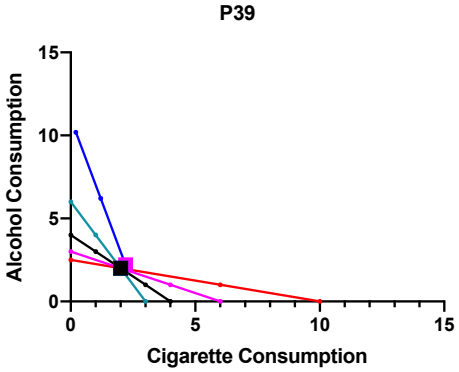
Alcohol Consumption
Cigarette Consumption
0
20
40
60
0
20
40
60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Cigarette Consumption
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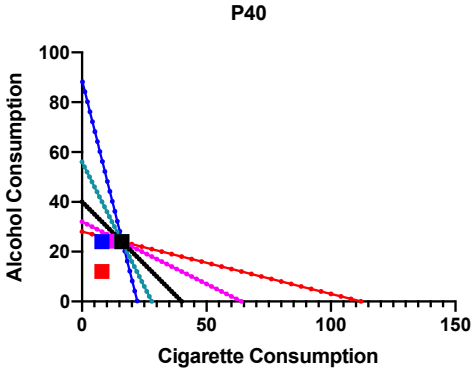
5
10
15
0
5
10
15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Cigarette Consumption
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20
40
60
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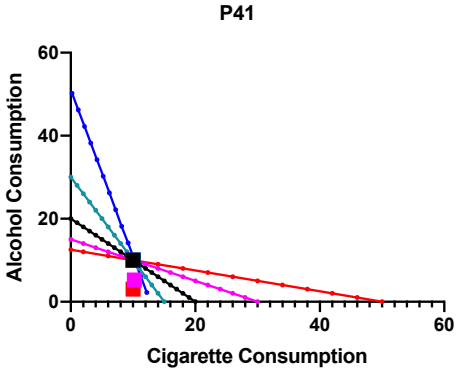
100
0
50
100
150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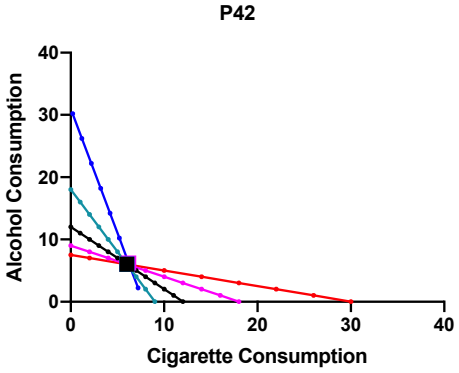
Cigarette Consumption
0
20
40
60
0
20
40
60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Alcohol Consumption
Cigarette Consumption
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10
20
30
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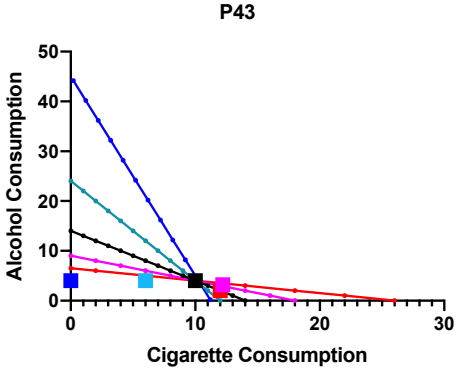
0
10
20
30
40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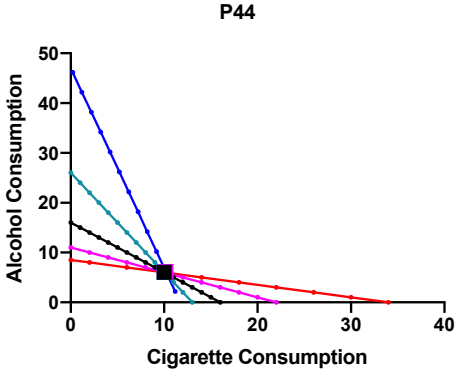
Alcohol Consumption
Cigarette Consumption
0
10
20
30
40
50
0
10
20
30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Alcohol Consumption
Cigarette Consumption
0
10
20
30
40
50
0
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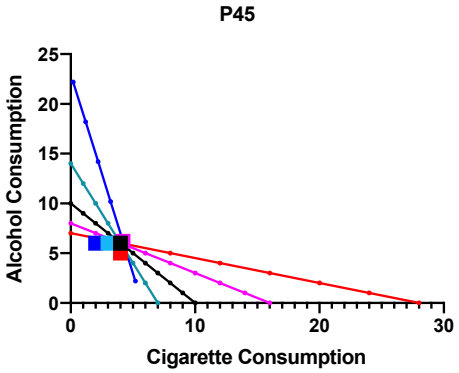
20
30
40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Alcohol Consumption
Cigarette Consumption
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5
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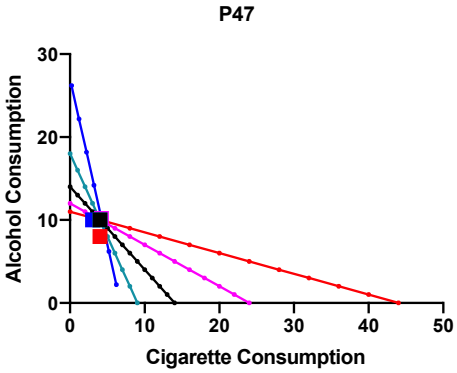
10
20
30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Alcohol Consumption
Cigarette Consumption
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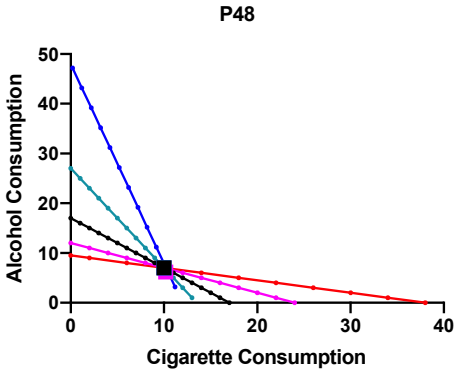
10
20
30
0
10
20
30
40
50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Alcohol Consumption
Cigarette Consumption
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20
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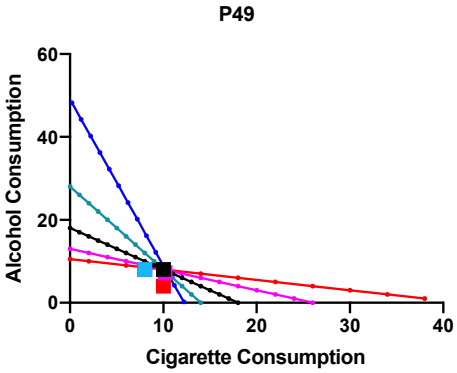
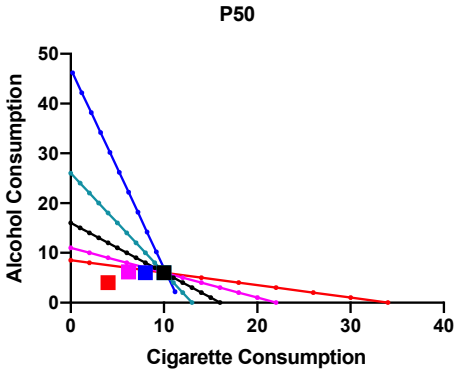
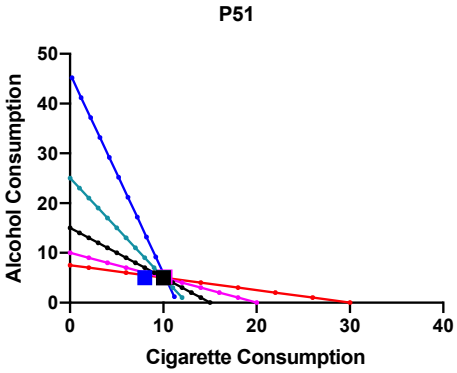
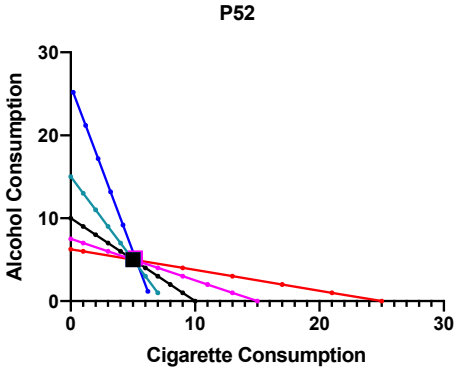
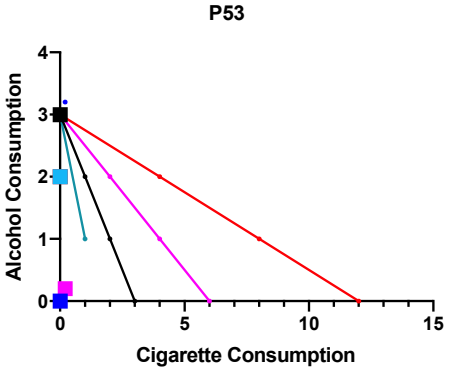
10
20
30
40

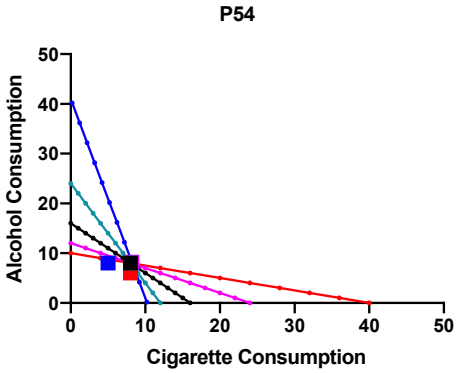

P49
Alcohol Consumption
Cigarette Consumption
0
20
40
60
0
10
20
30
40

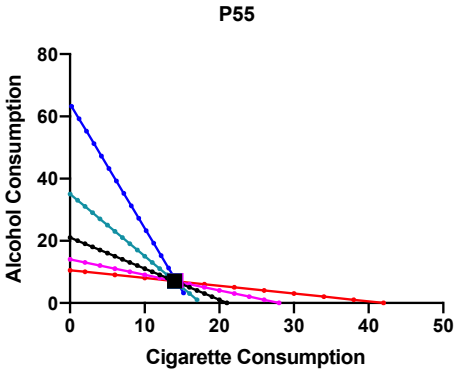

P50
Alcohol Consumption
Cigarette Consumption
0
10
20
30
40
50
0
10
20
30
40

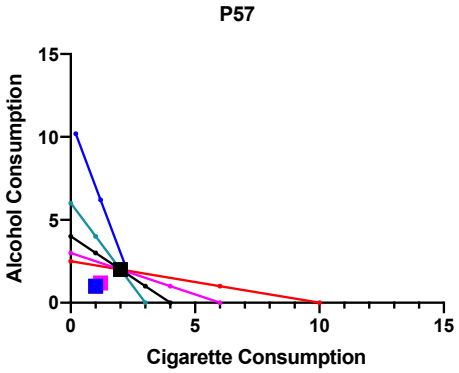

P51
Alcohol Consumption
Cigarette Consumption
0
10
20
30
40
50
0
10
20
30
40

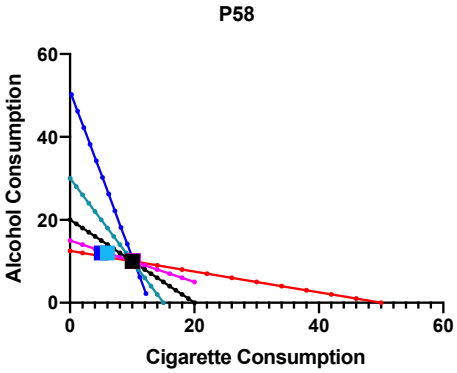

P52
Alcohol Consumption
Cigarette Consumption
0
10
20
30
0
10
20
30

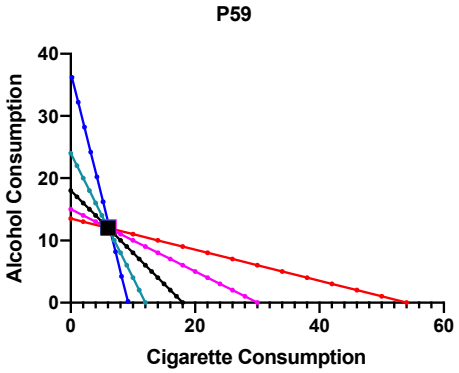

P53
Alcohol Consumption
Cigarette Consumption
0
1
2
3
4
0
5
10
15

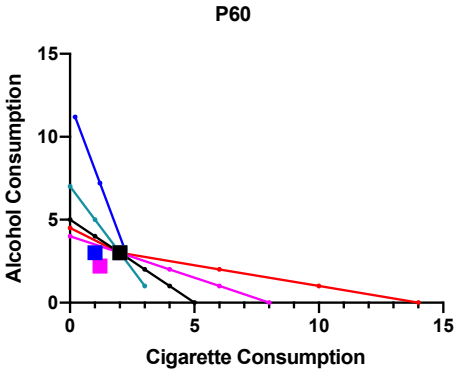

P54
Alcohol Consumption
Cigarette Consumption
0
10
20
30
40
50

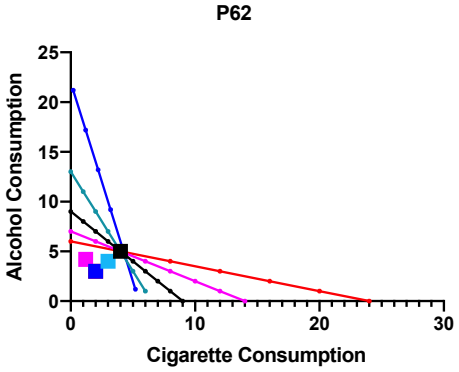

P55
Alcohol Consumption
Cigarette Consumption
0
20
40
60
80
10
30
50

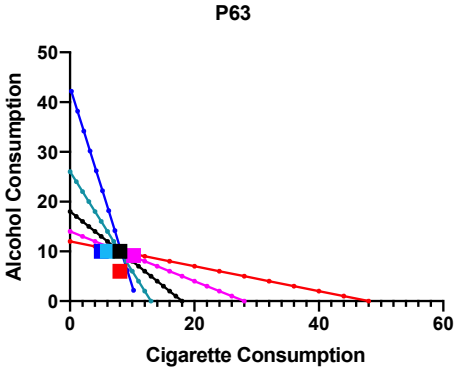

P57
Alcohol Consumption
Cigarette Consumption
0
5
10
15


P58
Alcohol Consumption
Cigarette Consumption
0
20
40
60

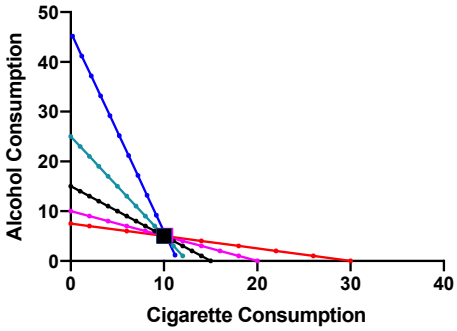

P59
Alcohol Consumption
Cigarette Consumption
0
10
20
30
40
60


P60
Alcohol Consumption
Cigarette Consumption
0
5
10
15


P62
Alcohol Consumption
Cigarette Consumption
0
5
10
15
20
25
30


P63
Alcohol Consumption
Cigarette Consumption
0
10
20
30
40
50
60

P64



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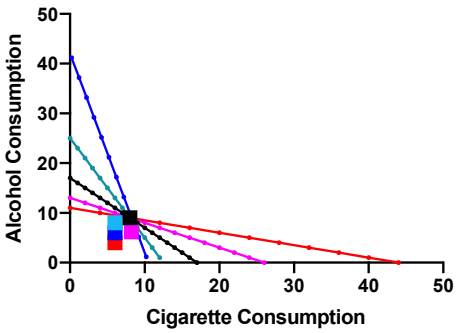

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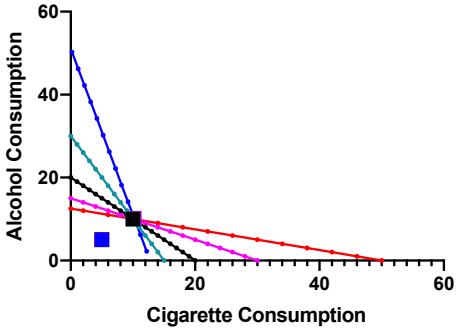

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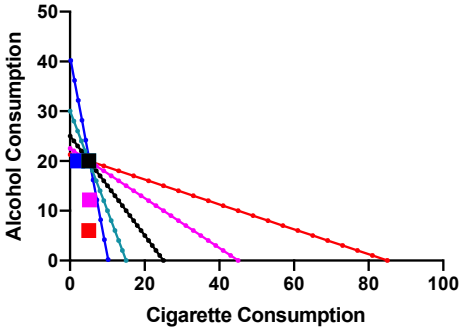

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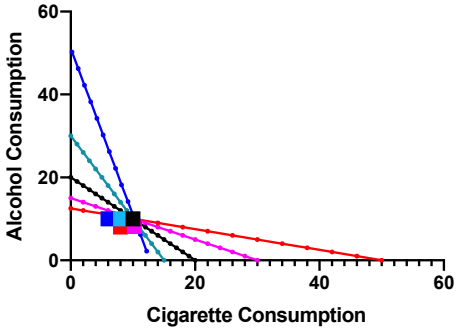

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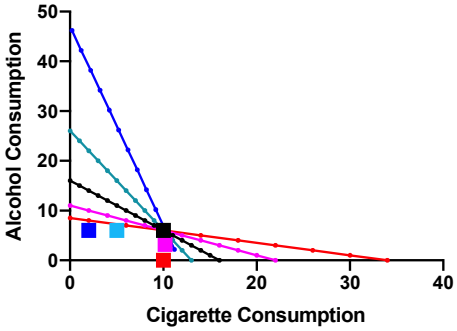

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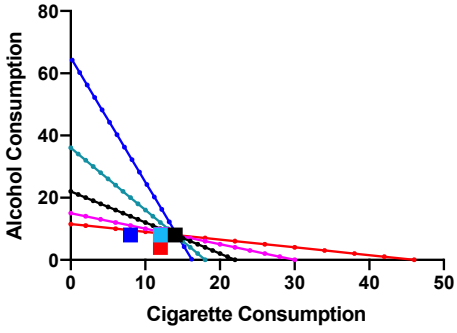

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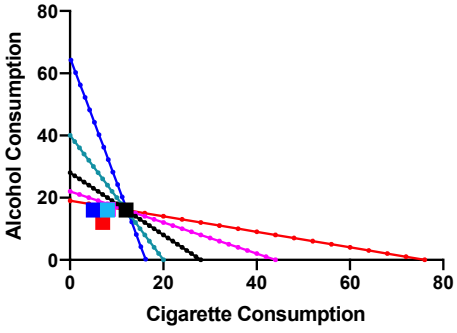
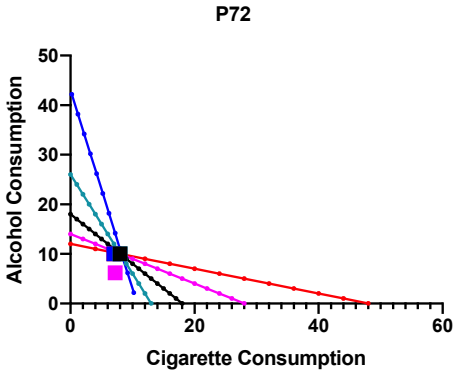
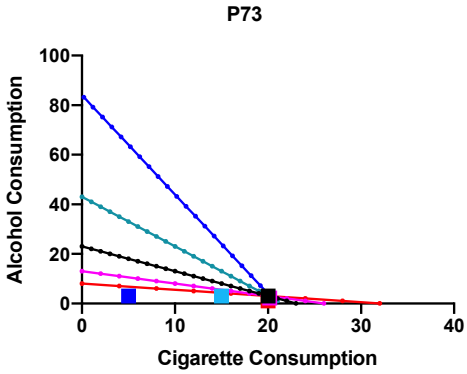
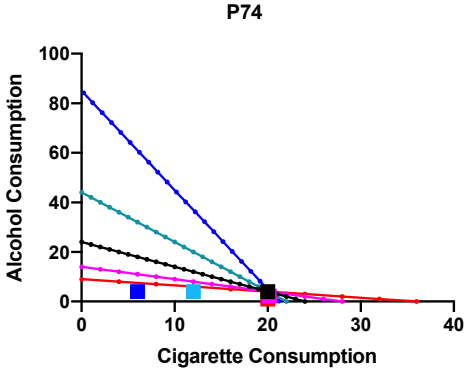
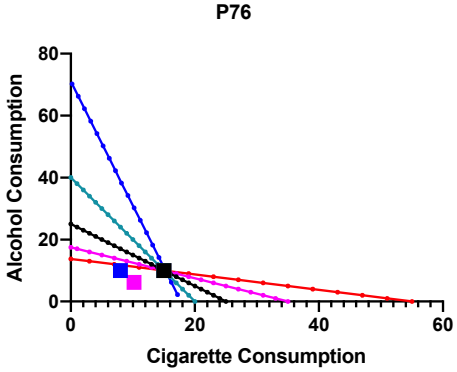
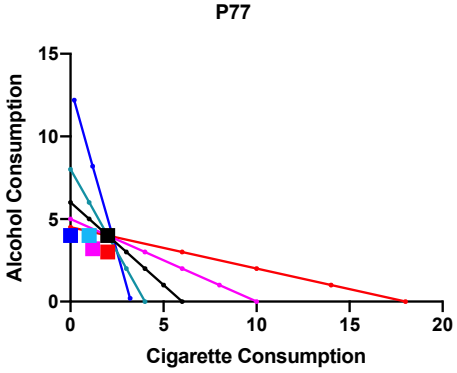


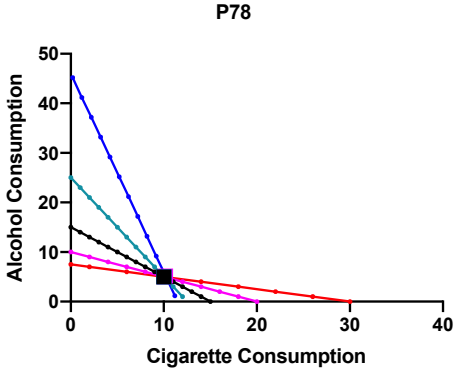

P72
Alcohol Consumption
Cigarette Consumption
0
10
20
30
40
50
0
20
40
60

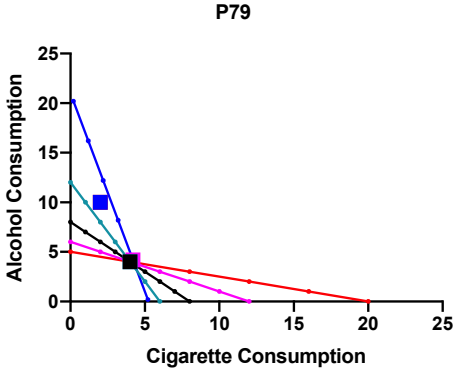

P73
Alcohol Consumption
Cigarette Consumption
0
20
40
60
80
100
0
10
20
30
40

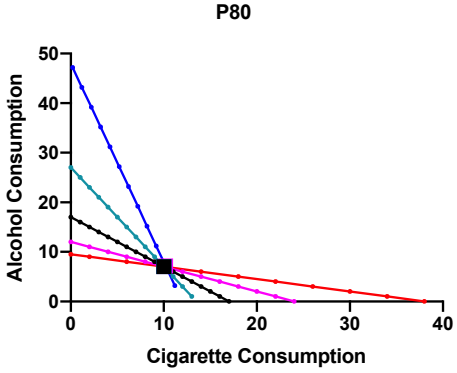

P74
Alcohol Consumption
Cigarette Consumption
0
20
40
60
80
100
0
10
20
30
40


P76
Alcohol Consumption
Cigarette Consumption
0
20
40
60
80
0
20
40
60

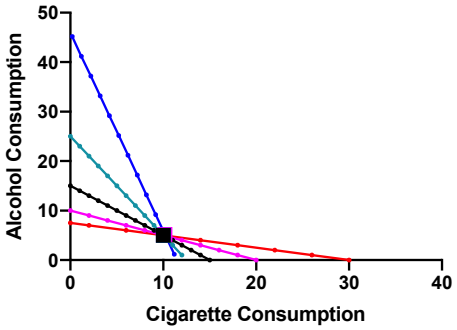

P77
Alcohol Consumption
Cigarette Consumption
0
5
10
15
0
5
10
15
20


P78
Alcohol Consumption
Cigarette Consumption
0
10
20
30
40
50
0
10
20
30
40

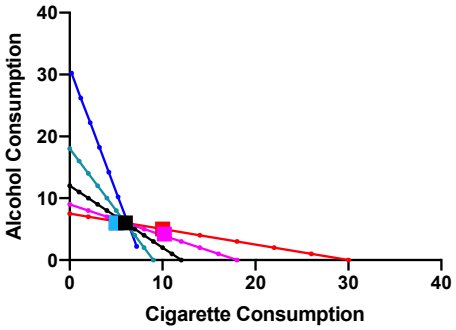

P79
Alcohol Consumption
Cigarette Consumption
0
5
10
15
20
25
0
5
10
15
20
25


P80
Alcohol Consumption
Cigarette Consumption
0
10
20
30
40
50
0
10
20
30
40

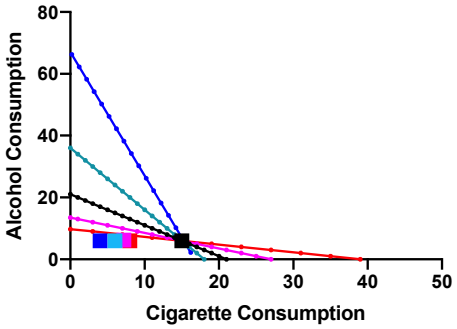
P81



P84



P85



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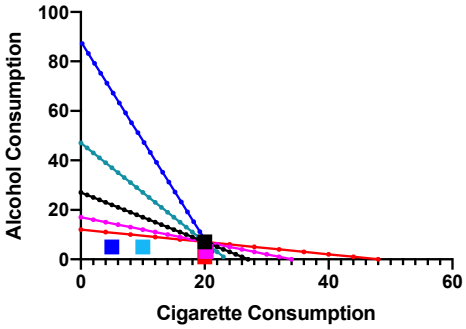

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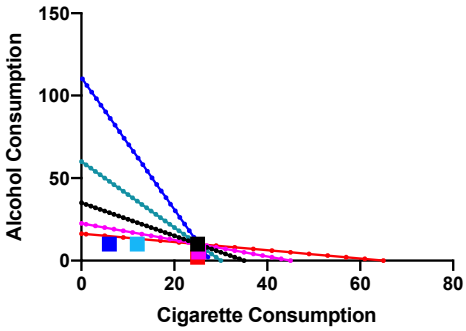

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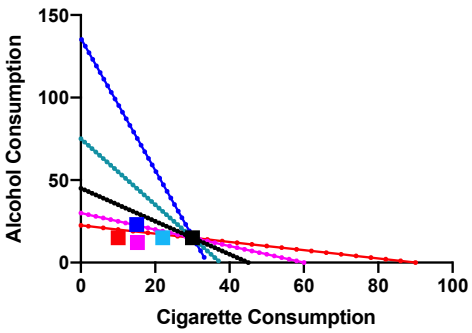

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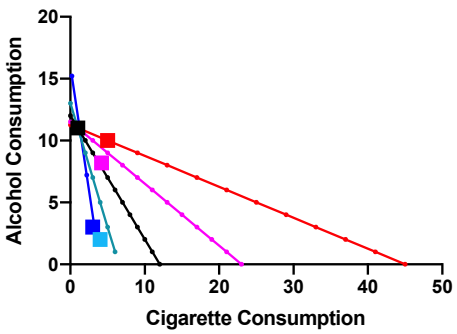
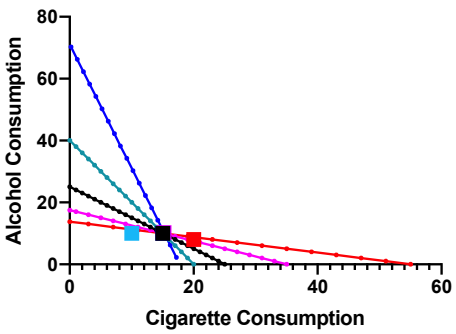
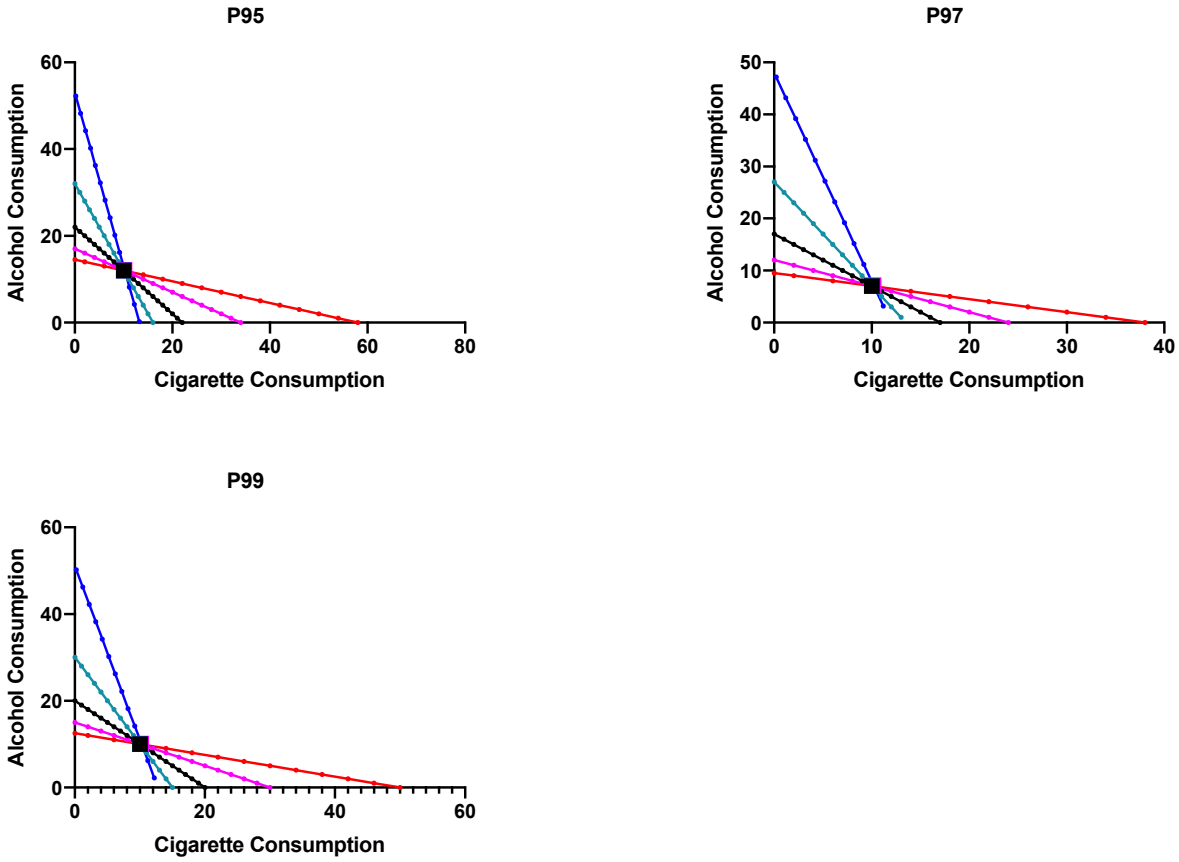


P94





In these graphs, alcoholic beverage consumption is plotted as a function of cigarette consumption for each condition and each participant. The black data path represents the potential bundle of cigarettes and alcoholic beverages that could have been purchased given the total number of tickets spent in the initial condition (when both goods cost 1 ticket each) and the black square indicates the actual bundle purchased. The light blue data path represents the potential bundles of cigarettes and alcoholic beverages that could have been purchased if participants spent all of their allotted tickets, when cigarettes cost 1 ticket and alcohol cost 2 tickets each. The light blue square indicates the actual bundle purchased. The dark blue data path represents the potential bundles of cigarettes and alcoholic beverages that could have been purchased if participants spent all of their allotted tickets, when cigarettes cost 1 ticket and alcohol cost 4 tickets each. The dark blue square indicates the actual bundle purchased. The pink data path represents the potential bundles of cigarettes and alcoholic beverages that could have been purchased if participants spent all of their allotted tickets, when cigarettes cost 2 tickets and alcohol cost 1 ticket each. The pink square indicates the actual bundle purchased. The red data path represents the potential bundles of cigarettes and alcoholic beverages that could have been purchased if participants spent all of their allotted tickets, when cigarettes cost 4 tickets and alcohol cost 1 ticket each. The red square indicates the actual bundle purchased.

Charles C. J. Frye

Office Address
USU Behavior Lab
Apt 49 432B Education Building
Utah State University
Logan, UT 84321
ccjfrye@gmail.com

Home Address
17441 SE Division
Portland, OR 97236
Phone: 765-585-0790
E-mail:

Education

2013 - Aug 2020 (Expected)		Utah State University PhD *Program:* Behavior Analysis *Advisor:* Dr. Amy Odum
2010	B.S.	Purdue University *Major:* Psychology *Specialization:* Psychobiology of Addictions *Advisors:* Dr. Nicholas Grahame
	B.A.	Indiana University *Major:* Philosophy

Research Experience

2013-2020 **USU Behavior Lab and Human Operant Lab**
My responsibilities include scheduling and conducting research for grant-related projects, co-management of the rat and pigeon laboratory, fixing any equipment/wiring malfunctions and ordering all lab-related supplies and non-human subjects. I was in charge of recruiting undergraduate research assistants for the animal lab, organizing a reading group that meets bi-monthly with graduate and undergraduate students who work in the lab, and evaluating undergraduate researchers' performance in the behavior lab. I have extensive experience programming experiments in med-state notation (behavior lab) and visual basic.net (human operant lab).

2008- 2010 **Dr. Nicholas Grahame's Behavioral Neuroscience Laboratory**
My responsibilities include conducting data analysis of delay discounting research in selectively-bred mouse lines (High-Alcohol Preferring and Low-Alcohol Preferring). Daily running of mice. Daily preparation of syringes for drug studies. Cleaning operant chambers. Weighing Mice. Feeding mice and providing access to water 2-hrs per day. Preparation of surgically-implanted saddles for alcohol self-administration through an infusion pump

into the aorta (saddles served to bypass the effect of taste in a study to assess the development of alcohol dependence). Training incoming undergraduate assistants and graduate students in the lab.

Awards and Grants

BORG Scholarship for research excellence
Grant Funded by Society for the Advancement of Behavior Analysis (SABA, 2016)
Teacher of the Year – Utah State University, College of Education (2017)
Teacher of the Year – Utah State University, Department of Psychology (2017)

Teaching Experience

Summer 2019 **Instructor of Record, Psyc 3500, Research Methods online – Utah State University**
My responsibilities included organizing the overarching structure of the course, assigning grades, overseeing a graduate teaching assistant, organizing lectures, and instructing students on a written research proposal

Spring 2019 **Instructor of Record, Psyc 3500, Research Methods – Utah State University**
My responsibilities included organizing the overarching structure of the course, assigning grades, overseeing a graduate teaching assistant, organizing lectures, and instructing students on a written research proposal

Spring 2018 **Instructor of Record, Psyc 3460, Neuroscience 1 – Utah State University**
My responsibilities included organizing the overarching structure of the course, assigning grades, overseeing a graduate teaching assistant, organizing lectures, and laboratory assignments.

Fall 2017 **Instructor of Record, Psyc 3010, Psychological Statistics – Utah State University**
My responsibilities included organizing the overarching structure of the course, assigning grades, overseeing two graduate teaching assistants and seven undergraduate tutors, and organizing lectures and laboratory assignments.

Summer 2017 **Instructor of Record, USU 1010, Connections – Utah State University**

My responsibilities included organizing the overarching structure of the course, assigning grades, overseeing two undergraduate teaching assistants and peer mentors, organizing lectures and assignments, and organizing activities with the community.

Summer 2017 **Instructor of Record, Psyc 3010 online, Psychological Statistics – Utah State University**
My responsibilities included organizing the overarching structure of the course, assigning grades, answering student questions, making and grading exams.

Summer 2016 **Instructor of Record, Psyc 3400 – online, Advanced Behavior Analysis – Utah State University**
My responsibilities included organizing the overarching structure of the course, assigning grades, providing feedback on students' work, making weekly announcements and online group chats with students, and creating online lectures.

Fall 2015- **Instructor of Record, Psyc 3400, Advanced Behavior Analysis – Utah**
Spring 2017 **State University**
My responsibilities included organizing the overarching structure of the course, assigning grades, lecturing 2 times per week, overseeing a graduate student teaching assistant, creating and programming a laboratory experiment in a pigeon lab for the students run birds, analyze data and write a lab report.

Fall 2014- **Teaching Assistant and Guest Lecturer, Psyc 3400,**
Spring 2015 **Advanced Behavior Analysis – Utah State University**
My responsibilities included organizing the lab portion of the class. I installing the newest version of Med-PC in the lab and the new interface system. I programmed all of the conditions for the experiment that was conducted throughout the semester. I was also in charge of training three undergraduate teaching assistants who assisted in maintaining the lab and supervising students. I was directly responsible for the health and overseeing of the pigeons in the colony. I provided feedback on students' writing and graded a lab report in APA format.

Fall 2012- **Lecturer, Psyc 102, Introduction to Psychology – Southern Illinois**
Summer 2013 **University**
My responsibilities included creating powerpoint presentations, preparing
and presenting lectures twice a week, holding office hours, grading quizzes, and mentoring 22 TAs (12 first-year graduate students and

10 senior undergraduate students). There was a total of 242 students in my section of the class and a total of 890 students in the class (Fall 2012).

Fall 2011-
Spring 2012 **Graduate Teaching Assistant and Lab Coordinator, Psyc 211, Research Methods – Southern Illinois University**
My responsibilities included leading two lab sections of 30 students each in a weekly two-hour meeting. The first hour consisted of lecture and the second hour consisted of a computer lab demonstration using Microsoft Excel to perform descriptive and inferential analyses. I also shaped successful writing in APA format, graded papers that were written in a manuscript format, proctored exams, maintained the lab portion of the grade book, held office hours, and coordinated activities within the lecture portion of the class.

Fall 2010-
Spring 2011 **Graduate Teaching Assistant and Discussion Leader, Psyc 102, Introduction to Psychology – Southern Illinois University**
My responsibilities included leading two sections of 30 students in a one-hour discussion over class material each semester, coordinating discussion and activities related to class material within a classroom setting, proctoring exams, mentoring and shaping successful writing, grading research papers and providing feedback on drafts, coordinating a grade book (electronic and hard copy), and conducting academic counseling sessions.

Spring 2010 **Undergraduate Teaching Assistant, Psyc-B105, Psychology as a Biological Science - IUPUI**
Responsibilities included leading a section of 50 students in review sections, grading papers/tests, working two hours a week in the psychology resource center (PRC), and meeting with students who required additional mentoring.

Fall 2009- **STAR (Students Taking Academic Responsibility) Program Mentor** –
Spring 2010 **IUPUI**
The program recruits successful upperclassmen for mentoring students on academic probation for the first time in a one-on-one setting to provide academic support and to act as a source of contingency management to encourage good academic behavior.

Fall 2008 - **Undergraduate Teaching Assistant, Psyc-B103, Introduction to a**
Spring 2010 **Major in Psychology- IUPUI**
My responsibilities for this class included overseeing the work of six to eight students, depending on the semester. Each student had

to submit a 6-10-page chapter each week written in APA format. It was my job to grade each chapter and mentor them in the process of writing each chapter (e.g. aiding them in setting up interviews and finding proper research material) and grade each chapter. By the end of the semester each student had a book (approximately 100 pages in length) illustrating what they can do with a bachelor's degree in psychology, resources on campus, the steps they must take to get into graduate school, different graduate degrees available in psychology, what it is like to be a professor, and how to make the most out of their undergraduate experience.

University Service

2010-2012	Judge for Illinois Junior Academy of Sciences Region 8 Science Fair Southern Illinois University at Carbondale	
2010-2012	Member of SIUC Cognitive Sciences Registered Student Organization	
	Treasurer	2010-2011
	Vice President	2011-2012
2010-2011	SIUC Brain and Cognitive Sciences Proseminar Coordinator	

Professional Memberships

Association for Behavior Analysis International
Mid-American Association for Behavior Analysis
Society for the Quantitative Analysis of Behavior
South Eastern Association for Behavior Analysis
Four Corners Association for Behavior Analysis
Society for Neuroscience
Research Society on Alcoholism

Publications

Friedel, J. E., Galizio, A., **Frye, C. C. J.**, DeHart, W. B., & Odum, A. L. (In Preparation). Rapidly obtaining indifference points: Measures of delay discounting from a visual analogue scale and a survey. *Journal of the Experimental Analysis of Behavior*

Frye, C. C. J., Rung, J. M., Galizio, A., Haynes, J. M., DeHart, W. B., Friedel, J. E., & Odum, A. L. (In Preparation). The influence of within-session contrast on the magnitude effect in delay discounting.

Haynes, J. M., Galizio, A., **Frye, C. C. J.**, Towse, C., Morrissey, K., Serang, S., & Odum, A. L. (Accepted pending revisions). Discounting of food and water in rats shows trait- and state- like characteristics. *Journal of the Experimental Analysis of Behavior.*

DeHart, W. B., Friedel, J. E., Berry, M. S., **Frye, C. C. J.**, Galizio, A., & Odum, A. L. (In Press). Delay discounting in cigarette, smokeless tobacco, and electronic cigarette users: No differences across types of nicotine use. *Journal of the Experimental Analysis of Behavior*.

Odum, A. L., Becker, R. J., Haynes, J. M., Galizio, A., **Frye, C. C.** J., Downey, H., ... & Perez, D. M. (2020). Delay discounting of different outcomes: review and theory. *Journal of the experimental analysis of behavior*, *113*(3), 657-679.

Rung, J. M., **Frye, C. C. J.**, DeHart, W. B., & Odum, A. L. (2019). Evaluating the effect of delay spacing on delay discounting: carry-over effects on steepness and the form of the discounting function. *Journal of the experimental analysis of behavior*, *112*(3), 254-272.

Frye, C. C. J., Rung, J. M., Nall, R. W., Galizio, A., Haynes, J. M., & Odum, A. L. (2018). Continuous nicotine exposure does not affect resurgenc of alcohol seeking in rats. *PLoS ONE*, 13(8): e0202230.

Frye, C. C. J., Galizio, A., Haynes, J. M., DeHart, W. B., & Odum, A. L. (2018). The effect of nicotine and nicotine + MAOI on the value of alcohol: A short report. *Behavioural Pharmacology*. Advance online publication. doi: 10.1097/FBP.0000000000000438

Galizio, A., **Frye, C. C. J.**, Haynes, J. M., Friedel, J. E., Smith, B. M., & Odum, A. L. (2018). Persistence and relapse of reinforced behavioral variability. *Journal of the Experimental Analysis of Behavior, 109*, 210-237. doi:10.1002/jeab.309

DeHart, W. B., Friedel, J. E., **Frye, C. C. J.**, Galizio, A., & Odum, A. L. (2018). A fistful of quarters: The effects of outcome unit framing on delay discounting. *Journal of the experimental analysis of behavior*, *110*(3), 412-429.

Frye, C. C. J., Galizio, A., Friedel, J. E., DeHart, W. B., Odum, A. L. (2016). Measuring delay discounting in humans using an adjusting amount task. *Journal of Visualized Experiments, (107)*, e53584-e53584.

Friedel, J. E., DeHart, W. B., **Frye, C. C. J.**, Rung, J. M., & Odum, A. L. (2015).

Discounting of qualitatively different delayed health outcomes in current and never smokers. *Experimental and Clinical Psychopharmacology, 24*(1), 18-29. http://doi.org/10.1037/pha0000062

Symposia Chaired

Symposium Organizer "Explorations of the Magnitude Effect in Delay Discounting
Research in Various Species and Domains". 2017. Association for Behavior Analysis International Annual Meeting, Denver, CO.

Paper Presentations at Professional Meetings

Stuart, I., **Frye, C. C. J.**, & Odum, A. L. (2018, February). The effect of nicotine administration on maladaptive alcohol drinking. Winter Conference for Animal Learning and Behavior, Logan, Utah.

Odum, A. L., Bevins, R. A., Galizio, M., Serang, S., Whitmore, S. A., **Frye, C. C. J.**, DeHart, W. B., Galizio, A., Friedel, J. E., Haynes, J. M., Berry, M. S., & Becker, R. J. (2019, Feb). The relation between delay discounting and e-cigarette use: Human and rat studies. *Oral presentation at the Winter Conference on Learning and Behavior, Logan, UT.*

Haynes, J. M., **Frye, C. C. J.**, Galizio, A., Nall, R. W., Rung, J. M., & Odum, A. L. (2018, February). The effects of continuous nicotine administration on alcohol relapse. Paper presentation delivered at the annual Winter Conference for Animal Learning and Behavior held at the University Inn and Conference Center, Logan, Utah.

Frye C. C. J., Galizio, A., Haynes, J. M., DeHart, W. B., & Odum, A. L. (2017). *Investigation of the magnitude effect: It is all about the contrast.* Paper presentation at Association for Behavior Analysis International annual conference, Denver, CO.

Galizio, A., **Frye, C. C. J.**, Haynes, J. M., Friedel, J. E., & Odum, A. L. (2017). *Relapse and Operant Variability*. Paper presentation at Association for Behavior Analysis International annual conference, Denver, CO.

DeHart, W. B., Friedel, J. E., **Frye, C. C. J.**, Galizio, A., Haynes, J. M., & Odum, A. L. (2017). Delay discounting of non-monetary outcomes: The effects of different magnitudes and delay distributions. Paper presentation at

Association for Behavior Analysis International annual conference, Denver, CO.

Odum, A. L., DeHart, W. B., Friedel, J. E., Galizio, A., & **Frye, C. C. J.** (2016). *Organismic and environmental influences on delay discounting: Evidence for a general process.* Paper presentation at Winter Conference on Animal Learning and Behavior, Winter Park, CO.

Frye, C. C. J. & Jacobs, E. A. (2012). *Percentile reinforcement of lever holding in rats: Preliminary data on the effects of manipulating reinforcement magnitude.* Paper presentation at Neuroscience Retreat, Collinsville, IL.

Frye, C. C. J. & Jacobs, E. A. (2012). *Molar versus molecular control over behavior using a percentile schedule and lever-hold duration on a single manipulandum procedure: Effects of a magnitude manipulation.* Paper presentation at the sixth annual Illinoisy Data Conference, Edwardsville, IL.

Frye, C. C. J., Jacobs, E. A., Young, M. E., & Zhu, J. (2011). *Differential reinforcement of lever holding when parameters are continuously changing: Assessing a novel single manipulandum procedure for measuring "impulsive" behavior in rats.* Paper presented at the fifth annual Illinoisy data conference, Carbondale, IL.

Poster Presentations at Professional Meetings

Haynes, J. M., **Frye, C. C. J.**, Galizio, A., Becker, R. J., Perez, D., & Odum, A. L. (2019, May). Defecting during the delay: Delay maintenance in rats. *Poster presented at the Annual Meeting of the Society for the Quantitative Analysis of Behavior, Chicago, IL.*

Galizio, A., **Frye, C. C. J.**, Haynes, J. M., Friedel, J. E., & Odum, A. L. (2019, Feb). Effects of *d*-amphetamine and nicotine on remembering and motivation in pigeons. *Poster presented at the California Association for Behavior Analysis Annual Western Regional Conference on Behavior Analysis, Long Beach, CA.*

Frye, C. C. J. & Odum, A. L. (2018, May). The effect of nicotine and nicotine in combination with MAOI on breakpoint for ethanol. Poster presented at the annual Research Society on Alcoholism conference, San Diego, CA.

Haynes, J. M., **Frye C. C. J.**, Galizio, A., & Odum, A. L. (2017, May). Effects of nicotine and nicotine with MAOI on alcohol valuation. Poster presented at the annual Society for Quantitative Analysis of Behavior convention, Denver, CO.

Frye, C. C. J., Rung, J. M., Galizio, A., Friedel, J. E., DeHart, W. B., & Odum, A. L. (2016, May). Explaining the magnitude effect in delay discounting research: It is all about the contrast. Poster to be presented at the annual Association for Behavior Analysis International convention, Chicago, IL.

Galizio, A., **Frye, C. C. J.**, Friedel, J. E., DeHart, W. B., & Odum, A. L. (2016, May). Timing and delay discounting. Poster to be presented at the annual Association for Behavior Analysis International convention, Chicago, IL.

Frye, C. C. J., Friedel, J. E., Galizio, A., & Odum, A. L. (2015, May). Resurgence of operant variability. *Poster presented at the Annual Convention of the Association for Behavior Analysis International, San Antonio, TX.*

Friedel, J. E., DeHart, W. B., **Frye, C. C. J.**, Galizio, A., & Odum, A. L. (2015, May). Impulsivity and tobacco use: Discounting of qualitatively different outcomes in non-smokers, cigarette smokers, and smokeless tobacco users. *Poster presented at the Annual Meeting of the Society for the Quantitative Analysis of Behavior, San Antonio, TX*.

Galizio, A., Friedel, J. E., Smith, B. M., **Frye, C. C. J.**, McIntyre, S., & Odum, A. L. (2015, May). Reinforced behavioral variability is resistant to change under extinction and reinstatement. *Poster presented at the Annual Convention of the Association for Behavior Analysis International, San Antonio, TX.*

Nelsen, S. A., Craig, A. R., Nall, R. W., Cunningham, P. J., **Frye, C. C. J.** & Shahan, T. A. (2015, May). Resurgence of alcohol seeking: effects of length of exposure to extinction plus alterative reinforcement. Poster presented at Society for the Quantitative Analysis of Behavior Annual Conference, San Antonio, TX.

Frye, C. C. J., Craig, A. R., Friedel, J. E., & Odum, A. L. (2014). *Are the impulsive persistant? Investigating the relation between delay discounting and behavioral momentum performance.* Poster presented at the annual meeting of the Society for Quantitative Analyses of Behavior, Chicago, IL.

Frye, C. C. J., Rung, J. M., Friedel, J. E., DeHart, W. B., & Odum, A. L. (2014). *Assessing difference in discounting using linear vs. exponential delay progressions.* Poster presented at the annual meeting of the Association for Behavior Analysis International, Chicago, IL.

Frye, C. C. J., Jacobs, E. A., & Young, M. E. (2014). *Holding for a better outcome: Assessing the effects of continuously changing probabilistic and magnitude contingencies in an accumulation task with rats.* Poster

presented at the annual meeting of the Association for Behavior Analysis International, Chicago, IL.

Frye, C. C. J. & Jacobs, E. A. (2013). *Percentile reinforcement of lever holding in rats: Increasing reinforcement magnitude decreases latency to respond, but does not systematically affect on hold duration.* Poster presented at the annual meeting of the Association for Behavior Analysis International, Minneapolis, MN.

Frye, C. C. J. & Jacobs, E. A. (2013). *Differential reinforcement of lever holding in rats: Assessing the effects of probabilistic reinforcement on temporal discounting in a single manipulandum procedure.* Poster presented at the annual meeting of the Society for the Quantitative Analysis of Behavior, Minneapolis, MN.

Smith, T. R., **Frye, C. C. J.**, Peterson, T. & Jacobs, E. A. (2013). *Effects of a Lesion to the Core of the Nucleus Accumbens on Concurrent Schedule Performances.* Poster presented at the annual meeting of the Society for the Quantitative Analysis of Behavior, Minneapolis, MN.

French, E. J., **Frye, C. C. J.,** Baumgartner, A., & Jacobs, E. A. (2013). *Rats foraging in a rapidly changing environment*. Poster presented at the annual meeting of Society for the Quantitative Analyses of Behavior, Minneapolis, MN.

Frye, C. C. J. & Jacobs, E. A. (2012). *Hold duration as a dependent measure: Effects of using a percentile schedule of reinforcement and manipulating reinforcement magnitude*. Poster presented at the annual meeting of the Mid-American Association for Behavior Analysis, Minneapolis, MN.

Mendez, V. R., Baumgartner, A., French, E., **Frye, C. C. J.**, & Jacobs, E. A. (2012). *Rats foraging in a rapidly changing environment.* Poster presented at the annual meeting of the Mid-American Association for Behavior Analysis, Minneapolis, MN.

Frye, C. C. J., Jacobs, E. A., Young, M. E., & Zhu, J. (2012). *Differential reinforcement of lever holding in rats: Hold duration as a dependent measure to assess temporal discounting.* Poster presented at the annual meeting of the Association for Behavior Analysis International, Seattle, WA.

Frye, C. C. J., Jacobs, E. A., Young, M. E., & Zhu, J. (2011). *Differential reinforcement of lever holding in rats: Hold duration as a dependent measure to assess temporal discounting.* Poster presented at the annual meeting of the Southeastern Association for Behavior Analysis, Charlotte, NC.

Frye, C. C. J., Jacobs, E. A., Young, M. E., & Zhu, J. (2011). *Differential reinforcement of lever holding in rats: Hold duration as a dependent measure to assess temporal discounting.* Poster presented at the annual meeting of the Mid-American Association for Behavior Analysis, Bloomingdale, IL.

Frye, C. C. J., Jacobs, E. A., Young, M. E., & Zhu, J. (2011). *Differential reinforcement of lever hold in rats: Assessing temporal discounting on a single manipulandum*. Poster presented at the annual meeting of the Association for Behavior Analysis International, Denver, CO.

Frye, C. C. J., & Grahame, N. J. (April 2010). *Responding for ethanol reduces impulsivity in cHAP and HAPI mice in a delay discounting task.* Poster presented at a campus poster presentation session for the honor's thesis, IUPUI, Indianapolis, IN.

References

Excellent references available upon request