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The Value Enhancing Effects of Nicotine Across Complex Reinforcers

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Abstract

Smoking increases one's risk for a number of fatal diseases. Most smokers report wanting to quit but very few are successful. The main active ingredient in cigarettes, nicotine, plays multiple roles in addiction. Animal studies have found that nicotine enhances the value of highly preferred reinforcers. This study expands on this research with humans. In Experiment I, reinforcer value was measured across three categories of reinforcers by progressive ratios and breakpoints (BP), purchase tasks (PT), preference ranking, and delay discounting across three participants. Results indicate multiple relationships, both positive and negative, between PT results and BPs. Rankings of reinforcers corresponded with results from PT. Experiment II examined the role of nicotine and reinforcer value using an ABA withdrawal design with two experimental participants and two control group participants. One experimental participant demonstrated a consistent pattern of responding suggesting nicotine influences responding on PT, however, it did not always increase value. For all experimental participants the demand for social reinforcers was less in the nicotine conditions. The use of PT for examining the effects of nicotine on reinforcer value is promising. It provides an efficient and cost-effective method for studying elements of reinforcer value with humans. The category of reinforcers was found to be

important to how nicotine interacts. This effect extends beyond ranked reinforcer preference.

Keywords: reinforcer value, purchase tasks, progressive ratios, nicotine

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Mortality rates for smokers are about 3 times higher than those for individuals who have never smoked (U.S. Department of Health and Human Services [HHS], 2014). Causes of death include several smoking related diseases including cancer, respiratory disease, and vascular disease. Not only does smoking hurt the individual engaging in the behavior but it hurts anyone around them. In the U.S., there are more than 480,000 smoking related deaths annually and of those, 41,000 are deaths related to secondhand smoke (HHS, 2014). Additionally, the costs of smoking related illnesses in the U.S. are huge; annually nearly $170 billion for direct medical care for adults, and $156 billion in lost productivity (Xu, Bishop, et al., 2014).

Risk and severity of disease is directly related to the length of time a person smokes (HHS, 2010). Reductions in risk of heart attack and other smoking related illnesses begin to drop after just one year of smoking abstinence (HHS, 2000). According to a U.S. Department of Health and Human Services report released in 2000, most smokers report wanting to quit, yet only 2% of smokers quit every year; and most require multiple attempts.

Given these statistics it is clear that a better understanding of smoking behavior is necessary. How the main active ingredient in tobacco products, nicotine, promotes addiction has not been clearly identified. According to the

National Institute on Drug Abuse (NIDA), nicotine is what makes tobacco addictive, and it is also considered the primary reinforcing component (NIDA, 2019; Picciotto & Mineur, 2014).

Nicotine as a Primary Reinforcer

In one of the first studies examining the primary reinforcing properties of nicotine, Clark (1969) found that rats preferred self-administered nicotine over water and saline. The author concluded in this study that nicotine is at least partially responsible for the appeal of tobacco. Several years later, after some mixed results in this area, Lang et al. (1977) conducted a pioneering study which found that when rats accessed injections of nicotine for completing lever presses, responding was very similar to controls receiving saline. These results suggested that nicotine did not operate as a primary reinforcer. It was found that responding for nicotine increased if the rats were reduced to 80% of their free feeding weight prior to the start of the experiment and responding increased significantly more when food reinforcement was also provided. This study suggested that very particular environmental variables were crucial for nicotine to operate as a reinforcer.

Slifer (1983) followed up on these results with rhesus monkeys. This study manipulated the mode of delivery: inhalation, ingestion, and intravenous injection. As well as the presence or absence of nondrug stimuli available

concurrently, both contingently and noncontingently. It was found that regardless of method of delivery the addition of either noncontingent or contingent nondrug stimuli led to quicker acquisition of nicotine self-administration relative to conditions without these stimuli.

Following this work, similar results were found suggesting nicotine was only a fragile primary reinforcer in isolation. Nicotine was found to support self-administration, without additional stimuli, only when doses were high (0.09 mg/kg; Chaudhri et al., 2007). Palmatier et al. (2007) demonstrated that responding for nicotine was also easily extinguished. What many of these studies found was that the inclusion of additional nondrug stimuli in conjunction with nicotine increased responding. This indicated to many researchers that nicotine was capable of establishing very effective conditioned reinforcers. Following this logic several studies have shown that the physical sensations associated with smoking (motor movements, throat sensations etc.) become reinforcers in their own right when paired with nicotine (Caggiula et al., 2001).

Overall, nicotine is described as a weak primary reinforcer which seems paradoxical considering how difficult it is for individuals to quit using the drug in the natural environment. While it seems that conditioned reinforcement is an important component, the work with noncontingent stimuli and noncontingent delivery of nicotine suggests there is still more to this interaction.

Value-Enhancing Effects of Nicotine

The paradox of nicotine being a weak reinforcer while simultaneously maintaining high rates of smoking in humans has led researchers to focus on other interactions nicotine has with organisms and their environment. For much of drug research the principle of contingency plays a central role; it is expected that responses will be more robust when the drug is presented contingently than when the drug is delivered noncontingently (Donny et al., 2003). Nicotine has demonstrated a more complex interaction.

Across a series of five experiments with rats, Donny and colleagues (2003) demonstrated that nicotine delivered noncontingently supported increased responding for nondrug stimuli. Experiment 1 examined the effects of contingent and noncontingent nicotine in combination with the presence or absence of an unconditioned reinforcer – in this case a light (visual stimulus, VS) – that was contingent on responding. The highest levels of responding were observed in groups that included both contingent nicotine and the VS. Experiment 2 examined the noncontingent delivery of nicotine more closely by comparing conditions with noncontingent nicotine or saline in the absence or presence of the VS, and noncontingent food delivery with the presence or absence of the VS. Responding was once again found to be highest in conditions including both nicotine and the VS. Responding in conditions with noncontingent food and the

VS was found to be similar to response levels in the saline and VS condition, indicating that the effect found with nicotine is not present with other types of primary reinforcers. In Experiments 3 through 5, the experimenters manipulated delivery and dose of noncontingent nicotine or saline using both the original yoked schedule and continuous infusion. The results from these experiments demonstrate similar levels of responding with continuous and noncontingent yoked delivery of nicotine, with higher doses producing a stronger effect. The authors highlight that "operant responding was maintained at high levels by nicotine that was neither temporally nor causally associated with behavior, indicating this effect is distinct from the actions of nicotine as a primary reinforcer" (p.74). The suggestion made by these authors and others is that nicotine operates in a number of ways, including as a primary reinforcer and by enhancing the value of nondrug reinforcers (Chaudhri et al., 2006; Donny et al., 2003).

Chaudhri and colleagues (2005) examined sex differences in self-administration in rats by manipulating dosage, and the presence or absence of a nondrug stimulus. Using the same nondrug stimulus as Donny et al. (2003) the rats were exposed to three increasing fixed ratio (FR) reinforcement schedules. Each schedule was run with three different doses of nicotine ranging from 0.03-0.15 mg/kg. Responding on both the active and inactive lever was monitored, but

only responses on the active lever resulted in reinforcement. At the lowest dose (0.03 mg/kg) responding in the nicotine only condition was equivalent on the inactive and active lever suggesting nicotine was not reinforcing at this dosage. In comparison, rats exposed to the 0.06 mg/kg and 0.15 mg/kg rats showed a clear preference for the active lever in the nicotine only condition, indicating nicotine did function as a reinforcer. The addition of the VS led to different responding across the three nicotine dosages. At the lowest dose responses dramatically increased immediately. At the middle dose there was a slower increase in responding. Finally, at the highest dose responding remained at the same level as the nicotine only phase. This result is inconsistent with the seemingly dose dependent changes in responding in the phase assessing nicotine as a primary reinforcer suggesting the enhancing effect operates differently. Additionally, at the two higher doses the females consistently responded more on both levers than males across all phases. The results indicate three findings: that nicotine does function as a primary reinforcer, at particular doses responding is increased by additional nondrug stimuli (although not in the expected way), and finally there are sex differences in responding.

Many studies with animals have demonstrated this reinforcer-enhancing effect on nondrug stimuli including: sucrose, food pellets, and lights (Chaudhri et al., 2007, 2006; Donny et al., 2011; Donny et al., 2003; Palmatier et al., 2007;

Raiff & Dallery, 2006, 2008, 2009). While the number of studies examining this effect with animals is both impressive and important there is still work to be done to make this knowledge applicable to humans.

Human Studies

Most studies examining the reinforcer-enhancing effects of nicotine have been done with animals, however, there have been a few studies examining this effect with human smokers (Perkins, 2009; Perkins et al., 2009; Perkins et al., 2017; Perkins & Karelitz, 2013). Perkins and Karelitz (2013) conducted a within-subject study where smokers were exposed to four counterbalanced conditions after abstaining from smoking for 12 hours. Participants experienced two different doses of nicotine and one condition without nicotine. In one nicotine condition participants engaged in eight guided puffs at the start of the session followed by two more prior to each trial, in the second condition participants engaged in only two guided puffs prior to each trial. Across all conditions participants then earned access to music clips, that they had previously ranked in order of preference, by clicking a target in a field. Once ratio requirements were met on a progressive ratio schedule that increased by 30% (PR30%) each trial, participants gained access to the music clips. Significantly higher levels of responding were demonstrated in the condition with the largest dosage of nicotine and the most preferred music clips. All other conditions showed no significant differences

between the different levels of nicotine and no nicotine indicating no enhancing effect. These results suggest that dosage and initial value of the reinforcer are important components for this effect and that dosage interaction may be different for humans and rats.

The animal research, and the limited human research have only examined a qualitatively distinct but narrow set of reinforcers. Animal research has not examined reinforcers beyond sucrose, food pellets, and lights. Meanwhile human research has not gone beyond music, video clips, and money. This leaves a significant gap in the understanding of the effects of nicotine. Many putative reinforcers relevant to factors involved in what makes quitting so hard (weight gain, stress etc.), have not been examined.

Physical Activity and Nicotine

Weight gain is commonly cited as a barrier to quitting smoking (HHS, 2014), and while nicotine use and food intake have been examined in this context, the other part of weight management, physical activity, has not been examined. There is some evidence that nicotine and physical activity may interact in important ways. For instance, nicotine doping in elite sports has increased according to the World Anti-Doping Association (Johnston et al., 2017). Currently there has been some limited research demonstrating an increase in endurance in human participants while under the influence of nicotine (Mündel

& Jones, 2006). While studying the physiological components are important in determining if nicotine is an effective ergogenic aid, it seems that given the current evidence, examining if nicotine increases the reinforcing properties of physical activity would also provide useful information regarding this interaction.

A recent poll found that 51.6% of U.S. adults engage in consistent exercise, meaning they exercise a minimum of 3 days a week for 30 minutes (Sharpe, 2013). Additionally, a wide variety of structured ways to engage in physical activity are available in most U.S. cities (e.g. gyms, team sports, rock climbing gyms, running clubs, dancing, etc.) so it seems that for many people physical activities are reinforcing. Although why people exercise and to what extent may differ across individuals. At the most basic level, wheel running has been shown to function as a reinforcer for rats (e.g., Belke & Pierce, 2016), and studies have shown exercise to be a reinforcer for humans in experimental environments (Azrin et al., 2006). Knowing whether or not nicotine can increase the reinforcing value of physical activity could have implications not only for tobacco users but for the use of nicotine in sports as well.

Social Interaction and Nicotine

Social interaction is frequently paired with nicotine use, whether it be taking a break to smoke with friends and colleagues or taking a moment to have a

cigarette during a social engagement. Additionally, social interactions have many implications for health and the continued use of tobacco products. There is empirical evidence supporting the benefits of social interaction on physical and mental health; in particular, social interaction has been shown to play an important role in stress reduction (Cohen, 2004; Umberson & Karas Montez, 2010). Furthermore, stress is associated with engaging in a variety of detrimental behaviors, including smoking (Cohen, 2004). The connection between stress levels, social interactions, and nicotine is especially relevant since one of the most commonly cited reasons for returning to smoking is stress (HHS, 2014). Research has shown that those with social anxiety use cigarettes to cope, and have increased cravings for cigarettes while under stress from social interactions (Watson et al., 2018). Studies with rats found that social rewards and nicotine operate synergistically, increasing the value of these reinforcers (Thiel et al., 2009).

Social interaction is a reinforcer for most people. This can be seen by how many people spend their time and the lengths that are taken to engage with others (e.g, the use of social media and other forms of communication). Social interaction is also a reinforcer for rats (Evans et al., 1994). It follows that the value of social interaction as a reinforcer could also be influenced by nicotine use. If nicotine enhances the value of social interaction it would suggest that quitting

smoking could lead to social interaction becoming less valuable. This reduction in value could lead to a decrease in social interactions, possibly contributing to feelings of isolation and increased stress levels which could then result in relapse.

Assessing Reinforcer Value

The use of schedules of reinforcement in research continues to be the bedrock of the experimental analysis of behavior. Schedules are frequently used to determine the "strength" or "value" of reinforcers. There are several ways of measuring reinforcer value. Some include: conditioned place preference (Thiel et al., 2009), rate of response, and behavioral momentum (Raiff & Dallery, 2008). It is common for these analyses to involve comparing rates of behavior on different schedules; higher rates of behavior indicate stronger or more valuable reinforcers.

Many studies with animals and humans have used progressive ratio (PR) schedules and breakpoints (BPs) to measure value. With this schedule, participants start with a ratio requirement that is relatively low (for example, FR 5). The ratio is increased after reinforcement is earned. In a PR 100% the next requirement would be doubled (in this case, FR 10). This increase will continue until the participant is inactive for some preestablished length of time; the last completed ratio is the BP (Stafford & Branch, 1998). The use of PR schedules to

establish a BP provides the experimenter with opportunity to collect relative rates of behavior, and also establishes how many responses an organism will engage in to obtain a reinforcer before a significant period of inactivity (BP); providing an additional aspect of value (Hursh & Silberberg, 2008). Most of the research examining the reinforcer enhancing effects of nicotine have used progressive ratios and BPs to evaluate value. In the field of behavioral pharmacology the ratio BP is widely seen as being optimal for these types of analyses (Hursh & Silberberg, 2008).

Behavioral economics has provided alternative methods of assessing the value of stimuli. Delay discounting refers to the devaluation of outcomes as a function of how far in the future their receipt is (Green & Myerson, 2004). Measures of delay discounting with humans usually consist of questionnaires where participants are asked to repeatedly choose between a small immediate outcome (smaller-sooner, SS) and a larger delayed outcome (larger-later, LL). The SS and delays are manipulated across questions and when participants change from selecting the SS to the LL (or vice versa), the SS values are averaged, and an indifference point is established. The indifference point is the point at which the value of the delayed outcome is equal to an immediately available outcome. For example, if a participant selects $550 available now over $1000 in one month and then chooses $1000 available in one month over $600 available

now, the indifference point would be $575. The indifference points can then be graphed and analyzed a number of ways to assess level of discounting. High levels of discounting have been shown to correlate with a number of maladaptive behaviors outside of the laboratory environment: excessive gambling, drug use, overeating, and hyperactivity (Bickel et al., 2014; Dixon, Marley, & Jacobs, 2003; Kirby et al., 1999; Wilson et al., 2011).

Although measures of monetary discounting are the most common, other types of commodities have been assessed and compared using delay discounting questionnaires. Most consumable commodities like cigarettes (e.g. food, alcohol) are discounted at higher rates than money (Odum et al., 2006; Odum & Rainaud, 2003). Studies with these results are looking at the value of cigarettes compared to other commodities not how nicotine changes the value of commodities. While monetary discounting rates for smokers, former smokers, and nonsmokers have been compared (Bickel et al., 2012; Odum et al., 1999; Reynolds, 2004), the value enhancing effects of nicotine have not been examined using this measure. Studies do not report or compare levels of nicotine in the smoker's system prior to completing the discounting measure.

From a behavioral economic perspective, demand is another way to study value. Demand refers not only to the total amount of the commodity consumed but also "the total level of resources allocated toward obtaining the substance

and to the extent to which consumption is sensitive (or insensitive) to a change in price" (Bickel et al., 2014, p. 643). This definition is similar to how value is viewed in behavioral studies where response requirements can be considered the unit price for a reinforcer. Purchase tasks are commonly used as a measure of demand. This measure requires participants to report the amount of a commodity they would purchase at a range of prices given a budget and timeframe (Jacobs & Bickel, 1999). The demand curves produced by these tasks have been shown to mimic actual consumption of the commodity (Wilson et al., 2016). Similar to the discounting research, purchasing tasks are commonly used to examine demand for cigarettes; these results are compared with other commodities with smokers and nonsmokers (Nighbor et al., 2019; Stein et al., 2017; Wilson et al., 2016). The value enhancing effect of nicotine has not been studied with purchase tasks.

Both purchasing tasks and delay discounting measures have shown to be reliable measures and results are reflected in real world behavior (Higgins et al., 2017; Mackillop et al., 2016; Matusiewicz et al., 2013; Stanger et al., 2012; Strickland et al., 2019; Yoon et al., 2007). Using these methods to measure value allow for researchers to save a number of resources. Using PR schedules and BPs is time consuming. Sessions may need to last hours and even then, there is no guarantee there will be BPs established for all participants. In addition, they

require the stocking and management of the putative reinforcers, and the manpower to run the study to power. The question is whether these measures are sensitive enough to assess the reinforcer enhancing effect of nicotine which has already been demonstrated with PR schedules and BPs.

The Current Studies

While there has been extensive research examining the reinforcer enhancing effects of nicotine with animals, only limited work has been done with humans. All such studies have used progressive ratios and BPs as the measure of value. Thus far music, video, and money have been examined. Only the value of the most highly preferred video and music clips has been changed in these studies. Furthering this analysis with additional qualitatively different types of reinforcers will provide a clearer picture of responding under the influence of nicotine. The current study examined social interaction, physical activity, and beverages that contain sugar. The first two categories are particularly relevant to barriers to quitting, and the last category is the most similar to animal preparations. The addition of purchasing tasks and commodity delay discounting will provide additional information on the best methodology for examining this effect. Regardless of outcome this research helps to further characterize the components of nicotine's effect on responding for reinforcers.

Experiment I

Methods

The purpose of this experiment was two-fold. The first was to examine the relationship between responding on discounting and purchase tasks to responding on the progressive ratio tasks across reinforcer categories. The second purpose was to evaluate the relationship between the participants ranking of preferred categories of reinforcers and the other measures of value.

Participants

Three participants were recruited from the University of Nevada, Reno campus. All three were nonsmokers with no history of nicotine use. Two participants (age 19 and 27) identified as female and one identified as male (age 67).

Procedures

Prior to the study, participants answered several questions aimed at measuring current levels of interactions with putative reinforcers to be used in the study (e.g. how often they spend time with friends, drink sugary beverages, and exercise; Appendix B). Participants then signed up for two sessions. The first session consisted only of the discounting and purchase task (see Table 1). The second session repeated the discounting and purchase task, however, in this session these tasks were followed by the progressive ratio task. Breaks were

provided throughout the session to mimic breaks taken by smokers in Experiment II.

Delay Discounting Questionnaires. Participants completed monetary and commodity delay discounting questionnaires. Delays for all questionnaires included: 1 week, 1 month, 6 months, 3 years, and 10 years. The delayed value for the monetary version was $200. Immediate values were determined based on the distribution outlined by Rachlin, Raineri, and Cross (1991). Three commodities were assessed: 30-minute exercise sessions, 30-minute social engagements, and 12 ounces of a preferred sugary beverage. Participants were asked what amount of each commodity would be equivalent to $200, if for the next month if they had no other access to these commodities (see Appendix C for an example of instructions). This number was then used to calculate delayed and immediate amounts of the putative reinforcers in the questionnaire. To avoid partial units of each commodity the immediate values were rounded up to the nearest whole number.

Purchase Task. Participants completed purchase tasks for all categories of reinforcers. The participant was asked for the average cost of one unit of their most preferred item in each category. They were told they had the same income and savings they have currently but would have to use the purchased units within 7 days (see Appendix D). They were then asked to indicate how many

units of each reinforcer they would purchase at 16 price points. Prices were calculated in terms of percentages of the average cost of one unit of the reinforcer for each category as provided by the participant. The percentages ranged from 1%-1000%. The unit sizes were the same as those used in the commodity discounting task: 30-minute exercise sessions, 30-minute social engagements, and 12 ounces of a preferred sugary beverage

Progressive Ratios and Break Points (BPs). Participants started the session selecting reinforcers from several options in each category for the PR task. Prior to the start of the computer tasks, participants were informed that regardless of how they chose to spend their time (computer task or break activity) this part of the study was going last a total of 2-hours. They were instructed that when they found acorns during the task, they would gain access to the activities that were chosen at the start of the session. Participants were told that if they no longer wished to respond to the computer task, they may look through the available magazines (mundane farming magazines), however this time would not lead to them gaining access to any other activities (provided opportunity for BP). An image of the activity they were working for was present on the screen during the Acorn Finder task. The program prompted the participant to engage with the appropriate category of reinforcers located behind the participant when they completed the response requirement for that trial. A

research assistant (RA) monitored the participant from across the room with their back to the participant. The program made audible sounds when it prompted the participant to change activities in order to alert the RA to provide additional prompts if the participant did not follow the instruction. The RA kept all verbalizations to an absolute minimum (outside of the social interaction sub-condition). Scripted responses were provided if the participant stayed too long in the reinforcement area or engaged with the wrong category of reinforcers.

Progressive ratio responses consisted of clicking a target on screen as part of the Acorn Finder task. BPs, IRTs, and/or rates were obtained for each category of reinforcer. Reinforcer categories alternated across trials (after each reinforcer delivery) and were counterbalanced across participants (see Figure 1). A BP was established when the participant engaged with magazines (selected to be mundane) for five minutes rather than responding to the Acorn Finder task; this led to the end of that trial and the start of the next trial. Once a BP was established for a category of reinforcement it was removed from the rotation. Once all BPs were established the rotation started again with the first FR being 50% of the previous BP. This continued until the two-hour session was over.

Apparatus, Materials, and Setting

Participants were seated at a desk with a laptop computer for most of the study. The delay discounting and purchase tasks were experienced first. During

the PR portion of the study, responses on the "Acorn Finder" task were tracked and resulted in access to reinforcers. This program involved the participant moving the cursor around the image of a tree and clicking on leaves to find acorns. The Applepicker task that this activity was based on has been used in several studies with human participants, including those using progressive ratio schedules and BPs (Perkins et al., 2009, 2017; Perkins & Karelitz, 2013). The number of responses required to obtain reinforcement doubled after each trial beginning with an FR 5 (adapted from Perkins et al., 2013). The ratio before a five-minute break in responding was considered the BP and was used as a measure of the value for that reinforcer. A five-minute BP has been found to be nearly equivalent to longer BPs (Stafford & Branch, 1998).

All participants were exposed to the withdrawal questionnaire prior to starting the session to allow assessment of any withdrawal effect on responding across Experiment I and II. The post-session questionnaire asked participants to rank the reinforcers experienced and those used in the discounting/purchase tasks during the session in order of most preferred to least preferred. There were also questions assessing the quality of the reinforcers experienced in the PR task and the resemblance to their preferred items in these categories outside of the laboratory.

Results

Data for the purchase task were analyzed using the Demand Curve Analyzer (Gilroy et al., 2018). The exponentiated version of Hursh and Silberberg's (2008) exponential equation was used for all analyses (Koffarnus et al., 2015):

$$C = Q_0 * 10^{k(e^{-\alpha Q_0 P} - 1)}$$

The Q_0 parameter is the number of units consumed if the price was \$0. The scaling parameter *k* was determined by taking the difference between the $\log_{10}$ of the highest and lowest consumption values in the data set (Koffarnus et al., 2015) which equaled 1.39. By holding *k* constant comparisons can be made between αs as a measure of elasticity or sensitivity to price. Demand curves are characterized by two sections: the inelastic and elastic range (see Figure 2). The inelastic range refers to the section of the demand curve where fitted responding is insensitive to increases in price. The elastic range is the section of the curve where there are large changes in consumption as price increases (Gilroy et al., 2018).The P_{MAX} is the point at which responding changes from inelastic to elastic. It is the highest price with inelastic responding. A higher P_{MAX} indicates that demand for a commodity was not affected until higher prices were reached. The O_{MAX} value is the highest level of expenditure (e.g., the number of responses

when responses/reinforcer is at P_{MAX}), which can be calculated by multiplying P_{MAX} by consumption (Wilson et al., 2016).

Ideally a Pearson correlation coefficient would be computed to assess the relationships between the demand curve analysis results and the BPs for each category of reinforcer for each participant. However, due to the need to stop data collection due to social distancing requirements related to COVID-19 there were not enough data to give a full statistical report of these analyses. Instead we can report on visual analysis of the relationships between BPs and the demand curve results. Additionally, we reported on clarity by running a preliminary Pearson correlation and used the results to categorize potentially significant results as being "strong" and nonsignificant relationships as being "weak" in terms of clarity. Results are summarized in Table 2. There was a strong positive relationship between α values and the breakpoints for participant 25, Meaning that when BPs increased so did the overall sensitivity to price. However, there was a strong negative relationship between α and the BPs for participant 20. For this participant as the BPs increased, the sensitivity to price reduced. For the third participant there was no clear relationship between these variables. Participant 25 was the only participant to have a strong negative relationship between P_{MAX} and BPs. As BPs increased the price supporting the highest level of responding reduced. All other participants did not have strong relationships

between these variables; however, all weak correlations were negative. The O_{MAX} for participant 20 was positively related to BPs. As BPs increased so did the maximum amount of hypothetical expenditures reported on the purchase task. There were weak negative correlations between these variables for the other participants. There was a positive relationship between the Q_0 and BPs for participant 30. This indicates that as BPs increased then so did the number of units purchased at $0. Only weak negative correlations were found for the remaining participants.

The results from the commodity discounting task were unsystematic making comparison across measures impossible. It was determined that the individual price of each commodity needed to be recorded in order to provide additional methods for analysis. Edits to the procedure were made for Experiment II based on this. Results from the monetary delay discounting task were analyzed. Pearson correlations were conducted to determine the relationship between discounting rate *(k)* and the sensitivity to price (α) for each of the reinforcer categories. All correlations were positive but not strong.

At the end of the session participants were asked to rank by preference both the hypothetical reinforcers (those imagined for the purchase and commodity discounting tasks) and the experienced reinforcers (those physically contacted in the PR task). Surprisingly very few of the rankings for the

experienced reinforcers matched the relative BPs. However, for two out of three participants the ranking of the hypothetical reinforcers did match relative P_{MAX} values.

Discussion

Demand curve analysis provides many different components for assessing demand. While it seems logical for these measures to correlate with BPs acquired via PR schedules these data paint a complicated picture. Whether the components of the demand curve correlated, and to what extent, differed across individuals. The nature of these relationships also varied, with some demonstrating a positive correlation and others a negative correlation for the same set of components. Participant 20's data demonstrated the highest levels of relatedness between all variables with all but the P_{MAX} being strongly related. All strong relationships seemed to be in a logical direction. As BPs increased (the largest number of responses given to acquire the reinforcer) sensitivity to price (α) went down, which is logical: the more an organism works for a reinforcer it would seem to indicate less sensitivity to price. Price being analogous with number of responses required per reinforcer. This participant also indicated in the post session questionnaire the highest level of similarity between the experienced reinforcers and reinforcers of the same category that she experienced outside of the laboratory environment.

It was interesting to see that rankings of preferred experienced reinforcers did not match with BPs established for those same reinforcers. Participant 30 indicated that the exercise task he chose was "dull" and ranked it as the least preferred. Yet he had twice the level of responding for that reinforcer. This indicates that verbal behavior in this instance failed to capture the effectiveness of the experienced reinforcers. Another reason one would expect these rankings to match better than the hypothetical rankings was that the experienced reinforcer rankings were made closer in time to the PR task then the rankings of the hypothetical reinforcer tasks. For most of the participants, however, responding on the purchase tasks matched the rankings of those same reinforcers: indicating this gap in time was not an issue.

While it seems reinforcer efficacy was not fully described by verbal reports, it does seem there is a useful relationship between elements of reinforcer value and the results of hypothetical tasks such as the Purchase Task. This indicates that these types of tasks could be useful when examining the reinforcer enhancing effects of nicotine with humans, which will be explored in Experiment II.

There are several important limitations for Experiment I. First there were only three participants, this was due to COVID-19 social distancing requirements being put in place during the course of the study. Correlations between demand

curve components and BPs were only calculated using 3 BPs for each of the three participants and could have benefitted from more. While every effort was made to make experienced reinforcers in the study as similar as possible to those in the natural environment for participants, there were limitations that could not be overcome. For example, one participant's main source of preferred exercise was riding his bike outside. This simply was not possible in the laboratory environment available for this study. Since the data suggest similarity may be important for this analysis, future studies should examine this further.

Experiment II

Methods

The purpose of this experiment was to examine the effects of nicotine on demand and delay discounting.

Participants

Two participants who smoked a minimum of 5 cigarettes per day and met DSM-V criteria for nicotine dependence, according to a structured interview (Appendix A) based on Breslau et al. (1994), were recruited for this study. Both smokers were females (ages 32 and 35). Two nonsmokers were also recruited: one male and one female (ages 29 and 36).

Procedures

Prior to the study, participants answered several questions aimed at measuring current levels of interactions with putative reinforcers to be used in the study (e.g. how often they spend time with friends, drink sugary beverages, and exercise; Appendix B). Attitudes about smokers and nonsmokers were also assessed. Smokers were asked about their smoking habits and preferred cigarettes.

All nonsmokers were not exposed to nicotine during the study (see Table 4) and they repeated the same condition 3 times. Smokers were exposed to an ABA reversal design. Smokers abstained from smoking for the 11+ hours leading up to the sessions. Abstinence was confirmed via a carbon monoxide monitor. The participants' most preferred cigarette brand and type were provided. Both chose cigarettes that contained .9 mg of nicotine per cigarette. During the baseline condition, participants smoked half a cigarette before starting the purchase task. In addition, prior to the discounting task they smoked another quarter of a cigarette (see Table 4). The cigarettes were cut using a ruler to ensure the correct quantity. The dosage was adapted from those used in previous human studies (Perkins & Karelitz, 2013) across conditions for smokers and nonsmokers.

Delay Discounting Questionnaires. Participants completed the same monetary and commodity delay discounting questionnaires as described in Experiment I. Delays and values used were established using the previously described procedures.

Purchase Task. Participants completed purchase tasks for all categories of reinforcers. As described in Experiment 1 all prices were calculated in terms of percentages of average cost of one unit of the reinforcer for each category as provided by the participant. A total of 16 price points were measured for each reinforcer.

Apparatus, Materials, and Setting

In order to stick to social distancing requirements related to COVID-19, nonsmokers participated via Zoom. The experimenter had the participants join the Zoom video chats on their own laptops. The experimenter then shared her screen with the program hosting the questionnaire tasks. The experimenter would select the choice indicated by the participant. Strict guidelines regarding verbalizations during tasks and mouse placement between questions were used to standardize experiences across participants.

Carbon monoxide measures were needed for smokers – making a completely online delivery not an option. Therefore, the experimenter would complete this part in-person while maintaining the most distance possible. Two

laptops were provided and the procedure for completing the purchase and commodity discounting task was the same as for nonsmokers. A Zoom meeting was used, and the experimenter selected the choice indicated by the participant. The only difference in procedure for the questionnaire tasks for smoker versus nonsmokers was that instead of the participant completing the Zoom appointment from a different house than the experimenter, smokers were in the same house, with as much distance as possible between them.

Prior to the start of every session for smokers, measures of carbon monoxide were taken via a Smokerlyzer monitor (Santa Barbara, CA) to check CO level (CO ≤ 10 ppm) for each smoker. For all sessions smokers were within the acceptable range and no session had to be rescheduled due to noncompliance. In addition, nicotine withdrawal symptoms were assessed via Minnesota Nicotine Withdrawal Scale (Appendix E; Hughes & Hatsukami, 2007) at the start and finish of each session; this occurred for all participants regardless of smoking status to keep procedures as similar as possible.

Results

The same equation and strategies identified in Experiment I were used to analyze the demand curves for this experiment. These data were well described by the exponentiated equation with a median R^2=.94.

P_{MAX} and α were compared across sessions for each set of reinforcers. Upon initial analysis there appear to be orderly fluctuations in responding across the conditions (see Figure 3). Participant 1 demonstrated changes that correlate with the presence and absence of nicotine for all reinforcers, although the changes were not always in the same direction. With coffee, sensitivity to price increased (α) in the no nicotine condition and the point at which responding changed from inelastic to elastic decreased (P_{MAX}). In other words, the highest level of consumption at the highest price went down when there was reduction of nicotine in the participant's system. For walking, there was a slight reduction in the P_{MAX}; however, this change in responding was not reflected in the α value – which did not change consistently across conditions. With parties, the α decreased in the nicotine condition and the P_{MAX} increased. This suggests demand for parties increased in the no nicotine condition, which was the opposite of what was seen with coffee across all measures and differed from the change in P_{MAX} value for walking. This same pattern of responding was observed in the same category of reinforcer for Participant 2, going out.

While these results seemed initially indicative of a strong effect, analysis of the control participants revealed something slightly less convincing. Fluctuations across the sessions occurred despite no change in condition (see Figure 4). Additionally, for each participant there was at least one instance of a

pattern suggestive of what one would expect if the middle session in fact included a manipulation. Although, such patterns were less prominent: None of the control participants demonstrated this pattern across all reinforcer categories and these patterns did not replicate within the same category across participants.

There were overall differences in responding for smokers and nonsmokers. A total of 83% of P_{MAX} values were under 30 for the nonsmokers compared to 33% of P_{MAX} values for smokers. Similarly, the nonsmokers were more sensitive to price changes overall with 66% of α being above .0022, whereas all α were below .0022 for smokers.

Both commodity and monetary delay discounting data were analyzed for each participant. Overall median AUC for the monetary discounting measure was higher for nonsmokers than for smokers, which is consistent with past research indicating that smokers discount future outcomes at higher rates (Odum et al., 1999). Monetary discounting measured by AUC was stable for Participant 1 across all conditions. Responding was also stable (AUC) for the first two sessions (nicotine and no nicotine) for participant 2 indicating that nicotine did not interact with responding on this measure. Commodity delay discounting data were characterized by either a lack of discounting or unsystematic data.

Discussion

While fluctuations in responding were evident across sessions for both the smokers and nonsmokers, the findings for Participant 1 are promising. None of the controls showed a consistent change in responding across the three reinforcers, suggesting the change in condition influenced responding. This finding is strengthened by the replication of the effect for the social reinforcer by Participant 2. This replication suggests a consistent effect with the type of reinforcer. This is particularly interesting for a number of reasons. First, in past research, the level of preference contributed to the change in value of the reinforcer. The social reinforcers were rated second and third for participants 2 and 3 respectively, yet both show a large change in value. Second, this effect was opposite of what was expected, suggesting nicotine actually reduced demand for this reinforcer. Previous studies have shown only self-rated highly preferred reinforcers were enhanced by nicotine (for a review see Perkins et al., 2017). The present results suggest that nicotine might have an opposite effect on less preferred reinforcers. Another explanation for this response pattern could be the type of reinforcer itself could influence responding differently regardless of preference. This should be examined thoroughly in studies going forward.

Participant 1's most preferred reinforcer was the beverage, in this case coffee, and her responding showed an increase in demand for coffee during the nicotine condition. This result is exactly what one would expect if nicotine enhances the reinforcing value of highly preferred items. This condition was also the most similar to reinforcers used in rat studies, consumable liquids. Participant 2 did not demonstrate the same effect for her most highly preferred item which, coincidentally, was also coffee. One explanation for this could be found in Participant 2's CO levels at the start of the session across all three days. While all readings were within required limits, she was consistently at the higher end of the range (indicating relatively less nicotine deprivation) with the last day being the highest acceptable value. P_{MAX} values for that day were the lowest for each reinforcer category, however this was not reflected in higher α levels. Withdrawal symptoms could also be why Participants 1 shows a stronger effect compared to Participant 2. Participant 2 demonstrated more consistent levels of withdrawal across sessions as measured by the Minnesota Nicotine Withdrawal Scale (Appendix D; Hughes & Hatsukami, 2007). Consistent with her lower CO level, Participant 1 demonstrated substantially more withdrawal symptoms at the end of the no nicotine session. A further study examining levels of CO and withdrawal symptoms could be useful in determining why this effect may be seen with some smokers and not with others.

One limitation is the number of participants included in the study; researchers should include more participants going forward. We were only able to replicate the nicotine condition once and were unable to replicate the no nicotine condition due to COVID-19, future research should include more replications of the nicotine and no nicotine conditions to confirm the effect.

General Discussion

The results of this study suggest that hypothetical purchase tasks and demand curve analysis could be a useful tool for measuring changes to reinforcer value in the presence and absence of nicotine. This approach is must faster to deliver and requires fewer resources than PR schedules and BPs. Additionally, the outputs of the demand curve provide more options for analysis than a single BP. Using this analysis we were able to see not only increases in demand but also the opposite effect, which was surprising, suggesting a much more complex interaction between reinforcers and nicotine than originally thought.

The results of the commodity discounting task did not produce useful data for this analysis. For many of the commodities across participants there simply was no discounting, in other instances responding was not systematic. It is unclear if the COVID-19 crisis was partially to blame for these issues, it would be ideal if these participants could complete the tasks again once the pandemic has passed. However, the monetary delay discounting data were more

systematic and allowed for analysis. The difference between the quality of the commodity delay discounting data and the monetary discounting data is not easily explained by the COVID-19 crisis.

There are several other potential explanations more specific to the procedure that could account for the lack of useful commodity discounting data. One being that, in the case of the purchase task, a more objective price was asked for, essentially how much on average do you spend on one unit of X. Whereas in the commodity discounting task participants were asked how many units of X were equal in value to the delayed amount ($200); this can be viewed as a more subjective question. Finally, higher valued items meant very few units were equivalent to $200, therefore there were very few questions since all partial units were rounded up and duplicate values were removed. This would make the analysis less sensitive and give very little room for error in terms of systematic indifference points. If a group design was used and median indifference points were the main subject of analysis, as they typically are in discounting research, this issue may be less pronounced.

The results also demonstrate that the effect of nicotine on reinforcers can potentially be observed in reinforcers that vary widely in form and function from what has been studied thus far. Finally, the study was originally proposed as a group design, however it was modified to account for COVID-19; it seems that

the within subjects design allowed for a much more thorough analysis of the data leading to the discovery of nuances such as changes occurring in the opposite direction for some participants across different reinforcers. These findings might have been washed out in a group analysis. The low number of participants and too few replications of the phases make this study preliminary but suggestive of the need for further research. Future research should also aim to solve the issues discussed in regard to the commodity discounting comparison.

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Table 1

Task Order for Experiment I

		Session I	Session II
Step 1	Withdrawal Questionnaire	Yes	Yes
		Break	
Step 2	Discounting Tasks	Yes	Yes
		Break	
Step 3	Purchase Tasks	Yes	Yes
			Break
Step 4	Progressive Ratio Schedule (break every 15 minutes)	No	Yes
Step 5	Post Session Questionnaire	Yes	Yes

Table 2

Relationships Between BPs and Demand Measures

Participant		Direction of Relationship	Clarity of Relationship
25	α	+	Strong
	P_{MAX}	-	Strong
	O_{MAX}	-	Weak
	Q_0	-	Weak
30	α	-	Weak
	P_{MAX}	-	Weak
	O_{MAX}	-	Weak
	Q_0	+	Strong
20	α	-	Strong
	P_{MAX}	+	Weak
	O_{MAX}	+	Strong
	Q_0	-	Strong

Note. These are preliminary data therefore a Pearson Correlation should not be calculated. A "+" indicates a positive relationship meaning as one measure increased so did the other. A "-" indicates a negative relationship meaning as one measure increased the other decreased. Clarity was determined by visually analyzing the data and running preliminary Pearson correlations and indicating those marked as significant as being strongly suggestive of having a relationship.

Table 3

Ranking Reinforcers Compared with Measure Outcomes

20	Social	Beverage	Exercise
Ranking of Hypothetical Reinforcer	1	3	2
P_{MAX}	32	.74	22.89
Ranking of Experienced Reinforcer	1	2	3
BP	1280	640	1280
25	Social	Beverage	Exercise
Ranking of Hypothetical Reinforcer	1	2	3
P_{MAX}	17.6	2.1	17.1
Ranking of Experienced Reinforcer	2	1	3
BP	40	1280	40
30	Social	Beverage	Exercise
Ranking of Hypothetical Reinforcer	1	3	2
P_{MAX}	129.3	1.8	3.25
Ranking of Experienced Reinforcer	1	2	3
BP	640	640	1280*

*Note.**This is the highest ratio completed but a BP was not established within the 2-hour period.

Table 4

Task Order for Experiment II

Type of Participant/Condition		Nonsmokers All 3 Conditions	Smokers 1st & 3rd Conditions	Smokers 2nd Condition (No Nicotine)
Step 1	Check for 12-hour Abstinence from Smoking	No	Yes	Yes
Step 2	Withdrawal Questionnaire	Yes	Yes	Yes
Step 3	Nicotine Administered or Break	Break	1/2 cigarette	Break
Step 4	Purchase Tasks	Yes	Yes	Yes
Step 5	Nicotine Administered or Break	Break	¼ cigarette	Break
Step 6	Delay Discounting Tasks	Yes	Yes	Yes
Step 9	Withdrawal Questionnaire	Yes	Yes	Yes

Note. This table shows the step-by-step procedures experienced by participants

Figure 1

Schematic of Sub-Conditions

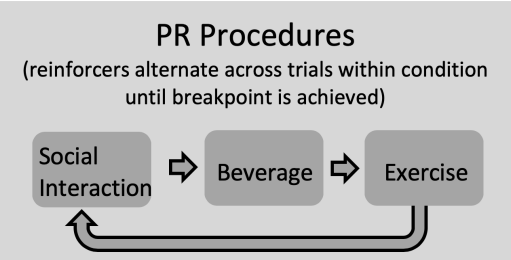
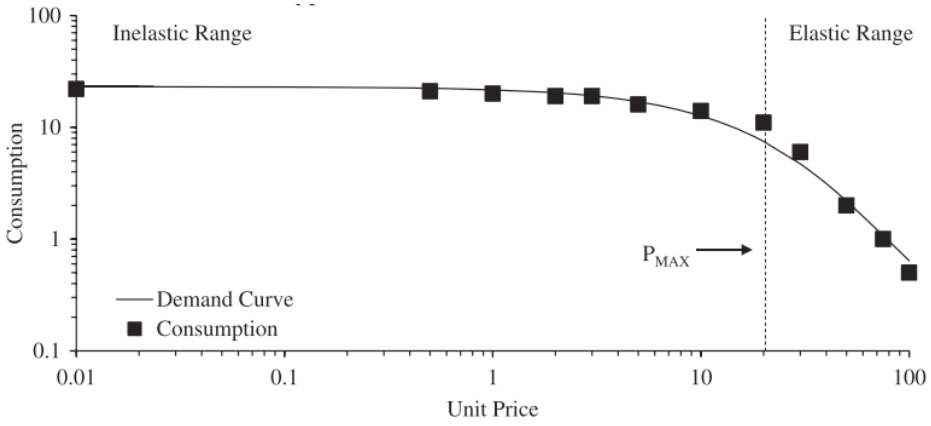


Figure 1. Schematic of sub-conditions for PR procedure (sub-conditions were counterbalanced).

Figure 2

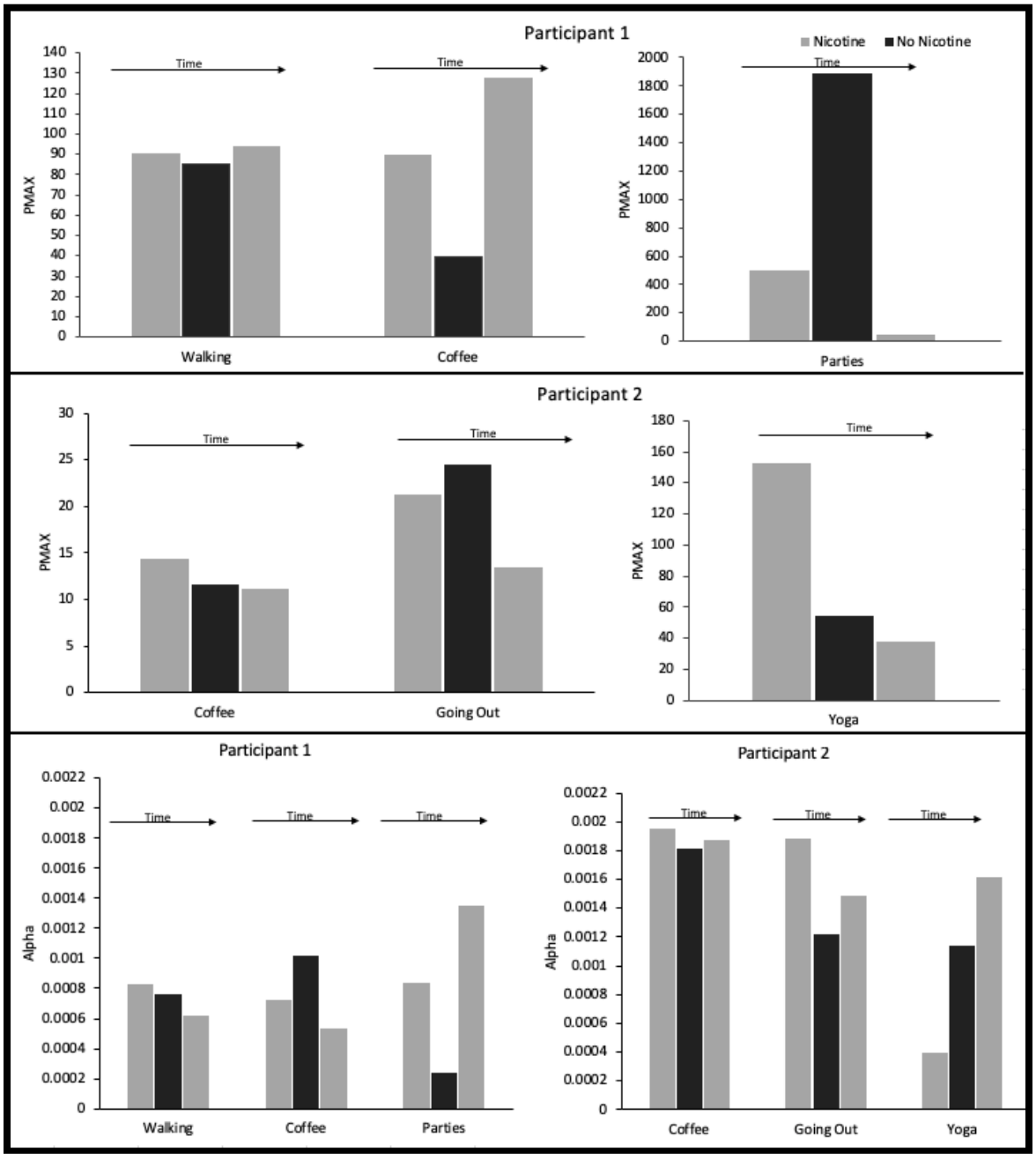
Hypothetical Demand Curve Series



Note. Example of a demand curve using hypothetical data provided by Gilroy et al. (2018).

Figure 3

Changes in P_{MAX} and Alpha Across Conditions for Smokers

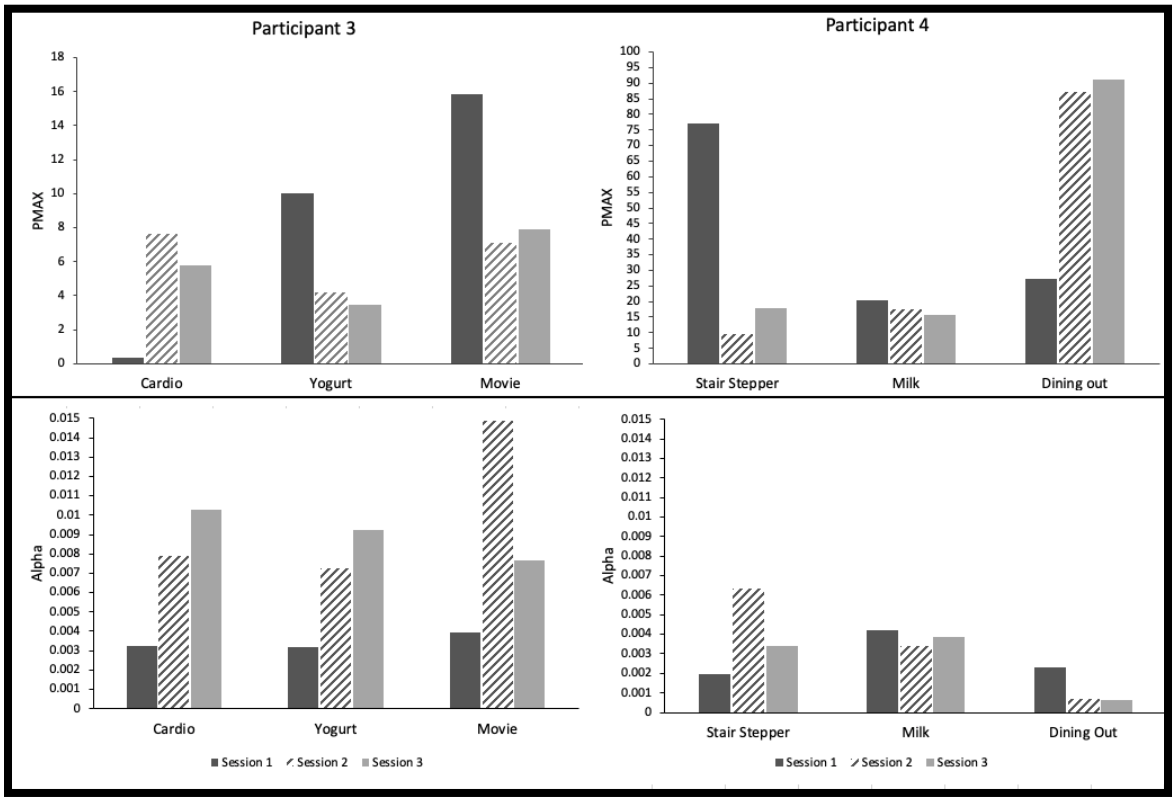


Note. The top two panels show the P_{MAX} values for Participant 1 (top panel) and Participant 2 (middle panel). A higher PMAX indicates a higher price the participant pays before responding reduces (more inelastic demand). Each bar

represents responding during a condition in order of experience across time. The bottom panel shows α values for both participants using the same format. Higher α values indicate more sensitivity to price (more elastic demand).

Figure 4

Changes in P_{MAX} and Alpha Across Sessions for Nonsmokers



Note. The top panel displays the P_{MAX} values for both participants across sessions. The bottom panel shows the α values.

Appendix A

Structured Interview

Please rate yourself on the following behaviors regarding your cigarette use for the
previous X time.

0= none, 1= slight, 2= mild, 3= moderate, 4= severe

1. I smoked more cigarettes than I intended to. (0/1/2/3/4)
2. I smoked cigarettes for a longer period of time than I intended to. (0/1/2/3/4)
3. I had a strong desire to reduce my cigarette use. (0/1/2/3/4)
4. I had unsuccessful efforts to reduce my cigarette use. (0/1/2/3/4)
5. I had a strong craving for cigarettes when none were present. (0/1/2/3/4)
6. My cigarette smoking has made it difficult for me to fulfill obligations at home, work, or school. (0/1/2/3/4)
7. My cigarette use caused social problems with people I know (for example, arguments about smoking). (0/1/2/3/4)
8. I gave up on activities that are important to me because of my cigarette use. (0/1/2/3/4)
9. I continued to smoke cigarettes despite knowing that it causes problems for me or makes problems worse. (0/1/2/3/4)
10. I needed more cigarettes than usual to feel the way I wanted to feel. (0/1/2/3/4)
11. I experienced withdrawal symptoms when not smoking cigarettes, like intense
cravings for nicotine, sweating, headaches, and nausea. (0/1/2/3/4)
12. I smoked cigarettes in order to get rid of withdrawal symptoms. (0/1/2/3/4)

Appendix B

Present Levels Prescreening (delivered via Qualtrics)

1. How often do you exercise?

- ○ never
- ○ less than 1 day per week
- ○ 1 day per week
- ○ 2-3 days per week
- ○ 4-5 days per week
- ○ 6-7 days per week

2. What type of exercise do you prefer?

- ○ running
- ○ weightlifting
- ○ stair stepper
- ○ yoga
- ○ organized sports. Type?

  _____

- ○ other _____

3. Why do you exercise?

Please rank order the options that best answer this question, 1 indicating the response that best fits.

Why do you exercise?

_____ I like how it feels to exercise

_____ I enjoy the health benefits

_____ I like how it changes how my body looks

_____ I am required to by my doctor

_____ I do not exercise

_____ I do it because I have to

_____ other

4. What type of beverages do you drink that contain sugar?

Please rank order the options, 1 being your most preferred drink.

_____ I do not drink sugary beverages

_____ Juice, please state the type.

_____ Soda, please list the type

_____ Sports drinks, please list type and flavor

_____ Other

5. How often do you drink beverages that contain sugar (soda, juice, gatorade etc.)?

- ○ never
- ○ less than once per week
- ○ 1 per week
- ○ 2-3 per week
- ○ 4-5 per week
- ○ 6-7 per week

6. How often do you interact with others for fun?

- ○ never
- ○ less once per week
- ○ once per week
- ○ 2-3 times a week
- ○ 4-5 times per week
- ○ 6-7 times per week

7. Indicate the level to which you agree with the following statement.

I enjoy interacting with friends in my free time.

- ○ Strongly agree
- ○ Agree
- ○ Somewhat agree
- ○ Neither agree nor disagree
- ○ Somewhat disagree
- ○ Disagree
- ○ Strongly disagree

8. What type of things do you do when you spend time with friends?

_____

9. Do you ever play games with friends when you are together?

- ○ Yes
- ○ No

10. Please rank order the following items, 1 being the most preferred

Enjoyable activities

_____ playing card games

_____ playing board games

_____ other game please list

11. Do you have an interest in agriculture or growing vegetables?

- ○ Yes
- ○ Maybe
- ○ No

12. Please explain what interest you have in agriculture or growing vegetables?

_____

_____

_____

_____

_____

What words do you associate to being a Smoker and being a Non-smoker? If words apply to both groups, drop the word in the 'Both' box. If you feel like the word does not apply to either, leave it in the column.

Items

Late

Unhealthy

Clean

Agressive

Healthy

Messy

Punctual

Inactive

Dirty

Active

Organized

Friendly

Smokers

Non-smokers

Both

Appendix C

Commodity Discounting Instructions

For the next month you will not have access to any beverages other than water. You are then given the opportunity to have a 12-ounce glass of your most preferred beverage that contains sugar. How many servings of 12 ounces of your most preferred beverage would be equal in value to $200 given this scenario?

As an example, entering 15 means you would consider 15 12-ounce beverages to be equal to receiving $200.

Appendix D

Think about how you are feeling right now. The following questions ask how many _____ you would purchase at various price points.

Assume that:

(1) The available _____are your preferred _____

(2) You have the same income/savings that you have now and no access to any of these _____ other than those offered at these prices.

(3) You would need to use the _____ over the course of the next week and cannot stockpile them for later than that.

(4) You can engage with _____without any restrictions and without factoring in what might occur in the next week related to your participation in the study.

Appendix E

Minnesota Withdrawal Scale

Subject ID_____

Date _____

Behavior Rating Scale
Self-Report

Please rate yourself for the period for the last_____

0 = none, 1 = slight, 2 = mild, 3 = moderate, 4 = severe

DSM-5 Symptoms
1. Angry, irritable, frustrated 0 1 2 3 4
2. Anxious, nervous 0 1 2 3 4
3. Depressed mood, sad 0 1 2 3 4
4. Difficulty concentrating 0 1 2 3 4
5. Increased appetite, hungry, weight gain 0 1 2 3 4
6. Insomnia, sleep problems, awakening at night 0 1 2 3 4
7. Restless 0 1 2 3 4

Other Validated Symptom
8. Desire or craving to smoke 0 1 2 3 4

Other Possible Symptoms
9. Constipation 0 1 2 3 4
10. Coughing 0 1 2 3 4
11. Decreased pleasure from events 0 1 2 3 4
12. Dizziness 0 1 2 3 4
13. Drowsy 0 1 2 3 4
14. Impatient 0 1 2 3 4
15. Impulsive 0 1 2 3 4