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Sex differences in nicotine-induced impulsivity and its reversal with bupropion in rats

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Abstract

Background: Enhancement in cognitive impulsivity and the resulting alterations in decision making serve as a contributing factor for the development and maintenance of substance use disorders. Nicotine-induced increases in impulsivity has been previously reported in male humans and rodents. Although the potential for sex differences in nicotine-induced impulsivity has not been examined.

Aims and Methods: In the present study, male and female Sprague Dawley rats were submitted to a delay discounting task, in which several consecutive measures of self-control were taken. Firstly, rats were tested with vehicle, and next with nicotine doses of 0.4 and 0.8 mg/kg. Thereafter, chronic treatment with bupropion started, and the animals were tested again. Half the animals continued to receive 0.8 mg/kg of nicotine, while the rest received nicotine and also a daily dose of 30 mg/kg of bupropion.

Results: When the animals were first tested with nicotine, female rats showed a significant nicotine dose dependent increase of impulsive behavior, whereas male rats only showed a decrease on their elections of the larger but delayed reward under the highest dose of 0.8 mg/kg of nicotine. Treatment with bupropion blocked the effect of nicotine on decision making in female rats, as they showed results close to their baseline levels. On the other hand, bupropion did not affect the nicotine-induced delay discounting in male rats.

Conclusion: These findings demonstrate sexually dimorphic effects of nicotine on cognitive impulsivity which may help to shed light nicotine use vulnerabilities observed in women.

Keywords

Nicotine; delay discounting; impulsivity; sex differences; bupropion

Introduction

Impulsivity can be described as a characteristic of normal personality, but when levels of impulsiveness prove extreme, they are associated with psychiatric disorders such as attention-deficit hyperactivity disorder (ADHD), mania, substance abuse and other

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personality disorders (Dickman 1990; Ibias and Pellón 2011; Moeller et al. 2001). Impulsivity results in a wide spectrum of behavioral responses such as deficits in inhibitory control, intolerance to delay for reward, precipitated decisions, and short attention span (Evenden 1999). Thus, impulsivity can be divided in two types: “motor impulsivity”, consisting of a behavioral excess, and “cognitive impulsivity”, which entails precipitated decision making that tends to lead to undesired consequences for the individual (Brunner and Hen, 1997). The delay discounting task (Mazur, 1987) consist of choosing between a small immediate reward and a delayed reward of greater magnitude. This task provides direct measures of cognitive impulsivity since each choice is marked by a single response (Winstanley et al., 2006). Increases in delay discounting occur when choices giving access to the larger but delayed reward decrease as the delay to obtain it is becoming increasingly longer. Thus, increases in delay discounting may be operationalized as impulsive behavior, and are expected in the acquisition and maintenance of addictive behaviors (Bickel et al., 2007; Mach, 2003; Rachlin, 1997)

Use of tobacco products containing nicotine leads to nicotine addiction which results in notable health and economic costs (Britton, 2017; Dai and Hao, 2018; Peto et al., 1996; Warner and Mendez, 2010). Impulsivity has been shown to be a contributing factor to drug abuse (De Witt, 2009; Moeller and Dougherty 2002; Perry and Carroll, 2008); and importantly for the present study, drug use has been shown to enhance impulsivity (MacKillop et al., 2011). Studies in humans and animals demonstrate that nicotine use increases impulsivity. For example, smokers tend to show higher levels of impulsivity compared to non- and ex-smokers when discounting targets are stimulus linked with tobacco consumption, but they don’t act more impulsive before other stimulus like monetary rewards (Baker et al., 2003; Bickel et al., 1999; Mitchell, 1999). Rodent studies have shown that nicotine administration can increase delay discounting in a dose dependent manner in Long Evans, Lewis, and Lister hooded male rats, but a slight decrease in Fisher male rats have also been found (Anderson and Diller, 2010; Dallery and Locey, 2005; Kelsey and Niraula, 2013; Kolokotroni et al., 2011). In addition to the effects of nicotine on impulsivity, sexually dimorphic effects of smoking and nicotine has been reported in humans and rodents. Women have more difficulty with smoking cessation and are less likely to quit smoking (Fortman and Killen 1994; Perkins et al., 1999; Rahmanian et al., 2011). Women also show lower rates of cessation when receiving nicotine replacement (Killen et al. 1990), but treatments with drugs like clonidine or bupropion appear to be more effective in women than in men (Glasman et al. 1988; Jamerson et al. 2001; Smith et al. 2003). In rats, females exhibit a greater motivation to lever press for nicotine and at lower doses than males (Chaudhri et al., 2005; Donny et al., 2000; Flores et al., 2016; Lanza et al, 2004; Rezvani et al., 2008). Female rats also tolerate higher doses of nicotine before experiencing negative aversive effects (Torres et al., 2009).

Bupropion is a dopamine and norepinephrine reuptake inhibitor and a nicotinic receptor antagonist (Carroll et al., 2014; Slemmer et al. 2000), which is used as a treatment option for smoking cessation and depression (Hurt et al. 1997). In humans, bupropion decreases nicotine withdrawal symptoms, craving and reactivity to nicotine associated stimuli (Brody et al. 2004; Jorenby et al. 1999; Shiffman et al. 2000). In addition, bupropion does not affect delay discounting when given alone (Acheson and Wit, 2008), except in patients with

depressive symptoms and ADHD (Barrickman et al., 1995; Wilens et al., 2005). Research with animals has shown that bupropion reverses the affective and somatic aspects of nicotine withdrawal via the enhancement of brain reward function (Cryan et al. 2003).

The current study aims to determine whether sex differences exist in delay discounting to nicotine and whether bupropion could block nicotine delay discounting in male and female rats. When considering the contribution of impulsivity to nicotine use, sexually dimorphic effects of nicotine, and effects of bupropion on nicotine cessation, we hypothesize that nicotine will increase delay discounting, with female rats potentially having a more robust discounting than their male counterparts. Furthermore, if the effects of bupropion are in line with human results, then we predict that bupropion will reduce delay discounting for nicotine in rats.

Methods

Subjects

Fifteen-week-old male and female Sprague Dawley rats that were bred in-house from Envigo stock (Envigo, Indianapolis, IN, USA) were used. Rats were housed in groups of 2–3 per cage in an environmentally controlled room with a 12-hour light-dark cycle (light on at 06:00), an ambient temperature of 20–22°C, and 65% relative humidity. At the start of the procedure, the mean weight of male rats was 393±9 g, and the mean weight of female rats was 233±3 g. Weights were reduced in proportion to standard growth curves for Sprague Dawley rats to 85±2.5% of free-feeding weight using a controlled diet that was maintained throughout the study. Each rat was weighed daily before the experimental session, and a minimum of 20 minutes after the experimental session each animal received the appropriate food supplement to maintain its weight within the criterion-based range. Water was freely available to all animals in their home cages, and food supplements were daily calculated for every animal depending on their body weight and an estimation of the food pellets amount provided in each procedure. The entire study was performed on consecutive days. All animal care procedures were approved by the Institutional Animal Care and Use Committee at Western University of Health Sciences.

Apparatus

Sixteen Med Associates ENV-007 modular conditioning chambers measuring 31.8 × 25.4 × 34.3 cm enclosed in soundproofed housing were used. Each chamber had two retractable levers available, situated on the front panel and at either side of the food tray. Lever presses required a force of approximately 0.5 N to be activated. Data were recorded using a MED-PC software under a Windows environment, and 45 mg food pellets were dispensed (F0021, Bio-Serv, Frenchtown, NJ, USA) in an aperture in the chamber's front wall, situated between the two levers. The chambers were lit by three 3W lamps, one situated above each lever and another situated on the top of the back wall as a chamber light. Exterior sound was masked by a fan that produced an ambient noise of approximately 60 dB in each chamber.

Drugs

The nicotinic acetylcholine receptor agonist, nicotine hydrogen tartrate salt was purchased from Sigma-Aldrich (St. Louis, MO, USA) and dissolved in saline (pH 7.4). Nicotine dose is expressed as free base in this study. Bupropion hydrochloride was purchased from Spectrum Chemical (New Brunswick, NJ, USA), and was dissolved in saline.

Acquisition of lever-pressing behavior (Autoshaping & training)

Four consecutive autoshaping sessions were conducted once the animals' weight had been reduced to criterion. A food pellet was delivered after pressing the available lever under a continuous fixed ratio 1 (FR1) reinforcement schedule. If the animal passed through to the schedule and completed it, the same procedure on the opposite lever was conducted. All rats completed the schedule on both levers (40 pellets on each lever) by the 4^{th} day of autoshaping sessions. Training began the day after the completion of autoshaping and consisted of daily sessions of 50 trials. Each trial commenced with the activation of one of the levers (right or left) and the light over that lever, which was turned on. Upon pressing the lever, the lever was retracted, a food pellet was dispensed and all lights in the experimental chamber switched off during an inter trial interval (ITI) of 30 s, until the start of the next trial, which might be on the same or on the opposite lever. The trial was computed as an omission if the animal took more than 10 seconds to respond following the presentation of a trial, in which case a new 30 s ITI ensued. This training procedure lasted for 4 consecutive sessions.

Delay discounting

The delay discounting procedure was adapted from those used by Winstanley et al. (2004); Fox et al. (2008); and Íbias and Pellón (2014). Each session consisted of 40 trials (24 free-choice and 16 forced-choice trials). Forced trials consisted of one of the levers available and the light above that level, as well as the chamber light, being switched on. The forced trials on lever A led to a reward of 4 food pellets (one every 0.5 seconds) for the first lever press after a given delay. The forced trials on lever B led to a single food pellet delivered immediately after the response. The free-choice trials consisted of both levers A and B available, and the lights above the levers as well as the chamber light being switched on, thereby permitting the animal to choose between the levers. After pressing either lever, and after the food delivery, the lights were switched off. Each trial was separated from the next by an ITI of 45 s during which the chamber light remained switched off. The position of levers A and B was balanced between the chambers, by assigning A as the right lever and B as the left lever in half the chambers, and reversing the order in the other half. During all forced- and free-choice sessions, food reward was dispensed using a FR1 schedule. Each session was divided into 4 blocks of 10 trials each. Each block commenced with 4 forced-choice trials (randomly 2 on each lever) and continued with 6 free-choice trials. If the animal took more than 10 seconds to respond after the respective lever light had turned on, the current trial was counted as an omission, the lever was retracted, the lights of the experimental chamber were switched off and the following trial began after the ITI. The rate of reinforcement was always higher for the delayed option regardless of the increase of the delay (Smethells and Reilly, 2015).

In the first phase of the study, 10 sessions were conducted without any delay (0 s), with the larger reward immediately following the response on lever A. Once all the animals had achieved a lever A preference criterion of 80% or more during the free-choice trials, a baseline estimate of impulsivity was made. Thereafter, twelve consecutive sessions (4 blocks of 3 sessions) were held, in which the value of the delay for lever A was doubled with delay values of 6, 12, 24 and 48 seconds needed to obtain the larger reward. Next, the preference for lever A was reset by means of 5 new sessions without any delay (0 s), in order to return the animals to an almost exclusive preference criterion for this lever. Overall, the sessions lasted between 27min (for delay 0) to 42min (for delay 48). In order to examine the effects of nicotine on impulsive choice, nicotine (0.4 mg/kg, sc) was administered, immediately prior to each experimental session, at approximately 11:00am. Animals were exposed to twelve consecutive sessions of delays (6–48sec), followed by five sessions of delay 0 under the effect of nicotine to reset lever preference to criterion. This procedure was repeated once again with the exception that rats were injected with 0.8 mg/kg of nicotine. Nicotine doses of 0.4 and 0.8 mg/kg were chosen based on their ability to produce rewarding/reinforcing effects in rats and also approximates to levels of nicotine intake in humans (LeSage et al., 2003; for a review see O'Dell & Khroyan, 2009).

In the second phase of the study, male and female rats were divided in four groups of 8 rats, half of the animals continued with the same treatment, a daily dose of 0.8 mg/kg of nicotine just before the experimental session, at approximately 11:00am. The other half received 0.8 mg/kg nicotine and a supplementary treatment consisting of a daily dose of 30 mg/kg of bupropion, administered by means of two daily doses of 15 mg/kg at 9:00am and 5:00pm. Similar to the first phase, 5 new sessions without any delay (0 s), and again 4 blocks of 3 sessions with delays of 6, 12, 24 and 48 seconds were performed. The bupropion dose was selected according to previous findings showing its effects in reducing nicotine self-administration and withdrawal (Bruijnzeel and Markou, 2003; Cryan et al., 2003; Hall et al., 2015). The bupropion administration regimen was selected to reflect the method given in human smokers that undergo nicotine cessation therapy (DynaMed, 2020).

In each session, the proportion of choice of levers A and B, number of omissions, latency of each lever press depending on different type of trial, and the head entries made during the delay and during the ITIs were recorded. The delay discounting procedure lasted for 78 consecutive sessions, and data from the last session of each delay condition were taken into analysis. Task parameters, delays and number of sessions, were chosen in order to minimize possible effects of satiation due to food deliveries and estimating a time window within 20 and 40 minutes for nicotine effect. All rats showed a successful performance throughout the entire study, as the omissions happened sporadically, and their number was always below 1 on average. Table 1 shows the experimental design.

Statistical analysis

All measures involved in delay discounting in the first phase of the study (before bupropion treatment) were analysed using ANOVA tests with a between subjects *Sex* factor (male and female rats), and two repeated measure factors *Dose* (Vehicle, 0.4, and 0.8mg/kg of nicotine) and *Delay* (0-, 6-, 12-, 24-, and 48-s). In the second phase of the study, analysis of bupropion

data was carried out using ANOVA analysis with the between subjects *Sex* factor, and *Treatment* factor (nicotine 0.8 mg/kg, or nicotine 0.8 mg/kg+ bupropion 30 mg/kg), and the repeated measure *Delay* factor. Data obtained from delay discounting were fitted using the following formula (Mazur, 1987): $Y = A/1+KD$, where Y is the mean proportion of choices of the delayed reward of greater magnitude, A is a free parameter for designing the beginning of the curve (asymptote), K is a parameter that reflects the slope of the discount function, and D corresponds to the delay used. As the value of the estimate of K increases, the curve becomes more pronounced, so that higher K estimates reflect greater impulsivity. Mean K estimations for each group and nicotine dose were compared using ANOVA with the between subjects *Sex* factor, and the repeated measure *Delay* factor. Post-hoc comparisons, when needed, were made using pairwise comparisons with a Bonferroni correction. Minimum significance was set at 0.05. The statistical analyses were performed using the SPSS 24.0 software package.

Results

Figure 1 shows the effects of nicotine and delays on the mean (±SEM) proportion of choices on the delayed lever made by male (Fig. 1A), and female rats (Fig. 1B). The analysis revealed a *Sex* × *Dose* × *Delay* interaction effect [$F(8,240)= 2.41$, $p< 0.03$]. Vehicle treated male and female rats decreased their proportion of delayed choices as the delay increased. The choices on the delayed lever decreased to approximately 60% of the possible delayed rewards at the longest delay of 48 s.

Nicotine 0.4 mg/kg treatment in male rats produced a similar decrease in the proportion of delayed choices as observed upon vehicle treatment. However in female rats, nicotine 0.4 mg/kg produced a decrease in the proportion of delayed choices that differed from vehicle treatment at the 6, 12 and 24 s delay sessions, and ultimately, at the 48 s delay, the choice on the delayed lever fell to 40%. A Further decrease in proportion of delayed choices was detected when rats were treated with nicotine 0.8 mg/kg. Nicotine 0.8 mg/kg treatment in male rats produced a gradual decrease in the proportion of delayed choices that differed from vehicle treatment at the 6, 12 and 24 s delay sessions, and at 48 s delay, the choice for the delayed lever was decreased to 40% of the possible delayed rewards. In female rats, nicotine 0.8 mg/kg produced a robust decrease in the proportion of delayed choices with all delay sessions (6–48 s) that were reduced as compared to vehicle treatment. At 0 s, there was a non-significant small reduction in the choice for the delay lever which is likely due to a slight shift in baseline, rather than anorexic effects of nicotine, as rats ate all food pellets, or an increase in omissions. At the 48 s delay session, the choice for the delay lever was attenuated to 15% of the possible delayed rewards. Sex differences were detected in both nicotine doses tested. Female rats treated with 0.4 mg/kg of nicotine had lower proportion of delayed choices at the 6 and 24 s delays compared to similarly treated male rats. Likewise, female rats treated with 0.8 mg/kg of nicotine had lower proportion of delayed choices during all delay periods as compared to their male counterparts.

Figure 2 shows the effects of nicotine and delays on mean (±SEM) latency made by male, and female rats during the immediate (Figures 2A, and 2B), and delayed (Figures 2C, and 2D) free choice trials. The analysis showed longer latencies for female rats when they were

injected with nicotine, as revealed by a *Sex* x *Dose* interaction effect [$F(2,60)= 9.36$, $p< 0.01$]. In male rats, nicotine treatment modestly increased latencies compared to vehicle at delay 0 s. In female rats, nicotine 0.8 mg/kg increased latencies as compared to vehicle treatment at all delays with the exception of 24 s. Overall, female rats treated with nicotine had longer latencies than similarly treated male rats. Analysis of latencies with choice on the delayed lever did not reveal any statistical differences for *Sex* [$F(1,30)= 3.01$, $p= 0.09$], *Dose* [$F(2,60)= 0.93$, $p= 0.91$], or *Delay* [$F(4,120)= 0.82$, $p= 0.51$].

Figure 3 shows the effects of nicotine and delays on mean (±SEM) head entries made by male (Figs. 3A, and 3C), and female rats (Figs. 3B, and 3D). The analysis of head entries during the delay revealed a *Sex* × *Dose* × *Delay* interaction effect [$F(8,176)= 3.35$, $p< 0.01$]. Head entries in vehicle treated male and female rats increased as the delay increased with all delays (6–48 s) being different from delay 0 s. Moreover, vehicle treated female rats had more head entries than male rats at the 6 s delay. Nicotine treatment did not change head entries in male rats; whereas in female rats, both doses of nicotine reduced head entries across delays 6–48 s when compared to vehicle treated rats. At 48 s delay, female rats treated with 0.4 mg/kg nicotine had fewer head entries than similarly treated male rats.

The analysis of head entries during the ITI revealed a *Sex* × *Dose* × *Delay* interaction effect [$F(8,240)= 6.88$, $p< 0.01$]. In vehicle treated male rats, head entries gradually increased as delays increased at delays 12–48 s being different from delay 0 s. Both doses of nicotine decreased head entries as compared to vehicle treatment between delays 12–48 s. Vehicle treated female rats had similar number of head entries across all delays, and at delays 0 and 6 s female rats had more head entries than their male counterparts. Both doses of nicotine treatment decreased head entries in female rats as compared to vehicle treatment across all delays. Moreover, 0.8 mg/kg nicotine reduced head entries in female rats more than in male rats at delays 0, 6 and 12 s, while both doses of nicotine reduced head entries in female rats more than in male rats at delays 24 and 48 s.

Figure 4 shows the effects of bupropion, nicotine and delays on the mean (±SEM) proportion of choices on the delayed lever made by male (Fig. 4A), and female rats (Fig. 4B) The analysis revealed a *Sex* x *Treatment* x *Delay* interaction effect [$F(4,112)= 2.52$, $p< 0.05$]. Nicotine treated male and female rats decreased their proportion of delayed choices as the delay increased with choices being lower starting at delay 12 s in male rats and at 6 s in female rats as compared to their respective delay 0 s values. Moreover, female rats had lower proportion of delayed choices than male rats at 12 and 24 s delays. In male rats bupropion did not alter proportion of delayed choices in nicotine treated rats. However in female rats, bupropion produced a significant increase in the proportion of delayed choices between 12 and 48 s delays. At 48 s delay, female rats had higher proportion of delayed choices than similarly treated male rats.

Figure 5 shows the effects of bupropion, nicotine and delays on mean (±SEM) latency made by male, and female rats during the immediate (Figures 5A, and 5B), and delayed (Figures 5C, and 5D) free choice trials. The analysis of latencies with choices on the immediate lever showed longer latencies for female rats as revealed by a *Sex* x *Delay* interaction effect [$F(4,112)= 5.13$, $p< 0.01$]. Female rats had longer latencies than male rats at delays from 6

to 48 s. In addition, significant differences were found for female rats given bupropion at delay 6 s, and for female rats given only nicotine at delay 12 s when compared to delay 0 s respectively. The analysis of latencies that led to choices on the delayed lever also revealed a *Sex* effect [$F(1,28)= 12.32$, $p< 0.01$]. Regardless of treatment, female rats had longer latencies than male rats at from delays 6 to 48 s.

Figures 6A and 6B show the effects of bupropion, nicotine and delays on mean (±SEM) head entries by male and female rats, respectively. The analysis of head entries during the delay revealed a *Sex* x *Delay* interaction effect [$F(4,112)= 3.61$, $p< 0.01$]. Regardless of treatment, male and female rats made more head entries as the delay increased. Male rats had more head entries at 48 s delay than female rats. Figures 6C and 6D show the effects of bupropion, nicotine and delay on mean (±SEM) head entries during the ITI period. The analysis revealed a *Sex* x *Delay* interaction effect [$F(4,112)= 13.47$, $p< 0.01$]. Male rats had more head entries than female rats during the ITI period.

Figure 7 shows mean (±SEM) estimates of *K* parameter for each group of male and female rats at each dose of nicotine from data shown on Figure 1 (Figure 7A), and also depending on the combined treatment of nicotine and bupropion or only nicotine from data shown on Figure 4 (Figure 7B). The analysis of *K* estimates showed bigger coefficients of impulsivity for female rats injected with nicotine when compared to male rats, as revealed by a *Sex* x *Dose* interaction effect [$F(2,90)= 186.60$, $p< 0.01$]. Nicotine increased the steepness of the hyperbolic functions of female rats describing the decrease of self-control on decision making due to the delays. On the other hand, treatment with bupropion produced a significant decrease on these impulsivity indexes on female rats, as revealed by a *Sex* x *Treatment* interaction effect [$F(1,28)= 100.20$, $p< 0.01$]. Female rats given nicotine were more impulsive than male rats, as it had been shown in the first part of the study, but treatment with bupropion successfully reduced the impulsive behavior of female rats, that showed lower impulsivity indexes than male rats given bupropion or only nicotine.

Discussion

The present study sought to examine differences in impulsivity between male and female Sprague Dawley rats injected daily with nicotine and evaluate whether chronic treatment with bupropion could reverse these differences. Rats were tested with vehicle and nicotine at doses of 0.4 and 0.8 mg/kg. Male and female rats showed similar levels of delay discounting when tested with vehicle, while delay discounting after nicotine administration produced a sexually dimorphic response. Female rats showed a significant increase in delay discounting when given 0.4 and 0.8 mg/kg of nicotine, as well as significant increases in the steepness of their respective discounting functions expressed by means of *K* parameters. On the other hand, male rats only showed increases in delay discounting and their *K* parameters only when 0.8 mg/kg of nicotine was given. The delay discounting observed at 0.8mg/kg nicotine in males was similar to levels observed with 0.4mg/kg in females.

Our results provide evidence in line with previous literature on sex differences in the vulnerability to drug effects. Female rats show higher density of neuronal acetylcholine nicotinic receptors (nAChRs), which could be responsible for sex differences in response to

nicotine (Koylu et al., 1997) by increasing nicotine-evoked impulsive behavior (Mendez et al., 2013; Ohmura et al., 2012). In addition, sex differences in neurotransmission in brain regions are also relevant, as nicotine either directly or indirectly increases dopamine (DA) release in the ventral striatum (Mansvelder et al., 2003; Rice and Cragg, 2004). In fact, female rats tend to display lower dopamine levels than males in the ventral striatum (Cummings et al., 2014), which in turn may contribute to increased levels of impulsivity (Gan et al., 2010; Saddoris et al., 2015; Moschak and Carelli, 2017). Moreover, pharmacokinetic factors could contribute to our findings as females accumulate nicotine in the brain faster and at higher levels than males (Rosecrans and Schechter, 1972) and metabolize nicotine slower than males (Kyerematen et al., 1988; Nwosu and Crooks, 1988). The role of ovarian hormones has also been investigated as a possible source of sex differences on drug effects. In case of nicotine, elimination of ovarian hormones by the way of ovariectomy decreases the rewarding effects of nicotine, which is reversed upon estradiol supplementation (Flores et al., 2016); although nicotine reward is not altered across the estrous cycle (Torres et al., 2009). It is presently not known whether ovarian hormones can modify nicotine-induced impulsivity. We did not observe changes on the behavior of our female rats that could be indicating cyclic variations, and unsurprisingly, changes on the proportion of delayed choices throughout the study were consistent with the drug treatments and the delay used.

The increase in delay discounting observed in female rats due to nicotine was also accompanied by sex differences in the topography of the animals' behavior. The analysis of other variables such as lever response latencies for immediate versus delay lever, or the number of head entries during delays and ITI can be indicative of differences in attention, arousal or motivation, and/or psychomotor processes that may suggest complementary or global behavioral effects (Cardinal et al., 2000; Mar and Robbins, 2007). Latencies provide a direct measure of the drug's power affecting the haste of the rats' responses over the two levers during the free choice trials. Our results showed that latencies to choose the delayed reward were not affected by the nicotine dose or the delay, even when the preference for the delayed reward had decreased because of the length of the delay. Although, both male and female rats showed a dose dependent increase on their latencies to choose the immediate lever during the delay 0 s condition. This result may indicate that nicotine selectively increased the rats' sustained attention (Mirza and Stolerman, 1998) for the delayed option. Furthermore, the increased latencies showed by female rats given 0.8 mg/kg of nicotine could be reflecting a resistance to change from the delayed to the immediate lever, as they were contingent with a significant decrease on the proportion of delayed choices and its consequent increase of choices on the immediate lever at delays of 6 and 12 s.

Head entries provide a quantitative measure of the number of times the animal inspects the food hopper, which may increase as a function of increasing delays, and be low during the ITI (Cardinal et al., 2000). In the present study, the number of head entries during the delays increased with the length of the delay in all the animals, but decreased in female rats given nicotine when compared to vehicle and when compared to male rats. This result was observed in all the delay conditions, and is in line with similar results in rats performing delay discounting under the effects of amphetamine (Cardinal et al., 2000). In addition, male and female rats showed a very low rate of head entries during the 45 s ITI periods, but

nicotine reduced even more than residual magazine behavior to an extent that it practically disappeared in female rats given 0.8 mg/kg of nicotine, which may reflect dose dependent anxiolytic like effects (Hendry and Rosecrans, 1982; Stolerman et al. 1995). Acute administration of nicotine at the doses used in our study are anxiolytic (File et al. 1998) that could be modulating our rats' performance on the delay discounting task, partially preventing the animals from an excessive checking of the food hopper. In addition, we did not observe any anorexic effect due nicotine administration, as rats always ate their food provided in their home cage, as well as all the food pellets dispensed during the experimental session. It is noteworthy that some studies have suggested that nicotine alters food reward value, which might be reflected in choice response, under a modified impulsive choice paradigm (Locey & Dallery, 2009, 2011).

After the evaluation of delay discounting with nicotine, half of the animals continued to receive a daily dose of 0.8 mg/kg of nicotine, while the other half received daily 0.8 mg/kg nicotine and a daily dose of 30 mg/kg of bupropion. Treatment with bupropion significantly decreased delay discounting in female rats to a degree similar to vehicle-treated baseline levels. Bupropion differs in its pharmacokinetic properties from men to women, and their normalized volume of distribution and half-life is larger for women, while they show a smaller terminal elimination rate (Stewart et al., 2001). In addition, a more pronounced antidepressant effect elicited by chronic bupropion treatment has been also observed in female mice (Radhakrishnan et al., 2013). Thus, a decrease in delay discounting due to the chronic treatment with bupropion could be based on its antidepressant effects mediated by its stimulatory action on the DA and norepinephrine (NE) systems, as well as on its anti-nicotinic receptor activity (Arias, 2009; Dwoskin et al., 2006). As such, the ability of bupropion to normalize impulsivity induced by nicotine could be due to catecholaminergic or cholinergic mechanisms. Increase in dopamine and norepinephrine levels have been implicated in decreasing impulsivity (Navarra et al., 2008; Pattij et al., 2007; Robinson et al., 2008; Tsutsui-Kimura et al., 2009). Additionally, antagonism of nicotinic receptor can reduce delay discounting given nicotine (Kolokotroni et al., 2011; Tsutsui-Kimura et al., 2010a; Tsutsui-Kimura et al., 2010b). On the other hand, bupropion did not alter the topography of the animals' behavior. This drug can decrease lever pressing to obtain nicotine, but without interfering other behaviors as lever pressing to obtain food (Bruijnzeel and Markou, 2003). In our study, bupropion did not alter the behavioral patterns for latencies and head entries previously shown when 0.8 mg/kg of nicotine had been given, suggesting that bupropion acts primarily to modify impulsive choice more so than interfering with topographic behaviors.

Conclusion

Our study has shown a common behavioral correlate of drug abuse, a decrease on self-controlled behavior related to nicotine consumption. Nicotine produced impulsive behavior similar to other drugs of abuse (Perry and Carroll, 2008). Sex differences in delay discounting could have been produced by a greater responsiveness to the effect of nicotine via cholinergic system, an increase of DA in striatum contingent with nicotine administration, and also because of sex differences on nicotine pharmacokinetics. The fact that bupropion blocked the effect of nicotine, reversing the impulsive behavior in our female

rats is likely due to one or more of the above noted mechanisms. Our results demonstrate that the activation of the cholinergic system by nicotine plays a critical role in nicotine-induced impulsive behavior and the observed sex differences. In addition, the sexually dimorphic effects of bupropion in the present study is in line with results observed in women given bupropion to quit smoking when compared to men (Smith et al. 2003). The present study introduces impulsivity as a factor to consider when examining nicotine use behaviors and nicotine cessation efforts between men and women.

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References

Acheson A, & de Wit H (2008). Bupropion improves attention but does not affect impulsive behavior in healthy young adults. Experimental and clinical psychopharmacology, 16(2), 113. [PubMed: 18489015]

Anderson KG, & Diller JW (2010). Effects of acute and repeated nicotine administration on delay discounting in Lewis and Fischer 344 rats. Behavioural pharmacology, 21(8), 754. [PubMed: 20944502]

Arias HR (2009). Is the inhibition of nicotinic acetylcholine receptors by bupropion involved in its clinical actions?. The international journal of biochemistry & cell biology, 41(11), 2098–2108. [PubMed: 19497387]

Arias HR, Biala G, Kruk-Słomka MKS, & Targowska-Duda K (2014). Interaction of nicotinic receptors with bupropion: Structural, functional, and pre-clinical perspectives. Receptors & Clinical Investigation, 1(1).

Baker F, Johnson MW, & Bickel WK (2003). Delay discounting in current and never-before cigarette smokers: similarities and differences across commodity, sign, and magnitude. Journal of abnormal psychology, 112(3), 382. [PubMed: 12943017]

Barrickman LL, Perry PJ, Allen AJ, Kuperman S, Arndt SV, Herrmann KJ, & Schumacher E (1995). Bupropion versus methylphenidate in the treatment of attention-deficit hyperactivity disorder. Journal of the American Academy of Child & Adolescent Psychiatry, 34(5), 649–657. [PubMed: 7775360]

Bickel WK, Odum AL, & Madden GJ (1999). Impulsivity and cigarette smoking: delay discounting in current, never, and ex-smokers. Psychopharmacology, 146(4), 447–454. [PubMed: 10550495]

Bickel WK, Miller ML, Yi R, Kowal BP, Lindquist DM, & Pitcock JA (2007). Behavioral and neuroeconomics of drug addiction: competing neural systems and temporal discounting processes. Drug and alcohol dependence, 90, S85–S91. [PubMed: 17101239]

Britton J (2017). Death, disease, and tobacco. The Lancet, 389(10082), 1861–1862.

Brody AL, Mandelkern MA, Lee G, Smith E, Sadeghi M, Saxena S, … & London ED (2004). Attenuation of cue-induced cigarette craving and anterior cingulate cortex activation in bupropion-treated smokers: a preliminary study. Psychiatry Research: Neuroimaging, 130(3), 269–281.

Bruijnzeel AW, & Markou A (2003). Characterization of the effects of bupropion on the reinforcing properties of nicotine and food in rats. Synapse, 50(1), 20–28. [PubMed: 12872290]

Brunner D, & Hen R (1997). Insights into the neurobiology of impulsive behavior from serotonin receptor knockout mice. Annals of the New York Academy of Sciences, 836(1), 81–105. [PubMed: 9616795]

Cardinal RN, Robbins TW, & Everitt BJ (2000). The effects of d-amphetamine, chlordiazepoxide, alpha-flupenthixol and behavioural manipulations on choice of signalled and unsignalled delayed reinforcement in rats. Psychopharmacology, 152(4), 362. [PubMed: 11140328]

Carroll FI, Blough BE, Mascarella SW, Navarro HA, Lukas RJ, & Damaj MI (2014). Bupropion and bupropion analogs as treatments for CNS disorders. In Advances in Pharmacology (Vol. 69, pp. 177–216). Academic Press.

Chaudhri N, Caggiula AR, Donny EC, Booth S, Gharib MA, Craven LA, … & Perkins KA (2005). Sex differences in the contribution of nicotine and nonpharmacological stimuli to nicotine self-administration in rats. Psychopharmacology, 180(2), 258–266. [PubMed: 15682294]

Cryan JF, Bruijnzeel AW, Skjei KL, & Markou A (2003). Bupropion enhances brain reward function and reverses the affective and somatic aspects of nicotine withdrawal in the rat. Psychopharmacology, 168(3), 347–358. [PubMed: 12698231]

Cummings JA, Jagannathan L, Jackson LR, & Becker JB (2014). Sex differences in the effects of estradiol in the nucleus accumbens and striatum on the response to cocaine: neurochemistry and behavior. Drug and alcohol dependence, 135, 22–28. [PubMed: 24332790]

Dai H, & Hao J (2018) Temporal Trends of Sources of Cigarettes among US High School Students: 2001–2015. Nicotine & Tobacco Research.

Dallery J, & Locey ML (2005). Effects of acute and chronic nicotine on impulsive choice in rats. Behavioural pharmacology, 16(1), 15–23. [PubMed: 15706134]

De Wit H (2009). Impulsivity as a determinant and consequence of drug use: a review of underlying processes. Addiction biology, 14(1), 22–31. [PubMed: 18855805]

Dickman SJ (1990). Functional and dysfunctional impulsivity: Personality and cognitive correlates. Journal of Personality and Social Psychology, 58(1), 95–102. [PubMed: 2308076]

Donny EC, Caggiula AR, Rowell PP, Gharib MA, Maldovan V, Booth S, … & McCallum S (2000). Nicotine self-administration in rats: estrous cycle effects, sex differences and nicotinic receptor binding. Psychopharmacology, 151(4), 392–405. [PubMed: 11026746]

Dwoskin LP, Rauhut AS, King-Pospisil KA, & Bardo MT (2006). Review of the pharmacology and clinical profile of bupropion, an antidepressant and tobacco use cessation agent. CNS drug reviews, 12(3-4), 178–207. [PubMed: 17227286]

DynaMed. (2020, 2 6). Bupropion Hydrochloride. Ipswich, MA: EBSCO Information Services Retrieved March 25, 2020, from https://www.dynamed.ebsco.healthcare/drugs/bupropion

Evenden JL (1999). Varieties of impulsivity. Psychopharmacology, 146(4), 348–361. [PubMed: 10550486]

File SE, Kenny PJ, & Ouagazzal AM (1998). Bimodal modulation by nicotine of anxiety in the social interaction test: role of the dorsal hippocampus. Behavioral neuroscience, 112(6), 1423. [PubMed: 9926824]

Flores RJ, Pipkin JA, Uribe KP, Perez A, & O'Dell LE (2016). Estradiol promotes the rewarding effects of nicotine in female rats. Behavioural brain research, 307, 258–263. [PubMed: 27059334]

Fortmann SP, & Killen JD (1994). Who shall quit? Comparison of volunteer and population-based recruitment in two minimal-contact smoking cessation studies. American Journal of Epidemiology, 140(1), 39–51. [PubMed: 8017402]

Fox AT, Hand DJ, & Reilly MP (2008). Impulsive choice in a rodent model of attention-deficit/hyperactivity disorder. Behavioural brain research, 187(1), 146–152. [PubMed: 17950930]

Gan JO, Walton ME, & Phillips PE (2010). Dissociable cost and benefit encoding of future rewards by mesolimbic dopamine. Nature neuroscience, 13(1), 25–27. [PubMed: 19904261]

Glassman AH, Stetner F, Walsh BT, Raizman PS, Fleiss JL, Cooper TB, & Covey LS (1988). Heavy smokers, smoking cessation, and clonidine: results of a double-blind, randomized trial. Jama, 259(19), 2863–2866. [PubMed: 3367452]

Hall BJ, Slade S, Wells C, Rose JE, & Levin ED (2015). Bupropion–varenicline interactions and nicotine self-administration behavior in rats. Pharmacology Biochemistry and Behavior, 130, 84–89.

Hendry JS, & Rosecrans JA (1982). Effects of nicotine on conditioned and unconditioned behaviors in experimental animals. Pharmacology & therapeutics, 17(3), 431–454. [PubMed: 6761718]

Hurt RD, Sachs DP, Glover ED, Offord KP, Johnston JA, Dale LC, … & Croghan IT (1997). A comparison of sustained-release bupropion and placebo for smoking cessation. New England Journal of Medicine, 337(17), 1195–1202. [PubMed: 9337378]

Ibias J, & Pellón R (2011). Schedule-induced polydipsia in the spontaneously hypertensive rat and its relation to impulsive behaviour. Behavioural brain research, 223(1), 58–69. [PubMed: 21540060]

Íbias J, & Pellón R (2014). Different relations between schedule-induced polydipsia and impulsive behaviour in the Spontaneously Hypertensive Rat and in high impulsive Wistar rats: Questioning the role of impulsivity in adjunctive behaviour. Behavioural brain research, 271, 184–194. [PubMed: 24931797]

Jamerson BD, Nides M, Jorenby DE, Donahue R, Garrett P, Johnston JA, … & Leischow SJ (2001). Late-term smoking cessation despite initial failure: an evaluation of bupropion sustained release, nicotine patch, combination therapy, and placebo. Clinical Therapeutics, 23(5), 744–752. [PubMed: 11394732]

Jorenby DE, Leischow SJ, Nides MA, Rennard SI, Johnston JA, Hughes AR, … & Fiore MC (1999). A controlled trial of sustained-release bupropion, a nicotine patch, or both for smoking cessation. New England Journal of Medicine, 340(9), 685–691. [PubMed: 10053177]

Kelsey JE, & Niraula A (2013). Effects of acute and sub-chronic nicotine on impulsive choice in rats in a probabilistic delay-discounting task. Psychopharmacology, 227(3), 385–392. [PubMed: 23340981]

Killen JD, Fortmann SP, Newman B, & Varady A (1990). Evaluation of a treatment approach combining nicotine gum with self-guided behavioral treatments for smoking relapse prevention. J Consult Clin Psychol, 58(1), 85–92. [PubMed: 2319049]

Kolokotroni KZ, Rodgers RJ, & Harrison AA (2011). Acute nicotine increases both impulsive choice and behavioural disinhibition in rats. Psychopharmacology, 217(4), 455–473. [PubMed: 21503608]

Koylu E, Demirgören S, London ED, & Pöğün S (1997). Sex difference in up-regulation of nicotinic acetylcholine receptors in rat brain. Life sciences, 61(12), PL185–PL190.

Kyerematen GA, Owens GF, Chattopadhyay B, & Vesell ES (1988). Sexual dimorphism of nicotine metabolism and distribution in the rat. Studies in vivo and in vitro. Drug metabolism and disposition, 16(6), 823–828. [PubMed: 2907460]

Lanza ST, Donny EC, Collins LM, & Balster RL (2004). Analyzing the acquisition of drug self-administration using growth curve models. Drug & Alcohol Dependence, 75(1), 11–21. [PubMed: 15225885]

LeSage MG, Keyler DE, Collins G, & Pentel PR (2003). Effects of continuous nicotine infusion on nicotine self-administration in rats: relationship between continuously infused and self-administered nicotine doses and serum concentrations. Psychopharmacology, 170(3), 278–286. [PubMed: 12898121]

Locey ML, & Dallery J (2009). Isolating Behavioral Mechanisms of Intertemporal Choice: Nicotine Effect on Delay Discounting and Amount Sensitivity. Journal of the experimental analysis of behavior, 91(2), 213–223. [PubMed: 19794835]

Locey ML, & Dallery J (2011). Nicotine and the behavioral mechanisms of intertemporal choice. Behavioural Processes, 87(1), 18–24. [PubMed: 21354278]

Mach E (2003). Delay discounting: A fundamental behavioral process of drug dependence.

MacKillop J, Amlung MT, Few LR, Ray LA, Sweet LH, & Munafò MR (2011). Delayed reward discounting and addictive behavior: a meta-analysis. Psychopharmacology, 216(3), 305–321. [PubMed: 21373791]

Mansvelder HD, De Rover M, McGehee DS, & Brussaard AB (2003). Cholinergic modulation of dopaminergic reward areas: upstream and downstream targets of nicotine addiction. European journal of pharmacology, 480(1–3), 117–123. [PubMed: 14623355]

Mar AC, & Robbins TW (2007). Delay discounting and impulsive choice in the rat. Current Protocols in Neuroscience, 8–22.

Mazur JE (1987). An adjusting procedure for studying delayed reinforcement. Commons, ML.; Mazur, JE.; Nevin, JA, 55–73.

Mendez IA, Damborsky JC, Winzer-Serhan UH, Bizon JL, & Setlow B (2013). α4β2* and α7 nicotinic acetylcholine receptor binding predicts choice preference in two cost benefit decision-making tasks. Neuroscience, 230, 121–131. [PubMed: 23159316]

Mitchell SH (1999). Measures of impulsivity in cigarette smokers and non-smokers. Psychopharmacology, 146(4), 455–464. [PubMed: 10550496]

Mirza NR, & Stolerman IP (1998). Nicotine enhances sustained attention in the rat under specific task conditions. Psychopharmacology, 138(3–4), 266–274. [PubMed: 9725748]

Moeller FG, Barratt ES, Dougherty DM, Schmitz JM, & Swann AC (2001). Psychiatric aspects of impulsivity. American journal of psychiatry, 158(11), 1783–1793. [PubMed: 11691682]

Moeller FG, & Dougherty DM (2002). Impulsivity and substance abuse: what is the connection?. Addictive Disorders & Their Treatment, 1(1), 3–10.

Moschak TM, & Carelli RM (2017). Impulsive rats exhibit blunted dopamine release dynamics during a delay discounting task independent of cocaine history. ENeuro, 4(2).

Navarra R, Graf R, Huang Y, Logue S, Comery T, Hughes Z, & Day M (2008). Effects of atomoxetine and methylphenidate on attention and impulsivity in the 5-choice serial reaction time test. Progress in Neuro-Psychopharmacology and Biological Psychiatry, 32(1), 34–41. [PubMed: 17714843]

Nwosu CG, & Crooks PA (1988). Species variation and stereoselectivity in the metabolism of nicotine enantiomers. Xenobiotica, 18(12), 1361–1372. [PubMed: 3245230]

O'Dell LE, & Khroyan TV (2009). Rodent models of nicotine reward: what do they tell us about tobacco abuse in humans?. Pharmacology Biochemistry and Behavior, 91(4), 481–488.

Ohmura Y, Tsutsui-Kimura I, & Yoshioka M (2012). Impulsive behavior and nicotinic acetylcholine receptors. Journal of pharmacological sciences, 118(4), 413–422. [PubMed: 22447304]

Pattij T, Janssen MC, Vanderschuren LJ, Schoffelmeer AN, & Van Gaalen MM (2007). Involvement of dopamine D 1 and D 2 receptors in the nucleus accumbens core and shell in inhibitory response control. Psychopharmacology, 191(3), 587–598. [PubMed: 16972104]

Perkins KA, Donny E, & Caggiula AR (1999). Sex differences in nicotine effects and self-administration: review of human and animal evidence. Nicotine & tobacco research, 1(4), 301–315. [PubMed: 11072427]

Perry JL, & Carroll ME (2008). The role of impulsive behavior in drug abuse. Psychopharmacology, 200(1), 1–26. [PubMed: 18600315]

Peto R, Lopez AD, Boreham J, Thun M, Heath C Jr, & Doll R (1996). Mortality from smoking worldwide a. British medical bulletin, 52(1), 12–21. [PubMed: 8746293]

Rachlin H (1997). Four teleological theories of addiction. Psychonomic bulletin & review, 4(4), 462–473.

Radhakrishnan R, Santamaría A, Escobar L, & Arias HR (2013). The β4 nicotinic receptor subunit modulates the chronic antidepressant effect mediated by bupropion. Neuroscience letters, 555, 68–72. [PubMed: 23981664]

Rahmanian SD, Diaz PT, & Wewers ME (2011). Tobacco use and cessation among women: research and treatment-related issues. Journal of Women's Health, 20(3), 349–357.

Rezvani AH, Eddins D, Slade S, Hampton DS, Christopher NC, Petro A, … & Levin ED (2008). Neonatal 6-hydroxydopamine lesions of the frontal cortex in rats: persisting effects on locomotor activity, learning and nicotine self-administration. Neuroscience, 154(3), 885–897. [PubMed: 18511204]

Rice ME, & Cragg SJ (2004). Nicotine amplifies reward-related dopamine signals in striatum. Nature neuroscience, 7(6), 583. [PubMed: 15146188]

Robinson ES, Eagle DM, Mar AC, Bari A, Banerjee G, Jiang X, … & Robbins TW (2008). Similar effects of the selective noradrenaline reuptake inhibitor atomoxetine on three distinct forms of impulsivity in the rat. Neuropsychopharmacology, 33(5), 1028. [PubMed: 17637611]

Rosecrans JA, & Schechter MD (1972). Brain area nicotine levels in male and female rats of two strains. Archives internationales de pharmacodynamie et de thérapie, 196(1), 46–54. [PubMed: 5059368]

Saddoris MP, Sugam JA, Stuber GD, Witten IB, Deisseroth K, & Carelli RM (2015). Mesolimbic dopamine dynamically tracks, and is causally linked to, discrete aspects of value-based decision making. Biological psychiatry, 77(10), 903–911. [PubMed: 25541492]

Shiffman S, Johnston JA, Khayrallah M, Elash CA, Gwaltney CJ, Paty JA, … & DeVeaugh-Geiss J (2000). The effect of bupropion on nicotine craving and withdrawal. Psychopharmacology, 148(1), 33–40. [PubMed: 10663415]

Slemmer JE, Martin BR, & Damaj MI (2000). Bupropion is a nicotinic antagonist. Journal of Pharmacology and Experimental Therapeutics, 295(1), 321–327. [PubMed: 10991997]

Smethells JR, & Reilly MP (2015). Intertrial interval duration and impulsive choice. Journal of the experimental analysis of behavior, 103(1), 153–165. [PubMed: 25533662]

Smith SS, Jorenby DE, Leischow SJ, Nides MA, Rennard SI, Johnston JA, … & Baker TB (2003). Targeting smokers at increased risk for relapse: treating women and those with a history of depression. Nicotine & Tobacco Research, 5(1), 99–109.

Stewart JJ, Berkel HJ, Parish RC, Simar MR, Syed A, Bocchini JA, … & Manno JE (2001). Single-dose pharmacokinetics of bupropion in adolescents: Effects of smoking status and gender. The Journal of Clinical Pharmacology, 41(7), 770–778. [PubMed: 11452710]

Stolerman IP, Mirza NR, & Shoaib M (1995). Nicotine psychopharmacology: addiction, cognition and neuroadaptation. Medicinal research reviews, 15(1), 47–72. [PubMed: 7898169]

Torres OV, Natividad LA, Tejeda HA, Van Weelden SA, & O'Dell LE (2009). Female rats display dose-dependent differences to the rewarding and aversive effects of nicotine in an age-, hormone-, and sex-dependent manner. Psychopharmacology, 206(2), 303–312. [PubMed: 19629450]

Tsutsui-Kimura I, Ohmura Y, Izumi T, Yamaguchi T, Yoshida T, & Yoshioka M (2009). The effects of serotonin and/or noradrenaline reuptake inhibitors on impulsive-like action assessed by the three-choice serial reaction time task: a simple and valid model of impulsive action using rats. Behavioural pharmacology, 20(5–6), 474–483. [PubMed: 19730368]

Tsutsui-Kimura I, Ohmura Y, Izumi T, Yamaguchi T, Yoshida T, & Yoshioka M (2010a). Endogenous acetylcholine modulates impulsive action via α4β2 nicotinic acetylcholine receptors in rats. European journal of pharmacology, 641(2), 148–153. [PubMed: 20639140]

Tsutsui-Kimura I, Ohmura Y, Izumi T, Yamaguchi T, Yoshida T, & Yoshioka M (2010b). Nicotine provokes impulsive-like action by stimulating α4β2 nicotinic acetylcholine receptors in the infralimbic, but not in the prelimbic cortex. Psychopharmacology, 209(4), 351–359. [PubMed: 20238211]

Warner KE, & Mendez D (2010). Tobacco control policy in developed countries: yesterday, today, and tomorrow. Nicotine & Tobacco Research, 12(9), 876–887. [PubMed: 20702814]

Wilens TE, Haight BR, Horrigan JP, Hudziak JJ, Rosenthal NE, Connor DF, … & Modell JG (2005). Bupropion XL in adults with attention-deficit/hyperactivity disorder: a randomized, placebo-controlled study. Biological psychiatry, 57(7), 793–801. [PubMed: 15820237]

Winstanley CA, Theobald DE, Cardinal RN, & Robbins TW (2004). Contrasting roles of basolateral amygdala and orbitofrontal cortex in impulsive choice. Journal of Neuroscience, 24(20), 4718–4722. [PubMed: 15152031]

Winstanley CA, Eagle DM, & Robbins TW (2006). Behavioral models of impulsivity in relation to ADHD: translation between clinical and preclinical studies. Clinical psychology review, 26(4), 379–395. [PubMed: 16504359]

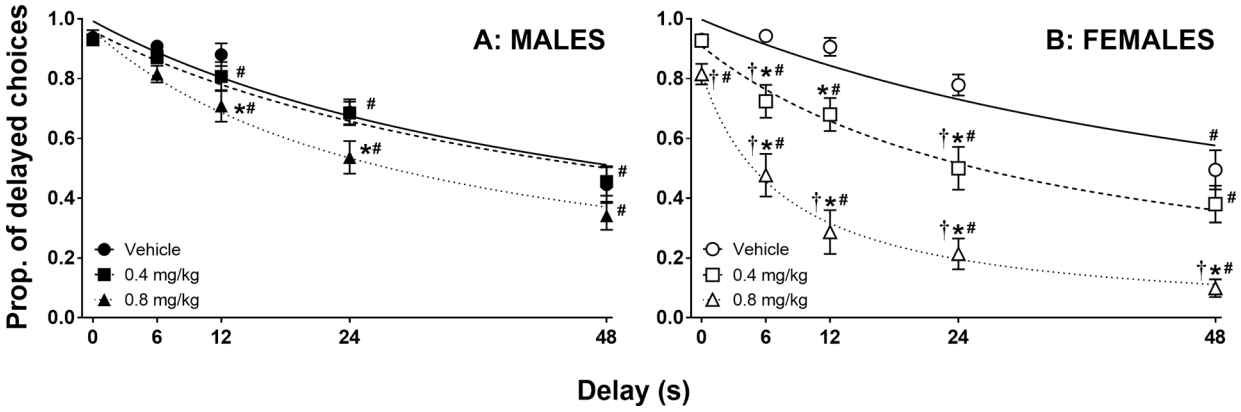

Figure 1.

shows the mean (±SEM) proportion of delayed choices made by male rats (Fig. 1A), and female rats (Fig. 1B) by reference to the delays (0, 6, 12, 24, and 48 s), and the different doses of nicotine used in the study (Vehicle, 0.4, and 0.8 mg/kg), n=16. †= $p< 0.05$ for *Sex* differences. *= $p< 0.05$ for *Dose* differences versus vehicle. #= $p< 0.05$ for *Delay* differences versus delay 0.

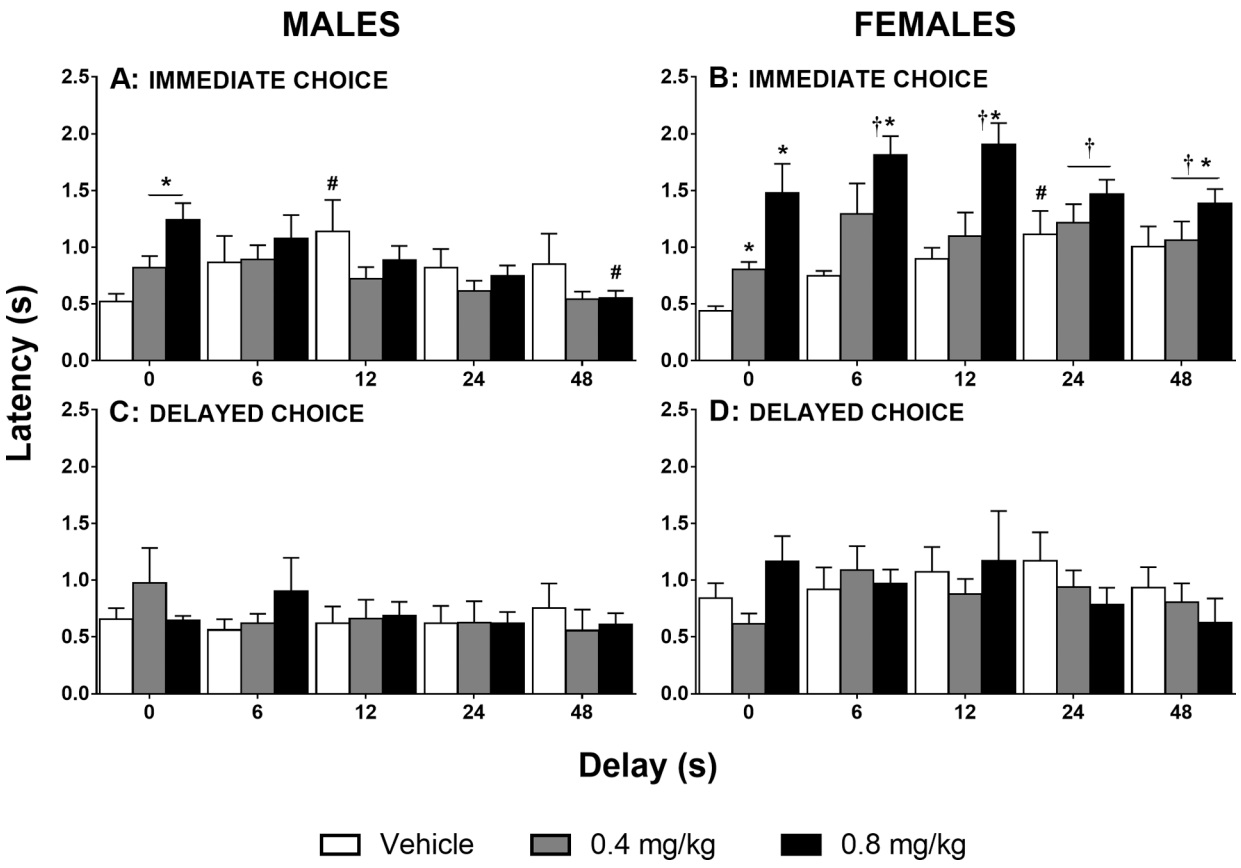

Figure 2.

shows the mean (±SEM) latency made by male, and female rats during the immediate (Figures 2A, and 2B), and delayed (Figures 2C, and 2D) free choices by reference to the delays (0, 6, 12, 24, and 48 s), and the different doses of nicotine used in the study (Vehicle, 0.4, and 0.8 mg/kg), n=16. †= $p< 0.05$ for *Sex* differences. *= $p< 0.05$ for *Dose* differences versus vehicle. #= $p< 0.05$ for *Delay* differences versus delay 0.

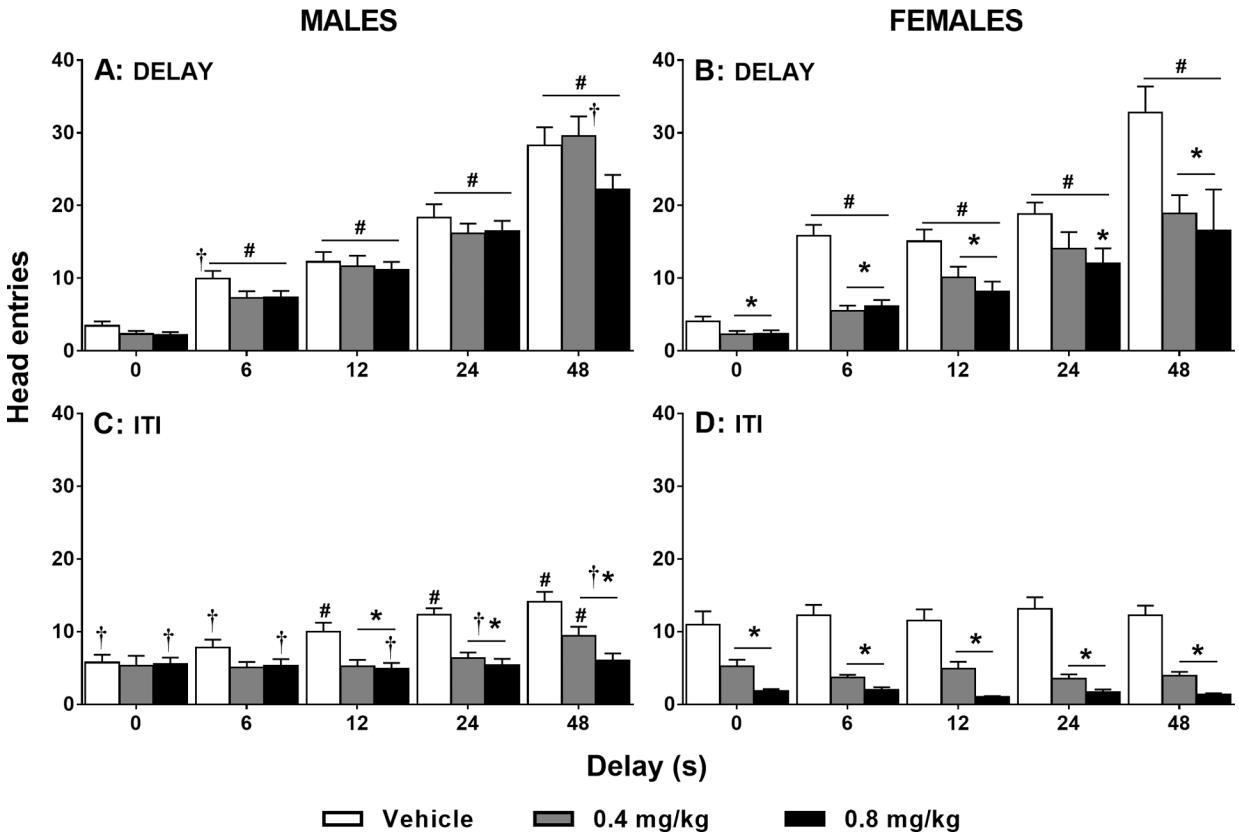

Figure 3.

shows the mean (±SEM) head entries made by male rats (Figs. 3A, and 3C), and female rats (Figs. 3B, and 3D) during the delay and the ITI by reference to the delays (0, 6, 12, 24, and 48 s), and the different doses of nicotine used in the study (Vehicle, 0.4, and 0.8 mg/kg), n=16. †= $p< 0.05$ for *Sex* differences. *= $p< 0.05$ for *Dose* differences versus vehicle. #= $p< 0.05$ for *Delay* differences versus delay 0.

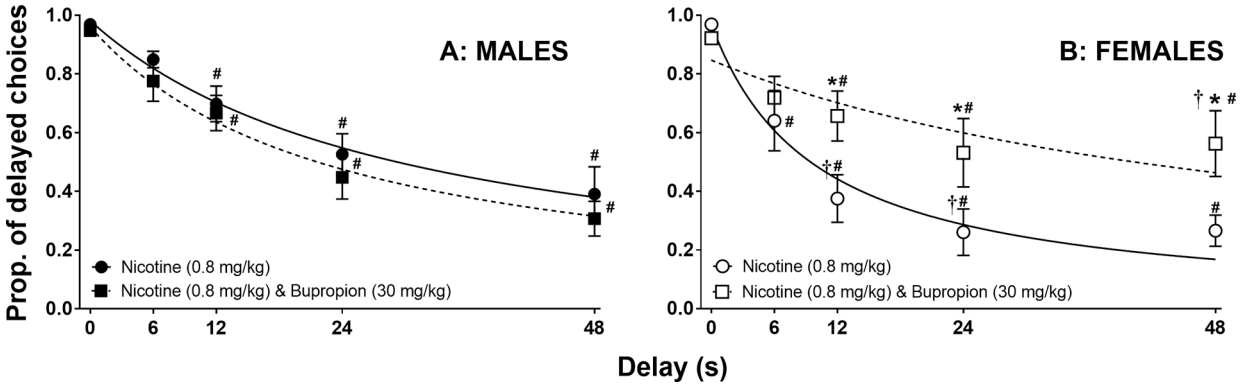

Figure 4.

shows the mean (±SEM) proportion of delayed choices made by male rats (Fig. 1A), and female rats (Fig. 1B) by reference to the delays (0, 6, 12, 24, and 48 s), and the different treatments used in the study (nicotine (0.8 mg/kg), or nicotine (0.8 mg/kg) & bupropion (30 mg/kg)), n=8. †= $p< 0.05$ for *Sex* differences. *= $p< 0.05$ for *Treatment* differences. #= $p< 0.05$ for *Delay* differences versus delay 0.

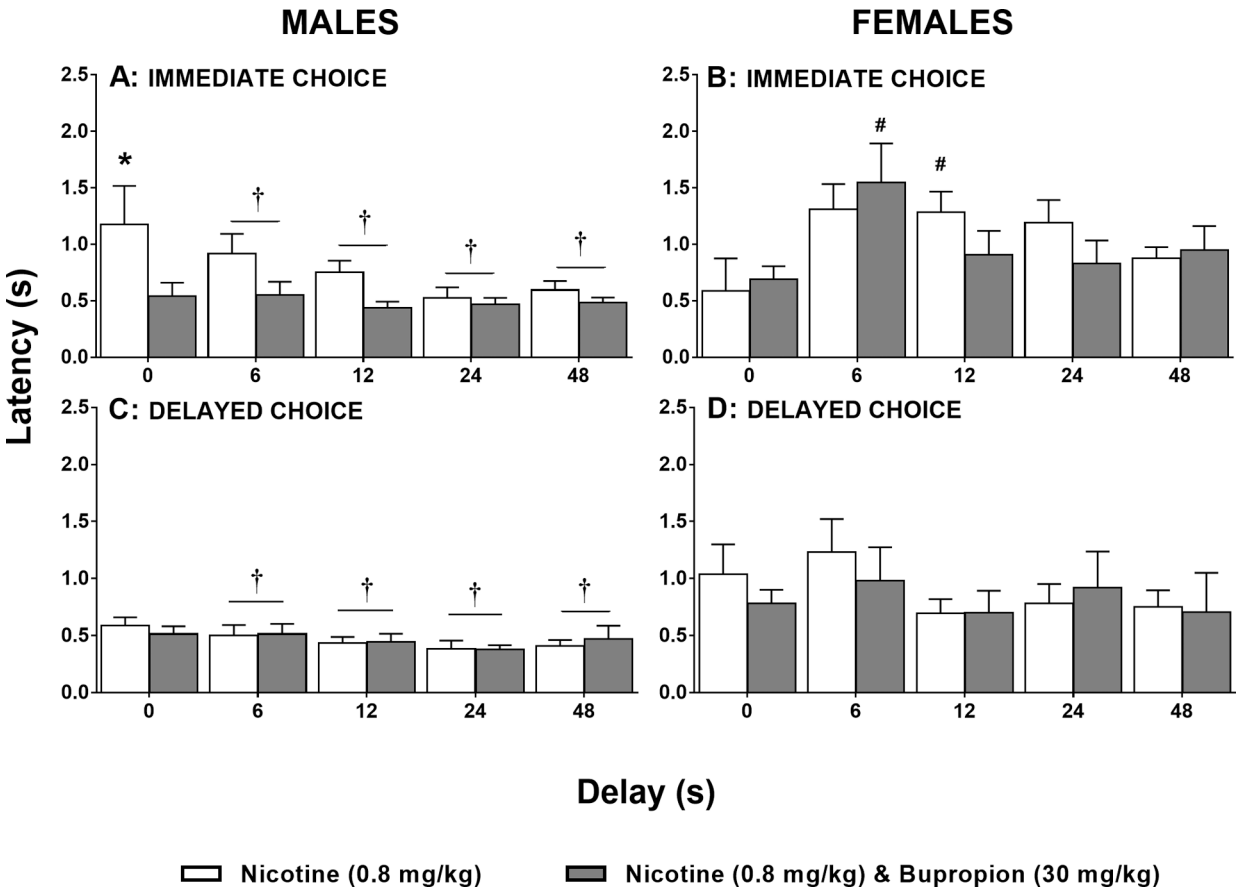

Figure 5.

shows the mean (±SEM) latency made by male, and female rats during the immediate (Figures 5A, and 5B), and delayed (Figures 5C, and 5D) free choices by reference to the delays (0, 6, 12, 24, and 48 s), and the different treatments used in the study (0.8 mg/kg of nicotine, and 0.8 mg/kg of nicotine + a daily dose of 30 mg/kg of Bupropion) (n=8). †= $p<$ 0.05 for *Sex* differences. *= $p<$ 0.05 for *Treatment* differences. #= $p<$ 0.05 for *Delay* differences versus delay 0.

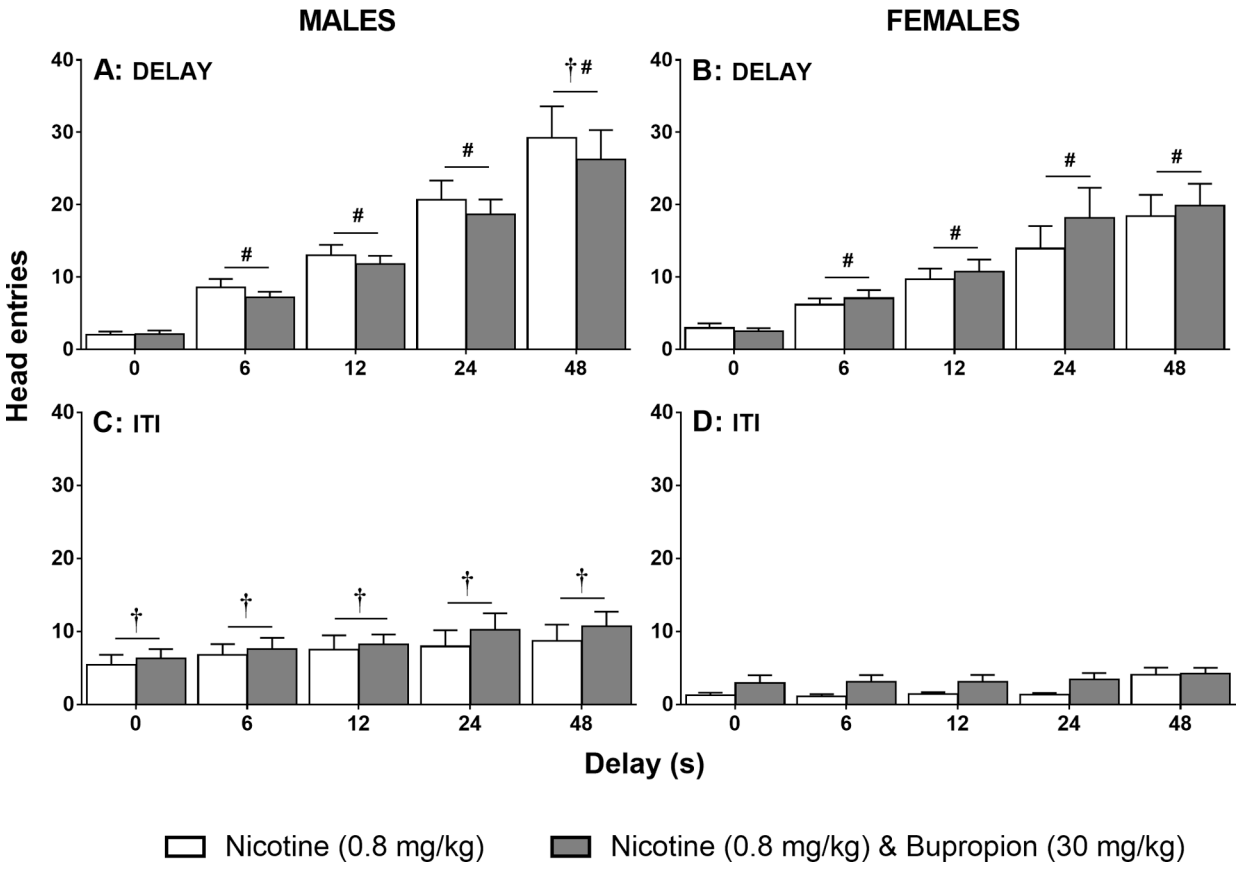

Figure 6.

shows the mean (±SEM) head entries made by male rats (Figs. 6A, and 6C), and female rats (Figs. 6B, and 6D) during the delay and the ITI by reference to the delays (0, 6, 12, 24, and 48 s), and the different treatments used in the study (nicotine (0.8 mg/kg), or nicotine (0.8 mg/kg) & bupropion (30 mg/kg)), (n=8). †= $p< 0.05$ for *Sex* differences. *= $p< 0.05$ for *Treatment* differences. #= $p< 0.05$ for *Delay* differences versus delay 0.

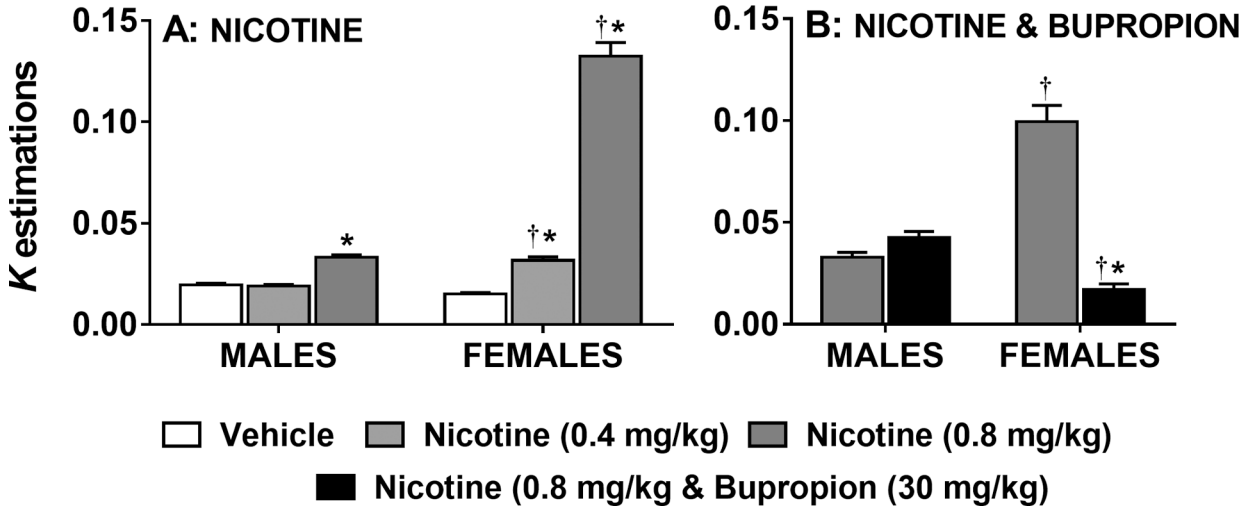

Figure 7.

shows mean (±SEM) estimations of *K* parameters for each group of male and female rats at each dose of nicotine (Figure 7A, n=16, †= $p < 0.05$ for *Sex* differences, *= $p < 0.05$ for *Dose* differences); as well as estimations of *K* depending on the combined treatment of nicotine and bupropion or only nicotine (Figure 7B, n=8, †= $p < 0.05$ for *Sex* differences, *= $p < 0.05$ for *Treatment* differences).

Table 1

shows the experimental design.

	Procedure	Treatment	Sessions
Autoshaping & Training	**(4 Autoshaping & 4 Training sessions)**		**8**
↓	**Delay 0-s** (Criterion >80% of free choices on the delayed lever)	***Vehicle***	10
	Test 3 Sessions X 4 Delays (6-, 12-, 24-, 48-s)		12
	Delay 0-s (Criterion >80% of free choices on the delayed lever)		5
Delay Discounting	**Test** 3 Sessions X 4 Delays (6-, 12-, 24-, 48-s)	***Nicotine (0.4 mg/kg)***	12
	Delay 0-s (Criterion >80% of free choices on the delayed lever)		5
	Test 3 Sessions X 4 Delays (6-, 12-, 24-, 48-s)	***Nicotine (0.8 mg/kg)***	12
↓	**Delay 0-s** (Criterion >80% of free choices on the delayed lever)		5
	Delay 0-s (Criterion >80% of free choices on the delayed lever)	***Nicotine (0.8 mg/kg)*** ***or*** ***Nicotine (0.8 mg/kg) & Bupropion (30 mg/kg)***	5
	Test 3 Sessions X 4 Delays (6-, 12-, 24-, 48-s)		12