Revista Argentina de Ciencias del Comportamiento

ISSN 1852-4206

Diciembre 2024, Vol. 16, N°4, 86-95

revistas.unc.edu.ar/index.php/racc

Effects of chronic nicotine on autoshaping acquisition and extinction

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Artículo Original

Abstract

Learning and motivational processes have been central to a modern understanding of tobacco addiction. In particular, there is growing evidence highlighting the importance of incentive motivational processes for the maintenance of tobacco addiction. The present experiment evaluated the effects of chronic nicotine on the incentive value of a natural reward paired with an environmental cue during acquisition and extinction in a Pavlovian autoshaping procedure with rats. We found that chronic administration of a nicotine dose with translational value for human research had an enhancing effect on responding to an environmental cue during late autoshaping acquisition, but there was no evidence that it affected extinction. Our results are consistent with the role of nicotine enhancing the incentive value of stimuli during acquisition on a Pavlovian autoshaping task and suggest future research on the conditions necessary for the expression of nicotine enhancement in Pavlovian autoshaping tasks.

Keywords:
Nicotine addiction, acquisition, extinction, incentive motivation.

Resumen

Efectos de la nicotina crónica en la adquisición y extinción en una tarea de automoldeamiento. Los procesos de aprendizaje y motivación son fundamentales para la comprensión moderna de la adicción al tabaco. En particular, existe creciente evidencia destacando la importancia de procesos de motivación de incentivos. El presente experimento evaluó los efectos de la nicotina crónica sobre el valor de incentivo de una recompensa natural, combinada con una señal ambiental, durante la adquisición y extinción en un procedimiento de automoldeamiento pavloviano con ratas. Se encontró que la administración crónica de una dosis de nicotina con valor traslacional para la investigación en humanos tuvo un efecto potenciador en la respuesta a una señal ambiental durante la adquisición tardía en automoldeamiento, pero no hubo evidencia de efectos durante la extinción. Estos resultados son consistentes con un fortalecimiento del valor de incentivo de los estímulos durante la adquisición por nicotina en una tarea de automoldeamiento y sugieren investigación futura sobre las condiciones necesarias para la expresión estos efectos.

Palabras clave:
Adicción a la nicotina, adquisición, extinción, motivación de incentivos.

Tabla de Contenido

Recibido el 03 de junio de 2023; Aceptado el 28 de enero de 2024
Editaron este artículo: Florencia Sanmartino, Debora Mola, Carolina Cárdenas y Paula Aguirre

Smoking dependence is still one of the major preventable health problems worldwide, particularly in developing countries (Pichon-Riviere et al., 2020). Nicotine seems to be the main active component in maintaining smoking dependence (United States Department of Health and Human Services, 2014). Current psychobiological theories of substance addiction focus on learning and motivational processes (e.g., Everitt & Robbins, 2016; Robinson & Berridge, 2000). Consistent with this view, several studies suggest that the complex and multifaceted role of nicotine on addiction can be understood according to learning and motivational processes. A sizeable amount of research has focused on nicotine as a primary reinforcer, a role associated with its ability to maintain operant behavior via self-administration (Corrigall & Coen, 1989) and the Pavlovian conditioning of contextual stimuli that can then act as conditioned reinforcers (Fudala & Iwamoto,

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Citar este artículo como: Ortega, L. A., & Papini, M. R. (2024). Effects of chronic nicotine on autoshaping acquisition and extinction. *Revista Argentina de Ciencias del Comportamiento, 16*(4), 86-95.

1986). However, nicotine alone seems to be a relatively weak reinforcer (Donny et al., 2003). Indeed, Palmatier et al. (2006) reported that a combined reinforcer including nicotine and a visual stimulus resulted in enhanced responding, when compared to performance supported by either nicotine or the visual stimulus alone. Together, this evidence suggests that subtle nonpharmacological factors related to other sources of reward concurrent with the context in which nicotine is administered, play a key role in nicotine addiction (Bevins & Palmatier, 2004; Donny et al., 2003). This notion has stimulated research evaluating a second reinforcing role for nicotine, that is the establishment and maintenance of incentive and reinforcing properties of naturally rewarding stimuli associated with nicotine administration. According to this view, nicotine's psychobiological effects on addiction are better understood using a dual reinforcement model according to which nicotine can act both as a primary reinforcer and as an enhancer of reinforcers (Chaudhri et al., 2006).

Autoshaping Pavlovian procedures have been widely used to understand drug abuse (Tomie et al., 2008), the incentive processes underlying the enhancing effects of nicotine on natural reinforcers (Bevins & Palmatier, 2004), and as a useful translational approach to clarify the psychobiological causal mechanisms underlying drug abuse (Colaizzi et al., 2020). Research on the effects of nicotine on the incentive value of natural reinforcers is usually performed during the acquisition phase of training. During this phase, a conditioned stimulus (CS) precedes by a few seconds the presentation of an unconditioned stimulus (US), and the effect of the association is evaluated on conditioned responding (CR). Nicotine seems to enhance the incentive value of CS-US pairings when administered during or prior to training, as suggested by an elevated CR level (Olausson et al., 2004a; 2004b). Robinson and Berridge (2000) proposed that such an enhancing effect could be related to the acquisition of the incentive salience value of the CS, a proposal that could be tested by the developed attractiveness of the CS, the energizing effects on the CR, and the CS's function as a conditional reinforcer. This proposal is also relevant for general substance addiction, as incentive stimuli could play an essential role in underlying drug-seeking behaviors and relapse contexts (Robinson & Berridge, 1993). Consistent with this proposal, Pavlovian sign-tracking CRs (i.e., contact with the lever CS during autoshaping training) have been proposed as a model to understand the development of impulsive drug use behaviors and their control by environmental stimuli (Tomie et al., 2008). However, little is known about the effects of chronic nicotine on the incentive value of a CS paired with a natural US, as well as on CRs during the extinction of the CS-US pairing. A role of chronic nicotine on the incentive value acquisition and extinction of Pavlovian autoshaping is suggested by: (a) the enhancing effects of nicotine on CS-US incentive value mentioned above; (b) previous research with operant procedures reporting that nicotine administration during acquisition and extinction enhanced responding during extinction (Barret & Bevins, 2013; Ramírez & Ortega, 2021; but see Raiff & Dallery, 2008, for negative results); (c) enhanced reinstatement responding after extinction in a Pavlovian task (Guy & Fletcher, 2014); and (d) modulation of fear extinction by simultaneous nicotine administration (Elias et al., 2010; Tian et al., 2008).

The present experiment has two goals. First, to evaluate the effects of chronic nicotine on the reinforcer value of a CS paired with food as a natural reward. We used a Pavlovian autoshaping procedure to evaluate the effects of chronic nicotine on both the incentive value of the CS paired with the US (primary reinforcer) during acquisition and a novel evaluation of the incentive value of the CS during the loss of the primary reinforcer in extinction. A previous study showed inconsistent effects of acute nicotine on autoshaping (Palmatier et al., 2013). Also, the effects of nicotine and learning on autoshaping acquisition have been evaluated mainly using acute administration; we found no studies evaluating the effect of chronic nicotine on autoshaping acquisition and extinction using a dose with translational value for human smoking dependence. Second, to evaluate the effect of chronic nicotine on autoshaping extinction and the extinction spike. A transition from acquisition to extinction in the autoshaping procedure is usually accompanied by an increase in lever pressing during early extinction trials, a phenomenon called the extinction spike, which is defined as a tendency for higher levels of lever pressing behavior early in extinction when compared to late extinction responding (Thomas & Papini, 2001). This effect is dependent upon circulating stress

hormones as it is eliminated by adrenalectomy (Thomas & Papini, 2001) and it fails to occur when acquisition involves partial reinforcement training (Torres et al., 2016) both results link the extinction spike to motivational processes, although there are interesting debates regarding the definition of the extinction spike and its proposed behavioral mechanisms (Katz & Lattal, 2021). This would expand research from conflicting reports of repeated injections of nicotine modulating operant extinction (Barret & Bevins, 2013; Raiff & Dallery, 2008), using chronic nicotine administration with mini-osmotic pumps, which maintain consistent delivery and plasma levels of cotinine, the major metabolite of nicotine (Murrin et al., 1987), and allow to evaluate the effect of chronic nicotine without the stress-induced factors underlying repeated injections.

Method

Subjects

Nineteen experimentally naïve, Wistar male rats (National Institute of Health, Bogota, Colombia), approximately 110 days old at the start of the experiment were individually housed in clear polycarbonate tubs in a colony that provided control for temperature and humidity, and under a 12:12 h light/dark cycle (lights on at 07:00 h). Animals were habituated to the lab environment for three weeks before the start of food deprivation. Before training, animals were deprived of food to 85% of their free-food weight. Training was performed during the light phase of the daily cycle. Water was freely available in each home cage. The Fundación Universitaria Konrad Lorenz Institutional Committee for Care and Use of Laboratory Animals approved the experimental protocol.

Apparatus

Six standard operant chambers (MED Associates) were used, each enclosed in a sound-attenuating chamber. Each box was (32 cm x 25 cm x 25 cm; h x l x w), with a grid floor consisting of stainless-steel bars. The food cup was located on the front wall of the chamber 2 cm above the floor. Two retractable levers were located 1 cm to the right and left of the feeder, and 6 cm above the floor. Pellet dispensers delivered 45-mg food pellets (Bio-Serv #F0165, Flemingtown, NJ). A computer, located in the same room as the chambers, controlled autoshaping training and data collection.

Procedure

Training consisted of 17 daily sessions. Each session started when the house light was turned on and ended when the house light was turned off. Each session consisted of 10 trials, separated by a variable intertrial interval averaging 90 s (range: 60-120 s). Regular intertrial intervals were presented before the first and after the last trial of each session. Each trial started with the insertion of a retractable lever. Lever-pressing responses during the 10 s of lever presentation were recorded by a computer. There were 12 acquisition sessions, in which each lever presentation resulted in the response-independent delivery of five food pellets on the magazine cup. Then, all animals received five extinction sessions, each under the same conditions as during acquisition, except that no food pellets were delivered. Animals were matched by weight and randomly assigned to one of two groups: chronic saline (Group S, n = 9) and chronic nicotine (Group N, n = 10). Animals underwent surgical procedures before training, as described below.

Animals received continuous nicotine during the experiment. Mini-osmotic pumps were used for nicotine administration (Model 2 ML4, pumping rate of 2.5 µl/h, and 28 days duration; ALZET, Cupertino, CA). This type of pump allows accurate and constant systemic release rates of nicotine administration. Animals were anesthetized using intraperitoneal ketamine (50 mg/kg) and xylazine (4 mg/kg), and surgically implanted with a mini-osmotic pump subcutaneously, 2-3 days before training. A lateral incision (2 cm) was performed to place a mini-osmotic pump in the subcutaneous space caudal to the incision and parallel to the spine. The incision was closed using a surgical suture. Each pump was filled with either saline or nicotine hydrogen tartrate dissolved in saline. The dose of nicotine was 3.6 mg/kg/day (dose reported as free base). The dose was selected to model the state of nicotine dependence observed in heavy smokers (Kolokotroni et al., 2012; Murrin et al., 1987). Half the animals in Group S received sham surgery, in which they underwent surgery procedures but there was no implantation of a mini-osmotic pump. The other half were implanted with mini-osmotic pumps containing saline solution.

Data analyses were performed using a repeated measures analysis of variance (ANOVA). Pairwise comparisons post hoc tests were

performed using the Fisher's Least Significant Difference (LSD) test. An alpha value $p < .05$ was used for all statistical tests. Independent statistical analyses were conducted on data from the acquisition and extinction phases. All analyses were performed using SPSS.

Results

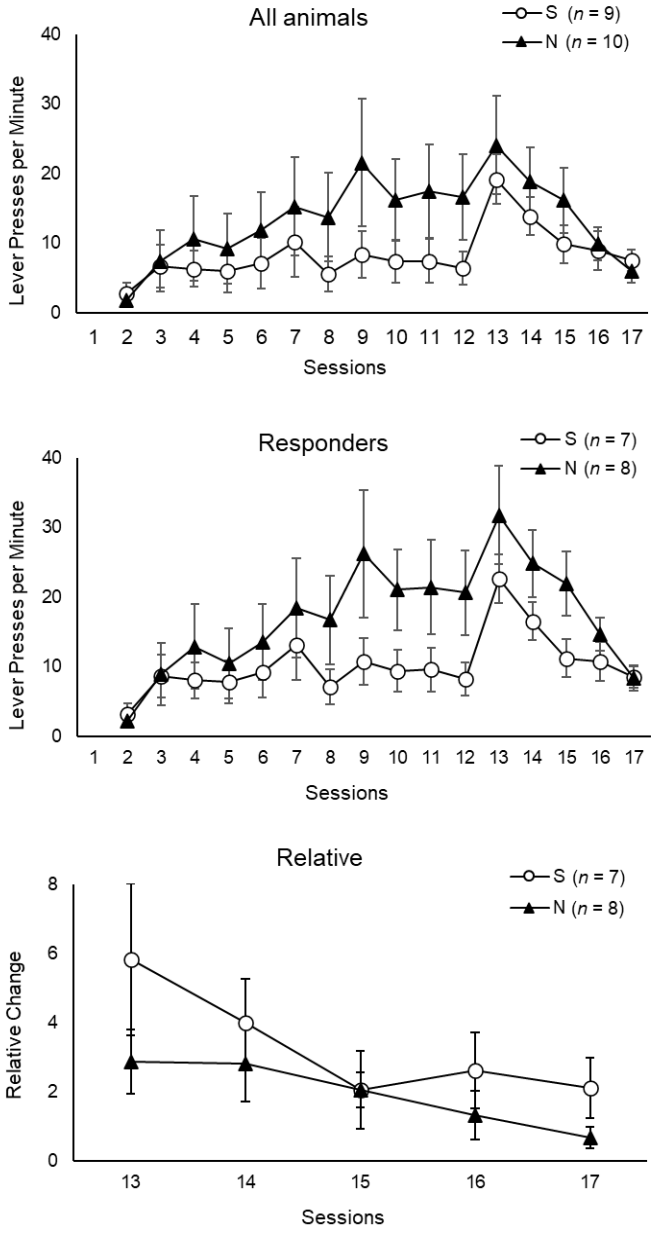
Due to a computer malfunction, data from session 1 of acquisition were lost, although animals underwent normal training. Analyses of acquisition and extinction for animals in Group S that received the sham operation vs. those that were implanted with saline mini-osmotic pumps showed no statistical differences, *F*s < 2.42, *p*s > .07.

The results are shown in Figure 1. The top panel shows lever pressing in all animals. As can be seen in the figure, chronic nicotine potentiated lever pressing responding toward the end of acquisition. A Group (S, N) by Session (2-12) analysis supported this conclusion with a significant interaction, $F(10, 170) = 1.95$, $p < .05$. There was also a significant acquisition effect, $F(10, 170) = 4.73$, $p < .001$, but the main group effect was nonsignificant, $F(1, 17) = 1.04$, $p > .32$. Although the divergence of the two groups is clear in the figure, LSD pairwise tests did not find any significant difference between groups at any session, *F*s(1, 17) < 2.73, *p*s > .11. The extinction results are also shown in Figure 1, top panel. There was a tendency for higher responding in Group N, but a Group by Session (13-17) analysis uncovered only a significant extinction effect, $F(4, 68) = 15.26$, $p < .001$. The other factors were not significant, *F*s < 1.25, *p*s > .27. As for the extinction spike, there was an obvious increase in responding from session 10 to session 11 which was significant, $F(1, 17) = 21.64$, $p < .001$, but there were no effects associated with the chronic nicotine treatment, *F*s < 1.65, *p*s > .21.

Some animals failed to acquire lever pressing. An analysis of autoshaping performance including only responders (eliminating animals that failed to respond in five or more acquisition sessions: Two animals for Group S and two animals for Group N), yielded the following results. There was a significant group by acquisition session interaction, $F(10, 130) = 2.00$, $p < .04$, as well as a significant acquisition across sessions 2-12, $F(10, 130) = 5.17$, $p < .001$. The main effect of chronic nicotine did not achieve significance, $F(1, 13) = 1.13$, $p > .30$. LSD pairwise tests still failed to find any significant difference between groups at any given session, *F*s(1, 13) < 3.12, *p*s > .10. As for extinction results, a similar analysis showed again

Figure 1

Effects of chronic nicotine in autoshaping performance.



Note. Mean (± SEM) lever presses per minute for all animals during acquisition and extinction in the autoshaping procedure. Middle: Mean (± SEM) lever presses per minute excluding animals that failed to acquire lever pressing. Bottom: Mean (± SEM) ratio of relative change scores for extinction. Animals received chronic nicotine (Group N, 3.6 mg/kg/day, dose reported as free base) or saline (Group S) during the experiment. See text for further details.

a significant reduction in lever pressing, $F(4, 52) = 19.02$, $p < .001$, but no effect of the chronic nicotine treatment, Fs < 1.87, ps > .13. As usual, we observed a strong extinction spike, $F(1, 13) = 22.13$, $p < .001$, but this effect was not affected by chronic nicotine, Fs < 2.52, ps > .13 (Figure 1 middle panel).

Figure 1, bottom panel, shows the extinction data. Because the terminal acquisition performance differed across groups, we also looked at the extinction results in relative terms, as typically done in similar studies (e.g., Ortega et al., 2014; Wagner, 1961). Only responders during acquisition sessions were used in this analysis of extinction. The performance of each animal in each extinction session was divided by the average responding of that animal during acquisition sessions 10 to 12. Thus, a ratio greater than one implies an increase in responding from acquisition to extinction, whereas a ratio between zero and one implies lower extinction responding relative to acquisition. There was only an extinction effect, $F(4, 48) = 6.59$, $p < .001$. There was no reliable information suggesting that the chronic nicotine treatment affected autoshaping extinction, Fs < 3.53, ps > .08.

Discussion

The present experiment assessed the effects of chronic nicotine on an autoshaping task using food pellets, a natural reward, during acquisition. This is the first report showing that chronic administration of nicotine had an enhancing effect on lever pressing late in autoshaping acquisition, although there was no evidence that it affected extinction. There was evidence of the extinction spike, but there was no evidence that the nicotine treatment modulated this effect.

An enhancing effect of chronic nicotine on lever responding from Pavlovian autoshaping using food as a reward is consistent with previous research reporting an enhancing effect of prior and concurrent administration of nicotine on Pavlovian approach responding using water as a reward (Guy & Fletcher, 2013; 2014; Olausson et al., 2003). The present study advances our knowledge about the enhancing effects of nicotine over the nonassociative incentive and reinforcing properties of naturally rewarding stimuli in three ways. First, using food as a reward expands the kind of reinforcement for which chronic nicotine enhances the incentive value of natural rewards. Second, by using mini-osmotic pumps for chronic nicotine delivery it is possible to administer a controlled and consistent dose of nicotine during the experiment, as well as a dose known to have translational value (Kolokotroni et al., 2012; Murrin et al., 1987). This type of administration also controls for the confounding stress effects of repeated injections associated with previous research on the incentive effects of chronic nicotine on acquisition and extinction of an operant task (Raiff & Dallery, 2008). Third, it suggests that for nicotine to have an effect, prior experience with nicotine is needed, which is, in turn, consistent with upregulation of cholinergic receptors only after several days of chronic nicotine administration (Sanderson et al., 1993; Schwartz & Kellar, 1983). Fourth, the differential results for the acquisition and extinction phases suggest that the modulatory role of chronic nicotine in the incentive value of the CS occurs only when the CS is accompanied by the US (acquisition).

The enhancing effects of chronic nicotine on behavior were dissociated for the training phases, acquisition and extinction, a fact suggesting that the effects of nicotine cannot be simply explained in terms of nicotine-induced generalized hyperactivity (e.g., Clarke & Kumar, 1983). If chronic nicotine were to induce generalized hyperactivity, an enhancing effect on behavior would be seen during both acquisition and extinction, which was not the case. This would be especially true in terms of the extinction spike, which seems to reflect a degree of emotional activation induced by reward loss. Although it is possible that nicotine-induced hyperactivity plays a role in the incentive-enhancing effects of nicotine on operant and Pavlovian tasks, it does not seem that hyperactivity is important for the expression of incentive-enhancement effects in operant (Barret & Bevins, 2013) or Pavlovian tasks (present experiment).

There were no detectable effects of nicotine at the beginning (extinction spike) and during extinction in the present autoshaping task. This suggests that the controlled administration of chronic nicotine using mini-osmotic pumps does not affect the incentive value of the CS in the absence of the US, as during the initial phases of extinction. However, this hypothesis requires further research. This lack of effect is also consistent with the inability of repeated nicotine administration to affect extinction of operant

behavior, but to enhance responding to visual stimuli associated with food during acquisition (Raiff & Dallery, 2008). However, Barret and Bevins (2013) reported that nicotine administration during both maintenance and extinction resulted in enhanced response rates during extinction. This suggests a need for future parametric research focusing on a careful evaluation of the conditions necessary for the expression of chronic nicotine enhancement of a CS's incentive value both during acquisition and extinction of Pavlovian tasks.

Pavlovian autoshaping procedures are related to competing responses between approaching and pressing the lever and entering and exploring the magazine. These responses were defined as sign-tracking and goal-tracking responses, respectively (Boakes, 1977). Such competing responses are also related to individual differences in the development of sign-tracking or goal-tracking CRs (Meyer et al., 2012), which could be important to clarify the role of individual differences as a risk factor in the development of addictive behaviors (Robinson & Flagel, 2009). As reported in the Method, the present study only recorded sign-tracking behaviors because of equipment limitations to measure goal-tracking behaviors. Future studies need to assess the effects of chronic nicotine with a translational value on goal-tracking behaviors during both the acquisition and extinction phases.

Incentive processes underlying nicotine effects have been recently connected to tobacco addiction via nonassociative incentive mechanisms that are always present in the smoking context (Bevins & Palmatier, 2004). Research using Pavlovian autoshaping procedures could help clarify the psychobiological basis of individual differences in the vulnerability to develop dependence from an initial drug use (Berridge & Robinson, 2016).

Acknowledgments

Financial support for this research was provided by Fundación Universitaria Konrad Lorenz. The authors would like to thank Angelo Cardona for his assistance with the experiment, and Alejandra Muñoz for her assistance with surgeries.

Data availability statement

The complete data set supporting the results of this study was published in the present article, in the annex.

Analytic methods statement

The entire set of analytical methods supporting the results of this study are available through request to contact author Leonardo A. Ortega (leonardoa.ortegam@konradlorenz.edu.co). The set of analytical methods is not publicly available due to SPSS copyright restrictions by IBM Corp.

Materials statement

The complete description of materials supporting the results from this study was published in the article.

Conflict of interest.

None.

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Annex 1

Effects of chronic nicotine in autoshaping performance autoshaping acquisition and extinction. Complete data set

		Acquisition											Extinction				
Animal	Group	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
A31	Sal	0	0	0.6	0	0	0	0	0	0	0	0	14.4	7.2	8.4	4.8	7.8	
A34	Sal	0	18	16.8	17.4	12.6	1.8	1.8	17.4	21.6	27	21.6	37.2	27.6	28.8	25.8	16.8	
A37	Sal	1.8	3.6	3.6	0.6	2.4	1.2	2.4	1.2	1.2	1.8	1.8	18	9	6	8.4	3	
A39	Sal	14.4	22.2	17.4	22.8	31.8	46.8	1.8	25.2	16.2	14.4	11.4	24	22.8	7.2	2.4	8.4	
A41	Sal	0	0.6	0	0	0.6	2.4	1.2	0	.6	3	3	1.2	13.2	4.8	3	6.6	
A44	Sal	0.6	0	0	0	0	5.4	4.8	1.8	1.2	0	2.4	19.8	12	4.8	9.6	8.4	
A45	Sal	2.4	0	0	0	0	0	0	0	0	0	0	0	1.8	1.8	0	0	
A47	Sal	5.4	16.2	15.6	13.8	15	18	23.4	2.4	19.8	15	7.2	26.4	11.4	15	18.6	1.8	
A49	Sal	0.6	0	3	0	1.8	7.2	5.4	9	5.4	6	1.2	22.8	19.8	12	7.8	6	
	M	2.8	6.7	6.3	6.1	7.1	10.2	5.5	8.3	7.3	7.5	6.4	19.2	13.9	9.9	8.9	7.5	
	SD	1.6	3.1	2.6	3.1	3.6	5	2.5	3.4	3	3.1	2.4	3.5	2.7	2.7	2.8	1.6	
A32	Nic	1.2	4.2	7.8	1.2	1.8	1.2	1.2	16.2	22.2	14.4	16.8	41.4	34.8	34.8	32.4	19.8	
A33	Nic	3	9.6	9.6	9	1.8	19.2	16.2	16.2	22.2	19.8	21.6	46.8	30	33	14.4	1.2	
A36	Nic	2.4	1.8	5.4	0	0.6	1.8	5.4	0	0.6	2.4	3.6	7.8	2.4	21.6	13.2	6	
A38	Nic	2.4	3.6	8.4	1.2	14.4	9.6	3	14.4	15	13.2	8.4	27	13.8	9.6	7.8	5.4	
A40	Nic	0	0.6	0	0	0.6	1.8	1.2	2.4	0	0	0.6	1.8	1.2	0	0	0	
A42	Nic	3	6.6	8.4	7.8	38.4	42	39.6	55.8	42	43.2	37.8	54.6	38.4	31.8	18	1.2	
A43	Nic	4.8	42	58.2	48	39.6	58.8	52.2	75.6	39.6	55.2	51	35.4	24.6	12	13.8	16.8	
A46	Nic	0	0	0	1.2	0	0	0	0	0	0	1.8	3	6	3	4.2	4.8	
A48	Nic	0.6	0	.6	0	0	0	0	0	0	0	0	.6	0	1.2	0	2.4	
A50	Nic	0.6	3	5.4	7.2	2.4	4.2	6	29.4	27	23.4	25.2	39.6	35.4	33	18	7.2	
	M	1.9	7.5	10.7	9.3	11.9	15.3	13.7	21.5	16.3	17.5	16.7	24.1	18.9	16.1	9.9	6	
	SD	0.6	4.4	6.1	5	5.4	7.1	6.4	9.1	5.8	6.8	6.1	7.1	4.8	4.7	2.4	1.7	

Note. Responses per minute. Sal (*n* = 9); Nic (*n* = 10). *M* = Mean, *SD* = Standard deviation.

Annex 2

Effects of chronic nicotine in autoshaping performance autoshaping acquisition and extinction. Complete data set. Excluding nonresponders - no responding in 5 or more

		Acquisition												Extinction				
Animal	Group	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
A34	Sal		0	18	16.8	17.4	12.6	1.8	1.8	17.4	21.6	27	21.6	37.2	27.6	28.8	25.8	16.8
A37	Sal		1.8	3.6	3.6	0.6	2.4	1.2	2.4	1.2	1.2	1.8	1.8	18	9	6	8.4	3
A39	Sal		14.4	22.2	17.4	22.8	31.8	46.8	1.8	25.2	16.2	14.4	11.4	24	22.8	7.2	2.4	8.4
A41	Sal		0	0.6	0	0	0.6	2.4	1.2	0	0.6	3	3	1.2	13.2	4.8	3	6.6
A44	Sal		0.6	0	0	0	0	5.4	4.8	1.8	1.2	0	2.4	19.8	12	4.8	9.6	8.4
A47	Sal		5.4	16.2	15.6	13.8	15	18	23.4	2.4	19.8	15	7.2	26.4	11.4	15	18.6	1.8
A49	Sal		0.6	0	3	0	1.8	7.2	5.4	9	5.4	6	1.2	22.8	19.8	12	7.8	6
	M		3.3	8.7	8.1	7.8	9.2	13.1	7.1	10.7	9.4	9.6	8.2	22.6	16.5	11.2	10.8	8.6
	SD		1.9	3.7	3.1	3.7	4.4	6	2.9	3.9	3.6	3.7	2.7	3.1	2.6	3.3	3.2	1.6
A32	Nic		1.2	4.2	7.8	1.2	1.8	1.2	1.2	16.2	22.2	14.4	16.8	41.4	34.8	34.8	32.4	19.8
A33	Nic		3	9.6	9.6	9	1.8	19.2	16.2	16.2	22.2	19.8	21.6	46.8	30	33	14.4	1.2
A36	Nic		2.4	1.8	5.4	0	0.6	1.8	5.4	0	0.6	2.4	3.6	7.8	2.4	21.6	13.2	6
A38	Nic		2.4	3.6	8.4	1.2	14.4	9.6	3	14.4	15	13.2	8.4	27	13.8	9.6	7.8	5.4
A40	Nic		0	0.6	0	0	0.6	1.8	1.2	2.4	0	0	0.6	1.8	1.2	0	0	0
A42	Nic		3	6.6	8.4	7.8	38.4	42	39.6	55.8	42	43.2	37.8	54.6	38.4	31.8	18	1.2
A43	Nic		4.8	42	58.2	48	39.6	58.8	52.2	75.6	39.6	55.2	51	35.4	24.6	12	13.8	16.8
A50	Nic		0.6	3	5.4	7.2	2.4	4.2	6	29.4	27	23.4	25.2	39.6	35.4	33	18	7.2
	M		2.2	8.9	12.9	10.4	13.6	18.5	16.7	26.3	21.1	21.5	20.6	31.8	24.8	22	14.7	8.3
	SD		0.5	4.8	6.6	5.6	5.8	7.4	6.7	9.4	5.5	6.8	6.1	6.6	4.5	4.7	3.3	2.5

Note. Responses per minute. Sal (*n* = 7); Nic (*n* = 8). *M* = Mean, *SD* = Standard deviation.