



Acquisition, Inhibitory Control, and Restoration of Lever Pressing in Spontaneously Hypertensive (SHR) and Lewis (LEW) Rats¹

Carlos F. Aparicio²

Malana Malonson

Tyler Pierce

Salem State University

Abstract

The spontaneously hypertensive (SHR) and the Lewis (LEW) rats have been proposed as possible animal models of attention-deficit/hyperactivity disorder. Because the rats in these two strains do not differ in genotype, using the SHR and LEW rats as experimental subjects allow researchers to observe possible dissociations between genetic and environmental aspects of impulsive behavior. In the present study, we examined response acquisition, inhibitory control, and response restoration in SHRs and LEWs. Both strains showed similar acquisition and maintenance of lever pressing along trials of a positive automaintenance procedure. The SHRs showed less inhibitory control of lever pressing along trials of a negative automaintenance procedure, which resulted in more omissions of food reinforcers as compared to the LEWs. In a final phase of positive automaintenance, lever pressing restored faster in the SHRs. Also, rats in both strains pressed on a lever that was never paired with food delivery. These findings suggest a learning deficit or memory insufficiency in the SHRs, which showed more impulsivity and less behavioral inhibition than the LEWs.

Key words: *Lever pressing, acquisition, inhibition, impulsivity, SHR, LEW, rats*

Resumen

Las ratas espontáneamente hipersensitiva (SHR) y las Lewis (LEW) se han propuesto como posibles modelos animales del trastorno por déficit de atención e hiperactividad. Dado que las ratas de esas cepas no difieren en genotipo, el uso de las ratas SHR and LEW como sujetos experimentales permite a los investigadores disociar a los aspectos genéticos de los factores ambientales de la conducta impulsiva. En este estudio examinamos la adquisición, el control inhibitorio y la restauración de respuestas en ratas SHR y LEW. Las dos cepas revelaron similar adquisición y mantenimiento de respuestas en ensayos de automantenimiento positivo. El control inhibitorio de respuestas en ensayos de automantenimiento negativo fue menor en las ratas SHR que en las ratas LEW, resultando en una mayor omisión de

¹ La referencia del artículo en la Web es: https://conductual.com/articulos/Acquisition_inhibitory_control_and_restoration_of_lever_pressing_in_spontaneously_hypertensive_and_Lewis_rats.pdf

² Correspondence: Salem State University, Department of Psychology, 352 Lafayette Street, Salem, Massachusetts 01970-5353. Email; caparicio@salemstate.edu.



reforzadores en las ratas SHR. En una fase final de automantenimiento positivo, las ratas SHR restauraron las respuestas más rápido que las ratas LEW. Las dos cepas presionaron una palanca que nunca se asoció con la presentación de reforzadores. Estos hallazgos sugieren una deficiencia en la memoria, o en el aprendizaje, de las ratas SHR que mostraron más impulsividad y menos control inhibitorio que las ratas LEW.

Palabras clave: *Presión de palanca, adquisición, inhibición, impulsividad, SHR, LEW, ratas*

The study of impulsive actions is important in understanding a variety of issues such as drug abuse, gambling, suicide, aggression, and psychiatric conditions such as attention-deficit/hyperactivity disorder (ADHD: American Academy of Pediatrics, 2000; Biederman, Petty, Evans, Small, & Faraone, 2010; Bridge, et al., 2015; Harris & Madden, 2002; Ng, Ho, Chan, Yong, & Yeo, 2017; Weiss, 1985). For example, impulsive behavior characterizes drug abusers who are unable to delay gratification (Grant, & Chamberlain, 2014; Reynolds, 2006) as well as children diagnosed with ADHD who choose smaller-sooner reinforcers over larger-later reinforcers (Winstanley, Eagle, & Robbins, 2006). Despite this range of applications (Evenden, 1999; Mitchell & Potenza, 2014; Winstanley, Eagle, & Robbins, 2006), impulsivity does not seem to be a unitary construct: it can be examined in terms of “cognitive impulsivity” and/or “motor impulsivity” (Evenden, 1999). The former sort of impulsivity, often termed “impulsive choice,” consists of choosing a smaller, immediate rewards over larger rewards that are more distant (Ainslie, 1975). The latter sort of impulsivity, often called “impulsive action” is the inability to withhold a pre-potent response (cf. Barkley, 1997; Chambers, Garavan, & Bellgrove, 2009; Winstanley, Eagle, & Robbins, 2006).

Impulsive choice in animals has been studied with concurrent schedules that arrange choices between smaller-sooner vs. larger-later reinforcers (e.g., Aparicio, Hennigan, Mulligan, & Alonso-Alvarez, 2019; Fox, Hand, & Reilly, 2008), whereas impulsive action has been studied either with differential-reinforcement-of-low-rate (DRL) schedules or with autoshaping. For example, on DRL schedules that range from 2 to 60 s, spontaneously hypertensive rats (SHR) learn to inhibit the responses that cause the omission of reinforcers (Bull, Reavill, Hagan, Overend & Jones, 2000). By contrast, rats injected with 5,7-dihydroxytyptamine on the dorsal or median raphe nuclei, show poor inhibitory control of responding on DRL 20-s schedules (Fletcher, 1995). Autoshaping procedures measure the inability to learn associations between stimuli and negative response-consequence contingencies more explicitly than DRL schedules (Kearns, Gómez-Serrano, Stanley, & Riley, 2006; Tomie, Aguado, Pohorecky, & Benjamin, 1998; Winstanley, Dailley, Theobald, & Robbins, 2004). Autoshaping (Brown & Jenkins, 1968) or sign tracking (Hearst & Jenkins, 1974) methods have proved ideal for this purpose, because the organism’s behavior is not required to produce the reinforcer. For example, autoshaping procedures have been successfully used to train rats to approach, make contact, and press on a lever paired with food after a delay of 15 s (Kearns, Gómez-Serrano, Weiss, & Riley, 2006). Responding persists even when contacting that stimulus causes the omission of the reinforcer (i.e., negative automaintenance: Williams & Williams, 1969), which suggests that autoshaped responding is impulsive behavior (Monterroso & Ainslie, 1999).

By focusing on impulsive choice and/or impulsive action, basic laboratory research has already documented a plausible genetic basis of impulsivity in inbred strains of mice (Isles, Humby, Walters, & Wilkinson, 2004) and rats (Anderson & Woolverton, 2005; Perry, Nelson, Anderson, Morgan, & Carroll,



2007; Wilhelm & Mitchell, 2008; 2009). It seems, therefore, that some aspects of impulsivity are measurable behavioral traits present in both human and nonhuman animals (Dalley, Mar, Economidou, & Robbins, 2008; Evenden, 1999; Ho, Mobini, Chiang, Bradshaw, & Szabadi, 1999). In this context, spontaneously hypertensive (SHR) and Lewis (LEW) rats have been proposed as animal models of the impulsivity that characterizes ADHD (e.g., Mook, Jeffery & Neuringer, 1993; Paule, Rowland, Ferguson, Chelonis, Tannock, Swanson, & Castellanos, 2000; Russell, de Villiers, Sagvolden, 2000, 2001; Winstanley, Dailey, Theobald, & Robbins, 2003; Winstanley, Theobald, Dalley, Cardinal, & Robbins, 2006; Wogar, Bradshaw, & Szabadi, 1993).

The SHR is so far the most prevalent model of ADHD (Sagvolden & Johansen, 2011), but some evidence also supports the use of the LEWs as an alternative (Garcia & Kirkpatrick, 2013). The cumulative body of evidence shows that both strains exhibit delay discounting (Anderson & Diller, 2010; Anderson & Woolverton, 2005; Aparicio, Elcoro, & Alonso-Alvarez, 2015; Aparicio, Hughes, & Pitts, 2013; Fox, Hand, & Reilly, 2008; Garcia Lecumberri, Torres, Martin, Crespo, Miguens, Nicanor, Higuera-Matas, & Ambrosio, 2010; Hand, Fox, & Reilly, 2009; Huskinson, Krebs, & Anderson, 2012; Madden, Smith, Brewer, Prinkston, & Johnson, 2008; Stein, Pinkston, Brewer, Francisco, & Madden, 2012). The SHR and the LEW differ from each other in indices of anxiety-related behavior, with the LEWs showing higher basal indices of anxiety-related behavior (e.g., Ramos, Berton, Mormede, & Chaouloff, 1998; Ramos, Kangerski, Basso, Da Silva Santos, Assreuy, Vedrusco, & Takahashi, 2002), but SHRs and LEWs do not seem to differ from each other in overall level of activity (Bruske, Vendruscolo, & Ramos, 2007). Which strain of rats serves as better model of impulsive action remains unclear. The SHR chooses more impulsively on delay discounting tasks than its normotensive control, the WKY (e.g., Aparicio, et al., 2019), but the LEW also chooses more impulsively than its control, the Fisher 344 rat (e.g., Garcia & Kirkpatrick, 2013; Kirkpatrick, Marshall, & Smith, 2015). Also, both SHRs and LEWs are capable of inhibiting responses that cause the omission of reinforcers (Bull et al., 2000; Kearns, et al., 2006).

To summarize, data exist showing that: (1) the LEWs and the SHRs display impulsive behavior on a variety of tasks; (2) both strains undergo irregularities in dopamine (DA) and serotonin (5-HT) activity in some areas of the brain; (3) the SHRs and the LEWs are potential rodent models of ADHD choosing impulsively on delay discounting tasks; (4) the SHR and the LEW do not differ from each other in levels of activity; and (5) both strains are able of inhibiting responses causing the omission of food reinforcer. Based on these findings and the hypothesis that autoshaped responding is a form of impulsive behavior, one may predict that: (a) there will be no differences in lever pressing acquisition between the SHR and the LEW on a positive automaintenance procedure; (b) both strains will inhibit responses that cause the omission of food in a negative automaintenance procedure; and (c) both strains will develop similar restoration of responding in the redetermination phase of the positive automaintenance procedure. By contrast, if motor impulsivity affects only response acquisition, and if a more complex process of attention, learning, or memory is needed to inhibit the responses that lead to reinforcer, then the LEWs will develop more inhibitory control of responses than the SHRs due to LEW's better sustained attention (Diana, 2002), better memory (Meneses, Castillo, Ibarra, & Hong 1996), and better learning ability (Meneses & Hong, 1998).

The present study evaluated these hypotheses by implementing three phases of automaintenance (positive, negative, then again positive) in SHRs and LEWs. The response rates emitted on two levers paired with food in trials of positive and negative automaintenance were compared among strains. To this end, we used a 4-parameter logistic (4PL) nonlinear regression model:



$$y = \frac{A_1 - A_2}{1 + (x/x_0)^s} + A_2 \quad (1)$$

where x is the independent variable (automaintenance trial number), y the dependent variable (response rate), A_1 the lower asymptote of the response rate, A_2 the higher asymptote of the response rate, s the slope of the curve, and x_0 its inflection point.

Method

Subjects

The subjects were sixteen experimentally naïve male rats (Charles River, Wilmington, MA), eight SHR_s numbered 201 to 208 and eight LEW_s numbered 101 to 108, of approximately 93 days old at the beginning of the experiment. Upon arrival, the rats were individually housed in plastic cages with water permanently available in a temperature-controlled vivarium maintaining a 12:12-h light / dark cycle (lights on at 0700). Animals were maintained on some ad libitum feeding regimen of Purina Chow (Mazuri) for three weeks, allowing habituation to the colony room. The weights of the SHR_s ranged from 268 to 315 g and those of LEW_s from 307 to 340 g. On the day before the experiment started, the feeders of all cages were emptied, and the rats were placed on a regimen of food restriction (no weight reduction was attempted). The sessions were conducted daily at about the same time (12:00), and each rat received a supplementary feeding of Purina® Chow of approximately 10 g (+/- 2 g) at the end of each session.

Apparatus

Eight Coulbourn Instruments® (Whitehall, PA) modular chambers for rats (E10-11R TC), 30 cm x 33 cm x 25 cm, were contained in sound-attenuating boxes (E10-23), 79 cm x 51 cm x 53 cm, equipped with exhaust fans. The front and back walls of each chamber were made of stainless steel, the sidewalls and the ceiling of Plexiglas, and the floor of stainless steel (E10-18NS). Two retractable levers (E23-17RA), 3.3 cm x 1.5 cm, were mounted on each front panel 6 cm above the floor; the edge of each lever was 2.3 cm from its respective left and right sidewall. Lever extension / retraction required approximately 1 s. Two 24-V DC stimulus lights (H11-03R) were installed 3.5 cm above the levers. A dry-food dispenser (H14-23R), positioned behind the front wall, delivered 45-mg grain-based pellets (BioServ, F0165) into a 3 cm x 4 cm hopper (E14-01R) centered between the retractable levers, 4.5 cm from the left- and 4.5 cm from the right-lever at 2 cm from the floor. A third non-retractable or back lever (H21-03R) 3.4 cm x 1.5 cm, was centered on the back wall and mounted 6.0 cm above the floor. All levers required a force of approximately 0.2 N to register a response. A 24-V DC house light (H11-01R) centered on the rear wall, 19 cm above the back lever, provided the illumination of the chamber. A 2.6 cm x 4.0 cm speaker (H12-01R), mounted on the rear wall at 20 cm from the floor, 1 cm from the left sidewall and 1 cm below the ceiling, was connected to a white noise generator (E12-08) providing a constant white noise. The experimental events were programmed, and the data were recorded by Windows®-controlled computers executing Coulbourn Instruments® software (Graphic State Notation, version 3.03) interfacing equipment operating at .01-s resolution. All animals used and procedures implemented in this study were approved by Salem State University, Institutional Animal Care and Use of Laboratory Animals (IACUC 011817-2), according to the guidelines of NIH (No. 8023). There is no conflict of interest that should be reported in this manuscript.

Procedure



The general procedure used two response-independent variable time 50 s schedules operating concurrently (Conc VT 50 s VT 50 s) to arrange 60 trials in each session. In each trial, only one lever (the left- or the right-lever) was extended into the chamber with the light above it turned on, signaling the trial lasting 15 s. The other inactive left lever or right lever remained retracted from the chamber with the light above it turned off. The inter-trial interval, averaging 50 s and ranging from 2 to 120 s, was set by a constant-probability algorithm (Catania & Reynolds, 1968). During the inter-trial interval, the lever for the next trial (either the same or the opposite left-or right-lever) was randomly selected and extended into the chamber with the light above it turned on for the next 15-s trial. A nonretractable lever was always available in the back wall of the chamber. It was not paired with food delivery but presses on that lever were recorded during the session.

Lever-pressing acquisition. For 30 consecutive sessions, all rats were directly exposed to trials of a positive automaintenance procedure like that introduced by Williams and Williams (1969, Experiment III). Each session consisted of 60 trials, 30 trials with the left- and 30 trials with the right-lever. All trials lasted 15 s, regardless of whether the rats pressed on the extended left- or right-lever. Lever presses on the extended lever during the 15 s trial did not finish with the trial, nor did they produce food immediately. Only at the end of each 15 s trial, 1 food pellet was delivered into the hopper, causing the active lever to retract from the chamber, turning off the light above it, and signaling the beginning of the inter-trial interval. Each session lasted 60 minutes or ended when the 60 trials were completed.

Lever-pressing inhibition. The SHRs and LEWs were exposed to 31 consecutive sessions of the negative automaintenance procedure. Each session consisted of 60 trials arranging a negative contingency between lever presses and food deliveries. Each trial lasted 15 s in the absence of responses. A single press on the extended lever during the 15 s of the trial turned off the light above it, retracted the lever from the chamber, and canceled the delivery of the food pellet that was scheduled to occur at the end of the trial. Lever presses did not alter the inter-trial interval, nor did they affect the onset of the next trial.

Lever-pressing restoration. All rats were re-exposed to the positive automaintenance procedure for another 30 consecutive sessions. Each session consisted of 60 trials identical to the trials that the SHRs and the LEWs experienced in the acquisition of lever pressing. Accordingly, the present study implemented an ABA reversal design to analyze the acquisition of responses on two levers paired with food in trials arranged by a positive automaintenance procedure (A), the inhibitory control of lever presses causing the omission of food in trials arranged by a negative automaintenance procedure (B), and the restoration of lever presses in redetermination trials of a positive automaintenance procedure (A).

Data Analysis

The data from all sessions of each condition were analyzed. The number of responses that each rat emitted on the left lever, right lever, and back lever were counted separately to compute the responses rates per minute corresponding to each session. Accordingly, the response rates on the left lever were computed with the number responses emitted on that lever during the session, divided by the times of all trials where the left lever was extended into the chamber. The response rates on the right lever were computed with the number responses emitted on that lever during the session, divided by the total time during which the left lever was extended into the chamber. Lastly, the response rates on back-lever response were computed with the number responses emitted on that lever during the session, divided by the duration of the session. Between strains differences in response rates of responses were assessed with



nonparametric Mann-Whitney U-tests at the alpha level of 0.05. Nonlinear regression analyses and Mann-Whitney U-tests were implemented with Origin®.

Results

Lever pressing acquisition. Figure 1 shows the response rates per minute that the SHRs (left graphs) and the LEWs (right graphs) emitted on the left lever (LL), right lever (RL), and back lever (BL) in 30 sessions of positive automaintenance procedure. The unfilled symbols stand for response rates emitted by the individuals and the filled symbols with error bars for the means of response rates produced by the group of SHRs (circles) and the group of LEWs (squares). The line is the best fit of Eq. 1 to the means of response rates. Note the base-10 logarithmic scale on the y-axis. Table shows the results from Eq. 1 fitting the groups' means of response rates.

Table 1. Parameters from Eq. 1 fitting mean data produced by the SHRs and LEWs.

Lever	Strain	A_1	SE	A_2	SE	x_0	SE	s	SE	R^2
<i>Acquisition</i>										
Left	SHR	0.29	0.04	37.04	10.46	22.58	5.30	2.45	0.28	0.945
	LEW	0.02	0.04	19.16	1.48	12.35	1.18	2.44	0.21	0.975
Right	SHR	0.18	0.05	111.63	171.84	40.51	27.35	3.19	0.63	0.875
	LEW	0.02	0.01	7.25	0.69	10.64	0.89	4.37	0.60	0.910
Back	SHR	0.19	0.02	1.12	0.22	19.01	3.00	3.52	0.89	0.910
	LEW	0.01	0.00	0.21	0.02	9.97	1.02	3.46	0.78	0.890
<i>Inhibition</i>										
Left	SHR	58.43	21.21	0.91	0.20	4.77	0.86	6.97	3.09	0.276
	LEW	3.07	0.60	0.52	0.05	11.58	0.90	9.92	4.23	0.458
Right	SHR	17.12	4.71	1.22	0.14	7.80	0.56	20.18	12.63	0.290
	LEW	2.E+03	3.E+05	0.28	0.05	0.06	5.36	1.78	0.58	0.613
Back	SHR	1.20	0.06	6.50	1.81	21.59	3.96	4.22	1.13	0.817
	LEW	0.14	0.01	0.36	0.04	20.91	1.92	7.96	3.87	0.767
<i>Restoration</i>										
Left	SHR	-6.E+00	2.E+02	5.E+02	6.E+04	2.E+06	1.E+09	0.24	3.12	0.755
	LEW	2.38	0.42	10.10	3.24	16.80	6.07	2.66	1.32	0.758
Right	SHR	-1.E+03	6.E+05	24.21	28.09	0.00	0.11	0.46	3.18	0.393
	LEW	0.14	0.27	1.22	1.47	13.88	31.15	1.12	1.74	0.593
Back	SHR	2.05	0.52	3.40	0.16	3.63	1.56	4.62	7.60	0.351
	LEW	38.11	7.E+04	0.20	0.19	0.00	0.51	0.62	4.29	0.118

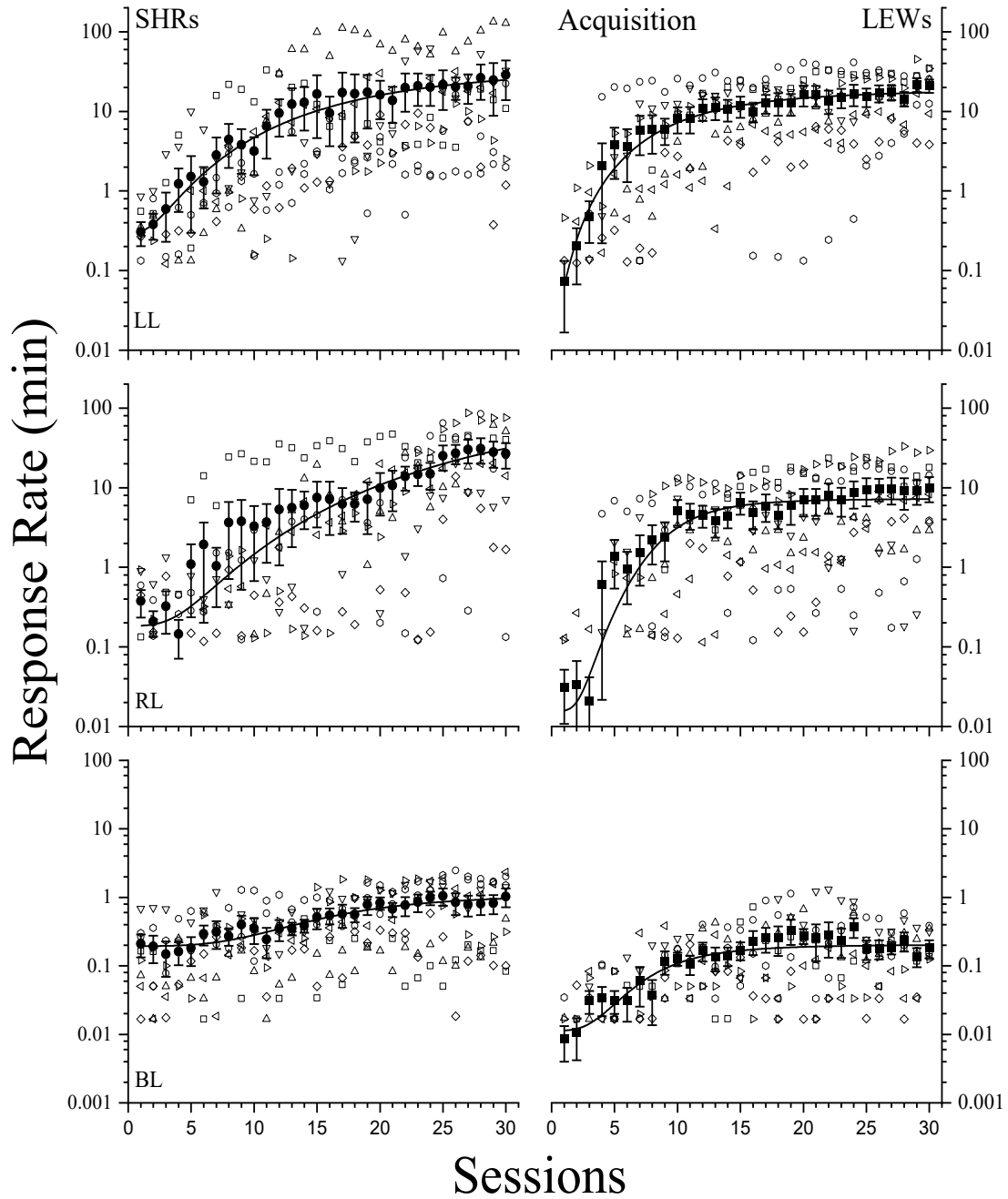


Figure 1. Acquisition of lever pressing. Response rates per min emitted on the back lever (BL), left lever (LL), and right lever (RL) as a function of the number sessions of the positive auto-maintenance procedure. Unfilled symbols stand for individual data and the filled circles and squares with error bars for group data of SHRs (left graphs) and LEWs (right graphs), respectively. The line is the best fit of Eq. 1 to the mean of the group.

In sessions 1 to 30 of positive automaintenance procedure, the SHRs and the LEWs developed similar acquisition and maintenance of lever presses on the left lever paired with food. The SHRs’ means of response rates increased from 0.31 to 28.7 responses per minute and the LEWs’ means of response rates increased from 0.07 to 21.1 responses per minute. An analysis of individual data revealed that the



LEWs (Mdn = 7.33) responded more ($U = 25276.5$, $p = .02$) than the SHRs (Mdn = 2.89). Eq. 1 fitted the mean data from the SHRs and LEWs well, accounting for changes in the SHRs' response rates along sessions ($R^2 = .945$ and $.975$, respectively). The lower ($A_1 = 0.29$) and higher ($A_2 = 37.04$) asymptote of response rates that Eq. 1 estimated for the mean data from the SHRs were larger than the lower ($A_1 = 0.02$) and higher ($A_2 = 19.16$) asymptote of response rates that it estimated for the mean data from the LEWs. The slope of the curve fitting the SHRs' means of response rates ($s = 2.45$), was like the slope of the curve fitting LEWs' means of response rates ($s = 2.44$), showing similar trends in response rates. The inflection points of the curves indicated that LEWs' means of response rates ($X_0 = 12.35$) progressed to asymptotic level sooner than the SHRs' means of response rates ($X_0 = 22.58$).

The SHRs developed faster acquisition of lever pressing and emitted more responses on the right lever than the LEWs. The SHRs' means of response rates increased from 0.37 to 26.8 responses per minute and the LEWs' mean of response rates from 0.03 to 10.1 responses per minute. Eq. 1 fitted the mean data from the SHRs ($R^2 = .875$) and the LEWs ($R^2 = .910$) well. Estimates of the lower ($A_1 = 0.18$) and higher ($A_2 = 111.63$) asymptote of response rates for the SHRs, were larger than those estimated for the LEWs (0.02 and 7.25, respectively). However, the analysis of individual data showed that the SHRs' response rates (Mdn = 1.23) were like ($U = 29712.5$, $p = .55$) the LEWs' response rates (Mdn = 1.97). The slope of the curve fitting the LEWs' response rates ($s = 4.37$) was steeper than the slope of the curve ($s = 3.19$) fitting the SHRs' response rates, indicating that the LEWs' response rates increased faster than the SHRs' response rates. Thus, the LEWs' response rates progressed to asymptotic level ($X_0 = 10.64$) sooner than the SHRs' response rates ($X_0 = 40.51$).

The SHRs pressed the back lever not paired with food, more than the LEWs. The SHRs' means of response rates increased from 0.2 to 1.0 responses per minute and the LEWs' means of response rates from 0.01 to 0.18 responses per minute. The responses emitted by the individuals revealed that the SHRs' response rates (Mdn = 0.31) were higher ($U = 43393.5$, $p < .001$) than the LEWs' response rates (Mdn = 0.08). Eq. 1 fitted the mean data from the SHRs' ($R^2 = .910$) and LEWs' ($R^2 = .890$) well. The slope of the curve fitting the SHRs' response rates ($s = 3.52$) was like that fitting the LEWs' response rates ($s = 3.46$), indicating similar trends in their response rates. Estimates of the lower ($A_1 = 0.19$) and higher ($A_2 = 1.12$) asymptote of response rates for the SHRs, were larger than estimates corresponding to the LEWs' response rates (0.01 and 0.21, respectively). Yet, the LEWs' response rates progressed to asymptotic level ($X_0 = 9.97$) sooner than the SHRs' response rates ($X_0 = 19.01$).

Lever pressing inhibition. Both strains of rats developed inhibitory control of lever pressing along negative automaintenance trials. Figure 2 plots the response rates that the SHRs and the LEWs emitted on the left lever, right lever, and back lever in 31 sessions of negative automaintenance procedure.

On the left lever, mean response rate for the SHRs decreased from 65.6 to 2.1 responses per minute and for the LEWs mean response rate decreased from 30.7 to 0.6 responses per minute (the filled circles). The analysis of individual data from each strain (unfilled symbols), revealed that the SHRs' response rates (Mdn = 1.07) were higher ($U = 27334.5$, $p = .006$) than the LEWs' response rates (Mdn = 0.41). Eq. 1 fitted the mean data from the SHRs ($R^2 = .276$) and the LEWs ($R^2 = .458$), accounting for more variability in the response rates emitted by the latter than in the response rates emitted by the former strain.

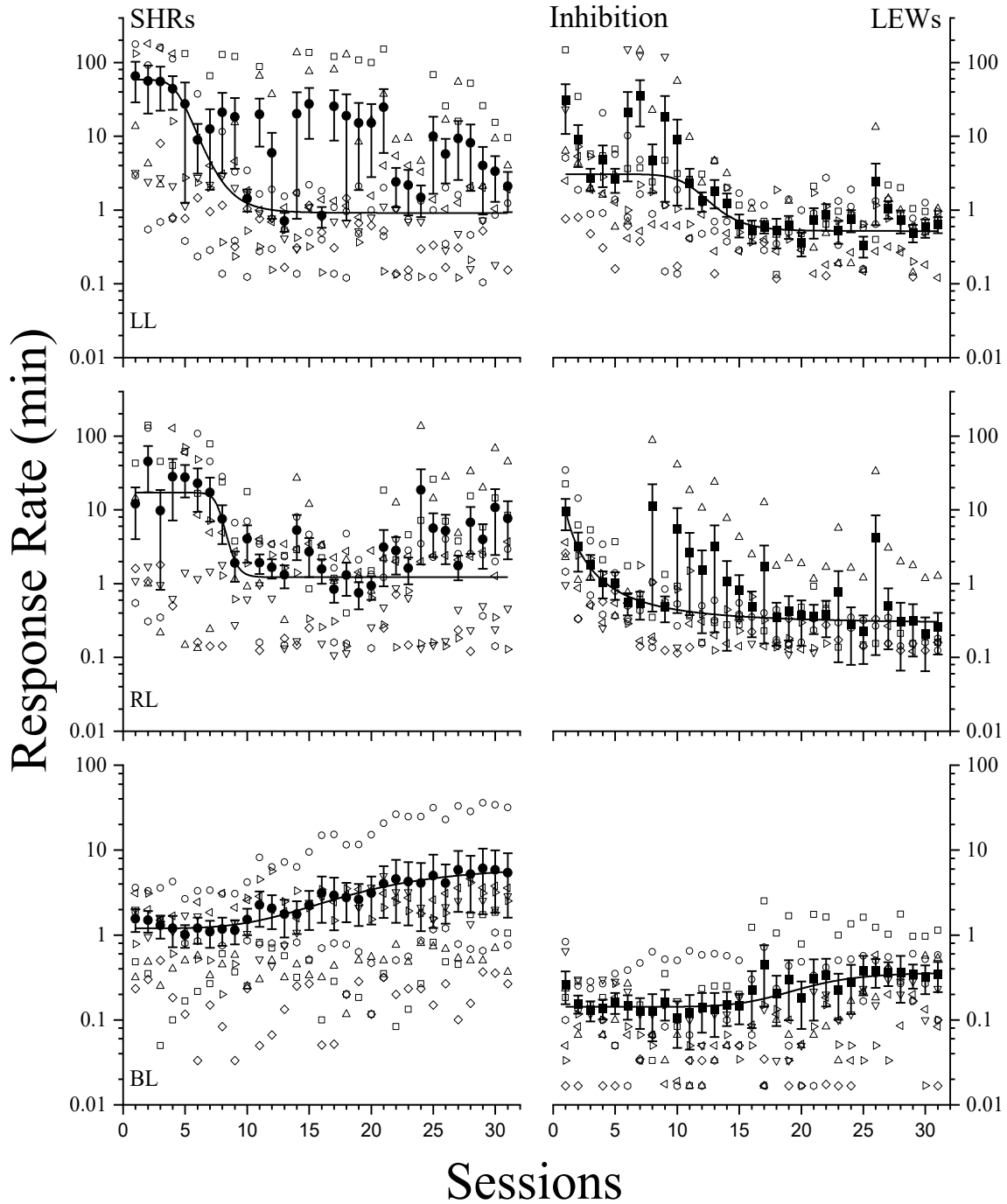


Figure 2. Inhibition of lever pressing. Response rates per min emitted on the back lever (BL), left lever (LL), and right lever (RL) as a function of the number sessions of the negative auto-maintenance procedure. Other details as in Fig. 1.

The slope of the curve fitting the LEWs' response rates ($s = 9.92$) was steeper than the slope of the curve fitting the SHRs' response rates ($s = 6.97$), indicating that the LEWs' response rates decreased faster than the SHRs' response rates. The SHRs' response rates advanced to asymptotic level ($X_0 = 4.77$) sooner than the LEWs' response rates ($X_0 = 11.58$). Estimates of the starting ($A_1 = 58.4$) and ending ($A_2 = 0.91$) points of the curve fitting the response rates that the SHRs emitted on the left lever, were larger



than those Eq. 1 estimated for the response rates the LEWs emitted on the left lever ($\mathcal{A}_1 = 3.07$ and $\mathcal{A}_2 = 0.52$, respectively), suggesting that the SHRs developed less inhibitory control of responses than that the LEWs attained. Yet, there were no between strain differences ($U = 28336$, $p = 0.1$) in the number of food pellets that the SHRs (Mdn = 21) and the LEWs (Mdn = 22) obtained with the left lever in 30 sessions of negative automaintenance procedure.

On the right lever, mean response rate for the SHRs decreased from 12.1 to 7.6 responses per minute and for the LEWs mean response rate decreased from 9.7 to 0.3 responses per minute (middle graphs). The analysis of individual data revealed that the SHRs' response rates (Mdn = 1.12) were higher ($U = 38429.5$, $p < .001$) than the LEWs' response rates (Mdn = 0.23). Eq. 1 fitting the mean data from the LEWs and SHRs, accounted for more variability in the LEWs' response rates ($R^2 = .613$) than in the SHRs' response rates ($R^2 = .290$). The LEWs' response rates progressed to asymptotic level ($X_0 = 0.06$) sooner than the SHRs' response rates ($X_0 = 7.80$). The slope of the curve fitting the SHRs' response rates ($s = 20.18$) was steeper than that fitting the LEWs' response rates ($s = 1.78$), indicating the SHRs' response rates decreased abruptly and the LEWs' response rates decreased gradually. Eq. 1 estimated that the lower asymptote of the LEWs' response rates ($\mathcal{A}_1 = 2E+03$) was larger than that of the SHRs' response rates ($\mathcal{A}_1 = 17.12$). Yet, Eq. 1 estimated that the higher asymptote of the LEWs' response rates ($\mathcal{A}_2 = 0.28$) was smaller than that of the SHRs' response rates ($\mathcal{A}_2 = 1.22$). Thus, the number of food deliveries that the LEWs obtained with the right lever (Mdn = 26) was greater ($U = 21557$, $p < .001$) than that the SHRs obtained (Mdn = 21), with the LEWs showing more inhibitory control of responses than the SHRs.

On the back lever, mean response rate for the SHRs increased from 1.6 to 5.4 per minute and for the LEWs mean response rate increased from 0.26 to 0.35 responses per minute. The analysis of individual data revealed that the SHRs' response rates (Mdn = 1.06) were higher ($U = 54431.5$, $p < .001$) than the LEWs' response rates (Mdn = 0.10). Eq. 1 fitted the LEWs' means of response rates ($R^2 = .767$) and the SHRs' means of response rates ($R^2 = .817$) well. The slope of the curve fitting the LEWs' means of response rates ($s = 7.96$), was steeper than the slope of the curve fitting the SHRs' means of response rates ($s = 4.22$), indicating that the LEWs' means of response rates increased faster than the SHRs' means of response rates. Thus, the LEWs' response rates advanced to asymptote level ($X_0 = 20.91$) sooner than the SHRs' means of response rates ($X_0 = 21.59$). Eq. 1 estimated that the SHRs' lower ($\mathcal{A}_1 = 1.20$) and higher ($\mathcal{A}_2 = 6.50$) asymptote of response rates, were larger than those corresponding to the LEWs' (0.14 and 0.36, respectively), indicating that the SHRs emitted more responses on the back lever than the LEWs.

Lever-pressing restoration. In the last, positive automaintenance, phase the SHRs' responses rates on the left lever, right lever, and back lever were higher than the LEWs' response rates, indicating that the SHRs reinstated higher responses on the levers than the LEWs. Figure 3 plots the response rates that the SHRs and the LEWs emitted on the left lever, right lever, and back lever in 30 sessions of the redetermination of positive auto-maintenance procedure.

On the left lever, mean response rate for the SHRs increased from 5.7 to 25.5 responses per minute and for the LEWs mean response rate increased from 3.2 to 11.7 responses per minute. The analysis of the response rates that the individuals emitted on the left lever, revealed that the SHRs' response rates (Mdn = 5.49) were higher ($U = 35579$, $p < .001$) than the LEWs' response rates (Mdn = 0.98). Eq. 1 fitted the mean data from the SHRs ($R^2 = .755$) and LEWs ($R^2 = .758$) well. The slope of the curve fitting the LEWs' means of response rates ($s = 2.66$) was steeper than the slope of the curve fitting the SHRs' means of response rates ($s = 0.24$), indicating that the LEWs' response rates increased faster than the SHRs' response rates.

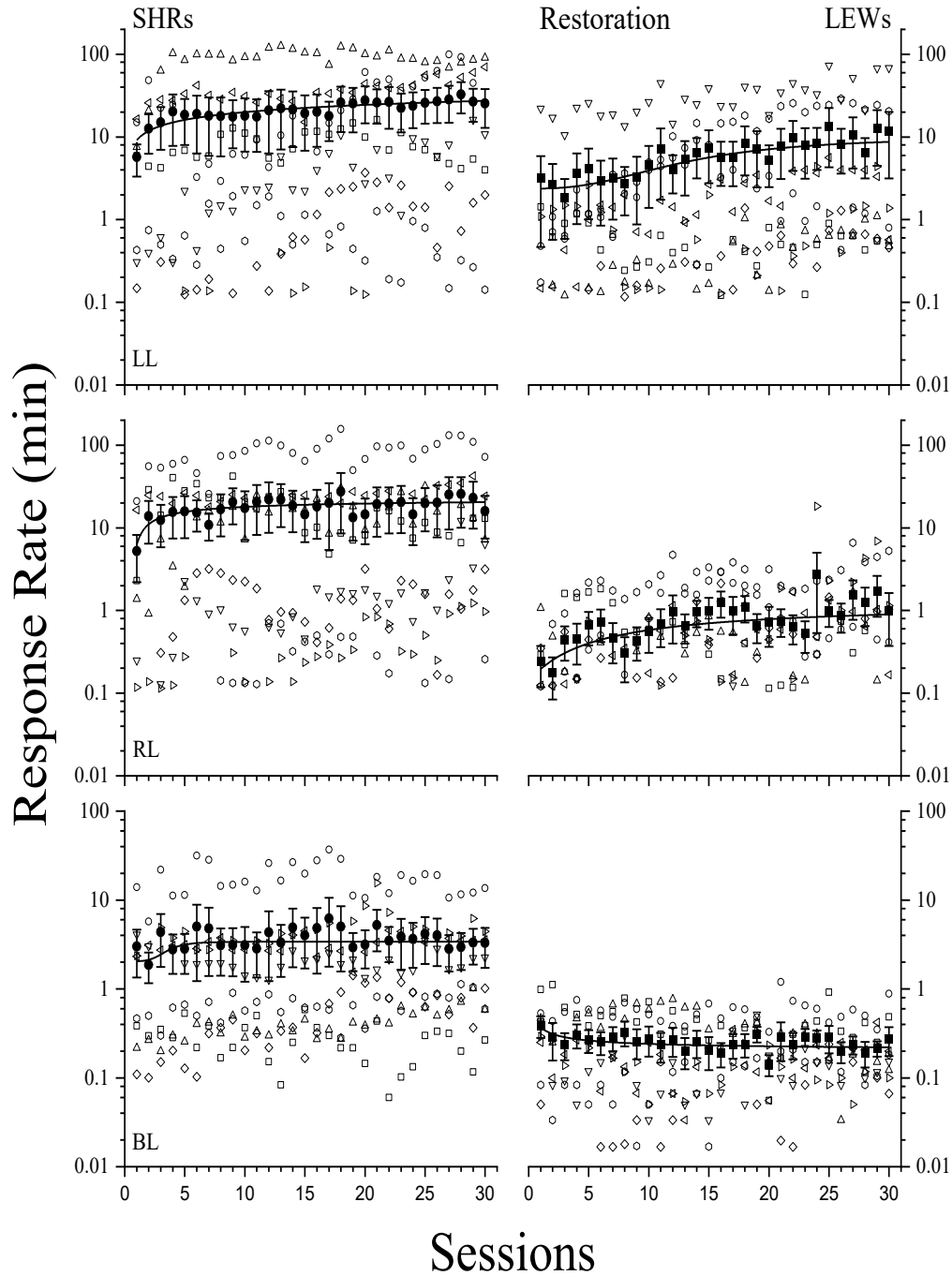


Figure 3. Restoration of lever pressing. Response rates per min emitted on the back lever (BL), left lever (LL), and right lever (RL) as a function of the number sessions of the re-determination to the positive auto-maintenance procedure. Other details as in Fig. 1.

Also, the LEWs' response rates progressed to asymptotic level ($X_0 = 16.8$) sooner than the SHRs' response rates ($X_0 = 2E+06$). The lower asymptote of the response rates that Eq. 1 estimated for the SHRs ($A_1 = -6E+00$) was smaller than that it estimated for the LEWs ($A_1 = 2.38$). Yet, the SHRs emitted more responses on the left lever than the LEWs, with Eq. 1 estimating that the lower asymptote of



response for the SHRs ($\lambda_2 = 5E+02$) was considerably larger than that corresponding to the LEWs ($\lambda_2 = 10.10$).

On the right lever, mean response rate for the SHRs increased from 5.2 to 15.9 responses per minute and for the LEWs mean response rate increased from 0.2 to 1.0 response per minute. Also, the response rates that the individual SHRs emitted on the right lever (Mdn = 3.2) were higher ($U = 44374$, $p < .001$) than the response rates that the individual LEWs emitted (Mdn = 0.41) on that lever. Eq. 1 fitted the mean data from the SHRs and the LEWs, accounting for more variability in the LEWs' response rates ($R^2 = .593$) than in the SHRs' response rates ($R^2 = .393$). The slope of the curve fitting the LEWs' response rates ($s = 1.12$) was steeper than the slope of the curve fitting the SHRs' response rates ($s = 0.46$), showing that the LEWs' response rates increased faster than the SHRs' response rates. However, the SHRs' response rates reached asymptotic level ($X_0 = 0$) sooner than the LEWs' response rates ($X_0 = 13.88$). The lower asymptote of response rates that Eq. 1 estimated for the SHRs ($A_1 = -1E+03$) was smaller than that it estimated for the LEWs ($A_1 = 0.14$). But the higher asymptote of response rates that Eq. 1 estimated for the SHRs ($\lambda_2 = 24.21$) was larger than that it estimated for the LEWs ($\lambda_2 = 1.22$), showing that the SHRs emitted more responses on the right lever than those the LEWs emitted.

On the back lever, mean response rate for the SHRs increased from 2.99 to 3.29 responses per minute, contrasting with mean response rate for the LEWs that decreased from 0.39 to 0.27 responses per minute. The analysis of individual data revealed that the SHRs' response rates (Mdn = 1.34) were higher ($U = 50407.5$, $p < .001$) than the LEWs' response rates (Mdn = 0.18). Eq. 1 fitted the SHRs' means of response rates ($R^2 = .350$) and the LEWs' means of response rates ($R^2 = .118$), accounting for more variability in the SHRs' response rates than in the LEWs' response rates. The slope of the line fitting the SHRs' means of response rates ($s = 4.62$) was steeper than the slope of the line fitting the LEWs' means of response rates ($s = 0.62$), indicating that SHRs' response rates increased faster than the LEWs' response rates. Thus, the LEWs' response rates advanced to asymptotic level ($X_0 = 0$) sooner than the SHRs' response rates ($X_0 = 3.63$). The SHRs' lower asymptote of response rates ($\lambda_1 = 2.05$) was smaller than the LEWs' lower asymptote of response rates ($\lambda_1 = 38.11$), and the SHRs' higher asymptote of response rates ($A_2 = 3.40$) was larger than the LEWs' higher asymptote of response rates ($A_2 = 0.20$), suggesting that the SHRs restored the responses on the back lever faster than the LEWs.

Discussion

The acquisition of responses on two levers paired with food delivery, and the inhibition of responses causing the omission of food, were analyzed in the case of SHRs and LEWs exposed to positive and negative automaintenance trials (Williams & Williams, 1969). By including an initial phase of positive automaintenance, we assessed the possibility that the SHRs and the LEWs do not differ from each other with respect to motor activity in novel environments (Bruske, Vendurscolo, & Ramos, 2007). By including a phase of negative automaintenance, we confirmed that both strains are able of inhibiting lever presses causing the omission of food (e.g., Bull, Reavill, Hagan, Overend, & Jones, 2000; Kearns, Gomes-Serrano, Stanley, & Riley, 2006). Based on research showing that the SHR undergoes irregularities in glutamate, dopamine, and norepinephrine activities in some areas of the brain (e.g., Heal, Smith, Kullkarni, & Rowley, 2008), whereas the LEW rat bears low levels of dopamine (DA) and serotonin (5-HT) activities (e.g., Flores, Wood, Barbeau, Quiron, & Srivastava, 1998; Lindley, Bengoechea, Wong, & Schatzberg, 1999; Selim & Bradberry, 1996), we predicted the following: (1) The SHRs and LEWs will show similar acquisition of responses on two levers paired with food in trials of a positive automaintenance procedure;



(2) The LEWs will develop more inhibitory control of responses causing the omission of food reinforcers in trials of a negative automaintenance procedure than the SHRs, due to learning deficits (Meneses & Hong, 1998) and poor sustained attention characterizing the SHRs (Diana, 2002); (3) the SHRs will show faster restoration of lever presses in redetermination trials of positive automaintenance procedure than the LEWs, due to motor impulsivity (Winstanley, Eagle, & Robbins, 2006); and (4) both strains will press on the back lever, because the food delivered with the left and right levers will act as a phylogenetically important event to induce food related activity (Baum, 2012).

The SHRs and the LEWs developed similar acquisition of responses on two levers paired with food in trials of positive automaintenance procedure (Fig. 1). All rats pressed on the left lever and the right lever in the first session of positive automaintenance procedure, with response rates on both levers that gradually increased with increasing sessions of training. Eq.1 fitted the mean data from both strains well, estimating that the lower and higher asymptote of the response rates that the SHRs emitted on the left lever and the right lever were larger than those corresponding to the LEWs' response rates. Thus, the idea that the SHRs and the LEWs do not differ from each other in motor activity performing on novel settings (Bruske, Vendurscolo, & Ramos, 2007) is not supported by the present results showing that the response rates that the SHRs maintained on the left and right levers are higher than the response rates that the LEWs maintained. It is concluded that the SHRs and the LEWs developed similar acquisition of lever-pressing on two levers paired with food, but the SHRs' response rates on the levers were higher than the LEWs' response rates, indicating more motor activity in the SHRs than in the LEWs. Overall the present results are consistent with those documented in studies that used a similar procedure to train LEWs and F344s to press on a lever signaling food that was delivered 15 s after the insertion of that lever into the chamber (Kearns, Gómez-Serrano, Weiss, & Riley, 2006); supporting the idea that nonhuman animals detect, approach, and make contact with brief-localized stimuli that are paired with food (Brown & Jenkins, 1968; Aparicio & Mario, 2014), food and water (Hearst & Jenkins, 1974), and food and cocaine (Kearns & Weiss, 2004). While sign-tracking behaviors qualify as conditioned responses elicited by conditioned stimuli, some studies suggest that sign tracking behaviors are shaped by positive reinforcement in autoshaping procedures (Wessels, 1974). For example, a response on either the left lever or the right lever at the end of the 15-s trial might be accidentally reinforced by temporal contiguity between the response and food delivery (Skinner, 1948). While this possibility was not formally analyzed in the present study, we have no evidence indicating that any response occurred at the end of the trial. The responses occurred either at the beginning of the trial or during the first 10 s of the trial, ruling out the possibility that responses are fortuitously reinforced by food delivery (Wessels, 1974). Delayed reinforcement may be more promising explanation for lever pressing acquisition in our study, with most lever presses occurring either at the beginning of the trial or before the end of the 15-s trial. Our data are consistent with the notion that lever pressing can be established with delayed reinforcement (Anderson & Elcoro, 2007; Bruner, Avila, Acuña, & Gallardo, 1998; Critchfield & Lattal, 1993; Hand, Fox, & Reilly, 2006; 2010; Lattal & Metzger, 1994; van Haaren, 1992), even when lever pressing is not explicitly shaped and the reinforcement is delayed (Lattal & Gleeson, 1990).

The LEWs developed more inhibitory control of lever presses canceling food deliveries in trials of negative automaintenance procedure, than the SHRs. The means of response rates that the SHRs emitted on the left and right levers, were higher than the means of response rates that the LEWs emitted (Fig. 2). This result was confirmed with individual data showing that the SHRs' response rates on the left and right levers were higher than the LEWs'. Thus, the autoshaped lever pressing persisted in the SHRs



and the LEWs despite the negative contingency between responses and reinforcers (Monterroso & Ainslie, 1969). However, in both strains, response rates eventually decreased along negative automaintenance sessions, supporting the notion that the SHRs and the LEWs are able of inhibiting responses causing the omission of reinforcers (Bull, Reavill, Hagan, Overend, & Jones, 2000; Kearns, Gomes-Serrano, Stanley, & Riley, 2006). Although the LEWs obtained more food reinforcers per session with the left lever than those the SHRs obtained, both strains obtained a similar number of food reinforcers per session with the right lever. Thus, the result showing that the SHRs' response rates were higher than the LEWs' response rates supports the idea that the SHR shows deficits in inhibitory control of responses (Barkley, 1997; Evenden, 1999) and limitations in the capacity to inhibit behavior (Chambers, Garavan, & Beligrove, 2009), due to learning deficits (Meneses & Hong, 1998), poor sustained attention (Diana, 2002), or memory insufficiency characterizing the SHR (Meneses, et al., 1996).

The redetermination of positive automaintenance procedure allowed us to assess the re-acquisition of lever pressing, looking for potential carry over effects of the inhibitory control of responses that the rats attained in trials arranged by negative automaintenance procedure. The negative contingency between lever pressing and the omission of food delivery was removed to study possible between strains differences in motor impulsivity, or in memory deficit. The results showed that the SHRs reinstated the response rates on the left and right levers faster than the LEWs (Fig. 3). Session 1 of the redetermination of positive automaintenance procedure showed that the SHRs' response rates on the left and right levers were higher than the LEWs' response rates, and sessions 2 to 30 showed that the SHRs' responses rates on the left and right levers increased more than the LEWs' response rates. The analysis of the response rates emitted by the individuals confirmed that the SHRs' response rates on the left and right levers were higher than the LEWs' response rates. Together, these results suggest that the LEWs showed stronger carry over effects of the inhibitory control of responses that they acquired in the sessions of negative automaintenance procedure, than the SHRs. It could be said that the SHRs developed faster re-acquisition of lever pressing in the redetermination of positive auto-maintenance procedure than the LEWs, due to motor impulsivity describing the SHRs (Winstanley, Eagle, & Robbins, 2006).

A remarkable result was that both strains of rats pressed on the back lever in sessions of positive and negative automaintenance procedures. This finding is important because the back non-retractable lever was always available in the chamber with no scheduled consequences, it did not provided food. Thus, the responses on the back lever were the product of either the rats' general motor impulsivity, or of the food deliveries themselves, acting as a phylogenetically important event that induce food related activity (Baum, 2012). These possibilities were examined with the response rates that the SHRs and the LEWs emitted on the back lever in the sessions of positive automaintenance procedure. The SHRs' means of response rates on the back lever were higher than LEWs' means of response rates (Fig. 1). This result was verified with the analysis of individual data showing that the SHRs' response rates were higher than the LEWs' response rates. Interestingly, the response rates that the LEWs emitted on the back lever in sessions of negative automaintenance procedure (Fig. 2) were lower than the response rates that they emitted on the back lever in the sessions of positive automaintenance procedure. In contrast, the response rates that the SHRs emitted on the back lever in the sessions of negative automaintenance procedure, were like the response rates that they emitted on the back lever in the session of positive automaintenance procedure. This finding suggests that the SHRs emitted high response rates on the back lever to dissipate the uncontrollable motor impulsivity to press on the left and right levers causing the omission of food reinforcers, contrasting with the LEWs that did not need to emit high response rates on the back lever to



inhibit the impulsive behavior of pressing on the left and right levers. This conclusion gained support from the redetermination of positive automaintenance procedure showing that the SHRs' response rates on the back lever were noticeably higher than the LEWs' response rates (Fig 3). Together, these findings suggest that the SHRs' motor impulsivity was higher than the LEWs' motor impulsivity, where high response rates on back lever represent the impulsive action describing the SHRs (Winstanley, Eagle, & Robbins, 2006). An alternative interpretation is that the responses on back lever were induced by the food delivered with the left and right levers, with food acting as a phylogenetically important event to induce related activity (Baum, 2012). Because induction is a process that extends on time, the food delivered in a situation contingent or no contingent upon responding, induces food related activity in that situation (Baum, 2012). However, Baum's idea of induction is like that of stimulus control, where food is a phylogenetically important event that controls behavior in the similar way to how a discriminative stimulus modulates behavior (Baum, 2012). Further research, however, is granted to clarify whether motor impulsivity, or food acting as a phylogenetical important event to induce activity, accounts for the behavior of pressing on a lever with no scheduled consequences.

Lastly, the present study showed that a 4-parameter (4PL) nonlinear model fits the autoshaping data from the SHRs and the LEWs well, providing empirical parameters to estimate the lower (A_1) and higher (A_2) asymptote of response rates, the inflection point of the curve (X_0) where response rates change to reach asymptote, and the slope of the curve (s) estimating changes in response rate. The 4-parameter nonlinear model was successfully used to assess the inhibition of responses in nonhuman animals (Elcoro, Aparicio, Kelly, and Thompson, 2016), and the present study extends its generality to analyzing the acquisition, behavioral inhibition, and restoration of responses in SHRs and LEWs. Future research using autoshaping procedures to examine the acquisition and maintenance of responses might find the empirical parameters from Eq.1 useful in assessing the effects of dopamine agonists and dopamine antagonists on impulsive behavior.

Conclusions

One contribution of the present study is to show that lever pressing acquisition in SHRs, is like that observed in LEWs responding to trials of positive automaintenance procedure. The behavior of pressing on two levers paired with food was autoshaped by successive trials of positive automaintenance procedure, with both strains of rats showing a similar process in the acquisition of lever pressing. The idea that the SHRs and the LEWs do not differ from each other in motor activity (Bruske, Vendurscolo, & Ramos, 2007), was not supported by the present results showing that the response rates that the SHRs maintained on the left and right levers, were higher than the response rates that the LEWs maintained on the left and right levers. Our second contribution is to show that both strains are able of inhibiting the responses causing the omission of reinforcers (Bull, Reavill, Hagan, Overend, & Jones, 2000; Kearns, Gomes-Serrano, Stanley, & Riley, 2006). Yet, the LEWs developed more inhibitory control of responses during negative automaintenance procedure than the SHRs developed. This result is consistent with the idea that the LEWs are able of inhibiting responses causing the omission of food reinforcers (Kearns, Gomes-Serrano, Weiss, & Riley, 2006). The SHRs developed poor inhibitory control of lever presses due to their impulsive action (Winstanley, Eagle, & Robbins, 2006), deficit in inhibitory control (Barkley, 1997; Evenden, 1999), or in the capacity to inhibit responses (Chambers, Caravan, & Belluove, 2009). These results suggest that the SHR might be a better rodent model of impulsive action than the LEW. The notion that food is a phylogenetically important event that induces activity (Baum, 2012), was supported by the present study showing that both strains of rats pressed on the back lever, even though pressing on



the back lever had no scheduled consequences. The result showing that the SHRs emitted more responses on the back lever than the LEWs suggests that pressing on that lever was facilitated in the SHRs by the motor impulsivity characterizing this strain of rats. A final contribution is to show that a 4-parameter (4PL) nonlinear model fits autoshaping data from the SHRs and the LEWs well, providing empirical measures that can be useful to assess the effects of dopamine agonists and dopamine antagonists on impulsive behavior.

References

- American Academy of Pediatrics (2000). Clinical practice guideline: diagnosis and evaluation of the child with attention-deficit/hyperactivity disorder. *Pediatrics*, *105*, 1158-1170.
- Ainslie, G. (1975). Specious reward: a behavioral theory of impulsiveness and impulsive control. *Psychological Bulletin*, *82*(4), 463-496.
- Anderson, K. G. & Elcoro, M. (2007). Response acquisition with delayed reinforcement in Lewis and Fischer 344 rats. *Behavioural Processes*, *74*, 311-318. doi.10.1016/j.beproc.2006.11.006.
- Anderson, K. G. & Diller, J. W. (2010). Effects of acute and repeated nicotine administration on delay discounting in Lewis and Fischer 344 rats. *Behavioural Pharmacology*, *21*(8), 754-764. doi.10.1097/FBP.0b013e328340a050
- Anderson, K. G. & Woolverton, W. L. (2005). Effects of clomipramine on self-control choice in Lewis and Fischer 344 rats. *Pharmacology Biochemistry and Behavior*, *80*, 387-393.
- Aparicio, C. F., Elcoro, M., & Alonso-Alvarez, B. (2015). A long-term study of the impulsive choices of Lewis and Fischer 344 rats. *Learning and Behavior*, *43*(3), 251-271. doi.10.3758/s13420-015-0177-y
- Aparicio, C. F., Hennigan, P. J., Mulligan, L. J., & Alonso-Alvarez, B. (2019). Spontaneously hypertensive (SHR) rats choose more impulsively than Wistar-Kyoto (WKY) rats on a delay discounting task. *Behavioural Brain Research*, *364*, 480-493.
- Aparicio, C. F., Hughes, C. E., & Pitts, R. C. (2013). Impulsive choice in Lewis and Fischer 344 rats: Effects of extended training. *Conductual*, *1*(3), 22-46.
- Aparicio, C. F. & Mario, C. J. (2014). Positive automaintenance in SHR and WKY rats: Faster acquisition of lever-pressing in the former strain suggests differences in impulsivity between strains. *Conductual*, *2*(3), 17-35.
- Baum, W. M. (2012). Rethinking reinforcement: Allocation, induction, and contingency. *Journal of the Experimental Analysis of Behavior*, *97*, 101-124.
- Barkley, R. A. (1997). Behavioral inhibition, sustained attention, and executive functions: constructing a unifying theory of ADHD. *Psychological Bulletin*, *121*(1), 65-94.
- Biederman, J., Petty, C. R., Evans, M., Small, J., & Faraone, S. V. (2010). How persistent is ADHD? A controlled 10-year follow-up study of boys with ADHD. *Psychiatry research*, *177*(3), 299-304.



- Bridge, J. A., Reynolds, B., McBee-Strayer, S. M., Sheftall, A. H., Ackerman, J., Stevens, J., ... & Brent, D. A. (2015). Impulsive aggression, delay discounting, and adolescent suicide attempts: effects of current psychotropic medication use and family history of suicidal behavior. *Journal of child and adolescent psychopharmacology*, 25(2), 114-123.
- Brown, P. L. & Jenkins, H. M. (1968). Auto-shaping of the pigeon's key-peck. *Journal of the Experimental Analysis of Behavior*, 11, 1-8.
- Bruner, C. A., Ávila, R., Acuña, L., & Gallardo, L. M. (1998). Effects of reinforcement rate and delay on the acquisition of lever pressing by rats. *Journal of the Experimental Analysis of Behavior*, 69, 59-75.
- Bruske, G. E., Vendruscolo, L. F., & Ramos, A. (2007). Two inbred rat strains for anxiety-related behaviors show similar levels of defensive responses to cat odor. *Behavioral and Brain Functions*, 3:17. doi:10.1186/1744-9081-3-17
- Bull, E., Reavill, C., Hagan, J. J., Overend, P., & Jones, D. N. C. (2000). Evaluation of the spontaneously hypertensive rat as a model of attention deficit hyperactive disorder: acquisition and performance of the DRL-60s test. *Behavioral Brain Research*, 109, 27-35.
- Catania, A. C., & Reynolds, G. S. (1968). A quantitative analysis of the responding maintained by interval schedules of reinforcement. *Journal of the Experimental analysis of Behavior*, 11(2), 327-383.
- Chambers, C. D., Garavan, H., & Bellgrove, M. A. (2009). Insights into the neural basis of response inhibition from cognitive and clinical neuroscience. *Neuroscience and Biobehavioral Reviews*, 33(5), 631-646. doi:10.1076/chin.7.1.32.3151.
- Critchfield, T. S. & Lattal, K. A. (1993). Acquisition of spatially defined operant with delayed reinforcement. *Journal of the Experimental Analysis of Behavior*, 59, 373-87.
- Dalley, J. W. Mar, A. C., Economidou, D., & Robbins, T. W. (2008). Neurobehavioral mechanisms of impulsivity: fronto-striatal systems and functional neurochemistry. *Pharmacology Biochemistry and Behavior*, 90(2), 250-260. doi:10.1016/j.pbb.2007.12.021.
- Diana, G. (2002). Does hypertension alone lead to cognitive decline in spontaneously hypertensive rats? *Behavioral Brain Research*, (134), 113-121.
- Elcoro, M., Aparicio, C. F., Kelly, S. P., & Thompson, T. (2016). Behavioral inhibition in rats after 6-hydroxydopamine lesions of the medial prefrontal cortex. *Psychology and Neuroscience*, 9(1), 125-138.
- Evenden, J. L. (1999). Varieties of impulsivity. *Psychopharmacology*, 146, 348-361.
- Fletcher, P. J. (1995). Effects of combined or separated 5,7-dihydroxytyptamine lesions on the dorsal or median raphe nuclei on responding maintained by a DRL 20 s schedule of food reinforcement. *Brain and Research*, 675, 45-54.
- Flores, G., Wood, G. K., Barbeau, D., Quiron, R., & Srivastava, L. K. (1998). Lewis and Fischer 344 rats: A comparison of dopamine transporter and receptors. *Brain Research*, 814, 34-40. doi:10.1016/S0006-8993(98)01011-7



- Fox, A. T., Hand, D. J., & Reilly, M. P. (2008). Impulsive choice in a rodent model of attention-deficit/hyperactivity disorder. *Behavioural Brain Research*, 187, 146-152. doi:10.1016/j.bbr.2007.09.008
- Garcia, A. & Kirkpatrick, K. (2013). Impulsive choice in four strains of rats: Evaluation of possible models of Attention-Deficit/Hyperactivity Disorder. *Behavioral Brain Research*, 238, 10-22. doi:10.1016/j.bbr.2012.10.017
- García-Lecumberri, C., Torres, I., Martín, S., Crespo, J. A., Miguens, M., Nicanor, C. Higuera-Matas, A., & Ambrosio, E. (2011). Strain differences in the dose-response relationship for morphine self-administration and impulsive choice between Lewis and Fischer 344 rats. *Journal of Psychopharmacology*, 25(6) 783-791. doi:10.1177/0269881110367444
- Grant, J. E., & Chamberlain, S. R. (2014). Impulsive action and impulsive choice across substance and behavioral addictions: cause or consequence? *Addictive behaviors*, 39(11), 1632-1639.
- Hand, D. J., Fox, A. T., & Reilly, M. P. (2006). Response acquisition with delayed reinforcement in a rodent model of attention deficit/hyperactive disorder (ADHD). *Behavioral Brain Research*, 175: 337-342.
- Hand, D. J., Fox, A. T., & Reilly, M. P. (2010). Response acquisition with signaled delayed reinforcement in a rodent model of attention deficit/hyperactive disorder (ADHD). *Behavioral Brain research*, 213: 155-160.
- Harris, A. C., & Madden, G. J. (2002). Delay discounting and performance on the prisoner's dilemma game. *The Psychological Record*, 52(4), 429-440.
- Hearst, E., & Jenkins, H. M. (1974). Sing tracking: the stimulus-reinforcer relation and directed action. Austin, TX: *The Psychonomic Society*.
- Heal, D. J., Smith, S. L., Kulkarni, R. S. & Rowley, H. L. (2008). New perspectives from microdialysis studies in freely moving, spontaneously hypertensive rats on the pharmacology of drugs for the treatment of ADHD. *Pharmacology Biochemistry and Behavior*, 90, 184-197.
- Ho, M. Y., Mobini, S., Chiang, T. J., Bradshaw, C. M., & Szabadi, E. (1999). Theory and method in the quantitative analysis of "impulsive choice" behavior: implications for psychopharmacology. *Psychopharmacology*, 146, 362-372.
- Huskinson, S. L., Krebs, C. A., & Anderson, K. G. (2012). Strain differences in delay discounting between Lewis and Fischer 344 rats at baseline and following acute administration of d-amphetamine. *Pharmacology, Biochemistry and Behavior*, 101(3), 403-416. doi:10.1016/j.pbb.2012.02.005
- Isles, A. R., Humby, T., Walters, E., & Wilkinson, L. S. (2004). Common genetic effects on variation in impulsivity and activity in mice. *Journal of Neuroscience*, 24, 6733-6740.
- Kearns, D. N., Gómez-Serrano, M. A., Weiss, S. J., & Riley, A. L. (2006). A comparison of Lewis and Fischer 344 rat strains on autoshaping (sign-tracking), discrimination reversal learning and negative automaintenance. *Behavioural Brain Research*, 169, 193-200.



- Kearns, D. N. & Weiss, S. J. (2004). Sign-tracking (autoshaping) in rats: a comparison of cocaine and food as unconditioned stimuli. *Learning and Behavior*, *32*, 463-476.
- Kirkpatrick, K., Marshall, A. T., & Smith, A. P. (2015). Mechanisms of individual differences in impulsive and risky choice in rats. *Comparative Cognition & Behavior Reviews*, *10*, 45-72. doi:10.3819/ccbr.2015.100003
- Lattal, K. A. & Gleeson, S. (1990). Response acquisition with delayed reinforcement. *Journal of Experimental Psychology: Animal Behavior Process*, *16*, 27-39.
- Lattal, K. A. & Metzger, B. (1994). Response acquisition by Siamese fighting fish (*Betta splendens*) with delayed visual reinforcement. *Journal of the Experimental Analysis of Behavior*, *61*, 35-44.
- Lindley, S. E., Bengoechea, T. G., Wong, D. L., & Schatzberg, A. F. (1999). Strain differences in mesotelencephalic dopaminergic neuronal regulation between Fischer 344 and Lewis rats. *Brain Research*, *832*, 152–158. doi: [10.1016/S0006-8993\(99\)01446-8](https://doi.org/10.1016/S0006-8993(99)01446-8)
- Madden, G. J., Smith, N. G., Brewer, A. T., Pinkston, J., & Johnson, P. S. (2008). Steady-state assessment of impulsive choice in Lewis and Fischer 344 rats: between-condition delay manipulations. *Journal of the Experimental Analysis of Behavior*, *90*, 333-344. doi:[10.1901/jeab.2008.90-333](https://doi.org/10.1901/jeab.2008.90-333)
- Meneses, A., Castillo, C., Ibarra, M., & Hong, E. (1996). Effects of aging and hypertension on learning, memory, and activity in rats. *Physiology & Behavior*, *60*, 341-345.
- Meneses A., & Hong, E. (1998). Spontaneously hypertensive rats: a potential model to identify drugs for treatment of learning disorders. *Hypertension*, *31*, 968-972.
- Mitchell, M. R. & Potenza, M. N. (2014). Recent insights into the neurobiology of impulsivity. *Current Addiction Reports*, *1*(4), 309-319.
- Monterroso, J. & Ainslie, G. (1969). Beyond discounting: possible experimental models of impulsive control. *Psychopharmacology*, *146*, 339-347.
- Mook, D. M., Jeffrey, J., & Neuringer, A. (1993). Spontaneously hypertensive rats (SHR) readily learn to vary but not repeat instrumental responses. *Behavioral and Neural Biology*, *59*, 126-135. doi:10.16/0163-1047(93)90847-B
- Ng, Q. X., Ho, C. Y. X., Chan, H. W., Yong, B. Z. J., & Yeo, W. S. (2017). Managing childhood and adolescent attention-deficit/hyperactivity disorder (ADHD) with exercise: A systematic review. *Complementary Therapies in Medicine*, *34*, 123-128.
- Paule, M. G., Rowland, A. S., Ferguson, S. A., Chelonis, J. J., Tannock, R., Swanson, J. M., & Castellanos, F. X. (2000). Attention deficit/hyperactivity disorder: characteristics, interventions and models. *Neurotoxicology and Teratology*, *22*, 631-651.
- Perry, J. L., Nelson, S. E., Anderson, M. M., Morgan, A. D., & Carroll, M. E. (2007). Impulsivity (delay discounting) for food and cocaine in male and female rats selectively bred for high and low saccharin intake. *Pharmacology Biochemistry and Behavior*, *86*, 822-837.



- Ramos, A., Berton, O., Morméde, P., & Chaouloff, A. (1998). A multiple-test study of anxiety-related behaviors in six inbred rat strains. *Behavioural Brain Research*, *85*, 57-69.
- Ramos, A., Kangerski, A. L., Basso, P. L., Da Silva Santos, J. E., Assreuy, J., Vendruscolo, L. F., & Takahashi, R. N. (2002). Evaluation of Lewis and SHR rat strains as a genetic model for the study of anxiety and pain. *Behavioural Brain Research*, *129*, 113-123.
- Reynolds, B. (2006). A review of delay discounting research with humans: relations to drug use and gambling. *Behavioural Pharmacology*, *17*, 651-667.
- Russell, V., de Villiers, A., Sagvolden, T., Lamm, M., & Taljaard, J. (1998). Differences between electrically-, Ritalin- and D-amphetamine-stimulated release of [³H]dopamine from brain slices suggest impaired vesicular storage of dopamine in an animal model of Attention-Deficit Hyperactivity Disorder. *Behavioural Brain Research*, *94*, 163-171. doi. 10.1016/S0166-4328(97)00177-0
- Sagvolden, T. (2000). Behavioral validation of the spontaneously hypertensive rat (SHR) as an animal model of attention-deficit/hyperactive disorder (ADHD). *Neuroscience and Behavioral Reviews*, *24*, 31-39.
- Sagvolden, T. (2001). The spontaneously hypertensive rat (SHR) as a model of ADHD. In M.V. Solanato-Gardner, A. F.T., Arnsten, & F. X. Castellanos (Eds.). *Stimulant drugs and ADHD: basic and clinical neuroscience* (pp. 221-237). Oxford: Oxford University Press.
- Sagvolden, T., & Johansen, E. B. (2011). Rat models of ADHD. In *Behavioral neuroscience of attention deficit hyperactivity disorder and its treatment* (pp. 301-315). Springer, Berlin, Heidelberg.
- Selim, M., & Bradberry, C.W. (1996). Effect of ethanol on extra cellular 5-HT and glutamate in the nucleus accumbens and prefrontal cortex: Comparison between the Lewis and Fischer 344 rat strains. *Brain Research*, *716*, 157-164. [doi.10.1016/0006-8993\(95\)01385-7](https://doi.org/10.1016/0006-8993(95)01385-7)
- Skinner, B. F. (1948). "Superstition" in the pigeon. *The Journal of Experimental Psychology*, *38*, 168-172.
- Stein, J. S., Pinkston, J. W., Brewer, A. T., Francisco, M. T. & Madden, G. J. (2012). Delay discounting in Lewis and Fischer 344 rats: steady-state and rapid-determination adjusting-amount procedures. *Journal of the Experimental Analysis of Behavior*, *97*, 305-321. doi.10.1901/jeab.2012.97-305
- Tomie, A., Aguado, A. S., Pohorecky, L. A., & Benjamin, D. (1998). Ethanol induces impulsive-like responding in a delay-of-reward operant choice procedure: impulsivity predicts autoshaping. *Psychopharmacology*, *139*, 376-382.
- van Haaren, F. (1992). Response acquisition with fixed and variable resetting delays of reinforcement in male and female Wistar rats. *Physiology and Behavior*, *52*, 769-772.
- Weiss, G. (1985). Pharmacotherapy for ADD-H adolescents workshop: follow-up studies on outcome of hyperactive children. *Psychopharmacology Bulletin*, *21*(2), 169-177.



- Wessels, M. G. (1974). The effects of reinforcement upon the prepacking behavior in pigeons in the autoshaping experiment. *Journal of the Experimental Analysis of Behavior*, 21, 125-144.
- Wilhelm, C. J. & Mitchell, S. H. (2008). Rats bred for high alcohol drinking are more sensitive to delayed and probabilistic outcomes. *Genes, Brain, and Behavior*, 7, 705-713. doi. 10.1111/j.1601-183X.2008.0046.x.
- Wilhelm, C. J. & Mitchell, S. H. (2009). Strain differences in delay discounting using inbred rats. *Genes, Brain, and Behavior*, 8, 426-434. doi.10.1111/j.1601-183X.2009.00484.x.
- Williams, D. R., & Williams, H. (1969). Automaintenance in the pigeon: Sustained pecking despite contingent non-reinforcement. *Journal of the Experimental Analysis of Behavior*, 12, 511-520.
- Winstanley, C. A., Dalley, J. W., Theobald, D. E. H., & Robbins, T. W. (2003). Global 5-HT depletion attenuates the ability of amphetamine to decrease impulsive choice on a delay-discounting task in rats. *Psychopharmacology*, 170(3). 320-331.
- Winstanley, C. A., Eagle, D. M., & Robbins, T. W. (2006). Behavioral models of impulsivity in relation to ADHD: translation between clinical and preclinical studies. *Clinical Psychology Review*, 26(4), 379-395.
- Wogar, A., Bradshaw, C. M., & Szabadi, E. (1993). Effects of lesions of the ascending 5-hydroxytryptaminergic pathways on choice between delayed reinforcers. *Psychopharmacology*, 111, 239-243.