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# Does Chronic Risperidone Administration Affect Food Reinforcement in Adulthood in Mice?

Francis Torres

Paul Soto

# DOES CHRONIC RISPERIDONE ADMINISTRATION AFFECT FOOD REINFORCEMENT IN ADULTHOOD IN MICE?

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Francis Rafael Torres
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B.S., University of South Florida, 2018
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# Abstract

Second-generation antipsychotics (SGAs) increase weight gain and food consumption in humans and non-human animals. It has been speculated that SGAs increase the reinforcing effects of food, which increases food consumption and drives weight gain. The current study evaluated the effects of risperidone on sucrose reinforcement in male and female C57BL/6J mice using economic demand assessments. Demand for sucrose was measured by varying the fixed ratio (FR) value required to produce sucrose delivery across experimental sessions using five FR values: 1, 5, 15, 30, and 45. The effects of acute risperidone administration on demand for sucrose were first assessed by orally administering risperidone or vehicle occasionally 30 min prior to experimental sessions. Next, the effects of chronic risperidone administration on demand for sucrose were assessed by orally administering risperidone after experimental sessions. During baseline (no vehicle or drug administration before or after) and vehicle sessions, the number of sucrose reinforcers obtained decreased as FR increased. Following acute, pre-session administration of 1 and 3 mg/kg risperidone, responding was substantially decreased, which reduced the number of sucrose reinforcers obtained across the different FR values. During the periods of chronic, post-session administration of 1 and 3 mg/kg risperidone, the number of sucrose reinforcers obtained at each FR value was not substantially changed relative to that observed following prior vehicle administration. Body weights were not affected by acute, pre-session, 1 or 3 mg/kg risperidone administration. Similarly, there was no significant effect on food consumption in male or female mice following acute pre-session 1 mg/kg administration, but food consumption in male mice decreased following acute pre-session administration of 3 mg/kg risperidone. Finally, chronic post-session administration of 1 mg/kg and 3 mg/kg risperidone increased the rate of weight gain in male and female mice, but there was no

significant effect on food consumption. These results suggest that neither acute, pre-session, nor chronic, post-session administration of risperidone increases the reinforcing effects of sucrose or food consumption.

# Introduction

Second-generation antipsychotics (SGAs) produce unwanted side effects such as weight gain (Bates et al., 2015). A metanalysis of 81 articles revealed that in the first ten weeks of treatment, weight gain across SGAs (clozapine, olanzapine, thioridazine, sertindole, chlorpromazine, and risperidone) varied from 0.04 kg to 4.45 kg. Over the ten weeks of treatment, weight continuously increased, suggesting that the amount of weight gained would have continued to grow with medication exposure duration (Allison et al., 1999). Further, a meta-analysis of 307 controlled clinical trials revealed that 81% of the reviewed studies reported that SGA treatment increased weight, and the amount of weight gained increased with treatment duration (Bak et al., 2014). SGA-induced weight gain may lead to metabolic problems, like metabolic syndrome (Starrenburg & Bogers, 2009).

SGAs increase the risk of developing metabolic abnormalities, which is associated with the risk of developing metabolic syndrome. In one study, the prevalence of metabolic syndrome in unmedicated schizophrenics was roughly 10%, while the prevalence of metabolic syndrome in medicated schizophrenics was 35.3% (Mitchell et al., 2013). Also, in a study of 30 schizophrenic patients receiving SGA treatment, 11.66% of the patients developed metabolic syndrome after four months of treatment (Gautam & Meena, 2011).

Metabolic syndrome is a cluster of conditions defined by high blood pressure, high blood sugar, high cholesterol levels, and weight increase. SGAs are known to impair glucose metabolism, increase cholesterol and triglyceride levels and cause arterial hypertension, leading to metabolic syndrome. (Correll et al., 2009; Lieberman, 2004). Patients diagnosed with metabolic syndrome have a five-fold increase in diabetes in the next 5 to 10 years (De Hert et al., 2011; Gami et al., 2007). Also, for non-diabetic individuals with metabolic syndrome and

hypertension, there is a 1.7-fold increase in heart and a 2-fold increase in cerebrovascular disease (Andreadis et al., 2007).

SGA medications can increase food consumption and binge eating in humans. A meta-analysis of 47 studies concluded that SGA-induced weight gain might be caused by increased food consumption (Benarroch et al., 2016). Further, in a study of 31 patients receiving olanzapine during their first schizophrenia episode, 58.1% reported increased feelings of hunger during the first four weeks of treatment and 77.4% by 12 weeks of treatment; those patients who reported increased appetite gained more weight than those who did not report increased appetite (Huang et al., 2020). Similarly, an analysis of 22 clinical studies revealed that patients increased food intake during SGA treatment, with some patients developing binge eating disorder (Cuerda et al., 2014). Finally, in male adolescent patients treated with olanzapine, SGA-induced weight gain resulted from increased caloric intake and not a diet change (Gothelf et al., 2002). Like humans, non-human animals experience SGA-induced weight gain and increased food consumption during SGA treatment.

SGA medications increase food consumption and weight gain in rodents. Female mice treated with olanzapine, quetiapine, ziprasidone, or risperidone exhibit increased weight gain and food consumption, with olanzapine and quetiapine causing the greatest increase in food consumption and weight gain (Cope et al., 2005). Similarly, female rats treated with olanzapine consumed more calories and gained more weight than controls (Arjona et al., 2004). Also, male rats treated with olanzapine and clozapine consume more high-fat food than controls, suggesting that SGAs may increase fat intake (Hartfield et al., 2003). The neural mechanisms underlying SGA-induced food consumption are not known but may involve antagonism of 5-HT2C and H1 receptors by SGA medications.

Two findings suggest that SGA antagonism of 5-HT2C receptors may play a role in SGA-induced weight gain and food consumption. First, olanzapine-induced weight gain and hyperphagia are absent in 5-HT2C receptor knockout mice, suggesting that olanzapine's effects on weight gain and food consumption is mediated by antagonism of 5-HT2C receptors (Lord et al., 2017). Second, lorcaserin, a 5-HT2C receptor agonist, attenuates risperidone-induced food consumption in mice (Wan et al., 2020), presumably by counteracting risperidone's antagonism of those receptors.

Other evidence suggests that short-term SGA-induced weight gain is predicted by SGA H1-receptor binding affinities with SGAs with higher H1-receptor binding affinities inducing greater weight gain (Goudie et al., 2003). In addition, H1-receptor antagonism by SGA medications may increase appetite and fat storage while decreasing energy expenditure (He et al., 2013). Also, H1-receptor antagonism activates AMP-activated protein kinase (AMPK), an enzyme that regulates energy homeostasis and is associated with increased caloric intake. Further, clozapine, olanzapine, and quetiapine increase levels of AMPK in the hypothalamus (Kim et al., 2007), a brain region closely tied to hunger, food consumption, and satiation. Further, administration of an H1 receptor agonist reduces olanzapine-induced food consumption and H1-AMPK signaling in the hypothalamus (He et al., 2014), suggesting that olanzapine-induced food consumption and weight gain involves antagonism of H1 receptors. Another mechanism that may affect SGA-induced weight gain and food consumption is dopamine receptor antagonism.

SGA medications bind to dopamine D2 receptors, and most SGA medications are antagonists at D2 receptors. Chronic SGA treatment may cause dopamine D2 receptor supersensitization, which is defined by an increased proportion of D2 receptors in a "high

affinity" state, which means that molecules such as dopamine and dopamine D2 receptor agonists bind to the receptor with higher binding affinity when the receptor is in the high-affinity state than other states (Samaha, 2014; Samaha et al., 2007). Additionally, dopamine supersenitization may occur relatively early during chronic SGA treatment as nine days of sertindole treatment have been shown to increase the proportion of D2 receptors with a high affinity for dopamine by as much as 186% to 215% in the striatum (Seeman, 2008b). Also, after nine days of treatment with bifeprunox, D2 receptors in the high-affinity state in the striatum of rats increased by 102-129%, and after seven days of treatment with aripiprazole, D2 receptors in the high-affinity state in the stratum increased by 108-188% (Seeman, 2008a). Upregulation of dopamine D2 receptors in the striatum and an increase in the proportion of dopamine D2 receptors in a high-affinity state may alter reward function (Bedard et al., 2011, 2013; Samaha, 2014). Specifically, such changes may increase the reinforcing effectiveness of food, which could increase food consumption.

Research suggests that acute SGA treatment increases the reinforcing effects of food. In marmosets, acute clozapine administration increased lever pressing for banana milkshake reinforcement under a progressive ratio schedule of reinforcement, suggesting that clozapine increased the banana milkshake's reinforcing effectiveness (Cilia et al., 2001). Further, acute dosing of clozapine dose-dependently increased lever pressing for sucrose under a progressive ratio schedule of reinforcement in rats, suggesting that clozapine increased the value of sucrose reinforcers (Mobini et al., 2000; Zhang et al., 2005). Also, acute and chronic clozapine treatment increased food-reinforced lever pressing under progressive and fixed-ratio schedules of reinforcement in rats (Abela et al., 2020; Abela et al., 2019). Other research has shown that ziprasidone, quetiapine, olanzapine, and clozapine increased sucrose-reinforced lever pressing in

a progressive ratio schedule of reinforcement in rats, but this effect was not seen with haloperidol or raclopride (Zhang et al., 2005). These findings suggest that some but not all SGAs increase the reinforcing effectiveness of foods. However, response rates on schedules of reinforcement are determined by several factors. An approach that examines changes in reinforcing effectiveness involves behavioral economic demand assessment.

Behavioral economic demand assessment measures the "strength" or value of a reinforcer by examining how consumption of goods changes as price increases (Hursh & Silberberg, 2008). The function relating the quantity consumed and the work required to obtain it is a demand curve. Demand curves plot reinforcers obtained as a function of price (the cost to acquire each reinforcer), and they let researchers access the elasticity of demand (the degree to which demand is decreased as price increases). Higher-valued reinforcers maintain less elastic demand (i.e., animals are more willing to work for the reinforcer as the price increases) than lower-valued reinforcers.

In human drug research, demand curves have been used to describe how alcohol consumption changes as a function of the price of a drink (Gray & MacKillop, 2015). Similarly, demand curve analysis has shown that self-administration of methamphetamine and heroin is affected by drug price and the level of participant's drug dependence (Chalmers et al., 2010). Further, demand for methadone and cigarettes decreases as price increases (Spiga et al., 2005). Under fixed-ratio schedules, rats are willing to work harder for heroin than saccharine (i.e., demand for heroin is less elastic than demand for saccharine), suggesting that the essential value of heroin is higher than saccharine (Schwartz et al., 2017). The examples provided illustrate that demand curves are used in multiple settings to determine the relationship between the price (cost or effort of a commodity) and the amount of that commodity that is consumed.

In behavioral economic analyses, fixed-ratio schedules of reinforcement are commonly used to vary the price of a reinforcer, and the number of reinforcers obtained at each fixed-ratio value is used as the measure of consumption. The exponential model of demand describes how consumption of a reinforcer changes as a function of the reinforcer's price according to the following equation: $\log Q = \log Q_0 + k(e^{-\alpha Q_0 C} - 1)$. In this equation, $Q$ specifies the total amount of a reinforcer that is consumed. $Q_0$, determines the highest consumption level (i.e., consumption at a price of zero responses). The range of the data, $k$ is set to a common constant across all comparisons. The elasticity of demand is determined by α, the log rate of decline in relative consumption with an increase in price. $C$ represents the cost of the reinforcer (i.e., fixed ratio value) (Hursh & Silberberg, 2008). The importance of this formula is that it normalizes demand curves based on $Q_0$ (Hursh & Silberberg, 2008).

One shortcoming of the exponential model of demand is that it cannot accommodate situations in which no reinforcers were obtained because the logarithm of 0 is undefined. Thus, we will use a modified equation: $\mathrm{Q} = Q_0 * 10^{k(e^{-\alpha Q_0 C}-1)}$, which exponentiates both sides of the exponential demand equation using a base of 10. Exponentiating the left side using a base of 10 allows the untransformed consumption values to be fitted, which allows the use of observations for which 0 reinforcers were obtained (Koffarnus et al., 2015).

The current study evaluated the effects of risperidone administration on the reinforcing effectiveness of sucrose using a behavioral economic demand analysis. First, the acute effects of risperidone on demand for sucrose were assessed using occasional pre-session administrations of risperidone. Second, the effects of chronic risperidone administration were assessed using daily, post-session administrations of risperidone. We predicted that risperidone might increase the

reinforcing effectiveness of sucrose, as measured by the demand elasticity of sucrose, following acute risperidone administration and/or during periods of chronic risperidone administration.

# Methods

## Subjects

Four female and four male C57BL/6J mice were purchased from The Jackson Laboratory (Bar Harbor, Me) and were single-housed in non-ventilated plastic cages. Animals were housed individually at 22±1 C, in a humidity-controlled room, under a 12-hour light/dark cycle (7AM/7PM). All methods performed were in accordance with the guidelines of the Institutional Animal Care and Use Committee of the Pennington Biomedical Research Center.

## Weight and Food Consumption

Bodyweight (grams) and food (grams) present in the cage hopper were measured every day. Food consumed (grams) was calculated by subtracting the weight of the food on each day from the weight of the food from the previous day, including any added food. Rodent chow (5001 Laboratory Rodent Diet, Fort Worth, TX) was given daily and kept above 40 grams in each microisolator cage throughout the experiment.

## Drugs

Risperidone (Cayman Chemical, Ann Arbor, MI) was administered in two doses, 1 and 3 mg/kg. 1 mg/kg Risperidone was chosen because this dose has been shown to affect behavior in a conditioned avoidance response test by inducing hyperlocomotion in rodents (Gao & Li, 2013). 3 mg/kg Risperidone was chosen because research has shown that it enhances locomotor activity in adult and juvenile rats (Moran-Gates et al., 2007).

Risperidone was administered in plain cookie dough. During the experiment, the drug dough (risperidone in plain cookie dough) and the plain dough were stored in air-tight containers in a refrigerator (Danby, model DAR026A1BDD, Findlay, OH). Each mouse received 6.25 grams of dough per kilogram of body weight. To administer drug or plain dough, each mouse

received a 25 ml glass bottle inside their housing cage, and the dough was applied inside the bottles.

The plain dough consisted of 17% unsalted Land O' Lakes Sweet Cream Butter (Land O' Lakes, Inc. Arden Hills, MN), 74% Betty Crocker Sugar Cookie Mix (General Mills, Inc, Minneapolis, MN), and 9% Eggbeaters (Con Agra Foods, Inc. Chicago, IL). The plain dough was made as follows: first, the butter was placed in a mixing bowl and left to soften. Next, the cookie mix was thoroughly mixed with the butter using a hand-mixer. Finally, Eggbeater was added by a syringe, and the whole mixture was blended using a hand-mixer.

A stock mixture of 10 mg of risperidone per gram of sugar cookie mix was used to make cookie dough for the delivery of 1 and 3 mg/kg risperidone. The concentration of risperidone in the dough for administering 1 mg/kg was 0.16 mg risperidone per g of dough, and for 3 mg/kg, it was 0.48 mg risperidone per g of dough. Dough containing risperidone was mixed as follows: first, the stock concentration of 10 mg risperidone per gram of sugar cookie powder was mixed thoroughly with plain sugar cookie powder (58% plain cookie powder and 16% 10 mg risperidone in cookie powder for administering 1 mg/kg or 26% plain cookie powder and 48% 10 mg risperidone in cookie powder for administering 3 mg/kg). After thoroughly mixing the stock concentration of risperidone in cookie powder with plain cookie powder, softened butter was added and mixed with a hand mixer. Finally, Eggbeater was added by a syringe, and the whole mixture was blended using a hand-mixer.

**Sucrose**

Sucrose solutions were made weekly. A concentration of 15% (w/v) sucrose was used for all operant sessions, and this concentration was chosen based on previous operant experiments.

The 15% sucrose concentration was made by mixing 135 grams of granulated sucrose in 900 ml of hot water.

**Apparatus**

Experimental sessions were conducted in eight operant conditioning chambers (Med-Associates, modified Model ENV307A, St Albans, VT) measuring 15.9 (length) x 14.0 (depth) x 12.7 (height) cm. Each chamber was equipped with two nose poke ports 2.5 cm above the floor. Each nose poke port contained a light-emitting diode (LED). A liquid dipper (ENV032M, St Albans, VT) delivery device was located between the nose ports and contained an LED. A mechanical relay provided audible clicks per nose poke port activation. Centered at the top of the front wall was a single house light that illuminated the chamber.

**Initial Training**

Experimental sessions were conducted once per day, five days a week. Sessions began five minutes after the mouse was placed inside the operant chamber with the illumination of the house lights and stimulus lights above the nose poke ports. At the start of training, there were response-independent sucrose deliveries, meaning that the liquid dipper delivered sucrose reinforcers every minute regardless of a nose poke response. Once mice made 15 nose poke responses, in either the left or right nose port, they were moved to FR 1, with one nose poke assigned as active and the other inactive. Only responses in the active nose poke produced reinforcer delivery. Sessions lasted one hour. Mice were moved from FR 1 to FR 2 after they received 15 reinforcers in two consecutive operant sessions. When mice received 15 reinforcers in two consecutive operant sessions of FR 2, they were moved to FR 3, and mice repeated this cycle until they reached FR 5.

**Demand Curve Assessment**

After the initial training procedure, operant sessions were conducted each day at the same time ±1 h. The FR value in effect during each session varied across days in the week (Monday – Friday) and were 1, 5, 15, 30, and 45 (FR 1 on Monday, FR 5 on Tuesday, and so on). Also, operant sessions lasted one hour.

The within-subject operant experiments consisted of multiple pre-session and post-session drug and vehicle administrations. For pre-session, acute drug administration, risperidone was administered every other day (7 days per week) Monday to Friday, risperidone administration occurred 30 minutes prior to operant sessions (Figure 1). Once pre-session, acute treatments ended, post-session, chronic treatments began (Figure 2). During post-session, chronic treatments, risperidone was administered every day (7 days per week) Monday to Sunday. On days animals had operant sessions (Monday to Friday), risperidone was administered after the animals finished their operant sessions. Additionally, after two weeks of post-session, chronic treatments, risperidone was administered, chronically, pre- or post-session, to determine if chronic treatments induce drug sensitization or tolerance (Figure 2). Weekly demand curves for each phase were created, and if operant behavior was still changing at the end of a chronic administration phase, then the phase was extended until behavior stabilized.

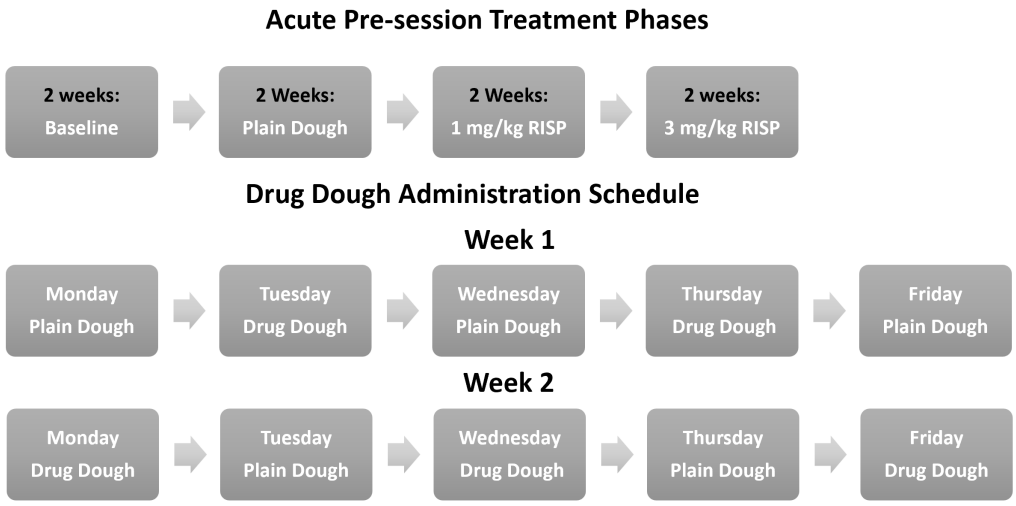


Figure 1. Pre-session, acute Drug Administration Dosing Schedules. At baseline, no vehicle or drug dough was administered. Pre-session, acute plain dough was administered for two weeks to determine if vehicle treatment would change sucrose responding. Pre-session, acute drug dough (1 mg/kg and 3 mg/kg risperidone [RISP]) was administered every other day with plain dough to create two demand curves (one for drug dough and another for plain dough) at the end of two weeks.

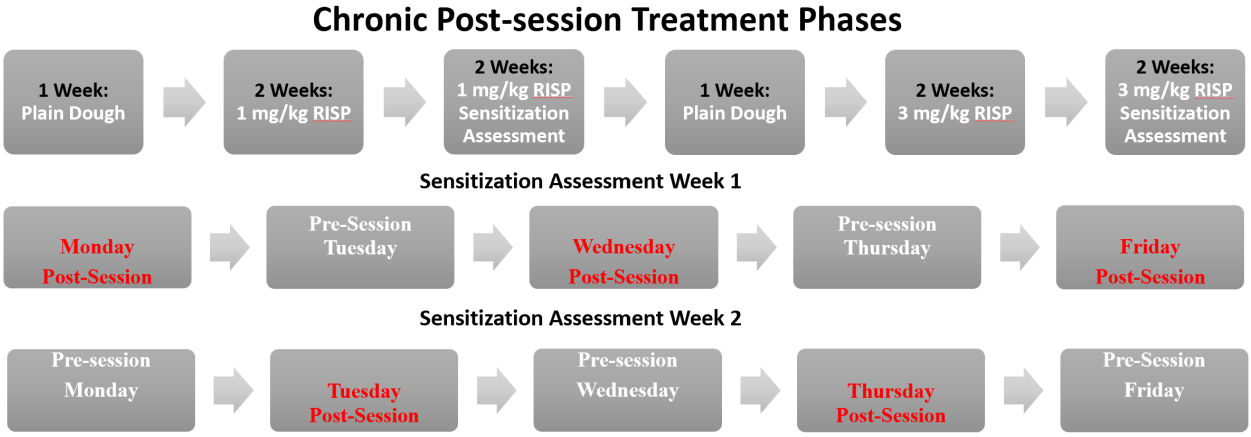


Figure 2. Post-Session Chronic Drug Administration Dosing Schedules. Post-session, chronic plain dough was administered for one week to determine if chronic vehicle administration affects sucrose responding. Post-session, chronic drug dough (1 mg/kg and 3 mg/kg risperidone [RISP]) was administered daily 7 days/week for 2 weeks because research suggests it takes 7 to 9 days of chronic treatment to increase D2-high receptors in the stratum during SGA administration (Seeman, 2008a, 2008b). Sensitization assessment consisted of two weeks of post and pre-session drug administration to determine if two weeks of drug treatments changed the demand for sucrose during pre-session drug administration.

**Data Analysis**

The number of sucrose reinforcers obtained at each FR value was analyzed via multilevel non-linear regression using the nlme function of the lme4 package (Bates et al., 2015) in the free, open-source statistical language R (R Development Core Team, 2020). The multilevel non-linear regression model was used to fit the number of reinforcers obtained as a function of FR using the exponentiated model of demand ($\mathrm{Q} = Q_0 * 10^{k(e^{-\alpha Q_0 C}-1)}$) using fixed effects estimates for $Q_0$ and α, for each dose and its corresponding vehicle sessions, and random effects estimates for $Q_0$ and α, for each mouse. $k$ was set as the mean range of log$Q$ values + 0.5 that was obtained for each drug vs. vehicle comparison in a multilevel non-linear regression formula by using the Getk function of the Beezdemand package (Kaplan et al., 2019).

Changes in body weight and food consumption following drug administration were analyzed using the lmer function of the lme4 package (Bates et al., 2015) in R (R Development Core Team, 2020). The multilevel linear function for body weight and food consumed included fixed effects predictors for postnatal day and dose and their interactions and random effects for postnatal day and dose and their interaction for each mouse. Bodyweight and food consumption values were obtained from days when the mice were dosed with vehicle (plain cookie dough) or drug (risperidone + cookie dough).

# Results

## Operant Data: Acute Phases

Decreases in total reinforcers obtained with increasing FR value were equivalent during the first two weeks of baseline (Figure 3). Multilevel fits of the exponentiated model of demand showed no statistically significant changes between the two weeks in $Q_0$ (baseline week 1= 62.34 and baseline week 2 = 67.59; t [69] = 1.33, p = .19) or α (baseline week 1= 0.00032 and baseline week 2 = 0.00034; t [69] = 0.58, p = .57).

Mice Reached a Stable baseline at Each FR

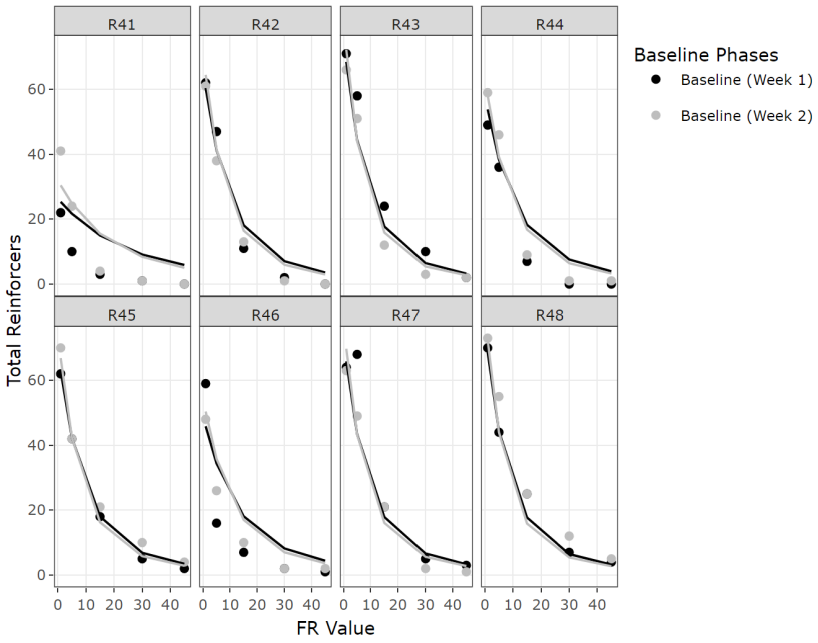


Figure 3. Changes in total reinforcers as a function of FR values for nose poking were reinforced by a 15% sucrose solution during the first week of baseline (black) and second week of baseline (gray). Each graph represents a different mouse. The alphanumeric label at the top of each graph indicates the mouse identification.

Decreases in total reinforcers obtained with increasing FR value were equivalent during the first week of pre-session vehicle and the second week of baseline (Figure 4). Multilevel fits of the exponentiated model of demand showed no statistically significant changes in $Q_0$ (baseline

week 2 = 67.59 and pre-session vehicle =60.59; t[69] = -1.76, p = .083) or α (baseline week 2 = 0.00037 and pre-session vehicle=0.00037; t[69] = 0.0092, p = .99).

Administration of Vehicle Did Not Increase Sucrose Reinforcement

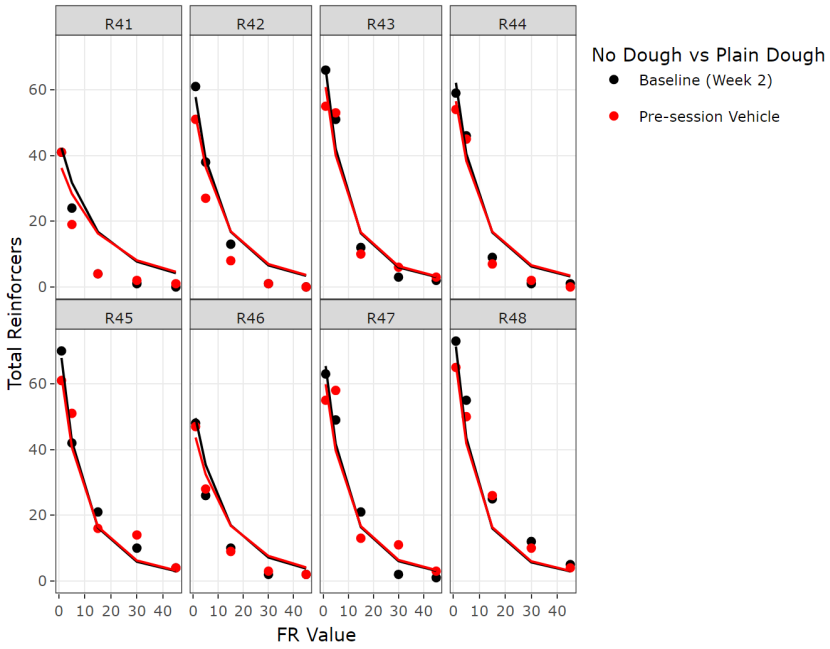


Figure 4. Changes in total reinforcers as a function of FR values for nose poking reinforced by a 15% sucrose solution during the second week of baseline (black) and first-week of pre-session plain dough (red). Other details as in Figure 3.

Pre-session 1 mg/kg risperidone administration decreased total reinforcers obtained substantially relative to the vehicle (Figure 5). Multilevel fits of the exponentiated model of demand showed that 1 mg/kg risperidone produced a statistically significant reduction in $Q_0$ (pre-session 1 mg/kg risperidone =19.98 and pre-session vehicle =61.15; t[69] = 10.11, p = .0001), and substantially increased α (pre-session 1 mg/kg risperidone =0.0011 and pre-session vehicle=0.00036; t[69] = -2.49, p = .015).

Pre-Session 1 mg/kg Risperidone Decreased Sucrose Reinforcement

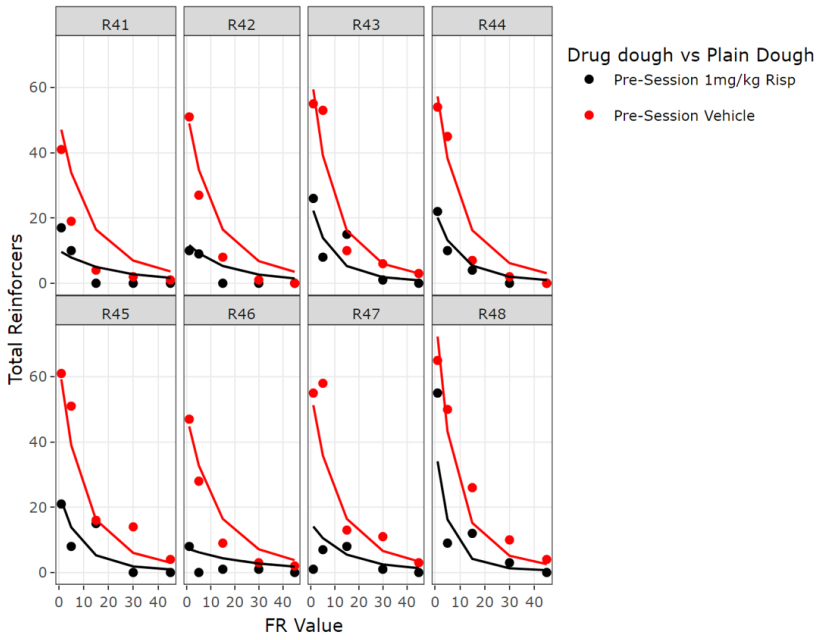


Figure 5. Total reinforcers as a function of FR values for nose poking reinforced by a 15% sucrose solution following pre-session 1 mg/kg risperidone (black) and pre-session plain dough (red). All other details as in Figure 3.

The effect of 3 mg/kg risperidone administration on sucrose demand relative to the vehicle (Figure 6) could not be assessed via fits of the exponentiated model of demand because total reinforcers obtained was close to 0 across all FR values following administration of 3 mg/kg risperidone, precluding reliable fits of the exponentiated model. However, a two-way repeated-measures ANOVA (Table 1) revealed a significant interaction between administration type (vehicle vs. 3 mg/kg risperidone) and FR values ($F[4, 28] = 80.31$, $p < .001$). Pre-session 3 mg/kg risperidone administration significantly reduced the number of reinforcers obtained compared to pre-session vehicle administration at all FR values, except FR 30, according to Bonferroni-adjusted p-values (<.001, <.001, .01, .05, and .04 for FR 1, 5, 15, 30, and 45, respectively).

Pre-Session 3 mg/kg Risperidone Decreased Sucrose Reinforcement

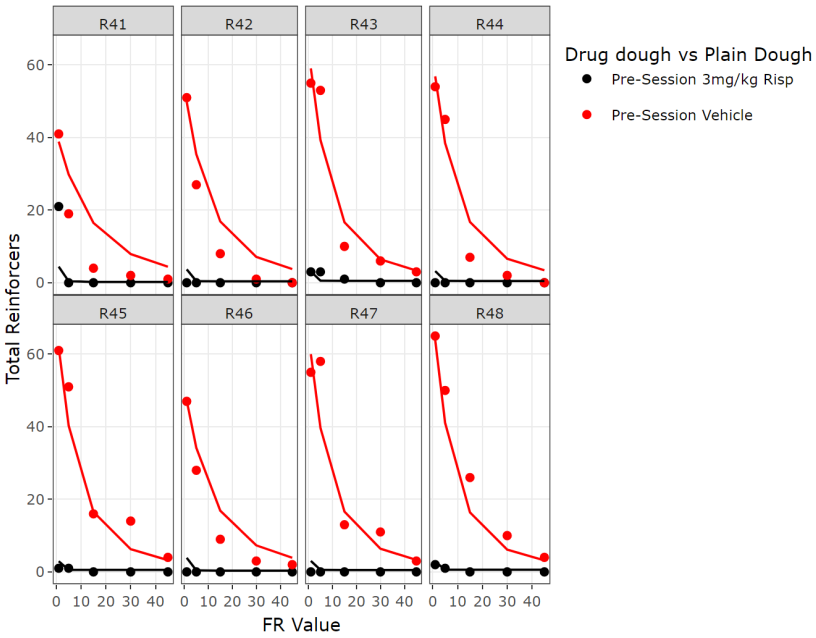


Figure 6. Total reinforcers as a function of FR value for nose poking reinforced by a 15% sucrose solution following pre-session 3 mg/kg risperidone (black) and pre-session plain dough (red). All other details as in Figure 3.

Table 1. Pre-Session 3 mg/kg Risperidone Decreased Sucrose Reinforcement

| Repeated-Measures ANOVA Results (Type III Tests) | | | | | | |
|---|---|---|---|---|---|---|
| Source of Variation | SS | DF | MS | F | P-Value | Effect Size |
| Treatment | 9812.45 | 1 | 9812.45 | 76.44 | < .001 | .780 |
| Treatment Residuals | 898.55 | 7 | 128.364 | | | |
| FR Value | 9443.575 | 4 | 2360.9 | 109.951 | < .001 | .773 |
| FR Value Residuals | 601.225 | 28 | 21.5 | | | |
| Interaction | 7627.175 | 4 | 1906.8 | 80.31 | < .001 | .734 |
| Interaction Residuals | 664.825 | 28 | 23.7 | | | |
| Subject | 603.4 | 7 | 86.2 | | | |

Note: Repeated-measures ANOVA results following pre-session, acute 3 mg/kg risperidone administration. Treatment in the repeated-measures ANOVA is a categorical variable encompassing pre-session 3 mg/kg risperidone and pre-session vehicle; similarly, FR value is a categorical variable encompassing FR 1-45.

**Operant Data: Chronic Phases**

Decreases in total reinforcers obtained with increasing FR value were equivalent during first week of post-session 1 mg/kg risperidone treatment relative to the vehicle (Figure 7). Multilevel fits of the exponentiated model of demand showed no statistically significant changes in $Q_0$ (post-session 1 mg/kg risperidone [week 1] =65.38 and post-session vehicle =77.26; t[69] = 1.60, p = .11) or α (post-session 1 mg/kg risperidone [week 1] =0.00021 and post-session vehicle =0.00010; t[69] = 1.86, p = .067).

The First Week of Chronic 1 mg/kg Risperidone Did Not Change Sucrose Reinforcement

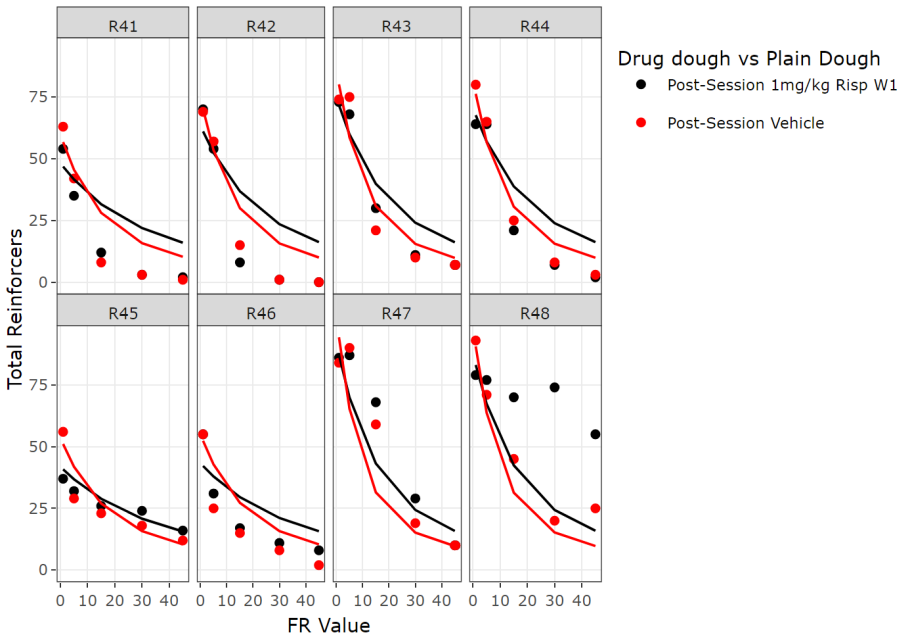


Figure 7. Total reinforcers as a function of FR values for nose poking reinforced by a 15% sucrose solution during post-session 1 mg/kg risperidone W1 (W1 stands for week one [black]) and post-session plain dough (red). All other details as in Figure 3.

Decreases in total reinforcers obtained with increasing FR value were equivalent during the second week of post-session 1 mg/kg risperidone treatment relative to that obtained during the week of vehicle administration (Figure 8). Multilevel fits of the exponentiated model of

demand showed no statistically significant changes in $Q_0$ (post-session 1 mg/kg risperidone [week 2] =77.74 and post-session vehicle=75.38; t[69] = 0.25, p = .81), or α (post-session 1 mg/kg risperidone (week 2) =0.00023 and pre-session vehicle=0.00013; t[69] = 1.32, p = .19).

The Second Week of Chronic 1 mg/kg Risperidone Did Not Change Sucrose Reinforcement

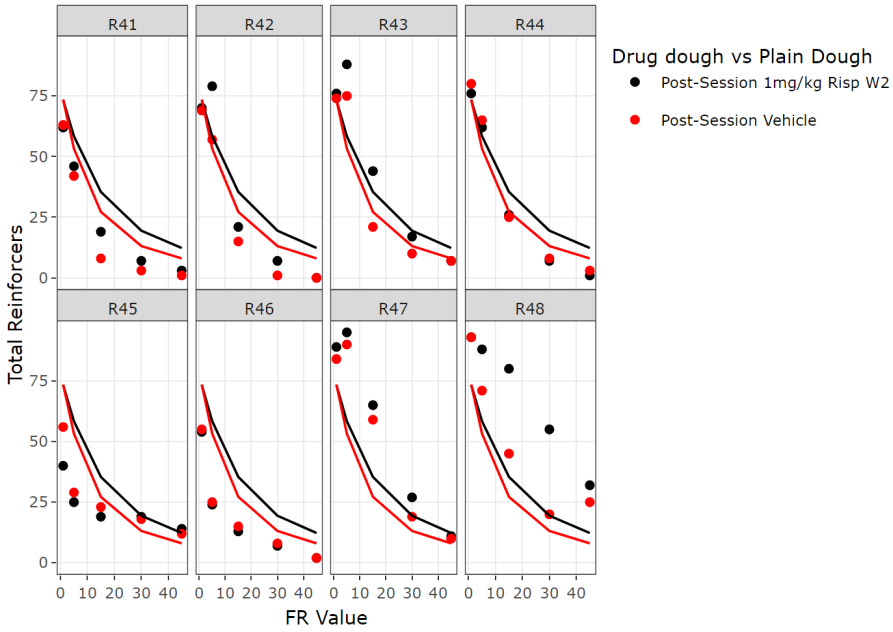


Figure 8. Total reinforcers as a function of FR values for nose poking reinforced by a 15% sucrose solution during the second week of post-session 1 mg/kg risperidone W2 (W2 stands for week two [black]) and post-session plain dough (red). All other details as in Figure 3.

Decreases in total reinforcers obtained with increasing FR value were not equivalent the first treatment of pre-session 1 mg/kg risperidone and the second treatment of pre-session 1 mg/kg after two weeks of chronic 1 mg/kg treatment (Figure 9). Multilevel fits of the exponentiated model of demand showed no statistically significant changes in $Q_0$ (first treatment of pre-session 1 mg/kg risperidone =23.45 and second treatment of pre-session 1 mg/kg risperidone =20.2; t[69] = -1.31, p = .19), but there was a reduction of α after the chronic drug administration (first treatment of pre-session 1 mg/kg risperidone =0.00091 and second treatment of pre-session 1 mg/kg risperidone =0.0019; t[69] = 3.4, p = .0011).

Chronic 1 mg/kg Risperidone Administration May Have Caused Drug Sensitization

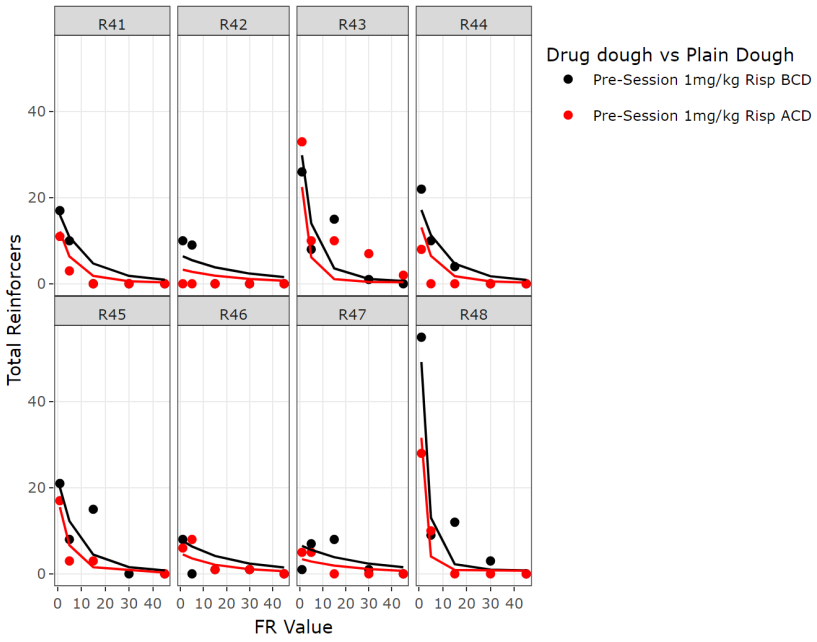


Figure 9. Total reinforcers obtained following pre-session 1 mg/kg risperidone administration before chronic dosing (BCD) and after chronic dosing (ACD) are displayed

Decreases in total reinforcers obtained with increasing FR value were equivalent the first week of post-session 3 mg/kg risperidone treatment relative to vehicle treatment (Figure 10). Multilevel fits of the exponentiated model of demand showed no statistically significant changes in $Q_0$ (post-session 3 mg/kg risperidone (week 1) =65.01 and post-session vehicle=76.72; t[69] = 1.53, p = .13), or α (post-session 3 mg/kg risperidone (week 1) =0.00013 and pre-session vehicle=0.00019; t[69] = 1.57, p = .12).

The First Week of Chronic 3 mg/kg Risperidone Did Not Change Sucrose Reinforcement

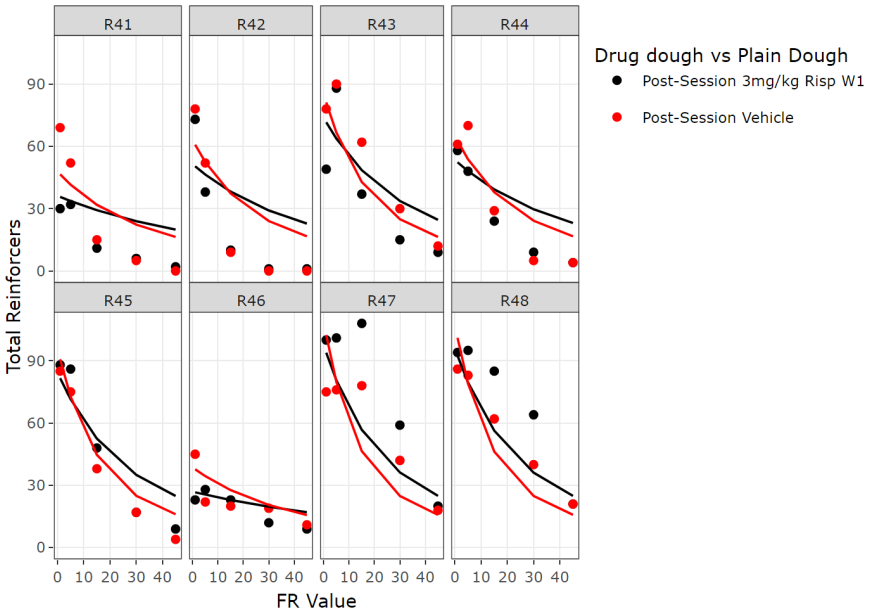


Figure 10. Total reinforcers as a function of FR value for nose poking reinforced by a 15% sucrose solution during the first week of post-session 3 mg/kg risperidone (W1 stands for week one [black]) and post-session plain dough (red). All other details as in Figure 3.

Decreases in total reinforcers obtained with increasing FR value were equivalent during the second week of post-session 3 mg/kg risperidone treatment relative to vehicle treatment (Figure 11). Multilevel fits of the exponentiated model of demand showed no significant changes in $Q_0$ (post-session 3 mg/kg risperidone (week 2) =74.05 and post-session vehicle=76.63; t[69] = 0.21, p = .83), or α (post-session 3 mg/kg risperidone (week 2) =0.00016 and pre-session vehicle=0.00018; t[69] = 0.51 p = .61).

The Second Week of Chronic 3 mg/kg Risperidone Did Not Change Sucrose Reinforcement

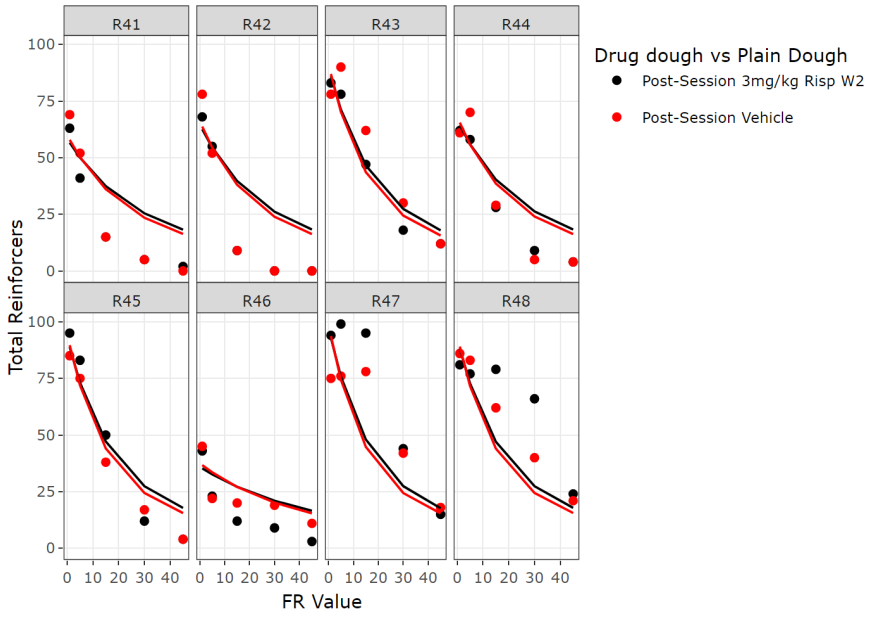


Figure 11. Total reinforcers as a function of FR values for nose poking reinforced by a 15% sucrose solution during the second week of post-session 3 mg/kg risperidone (W2 stands for week two [black]) and post-session plain dough (red). All other details as in Figure 3.

The effect of pre-session 3 mg/kg risperidone administration before chronic drug administration (BCD) relative to pre-session 3 mg/kg risperidone administration after chronic drug administration (ACD) (Figure 12) could not be assessed via fits of the exponentiated model of demand because total reinforcers obtained was close to 0 across all FR values following administration of 3 mg/kg risperidone. Additionally, a two-way repeated-measures ANOVA (Table 2) did not reveal a significant interaction between drug administration (pre-session 3 mg/kg BCD vs. pre-session 3 mg/kg ACD) and FR values ($F[1, 7] = 0.039$, $p = .839$).

Chronic 3 mg/kg Risperidone Administration Did Not Cause Drug Tolerance or Sensitization

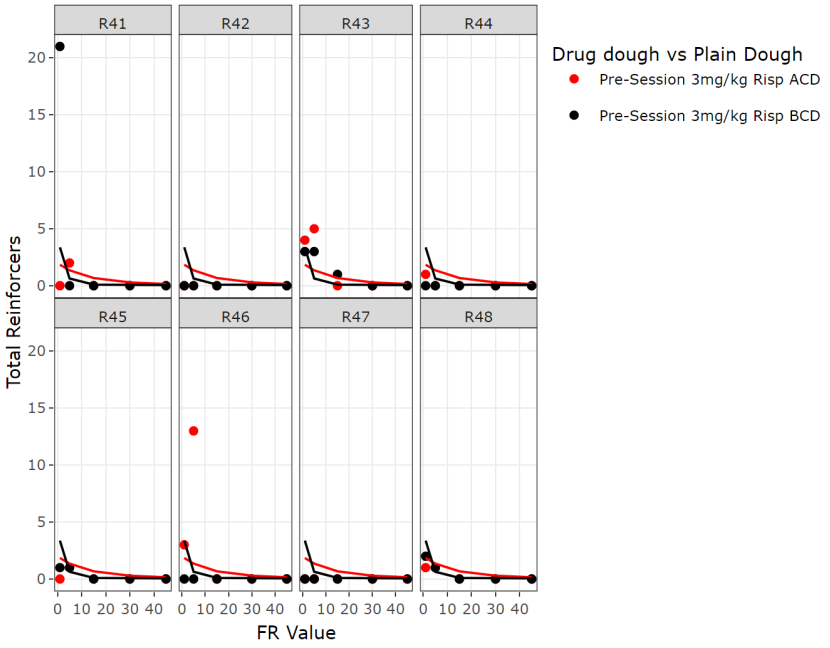


Figure 12. Total reinforcers as a function of FR values for nose poking reinforced by a 15% sucrose solution following 3 mg/kg risperidone administration before chronic dosing (BCD)and after chronic dosing (ACD). All other details as in Figure 3.

Table 2. Chronic 3 mg/kg Risperidone Administration Did Not Cause Drug Tolerance or Sensitization

| Repeated-Measures ANOVA Results (Type III Tests) | | | | | | |
|---|---|---|---|---|---|---|
| Source of Variation | SS | DF | MS | F | P-Value | Effect Size |
| Treatment | 0.05 | 1 | 0.050 | 0.006 | .942 | < .001 |
| Treatment Residuals | 62.35 | 7 | 8.907 | | | |
| FR Value | 75.43 | 4 | 18.856 | 2.708 | .0504 | < .001 |
| FR Value Residuals | 194.98 | 28 | 6.963 | | | |
| Interaction | 38.325 | 4 | 9.581 | 1.246 | .314 | < .001 |
| Interaction Residuals | 215.275 | 28 | 7.688 | | | |
| Subject | 56.4 | 7 | 8.057 | | | |

Note: Repeated-measures ANOVA results following pre-session, acute 3 mg/kg risperidone administration after chronic dosing. Treatment in the repeated-measures ANOVA is a categorical variable encompassing pre-session 3 mg/kg risperidone before and after chronic dosing; similarly, FR value is a categorical variable encompassing FR 1-45.

**Body Weight and Food Consumption Data: Acute Phases**

Pre-session, acute administration of 1 mg/kg risperidone did not significantly affect body weights (Figure 13 and Table 3) or food consumption (Figure 14 Table 4) for male mice. Similarly, pre-session, acute administration of 1 mg/kg risperidone did not significantly affect body weights (Figure 13 and Table 3) or food consumption (Figure 14 Table 4) for female mice.

Pre-Session 1 mg/kg Risperidone Administration Does Not Change Body Weights in Male or Female Mice

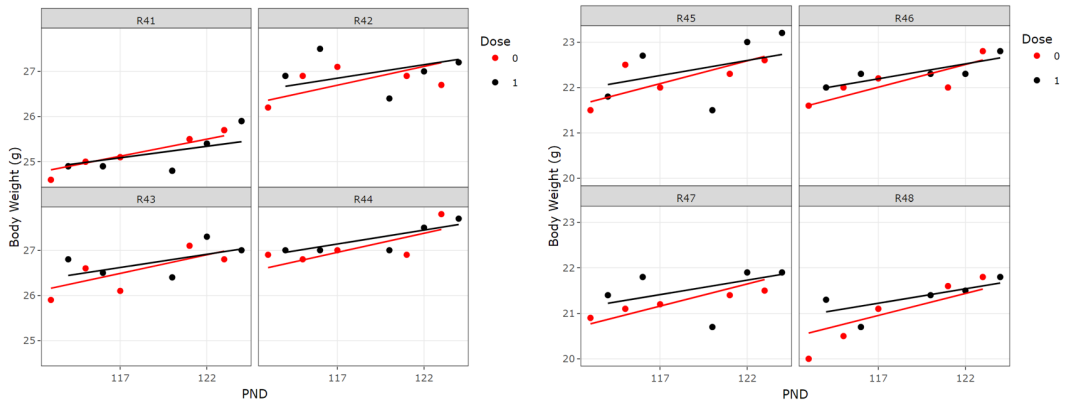


Figure 13. Body weights following administration of 1 mg/kg risperidone ("1"; black) and vehicle ("0"; red) as a function of postnatal day (PND). Males (R41-R44) are shown on the left, and females (R45-R48) are shown on the right.

Pre-Session 1 mg/kg Risperidone Administration Does Not Change Food Consumption in Male or Female Mice

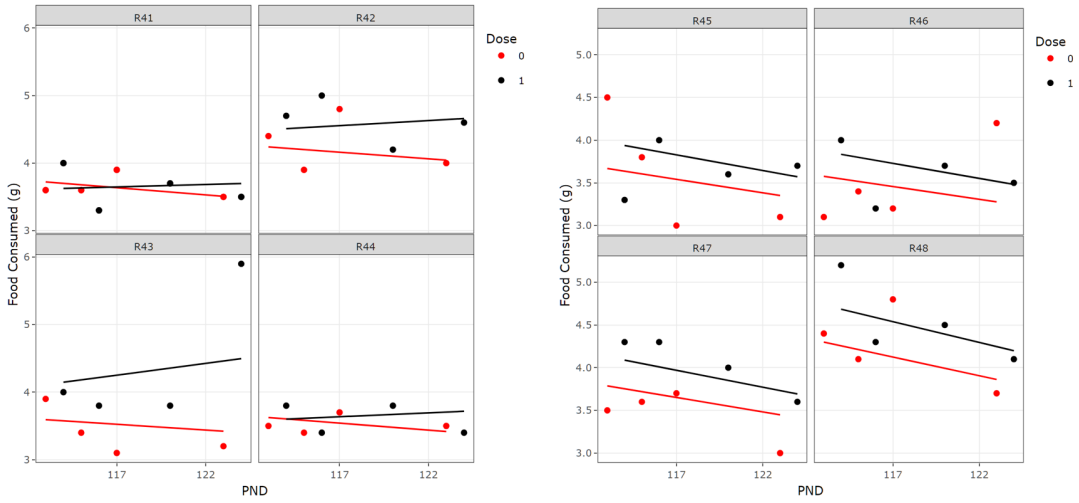


Figure 14. Food consumed following administration of 1 mg/kg risperidone ("1"; black) and vehicle ("0"; red) as a function of PND. Other details as in Figure 13.

Table 3. Pre-Session 1 mg/kg Risperidone Administration Did Not Change Body Weights in Male or Female Mice

| Regression Results | | | | Analysis of Variance using Type III Wald $X^2$ Tests | | |
|---|---|---|---|---|---|---|
| Predictor | Estimate | SE | T | Predictor | $X^2$ | P |
| Male Pre-Session 1 mg/kg Body Weight | | | | | | |
| Intercept | 16.789 | 1.930 | 8.699 | Intercept | 75.673 | < .001 |
| PND | 0.081 | 0.016 | 4.956 | PND | 24.563 | < .001 |
| Dose 1 | 2.877 | 2.740 | 1.050 | Dose 1 | 1.102 | .294 |
| PND: Dose 1 | -0.024 | 0.023 | -1.023 | PND: Dose 1 | 1.048 | .306 |
| Female Pre-Session 1 mg/kg Body Weight | | | | | | |
| Intercept | 10.021 | 2.639 | 31.833 | Intercept | 14.414 | < .001 |
| PND | 0.099 | 0.022 | 28.385 | PND | 19.435 | < .001 |
| Dose 1 | 4.167 | 3.750 | 30.303 | Dose 1 | 1.234 | .267 |
| PND: Dose 1 | -0.034 | 0.032 | 29.909 | PND: Dose 1 | 1.137 | .286 |

Note: Regression coefficients from multilevel linear model fits for body weight in males (top) and females (bottom) following pre-session, acute 1 mg/kg risperidone administration. Also shown is the analysis of variance type III Wald chi-square tests of statistical significance.

Table 4. Pre-Session 1 mg/kg Risperidone Administration Did Not Change Food Consumption in Male or Female Mice

| Regression Results | | | | Analysis of Variance using Type III Wald $X^2$ Tests | | |
|---|---|---|---|---|---|---|
| Predictor | Estimate | SE | T | Predictor | $X^2$ | P |
| Male Pre-Session 1 mg/kg Food Consumption | | | | | | |
| Intercept | 6.018 | 2.791 | 2.156 | Intercept | 4.647 | .031 |
| PND | -0.020 | 0.024 | -0.827 | PND | 0.683 | .409 |
| Dose 1 | -4.010 | 3.937 | -1.019 | Dose 1 | 1.038 | .308 |
| PND: Dose 1 | 0.037 | 0.033 | 2.328 | PND: Dose 1 | 1.204 | .272 |
| Female Pre-Session 1 mg/kg Food Consumption | | | | | | |
| Intercept | 7.768 | 3.317 | 2.342 | Intercept | 5.484 | < 0.01 |
| PND | -0.035 | 0.028 | -1.236 | PND | 1.529 | .216 |
| Dose 1 | 0.933 | 4.607 | 0.203 | Dose 1 | 0.041 | .839 |
| PND: Dose 1 | -0.005 | 0.039 | -0.134 | PND: Dose 1 | 0.018 | .894 |

Note: Regression coefficients from multilevel linear model fits for food consumption in males (top) and females (bottom) following pre-session, acute 1 mg/kg risperidone administration. Also shown is the analysis of variance type III Wald chi-square tests of statistical significance.

Pre-session, acute administration of 3 mg/kg risperidone did not significantly change body weights for male mice (Figure 15 and Table 5), but it significantly decreased food consumption mice by 0.072 grams per day (Figure 16 and Table 6). Pre-session, acute administration of 3 mg/kg risperidone did not significantly change body weight (Figure 15 and Table 5) or food consumption (Figure 16 Table 6) for female mice.

Pre-Session 3 mg/kg Risperidone Administration Did Not Change Body Weights in Male or Female Mice

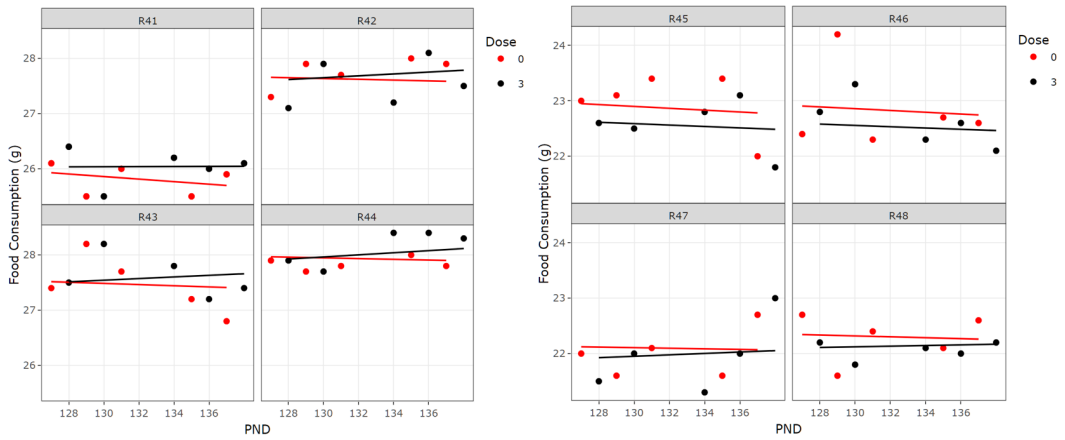


Figure 15. Body weights following administration of 3 mg/kg risperidone ("1"; black) and vehicle ("0"; red) following pre-session, acute dosing as a function of PND. All other details as in Figure 13.

Pre-Session 3 mg/kg Risperidone Administration Decreased Food Consumption in Males, but Not Females

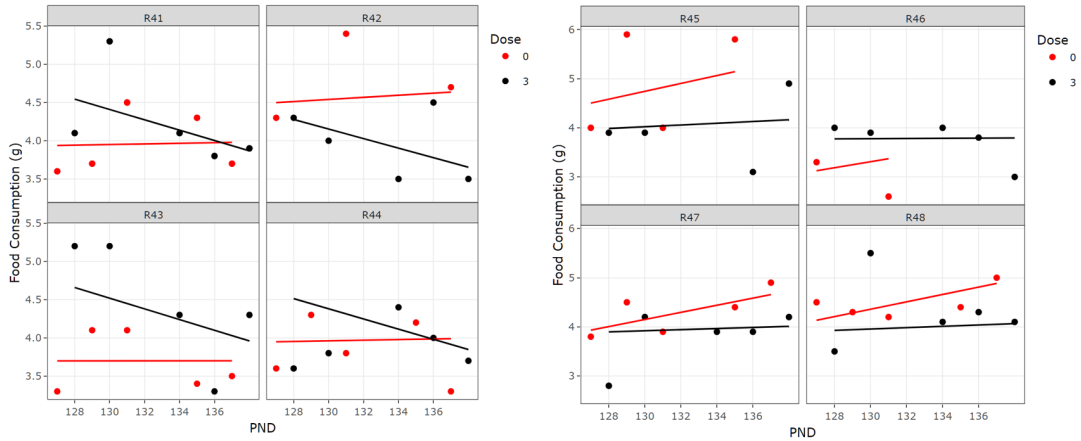


Figure 16. Food consumption following administration of 3 mg/kg risperidone ("1"; black) and vehicle ("0"; red) as a function of PND. For R46, data is missing because the mouse was munching on food and creating food crumbs that were not weighed. All other details are as in Figure 13.

Table 5. Pre-Session 3 mg/kg Risperidone Administration Did Not Change Body Weights in Male or Female Mice

| Regression Results | | | | Analysis of Variance using Type III Wald $X^2$ Tests | | |
|---|---|---|---|---|---|---|
| Predictor | Estimate | SE | T | Predictor | $X^2$ | P |
| Male Pre-Session 3 mg/kg Body Weight | | | | | | |
| Intercept | 28.880 | 2.428 | 11.897 | Intercept | 141.534 | < .001 |
| PND | -0.012 | 0.019 | -0.684 | PND | 0.468 | .494 |
| Dose 3 | -3.138 | 3.447 | -0.910 | Dose 3 | 0.829 | .363 |
| PND: Dose 3 | 0.025 | 0.026 | 0.949 | PND: Dose 3 | 0.90 | .343 |
| Female Pre-Session 3 mg/kg Body Weight | | | | | | |
| Intercept | 24.058 | 4.144 | 5.809 | Intercept | 33.740 | < .001 |
| PND | -0.012 | 0.031 | -0.372 | PND | 0.138 | .709 |
| Dose 3 | -1.564 | 5.844 | -0.268 | Dose 3 | 0.072 | .789 |
| PND: Dose 3 | 0.010 | 0.044 | 0.231 | PND: Dose 3 | 0.053 | .818 |

Note: Regression coefficients from multilevel linear model fits for body weights in males (top) and females (bottom) following pre-session, acute 3 mg/kg risperidone administration. Also shown is the analysis of variance type III Wald chi-square tests of statistical significance.

Table 6. Pre-Session 3 mg/kg Risperidone Administration Decreased Food Consumption in Males, but Not Females

| Regression Results | | | | Analysis of Variance using Type III Wald $X^2$ Tests | | |
|---|---|---|---|---|---|---|
| Predictor | Estimate | SE | T | Predictor | $X^2$ | P |
| Male Pre-Session 3 mg/kg Food Consumption | | | | | | |
| Intercept | 3.325 | 3.432 | 0.969 | Intercept | 0.939 | .333 |
| PND | 0.006 | 0.026 | 0.209 | PND | 0.044 | .834 |
| Dose 3 | 9.712 | 4.808 | 2.019 | Dose 3 | 4.075 | .043 |
| PND: Dose 3 | -0.072 | 0.036 | -1.987 | PND: Dose 3 | 3.948 | .047 |
| Female Pre-Session 3 mg/kg Food Consumption | | | | | | |
| Intercept | -5.268 | 5.909 | -0.892 | Intercept | 0.795 | .372 |
| PND | 0.072 | 0.045 | 1.597 | PND | 2.551 | .110 |
| Dose 3 | 7.735 | 7.672 | 1.008 | Dose 3 | 1.016 | .313 |
| PND: Dose 3 | -0.061 | 0.058 | -1.052 | PND: Dose 3 | 1.106 | .293 |

Note: Regression coefficients from multilevel linear model fits for food consumption in males (top) and females (bottom) following pre-session, acute 3 mg/kg risperidone administration. Also shown is the analysis of variance type III Wald chi-square tests of statistical significance.

**Body Weight and Food Consumption Data: Chronic Phases**

Post-session, chronic administration of 1 mg/kg risperidone significantly increased body weights for male mice by 0.016 grams per day (Figure 17 and Table 7) but not food consumption (Figure 18 and Table 8). Similarly, post-session, chronic 1 mg/kg risperidone significantly increased body weights for female mice by 0.026 grams per day (Figure 17 and Table 7) but not food consumption (Figure 18 and Table 8).

Post-Session 1 mg/kg Risperidone Administration Increased Rate of Body Weight Gain in Males and Females

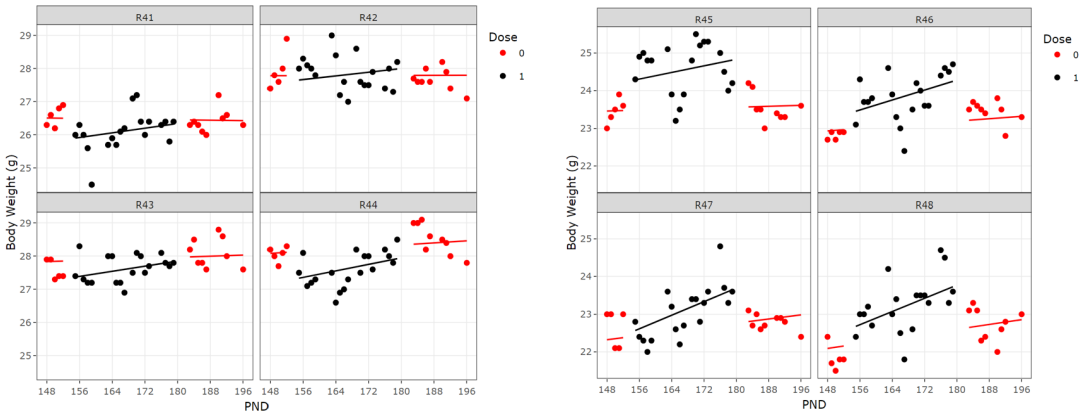


Figure 17. Body Weight for post-session 1 mg/kg risperidone ("1"; black) and vehicle ("0"; red) following post-session, chronic dosing as a function of PND. All other details as in Figure 13.

Post-Session 1 mg/kg Risperidone Administration Did Not Change Food Consumption in Male or Female Mice

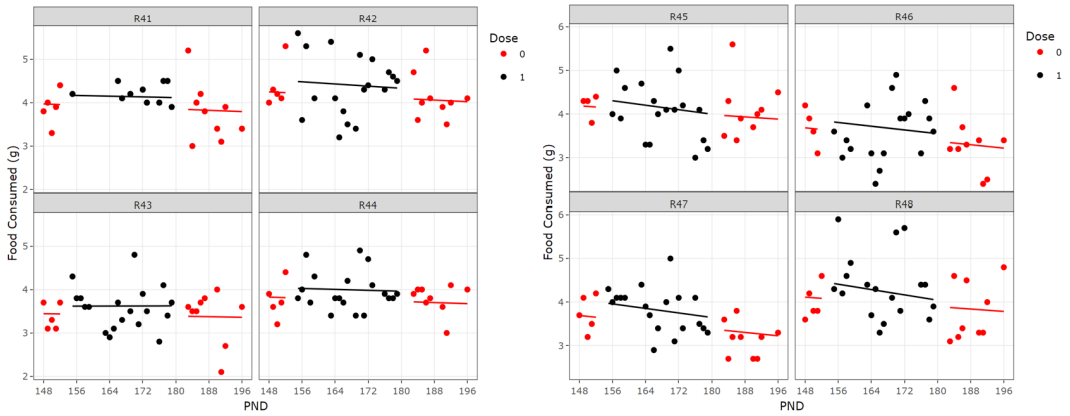


Figure 18. Food consumed values during chronic post-session 1 mg/kg risperidone ("1"; black) and vehicle ("0"; red) administration dosing as a function of PND. All other details as in Figure 13.

Table 7. Post-Session 1 mg/kg Risperidone Administration Increased Rate of Body Weight Gain in Males and Females

| Regression Results | | | | Analysis of Variance using Type III Wald $X^2$ Tests | | |
|---|---|---|---|---|---|---|
| Predictor | Estimate | SE | T | Predictor | $X^2$ | P |
| Male Post-Session 1 mg/kg Body Weight | | | | | | |
| Intercept | 27.165 | 0.546 | 49.753 | Intercept | 2475.392 | < .001 |
| PND | 0.002 | 0.004 | 0.718 | PND | 0.515 | .473 |
| Dose 1 | -3.014 | 1.186 | -2.541 | Dose 1 | 6.455 | .011 |
| PND: Dose 1 | 0.016 | 0.007 | 2.328 | PND: Dose 1 | 5.417 | .019 |
| Female Post-Session 1 mg/kg Body Weight | | | | | | |
| Intercept | 21.189 | 0.888 | 23.849 | Intercept | 568.766 | < .001 |
| PND | 0.010 | 0.004 | 2.314 | PND | 5.355 | .021 |
| Dose 1 | -3.509 | 1.551 | -2.262 | Dose 1 | 5.118 | .024 |
| PND: Dose 1 | 0.026 | 0.009 | 2.840 | PND: Dose 1 | 8.067 | .005 |

Note: Regression coefficients from multilevel linear model fits for body weight in males (top) and females (bottom) following post-session, chronic 1 mg/kg risperidone administration. Also shown is the analysis of variance type III Wald chi-square tests of statistical significance.

Table 8. Post-Session 1 mg/kg Risperidone Administration Did Not Change Food Consumption in Male or Female Mice

| Regression Results | | | | Analysis of Variance using Type III Wald $X^2$ Tests | | |
|---|---|---|---|---|---|---|
| Predictor | Estimate | SE | T | Predictor | $X^2$ | P |
| Male Post-Session 1 mg/kg Food Consumption | | | | | | |
| Intercept | 4.361 | 0.625 | 6.977 | Intercept | 48.675 | < .001 |
| PND | -0.003 | 0.003 | -1.011 | PND | 1.022 | .312 |
| Dose 1 | 0.124 | 1.507 | 0.082 | Dose 1 | 0.007 | .934 |
| PND: Dose 1 | 0.0006 | 0.009 | 0.074 | PND: Dose 1 | 0.005 | .941 |
| Female Post-Session 1 mg/kg Food Consumption | | | | | | |
| Intercept | 5.124 | 0.797 | 6.430 | Intercept | 41.342 | < .001 |
| PND | -0.008 | 0.005 | -1.763 | PND | 3.107 | .077 |
| Dose 1 | 1.018 | 1.826 | 0.557 | Dose 1 | 0.310 | .577 |
| PND: Dose 1 | -0.005 | 0.011 | -0.447 | PND: Dose 1 | 0.200 | .655 |

Note: Regression coefficients from multilevel linear model fits for food consumption in males (top) and females (bottom) following post-session, chronic 1 mg/kg risperidone administration. Also shown is the analysis of variance type III Wald chi-square tests of statistical significance.

Post-session, chronic administration of 3 mg/kg risperidone significantly increased body weights for male mice increased by 0.040 grams per day (Figure 19 and Table 9) but not food (Figure 20 and Table 10). Similarly, post-session, chronic 3 mg/kg risperidone significantly increased body weights for female mice by 0.031 grams per day (Figure 19 and Table 9) but not food consumption (Figure 20 and Table 10).

Post-Session 3 mg/kg Risperidone Administration Increased Rate of Body Weight Gain in Male and Female Mice

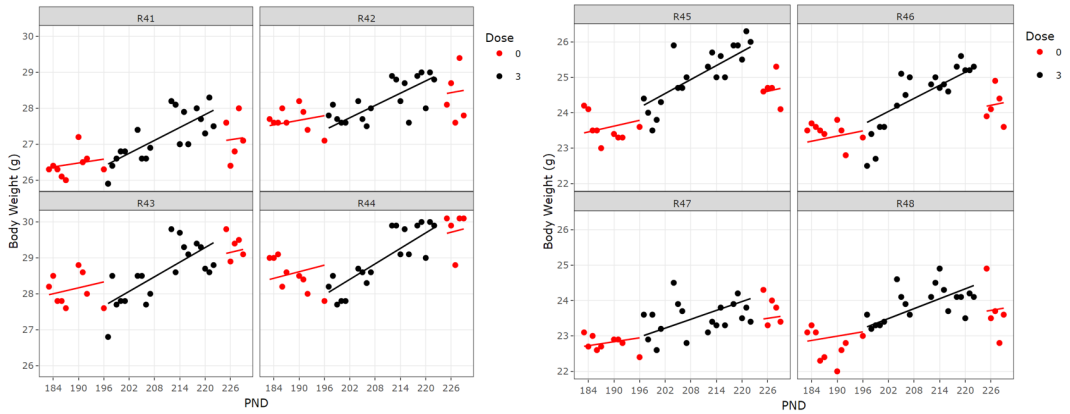


Figure 19. Body Weight for post-session 3 mg/kg risperidone ("1"; black) and vehicle ("0"; red) following post-session, chronic dosing as a function of PND. Other details as in Figure 13.

Post-Session 3 mg/kg Risperidone Administration Did Not Change Food Consumption in Male or Female Mice

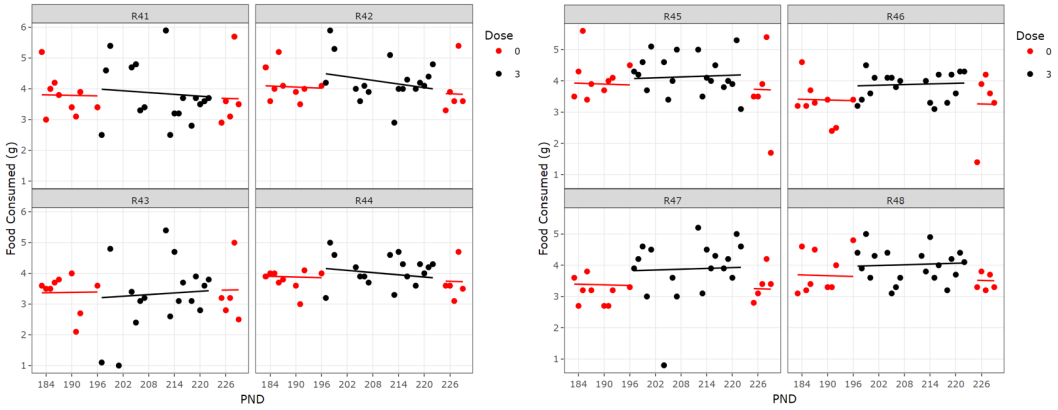


Figure 20. Food Consumption for post-session 3 mg/kg risperidone ("1"; black) and vehicle ("0"; red) following post-session, chronic dosing as a function of PND. Other details as in Figure 13.

Table 9. Post-Session 3 mg/kg Risperidone Administration Increased Rate of Body Weight Gain in Male and Female Mice

| Regression Results | | | | Analysis of Variance using Type III Wald $X^2$ Tests | | |
|---|---|---|---|---|---|---|
| Predictor | Estimate | SE | T | Predictor | $X^2$ | P |
| Male Post-Session 3 mg/kg Body Weight | | | | | | |
| Intercept | 23.109 | 0.660 | 35.007 | Intercept | 1225.482 | < .001 |
| PND | 0.024 | 0.004 | 5.735 | PND | 32.885 | < .001 |
| Dose 3 | -8.330 | 1.452 | -5.738 | Dose 3 | 32.921 | < .001 |
| PND: Dose 3 | 0.040 | 0.007 | 5.766 | PND: Dose 3 | 33.245 | < .001 |
| Female Post-Session 3 mg/kg Body Weight | | | | | | |
| Intercept | 18.918 | 0.709 | 26.699 | Intercept | 712.838 | < .001 |
| PND | 0.023 | 0.004 | 5.969 | PND | 35.629 | < .001 |
| Dose 3 | -5.985 | 1.664 | -3.599 | Dose 3 | 12.953 | < .001 |
| PND: Dose 3 | 0.031 | 0.008 | 3.895 | PND: Dose 3 | 15.172 | < .001 |

Note: Regression coefficients from multilevel linear model fits for body weight in males (top) and females (bottom) following post-session, chronic 3 mg/kg risperidone administration. Also shown is the analysis of variance type III Wald chi-square tests of statistical significance.

Table 10. Post-Session 3 mg/kg Risperidone Administration Did Not Change Food Consumption in Male or Female Mice

| Regression Results | | | | Analysis of Variance using Type III Wald $X^2$ Tests | | |
|---|---|---|---|---|---|---|
| Predictor | Estimate | SE | T | Predictor | $X^2$ | P |
| Male Post-Session 3 mg/kg Food Consumption | | | | | | |
| Intercept | 4.281 | 1.108 | 3.864 | Intercept | 14.927 | < .001 |
| PND | -0.003 | 0.005 | -0.504 | PND | 0.254 | .614 |
| Dose 3 | 1.285 | 2.668 | 0.482 | Dose 3 | 0.232 | .630 |
| PND: Dose 3 | -0.005 | 0.013 | -0.436 | PND: Dose 3 | 0.189 | .663 |
| Female Post-Session 3 mg/kg Food Consumption | | | | | | |
| Intercept | 4.340 | 1.008 | 4.305 | Intercept | 18.534 | < .001 |
| PND | -0.004 | 0.005 | -0.818 | PND | 0.669 | .414 |
| Dose 3 | -1.220 | 2.276 | -0.536 | Dose 3 | 0.287 | .592 |
| PND: Dose 3 | 0.008 | 0.011 | 0.744 | PND: Dose 3 | 0.554 | .457 |

Note: Regression coefficients from multilevel linear model fits for food consumption in males (top) and females (bottom) following post-session, chronic 3 mg/kg risperidone administration. Also shown is the analysis of variance type III Wald chi-square tests of statistical significance.

# Discussion

Regarding sucrose demand, acute pre-session 1 and 3 mg/kg risperidone administration decreased $Q_0$ and increased α, whereas chronic post-session 1 and 3 mg/kg risperidone administration did not change $Q_0$ or α. Additionally, two weeks of chronic post-session 1 mg/kg risperidone administration induced drug sensitization to pre-session 1 mg/kg; however, two weeks of chronic post-session 3 mg/kg administration did not induce risperidone sensitization or tolerance to pre-session 3 mg/kg.

The operant results are important for three reasons. First, acute risperidone administration decreases $Q_0$, which is a measure of *demand intensity* (an organism's consumption when a reinforcer is available at low prices (Koffarnus et al., 2015), suggesting that demand for sucrose at FR 1 (when a low effort was required to produce a reinforcer) was decreased by risperidone administration. Additionally, studies have used $Q_0$ as a measure of hedonic value (Bentzley et al., 2013; Fragale et al., 2017; Hursh & Silberberg, 2008), and since pre-session administration decreases $Q_0$, it would suggest that the reinforcing value of *liking and wanting* sucrose, was decreased by pre-session, acute risperidone administration. Second, acute drug administration increased α, which measures a reinforcer's *essential value* (defined as the parameter of the rate of decline in consumption as price changes (Hursh & Silberberg, 2008)), suggesting that sucrose demand decreased more rapidly following risperidone administration than it did following vehicle administration. Additionally, studies have used α as a measure of *demand elasticity* (inelastic demand occurs when the change in consumption is small as price increases and elastic demand when the change in consumption is large as price increases (Fragale et al., 2017; Hursh & Silberberg, 2008) as indicative of motivational change, and since pre-session administration of risperidone greatly increased α, it suggests that sucrose becomes more elastic or less motivating,

during risperidone administration. Third, responding for sucrose was eliminated following pre-session 3 mg/kg drug administration, suggesting that sucrose's ability to serve as a reinforcer was eliminated by risperidone administration or the animal's ability to nose poke was eliminated.

The results for chronic post-session 1 and 3 mg/kg risperidone administration are important for two reasons. First, chronic drug administration did not change the *demand intensity* of sucrose reinforcers, suggesting that when a low effort was required to produce a reinforcer, demand for sucrose was not changed by risperidone administration. Also, these results suggest that the hedonic value of sucrose was not changed by risperidone administration. Second, after chronic drug administration, α but not $Q_0$, increased during pre-session 1 mg/kg, relative to pre-session 1 mg/kg before the chronic drug administration, suggesting that chronic treatments sensitized mice to the effects of 1 mg/kg on sucrose demand.

In terms of body weight and food consumption, chronic risperidone administration increased body weights without affecting or even reducing food consumption. Acute pre-session 1 and 3 mg/kg risperidone administration did not change body weights, whereas chronic post-session 1 and 3 mg/kg risperidone administration increased body weights. With respect to food consumption, acute pre-session 1mg/kg risperidone administration did not change food consumption in males or females, whereas acute pre-session 3 mg/kg risperidone administration decreased food consumption in males but not females. Further, chronic post-session risperidone administration did not change food consumption in males or females. The results on body weight and food consumption are essential for one reason. Chronic post-session treatments induced weight gain in male and female mice in the absence of increased food consumption or sucrose reinforcement. These results suggest that risperidone can increase body weight for other reasons outside of food consumption.

One limitation of the current study is that two drug doses are insufficient to fully explore the effects of risperidone administration on sucrose reinforcement. It is not clear if doses lower than 1 mg/kg would decrease sucrose reinforcers obtained following pre-session risperidone administration or if these doses would increase sucrose reinforcers obtained (i.e., perhaps the effects of risperidone on sucrose reinforcement follow an inverted-U-shaped curve). In addition, a dose-effect curve for pre-session and post-session treatments may be beneficial for future risperidone studies using economic demand assessments with sucrose reinforcement. A second limitation was that motor movements inside the operant chambers were not measured. Currently, it is unknown if pre-session doses of 1 mg/kg and 3 mg/kg suppressed the value of reinforcers or if animals were too sedated to move efficiently in operant chambers to nose-poke for sucrose. Measuring motor movements inside the operant chambers during pre-session dosing should be explored in future analyses.

In addition to addressing the behavioral effects of risperidone, several avenues for future research are clear based on the current results. The present results suggest that risperidone affects weight gain regardless of food consumption and food reinforcement. Future research should repeat this experiment and address if biological mechanisms, such as D2 receptor antagonism, cause weight gain during risperidone treatment by using genetic manipulation. Additionally, future research should address if the current pre-session and post-session results will be replicated with other SGAs like olanzapine, clozapine, or aripiprazole. Notably, some studies using progressive ratio schedules of reinforcement have suggested that SGAs increase the reinforcing effects of food (Abela et al., 2020; Abela et al., 2019; Cilia et al., 2001; Mobini et al., 2000; Zhang et al., 2005). Possibly, specific binding affinities to D2, 5HT2C, or H1 receptors affect food reinforcement. Research has shown that acute risperidone administration does not

affect the breakpoint for food, while clozapine increases the breakpoint for food (Cilia et al., 2001). Future research should compare the binding affinities of different SGAs to D2, 5HT2C, or H1 receptors and assess if binding affinity to any of these receptor sites during acute or chronic drug administration affects sucrose reinforcement. Lastly, since the rate of weight gain during chronic dosing is independent of the value of sucrose reinforcers or food consumption, further metabolic analyses on risperidone-induced weight gain need to be explored to disentangle the biological and behavioral side effects of SGAs.

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# VITA

Born in Ponce, Puerto Rico, Francis Rafael Torres received his dual bachelors of Science and Arts from University of South Florida. During his undergraduate program, he volunteered in various traumatic brain injury ethanol research studies under Dr. Mark Kindy and Dr. Jessica Hoffman. After finishing his undergraduate program, he volunteered for the Tobacco Research and Intervention Program under Dr. Thomas Brandon in Moffitt Cancer Research Center and pursued a job as an Animal Care Technician at the University of South Florida. As his interest in animal and behavioral pharmacology research grew, he decided to enter the Department of Psychology at Louisiana State University under Dr. Paul Soto. Upon completion of his master's degree, he will begin to work on his doctorate's degree.