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Abstract

Haloperidol, a dopamine (DA) D2 receptor antagonist, is an antipsychotic drug which is commonly used to treat schizophrenia and other psychiatric disorders. These disorders are often characterized by elevated striatal dopamine, which is speculated to have a role in producing positive symptoms such as hallucinations, delusions, and paranoia, as well as symptoms related to motivational salience and reward prediction. Individuals with schizophrenia also exhibit negative symptoms, such as amotivation, anergia, fatigue, and apathy among others. While some negative symptoms of schizophrenia are inherent to the pathophysiology, other negative symptoms are hypothesized to be partially induced by chronic exposure to antipsychotic treatments, such as haloperidol. This may be due to the blockade of DA receptors in some striatal areas of the brain, as well as D2 receptor density changes as a result of chronic exposure to a DA D2 antagonist. Over the past several decades, effort-based decision making tasks have been used to model motivational symptoms of psychiatric disorders in rodents. Previous experiments have shown that DA depletions or antagonism in the nucleus accumbens (NAc) reduces the amount of effort animals will exert, biasing them towards the low-effort chow alternative. To elucidate the role of chronic DA D2 receptor antagonism on motivation in rats, this study assessed the impact of chronic haloperidol administration on cost-effort computing using the FR5/chow feeding choice task. It was hypothesized that we would see a bias in the group of rats receiving haloperidol towards the low-effort alternative. This study will be beneficial in understanding the impact of chronic, steady state administration of antipsychotics on cost-effort computing and effort-related choice behaviors, with further implications for treatment of schizophrenic patients.

I.   Introduction

Schizophrenia is a debilitating disease that affects 0.5 to 1.0 percent of people worldwide, often affecting not just the patients themselves, but their families, friends, and caregivers. It is not only a mentally and socially debilitating disease but also the seventh most costly medical disease to the US (Ross et al., 2006). Typically diagnosed between the late teens and early 30s, the cause of schizophrenia is still relatively unknown and seems to be a mix of various risk factors, ranging from genetics to environment and drug usage. The most notable genetic factors are mutations to neuregulin 1, dysbindin, DISC1, and translocations of chromosome 22 , and most notably a serine311cystiene polymorphism on dopamine (DA) D_2 receptors (Glatt and Jönsson, 2006; Howes and Kapur, 2009; Ross et al., 2006). When these genetic factors fall in place with increased stress and chronic cannabis or amphetamine use, the risk for schizophrenia markedly increases. Most of these risk factors result in an increased release of striatal dopamine and increased DA metabolites, especially in tandem with increased stress or drug use (Howes, 2009).

Unsurprisingly then, the current hypothesis for understanding schizophrenia is centered around DA. The DA hypothesis is the idea that excessive dopaminergic transmission causes schizophrenia, which can be seen as increased subcortical DA transmission due to prefrontal dysfunction, increased number of DA receptors, and increased DA in tissue (Freedman, 2003; Seeman 2006; Howes et al. 2017; Meltzer and Stahl 1976). It is understood that positive symptoms such as hallucinations and delusions are caused by an increase in DA in the striatum and negative symptoms such as apathy and amotivation are caused by an decrease of DA in the frontal cortex (Freedman, 2003; Ross et al., 2006). Schizophrenic patients have been shown to have elevated levels of presynaptic striatal dopamine, an increase in the synthesis and release of

dopamine, and increased baseline occupancy of DA D_2 receptors during acute psychotic episodes (Howes and Kapur, 2009; Seeman, 2006; Freedman, 2003). This elevated DA transmission is thought to be then filtered through each person's own cultural and cognitive schemas creating the unique clinical manifestations within the classic symptomology (Howes and Kapur, 2009).

DA is essential in the brain of every animal, playing roles in the execution of voluntary movement, activational aspects of motivation, reward processing, working memory, and emotional and cognitive functioning (Roeper, 2013; Liss, 2007). In addition to schizophrenia, DA is implicated in a wide variety of disorders ranging from Parkinson's disease and obsessive compulsive disorder, to addiction and depression (Poulin, 2014). Many drugs that increase DA transmission have been shown to induce psychosis in healthy individuals and heighten psychosis in people suffering from schizophrenia, further implicating excessive DA as a dominant factor in the symptomology of schizophrenia (Freedman, 2003; Ross et al., 2006). Part of schizophrenic pathology is not just a widespread increase of DA, but more specifically, an increase in striatal DA and striatal DA $D_{2/3}$ receptor density has been noted (Howes and Kapur, 2009; Seeman, 2006; Ross et al, 2006; Glatt, 2006). Of the five known DA receptor subtypes, the DA D_2 receptor is the most critical for schizophrenia symptom regulation (Seeman, 1984; Howes and Kapur, 2009). Effective antipsychotics are most active on DA D_2 receptors; there is a direct correlation between DA D_2 affinity and clinical potency of various antipsychotics, while there is no correlation between DA D_1 receptor occupancy and their clinical efficacy (Seeman, 2006; Howes and Kapur 2009).

There are two families of antipsychotics used to treat schizophrenia: typical and atypical antipsychotics. Atypical antipsychotics like clozapine block DA receptors, but often have additional mechanisms of action while typical antipsychotics are DA D_2 receptor antagonists or

monoamine storage inhibitors and effectively suppress delusions and hallucinations (Seeman, 2006; Ross, 2006; Howes and Kapur, 2009). As stated above, there is a direct correlation between DA D_2 receptor sensitivity and clinical potency; the therapeutic levels of antipsychotic drug occupancy is between 60-80% so the lower the K_d of the drug, the lower the dose required for efficacy (Seeman, 2006). Another biochemical property of relevance when comparing antipsychotics to one another is how loosely/tightly attached to the DA D_2 receptor they are and how rapidly they dissociate. Antipsychotics that elicit or exacerbate negative symptoms are more tightly bound and dissociate more slowly (Seeman, 2006; Ross et al., 2006). One of the most commonly used typical antipsychotics, haloperidol, falls under this category with a K_d between 0.4 and 0.74 and the time for 50% offset from D_2 at 38 minutes, one of the longest of antipsychotics (Seeman, 2006).

Even with the propensity to induce negative symptoms with prolonged use, haloperidol remains one of the most common antipsychotics as a DA D_2 antagonist with pronounced efficacy in treating positive symptoms (Beresford and Ward, 1987). It is typically administered in one of two ways: a daily oral dose or an injectable version of haloperidol decanoate, both of which have matched clinical safety and therapeutic reliability (Reyntjens, 1982; Tollefson et al. 1997; Zimbroff et al., 1997; Beresford and Ward, 1987). Patients given monthly injections had a slow, uniform release of haloperidol reaching a steady state after about 3 injections (Reyntjens, 1982). There have been several reported advantages to monthly chronic administration compared to oral administration: patients had better compliance, more reliable absorption of drug, and fewer, but still not absent, side effects such as avolition, blunted affect, and alogia (Beresford and Ward, 1987; Cobo et al., 2016). Compliance is hard to achieve for treatment of many diseases, but is especially difficult with patients suffering from paranoid delusions like those seen in

schizophrenia. A chronic administration regimen allows people with schizophrenia to less frequently be reminded of their condition and removes the intentional or unintentional skipping of treatments that patients who take a daily oral dose often experience (Beresford and Ward, 1987).

While, as stated above, chronic administration of haloperidol among other DA D_2 antagonists lessens the likelihood of noncompliance as compared to other methods of administration in the treatment of schizophrenia, it still decreases DA transmission and can therefore cause or exacerbate the negative symptoms of schizophrenia (Beresford and Ward, 1987; Cobo et al., 2016; Fibiger et al., 1976; Salamone et al., 2001; Yang et al., 2020; Koch, 2000; Walton et al., 2003). While schizophrenia is most commonly thought of, and treated for, the positive symptoms of hallucinations and delusions, the negative symptoms actually account for the poor functional outcome and lowered life expectancy (Buchanan, 2007; Mader and Galderisi, 2017). There are five main constructs that are considered negative symptoms: blunted affect (a decrease in the expression of emotion), alogia (reduction in the quantity of speech), anhedonia (a diminished ability to experience or anticipate pleasure), asociality (reduced social initiative), and avolition (decreased drive and lack of goal directed activity) (Buchanan, 2007; Marder and Galderisi, 2017). Many of these secondary symptoms overlap into other disorders. Blunted affect, anhedonia, asociality, and avolition are all characteristics commonly seen in depressed patients as well as in some people with Parkinson's Disease (Mader and Galderisi, 2017; Buchanan, 2007). The biggest predictor of the severity of real life function among these symptoms is avolition or amotivation (Marder and Galderisi, 2017).

Motivation can best be described as "the set of processes through which organisms regulate the probability, proximity, and availability of stimuli"(Salamone, 1992). Motivation is

predominantly thought to be controlled by nucleus accumbens dopamine by mediating the primary reinforcing properties of stimuli (Salamone and Correa, 2012, Salamone et al., 2002, Salamone 1994, and Salamone, 1992). DA in the nucleus accumbens is thought to be particularly important in relation to overcoming work-related response costs, essentially motivation to work harder for a higher reward (Salamone et al., 2002; Howes and Kapur 2009; Kurniawan et al., 2011).   Animal models for motivation have been around for decades and often utilize a high effort/high reward choice vs low effort/low reward choice. One of the more common models of motivation is giving an animal the option to lever press for a reward such as food pellets with some studies offering chow alternative and some offering no alternative (Koch, 2000; Salamone et al., 2001, Salamone et al., 1994). In studies where dopamine transmission was reduced via DA D_2 antagonists, rats showed decreased lever pressing, and therefore decreased motivation (Koch, 2000; Salamone et al., 2001) and as seen by Salamone et al., 1994, rats that had higher rates of responding had higher levels of nucleus accumbens dopamine. In a study by Yang et al., (2020), administration of the DA D_2 antagonist haloperidol to mice reduced their tendency to work for food, but did not decrease primary food motivation on a FR1 panel pressing/choice procedure. This finding resonates with a study that found that when administered to rats, the DA D_2 antagonist Sulpiride dose-dependently decreased lever press responses and increased consumption of concurrent chow; again showing a decrease in motivation with no impairment of primary food motivation (Koch, 2000). The respective increased or decreased rate of responding is not the result of reduced motivation for food or anorexia. In studies where rodents were given the option of a low effort/low reward alternative such as chow, the rodents with decreased rates of responding showed increased chow consumption (Fibiger et al., 1976; Koch, 2000; Salamone et al., 2001).

In the present study, rats were given the choice between a high effort alternative (lever pressing) for a highly valued reward (high carbohydrate pellets) and low-effort alternatives for a less valued reward (eating the chow in the operant box), akin to the methods seen in Fibiger et al. (1976), Koch (2000), and Salamone et al. (2001). Since chronic slow release of DA D_2 antagonists, such as haloperidol, is a typical method of drug administration in humans, a chronic administration method via iPRECIO pumps was used. Due to the fact that haloperidol reduces DA transmission and induces motivational dysfunctions in humans, it was hypothesized that the rats receiving haloperidol would be biased towards the low-effort/low-reward alternative, seen as a reduction in lever presses and an increase in chow consumption.

II.   Materials and methods
Subjects:

A total of 17 male Sprague Dawley rats (Harlan Spragye Dawley, Indianapolis IN, USA) were used for this experiment with initial weights between *279-299g*. The rats were pair-housed in a colony that was maintained at 23°C with a 12 hour light/dark cycle (lights on at 07:00). They were food restricted to 85% of their projected free-feeding weights during training periods and water was available ad libitum. The animal protocols were implemented in accordance with the University of Connecticut Institutional Animal Care and Use Committee.

Behavioral Training:

As depicted in Figure 1A, rats were initially trained on a continuous reinforcement fixed ratio 1 (FR1) schedule (one press delivers one high carbohydrate pellet (Bio-serv, Frenchtown, NJ, USA)) 30 minutes a day for one week, and then shifted to a FR5 schedule (five presses delivers one pellet). After five weeks of FR5 training or until a stable baseline was reached, rats were

shifted to a FR5/chow feeding choice schedule for approximately four weeks, in which the rats

had the option to lever press for pellets or eat the freely available chow (Laboratory Diet, 5P00

Problab RHM 3000, Purina Mills, St. Louis MO, USA; 15-20g) placed on the floor of the

chamber. The behavioral sessions took place in operant conditioning chambers (28 x 23 x 23cm,

Med Associates). After the training session, the rats were immediately removed from the

operant chambers and the food intake was determined by the difference in weights of the pre and

post chow (including spillage). Rats were trained until they established a stable baseline lever

pressing and chow intake level (consistently greater than 1,200 lever presses per 30 minutes;

approximately four weeks) before undergoing surgical procedures. On most days rats did not

receive additional chow in their home cage, but over weekends, after drug tests and during

recovery, rats typically did receive additional chow in their home cage to maintain predetermined
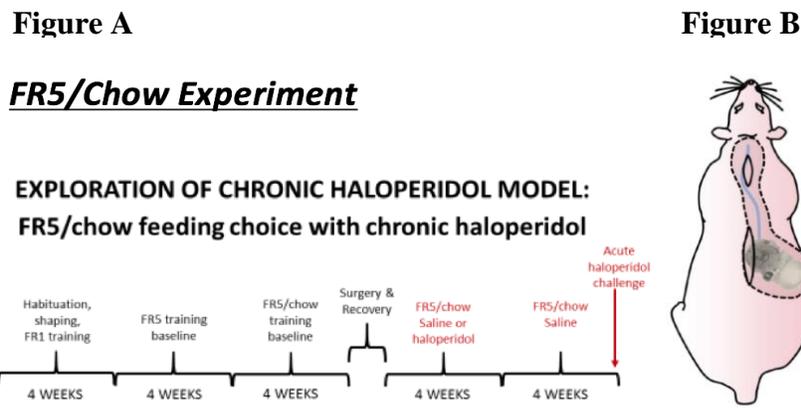
target body weights.

Figure A   **Figure B**

Figure 1. Schematic representations of experimental timeline and surgical methods. **(A)** The

experimental timeline of the behavioral training, surgery, drug treatment, washout period and

acute haloperidol challenge. **(B)** A representation of the iPRECIO pump that was surgically

implanted into the rats to facilitate chronic drug administration throughout the experiment.

Surgeries:

The rats underwent surgery after they had established a baseline of lever presses and chow intake (four weeks of training). Prior to surgery, each rat was placed into a chamber with a secure lid that was filled with isoflurane at 2-4% with a flow rate of 1-2 L/min to induce anesthesia. Then the rat was tested for reflexes (respiration rate, ocular reflex, and pedal reflex) prior to the surgery start, and every ten minutes thereafter. The rats remained on a pre-warmed circulating water heating pad with a nose cone fitted over their snout delivering the anesthesia for the entire procedure. Ocular lubricant was applied to the eyes and the rat's back was shaved around the insertion site. The shaved site was then cleaned with an antiseptic solution (betadine), and local analgesic (topical lidocaine) was applied to the site. A small incision was then made with a scalpel along the rat's back, and a subcutaneous pocket of approximately 5cm was made via a blunt hemostat. As seen in figure 1b, the pre-filled iPRECIO pump was then placed into the subcutaneous pocket, gently sutured to the muscle in two places, and the wound was closed with wound clips and sutures. The rat was then placed in a clean cage, over a heating pad and given unlimited chow and water. Rats were then housed individually for 7-10 days while they recovered, during which time they had ad libitum access to chow and water.

Drug Treatments:

For the twelve days following surgery, the pumps contained saline and the flow rate was set to 1 uL/hour while the rats recovered and re-established baseline behavior on the FR5/chow task. Once baseline criteria was met, the rats were randomly assigned to either a vehicle (0.3% tartaric acid solution), low dose (1.0 mg/ml haloperidol), or high dose (2.0 mg/ml haloperidol)

treatment group. The drug was administered subdermally through an osmotic mini pump with a flow rate of 3μL/hour. Testing was conducted daily, five to six days a week, for a total of 19 days during the drug exposure phase. Then, the solution inside the pumps was replaced with saline for a four week washout period, during which time the animals were trained five days a week. After the washout period, the solution inside the pumps of all three groups was replaced with a high dose (2.0 mg/ml haloperidol) for the acute haloperidol challenge and the rats were tested again.

III. Results

The data from the FR5/Chow experiment were analyzed via factorial analysis of variance (ANOVA) calculated using SPSS. The number of comparisons was limited to the number of comparisons minus one and a p value of <0.05 was considered statistically significant. The between-subjects factor is the treatment group and within-subject factor is week. Figure 2A shows the effect of chronic haloperidol administration on lever presses during the FR5/Chow feeding task. During the drug exposure phase there was a significant between subjects effects of treatment group on lever presses ($F_{(2,14)} = 20.498$, $p <0.001$) and during washout there was a significant effect of week on lever presses ($F_{(3,12)} =11.088$, $p = 0.001$) and week by treatment interaction effect on lever presses approached significance ($F_{(6,12)}=2.661$, $p =0.070$). Figure 2B shows the effect of chronic haloperidol administration on chow intake during the FR5/Chow feeding task. There was a significant between-subjects effect of treatment on chow intake during the drug exposure phase ($F_{(2,14)} = 18.574$, $p < 0.001$). During the washout period there was a significant effect of week ($F_{(3,12)} = 8.813$, $p=0.002$) and significant week by treatment interaction effect on chow intake ($F_{(6,12)} = 3.194$, $p = 0.041$).

The data from the acute haloperidol challenge was analyzed using a one way analysis of variance (ANOVA) in SPSS. In both figure 2A showing the effect of chronic haloperidol administration on lever presses and in figure 2B showing the effect of chronic haloperidol administration on chow intake, there was no significant effect of treatment in the acute haloperidol challenge.
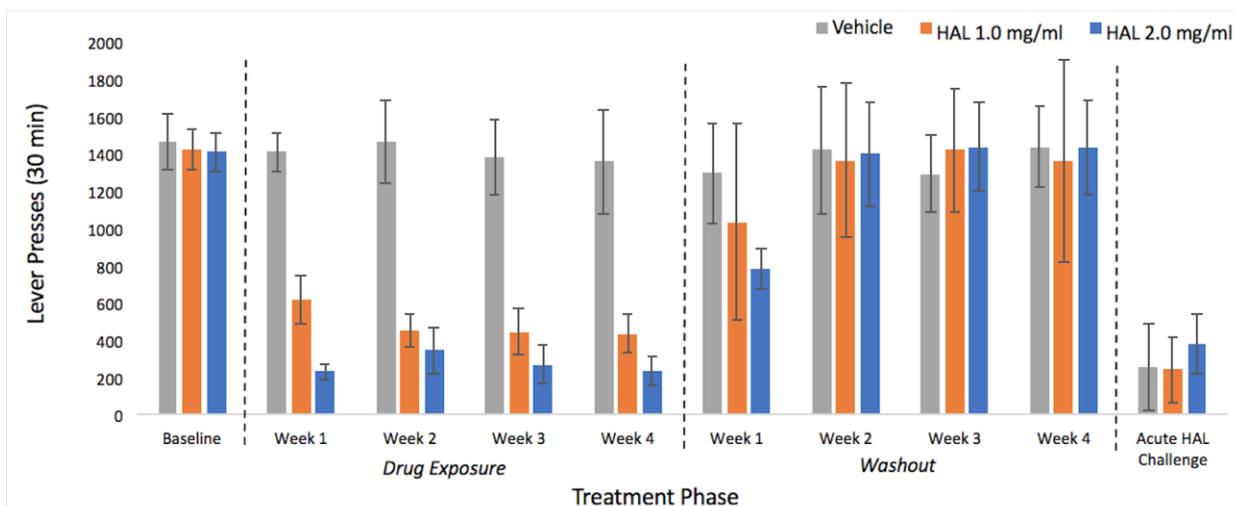

Figure 2A. The effect of chronic haloperidol administration on lever presses during the FR5/Chow feeding task. Drug exposure n = 17, washout and acute haloperidol challenge n = 7. Dashed lines represent separations between treatment phases. Bars represent mean lever presses (± SEM).
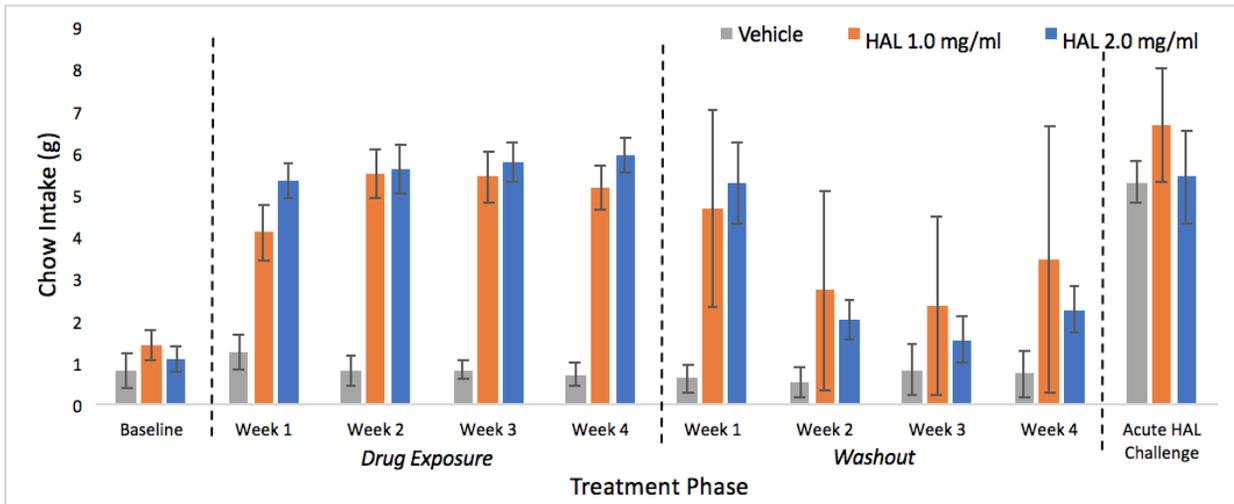
Figure 2B. The effect of chronic haloperidol administration on lever presses during the FR5/Chow feeding task. Drug exposure n = 17, washout and acute haloperidol challenge n = 7. Dashed lines represent separations between treatment phases. Bars represent mean chow intake (± SEM).

IV.   Discussion

The purpose of this study was to assess the effects of chronic DA D_2 blockade via haloperidol on cost-effort computing using a FR5/chow feeding choice task. This specific animal model was used to represent relative levels of motivation, and can be used to draw comparisons to the debilitating secondary negative symptoms of schizophrenia which can be induced or exacerbated by long term drug treatment. The results showed that chronic haloperidol administration significantly and dose dependently reduced lever presses and increased chow intake during the FR5/chow feeding choice task and that continuous subdermal infusion of haloperidol by the iPRECIO pumps provided a realistic model of chronic antipsychotic administration.

Schizophrenia treatment with DA D2 antagonists is most commonly administered chronically, so our study strove to mimic this through a continuous subdermal infusion of haloperidol via an iPRECIO pump. Utilizing implantable diffusion pumps offers distinct advantages over other methods of chronic drug infusions such as tethered infusion systems which restrict movement or vascular access ports that require regular cleaning and maintenance (Cobo et al., 2016). The iPRECIO pumps used in this study exert no significant impact on the rats physiological condition (Tsubio et al., 2016) and drastically reduces the amount of handling and stress, as well as the risk of infection for the rats (Tsung et al., 2011, Cobo et al., 2016). In this study the rodents underwent three unique testing periods: treatment, washout, and an acute haloperidol challenge. Using a method of chronic administration eliminated sources of unnecessary stress to the rodents such as additional surgeries to change the treatments or refill the pump reservoirs, thus minimizing possible mediating variables which may have influenced the results.

At baseline, the rodents in this study showed high levels of motivation via lever pressing. During the drug treatment phase of this study, we saw a significant dose-dependent decrease in lever presses in treatment groups receiving the DA D_2 antagonist, indicative of a decrease in motivation. Moreover, the rats that showed decreased lever pressing, showed an increase in their chow intake, indicating that the decrease in lever pressing for a food reward was not due to a decreased appetite and that the primary food reinforcement is still intact. This further corroborates our hypothesis that decreased DA via chronic DA D_2 antagonism leads to a significant decrease in motivation. Our results are consistent with results of previous studies that utilized cost-effort models and DA D_2 antagonists to show that chronic DA D_2 antagonism decreases motivation (Salamone et al., 2001; Fibiger et al., 1976; Koch, 2000; Yang et al., 2020;

Moore, 2019, unpublished thesis).   During the washout phase, the lever pressing and chow intake of the haloperidol treated groups regressed close to baseline and showed a significant effect of week as well as a week by treatment interaction effect for chow intake and a week by treatment effect that approached significance for lever pressing. By week two of washout, the treatment groups had both fallen back to baseline, and then remained fairly steady for week three and four indicating essentially a full recovery prior to the acute haloperidol challenge.

Due to a nationwide shutdown of laboratories because of COVID-19, we had to sacrifice 10 of our rodents prior to the washout and acute haloperidol challenge phases of this study, reducing the subjects from 17 to 7 and decreasing the power of our study. While the washout phase results of our study were fairly similar to previous studies, in this study we did not see any significant effects of the acute haloperidol challenge. This contrasts results found in a FR5 only (no concurrent chow) study where the high and low dose groups had more lever presses in a acute haloperidol challenge than the vehicle group, suggesting a tendency towards tolerance to haloperidol as a result of the four week drug phase (Moore, 2019, unpublished thesis). In a FR5/chow study we would expect to see more of an effect during the acute haloperidol experiment because the rats have the ability to eat the concurrent chow instead. Since the primary food reinforcement is not diminished in animals treated with haloperidol, giving the option of low effort/low reward chow as well as a high effort/high reward reinforcer, we would expect to see more significant effects. However, further tests with more subjects would be necessary for the washout and acute haloperidol challenge phases of this study to validate this hypothesis. Moreover, it would be beneficial in future studies to collect blood samples after the drug exposure and washout periods to analyze the serum drug concentrations and ensure that

there was complete washout prior to the acute haloperidol challenge. This is important to further validate the results from the acute haloperidol challenge.

Current treatment for schizophrenia is predominantly focused on alleviating positive symptoms, often at the expense of negative symptoms (Seeman, 2006; Ross, 2006; Howes and Kapur, 2009). These negative symptoms can be debilitating for patients, causing amotivation, flattened affect and reduced cognitive ability, effectively preventing them from leading a normal life (Buchanan, 2007; Freedman, 2003; Ross et al., 2006). These symptoms may be improved by further exploration of chronic administration models, which already have been shown to be beneficial in ensuring patient compliance (Beresford and Ward, 1987). This research has important implications in the clinical setting for the treatment of positive and negative symptoms of schizophrenia and other psychiatric disorders.

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