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Latent Inhibition and Extinction Rate of the Conditioned Stimulus in Long Evans and Brattleboro Rats Using Conditioned Taste Aversion

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by

Elizabeth Vu Tran

Committee in charge:

Professor David Feifel, Chair
Professor Takaki Komiyama, Co-Chair
Professor Jill Leutgeb

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Co-Chair

Chair

University of California, San Diego

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ABSTRACT OF THE THESIS

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Elizabeth Vu Tran

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Professor David Feifel, Chair

Professor Takaki Komiyama, Co-Chair

Brattleboro rats, a Long Evans strain with a single gene mutation in vasopressin, have inherent cognitive deficits in memory, emotional reactivity, motivation, attention, and social recognition, which are abnormalities associated with schizophrenia. Latent inhibition (LI) refers to a decrease in conditioned learning that occurs when the subject being tested is preexposed to the to-be-conditioned stimulus without the paired unconditioned stimulus. The LI deficit in schizophrenics has been used as evidence of a selective attention deficit in schizophrenia. Given that the Brattleboro rats display several natural deficits that are also seen in schizophrenics, this experiment investigated whether

Brattleboro rats also display deficient LI. We hypothesized that the Brattleboro rats will exhibit LI deficits compared to Long Evans rats.

The conditioned taste aversion paradigm was used to test LI. Analysis of the data showed that both the Long Evans and Brattleboro rats displayed LI ($p<0.05$), however, the Brattleboro rats showed reduced LI compared to the Long Evans rats ($p<0.05$). Also, we studied extinction of the conditioned stimulus and found the preexposed Long Evans rats extinguished it at a similar rate as the non-preexposed Long Evans rats ($p>0.05$). However, the preexposed Brattleboro rats extinguished it significantly slower than the non-preexposed Brattleboro rats ($p<0.01$); they inhibited extinction. Although the Brattleboro rats displayed LI, they will continue to serve as models for schizophrenia because of the other cognitive deficits observed in them.

1. Introduction

1.1 Schizophrenia

Schizophrenia is a chronic, severe, mental disorder commonly manifested as paranoid or bizarre delusions, disorganized speech or thinking, and auditory hallucinations (Van Os and Kapur, 2009). Schizophrenia tends to affect behavior and emotion in addition to cognition because those with schizophrenia are likely to have comorbid conditions where major depression and anxiety disorders are present (Buckley et al, 2009). Social withdrawal, lack of hygiene, and loss of motivation and judgment are all common in schizophrenia (Carson, 2000). Current treatment includes psychotherapy and antipsychotic medications which function to suppress dopamine and serotonin receptor activity (Becker and Kilian, 2006). Genetics, neurobiology, and psychological processes are factors that appear to contribute to this disorder, though no single cause has yet to be found.

Schizophrenia affects about 1% of people worldwide and the onset generally begins in late adolescence and early adulthood, which is a critical time in an individual's social and career development (Freudenreich et al, 2008). In schizophrenia, there are two categories of symptoms: positive and negative. Positive symptoms (delusions, thought disorders, hallucinations) are those that most individuals do not normally experience but are present in schizophrenics (Kneisl and Trigoboff, 2009). Those with positive symptoms generally respond well to medication. Negative symptoms (flat affect and emotion, inability to experience pleasure, lack of desire to form relationships, and lack of motivation) are deficits of normal emotional responses or of other thought processes, and

those with these symptoms respond less well to medication (Carson, 2000). Research shows that negative symptoms contribute to a poor quality of life and functional disability than do positive symptoms (Velligan and Alphs, 2008).

Studies have used brain imaging technologies like functional magnetic resonance imaging and positron emission tomography to look at the functional differences in brain activity between healthy controls and schizophrenics. More specifically, the dopamine function in the mesolimbic pathway of the brain has been an area of interest. It has been found that phenothiazine drugs reduce psychotic symptoms through blocking dopamine function, while amphetamines exacerbate the psychotic symptoms through triggering the release of dopamine (Laruelle et al, 1996). The dopamine hypothesis of schizophrenia arose and proposed that excessive activation of the dopamine receptor D2 led to the positive symptoms of schizophrenia (Carlsson, 1988).

1.2 Animal Models Relevant to Schizophrenia

Current animal models of schizophrenia are not intended to serve as the complete animal equivalent of the disorder, but instead, they are used to test hypotheses regarding factors or pathways that may contribute to schizophrenia (Marcotte et al, 2001). This is due to the inability to model the core symptoms of the disorder such as hallucinations and delusions in animals, and so, a solution was devised to model putative biological markers such as prepulse inhibition deficits. Some models are based on the manipulation of the neurotransmitter systems in order to elicit behavioral or neurochemical changes that are believed to be involved in schizophrenia (Marcotte et al, 2001), while other models

produce hippocampal lesions in the brain (Lipska, 2004). The models are then validated based on how well their performance in a given test corresponds to performance of schizophrenic patients. One model used in schizophrenia is based on the dopamine hypothesis, which states that a dysfunction in the dopamine neurotransmission leads to the symptoms observed in schizophrenia. Hyperactivity of the mesolimbic dopaminergic neurons possibly produces symptoms like psychosis (Seeman, 1987). Amphetamine administration produces excess dopamine release (Breier et al, 1997). Behavioral alterations like hyperlocomotion and stereotypy were seen in these animals and when they were treated with antipsychotics, reduced behavior was observed which further supports the validity of this model (Pijnenburg et al, 1975). In addition, altered prepulse inhibition of the startle (PPI) and latent inhibition (LI) are deficient in schizophrenics and are therefore considered important features in establishing the validity of animal models (Swerdlow and Geyer, 1998; Moser et al, 2000). Studying PPI and LI in animals and relating them to dysfunctions in schizophrenics provides an approach to modeling schizophrenia. PPI is a test of preattentional sensorimotor gating, which is impaired in schizophrenics (Braff et al, 1978). Using the dopamine agonists such as apomorphine, one can disrupt PPI in both humans and rats, thereby mimicking the PPI deficits observed in schizophrenics. With antipsychotic treatment, one can restore the PPI function in apomorphine-treated rats (Swerdlow et al, 1994). Also, another method to disrupt PPI in rats is to infuse dopamine directly into the nucleus accumbens (Swerdlow et al, 1994). The administration of antipsychotics will allow for PPI restoration. Schizophrenics are impaired in a number of experimental cognitive features of information processing and selective attention that includes sensorimotor gating and latent inhibition. Latent

inhibition is the retardation in learning of a stimulus to which there is prior exposure without any consequences (Weiner, 1990). LI reflects a form of selective attention where it corresponds to one's ability to attend to important information in one's environment and to ignore the unimportant information (Lubow, 1989). LI occurs when the subject learns to ignore a trivial stimulus that does not predict an important event and when the stimulus is later given meaning, the subject has to overcome their ignore response before conditioning can occur (Lubow, 1989). LI is important for understanding the cognitive deficits in schizophrenia. LI has been reported to be reduced in schizophrenia patients (Gray et al, 1991; Lubow and Gewirtz, 1995). This finding has been interpreted as the inability of schizophrenics to ignore irrelevant stimuli. In addition, LI in rats is sensitive to early developmental influences like isolation rearing and handling stress, so LI could be used as a cross-species model to study neurodevelopmental processes seen in schizophrenia (Weiner et al, 1985; Feldon and Weiner, 1988; Feldon et al, 1990). The LI deficit in schizophrenics has been used as evidence of a selective attention deficit in schizophrenia (Gray et al, 1991; Lubow and Gewirtz, 1995), although Swerdlow et al. (1996) failed to find an LI deficit in patients. LI deficits in schizophrenics are detectable early in the course of the disorder and before the administration of antipsychotic drugs (Baruch et al, 1988). In addition, when normal volunteers were given amphetamine, LI was also disrupted which was consistent with the hypotheses regarding dopamine hyperactivity in schizophrenia (Carlsson and Lindqvist, 1963; Carlsson and Carlsson, 1990). A study by Conti et al (2001) found that Brown Norway rats, another model for schizophrenia, displayed relatively low prepulse inhibition of the acoustic startle response as well as poor latent inhibition. Other studies which bred rodents for an altered

behavioral response to dopaminergic drugs seem to suggest that PPI and LI have common genetic substrates (Kline et al, 1998; Ellenbroek et al, 1995). Therefore, dopamine may possibly play a role in low PPI and LI. In rats, administration of amphetamine also disrupts LI and treatment with antipsychotic drugs reverses the effect. Since LI can be studied in both humans and animals and amphetamine can cause disruption in both species, LI has garnered interest as an important feature in establishing the validity of animal models.

1.3 Brattleboro Rat as Candidate Animal Model of Relevance to Schizophrenia

Brattleboro rats are Long Evans-derived rats with a single base pair mutation that prevents the proper synthesis of vasopressin. The Brattleboro rats that are homozygous for this mutation show some behaviors that are analogous to behaviors seen in schizophrenia, such as abnormalities in memory (Laycock et al, 1983), stress reactivity (Williams et al, 1985), social recognition (Engelmann and Landgraf, 1994), motivation (Williams et al, 1983) and attention (Williams et al, 1983). Studies have shown that vasopressin plays an important role in learning, memory processes, emotional behavior, and cognition and a null mutation in the vasopressin gene will lead to alterations in brain development, such that a vasopressin deficiency during the pre- and early postnatal periods contributed to brain abnormalities that persisted into adulthood (Jentsch et al, 2003; Boer, 1985). In addition, the Brattleboro rats have exhibited natural schizophrenia-like deficits in PPI, social recognition deficits, and natural social discrimination deficits (Engelmann and Landgraf, 1994; Feifel et al, 2009; Feifel and Priebe, 2001). Given that the Brattleboro rats display natural deficits that are also seen in schizophrenics, it is

important to determine if they display LI in order to assess their similarity to schizophrenics. A previous study showed that Brattleboro rats can acquire a conditioned taste aversion (CTA) as well as Long Evans rats and so, vasopressin is not necessary for normal acquisition of CTA (Yirmiya et al, 1987). Since the Brattleboro rats drink much more than the control Long Evans rats due to the vasopressin deficiency and the amount of drinking during acquisition could affect the strength of the CTA, Yirmiya et al found a way to equate the amount consumed by the two strains on acquisition day. The researchers found that after a three hour water deprivation, the Brattleboro rats drank the same amount of water as the Long Evans rats after a twenty four hour deprivation (Yirmiya et al, 1987). The CTA paradigm using lithium chloride, an illness-inducing agent as the unconditioned stimulus and saccharin water as the conditioned stimulus, tested for the presence or absence of LI.

In this study, LI was assessed in two strains of rats: Long Evans and Brattleboro rats. The Long Evans control rats, the wild type parental strain of the Brattleboro rats, have only shown age-related cognitive decline and therefore it was expected that normal LI would be observed consistent with what has been seen in other strains of rats (Loskutova et al, 1990). Previous research indicates that Brattleboro rats display similar cognitive deficits and neurotransmitter abnormalities that are also seen in humans with schizophrenia (Feenstra et al, 1990; Laycock et al, 1983). Deficits in LI of Brattleboro rats compared to Long Evans rats would add further support to the notion that Brattleboro rats share features with schizophrenia patients.

In addition to LI, extinction of the conditioned stimulus was studied by determining how quickly rats lose the learned association of saccharin water to sickness.

2. Materials and Methods

2.1 Animals

All experimental procedures were conducted in accordance with the University of California, San Diego guidelines for animal care and experimentation. In total, 15 male Long Evans rats and 15 male Brattleboro rats (170–350 grams at testing, Harlan Laboratories, San Diego) were housed in individual clear plastic chambers in a climate controlled room under a 12/12 h light/dark schedule (lights on/off – 0700/1900). They were allowed free access to food for the extent of the study. The Long Evans rats were separated into two groups: non-preexposed group contained 8 rats and preexposed group contained 7 rats. The Brattleboro rats were separated into two groups: non-preexposed group contained 8 rats and preexposed group contained 7 rats.

2.2 Duration and Water Deprivation

The Long Evans study lasted 10 days and Day 4 was the conditioning day. The rats underwent water deprivation for twenty four hours each day and at a specific time, they were given either 100 mL of water or 100 mL of saccharin water for 20 minutes. Previous studies indicate that Long Evans rats need only 20 minutes to drink all the water they need daily (Bennett). The non-preexposed group received 100 mL of water on Days 1, 2, 5, 7, and 9 and 100 mL of saccharin water on Days 3, 4, 6, 8, and 10. The preexposed group received 100 mL of water on Days 1, 2, 3, 5, 7, and 9 and 100 mL of saccharin water on Days 4, 6, 8, and 10.

The Brattleboro study lasted 10 days and Day 4 was the conditioning day. The rats underwent water deprivation for three hours per day and at the end of the three hours, they were given either 100 mL of water or 100 mL of saccharin water for 20 minutes. Because these rats are vasopressin deficient, they cannot fulfill their daily water needs in 20 minutes like the Long Evans rats can (Bennett). This is why they underwent 3 hours of water deprivation rather than 24 hours of water deprivation. After the 20 minutes, their normal water bottles were put back into their cages. The non-preexposed group received 100 mL of water on Days 1, 2, 5, 7, and 9 and 100 mL of saccharin water on Days 3, 4, 6, 8, and 10. The preexposed group received 100 mL of water on Days 1, 2, 3, 5, 7, and 9 and 100 mL of saccharin water on Days 4, 6, 8, and 10.

2.3 Saccharin Water

The saccharin water was prepared by adding 500 mL of water to 0.500 grams of saccharin (99% sodium salt hydrate, Acros Organics).

2.4 Lithium Chloride Preparation

The lithium chloride was prepared by combining 0.636 grams of Lithium chloride (99%, Strem Chemicals) with 100 mL saline (0.9% NaCl Irrigation, Baxter Healthcare Corporation). All rats will receive LiCl injections intraperitoneally on Day 4 right after the 20 minutes of saccharin. The weight in kilograms of a rat multiplied by 13.3 gave the amount of Lithium Chloride in mL to inject.

2.5 Statistical Analysis

Using the SPSS software, paired samples T-tests were used to confirm conditioned taste aversion and independent samples T-tests were used to confirm LI, difference scores, and extinction rates. To calculate the difference score, we calculated the difference between the amount of saccharin consumed by each rat in the preexposed group and the mean of the amount of saccharin consumed by the non-preexposed group of the same strain. Then, we proceeded further by calculating it into a percentage, allowing us to see how much each rat drank on the second day of reexposure to saccharin compared to the first day of reexposure. To calculate extinction rates, we inputted this equation [((Day 8 volume-Day 6 volume)/Day 6 volume) x 100%] and found how much more each rat drank on Day 8 in percentages.

3. Results

3.1 Latent Inhibition in Long Evans Rats

Using the SPSS statistical software, we performed a paired samples T-test and there was a statistical difference ($t(7) = 6.355$; $p<0.01$) between the mean volume intake of non-preexposed LE rats on their conditioning day (Day 4) and their first saccharin re-exposure day (Day 6), which confirmed that non-preexposed LE rats exhibited conditioned taste aversion. Likewise, for the preexposed LE, there was also a statistical difference ($t(7) = 7.485$; $p<0.01$) between the means indicating the preexposed LE on Day 6 drank significantly less than on Day 4 (Figure 1, denoted by hash marks). Since taste aversion was seen in both groups, we were able to confirm whether LI was present. Latent inhibition was seen on Day 6 when saccharin water was administered (Figure 1, denoted by asterisks). The preexposed group exhibited latent inhibition because there was a statistical difference in means of volume intake ($t(7) = 6.750$; $p<0.01$) for the non-preexposed group versus preexposed group. The preexposure to the saccharin on Day 3 affected the preexposed group's volume intake on Day 6.

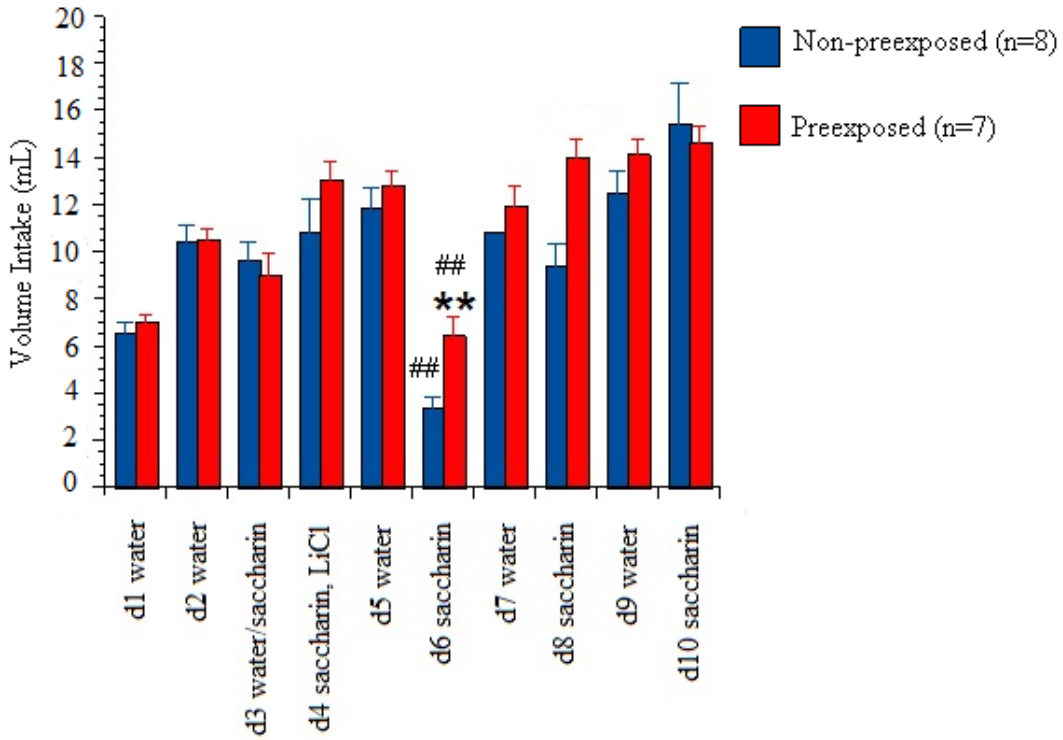

Figure 1: Results of LI experiment for Long Evans rats. ## represents significant difference (t (7) = 6.355, 7.485; p<0.01) from same group intake on conditioning day (Day 4). ** represents significant difference (t (7) = 6.750; p<0.01) from non-preexposed group on same day.

3.2 Latent Inhibition in Brattleboro Rats

Using the SPSS statistical software, we performed a paired samples T-test and there was a statistical difference (t (7) = 9.525; p<0.01) between the mean volume intake of non-preexposed BB rats on their conditioning day (Day 4) and their first saccharin re-exposure day (Day 6), which confirmed that non-preexposed BB rats exhibited conditioned taste aversion. Likewise, for the preexposed BB rats, there was also a statistical difference (t (6) = 4.694; p<0.01) between the means indicating the preexposed BB on Day 6 drank significantly less than on Day 4 (Figure 2, denoted by hash marks).

Since taste aversion was seen in both groups, we were able to confirm whether LI was present. Latent inhibition was seen on Day 6 when saccharin water was administered (Figure 2, denoted by asterisks). The preexposed group exhibited latent inhibition because there was a statistical difference in means of volume intake ($t(6) = 2.853$; $p<0.05$) for the non-preexposed group versus preexposed group. The preexposure to the saccharin on Day 3 affected the preexposed group's volume intake on Day 6.

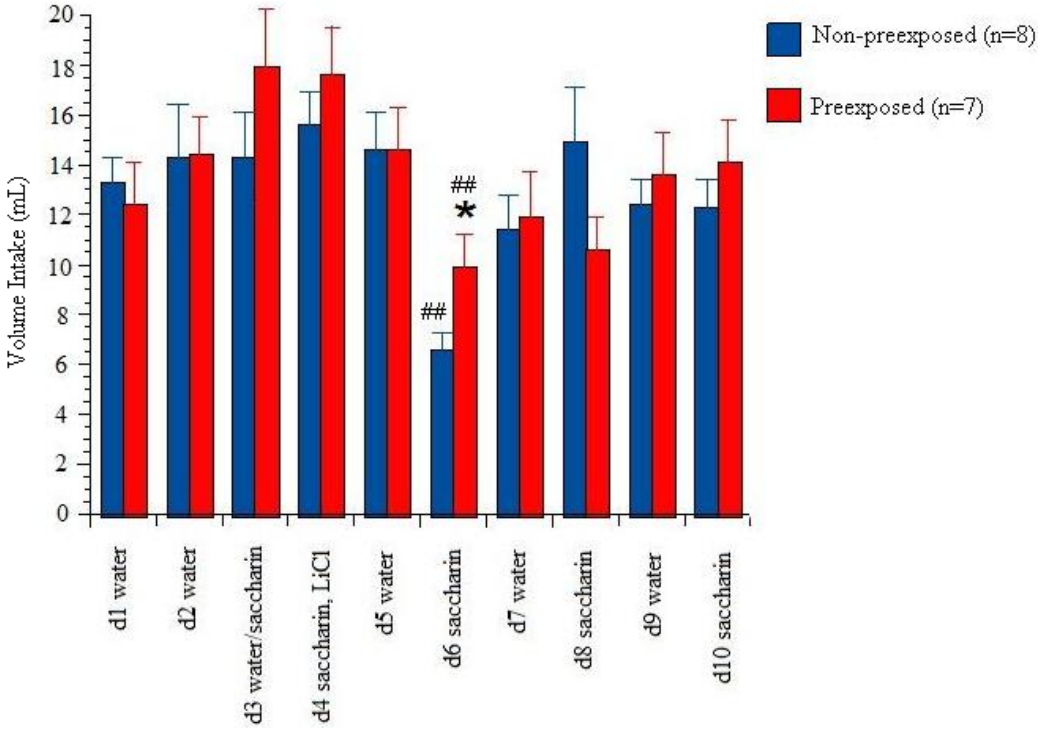

Figure 2: Results of LI experiment for Brattleboro rats. ## represents significant difference ($t(7) = 9.525$; $t(6) = 4.694$; $p<0.01$) from same group intake on conditioning day (Day 4). ** represents significant difference ($t(6) = 2.853$; $p<0.05$) from non-preexposed group on same day.

3.3. Comparison of Conditioned Learning and Latent Inhibition in Long Evans and Brattleboro rats

To compare the strength of conditioned learning (conditioned taste aversion) in LE and BB rats, the reduction in drinking on the first saccharin re-exposure day (Day 6)

compared to the conditioning day (Day 4) was calculated as a percentage by subtracting Day 6 volume ingested for each rat from their Day 4 volume ingested and dividing by their Day 4 volume and then multiplying by 100. The percent reduction for LE rats was compared to BB rats using an independent samples t-test. The results showed that the preexposed LE had weaker conditioned learning than the non-preexposed LE ($t(7) = 4.960$; $p < 0.01$), and the preexposed BB had similar conditioned learning as the non-preexposed BB ($t(6) = 2.281$; $p > 0.05$). Furthermore, our findings showed that there was a weaker conditioned taste aversion in the non-preexposed BB rats compared to the non-preexposed LE rats ($t(7) = 2.574$; $p < 0.05$).

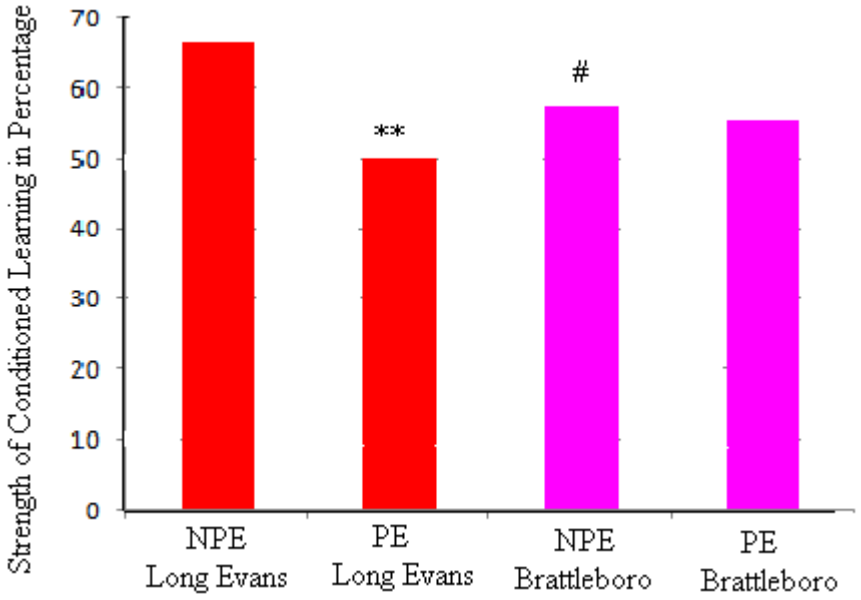

Figure 3: Results of the strength of conditioned learning. ** represents significant difference ($t(7) = 4.960$; $p < 0.01$) between non-preexposed Long Evans and preexposed (PE) Long Evans. # represents significant difference ($t(7) = 2.574$; $p < 0.05$) between non-preexposed Long Evans and non-preexposed Brattleboro rats.

To compare LI exhibited by LE and BB rats, a difference score was calculated for each preexposed rat based upon the method used in Philips et al (1996) and Conti et al (2001) where we calculated the difference between the amount of saccharin consumed by each rat in the preexposed group and the mean of the amount of saccharin consumed by the non-preexposed group of the same strain. Specifically, we looked at the first day of re-exposure to saccharin after the conditioning day. As seen in Figure 4 below, this difference was not significant between the Long Evans and Brattleboro rats ($t(7) = 2.105$; $p>0.05$). Furthermore, we converted the difference score into a percentage and found that this percentage difference was significantly greater in the Long Evans than the Brattleboro rats ($t(7) = 2.560$; $p<0.05$; Figure 5). This indicated that although the Brattleboro rats showed LI, it was reduced in comparison to the Long Evans rats.

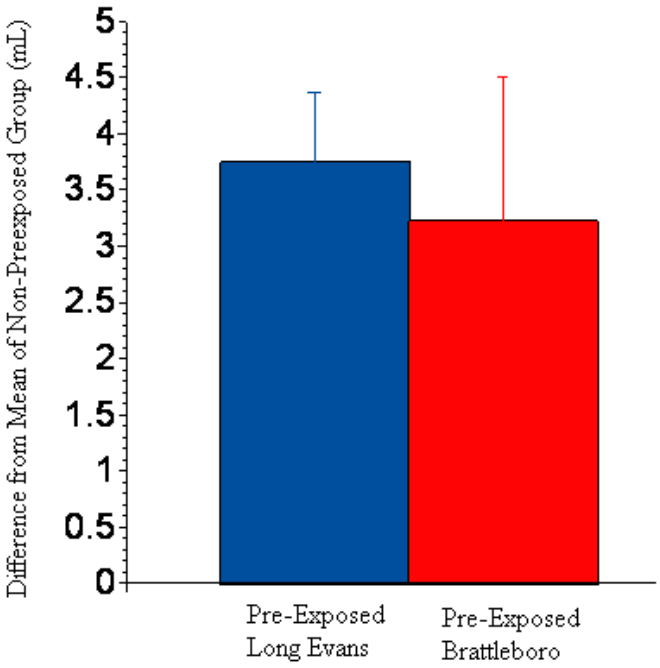

Figure 4: Mean +/- standard error difference score calculated for each preexposed rat of each strain. The score shows the difference between the amount of saccharin (mL) consumed by each preexposed rat and the mean amount of saccharin consumed by the non-preexposed group of the same strain. There was no significance between the two strains ($t(7) = 2.105$; $p>0.05$).

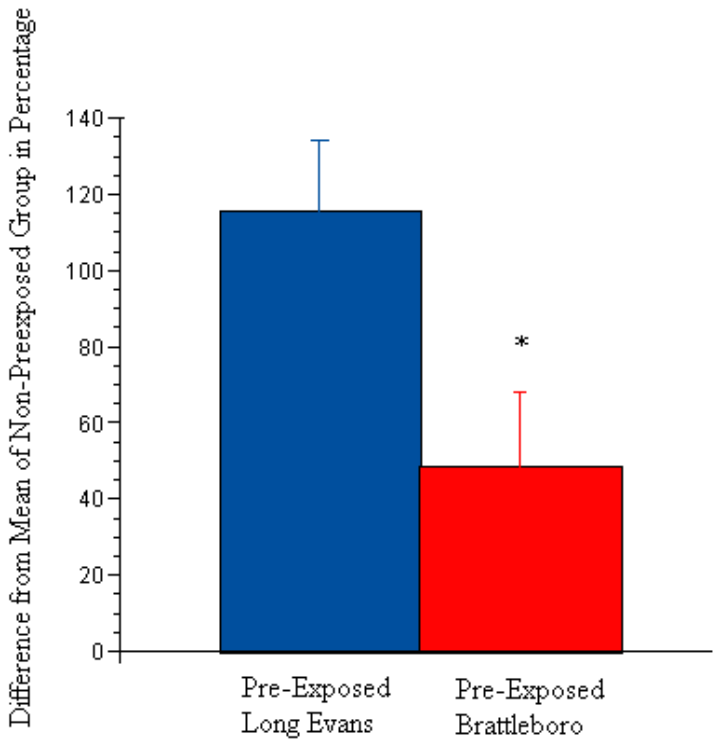

Figure 5: Mean +/- standard error difference score calculated for each preexposed rat of each strain in percentages. The score shows the percentage difference between the amount of saccharin (mL) consumed by each preexposed rat and the mean amount of saccharin consumed by the non-preexposed group of the same strain. There was a significance between the two strains ($t(7) = 2.560$; $p<0.05$).

3.4 Extinction Rates in Long Evans and Brattleboro Rats

In order to measure extinction rate, we calculated the percent increase in volume intake on second saccharin re-exposure day (Day 8) compared to first saccharin re-exposure day (Day 6) for each animal in the groups. Using the independent samples t-test in SPSS, we compared the means of the percentages between the non-preexposed LE (mean=214.17) and the preexposed LE (mean=165.35) and found that there was no statistical difference in the extinction rate between non-preexposed and preexposed LE

rats (Figure 6, t (7) = 2.145; p>0.05), whereas there was a statistical difference between the non-preexposed and preeexposed BB rats (t (7) = 5.230; p<0.01) such that the non-preexposed BB rats extinguished the conditioned stimulus quicker than the preexposed BB rats.

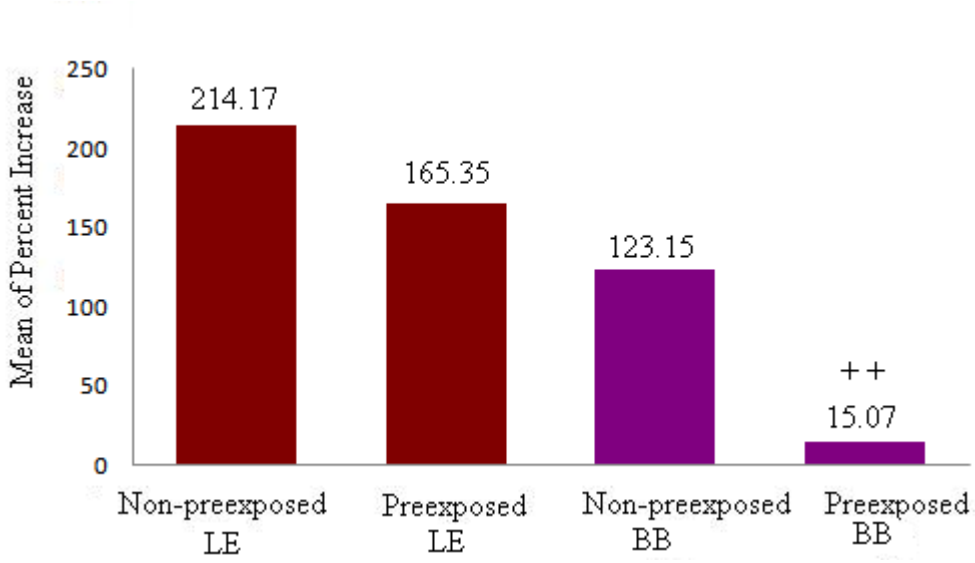

Figure 6: The extinction rate of Long Evans (LE) and Brattleboro (BB) rats measured as a means of percent increase between Day 8 and Day 6. ++ represents a significant difference from the non-preexposed Brattleboro rats.

4. Discussion

Latent inhibition has been thought to result from decreased attention to a conditioned stimulus made irrelevant by preexposure (Mackintosh, 1975). Therefore, there is slower learning of a preexposed conditioned stimulus than a non-preexposed conditioned stimulus. As we expected, the Long Evans rats displayed LI. We hypothesized that the Brattleboro (BB) rats would exhibit LI deficits compared to Long Evans (LE) rats and our results showed that the BB rats had an LI deficiency compared to their parental strain. In addition, other studies have found that the BB rats exhibit prepulse inhibition (PPI) and social discrimination deficits when compared to the LE rats (Feifel and Priebe, 2001; Feifel et al, 2009). This is similar to the Brown Norway rat which also shows PPI and LI deficits compared to the Wistar-Kyoto rats, their closest genetic strain (Conti et al, 2001). Other studies which bred rodents for an altered behavioral response to dopaminergic drugs seem to suggest that PPI and LI have common genetic substrates (Kline et al, 1998; Ellenbroek et al, 1995). For our study to find LI in the BB rats although reduced compared to LE rats, this suggests that PPI and LI may have different genetic substrates in BB rats. There could be other neurotransmitters besides dopamine or the presence of unknown receptors that could affect PPI and LI differently.

There are conflicting reports whether schizophrenia patients show LI. The LI deficit in schizophrenics has been used as evidence of a selective attention deficit in schizophrenia (Gray et al, 1991; Lubow and Gewirtz, 1995), although Swerdlow et al (1996) failed to find an LI deficit in patients. Using the same LI paradigm as the study that reported an LI deficit in schizophrenics (Baruch et al, 1988), Swerdlow et al (1996)

found schizophrenics exhibiting intact LI when they were tested in a new, easier-to-acquire computerized LI paradigm. Using an auditory LI task, Swerdlow et al (1996) replicated the methods and found that when comparing LI in normal control subjects to LI in schizophrenics, there was no difference. Furthermore, the effects of gender and age on LI were assessed and LI did not differ significantly between genders or age (Swerdlow et al, 1996). In addition, a visual LI task was given and LI was seen in both the control and schizophrenia groups (Swerdlow et al, 1996). Although these results differed from previous findings, they could be due to a greater sample size, different subject samples, and different medications currently used by the subjects (Swerdlow et al, 1996). It must be noted that schizophrenic patients show a relative deficit in associative learning and so, that is why patients appear to have an LI deficit (Swerdlow et al, 1996). In addition, our findings showed that there was a weaker conditioned taste aversion in the BB rats compared to the LE rats, which indicated that the BB rats may have deficits in associative learning. This is consistent with what Swerdlow et al (1996) found in schizophrenics. Furthermore, this may be the reason why the BB rats exhibited reduced LI compared to the LE rats. In addition, we looked at the extinction rate of the conditioned stimulus to confirm whether preexposure to the saccharin before the conditioning day affected extinction. Comparing between groups of each strain, the preexposed LE rats extinguished it at a similar rate as the non-preexposed LE rats. However, the preexposed BB rats extinguished it significantly slower than the non-preexposed BB rats. The preexposed BB rats inhibited extinction. This meant that on the second day of saccharin re-exposure after the conditioning day, the preexposed BB rats continued to hold onto the conditioned stimulus. The fact that the preexposed BB had LI showed that they learned to

ignore the trivial stimulus that did not predict an important event and when that stimulus was later given meaning, they overcame their ignore response so conditioning could occur (Lubow, 1989).

Extinction of LI has not yet been studied in schizophrenia and so it would be an interesting subject to look at and it would provide researchers with another opportunity to test the validity of BB rats as animal models of schizophrenia. Future studies could possibly look at extinction rate using the conditioned taste aversion model in schizophrenics and perhaps answer the question: will preexposed schizophrenics extinguish the conditioned stimulus slower than non-preexposed schizophrenics? Our study has shown that preexposed BB rats inhibit extinction, so it would be interesting to see if this is also the case for schizophrenics.

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