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Entitled
Genetic Correlation between Alcohol Preference and Motor Impulsivity with Genetically Selected High-Alcohol and Low-Alcohol Preferring Lines of Mice

For the degree of Master of Science

Is approved by the final examining committee:

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GENETIC CORRELATION BETWEEN ALCOHOL PREFERENCE AND MOTOR IMPULSIVITY WITH GENETICALLY SELECTED HIGH-ALCOHOL AND LOW-ALCOHOL PREFERRING LINES OF MICE

A Thesis

Submitted to the Faculty

of

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In Partial Fulfillment of the

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ABSTRACT

Novotney, Devon Michael. M.S., Purdue University, December 2011. Genetic Correlation between Alcohol Preference and Motor Impulsivity with Genetically Selected High-Alcohol and Low-Alcohol Preferring Lines of Mice. Major Professor: Nicholas Grahame.

Alcohol related problems and abuse continue to be serious problems in the U.S. today affecting nearly 17.6 million Americans. Understanding of the specific genes and related behaviors associated with alcohol use may provide substantial preventative measures for those who are at an increased risk. Genetically selected lines such as the high-alcohol preferring (HAP) and low-alcohol preferring (LAP) mice have been created to examine which endophenotypes co-segregate with alcohol preference. One behavioral trait that has been commonly associated with alcohol related problems is impulsivity. Impulsivity is the inability to withhold a response (motor impulsivity) or to act without forethought (cognitive impulsivity). The latter comprises much of the research and literature today using delay discounting models to tease out differences in subject's wiliness to discount larger reinforcers for smaller immediate reinforcers. This study utilized relatively two newer paradigms associated with motor impulsivity in attempt to test differences in response disinhibition between two independent replicate HAP and LAP lines. It is hypothesized that the genes responsible for alcohol preference would be genetically correlated with motor impulsivity as HAP mice would display a greater degree of response disinhibition.

Two independent replicates consisting of 48 mice (24 HAP II and 24 LAP II, representing the 37th generation; 24 HAP III and 24 LAP III, representing the 13th generation) were tested in two separate identical experiments. Each experiment was comprised of three phases. Phase I utilized a fixed interval (FI) 120s procedure for 30 days. After the 30 days of FI exposure mice were immediately moved to phase II for 10 days which implored a differential reinforcement of low rate procedure (DRL) at a time interval of 20s. Phase III used the same procedures as Phase II except the DRL was increased to 32s.

As hypothesized, there was a moderate genetic correlation between alcohol preference and impulsivity as the HAP II mice displayed greater response disinhibition throughout all three phases compared to the LAP II mice. No differences were observed amongst the replicate III mice in any of the three phases.

The findings from this study provide additional support that a genetic correlation between alcohol preference and impulsivity exists as seen in the delay discounting literature. Though this was observed in only one of the two replicates, interpretations must be taken at caution as the replicate III mice are still in the early stages of selection. It is possible at this stage in the selection process that increases in alcohol over successive generations are associated with selecting for taste until a threshold is met where selection shifts to pharmacologic drinking relevance. Until later generations of replicate III mice are studied where pharmacologic drinking occurs, conclusions from this study provide a moderate genetic correlation between alcohol preference and impulsivity.

INTRODUCTION

Alcoholism and alcohol related disorders, continue to be serious problems in the U.S. today affecting nearly 17.6 million Americans (NIAAA, 2008). Research in this field has proposed a multitude of potential causes for the development and maintenance of alcoholism while much of the remaining genetic variance is uncertain. Alcoholism is a heritable, problematic disorder that is correlated with many different psychological disorders and behavioral traits. Because of its' heritable nature, alcohol related genes from parents whom are alcoholics leave their children at an increased susceptible risk for developing this disease. Understanding of the specific genes and related behaviors for developing and maintaining alcohol use may provide substantial preventative measures for those who are at an increased risk.

Selection for Alcohol Preference

Genetically selected lines such as the high-alcohol preferring (HAP) and low-alcohol preferring (LAP) mice have been created to examine which endophenotypes co-segregate with alcohol preference (Grahame et al., 1999a). Over successive generations, specific trait behaviors that are heritable with high alcohol preference and low alcohol preference have been selected for, and may provide a much more clear understanding to potential underlying causes for the development and maintenance of alcoholism (Grahame et al., 1999b). At Indiana University-Purdue University Indianapolis (IUPUI),

three genetically independent replicate lines have been developed selecting for high- and low-alcohol preference. This study attempts to examine whether a genetic correlation exists between alcohol preference and impulsivity. All mice were derived from the same Hs/Ibg progenitors but come from different generations. The two replicate lines used in this study are the replicate II and replicate III high- and low-alcohol preferring mice representing the 37th and 13th generations, respectively. The addition of a second replicate line used in this study should provide further support that a genetic correlation exists between alcohol preference and impulsivity. Over successive generations, both trait-relevant and trait-irrelevant alleles become fixed possibly creating a false representation of genetic correlation due to trait-irrelevant alleles. The addition of a second replicate line minimizes the chances that the same trait-irrelevant alleles are selected thus increasing the likelihood that there is a true genetic relationship between alcohol preference and impulsivity (Crabbe et al., 1990).

Impulsivity

Recent evidence with both human and animal studies has provided substantial support for specific trait behaviors that are genetically correlated with alcoholism. This includes deficiencies in decision making, working memory, attention, and acquisition of learning rules with consequences (Hinson et al., 2003; Finn et al., 1999; Wittmann et al., 2007; Wultz & Sagvolden, 1992). Taken together, it is believed that these traits are the underlying causes for behavioral impulsivity. Individuals at risk for alcoholism display more frequent patterns of problematic, impulse related behaviors (Bobova et al., 2009). These impulse related patterns of behavior in both the absence and presence of

consequences compared to their control counterparts, will ultimately result in an accumulative loss of reinforcer (Bechara et al., 1994). Behavioral impulsivity can be broken down into two separate components: cognitive impulsivity which can be tested using a delay discounting (DD) model or the Iowa gambling task (IGT) (Oberlin & Grahame, 2009; Miranda et al., 2009, respectively), and motor impulsivity which can be measured by fixed interval (FI) or differential reinforcement of low rate (DRL) procedures (Sagvolden et al., 1993; Rubio et al., 2008, respectively).

Cognitive Impulsivity

Cognitive impulsivity examines the pattern of behavioral responses for a reward, and the choices made by either manipulating a time delay or introducing a consequence. In these particular experiments, cognitive impulsivity is observed when a subject chooses to adhere to a smaller immediate reinforcer or a large reinforcer paired with a consequence ultimately resulting in accumulative net loss (Hinson et al., 2003; Shead & Hodgins, 2009; Wilhelm et al., 2007). In DD studies, a subject is required to make a decision between two options: a small immediate reinforcer or a larger delayed reinforcer. Throughout an experimental session, the reinforcer values and the time delays fluctuate to provide a precise estimate for how much the subject is willing to discount for a given reinforcer. Greater discounting indicates a higher degree of impulsivity (Ainslie, 1975). Alcoholics display increases in cognitive impulsivity, which leads to difficulty thinking beyond immediate reinforcers and act on impulse without fully contemplating the potential consequences associated with their choices (Bobova et al., 2009). Delay discounting models do a fair assessment in finding differences in choice behavior

between alcoholics and controls. Delay discounting was first used as a method in explaining economic trends, but recently the DD model has been adapted to both human and animal studies to help explain differences in decision making processes among addictive personalities (Mitchell et al., 2005; Oberlin & Grahame, 2009).

Motor Impulsivity

The other component of impulsivity is motor impulsivity. Motor impulsivity examines the inability to withhold a response. Disinhibition of responding has been associated with deficiencies in working memory, attention, and temporal perception (Finn et al., 1999). Individuals diagnosed with attention deficit hyperactive disorder (ADHD) display variations of these deficits. ADHD subjects have a difficult time adhering to rules, often struggling to sit still and refrain from responding (Ryan et al., 2010). This pattern of behavior has been modeled at the animal level and can be measured using a fixed interval procedure. The spontaneous hypertensive rat (SHR) strain which is an animal model of ADHD has been used in behavioral procedures such as the fixed interval task. This procedure along with several others, are excellent models for behavioral impulsivity as supported by the ADHD literature (Sagvolden et al., 1992). Fixed interval procedures are designed to measure behavioral output, primarily at the point of increased response rate just prior to reinforcer availability. In these particular tasks, subjects are free to respond for a reinforcer without consequence, but only when the interval has elapsed, will the reinforcer become available. SHR rats display response patterns similar to controls however they increase their response rate much earlier in the inter-reinforcer interval (IRI) (Sagvolden et al., 1993). One possible explanation is that their inner clock or perception

of time is somewhat faster than control subjects. This underlying dysfunction may provide some explanation for why ADHD subjects exhibit greater levels of motor impulsivity over controls (Sagvolden et al., 1992). Likewise, disordered dopamine function has been implicated in a range of behavioral disorders such as addiction, compulsive gambling, and ADHD to name a few. In a recent study by Pine et al., found that altering the dopamine system by increasing the amount of dopamine transmission lead to an increase in impulsivity using an intertemporal choice task (2010). Thus hyperfunctioning dopamine may possibly lead to enhanced discounting of future reinforcers. This might provide some explanation for the differences seen between HAP and LAP mice in delay discounting. Furthermore, there's considerable support for similarities in impulsive behaviors associated with both ADHD subjects and alcoholics. Based on the human literature for cognitive impulsivity and alcoholism, incorporating the procedures used to measure impulsivity in the SHR strains may provide further support that alcohol preference and impulsivity are genetically correlated with HAP versus LAP mice.

The basic behavioral abnormalities previously mentioned that are associated with ADHD has been beneficial for alcohol researchers because most substance abusers exhibit similar behaviors in regards to motor impulsivity (Finn, 2002; Finn & Hall, 2004). In addition, the cognitive impulsivity presented in alcoholics is also a great way to measure differences in immediate versus delayed reinforcers in relation to their subjective consequences, however it is extremely difficult to determine whether or not delayed reinforcers receive the same allocation of attention as immediate reinforcers. Understanding the components that can explain motor impulsivity may provide further

support for understanding the development of alcoholism, while also providing us with some insight to why there are such apparent cognitive impulsivity differences between alcoholics and controls.

Fixed interval responding provides a simple measurement of motor impulsivity by examining response patterns for reinforcer with no immediate consequence. Responses for any given subject can be mapped over the duration of the fixed interval period. Patterns of response rates should increase as the fixed interval period elapses and reinforcer is available (Skinner & Morse, 1957). For subjects who display impulsive characteristics, response patterns should occur much earlier in the IRI than controls as was mentioned before. Differential reinforcement of low rate (DRL) procedures are another way of measuring motor impulsivity. In these DRL studies, subjects have to wait a specific amount of time before responding for a reinforcer. If a response is made before the time interval is up, the clock is restarted and no reinforcer is received. Thus the introduction of a consequence leads to a reduction in response rate once the subject has acquired the omission contingency (van den Broek et al., 1987). In order to be efficient in this type of procedure, responses must be kept to a minimum and timed accurately to ensure maximum efficiency. Alcoholics express profound deficits in these types of tasks compared to controls (Kirshenbaum et al., 2009; Rubio et al., 2008). Alcoholics display an increased number of responses which ultimately results in fewer numbers of reinforcers compared to controls. Efficiency values are smaller for alcoholics which provide considerable support for examining motor impulsivity. Because alcoholics exhibit a greater magnitude of motor impulsivity, they struggle at waiting and withholding their responses until the appropriate time. This may also characterize why

alcoholics discount to a greater extent for smaller immediate reinforcers over larger delayed reinforcers. Taken together, models for cognitive and motor impulsivity may provide substantial support for the genetic relationship between alcohol preference and impulsivity.

Aims and Hypothesis

In order to characterize the extent to which having a genetic predisposition for alcohol preference is correlated with impulsivity; three phases were implemented on selected high- and low-alcohol preferring lines of mice. Phase I incorporated a fixed interval 2 min procedure to assess the response patterns of the selected replicate II and replicate III lines and their abilities to withhold a response prior to reinforcer availability. This was done in two separate experiments using the exact same procedures. The use of a second replicate line provided stronger evidence that a genetic correlation between alcohol preference and impulsivity exists. During phase I it is hypothesized that similar patterns of responding should be evident between both replicate lines. Specifically, responses that characterize impulsive behavior such as responding earlier in the FI period prior to reinforcer availability should be apparent in the high-alcohol preferring lines. This would further exemplify impulsivity as an endophenotype for alcohol preference. Furthermore, the relationship between the two replicate lines, which comes from the same Hs/Ibg strain provides additional evidence that behavioral impulsivity co-segregates with alcohol preference (Crabbe et al., 1990). The response patterns of the high-alcohol preferring mice should mimic the response patterns seen in the SHRs, further validating this procedure as an appropriate measure for motor impulsivity. In addition to the

differences in response patterns mentioned above, there should be no differences in the number or reinforcers received for either replicate or line.

After completion of FI 2 min procedure, mice were immediately exposed to the phase II (DRL 20s) and phase III (DRL 32s) procedures, respectively. These two procedures assess differences in motor impulsivity between the two lines as well and implement a consequence not observed in the fixed interval procedure. During these two phases, both the replicate II and replicate III high-alcohol preferring lines will display deficits in withholding their responses, but over consecutive days, response rates should decrease while efficiency for obtaining a reinforcer should increase. This pattern of data should support learning of the DRL contigency and model differences in motor impulsivity for both lines. Once both of the lines have acquired the omission contingency, the low-alcohol preferring lines will display a greater degree of self control by inhibiting their responses, ultimately receiving more reinforcers per number of responses throughout the duration of the DRL procedure. As mice transition from phase II to phase III it is hypothesized that differences between HAP and LAP mice should be more apparent as the inter-reinforcer interval increases from 20s to 32s. Specifically, the increase for the time interval should constrain HAP mice from obtaining a reinforcer due to differences in response inhibition compared to LAP mice. Taken together, it is hypothesized that the genes responsible for alcohol preference are genetically correlated with increased levels of motor impulsivity. This prior experience with response inhibition should provide an excellent measure for examining motor impulsivity. In addition using the mice from phase I will also allow us to track the individual differences between each mouse. The data combined from the two experiments may further provide support for our

original hypothesis. Combination of the three phases allows us to further examine the relationship between temporal dysfunction (responding too early in the FI procedure) and response disinhibition (lower efficiency and higher response rate) and whether or not this is evident in the high-alcohol preferring lines on an individual subject level.

The mice used in this study were tested alcohol naïve and never have exposure to alcohol because previous studies examining impulsivity and alcohol intoxication have had mixed results. A study using 67 college students found that alcohol intoxication reduces impulsivity in a delay discounting task (Ortner et al., 2003). The findings from the previous study provide insights toward the effects of alcohol however the study was not conducted with alcoholics who may have a genetic predisposition for impulsive behavior. Furthermore, testing alcohol naïve mice allows us to examine this relationship and further provide evidence that the behavioral traits for alcohol preference are heritable with impulsivity in the absence of alcohol related effects.

METHODS

Experiment 1 & 2: Differences in Motor Impulsivity

Animals

24 HAP II and 24 LAP II male and female mice were used in this study. All animals were bred on site at Indiana University-Purdue University Indianapolis from the replicate II progenitors, and represent the 37th generation. All mice were counterbalanced by line, sex, and family for each of the four squads. Mice were individually housed in polycarbonate cages (27.9 x 9.5 x 12.7 cm) with Cellsorb bedding at an ambient temperature of 21 +/- 1 C. Mice were on a reverse light cycle where the light cycle is lights on from 2030 to 0830 (8:30pm to 8:30am). Prior to starting the experiment, all subjects were individually housed in their cages for one week to ensure that they are acclimated to the new colony room environment. The age at the start of the experiment was seven weeks. Water deprivation began at 5pm the previous day before a trial. In addition to the Line II mice used in the three phases of this study, a second experiment utilizing the same methods was conducted using replicate III mice. 24 HAP III and 24 LAP III mice were used. As previously mentioned, all line III mice were bred on site at Indiana University-Purdue University Indianapolis from replicate III progenitors, and represent the 13th generation.

Apparatus

Twelve identical boxes measuring 21.6 x 19.7 x 12.7 cm were used in all three phases of this experiment, each with 2 sides of clear acrylic and 2 sides of aluminum (Med Associates ENV 307W, St. Albans, VT). Operant boxes were contained in sound and light attenuated chambers equipped with fans. An LED nose-poke infrared detector is centered on the 19.7 cm of each box at 6.3 cm above the floor. Below this light is a sipper access hole. The sipper tubes that were used for this experiment were 10-ml graduated plastic serological pipettes fitted with stainless steel tips. All tubes were filled with 0.0316% (w/v) saccharin solution. This solution was selected because it is the lowest concentration that has been tested in our lab while also producing the smallest line difference compared to higher concentrations. Two levers were mounted in each operant chamber for the latter stages of shaping and testing, each 2.5 cm above the floor on either side of the sipper tube opening. Each of the levers had an LED 2.3 cm above them. Mice were assigned with one active lever and one inactive lever, and these assignments were fixed throughout the entire experiment. Operant boxes were controlled using MedPC IV software on a Windows computer.

Phase I: Fixed Interval 120s

Previous literature has shown that fixed interval tasks are an appropriate measure of motor impulsivity as displayed by inefficient response patterns of ADHD mice compared to controls. In order to validate the previous work done and to see if this can be generalized to alcohol models of impulsivity, an FI120 second task was used to test differences in response inhibition between the two lines and in addition a second replicate

line as well. HAP II mice in delay discounting tasks have shown impulsive decision making responses, and whether this can be attributed to deficits in response disinhibition, is supported in this experiment. Previous studies have also linked alcoholism with temporal dysfunction which may ultimately support the differences seen between alcoholics and controls in regards to this measure of impulsivity.

Procedure

The start of shaping began with both the HAP II and LAP II mice being placed in a fixed-time reinforcer duration task. After successful completion, the mice were moved respectively to a FR1 10s, FR1 2.5s, and finally a FR1 2s reinforcer task. In order to successfully complete each stage, each subject must respond at a minimum of 10 reinforcers while also consuming a minimum of 0.5 mL. The subjects that complete the current stage were not ran again until all mice had completed the above minimum requirement. The FR1 2s program was ran for only two consecutive days, and any mouse that did not complete the above minimum requirements was not used in the duration of the experiment. Finally for those mice that completed the shaping programs were ran in FI30s and FI60s tasks for 3 days each to acclimate them to the fixed interval procedure. All of the mice were then tested at a FI120s time schedule for 30 consecutive days. At which successful bar pressing after the time interval has elapsed yielded 2s of sipper access time. This particular FI duration has been used in previous studies with SHR rats and has been an appropriate time to measure motor impulsivity. The 30 day duration was first selected as an arbitrary number based on previous pilot work in the lab. However, during the pilot experiment only 15 days of the fixed interval procedure was run. At that

particular duration, minimal changes were observed over each successive day suggesting complete acquisition of the fixed interval procedure. Therefore doubling the amount of exposure to 30 days would eliminate or minimize the chances of terminating fixed interval exposure too early where acquisition may continue to occur. Linear regression analysis for experiment 1 displayed no differences between days 26-30 as the lines were collapsed on top of each other suggesting complete acquisition to the fixed interval procedure. To keep the analysis consistent with experiment 2, only 30 days of fixed interval was run as well.

On testing days, mice are moved in a light-tight box to the operant testing room. The operant boxes run the appropriate MEDPC-IV program assigned to each mouse. Each operant box is wiped with a wet sponge prior to running a mouse. All programs are loaded and wait for the start signal. After the one hour trial, the mice are removed from their boxes and put back into the light-tight transport box. After all mice are run, they are all transported back to the colony room. The mice are then provided with 2 hours of water access, after which time their water bottles are pulled off, and the procedure repeats.

Once a week their operant boxes are wiped down, and the bedding in the bottom is changed. Once a week their sipper tubes are drained, rinsed in bleach and allowed to air-dry overnight. The mice are tested in the operant chambers 5 days per week. Their water bottles are removed each night to ensure motivated responding prior to each procedure.

Data Analysis

A four-way mixed ANOVA was used to extrapolate the main effects of the FI120 procedure. The analysis examines the relationship between line x replicate x sex x bin. 24 5s bins were analyzed for each mouse to map out a precise time the lever was pressed. Over the course of the 1 hour session, each of the fixed interval trials were collapsed on top of each other, providing a complete summary of when each lever press occurred throughout the fixed interval session. During the original analysis no sex interactions were observed which resulted in sex being factored out of the original four-way analysis. This led to examining a three-way mixed ANOVA with line x replicate x bin. This was done for both day 1 and the average of days 26-30. To further examine individual line differences within each replicate, a two-way mixed ANOVA examining line by bin was used. Three different dependent variables were examined throughout all three phases; number of correct responses, number of reinforcers, and number of responses per reinforcer (efficiency). Independent samples t-test were used to analyze the aforementioned dependent measures to test differences between HAP and LAP mice.

Phase II & III: Differential Reinforcement of Low Rate 20s & 32s

The ability to withhold a response until a reinforcer becomes available has been shown to be an effective way of displaying or measuring impulsivity (Sagvolden et al., 1993). Several studies have demonstrated that there are significant differences in DRL tasks between Heavy Drinkers (HD) and controls. These findings implicate that HDs show increased sensitivity to impulsive decision making by disinhibition to respond for a reinforcer prior to reward availability compared to controls, respectively (Rubio et al.,

2008). As the time duration of the DRL increases over sessions, mice that fail to withhold a response results in a consequence of the inter-reinforcer interval to reset. Thus impulsive decision making results in fewer reinforcers and ultimately, a reduction in their reinforcer/response efficiency.

Procedure

After completion of phase I, mice were placed in a DRL 20s procedure for several weeks until neither line displays any improvement over successive days. The 20s interval is a relatively short duration compared to most DRL intervals commonly seen throughout the literature. As the mice progressed from fixed interval to DRL, using such a short interval allowed for an easy transition between two different types of experimental procedures as a consequence was introduced. Exposing mice to the fixed interval procedure over the 30 days should allow for simple acquisition of this DRL procedure. The 20s interval allows for maximum training of the DRL omission contingency by increasing the likelihood of obtaining a reinforcer. Therefore daily changes should be apparent as mice minimize responding while consequently increasing the number or reinforcers obtained. The criterion for continued exposure to DRL is based on evidence of learning the omission contingency and continued change in response behavior. Both the HAP and LAP mice need to show continued reduction in response rate which directly affects their efficiency for obtaining a reinforcer. Consequently, during experiment 1 replicate III mice displayed complete acquisition to DRL 20 after just 2 days of exposure. 10 days were run to verify that no additional changes would be observed. Again, to keep the analysis consistent 10 days were selected as the duration of the DRL 20 procedure.

Based on previous literature, the LAP mice should be more efficient at acquiring this task than the HAP mice, thus displaying greater response inhibition. The method of exposing the mice to FI prior to DRL provides the mice with some experience of inhibiting their responses in order to receive a reinforcer. However, phase I had no consequence for responding early within the IRI whereas responses in DRL procedures that occur within the IRI cause the clock to reset. Thus reinforcers can only be received once the IRI has elapsed.

After the 10 day exposure to DRL 20s, both the HAP and LAP mice were then exposed to DRL 32s. This particular duration is extremely common throughout the DRL literature. To further investigate differences in motor impulsivity, the exposure to a second DRL of a longer duration was used to tease apart additional differences between HAP and LAP mice. It is hypothesized that as the DRL increases, the differences between HAP and LAP mice should become more apparent. This is because increasing the length of the DRL should create a more difficult task for those subjects whom display response disinhibition. For comparability between phase II and phase III, the procedural methods and data analysis mentioned above for phase II were the exact same for phase III. The only difference between phase II and phase III is the increase in the omission contingency from 20s to 32s, respectively.

Data Analysis

A four-way mixed ANOVA was used to extrapolate the main effects of the DRL 20. The analysis examined the relationship between line x replicate x sex x day. As previously mentioned, no interactions in regards to sex were observed in analysis

therefore sex was factored out of the original four-way analysis. The study utilized a three-way mixed ANOVA with line x replicate x day to examine differences amongst replicate lines. Additionally to further examine individual line differences within each replicate, a two-way mixed ANOVA examining line by day was used. Similar to phase I, three different dependent variables were examined; number of correct responses, number of reinforcers, and number of active lever presses per reinforcer (efficiency). Independent samples t-test were analyzed to test the differences between HAP and LAP mice in regards to number of correct responses, number of reinforcers obtained, and overall efficiency.

RESULTS

Phase I: Fixed Interval 120s

Day 1: Percent Active Lever Press

After completion of fixed interval training, Day 1 of FI 120 displayed no differences between HAP and LAP mice for either replicate. There could be line differences at this point, however temporally appropriate responding is not expected because mice should not display any understanding of the fixed interval procedure. A horizontal line is indicative of behavior not responsive to the fixed interval contingency (See Figure 1, A & B). Based on previous pilot work with replicate II mice, HAP II mice respond at a significantly higher rate, so a percent transform was used to adjust for baseline differences in response rate, allowing for a more even comparison between the lines. After 30 days of exposure to the fixed interval procedure, days 26-30 were averaged across day. There were no significant main effects or interactions for sex in any of the analyses, therefore sex will not be a factor in this study.

Days 26-30: Percent Active Lever Press

A three way mixed ANOVA for days 26-30 examining replicate by line by bin for percent of active lever presses resulted in a significant main effect of replicate ($F(1,88) = 85.320$, $p < .001$)), but no main effect of line was observed. Replicate III mice did not

display any differences in their response patterns over the course of the 24 bins. There was a significant interaction for replicate by line by bin ($F(1,23) = 1.876$, $p < .01$)). However, in the absence of a main effect of line but a line by replicate interaction which was previously observed would signify that there is a moderate genetic correlation between alcohol preference and impulsivity if and only if there is a main effect of line. In addition, there was also a replicate by bin interaction ($F(1,23) = 5.908$, $p < .001$)), signifying that replicate II mice withheld responding to a greater extent at the beginning of the interval compared to replicate III mice. Thus follow up analysis examining each replicate separately would signify whether or not a genetic correlation exists. If only one of the two replicates result in a main effect of line, a moderate genetic correlation between alcohol preference and impulsivity will be observed for the percent adjusted fixed interval procedure.

Contrary to the original hypothesis, a replicate by line by bin interaction was not expected for days 26-30 therefore two separate analyses were conducted in order to examine each replicate separately. A three way mixed ANOVA for days 26-30 examining the effects of line II mice by sex by bin for percent of active lever presses failed to display a significant interaction, therefore sex was factored out of the analysis. A two way mixed ANOVA comparing line II mice and bin revealed a significant main effect of bin ($F(1,23) = 86.823$, $p < .001$)). The significant main effect of bin signifies an increase in response inhibition over successive bins for days 26-30. In agreement with the original hypothesis, the results of the two way mixed ANOVA also resulted in a significant line by bin interaction ($F(1,23) = 1.845$, $p < .01$)). Thus HAP II mice display greater response disinhibition compared to LAP II mice. Follow up independent samples

t-test examining the differences between line II mice and bin resulted in three significant data points. LAP II mice showed significantly lower relative rates of responding during the first three bins (0-15s) $p < .05$, compared to HAP II mice. After 15s, no other bins displayed significant line differences. As expected, LAP II mice during the first 15 seconds of the fixed interval procedure successfully inhibited their overall responding relative to HAP II mice. Though the differences at the last several were not significantly different, there is a general trend of LAP II mice responding at a higher rate than HAP II mice respectively. The differences between HAP II and LAP II mice for days 26-30 in regards to fixed interval responding is illustrated in Figure 2 A.

Analysis of the replicate III line also failed to observe a line by sex by bin interaction for days 26-30 and therefore sex was factored out of the analysis. A two way mixed ANOVA comparing line III mice and bin for percent of active lever presses revealed a significant main effect of bin ($F(1,23) = 32.875$, $p < .001$)), however contrary to the hypothesis no line by bin interaction was found that was previously seen in the replicate II mice (See Figure 2 B). Both HAP III and LAP III mice display very similar patterns of responding throughout the two minute interval thus demonstrating minimal differences in impulsivity. In the middle of the interval, differences between HAP III and LAP III mice are not necessarily important. Differences in impulsivity with fixed interval responding are primarily important during the first and last couple of bins where it's expected to see response inhibition early, and maximal responding toward the end just prior to reinforcer availability. The minimal differences observed between LAP III and HAP III mice are illustrated in Figure 2 B. The findings provide some support for and against a genetic correlation between alcohol preference and impulsivity. The findings

from replicate II mice in regards to the percent transform for days 26-30 in the fixed interval procedure do provide moderate correlative evidence for alcohol preference and impulsivity.

Days 26-30: Active Lever Press

The previous analysis examined replicate and line differences for each of the five second bins with a percent transform of the fixed interval period for days 26-30. Below is the same analysis for each five second bins for days 26-30 without a percent transform. By minimizing the large differences amongst HAP and LAP mice, the percent transform allows for an even comparison between the two lines. While examining the data, only HAP II mice exhibited these large response behaviors therefore requiring further analysis. Using a three way mixed ANOVA, replicate by line by bin for active lever presses resulted in a main effect of line ($F(1,88) = 6.322$, $p < .05$)). This was expected because HAP II mice respond at a significantly higher rate. There was also a main effect of replicate ($F(1,88) = 8.549$, $p < .01$)) and a significant interaction between replicate by line ($F(1,88) = 4.566$, $p < .05$)). Replicate II mice responded at a significantly higher rate than replicate III mice, but the overall difference was markedly driven by the HAP II mice. Because of the high response rates amongst HAP II mice, tests of within subjects effects revealed as was expected a significant interaction for line by bin ($F(1,23) = 2.126$, $p < .01$)) and a significant interaction for replicate by bin ($F(1,23) = 10.016$, $p < .001$)). There was not however, a significant interaction for replicate by line by bin. Follow up analysis examining each replicate separately will provide a more accurate assessment for the significant differences driven by the HAP II mice.

Using the same previous analysis for the percent transform data with days 26-30 averaged, a two way mixed ANOVA looking at line II mice by bin for active lever presses resulted in a significant main effect of bin ($F(1,23) = 42.507$, $p < .001$)) but did not display a significant interaction for line by bin (See Figure 3 A). In agreement with the previous pilot work HAP II mice responded more than the LAP II mice. Intuitively there was a main effect of line ($F(1,43) = 8.214$, $p < .01$)) which was expected because of the significantly higher responses emitted by the HAP II mice. Follow up independent samples t-test comparing line differences for each bin resulted in 19 out of 24 bins being significantly different. HAP II mice responded higher at all 24 bins respectively. Contrary to what was observed with the replicate II mice, a two way mixed ANOVA for replicate III mice did not exhibit a main effect for line or an interaction with line by bin for active lever presses on days 26-30. There was however a main effect of bin which signifies both HAP III and LAP III mice responding in a manner consistent with the contingencies of FI-120, during which no reinforcement is available initially (See Figure 3 B). The absence of a main effect of line between HAP III and LAP III mice contradicts the findings from the replicate by line by bin analysis above. Therefore, only a moderate genetic correlation for alcohol preference and impulsivity exists and this relationship is primarily driven by HAP II responding.

Three other dependent measures which included total active lever presses, total reinforcers, and number of responses per reinforcer were used to further examine differences in impulsive behavior. Similar to the analyses done with the bin data, all dependent measures were averaged over days 26-30. As previously mentioned, day 1 is not being included in these analyses because mice should not exhibit any apprehension of

the fixed interval contingency. Therefore, any differences that would have been observed at day 1 would likely be due to chance and thus can be factored out of the analysis.

Total Active Lever Presses

As hypothesized, a three way between subjects ANOVA examining replicate by line by active levers presses resulted in a significant main effect of replicate ($F(1,88) = 8.459$, $p < .01$)). Replicate II mice significantly responded more than the replicate III mice. There was also a significant main effect of line ($F(1,88) = 6.322$, $p < .05$)) and a significant interaction for replicate by line ($F(1,88) = 4.566$, $p < .05$)). Intuitively these results are not surprising because of the overall responding emitted by the HAP II mice. Follow up independent samples t-test for replicate II mice concludes that HAP II mice respond at a significantly higher rate ($M = 349.167$, SE 34.598) compared to LAP II mice ($M = 227.391$, $SE = 22.290$; $t = 2.866$, $p < .01$)). This difference is illustrated in Figure 4 A. HAP III mice did respond at a higher rate ($M = 217.074$, $SE = 16.828$) compared to LAP III mice ($M = 207.190$, $SE = 28.106$), but the difference was not significant (See Figure 4 B). It is interesting to note, the response rate for LAP II mice is fairly comparable to the response rate for both replicate III lines.

Total Reinforcers

Contrary to the original hypothesis, a three way between subjects ANOVA comparing replicate by line by number of reinforcers received for days 26-30 resulted in a significant main effect for line ($F(1,88) = 18.467$, $p < .001$)). As stated, the previous hypothesis did not expect there to be any line differences for total number of reinforcers

received for the fixed interval procedure. HAP mice received more reinforcers than LAP mice and this finding was observed in both replicates. A main effect for replicate nor a significant interaction for replicate by line was observed in the analysis. Follow up independent samples t-test for both replicate II and replicate III mice displayed HAP II mice receiving more reinforcers (M = 25.841, SE = .226) compared to LAP II mice (M = 24.762, SE .413, t = 2.363, p < .05). Figure 5 A illustrates the differences between HAP II and LAP II mice for total number of reinforcers. In addition, Figure 5 B illustrates HAP III mice receiving more reinforcers (M = 25.970, SE = .173) compared to LAP III mice (M = 24.700, SE = .270; t = 4.138, p < .001). Though the difference between HAP and LAP was significant for both replicates, the difference was less than one for 29 possible reinforcers that could be obtained.

Total Efficiency

Finally, the last analysis examines differences in number of responses emitted to obtain a reinforcer. This dependent measure is probably the most useful measure for examining impulsive behavior in relation to examining their response output. Any response that does not yield a reinforcer can be considered wasteful responding. It was hypothesized that LAP mice would be more efficient at withholding responses prior to reinforcer availability thus inhibiting the total number of responses per reinforcer received. A three way between subjects ANOVA comparing replicate by line by number of responses per reinforcer as was expected, exhibited a main effect of line ($F(1,88) = 5.369$, $p < .05$)). LAP mice significantly emitted fewer responses per reinforcer compared to HAP mice. There was no main effect for replicate. However, there was a significant

replicate by line interaction ($F(1,88) = 5.162$, $p < .05$)). The significant interaction illustrates the pattern of line differences was not the same in each replicate. Based on the minimal differences observed between HAP III and LAP III mice in total number of active lever presses, only replicate II mice should differ in regards to this dependent measure. Follow up independent samples t-test for replicate II mice with number of responses per reinforcer as a dependent measure resulted in LAP II mice emitting fewer number of responses per reinforcer ($M = 8.914$, $SE = .812$) compared to HAP II mice ($M = 13.290$, $SE = 1.234$; $t = 2.873$, $p < .01$). This is illustrated in Figure 6 A. However, contrary to the original hypothesis, LAP III mice did not emit fewer responses per reinforcer compared to HAP III mice, in fact, no difference was observed between the two lines (See Figure 6 B). In agreement with the original hypothesis, HAP II mice exhibited more impulsive like behavior than LAP II mice.

Phase II: DRL 20s

10 Day Active Lever Press

After exposure to 30 days of the fixed interval procedure, mice were then exposed to 10 days of DRL 20 A replicate analysis utilizing a three way mixed ANOVA with replicate by line by day comparisons for active lever presses resulted in a significant main effect of line ($F(1,88) = 8.089$, $p < .01$)) and a significant main effect of replicate ($F(1,88) = 17.761$, $p < .001$)). Replicate II mice significantly responded more than replicate III mice. This should not come as surprise due to the high response rates previously observed amongst the HAP II mice during the fixed interval procedure. In addition there

was also a significant main effect of day ($F(1,9) = 22.777$, $p < .001$)) which signifies apprehension of the DRL omission contingency. This resulted in a reduction of responding over days. There was not a significant interaction for replicate by line by day ($F(1,9) = .378$, $p = .946$)). In agreement with the original hypothesis there was a significant interaction for line by day as it was expected that LAP mice would significantly respond at a lower rate compared to HAP mice thus displaying lower levels of impulsivity ($F(1,9) = 1.919$, $p < .05$)). However, contrary to the hypothesis in question, there was a significant interaction for replicate by day ($F(1,9) = 8.660$, $p < .001$)), as replicate III mice tended to respond significantly less over days compared to replicate II mice. Further analysis examining the individual within replicate comparisons between the lines is mentioned below.

Using a two way mixed ANOVA for line II mice by day for active lever presses as was expected resulted in a significant main effect for line ($F(1,43) = 8.007$, $p < .01$)). Thus HAP II mice significantly responded at a higher rate compared to LAP II mice. A significant main effect of day was also observed ($F(1,9) = 4.849$, $p < .001$)) which provides evidence that the mice were able to learn the DRL omission contingency. Follow up independent samples t-test revealed that during 7 out of the 10 days, LAP II mice responded significantly less than HAP II mice. In fact, HAP II mice responded at a higher rate for all 10 days of the DRL 20 procedure (See Figure 7 A). The aforementioned analysis above which was predicted by the original hypothesis was not observed in the replicate III mice. A two way mixed ANOVA for line III mice and active lever presses over days failed to yield a significant main effect for line. There was however a significant main effect for day ($F(1,9) = 50.240$, $p < .001$)) signifying that the

replicate III mice did learn the DRL omission contingency (See Figure 7 B). It can be concluded based on this analysis that replicate III mice do not differ in regards to response disinhibition as measured by DRL 20. To further examine the differences of active lever presses, the last 5 days of DRL 20 were averaged. Using a two way ANOVA comparing replicate by line for active lever presses did not reveal a main effect of replicate, main effect of line, nor a line by replicate interaction suggesting minimal differences in active lever presses.

10 Day Reinforcers

Over the course of days during the DRL procedure, it is expected to see an overall decrease in responding as mice inherently learn to wait for the reinforcer to become available. As a consequence to this, a reduction in responding should lead to an increase over days for the number of reinforcers received. In agreement with the original hypothesis, as LAP mice become more efficient at this, their response rates should diminish and their number of total reinforcers should increase over days significantly more so than HAP mice. If HAP mice do display response disinhibition, then over days, LAP mice should ultimately receive a significantly greater number of reinforcers. However, this was not observed in the three way mixed ANOVA comparing replicate by line by day for reinforcers because there was no main effect of line. There was however a significant main effect for replicate ($F(1,88) = 49.595$, $p < .001$)) as replicate III mice significantly received more reinforcers than replicate II mice. As mice become more proficient at displaying response inhibition, a decrease in responding over days lead to an increase in number of reinforcers was received. This was apparent as a main effect of day

was observed ($F(1,9) = 6.335$, $p < .001$)). Contrary to the original hypothesis, there was a significant interaction for replicate by line by day ($F(1,9) = 3.050$, $p < .01$)) and a significant interaction as well for replicate by day ($F(1,9) = 8.976$, $p < .001$)).

A two way mixed ANOVA comparing replicate II mice by day for total reinforcers did not reveal a significant main effect for line ($F(1,43) = .566$, $p = .456$)). Consequently, dependent on the total number of reinforcers available, high responding can yield a similar amount of reinforcers relative to low responding only if the time elapsed after reinforcer availability is a significant amount of time. To elaborate, LAP II due to prior exposure to fixed interval training may be inhibiting their responses much longer than the 20 second DRL interval therefore minimizing the number of reinforcers that can obtained. A line by day interaction was also observed ($F(1,9) = 1.935$, $p < .05$)) which may explain why there wasn't a significant main effect of line. Figure 8 A illustrates the number of reinforcers both lines received and it appears that LAP II mice displayed a general trend of receiving a greater number of reinforcers. Likewise, analysis with replicate III mice revealed similar findings. Using a two way mixed ANOVA with line by day and number of reinforcers as a dependent measure, failed to produce a significant main effect for line. Though this finding is contrary to what the original hypothesis stated, it is not surprising because there was a lack of a main effect for in regards to active lever presses between HAP III and LAP III mice. Therefore, no differences between the two lines for number of reinforcers should be observed. Figure 8 B captures the significant interaction for line by day with the replicate III mice ($F(1,9) = 5.348$, $p < .001$)). After averaging the last 5 days of DRL 20, a two way between subjects ANOVA comparing replicate by line for reinforcers did not reveal a main effect of

replicate, main effect of line, nor a line by replicate interaction. Reinforcers as a measure in this particular procedure may have not been the most accurate portrayal of impulsive behavior, but when combined with the number of active lever presses per reinforcer received, a clearer picture is presented.

10 Day Efficiency

Efficiency, or number of active lever presses per reinforcer is the most appropriate measure for response inhibition because it adds a cost component. If the goal of the experiment is to minimize responding thus maximizing the total number of reinforcers possible, then low values are representative of response inhibition. In the aforementioned study, heavy drinkers failed to exhibit response inhibition compared to control subjects ultimately emitting a greater number of responses per reinforcer. In agreement with the original hypothesis and the findings from the Rubio et al. study, a three way mixed ANOVA comparing replicate by line by day for efficiency revealed a significant main effect of line ($F(1,88) = 7.219$, $p < .01$)). Thus LAP mice tended to be significantly more efficient than HAP mice however, this difference was mostly driven by the HAP II mice increased response rate. In addition to this finding and as was expected, a significant main effect of replicate was also observed ($F(1,88) = 16.537$, $p < .001$)). As seen during phase I with the fixed interval procedure, replicate II mice responded significantly more than replicate III mice which ultimately resulted in a greater number of responses per reinforcer received. An interaction between replicate by line by day for efficiency was not found to be significant, but there were interactions for line by day and replicate by day respectively ($F(1,9) = 2.439$, $p < .01$; $F(1,9) = 6.516$, $p < .001$)).

Based on the aforementioned analysis above, the differences are primarily driven by the HAP II mice because HAP III and LAP III mice did not differ for active lever presses nor total reinforcers received.

In agreement with the original hypothesis, a two way mixed ANOVA comparing replicate II mice and day for efficiency explains this relationship as there was a main effect of line ($F(1,43) = 5.069$, $p < .05$)). Follow up independent samples t-test for each day for individual line comparisons concludes that at each of the 10 days, LAP II mice emitted fewer responses per reinforcer thus displaying greater response inhibition. This explains why a significant interaction for line by day was not observed. Figure 9 A best illustrates the differences in response inhibition between HAP II and LAP II mice. Contrary to replicate II mice, a two way mixed ANOVA comparing replicate III mice by day for efficiency did not reveal a significant main effect for line (See Figure 9 B). Likewise it is not surprising that a line by day interaction was observed ($F(1,9) = 5.523$, $p < .001$)) signifying considerable overlap throughout the 10 days due to similar overall responding. Follow up independent samples t-test did reveal though that on the first day just after fixed interval exposure, LAP III mice significantly emitted fewer responses per reinforcer ($M = 6.851$, $SE = .968$) compared to HAP III mice ($M = 12.230$, $SE = 1.726$; $t = 2.473$, $p < .05$). This difference inherently may be due to differences in response patterns during the fixed interval days. Based on the findings from exposure to DRL 20, there is a moderate genetic correlation between alcohol preference and impulsivity. This relationship continues to hold considerable support as similar findings were found for the fixed interval procedure amongst replicate II mice. Finally, the last 5 days of DRL 20 were averaged and a two way between subjects ANOVA comparing replicate by line for

efficiency did not reveal a main effect of line, a main effect of replicate, nor a replicate by line interaction.

Phase III: DRL 32s

10 Day Active Lever Press

Phase III used the exact same procedure as the Phase II DRL 20, however the reinforcer interval was increased to 32 seconds. Replicate analysis using a three way mixed ANOVA comparing replicate by line by day for active lever presses did not reveal a main effect for replicate nor line. This was not expected based on the original hypothesis which predicted differences in overall responding between HAP and LAP mice. There was however, a significant interaction for replicate by line ($F(1,88) = 8.747$, $p < .01$)). As seen in the previous two phases, differences in responding are most likely attributed to the increased response rate observed in the HAP II mice. Within subjects analysis resulted in a significant interaction for replicate by day ($F(1,9) = 10.100$, $p < .001$)), as well as a significant interaction for replicate by line by day ($F(1,9) = 2.218$, $p < .05$)) which again suggests a difference in responding over days primarily driven by HAP II mice. Following up with the replicate analysis, a two way mixed ANOVA comparing replicate II mice and day for active lever presses resulted in a significant main effect of line ($F(1,43) = 8.422$, $p < .01$)) as HAP II mice continue to lever press significantly more so than LAP II mice (See Figure 10 A). As expected and previously seen in the previous phases, there was no interaction for line by day. Throughout the 10 day exposure to DRL 32, LAP II mice responded less than HAP II mice each of the 10

days. Independent samples t-test concluded that 7 out of the 10 days, LAP II mice significantly responded less than HAP II mice, but days 4, 9, and 10 did not result in a significant difference. Similar to the phase II DRL 20 procedure, a two way mixed ANOVA for replicate III mice by day for active lever presses did not result in a significant main effect for line. Again there are no differences observed between HAP III and LAP III mice in regards to active lever presses (See Figure 10 B). A significant interaction for line by day was observed ($F(1,9) = 2.122$, $p < .05$)) which would explain the absence of a main effect for line. Contrary to the original hypothesis, the inverse from what was predicted was observed as independent samples t-test revealed LAP II mice responding at a higher rate each of the 10 days compared to HAP II mice. There were no significant differences observed for active lever presses during any of the 10 days. To further examine possible differences between the replicates and lines, the last 5 days of DRL 32 were averaged. Using a two way between subjects ANOVA comparing replicate and line for total active lever presses did not result in a main effect of replicate or a main effect of line. However, there was a significant replicate by line interaction as LAP III mice responded higher than HAP III mice while the inverse was observed in the replicate II mice as HAP II mice responded higher than LAP II mice ($F(1,88) = 4.584$, $p < .05$)). This contradicts the original hypothesis as the HAP III mice were expected to respond at a much higher rate than LAP III mice. Follow up independent samples t-test did not reveal any significant differences between the lines for either replicate.

10 Day Reinforcers

Contrary to the analysis for the phase II DRL 20, there was a significant main effect for line for the number of reinforcers received over days. A three way mixed ANOVA comparing replicate by line by day for reinforcers resulted as previously stated, a main effect of line ($F(1,88) = 5.984$, $p < .05$)). In agreement with the original hypothesis, LAP mice received significantly more reinforcers, suggesting better response inhibition. In addition, there was also a significant main effect of replicate ($F(1,88) = 11.638$, $p < .01$)) where replicate III mice received significantly more reinforcers compared to replicate II mice. There was not an interaction for replicate by line signifying that both LAP II and LAP III mice received more reinforcers in general compared to their counterparts. This held true over successive days throughout the DRL 32 procedure as there was an absence of an interaction for replicate by line by day. A two way mixed ANOVA comparing replicate II mice by day for reinforcers did not result in a main effect of line (See Figure 11 A). In addition, there was an absence of an interaction for line by day. However, LAP II mice did receive more reinforcers throughout all 10 days compared to HAP II mice even though there was an absence of a main effect of line. Similar findings were observed with replicate III mice in that using the same analysis mentioned above, no main effect of line nor an interaction for line by day was found. LAP III mice received more reinforcers over each of the 10 days as well compared to HAP III mice (See Figure 11 B). Averaging the last 5 days of DRL 32 did not result in any significant findings. This was observed using a two way between subjects ANOVA comparing replicate and line for total reinforcers. The results did not reveal a main effect of replicate, a main effect of line, nor a line by replicate interaction.

10 Day Efficiency

Finally, in agreement with the original hypothesis and the findings from DRL 20, a three way mixed ANOVA comparing replicate by line by day for efficiency resulted in a significant main effect of line ($F(1,88) = 5.905$, $p < .05$)). LAP mice exhibited greater response inhibition compared to HAP mice by emitting fewer active lever presses per reinforcer. In addition, replicate III mice were significantly more efficient than replicate II mice as a main effect of replicate was observed ($F(1,88) = 7.133$, $p < .01$)). This also explains why there was a significant interaction between replicate and line ($F(1,88) = 4.538$, $p < .05$)).

The moderate genetic correlation between alcohol preference and impulsivity that has been observed in the previous two phases is once again supported by the replicate II mice. A two way mixed ANOVA comparing replicate II mice and day for efficiency did result in a significant main effect of line ($F(1,43) = 5.472$, $p < .05$)). LAP II mice were more efficient throughout all 10 days of the DRL 32 procedure emitting a fewer number of responses per reinforcer compared to HAP II mice. Thus LAP II mice display greater response inhibition or lower impulsive like behavior. Consequently, there was an significant line by day interaction ($F(1,9) = 1.965$, $p < .05$)). Though number of response per reinforcer should diminish over days as mice learn the DRL omission contingency, there was an increase in number of responses per reinforcer at days 6 and 7 (See Figure 12 A). Contrary to the replicate II mice, using a three way mixed ANOVA for replicate III mice and day for efficiency did not result in a significant main effect for line nor a line by day interaction. As seen throughout this experiment, HAP III and LAP III mice display very similar response patterns and receive similar number of reinforcers, thus it's

expected that there would not be any differences in their efficiency. There was a general trend however for LAP III mice emitting fewer number of active lever presses per reinforcer. Figure 12 B best illustrates this relationship. Finally, the last 5 days of DRL 32 were averaged and a two way between subjects ANOVA comparing replicate by line for efficiency did not reveal a main effect of line, a main effect of replicate, nor a replicate by line interaction. Based on the previous findings from the three phases for both replicate lines, it can be concluded that there is a moderate genetic correlation between alcohol preference and impulsivity, and this relationship is evident in the replicate II mice.

DISCUSSION

Experiments 1 & 2

General Discussion and Implications

The present findings from this study provide some support for the influence of one to multiple genes affecting multiple traits. In regards to this study, divergent selection for alcohol preference and testing mice alcohol naïve resulted in a moderate genetic correlation between alcohol preference and motor impulsivity. Thus mice selected for high alcohol preference tended to show significant deficits in response inhibition prior to reinforcer availability, and this deficit was primarily apparent in the replicate II line of the high-alcohol preferring mice. The HAP II mice in this study significantly responded more than the LAP II mice ultimately emitting a greater number of responses per reinforcer obtained. Similarly, HAP II mice failed to inhibit their responses at the beginning of the fixed interval periods compared to LAP II mice which significantly inhibited their overall responding. Though only one of the two replicates resulted in a significant difference between the high- and low-alcohol preferring lines, according to Crabbe et al., this still provides a moderate correlative relationship between alcohol preference and impulsivity (Crabbe et al., 1990).

Throughout the course of both experiments and during each of the three phases, all mice displayed responding appropriate to the fixed interval and DRL contingencies. In

the fixed interval phase, shifts in the slopes of their responding displayed minimal responding at the beginning of the interval and an increase over each successive bin throughout the two minute interval. This pattern of responding became apparent over successive days as mice learned to inhibit responding. Additionally, over successive days in the DRL phases, all mice inhibited their total number of responses as well. The replicate II high-alcohol preferring mice responded at a significantly higher rate in all three phases of the experiment compared to LAP II mice and in addition, both replicate III lines as well. In fact the observed differences were very similar in two separate pilot studies utilizing replicate II mice. The difference in overall responding that the HAP II mice display may provide the most support for a genetic relationship between alcohol preference and impulsivity.

Alcohol Related Background

Though delay discounting was not a measure used in this experiment it does provide further support that there is a genetic relationship between alcohol preference and impulsivity. As previously mentioned, delay discounting studies examine the amount a subject is willing to discount in order to receive a smaller immediate reward. Discounting for a smaller immediate reward does share some similarity to motor impulsivity procedures as impulsive subjects display deficits in response inhibition. This inability to inhibit a response may further explain why impulsive subjects prefer to have a smaller immediate reward compared to a larger delayed reward as the time delay may subjectively appear to be too long. In a recent delay discounting study using both HAP I and LAP I mice where the alleles for alcohol preference have been exhausted displayed

similar patterns for differences in both responding and impulsivity. As previously mentioned, the use of delay discounting comparing HAP I and LAP I mice tested alcohol naïve resulted in significant differences in cognitive impulsivity. HAP I mice significantly discounted to a greater extent compared to LAP I mice (Oberlin & Grahame, 2009). Additionally, the original HS/Ibg mice that were used for selection of high- and low-alcohol preference discounted significantly less than the HAP I mice used in the study. Similar to the findings from this study, selection to low drinking doesn't necessarily mean low impulsivity, but exhausted selection for high alcohol preference may lead to greater impulsive behavior. If true, then this would again provide further explanations for the differences observed between the replicate II and replicate III HAP lines. In addition to the previous study mentioned, a DD study comparing abstinent alcoholics to non-alcoholic controls found that abstinent alcoholics discount to a greater extent exhibiting significant deficits in inhibitory control (Mitchell et al., 2005). The inability to choose the higher valued delayed reinforcer exhibited amongst the abstinent alcoholics exemplifies that alcohol may not be the cause of the impulsive behavior. The genes responsible for alcoholism and impulsivity may in fact be inherently linked as they share a common set of genes. This relationship has also been observed in high-alcohol drinking rats as they significantly discount to a greater extent than low-alcohol drinking rats providing more support for the genetic relationship between alcohol preference and impulsivity (Wilhelm & Mitchell, 2008).

Motivation

A caveat to examining impulsivity is that the difference in response rate between HAP II and LAP II may be due to differences in motivation to obtain the reinforcer. For example, rats can easily be manipulated to alter their response rates for sucrose as the concentration is increased (Belke & Hancock, 2003). However, individual differences to the sensitivity of the reinforcer value may further explain the differences observed between HAP and LAP mice. The use of saccharin as a reinforcer solution is highly effective in reinforcing lever-press responding (Premack, 1965). Even at a very low saccharin concentration, 0.0316% (w/v) solution as previously mentioned was quite effective in reinforcing lever-press responding, but there are large differences in acquisition to lever press between HAP and LAP mice. This apparent difference is primarily observed in the replicate II mice whereas HAP III mice do acquire lever pressing at a slightly quicker rate compared to LAP III mice, while also exhibiting a much higher response rate during training. Though throughout the course of the experiment there were minimal differences in responding between replicate III mice, HAP III mice during training exhibited similar acquisition and response rates compared to HAP II mice. Deprivation prior to conditioning and testing has also been demonstrated to increase motivation and the value of the reinforcer itself (Timberlake & Allison, 1974). Though this is an effective training strategy in predicting response behavior, there is still a considerable amount of variation between the lines in their response behaviors. Because the HAP II mice respond at a much higher rate than the LAP II mice, they may in fact be more highly motivated. Moreover, the total difference of reinforcers received between the two lines during the fixed interval procedure was less than one, though HAP II mice

consumed significantly greater amounts of saccharin. The amount of access did not differ greatly between HAP and LAP mice, but the motivation to get to the sipper tube before it retracted provides some evidence for differences in motivated behavior as HAP mice consumed more saccharin solution.

Yet, it is difficult to assess based on this experiment whether or not differences in motivation was due to the reinforcer received. HAP mice based on previous work in the lab have demonstrated significantly higher levels of fluid intake compared to LAP mice (Oberlin et al., 2011). Likewise, differences in motivation may be linked to differences in time perception. That is, those subjects who display impulsive like behavior and/or tendencies may have profound deficits in their abilities to perceive time accurately. These deficits in timing have been demonstrated in subjects with ADHD, and this deficit is a core symptom commonly found with those that have the disorder (Ryan et al., 2010). Similar to ADHD subjects, impulsive individuals display response disinhibition, decreased tolerance to delays, overestimation of time, and poor temporal foresight. The fixed interval procedure was used to test these apparent differences in timing behavior in this study. HAP II mice exemplified deficits in timing, response disinhibition, and poor temporal foresight by responding much earlier in the inter-reinforcer intervals. Not being able to perceive time accurately when a reinforcer is available may explain the increase in response behavior. Motivation to respond for a reinforcer may then inherently be linked to poor timing for reinforcer availability. In a recent study examining the differences in time perception between those individuals whom scored high on impulsive behavior versus controls, found that impulsive individuals display deficits in timing and that this

deficit may explain why they overestimate the duration of future reinforcers (Wittmann et al., 2011).

Selecting for Alcohol Preference

There were no differences observed in any of the three phases between the replicate III mice, except that the HAP III mice did receive significantly more reinforcers than the LAP III but the difference was less than one reinforcer. In fact the responding between all replicate III mice and LAP II mice were very similar. Several possible explanations may provide some insight and further support for the genetic correlation seen in the replicate II mice. Because the replicate III mice are at an earlier point in the selection process, the additive effects of selecting for alcohol preference may not have been fully exhausted as seen in the replicate II mice (Crabbe et al., 1990). During selection, HAP II mice nearly drink twice as much alcohol as the HAP III mice. Furthermore, in a recent study examining differences in both alcohol and saccharin intake between replicate II and replicate III mice revealed an inverse relationship between these different solutions. Replicate II mice consumed significantly more alcohol compared to replicate III mice whereas replicate III mice consumed more saccharin. In addition, HAP mice consumed significantly more saccharin compared to LAP mice. Though the replicate III mice did consume more saccharin, it did not correlate to a greater number of responses as would be expected. Thus a conclusion can be drawn that saccharin intake doesn't necessarily correlate with motor impulsivity (Oberlin et al., 2011). One possible explanation for this discrepant difference is during selection there might be a threshold where earlier generations are selected for taste until a shift in selecting for pharmacologic

drinking relevance occurs. Currently, the replicate III mice are still at the early stages of selection which may explain the apparent difference, but their current selection progression is very similar to both replicate I and replicate II mice.

In addition as previously mentioned, it is possible that HAP III mice at this point during the selection process have not yet fully recruited all the genes responsible for alcohol preference. Therefore if there is a strong genetic relationship between alcohol preference and impulsivity, it will not be apparent until later generations when all additive effects have been exhausted thus maximizing the total amount of gene to gene interaction between the two traits. It is probable that the differences observed within the replicate II line may be a consequence of selecting for alcohol preference. In other words, by chance during the first divergent generation between HAP II and LAP II mice, some of the genes responsible for impulsive behavior may have been consequently selected for as well. These genes may share close proximity to the loci but may in fact share zero common genes. Therefore, some of the genetic variance between both traits may overlap due to the selection process providing a false genetic correlation that was observed by chance. Another possible explanation for the differences observed between replicate II and replicate III HAP mice may be due to sampling error or genetic drift. During the selection process there is the possibility of influencing gene or genes that are unique to the replicate that may contribute to the observed differences in the this study. Though only one of the replicates produced a significant difference in the post hoc analyses, according to Crabbe et al., the replicate that exhibits this difference is most likely an accurate assessment of a genetic correlation, and in this case between alcohol preference and impulsivity (Crabbe et al., 1990). However, both cases may be true if a replicate

loses a gene important to the trait during inbreeding which would then lead to differences in correlated responses. Therefore, conclusions concerning whether a genetic correlation exists for alcohol preference and impulsivity with the replicate III mice cannot be determined until later generations once the alleles for alcohol preference have been exhausted and fixed.

Conclusion

In agreement with the original hypothesis, the findings from this study provide a moderate genetic correlation between alcohol preference and impulsivity. Alcohol abuse and alcohol dependence have a multitude of traits and behaviors that can be attributed to the development and maintenance of alcoholism. However, it is important to note that not all individuals share the exact same course toward developing this disease. There is a considerable amount of variation between individuals similar to the large amounts of variation seen between our selected alcohol preferring lines. This genetic relationship between alcohol preference and impulsivity provides considerable support toward the understanding of multiple factors that influence and trigger an individual to develop and maintain alcohol related problem(s). For those individuals who have both a genetic background for alcohol and in addition, impulsive behaviors increases their risk of developing an alcohol related disorder. Because of alcohol's heritable nature, alcohol preference based on this study and on several others, provides a considerable amount of evidence that alcohol preference and impulsivity share a common set of genes. The relationship between preferring to consume alcohol over other alternatives and being impulsive in nature may provide some insight toward placing oneself in drinking

environments and the inability to inhibit one's behavior toward self-control. Thus, young individuals with parents with alcohol related problems may show early signs of impulsive like behavior which may lead to early intervention and prevention of future alcohol related problems within one's family.

FIGURES

A B

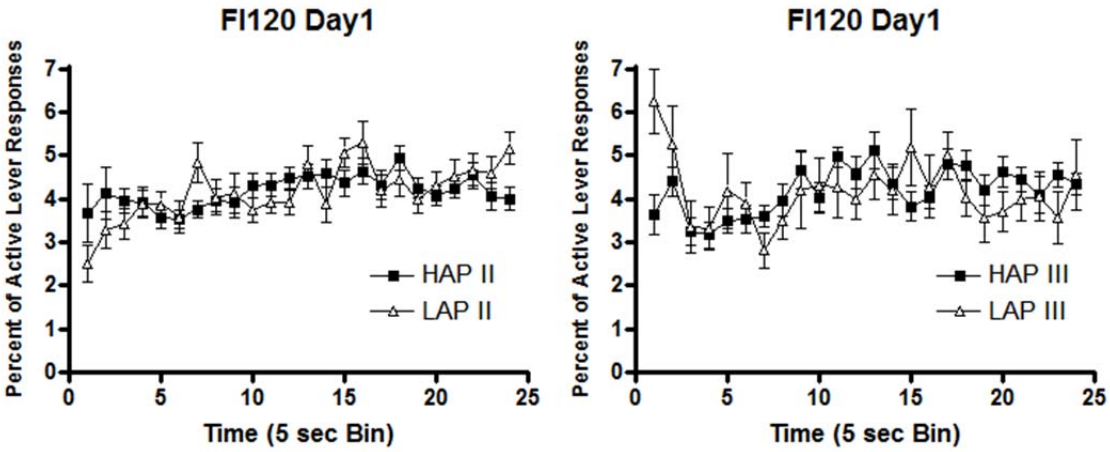

Figure 1. Phase I Day 1 Percent Active Lever Press. HAP and LAP mice for both replicates on day 1 using a percent transform do not exhibit differences in response inhibition. This is illustrated by a horizontal line indicating that mice do not have any prior experience with this procedure.

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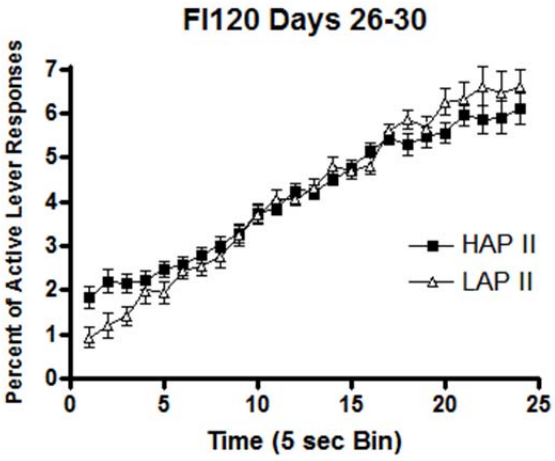

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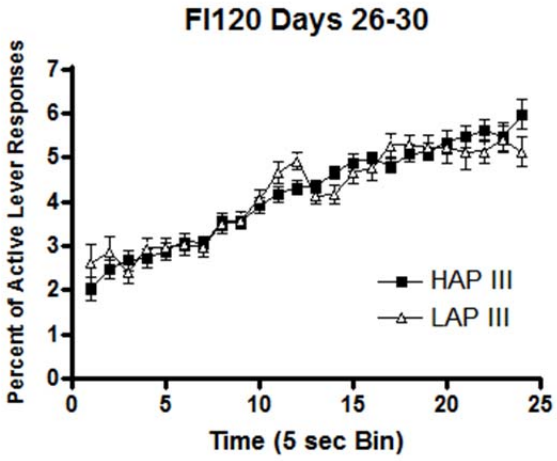

Figure 2. Phase I Days 26-30 Percent Active Lever Press. After 30 days of FI120 exposure, days 26-30 were averaged. Analysis using a percent transform revealed a significant line by bin interaction for the replicate II mice ($F(1,23) = 1.845$, $p < .01$)) indicating greater response inhibition amongst LAP II mice compared to HAP II mice. There was however, no differences observed between the replicate III mice.

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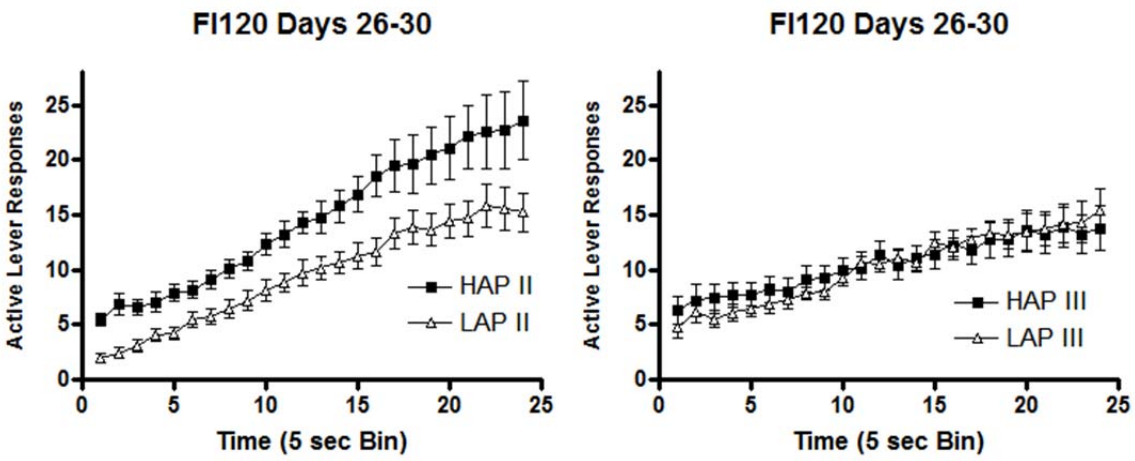

Figure 3. Phase I Days 26-30 Active Lever Press. HAP II mice respond at a significantly higher rate than LAP II mice ($F(1,43) = 8.214$, $p < .01$)). Independent t-test revealed significant differences for 19 out of the 24 bins amongst the replicate II mice, with HAP II mice responding at a higher rate at each of the 24 5s bins. There were no differences observed for active lever presses between replicate III mice.

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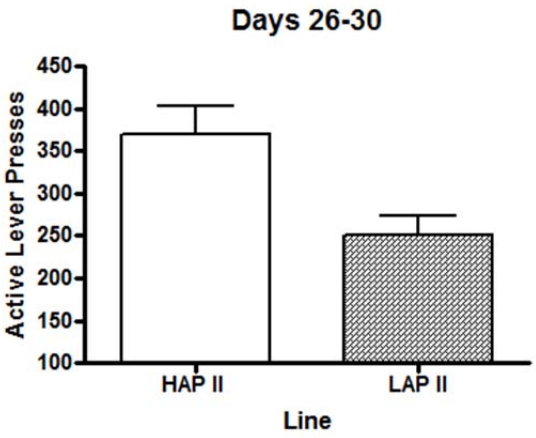

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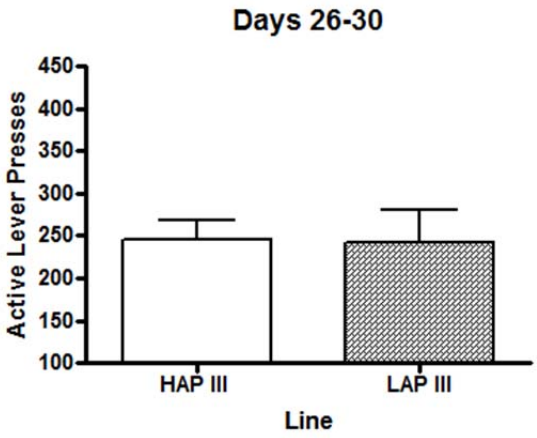

Figure 4. Phase I Days 26-30 Total Active Lever Press. Independent samples t-test for total active lever presses averaged across days 26-30 concluded that HAP II mice respond at a significantly higher rate (M = 349.167, SE 34.598) compared to LAP II mice (M = 227.391, SE = 22.290; t = 2.866, $p < .01$)). Again, no differences were observed between replicate III mice.

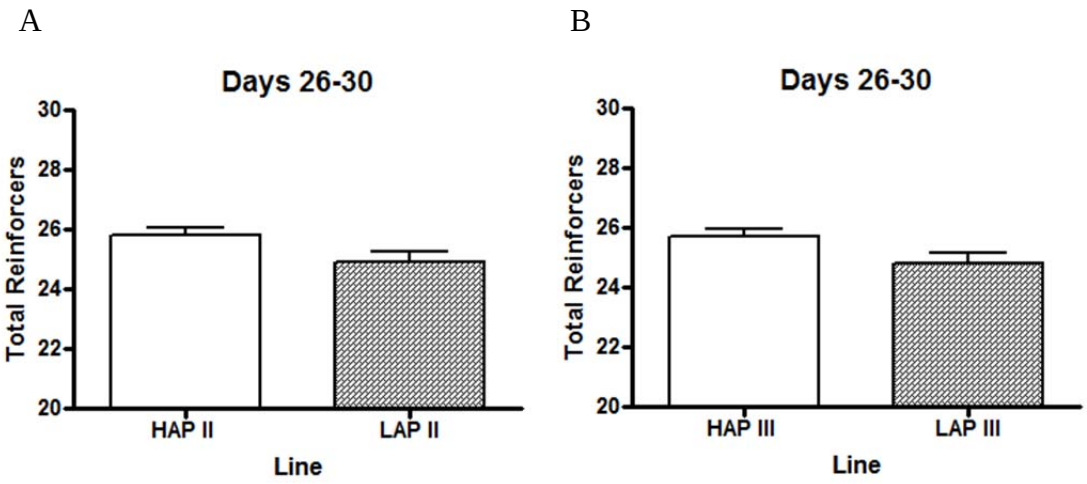

Figure 5. Phase I Days 26-30 Total Reinforcers. Contrary to the original hypothesis, HAP mice received more reinforcers than LAP mice. HAP II mice received significantly more reinforcers (M = 25.841, SE = .226) compared to LAP II mice (M = 24.762, SE .413, t = 2.363, $p < .05$), in addition HAP III mice also received significantly more reinforcers (M = 25.970, SE = .173) compared to LAP III mice (M = 24.700, SE = .270; t = 4.138, $p < .001$).

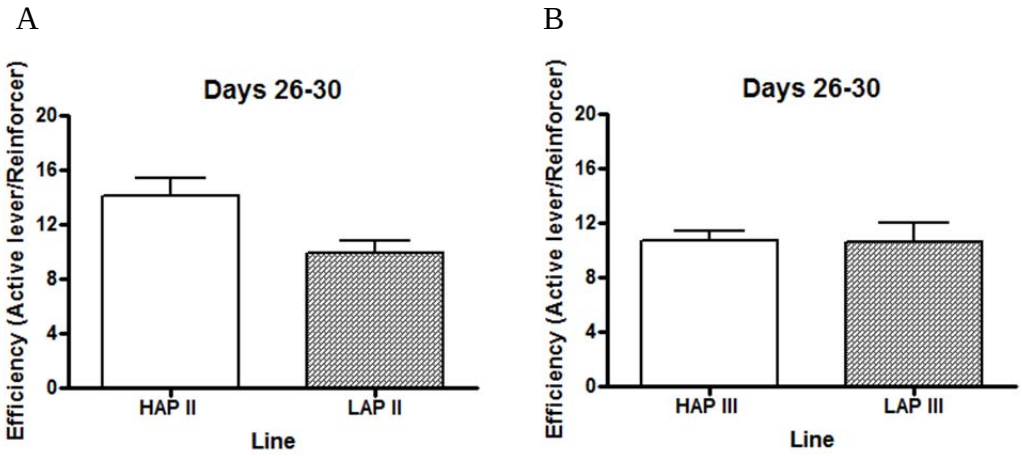

Figure 6. Phase I Days 26-30 Efficiency. The high response rate emitted by the HAP II mice led to a significantly higher number of active lever presses per reinforcer obtained (M = 13.290, SE = 1.234) compared to LAP II mice (M = 8.914, SE = .812; t = 2.873, p < .01), thus displaying poorer response efficiency. There were no differences observed between the replicate III mice.

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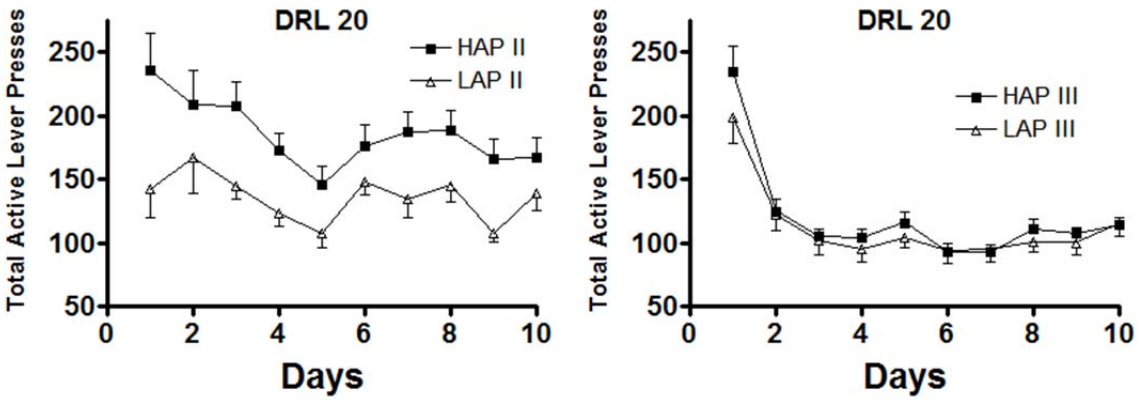

Figure 7. Phase II 10 Day Active Lever Press. During phase II, both replicates displayed apprehension of the omission contingency by reducing overall responding over days. There was a main effect of line over the 10 days as HAP II mice significantly responded higher ($F(1,43) = 8.007$, $p < .01$)) compared to LAP II mice. No differences were observed between replicate III mice.

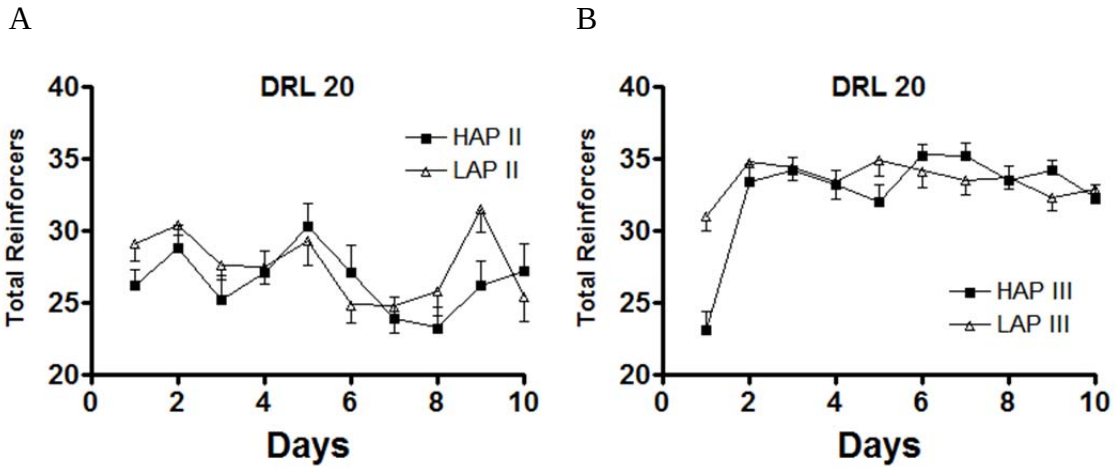

Figure 8. Phase II 10 Day Reinforcer. Contrary to the original hypothesis, HAP and LAP mice did not differ in the number of reinforcers received as there was an absence of a main effect of line for either replicate. Replicate III mice did however, receive significantly more reinforcers compared to replicate II mice ($F(1,88) = 49.595$, $p < .001$)).

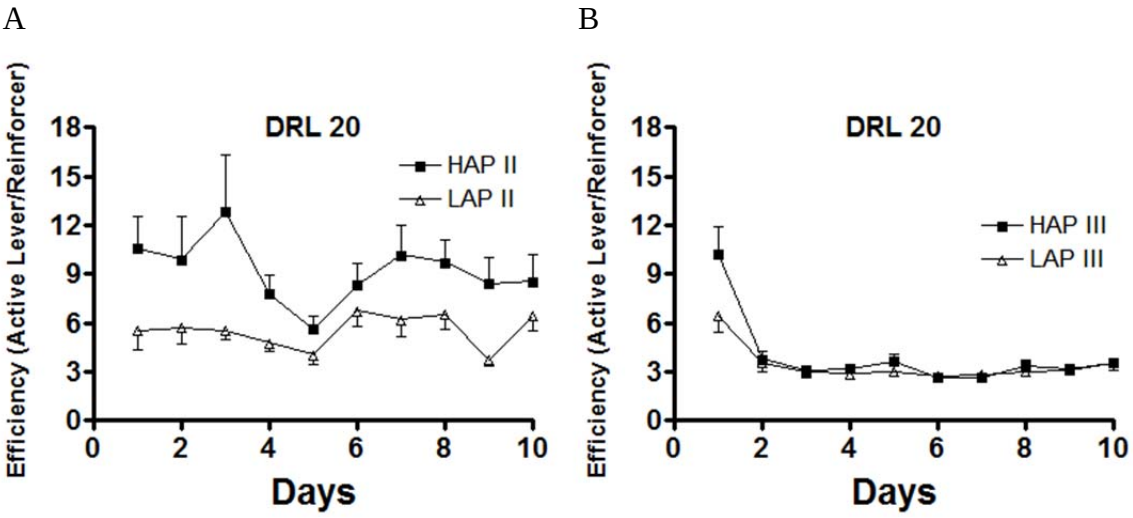

Figure 9. Phase II 10 Day Efficiency. As seen in phase I, HAP II mice significantly respond at a higher rate than LAP II mice. With minimal differences in number of reinforcers received, LAP II mice are significantly more efficient than HAP II mice ultimately emitting a fewer number of responses per reinforcer ($F(1,43) = 5.069$, $p < .05$)). Replicate III mice did not display any differences in efficiency after day 1.

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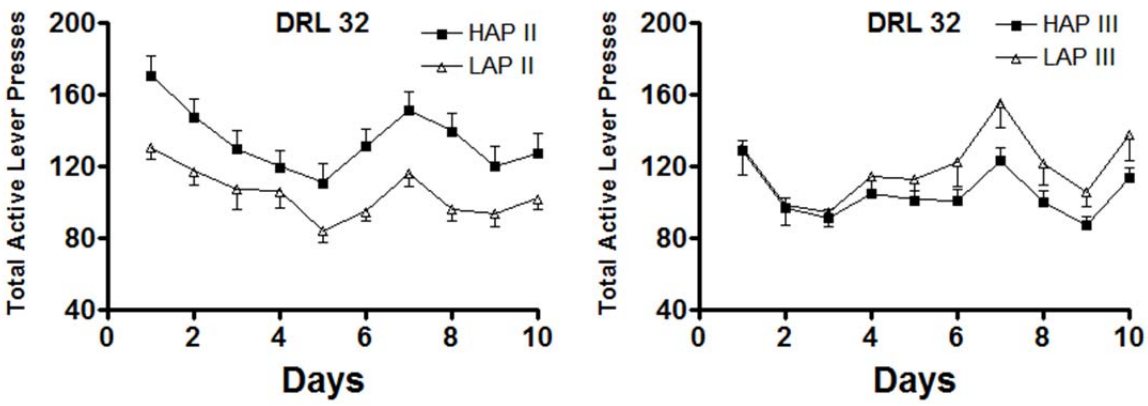

Figure 10. Phase III 10 Day Active Lever Press. Similar to the findings from phase II, phase III data for active lever presses resulted in a significant main effect of line over the 10 days as HAP II mice significantly lever pressed at a higher rate compared to LAP II mice ($F(1,43) = 8.422$, $p < .01$)). There were no significant differences observed between the replicate III mice however, LAP III mice tended to respond at a higher rate compared to HAP III mice on days 4-10.

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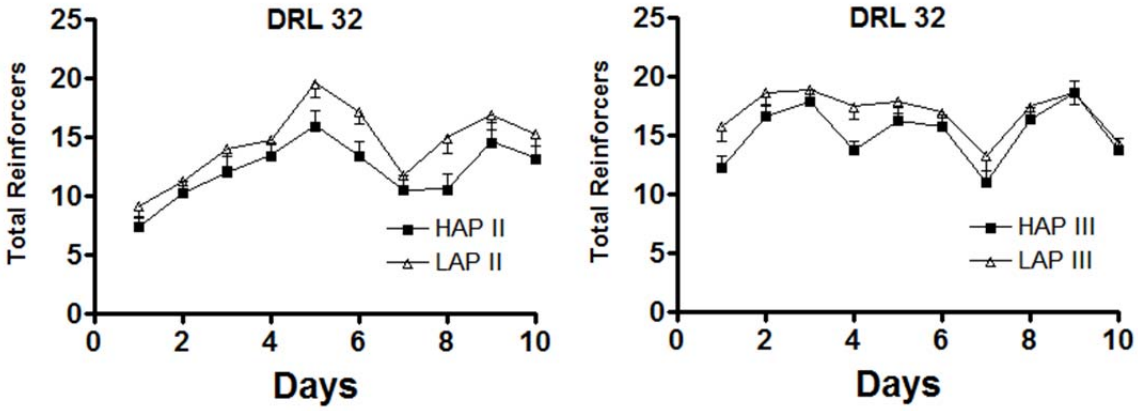

Figure 11. Phase III 10 Day Reinforcer. There was no main effect of line over days for the number of reinforcers between the lines for either replicate. However, LAP II and LAP III mice did tend to receive more reinforcers over each of the 10 days compared to their HAP mice counterparts respectively.

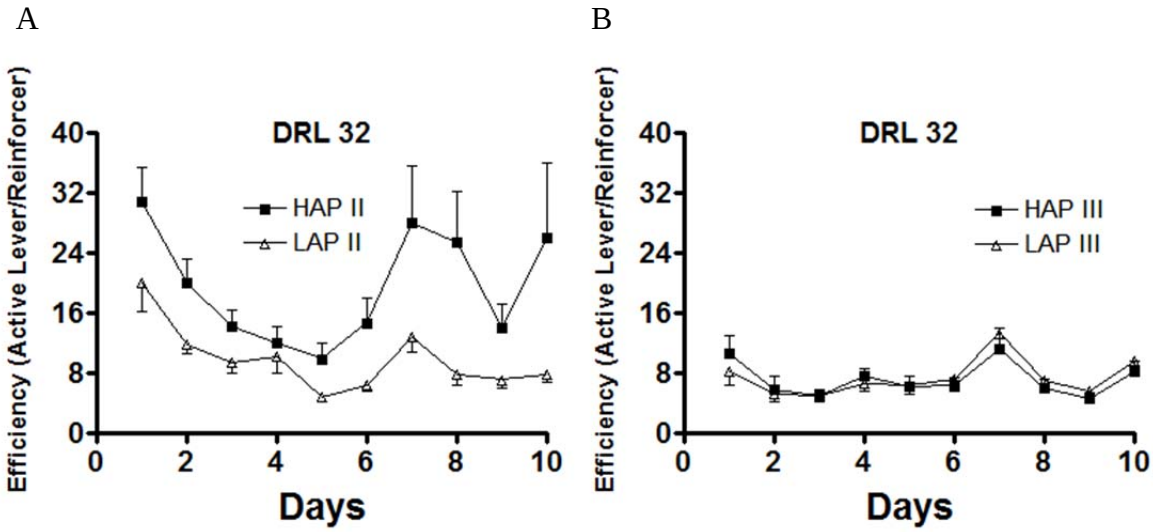

Figure 12. 10 Day Efficiency. As previously illustrated in the DRL 20 data, there was a significant main effect of line over days for active lever presses per reinforcer ($F(1,43) = 5.472$, $p < .05$)) as HAP II mice significantly pressed more to obtain a reinforcer compared to LAP II mice. No differences were observed between replicate III mice.

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VITA

VITA

Devon Michael Novotney

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Accepted Abstracts/Poster Presentations

Novotney, D.M., Villalta, N.A., Frye, C.J., Grahame, N.J. Fixed Interval and Differential Reinforcement of Low Rate as Potential Measures for Motor Impulsivity with Genetically Selected High-Alcohol Preferring Mice. (Research Society on Alcoholism Meeting, Atlanta, GA, June 2011)

Villalta, N.A., **Novotney, D.M.**, Grahame, N.J. Differences in Impulsivity Between High-Alcohol Preferring and Low-Alcohol Preferring Mice in a DRL Task. (Butler Undergraduate Research Conference, Indianapolis, IN, April 2011)

Villalta, N.A., **Novotney, D.M.**, Grahame, N.J. Selectively Bred High-Alcohol Preferring Mice Show Poor Response Inhibition in both Fixed Interval Reinforcement and Differential Reinforcement of Low Rate. (IUPUI Research Day, Indianapolis, IN, April 2011)

Novotney, D.M., Villalta, N.A., Frye, C.J., Grahame, N.J. Fixed Interval and Differential Reinforcement of Low Rate as Potential Measures for Motor Impulsivity with Genetically Selected High-Alcohol Preferring Mice. (Indianapolis Society for Neuroscience Local Neuroscience Meeting, Indianapolis, IN, October 2010)

Novotney, D.M., Grahame, N.J. Selectively Bred High-Alcohol Preferring Mice Show Poor Response Inhibition during Fixed Interval Reinforcement. (Research Society on Alcoholism Meeting, San Antonio, TX, June 2010)

Novotney, D.M., Grahame, N.J. Selectively Bred High-Alcohol Preferring Mice Show Poor Response Inhibition during Fixed Interval Reinforcement. (Indianapolis Society for Neuroscience Local Neuroscience Meeting, Indianapolis, IN, October 2009)

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