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Mice bred for severity of acute alcohol withdrawal respond differently in a Go/No-go task

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Abstract

Background—Mice selectively bred for high or low withdrawal to acute alcohol differ on a number of traits, including consumption of alcohol, conditioned place preference for alcohol, and sensitivity to alcohol-induced locomotor activity. One trait that has not been examined in these mice is behavioral inhibition.

Methods—High and low alcohol withdrawal mice (2nd replicate: [HAW-2/LAW-2]) were trained and tested in a Go/No-go task. Mice were administered 0.0, 0.5, 1.0, and 1.5 g/kg ethanol on 3 occasions according to an incomplete Latin Square. A separate cohort of C57BL/6J [B6] and DBA/2J [D2] mice (the progenitor strains for HAW-2/LAW-2 mice) underwent the same protocol, using the same ethanol doses.

Results—HAW-2 and LAW-2 mice did not differ in behavioral inhibition at baseline, although LAW-2 mice did have higher overall levels of responding in the task. Ethanol did not alter behavioral inhibition in these mice. However, it did decrease responses to the Go cue, and this effect was greater in HAW-2 mice than in LAW-2 mice. D2 mice had lower behavioral inhibition than B6 mice at baseline, and ethanol slightly decreased behavioral inhibition in both strains.

Conclusions—The findings with D2 and B6 mice generally fit with the existing literature. However, the lack of a difference in behavioral inhibition between HAW-2 and LAW-2 mice was unexpected, as well as the absence of any effect of these doses of ethanol on behavioral inhibition in these mice. Nonetheless, the findings do suggest that selectively breeding for high or low withdrawal to acute alcohol can lead to differences in operant behavior in the Go/No-go task.

Keywords

Alcohol; Behavioral Inhibition; Impulsivity; Selected lines; Go/No-go

Introduction

Alcohol is a commonly abused substance, and many studies have demonstrated that alcohol use increases impulsive and risk taking behaviors such as gambling, aggressive behavior, and unprotected sex (Erickson and Trocki, 1992; Fendrich et al., 1995; Goudriaan et al., 2005). One type of impulsive behavior is reduced behavioral inhibition (heightened

disinhibition), which can be measured with tasks that ask participants to withhold a response in order to receive a reward. Individuals that are unable to withhold responses are thought to be more impulsive. Interestingly, alcoholics tend to have less behavioral inhibition than controls (de Wit et al., 2000; Easdon et al., 2005). However, it is unknown whether this is due to chronic alcohol abuse, early environmental experience, or a genetic predisposition that influences alcohol drinking and behaving impulsively.

Because of the difficulty in directly examining genetic effects in humans, several lines of mice have been developed to help understand the genetic components of alcohol consumption. Such lines include the high- and low-alcohol preferring mice [HAP/LAP] (Grahame et al., 1999) and the high- and low-drinking short-term selected mice [STDRHI/STDRLO] (Phillips et al., 2005). In addition to consumption of alcohol, a number of mice have been selected on other alcohol-related traits, such as sensitivity to alcohol-induced stimulation (FAST/SLOW mice; Crabbe et al., 1987), sensitivity to alcohol-induced loss of righting reflex (short/long sleep mice [SS/LS]; Fuller, 1980), and severity of alcohol withdrawal (after chronic alcohol: Withdrawal Seizure Resistant/Prone mice [WSR/WSP], Kosobud and Crabbe, 1986; after acute alcohol: High- and Low-Alcohol Withdrawal mice [1streplicate: HAW-1/LAW-1], Metten et al., 1998a). Often, mice selected for a particular alcohol-related trait will also differ in consumption of alcohol, suggesting that common genes mediate both behaviors. For example, both WSR and LAW-1 mice consume significantly more alcohol than WSP and HAW-1 mice, respectively (Kosobud et al., 1988; Metten et al., 1998b).

In order to understand how behavioral inhibition might relate to these different traits, a recent study examined behavioral inhibition in 15 inbred strains (Gubner et al., 2010). Strain differences in behavioral inhibition were then correlated with strain differences found in other alcohol-related behavioral traits as reported in previous studies. Behavioral inhibition did not correlate with drinking, sedation, or ataxia, but low behavioral inhibition did correlate with high withdrawal from chronic and acute alcohol, suggesting that common genes may underlie these two traits. Thus, the WSR/WSP and HAW/LAW mice are prime candidates in which to examine behavioral inhibition, and we focus on the second replicate HAW-2/LAW-2 lines in this study, as the first replicate (HAW-1/LAW-1) were terminated in the late 1990's.

HAW-2 and LAW-2 mice are derived from an F2 cross between the commonly used inbred C57BL/6J [B6] and DBA/2J [D2] mice. Like HAW-1 and LAW-1 mice, B6 and D2 strains also have markedly different responses to ethanol. B6 mice will voluntarily drink more ethanol, display a smaller stress response to ethanol, and have less severe withdrawal seizures than D2 mice (Belknap, 1993; Roberts et al., 1992). However, D2 mice exhibit stronger conditioned placed preference for ethanol than B6 mice, paralleling a finding that HAW-1 mice exhibit stronger conditioned placed preference for ethanol than LAW-1 mice (D2/B6: Cunningham et al., 1992; HAW/LAW: Chester et al., 1998). Behavioral inhibition has been examined in B6 and D2 mice, and the literature suggests that D2 mice have less basal inhibition. For example, Patel et al (2006) found that D2 mice made more premature responses in the 5-choice serial reaction time task. In another study using a Go/No-go task, Loos et al. (2010) demonstrated drug naive D2 mice were less able to withhold responding

during the No-go signals and also made more premature responses in the 5-choice serial reaction time task. Gubner et al. (2010) compared D2 and B6 mice in the Go/No-go task and did not find significant differences, however trends were present where D2 mice responded more during the No-go signal (false alarms) and a higher rate of response in the period immediately prior to the onset of the Go and No-go cues.

Although some studies on basal behavioral inhibition have been examined in B6 and D2 mice, to our knowledge no studies have compared the effects of acute ethanol on behavioral inhibition in these strains. Nonetheless, some studies have examined these effects in other strains of mice. Oliver et al. (2009) demonstrated ethanol increased premature responding during inter-trial intervals in C57BL/6JOLA^{Hsd} and CD1 mice. Olmstead et al. (2009) used knockout and wild type mice with a B6 or 50% B6 background and found ethanol administration increased premature responding in the stop signal task.

The goal of this study was to determine if HAW-2 and LAW-2 lines differed in behavioral inhibition before ethanol administration, and then to examine how each line responded to ethanol. To accomplish this, we ran HAW-2 and LAW-2 subjects in the Go/No-go task and administered acute ethanol injections. We anticipated that the HAW-2 strain would have less behavioral inhibition both before and after receiving ethanol when compared to the LAW-2 strain. To compare these data with those of the progenitor strains, B6 and D2 mice completed the same procedure to compare HAW-2 and LAW-2 performance to the parent strains, and we hypothesized the B6 and LAW-2 strains would have similar responses.

Methods

Subjects

This research used naïve mice selected for high acute alcohol withdrawal (HAW-2) and low acute alcohol withdrawal (LAW-2), which were selectively bred for five generations from a C57BL/6J × DBA/2J population in the Portland Alcohol Research Center at the Portland VA Medical Center. Only replicate 2 lines were available for this study. The acute withdrawal response selected for was the area under the curve for the waxing and waning handling-induced convulsion score tested hourly for 12 hr after ip injection of 4 g/kg ethanol: these were corrected for baseline scores. Mice from this generation of HAW-2 and LAW-2 had acute withdrawal scores averaging 7.54 ± 0.75 and 2.41 ± 0.49, respectively ($F(1,136) = 30.7$, $P < 0.0001$) (Metten, Phillips, Crabbe and Belknap, unpublished data). The second group of mice consisted of male and female C57BL/6J and DBA/2J mice obtained from Jackson Laboratory (Bar Harbor, ME).

At the beginning of the study mice were between 5-8 weeks of age. The mice were weighed for 5 days to obtain their free-feeding weights. The first day of training occurred after a minimum of 48 hours on a food-restricted diet to ensure they would be motivated to respond using a sucrose reinforcer. Throughout the experiment mice were maintained at approximately 90% of their free-feeding weight with laboratory mouse chow.

Mice were housed 2-5 per cage under a 12:12-h light: dark cycle (lights on at 6 am) in a temperature-controlled vivarium ($21.7 \pm 1^\circ\text{C}$), and maintained according to guidelines

provided by the Oregon Health & Science University Department of Comparative Medicine. The Institutional Animal Care and Use Committee approved all procedures.

Apparatus

Behavior was assessed in sixteen identical Med-Associates (St. Albans, VT) operant conditioning chambers housed in sound-attenuating ventilated boxes. Mounted on the back panel outside the chamber was a 100 mA house light. The front panel contained 3 nosepoke holes mounted 1.27 cm above the grid floor. Above each of the nosepoke holes was a 0.50 cm diameter yellow LED light. Each nosepoke contained a liquid reward cup. Eighteen-gauge stainless steel pipes continuous with the cups fed into plastic tubing attached to a syringe, which was filled with 10% (w/v) sucrose solution and secured in a Med-Associates pump.

Procedure

The training procedure was the same as in Gubner et al. (2010); subjects completed two training phases before reaching the experimental phase (see Table 1 for training data.) Following training, subjects performed the Go/No-go task for 15 sessions. At this time, mice advanced to the injection phase of the study. All groups of mice could discriminate between the Go and No-go cues, as indicated by having a d-prime score significantly above zero (HAW: 0.71 ± 0.11 , LAW: 0.73 ± 0.11 , D2: 0.49 ± 0.13 , B6: 1.05 ± 0.14 ; one-sample t-tests comparing to zero: all $t_s > 3.81$, $p_s < .001$). D-prime is defined as the z-score transformation of the proportion of Go trials on which the animal responded (Hits/Go trials) minus the z-score transformation of the proportion of No-go trials on which the animal responded (False alarms/No-go trials).

Go No/Go Task—The Go/No-go task was identical to that used in Gubner et al. (2010). Each session lasted until 60 trials were completed (30 Go, 30 No-go) or until 40 min elapsed. The 1:1 ratio for Go:No-go trials was chosen (as opposed to higher ratios used in human studies) because preliminary research in our lab has shown that rodents have difficulty learning the task with higher ratios. Each trial began with a variable duration precue period of 9-24 seconds during which the house light was illuminated. If a response was made during the last 3 seconds of the precue period the trial was reset to prevent premature responding. The precue period was followed by a 5 sec cue period using distinct cues to differentiate Go trials from No-go trials. In a Go trial, the light above the left or right nosepoke hole was illuminated (counterbalanced between subjects). In a No-go trial a continuous 65-dB 2.9 kHz tone sounded. A nosepoke response during a Go trial ended the Go cue and was reinforced with 20 microliters of 10% sucrose solution (see Figure 1). A “click” signaled the delivery of the reward and the start of the 3 second reward period. This was followed by a 10 second inter-trial interval (ITI) in which the house light was off. If no nosepoke response was made during the No-go cue, a 20 μ l reinforcer was delivered at the end of the period, signaled by a click. After a 3-second reward period, the 10-second ITI began. If a nosepoke response was made during the No-go period the tone was terminated and the ITI began with no reinforcer delivered.

Ethanol administration—200 proof ethanol was mixed with 0.9% saline for a 20% v/v ethanol solution. Animals were administered 4 doses of ethanol: 0.0 g/kg, 0.5 g/kg, 1.0 g/kg, and 1.5 g/kg 3 times, on a Tuesday and Friday, creating an incomplete Latin square. Ethanol was administered intraperitoneally and the test session began immediately after the injection. No injection was provided prior to the Monday, Wednesday and Thursdays sessions.

A separate group of HAW-2 and LAW-2 mice were injected with ethanol without performing the task to test for differences of ethanol metabolism. Blood samples were drawn 40 minutes after injection and blood ethanol concentration was measured. This second group was used so anticipatory stress associated with the blood draw could not interact with the effects of ethanol on behavior in the task. Two-factor analyses of Variance (ANOVAs) indicated that there were no selected line differences present at any dose (0.5g/kg: LAW: 0.09 ± 0.05 g/kg, HAW: 0.16 ± 0.10 g/kg; $F(1, 14) = 0.09, p = .774$; 1.0 g/kg: LAW: 0.60 ± 0.4 g/kg, HAW: 0.76 ± 0.10 g/kg; $F(1, 14) = 1.53, p = .237$; LAW: 0.92 ± 0.14 g/kg, HAW: 0.99 ± 0.18 g/kg; 1.5 g/kg: $F(1, 14) = 0.02, p = .883$). Previous data indicate B6 and D2 mice do not differ markedly in BEC levels 30 minutes after receiving 1.0 and 2.0 g/kg ethanol (Crabbe et al, 1994).

Data Analysis

The Go/No-go task measures the ability to respond or withhold a response, depending on the cue presented. The two main measures of inhibition were false alarms (responses during the No-go cue) and precue response rate (responses made during the precue periods divided by the total precue time). Also analyzed were hits (responses during the Go cue).

To examine behavior prior to the administration of ethanol, sessions 11-15 were averaged and analyzed using two-factor ANOVAs: (mouse: HAW-2, LAW-2 or B6, D2) $\times$ (sex: male, female) ANOVAs. Injection data were analyzed by comparing the session before receiving drug with the session where drug was received using $2 \times 2 \times 4 \times 2$ ANOVAs (mouse $\times$ sex $\times$ dose $\times$ session). Because there were no systematic effects across the 3 separate occasions that each dose was administered, we averaged the data across these separate occasions to reduce the number of factors in the ANOVA.

Excluded Subjects and Sessions

Ten mice failed to pass either Phase 1 or Phase 2 of training and therefore did not complete the experiment (2 HAW-2 males, 4 LAW-2 females and 4 DBA/2J females). These mice are excluded from all analyses and are not represented in Table 1.

A total of 10 injections out of 1,744 were excluded from analyses due to subjects not receiving the full dose. For these data points, we substituted the mean score from the other 2 days on which that dose was administered.

All statistics were analyzed using PASW version 18 (SPSS Inc. Chicago, IL). Huynh-Feldt corrections were performed if there were violations of the sphericity assumption and, in those cases, the adjusted degrees of freedom are reported.

Results

HAW-2 and LAW-2

Baseline—HAW-2 and LAW-2 mice responded differently in the Go/No-go task in ways suggesting that LAW-2s were more predisposed to nosepoke than HAW-2s. The LAW-2 line had more false alarms than the HAW-2 line ($F(1, 50) = 5.39, p = .025$) and a higher precue response rate ($F(1, 50) = 7.17, p = .010$) suggesting LAW-2 mice were less inhibited at baseline (see Figure 2, Table 2). However, the LAW-2 line also had more hits ($F(1, 50) = 4.12, p = .048$), which suggests these differences in measures of inhibition reflect a higher level of operant activity. Male mice had a higher precue response rate and more hits than females ($F(1, 50) = 4.86, p = .032$; $F(1, 50) = 5.40, p = .024$), however false alarms did not differ between sexes. There were no significant line $\times$ sex interactions for any variable.

Ethanol Effects—Ethanol did not alter behavioral inhibition in either the HAW-2 or the LAW-2 mice, although there were significant ethanol dose $\times$ session interactions for each of the three task measures (precue response rate: $F(2.66, 132.86) = 2.81, p = .048$, false alarms: $F(3, 150) = 15.26, p = .012$, hits: $F(2.61, 130.37) = 31.00, p < .001$). The nature of these interactions differed for each measure (see Figure 3). Ethanol's effects on precue response rate were minimal, and the dose $\times$ session interaction appeared to be driven by differences between the pre-injection sessions (pre-injection sessions only: dose: $F(3, 150) = 5.76, p = .001$, injection sessions only (dose: $F(3, 150) = 0.75, p = .525$). However, the saline injection led to a significant increase in precue response rate (injection: $F(1, 50) = 101.80, p < .001$, significantly different from baseline at 0.0 g/kg). The saline injection also increased false alarms; however, this effect was dose-dependently blocked by ethanol (injection: $F(1, 50) = 13.16, p = .001$, significantly different from baseline at 0.0 g/kg, not different at 1.0 and 1.5 g/kg). Finally, hits were not affected by the saline injection, but they were decreased by ethanol at 1.5 g/kg. The decrease in hits was stronger in the HAW-2 mice (line $\times$ dose $\times$ session: $F(2.61, 130.37) = 5.93, p = .001$).

DBA/2J and C57BL/6J

Baseline—D2 exhibited lower behavioral inhibition in the Go/No-go task than B6 mice: D2 mice had more false alarms ($F(1, 50) = 43.90, p < .001$, see Figure 4, Table 2). The two strains responded similarly for hits and precue response rate. Additionally, males of both strains had more hits and false alarms than females (hits: $F(1, 50) = 9.10, p = .004$; false alarms: $F(1, 50) = 21.08, p < .001$). There were no strain $\times$ sex interactions for any variable.

Ethanol Effects—Ethanol decreased behavioral inhibition in these mice, as evidenced by the increased precue response rate and false alarms at the highest dose (precue response rate: $F(2.03, 101.31) = 7.48, p = .001$, false alarms: $F(3, 150) = 5.94, p = .001$, coupled with Bonferroni post hoc tests, see Figure 5). However, ethanol's effects on hits were opposite for the two strains. Ethanol led to a nonsignificant increase in hits for D2 mice, while it led to a significant decrease in hits for B6 mice at the highest dose (dose $\times$ injection $\times$ strain: $F(3, 150) = 4.38, p = .006$, followed by Bonferroni post hoc tests). Lastly, the saline injection significantly decreased hits, but only for the B6 mice (injection $\times$ group: $F(1, 50) = 33.10, p < .001$, significant decrease at 0.0 g/kg for B6 mice).

Discussion

HAW-2 and LAW-2 mice differed from each other and from their progenitor strains in several ways. First, LAW-2 mice responded significantly more than HAW-2 mice on the three primary measures of interest in the Go/No-go task at baseline. While one could interpret this as showing that LAW-2 mice had lower behavioral inhibition than HAW-2 mice (since they have more false alarms and a higher precue response rate), the fact that LAW-2 mice also had more hits complicates this finding. Because the difference between the strains is not specific to the measures of behavioral inhibition, it may reflect a difference in motivation to respond in the task, different motor capability in general, or a different strategy for responding in the task.

In contrast, D2 and B6 mice did show a difference specific to behavioral inhibition at baseline, since D2 mice had significantly more false alarms but similar numbers of hits compared to B6 mice. Therefore, we can conclude that D2 mice had lower behavioral inhibition than B6 mice in this task, which is consistent with previous findings (Loos et al., 2010; Patel et al., 2006). It should be noted that one study (Gubner et al., 2010) only found trends towards differences in false alarms, precue response rate, and hits, suggesting differences in overall response levels rather than behavioral inhibition. Nonetheless, it is possible that the Gubner et al. (2010) study was underpowered, as it only had 8 subjects for each group (for comparison, the current study used 29 B6 mice and 25 D2 mice).

The findings with the drug-naïve HAW-2 and LAW-2 mice were not what we expected given the Gubner et al. (2010) findings, which showed that mice with high ethanol withdrawal also had low behavioral inhibition. However, it should be noted that the correlation in that study was stronger for chronic withdrawal than acute withdrawal, and that the acute withdrawal correlation seemed to be driven primarily by one outlier strain. It may be that using mice selected for withdrawal after chronic ethanol would have yielded results more in line with our hypothesis; our lab is currently conducting a similar study using WSR/WSP mice.

Nonetheless, the findings are also unexpected based on the parallels seen between HAW-1/LAW-1 and D2/B6 mice in other behavioral assays. For example, both HAW-1 and D2 mice have more severe withdrawal seizures after ethanol (HAW-1/LAW-1: Metten et al., 1998a; D2/B6: Roberts et al., 1992), drink less ethanol (HAW-1/LAW-1: Metten et al., 1998b, D2/B6: Belknap, 1993), have high ethanol-induced locomotor activity (HAW-1/LAW-1: Chester et al., 1998; D2/B6: Phillips et al., 1994) and show strong CPP for ethanol (HAW-1/LAW-1: Chester et al., 1998; D2/B6: Cunningham et al., 1992), while LAW-1 and B6 mice show the opposite behavioral profile (one example where this does not hold is conditioned taste aversion: D2 mice show more conditioned taste aversion than B6 mice (Risinger and Cunningham, 1998), while HAW-1 and LAW-1 mice do not differ (Chester et al., 1998)). Although our data are from the second replicate HAW-2/LAW-2 lines, unpublished data suggests they have a withdrawal response profile similar to that of the original selected lines (see Methods and Metten et al, 1998a). They also resemble the HAW-1/LAW-1 in terms of their relative consumption of 10% ethanol (LAW-2 = 3.68 $\pm$ 0.71 g/kg vs HAW-2 = 1.76 $\pm$ 0.64 g/kg, $F(1,36) = 3.53$, $p < 0.05$, one tailed test; Metten, Phillips, Crabbe and

Belknap, unpublished data). Given this, we might have expected that HAW-2 mice, like D2 mice, would have had more false alarms than their counterparts. There are a number of possible explanations for our discrepant data, but at any rate it appears that any genetic link between behavioral inhibition, withdrawal to acute ethanol, and performance in the other tasks listed above is a complicated one.

Putting aside behavioral inhibition per se, it is clear that HAW-2 and LAW-2 lines responded differently in the task, suggesting, at the very least, that selecting for high or low withdrawal to acute ethanol also selects for genes important in operant responding. As mentioned previously, this could relate to motivation, locomotor capacity, or task strategy. HAW-1 mice have been shown to have more locomotor activity than LAW-1 mice (although this was after saline injection; Chester et al., 1998). Therefore, if HAW-2/LAW-2 mice are similar to HAW-1/LAW-1 mice in this regard, it may be that the comparatively higher locomotor activity of the HAW-2 mice interfered with their ability to respond in the task.

The effects of ethanol on task performance differed depending on the type of mouse being tested. Ethanol had no effect on false alarms or precue response rate in either HAW-2 or LAW-2 mice, although it did decrease hits for both lines at the highest dose. Because ethanol decreased hits, but not false alarms or precue response rate, it seems unlikely that a reduction in overall ability or motivation to respond is the sole effect of ethanol in this task (other studies where this is suspected to be the primary effect of a drug have seen all three measures decrease in concert; Moschak et al., 2012; Moschak and Mitchell, 2012). There are a number of reasons why ethanol might have affected hits without affecting precue response rate or false alarms. First, it may be that ethanol decreases responding more strongly in components of the task that yield a higher response rate (such as the Go signal elicits). There is some evidence for ethanol having this type of effect in other studies (Barrett and Stanley, 1980; Petry, 1998). It may also be that ethanol suppresses both activational (i.e. responding during Go cues) and inhibitory (i.e. not responding during No-go cues or before cues) processes. Because responding during no-go cues or before cues is presumably a composite of both behaviorally activating and inhibitory processes (unlike responding during Go cues, which presumably consists of primarily behaviorally activating signals), reduction of both processes could effectively cancel each other out and lead to no observable effect. Finally, it may be that ethanol decreased discrimination of the Go cue without affecting discrimination of the No-Go cue.

Although the two lines did not differ in their response to ethanol's effects (or lack thereof) on behavioral inhibition, the effect of ethanol on hits was significantly stronger in HAW-2 mice than in LAW-2 mice. The two lines did not differ in blood ethanol concentration after any dose, so the difference is probably not pharmacokinetic in nature. It is possible that HAW-2 mice are more sensitive to ethanol-induced reductions in locomotor activity or reductions in motivation for the reinforcer (perhaps due to stronger aversive properties of the drug in HAW-2 mice). The latter hypothesis would fit well with the observation that HAW-2 mice consume less ethanol.

Ethanol led to a small but significant decrease in behavioral inhibition for the B6 and D2 mice at the highest dose. Although this was a small effect, it does replicate previous work showing that ethanol decreases behavioral inhibition in mice (Oliver et al., 2009; Olmstead et al., 2009); to our knowledge this is the first time such an effect of ethanol has been shown using the Go/No-go task in mice. Neither strain was more sensitive to this effect than the other, although it is possible that a difference in sensitivities could have been elucidated with higher doses.

In conclusion, we have found that HAW-2/LAW-2 and B6 and D2 mice show different response profiles in this task, both basally and after administration of ethanol. Our findings with B6 and D2 mice generally fit with the existing literature, although it was a bit surprising that ethanol did not differentially affect behavioral inhibition in the two strains. Contrary to our expectations, HAW-2 mice did not show lower behavioral inhibition than LAW-2 mice, but instead had a lower level of responding overall in the task. HAW-2 mice were also more susceptible to ethanol's effects on hits in this task. In total, these results suggest that selectively breeding for differences in acute ethanol withdrawal can also select for differences in Go/No-go task performance, although not necessarily as one might expect given the existing literature.

Acknowledgments

SHM designed the study, KAS and TMM collected the data, and all authors were involved in data analysis and manuscript preparation.

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Go Trial: Reinforced for responding when *Cue Light* is present

Start

No-go Trial: Reinforced for *not* responding when *Tone* is present

Start

Figure 1.

The nose-poke contingencies of a single trial in the Go/No-Go procedure (Figure adapted from Gubner et al., 2010).

Figure 2. Mean ($\pm$ SEM) levels of responding (false alarms, precue response rate, hits) before receiving ethanol for HAW-2 and LAW-2 mice. * $p < .05$

Figure 3.

Mean ($\pm$ SEM) levels of responding (false alarms, precue response rate, hits) before receiving ethanol for C57BL/6J and DBA/2J mice. ** $p < .01$

Figure 4.

Mean ($\pm$ SEM) levels of responding (false alarms, precue response rate, hits) after receiving each dose of ethanol for HAW-2 and LAW-2 mice. Data for both the day prior (preinjection) and the day of (injection) are included. *** $p < .001$, both lines combined significantly lower than saline and preinjection day.

Figure 5.

Mean ($\pm$ SEM) levels of responding (false alarms, precue response rate, hits) after receiving each dose of ethanol for DBA/2J and C57BL/6J mice. Data for both the day prior (preinjection) and the day of (injection) are included. * $p < .05$, ** $p < .01$ *** $p < .001$, both strains combined significantly higher than saline and preinjection day. + $p < .05$, DBA/2J mice significantly lower than saline and preinjection day.

Table 1

Mean ($\pm$ SEM) number of sessions to complete training phases for Go/No-go task.

Strain		N	Phase 1 ^a	Phase 2 ^b
HAW-2	Female	14	6.21 $\pm$ 0.77	2.71 $\pm$ 0.37
	Male	15	5.60 $\pm$ 0.51	2.33 $\pm$ 0.23
LAW-2	Female	11	5.18 $\pm$ 0.60	2.18 $\pm$ 0.12
	Male	14	4.21 $\pm$ 0.47	2.07 $\pm$ 0.07
C57BL/6J	Female	16	5.63 $\pm$ 0.70	3.81 $\pm$ 0.53
	Male	13	6.00 $\pm$ 1.13	2.08 $\pm$ 0.83
DBA/2J	Female	12	5.08 $\pm$ 0.18	2.43 $\pm$ 0.61
	Male	13	6.08 $\pm$ 0.93	3.15 $\pm$ 0.52

^aMice advanced to the next stage according to the following criteria: Phase 1, completing 30 Go trials within 40 minutes for 2 consecutive days; Phase 2, completing 30 Go trials within 40 minutes for 2 consecutive days

^bNo-go trials were added in the experimental phase, cue light and tone had 5 second durations

Table 2

Mean ($\pm$ SEM) response rates for Precue, Go, and No-go periods at baseline.

Strain	Precue Response Rate (responses / s)	Go Cue Response Rate (responses / s)	No-go Cue Response Rate (responses / s)
HAW-2	0.06 ± 0.01	0.22 ± 0.02	0.10 ± 0.01
LAW-2	0.08 ± 0.01	0.26 ± 0.02	0.12 ± 0.01
C57BL/6J	0.06 ± 0.01	0.22 ± 0.03	0.06 ± 0.01
DBA/2J	0.07 ± 0.01	0.21 ± 0.02	0.12 ± 0.01