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Chronic periadolescent alcohol consumption produces persistent cognitive deficits in rhesus macaques

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Abstract

Background—Although human alcoholics exhibit lasting cognitive deficits, it can be difficult to definitively rule out pre-alcohol performance differences. For example, individuals with a family history of alcoholism are at increased risk for alcoholism and are also behaviorally impaired. Animal models of controlled alcohol exposure permit balanced group assignment, thereby ruling out the effects of pre-existing differences.

Methods—Periadolescent male rhesus macaques (N=5) consumed alcohol during 200 drinking sessions (M-F) across a 10-month period (mean daily alcohol consumption: 1.38 g/kg/day). A control group (N=5) consumed a fruit-flavored vehicle during the same period. Spatial working memory, visual discrimination learning and retention and response time behavioral domains were assessed with subtests of the Monkey CANTAB (CAmbridge Neuropsychological Test Automated Battery).

Results—Spatial working memory performance was impaired in the alcohol group after 120 drinking sessions (6 mo) in a manner that depended on retention interval. The chronic alcohol animals were also impaired in retaining a visual discrimination over 24 hrs when assessed 6-8 weeks after cessation of alcohol drinking. Finally, the presentation of distractors in the response time task impaired the response time and accuracy of the chronic alcohol group more than controls after 6 months of alcohol cessation.

Conclusions—Chronic alcohol consumption over as little as 6 months produces cognitive deficits, with some domains still affected after acute (6-8 wks) and lasting (6 mo) discontinuation

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Author Contributions
M.J.W., Jr. and M.A.T. designed the overall study, components of which were implemented and refined by M.J.W., Jr. under the supervision of M.A.T. Analysis of the data and creation of figures was conducted by M.J.W., Jr. with input from M.A.T. and drafting of the manuscript was by M.J.W., Jr. and M.A.T. Both authors have approved the manuscript.

from drinking. Animals were matched on alcohol preference and behavioral performance prior to exposure, thus providing strong evidence for the causal role of chronic alcohol in these deficits.

Keywords

ethanol; working memory; attention; withdrawal; binge drink

1. Introduction

Chronic heavy alcohol use in humans has been associated with differences in neuroanatomy and brain physiology as well as deficits of perception, learning and memory (Oscar-Berman M, 1997, George et al., 2001, Agartz et al., 2003, Harper et al., 2003, Pfefferbaum et al., 2009, Spreckelmeyer et al., 2011). While cognitive function is generally thought to improve in adult humans after extended abstinence from alcohol (Rosenbloom et al., 2004, Fein et al., 2006, Kopera et al., 2012), some cognitive deficits appear to persist after the cessation of alcohol consumption [see (Fein et al., 1990) for review] and the extent of any recovery may be related to age, length of abstinence and whether periods of abstinence were interrupted by alcohol consumption (Rourke and Grant, 1999, Munro et al., 2000, Zinn et al., 2004). A recent examination of a very large sample of 18-22 year-old men indicated that those who drank alcohol on a daily basis had the lowest IQ of any group examined (Müller et al., 2013). However, such findings could be confounded by a number of factors including pre-existing cognitive differences in those who end up drinking daily and the effect of cognition on willingness or ability to cease drinking. For example, better cognitive function at the time of treatment predicts abstinence in alcoholics (Abbott and Gregson, 1981, Parsons, 1994, Wehr and Bauer, 1999).

While the association of lower cognitive function with chronic alcohol exposure in humans is documented, it is difficult to exclude the contribution of other factors. There is evidence that poor pre-morbid cognitive function is a predictor of illicit drug use and alcohol abuse (Moriyama et al., 2006). In addition, individuals with alcoholic family members perform worse than control subjects on tests of verbal IQ, visuospatial perception, attention, memory, executive function and electrophysiological indices of cognitive function (Begleiter et al., 1984, Hill et al., 1990, Whipple et al., 1991, Polich et al., 1994, Harden and Pihl, 1995, Ozkaragoz et al., 1997) in the absence of chronic drinking.

The complexity of establishing causality between alcohol drinking and cognitive function can be circumvented by controlled studies in animal models. Due to their anatomical and physiological similarities to humans, relative alcohol preference and wide behavioral repertoires, monkey models provide a high level of validity for the cognitive impact of alcohol in humans (Tabakoff and Hoffman, 2000, Grant and Bennett, 2003). For instance, the role of the frontal cortex in working memory is well-established (Courtney et al., 1998a, Courtney et al., 1998b, Koch et al., 2005, Curtis, 2006). In monkeys (and other animal models), the working memory deficits that results from lesions to the frontal cortex (Collins et al., 1998) are similar to the deficits in adult humans that consume alcohol chronically (Townshend and Duka, 2005, Kopera et al., 2012). The extended period of adolescence in rhesus macaques (Lewis, 1997, Schwandt et al., 2010) makes them an excellent model for

human developmental psychopharmacology and we have recently shown that repeated consumption of alcohol alters several cognitive functions in periadolescent monkeys (Crean et al., 2011). Deficits in pattern-spatial associative memory that were identified were likely a result of changes in hippocampal neurodegeneration and neurogenesis (Taffe et al., 2010). Because the monkeys were matched on alcohol preference and general cognitive ability prior to exposure, those data support the conclusion that deficits in human alcoholics are produced by the alcohol consumption itself.

The studies in this current investigation sought to further determine the extent of cognitive deficits produced in male rhesus macaques that consumed alcohol chronically, five days per week, during the periadolescent epoch. We focus on the adolescent age range because evidence shows that over 90% of adult alcoholics started drinking before the age of 21 (SAMHSA, 2011) and 20% of US high-school seniors have consumed 5 or more standard drinks in one session within the 2 week interval prior to survey (Johnston et al., 2012a, Johnston et al., 2012b). Likewise, the study was conducted in males because in US 12th grade students, male rates for past-30-day alcohol use, past 2-week heavy drinking and daily alcohol use exceed the female rates (ibid). Thus we decided to focus on modeling the sex that is of greatest risk in the human target condition. It is also the case that the human brain exhibits significant changes in structure and function during adolescence (Huttenlocher, 1979, Huttenlocher et al., 1982, De Bellis et al., 2000, De Bellis et al., 2001, De Bellis et al., 2005). It is hypothesized that interference in the development of the prefrontal cortex (Pfefferbaum et al., 1994, Giedd et al., 1999, Thompson et al., 2000, Durston et al., 2001, Paus et al., 2001) may underlie impairments in visuospatial skills, attention and executive function which are observed in recently detoxified adolescents (Tapert and Brown, 1999, Brown et al., 2000). The focus of this study was therefore on behavioral domains that are associated with intact frontal cortical function including spatial working memory, retention of discrimination learning and performance of a response-time task. The alcohol exposure model for this study was selected to meet the binge criteria (of 5 standard drinks in a single ~hour long interval (see Crean et al., 2011, for discussion) in an attempt to model after school-day consumption. The behavioral assessment model used a computerized, touch-screen battery (Cambridge Neuropsychological Test Automated Battery; CANTAB) that has been designed with parallel versions suitable for human and nonhuman primate assessment (Weed et al., 1999). Studies using CANTAB measures in humans have identified deficits of reaction time, spatial working memory, spatial memory span and attentional set shifting in abstinent, previously alcohol dependent adults (Kopera et al., 2012). Female, but not male, binge drinkers were found to be impaired, relative to non-binge drinkers, on spatial working memory assessed with CANTAB (Townshend and Duka, 2005). Children with pre-natal alcohol exposure have been found impaired on reaction time, spatial working memory and spatial memory span (Rasmussen et al., 2011). The use of parallel behavioral assessment tools in monkeys in the present study greatly enhances the translational comparison of the findings.

2. Material and Methods

2.1 Subjects

These experiments were conducted using ten male rhesus macaques (*M. mulatta*; Primate Products, Inc., Immokalee, FL, USA); prior studies in these animals have been reported by Wright and colleagues (Wright et al., 2013a, Wright et al., 2013d). At the onset of the present studies, the median age of the monkeys was 58 months (range = 50-59 months) and 7 of the 10 monkeys were born within 60 days of each other. Animals were obtained as a single cohort with identical weaning and group housing conditions reported by the vendor, then treated identically on arrival in the laboratory. The mean weight was 8.3 kg (range = 6.2 - 9.4 kg). Previous work in this lab indicates the rate of bodyweight gains begins to increase at around 32 months of age for male rhesus macaques. Likewise, experience in this lab indicates that male rhesus macaques do not reach stable mature weight of 12-16 kg until about 8-9 years of age. These observations are consistent with an increase in plasma testosterone observed in intact male monkeys across the 34-50 month interval (Rose RM, 1978) and observation of brain growth tapering off at about 40-50 months of age (Knickmeyer, 2010). Thus, the age range of the monkeys used in these experiments is consistent with late adolescence into early adulthood, similar to the college-age population of humans.

Monkeys were maintained on a diet of standard nonhuman primate chow (Harlan Teklad 15% Monkey Diet #8714, Harlan Laboratories Inc., Madison, WI USA). Each monkey was fed sufficient to maintain normative growth and condition while still ensuring behavioral motivation (Taffe, 2004). Monkey chow was supplemented with fresh fruit or vegetables and a multi-vitamin tablet (Kirkland Signature Sugar-free Children's Chewable Vitamins, Seattle WA USA) each day. Monkeys were fed approximately 2-3 biscuits at least 1 hour before the morning testing sessions. The balance of their daily ration was divided across two feeding sessions conducted just after behavioral testing and again in the late afternoon. Water was available *ad libitum*. All of the monkeys were single-housed in a common colony room upon arrival in the laboratory.

2.2 Testing environment

The colony room was maintained between 22° C and 25° C on a 12-hour light cycle (lights on at 6:00 am). Alcohol consumption and behavioral testing took place in the home cages between 9:00 am and 3:00 pm. These experiments followed procedures consistent with the United States Public Health Service Policy on Humane Care and Use of Laboratory Animals and took place in a facility accredited by the Association for Assessment and Accreditation of Laboratory Animal Care International (AAALAC). The experimental protocol was approved by the Institutional Animal Care and Use Committee of The Scripps Research Institute.

2.3 Apparatus

Monkeys responded to visual stimuli presented on touch-sensitive LCD panels housed in stainless steel consoles as previously described (Weed et al., 1999). The testing system was controlled by Monkey CANTAB computer software (CAmbridge Neuropsychological Test

Automated Battery, Lafayette Instruments, Lafayette, IN, USA). The touch-sensitive LCD panels measured approximately 23 cm × 30 cm (~38 cm diagonally) and were positioned directly in front of the home cages. The home cages featured five strategically placed access ports that allowed the monkeys access to the touch-sensitive LCD panels and the collection cup into which rewards were dispensed.

2.4 Alcohol Consumption and Chronic Exposure Conditions

Alcohol (4% v/v) was added to a 6% (w/v) fruit-flavored solution (e.g, Tang, Kool-Aid, Country Time Lemonade; Kraft Foods, Glenville, IL, USA) to facilitate robust and consistent patterns of alcohol consumption using techniques previously described (Katner et al., 2004, Katner et al., 2007, Crean et al., 2011). In brief, graduated bottles were attached to the cage and consumption was individually recorded 5, 10, 15, 20, 30, 45 and 60 min after the beginning of the session. Spillage is rare in this model but when it occurs it is readily detected by the observer and subtracted from the consumption recorded for that session.

Group assignment was based on multiple performance parameters. Behavioral measures included initial touch screen training (sessions to criterion), 5-choice serial response time task (latency to make observing response on task initiation, target response latency and percent correct targets), reinforcers acquired under a progressive ratio schedule and latency to retrieve 16 raisins in a bimanual dexterity task; the behavioral procedures followed those previously described (Weed et al., 1999). Spontaneous alcohol preference measures (dose consumed and rate of consumption within the 30-60 minute access sessions) were derived from the subjects' participation in prior studies of the acute effects of alcohol on discrimination learning and reaction time measures (Wright et al., 2013a, Wright et al., 2013d). Groups were approximately balanced in terms of cognitive performance and alcohol preference with the relative rankings as depicted in Table 1. Animals were approximately matched on body weight before the chronic exposure and the caloric vehicle content available to the control group was yoked to the caloric intake of the experimental group during chronic drinking.

The timeline for the study is schematized in Figure 1. Monkeys in the experimental group (n = 5) consumed alcohol 5 days each week for approximately 10 months (200 drinking sessions). The Control group of monkeys (n = 5) consumed only the fruit-flavored solution during the same period. Drinking sessions were conducted in the afternoon, following the daily training/testing sessions. All animals received training and drinking sessions each test day and the individual's time of testing was randomized from day to day with an order that was balanced across the treatment groups. Afternoon feeding sessions were scheduled at least 1 hour after the completion of the drinking sessions to facilitate uniform alcohol absorption. Maximum daily alcohol doses were limited to 1.5 g/kg until the 99th drinking session, when the limit was gradually increased to 3.0 g/kg over 6 consecutive sessions. The approach was to limit variability in alcohol exposure via the daily consumption cap while modeling an escalation of intake over the course of chronic drinking. The increase in available alcohol dose was achieved by increasing the available volume while holding concentration steady. The amount of alcohol consumed by each monkey was recorded for each session.

Between the 144th and the 149th drinking sessions, a series of experiments were conducted to determine blood-alcohol levels (BAL). All monkeys (Experimental and Control) were allowed 30 minutes to consume up to 3.0 g/kg alcohol. Animals were immobilized with ketamine (10 mg/kg, i.m.) and blood samples were taken 30 minutes after the alcohol consumption interval. Blood-alcohol levels were determined using an Analox AM1 ethanol analyzer (Analox Instruments USA, Lunenburg, MA) and expressed as mg% (i.e., mg/dL).

After the 200 chronic exposure sessions, monkeys were no longer provided with alcohol. For three weeks, all animals continued to receive drinking sessions in which the former alcohol group and the control group received vehicle only. Thereafter the drinking sessions were discontinued.

2.5 Statistical Analyses

Behavioral data were analyzed with one-factor or two-factor (as appropriate) repeated measures analyses of variance (SigmaStat, ver. 3.5, Systat Software, Inc, Richmond, California, USA). Post-hoc analyses were conducted using the Holm-Sidak method with all possible comparisons. The criterion for significance was $p < 0.05$ for all tests. The mathematical relationship between ethanol dose and blood-ethanol concentration was determined by linear regression analysis.

2.6. Experiments

2.6.1 Experiment 1: Manipulation of retention interval within spatial working memory task—The influence of the duration during which working memory must be maintained on response accuracy was determined after 120 drinking sessions (~6 months). The procedure used was derived from the self-ordered spatial search (SOSS) task described in Weed *et al*. (1999) which is sensitive to amnestic drugs such as ketamine and scopolamine (Taffe et al., 1999, Taffe et al., 2002), as well as Δ^9-tetrahydrocannabinol (Taffe, 2012). Within each session, trials were presented in the following order: 15 2-stimulus trials → 15 3-stimulus trials → 15 2-stimulus trials → 15 3-stimulus trials. The screen consisted of pink stimuli, or boxes, (3 cm × 3 cm) set against a black background. Within each trial, monkeys were required to touch each box once and only once, although the order in which the boxes were touched was irrelevant to trial success. A trial ended when all of the boxes had been touched once, when any box was touched twice or if more than 30 seconds elapsed between responses. After each response, all stimuli disappeared and the screen went black. When the stimuli re-appeared, they were in the same position as they were at the beginning of the trial. Successful trial completion resulted in the delivery of two 190 mg fruit-flavored nonhuman primate pellets (Product #5TUR, TestDiet, Richmond, IN USA). If a monkey touched any stimulus twice or if more than 30 seconds elapsed between responses, then the trial ended without any further programmed consequences. Each trial was followed by a 5 second inter-trial interval during which the screen was completely black.

Animals had been under training on this task during the interval of chronic drinking with no group differences observed. For this challenge experiment, the duration of the black screen between responses was set to either 0.25 seconds or 2.5 seconds (the 0.25 second delay was

the standard delay used during all training sessions). This manipulation extends the interval of time over which the animal must remember prior responses in the trial and therefore increases the difficulty of the task.

2.6.2 Experiment 2: Retention of a previously established visual discrimination—The monkeys completed a series of visual discrimination tasks from six to eight weeks after the cessation of alcohol consumption. The task was derived from the 2-choice discrimination stages from the monkey CANTAB Intra-Dimensional/Extra-Dimensional Attentional Set Shift task previously described for use in nonhuman primates (Dias et al., 1996, Weed et al., 1999, Weed et al., 2008, Zurcher et al., 2010) and shown sensitive to acute challenge with Δ^9-tetrahydrocannabinol (Wright et al., 2013b) and alcohol (Wright et al., 2013a). These tasks involved successive discrimination learning stages in which responses on the reinforced stimulus resulted in a food reward (two 190 mg fruit-flavored nonhuman primate tablets, Product #5TUR, TestDiet, Richmond, IN USA). Visual stimuli were approximately 5 cm × 8 cm in size and consisted of 2 white lines superimposed over 2 purple shapes set against a black background. The positions of the lines and shapes were independent of each other and were varied in a pseudorandom fashion from trial to trial; thus, reinforcer delivery was uniquely associated either one of the shape elements or one of the line elements. Responses on one of the shapes were reinforced for one discrimination stage and responses on one of the lines for the other discrimination stage within a session. After the monkeys made at least 12 correct responses within 15 sequential trials (12/15 criterion) it was considered a successful acquisition of the discrimination; two stages were completed each day. The primary dependent variable for this test is the number of errors committed before reaching the criterion. These values are square root transformed prior to statistical analysis to normalize the distribution since extremely large numbers of errors-to-criterion are theoretically possible. All test sessions were limited to 240 trials.

For this experiment, another visual discrimination session was repeated 24 hours after completion of the first with the critical feature that one of the stages was identical to one of the ones from the prior day (order was randomized across individuals). A reduction in errors-to-criterion, and/or an increase in overall response accuracy for that stage, is interpreted as retention of the original discrimination problem (Wright et al., 2013a). The entire 24-hr retention experiment was repeated after 2 weeks later, but the order in which stimulus dimension was reinforced was reversed (e.g., if shapes were reinforced the first iteration, the lines were reinforced in the second and vice versa). Data from both experiments were combined to determine the influence of chronic alcohol consumption on retention of the discrimination.

2.6.3 Experiment 3: 5-choice serial response time performance with variable target stimuli duration and simultaneous visual distracters—Six months after the cessation of alcohol consumption, performance in a 5-choice serial response time task (5CSRTT) was determined using variable duration target stimuli and simultaneous visual distracters. Each 5CSRTT trial began with a sustained touch (observing response) on a centrally-located visual stimulus, described in (Wright et al., 2013d). The requirement for each observing response varied between 0.75 and 2.50 seconds from trial to trial to reduce

the probability of monkeys anticipating the subsequent appearance of the target stimulus. If the monkey failed to maintain the observing response for the required duration, the trial was terminated. The trial was also terminated if the monkey failed to emit an observing response within 30 seconds of central stimulus onset.

After each successful observing response, a single target stimulus appeared in 1 of 5 possible locations that were aligned in a radial pattern around the central observing stimulus. The target stimulus remained illuminated for a duration which varied pseudo-randomly (<2 cs, 10 cs, 100 cs and 200 cs). The shortest target was determined by the monitor refresh rate (~1.67 cs) and the 200 cs stimulus duration was the interval used during training sessions. For this experiment, two-thirds of the trials were conducted under standard conditions where the target stimulus was displayed in 1 of 5 possible positions and all other possible positions remained unfilled. In the remaining one-third of the trials, presentation of the target stimulus was accompanied by the simultaneous presentation of 4 visual distracter stimuli. The distractor stimuli were differentiated from the target stimulus by hue and the position of the target varied in each trial. Monkeys had 10 seconds to emit a target response before the trial ended. Correct target responses resulted in the delivery of two 190 mg fruit-flavored nonhuman primate tablets (Product #5TUR, TestDiet, Richmond, IN USA). Each 5CSRT session consisted of 90 trials.

3. Results

3.1 Alcohol Consumption and Blood-Alcohol Levels

As reported previously, mean *individual* daily alcohol consumption ranged from 0.74 g/kg (+/− 0.04 SEM) to 1.93 g/kg (+/− 0.04 SEM) with an overall group mean intake of 1.38 g/kg (+/− 0.02 SEM) for the entire chronic exposure interval. Consumption patterns were generally consistent within each monkey (Wright et al., 2013d) and blood-alcohol levels (BAL) were reliably related to the dose consumed (Wright et al., 2013d). In Figure 2, the BALs previously reported are identified by treatment group: the mean alcohol dose consumed during BAL determination was 1.41 g/kg (+/− 0.46 SEM) for the VEH group, producing a mean BAL of 81.94 mg% (+/− 22.36 SEM). For the EtOH group, mean alcohol dose consumed during BAL determination was 1.58 g/kg (+/− 0.32 SEM) and the mean BAL was 89.70 mg% (+/− 16.60 SEM). Linear regression analysis produced no evidence that chronic alcohol consumption altered alcohol absorption or metabolism (Fig 2).

3.2 Experiment 1: Manipulation of delay within spatial working memory task

Two-way repeated measures ANOVA failed to confirm the trend for an interaction of history of alcohol consumption and delay in presentation of stimuli on response accuracy for the 2 box trials, $F_{1,8} = 5.308$, $p = 0.05$ (Fig 3). No significant main effects were confirmed.

However, a two-way repeated measures ANOVA confirmed an interaction of a history of alcohol consumption and delay in presentation of stimuli on response accuracy for the more difficult 3 box trials, $F_{1,5} = 14.208$, $p = 0.013$ (Fig 3). Post-hoc analysis further confirmed that response accuracy declined reliably in monkeys with a history chronic alcohol consumption when the interval between presentation of the stimuli was increased from 0.25

(i.e., the standard delay used during training) to 2.5 seconds (p = 0.006). Similarly, response accuracy was lower in monkeys with a history of chronic alcohol consumption than in control monkeys at the longer delay (p= 0.019). No other statistically significant differences were confirmed.

3.3 Experiment 2: Retention of a previously established visual discrimination

Two-way repeated measures ANOVA confirmed a significant main effect of task repetition on response accuracy, $F_{3,24} = 7.173$, $p = 0.001$ (Fig 4). Subsequent post-hoc analysis confirmed that when monkeys in the control group were allowed to repeat a visual discrimination task after 24 hours, response accuracy improved reliably ($p < 0.05$). In contrast, monkeys with a history of chronic alcohol consumption did not exhibit a significant improvement in performance.

A separate two-way repeated measures ANOVA also confirmed a significant main effect of task repetition on errors committed before the learning criterion was satisfied, $F_{3,24} = 4.404$, $p = 0.013$ (Fig 4). Post-hoc analysis confirmed that errors were significantly lower in the control group when the discrimination learning task was repeated after 24 hours. Again, no such savings were evident in monkeys with a history of chronic alcohol consumption.

3.4 Experiment 3: Response time performance with variable target stimulus duration and simultaneous visual distracters

A two-way repeated measures ANOVA confirmed a significant main effect of target stimulus duration on response time under standard conditions, $F_{3,24} = 7.591$, $p < 0.001$. In these trials, response times increased as target stimulus duration decreased (Fig 5). Post-hoc analyses confirmed that response times were longer in the control group when the target stimulus duration was <2 cs than when the duration was 100 cs or 200 cs, $p < 0.05$ (Fig 5). A similar pattern was observed in monkeys with a history of chronic alcohol consumption, but the differences in response time were not statistically significant.

Two-way repeated measures ANOVA also confirmed a main effect of target stimuli duration on response time when visual distracters were presented, $F_{3,23} = 6.648$, $p = 0.002$ (Fig 5). Post-hoc analysis confirmed that, in monkeys with a history of chronic alcohol consumption, response times were longer when target stimulus duration was <2 cs than when duration was 100 cs or 200 cs, $p < 0.05$ (Fig 5). A non-significant tendency for response times to increase as target stimulus duration declined was observed in the control group.

Two-way repeated measures ANOVA also confirmed a significant main effect of visual distracters on response accuracy in the control group ($F_{1,12} = 9.156$, $p = 0.039$; Fig 6). Subsequent post-hoc analyses confirmed that visual distracters reduced response accuracy in the control group when target stimulus duration was 10 cs, $p < 0.05$.

A final two-way repeated measures ANOVA confirmed a main effect of target response duration ($F_{3,12} = 8.846$, $p = 0.002$) and the presentation of visual distracters ($F_{1,12} = 24.412$, $p = 0.006$) on response accuracy in monkeys with a history of chronic alcohol consumption (Fig 6). Post-hoc analysis confirmed that response accuracy was higher under the standard

condition than it was when visual distracters were present at <2 cs and 10 cs, $p < 0.05$. Post-hoc analysis also confirmed that when visual distracters were present, response accuracy was lower when the target duration was <2 cs or 10 cs than when it was 100 or 200 cs, $p < 0.05$.

4. Discussion

These data demonstrate that as little as 6 months of chronic, binge-level alcohol consumption (120 drinking sessions) produces working memory deficits as assessed with the Self-Ordered Spatial Search (SOSS) task in periadolescent rhesus macaques. It was further determined that 24-hr retention of a visual discrimination task was impaired after 6-8 weeks of discontinuation from drinking subsequent to 10 months of chronic alcohol. The study also found that the accuracy and response time in a 5-choice serial response time task declined as difficulty conditions were increased most consistently in the alcohol monkeys when evaluated after 6 months of discontinuation from chronic drinking. It was notable that these cognitive disruptions after alcohol cessation were observed in the absence of any somatic withdrawal signs in the days to weeks after alcohol discontinuation. Thus, lasting effects on cognition did not depend on levels of alcohol intake that produced substantial physical signs of withdrawal.

These data confirm and extend our prior results showing that chronic drinking impairs spatial delayed-response and visual-spatial associative memory in periadolescent monkeys (Crean et al., 2011); the latter finding was consistent with disruption of neurogenesis in the hippocampus of the alcohol group observed months after alcohol discontinuation (Taffe et al., 2010). Prior work has associated the perirhinal region of the anterior inferior temporal lobe (Miyashita et al., 1998, Mitchell et al., 2008) with the retention and retrieval of visual discriminations in macaque monkeys and, interestingly, young adolescent rats may be more sensitive than adults to neuronal damage in the perirhinal cortex following binge alcohol exposure (Crews et al., 2000, Obernier et al., 2002). Therefore the lasting effect of chronic alcohol on the retention and retrieval of a visual discrimination is likely a consequence of perirhinal insult, at least in part. This study also showed that a self-ordered spatial search task that depends on intact function of pre-frontal cortex (Collins et al., 1998) is disrupted by chronic alcohol consumption. A prior study found that N-methyl-D-aspartate (NMDA) receptor expression in dorsolateral prefrontal cortex is decreased by chronic alcohol (Acosta et al., 2010) and these receptors are integral for delay-related neuronal activity in this area during a spatial working memory task (Wang et al., 2013). The present results connect these two prior observations to explain the behavioral outcome of chronic alcohol exposure. Similar to the spatial-delayed response finding in Crean et al (2011), the deficit in the present chronic alcohol group was associated with the duration of time over which the subject was required to remember spatial information. Also, this deficit was present during the course of chronic exposure (but assessed a day after the prior drinking opportunity). Unlike the prior finding with the initial training of a stimulus-location memory task, the present study did not find any significant group differences in the acquisition (of the normal version) of the SOSS task over months of training during chronic drinking. This further highlights the specificity of the alcohol-associated deficit in the retention of information in

short term memory, rather than a deficit in learning or performing the basic task requirements.

One of the major strengths of the study is the fact that the treatment groups were similar across multiple performance parameters before chronic alcohol consumption began and were balanced for spontaneous alcohol preference. Thus, these data show that the effects were produced by chronic alcohol consumption itself and are not attributable to pre-existing factors such as those that complicate clear interpretation of human studies (Whipple et al., 1991, Polich et al., 1994, Tapert and Brown, 2000, Hill et al., 2001). The present conclusions are also consistent with other pre-clinical data from rodent models showing that repeated alcohol consumption during adolescence produces persistent cognitive deficits (Santin et al., 2000, Sircar and Sircar, 2005, Schulteis et al., 2008).

The results of this study align with findings in abstinent human alcoholics, and non-abstinent binge drinkers, who have been assessed on the parallel human versions of the CANTAB measures used here in the monkeys (Joyce and Robbins, 1991, Townshend and Duka, 2005, Kopera et al., 2012). Those studies identified deficits on the human version of the 5CSRT task and the SOSS task. It is also notable that the mean alcohol intake for these experiments (1.38 g/kg) is moderate in comparison with intakes in human alcoholics, even though binge criteria were met by design. It is clear from this study that persisting cognitive deficits can result from chronic consumption of alcohol in doses that are far from extreme and are consumed over a short (daily) interval. Likewise, despite evidence that recovery of cognitive function after chronic alcohol is slower as humans age (Rourke and Grant, 1999, Munro et al., 2000), the data presented here confirm that chronic alcohol consumption even during late adolescence can produce cognitive deficits that can last across many weeks to several months after discontinuation.

It is important to note that the cognitive deficits produced by chronic alcohol consumption were not global impairment of performance. Group differences were not observed in the training of the SOSS task, the bimanual motor skills procedure or the progressive ratio task (see (Weed et al., 1999, Wright et al., 2013c) for description). Instead, the observed deficits were most apparent as function of increased task difficulty. For instance, response accuracy in the SOSS task was indistinguishable between the groups for both the 2-stimulus and 3-stimulus trials when the delay between responses was equal to the training condition (Fig 3). Indeed the chronic alcohol group exhibited a numerical increase in response accuracy under training conditions (i.e., a 0.25 second delay) in both trial types. It was only when the duration over which working memory had to be maintained within a trial (2.5 sec between each response or about 5 sec for the 3-stimuli trials) increased that cognitive deficits became apparent in the group that consumed alcohol chronically; this is similar to a prior result with a 1-stimulus spatial-delayed response task in which a different cohort of chronic alcohol drinking monkeys were increasingly impaired as the retention interval stretched past 5 seconds (Crean et al., 2011).

Additional findings in this study underline alcohol-related liabilities that are only revealed with changes in task difficulty. The chronic alcohol group actually had fewer errors-to-criterion during the original discrimination learning trial of Experiment 2 (Fig. 4) as well as

similar response time and response accuracy in the 5CSRT (Experiment 3) when the trials were conducted under training conditions (i.e., 200 cs; Figs 5 and 6). Alcohol-related deficits were revealed in these tasks, however, when the discrimination had to be retained for 24 hrs and when non-target stimuli were introduced in the 5CSRT, respectively. The discrimination learning result points to a decreased consolidation of the visual discrimination into long term memory in the alcohol monkeys, particularly since response accuracy on the original discrimination learning problem was comparable to controls and the EtOH group had fewer errors-to-criterion. This contrasts with a prior study in which acute alcohol treatment did not appear to affect the consolidation of a visual discrimination, but did interfere with the retrieval of that information when confronted with reversal learning under acute intoxication (Wright et al., 2013a). There were no group differences found (data not shown) on the Intradimensional/Extradimensional Attentional Set Shift task which relies on the discrimination task outlined in this study.

The 5CSRT result indicates alcohol consumption and discontinuation decreased the ability to maintain attentional focus when stimuli must be rapidly processed. This follows up on the finding of an increase in the rightward skew (tau component) of the response time distribution (in the absence of any change in mean response time) of the chronic EtOH monkeys observed during the first month of alcohol discontinuation (Wright et al., 2013d). This change in the distribution has been interpreted as an indicator of inattentiveness. The distractor manipulation in this investigation shows that EtOH group was more consistently impaired by the presence of distractors, particularly when the stimulus presentation was short, compared with the VEH group monkeys. These results are consistent with indications of decreased vigilance in detoxified alcoholics (Duka et al., 2003) and delayed amplitudes and/or latencies of the vigilance-related P300 evoked-potential response (Emmerson et al., 1987, Fein and Chang, 2006). No group differences in performance of the normal version of the SOSS, of a bimanual motor skill task, nor of the progressive ratio task were observed during the discontinuation interval, thus the effects on retention of a discrimination and on the distractor version of the 5CSRT task were selective.

One minor caveat to this study is that the experiments do not directly determine the *minimum* amount of alcohol exposure required during adolescence to produce persistent cognitive deficits and do not address the role of alcohol consumption patterns. The model was selected to meet binge criteria of 5 standard drinks in a single ~hour long interval (see Crean et al. 2011 for discussion) in an attempt to model alcohol binging behavior reported for studies in human adolescents (Schweinsburg et al., 2005, Squeglia et al., 2014). This is only one plausible model, however, and it would be of interest to determine the role of longer, yet more intermittent, heavy drinking sessions to model weekend party consumption. It might also be of interest to determine if vulnerabilities to alcohol related cognitive impairment are identical in male and female monkeys. These questions are of highly related public health concern and represent an important area of future inquiry. Nevertheless, it is important to recognize that the total interval of chronic alcohol was relatively short compared with studies in adult alcoholics or even some studies of adolescents. The daily duration of alcohol intoxication was likewise abbreviated compared with some adult alcoholics that maintain high BALs throughout the day. These studies show that lasting

cognitive damage can be produced with less than a year of alcohol drinking and with episodes limited to a single hour long binge per day. The specific cognitive domains affected have been previously shown to be affected in abstinent adult alcoholics, therefore the present study shows that such findings are not the result of pre-existing differences in those who become alcoholic but likely result from the chronic alcohol drinking itself.

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Highlights

- Cognitive deficits in human alcoholics confounded by pre-existing differences
- Monkeys were balanced on behavior and alcohol preference prior to study
- Spatial working memory impaired by 6 mo of M-F binge drinking
- 24 h memory retention impaired in alcohol monkeys after 6 wks of abstinence
- Alcohol monkeys more distractible on a reaction time task after 6 mo of abstinence

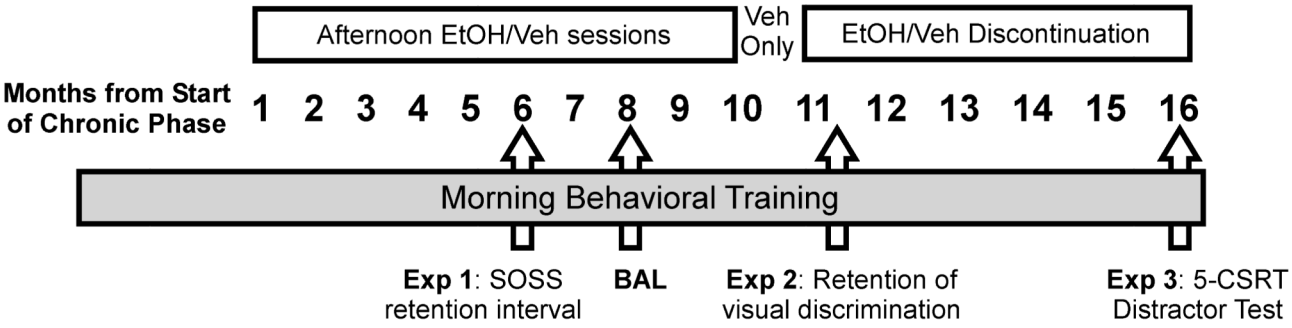

Figure 1. Timeline

The timeline for the experiments is outlined by month. The continued behavioral training and the intervals of chronic drinking/discontinuation are depicted in the horizontal bars. Vertical arrows indicate the approximate timing of the behavioral challenge experiments and the blood-alcohol level determination. 5-CSRT: 5-Choice Serial Reaction Time task; BAL: Blood Alcohol Level; EtOH: ethanol; SOSS: Self-Ordered Spatial Search task; Veh: Vehicle.

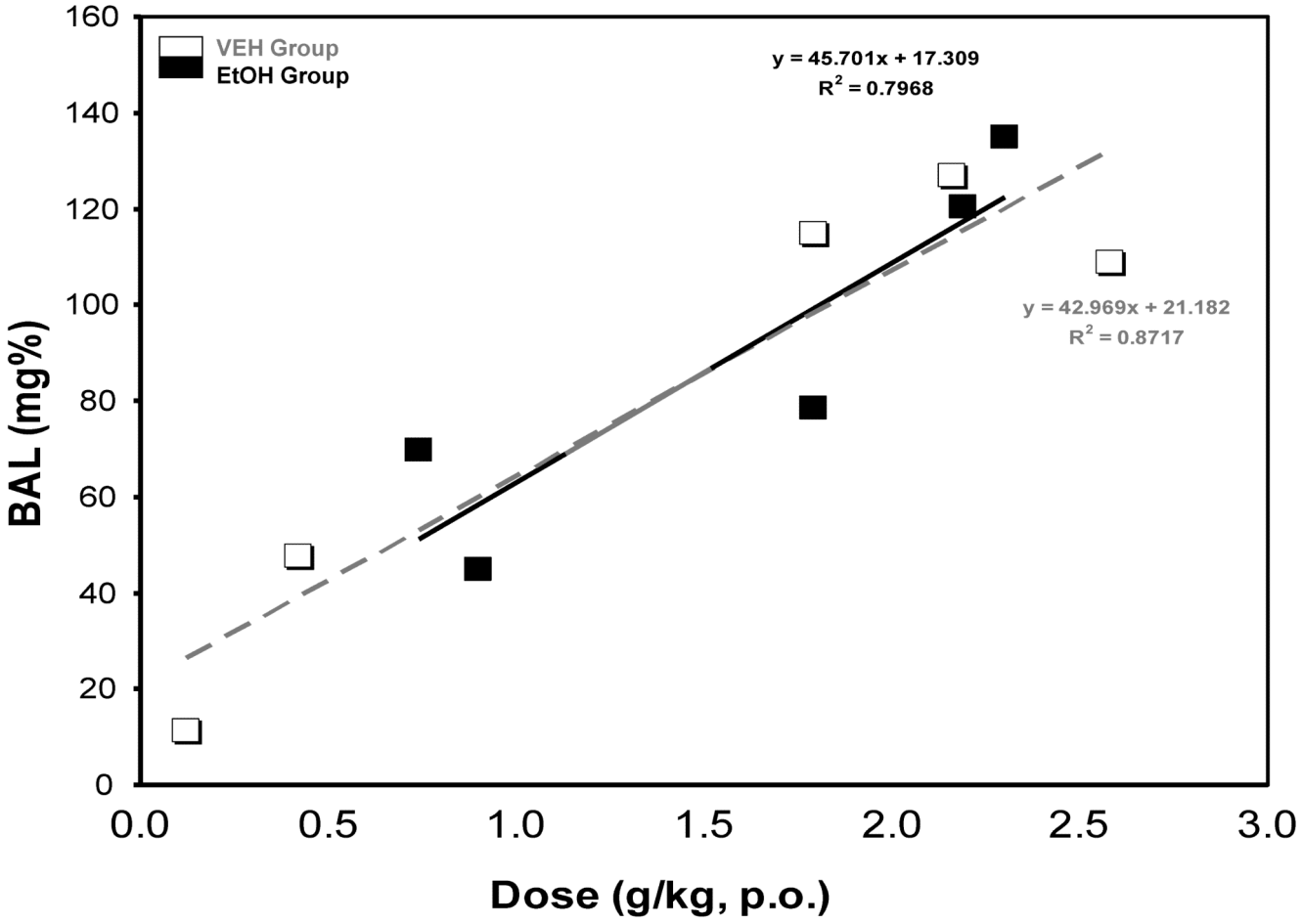

Figure 2. Blood-alcohol levels

Determination of BALs were conducted between the 144th and the 149th drinking sessions with both groups allowed to consume alcohol. For the VEH group, mean alcohol intake was 1.41 g/kg (+/− 0.46 SEM) and the mean BAL was 81.94 mg% (+/− 22.36 SEM). For the EtOH group, mean alcohol intake was 1.58 g/kg (+/− 0.32 SEM) and the mean BAL was 89.70 mg% (+/− 16.60 SEM). Linear regression analysis produced no evidence that chronic alcohol consumption altered either alcohol absorption or metabolism.

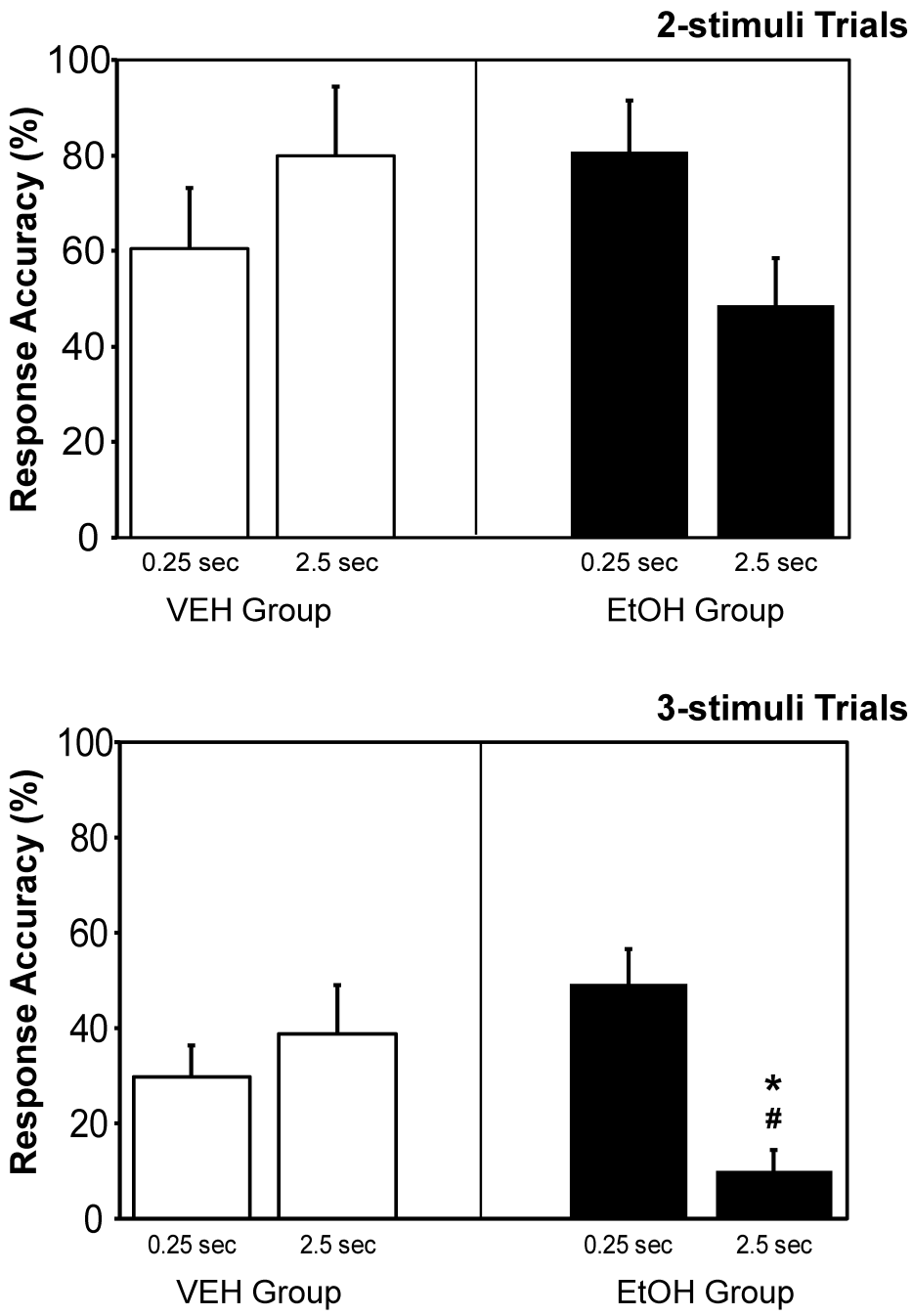

Figure 3. Self-Ordered Spatial Search Task

Mean (N = 5 per group; bars indicate SEM) response accuracy in the 2-stimuli (upper panel) and 3-stimuli (lower panel) trials of the Self-Ordered Spatial Search (SOSS) task is depicted for groups which consumed either alcohol (EtOH) solutions or the vehicle (VEH) 5 days per week for 120 sessions. The figure contrasts performance when the inter-response delay was 0.25 sec with when the interval was 2.5 sec. A significant difference between groups (within a difficulty condition) is indicated by * and a significant difference between inter-response delay conditions (within group) by #. (*$p<0.05$; **$p<0.01$)

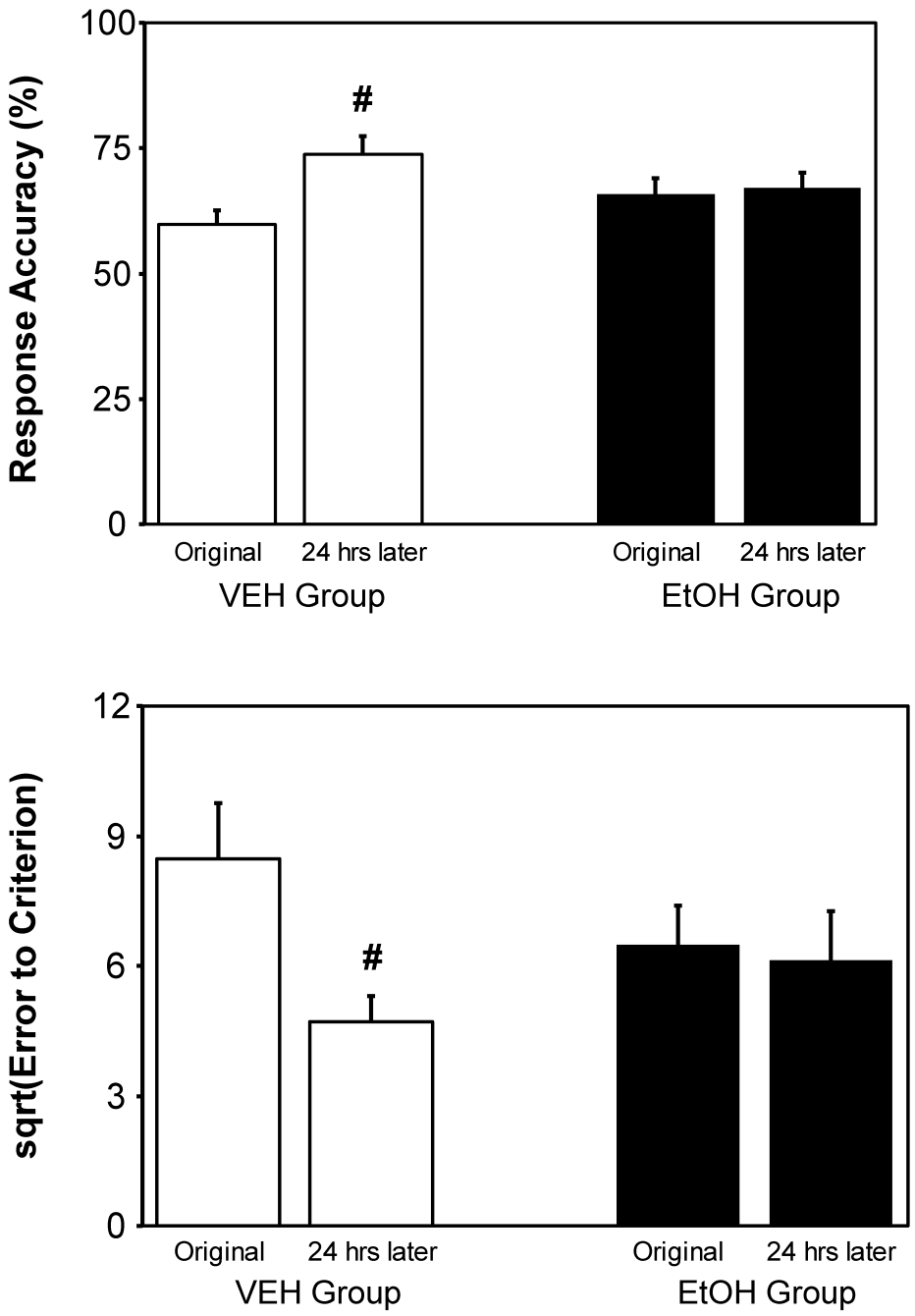

Figure 4. Discrimination Learning and Retention

Mean (N = 5 per group; bars indicate SEM) response accuracy (upper panel) and errors-to-criterion (lower panel; expressed as sqrt transformed errors to normalize variance) for a two-alternative visual discrimination task. Performance is depicted for the original learning session and then a repetition of the discrimination problem conducted 24-hours later for animals who had previously consumed alcohol (EtOH) or the vehicle (VEH) for 10 months. A significant difference between the original learning session and the repetition, within group, is indicated by #.

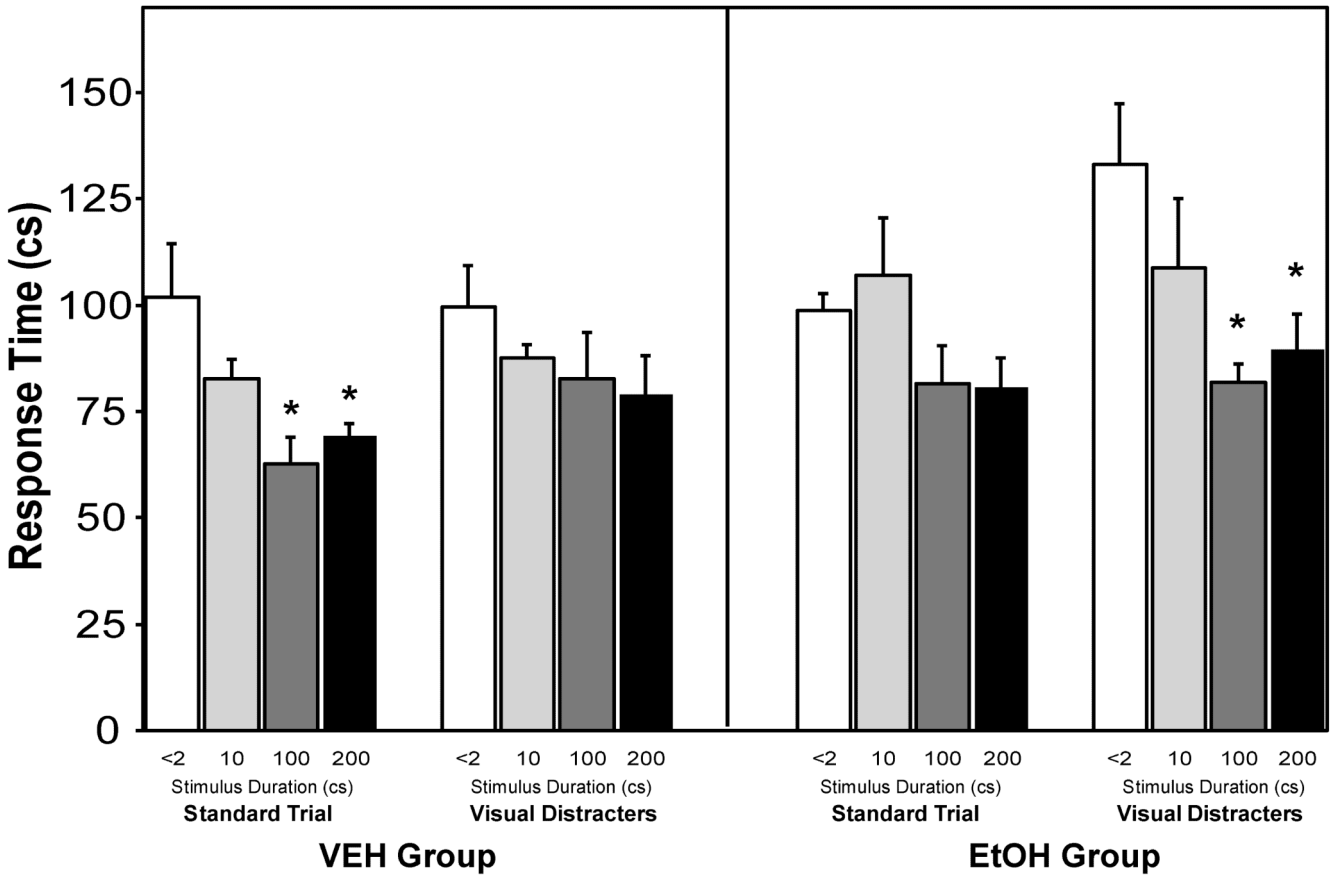

Figure 5.

5-Choice Serial Reaction Time: Mean (N = 5 per group; bars indicate SEM) response time in the 5CSRT task is depicted for animals who had consumed vehicle (VEH) or alcohol (EtOH) for 10 months. Performance is grouped for trials in which only a target stimulus appeared (Standard Trial) and trials in which a non-target distracting stimulus was presented (Visual Distractors). Within each distraction condition, the stimuli appeared for varying durations of time, as indicated. A significant difference from trials when stimulus duration was <2cs is indicated by *.

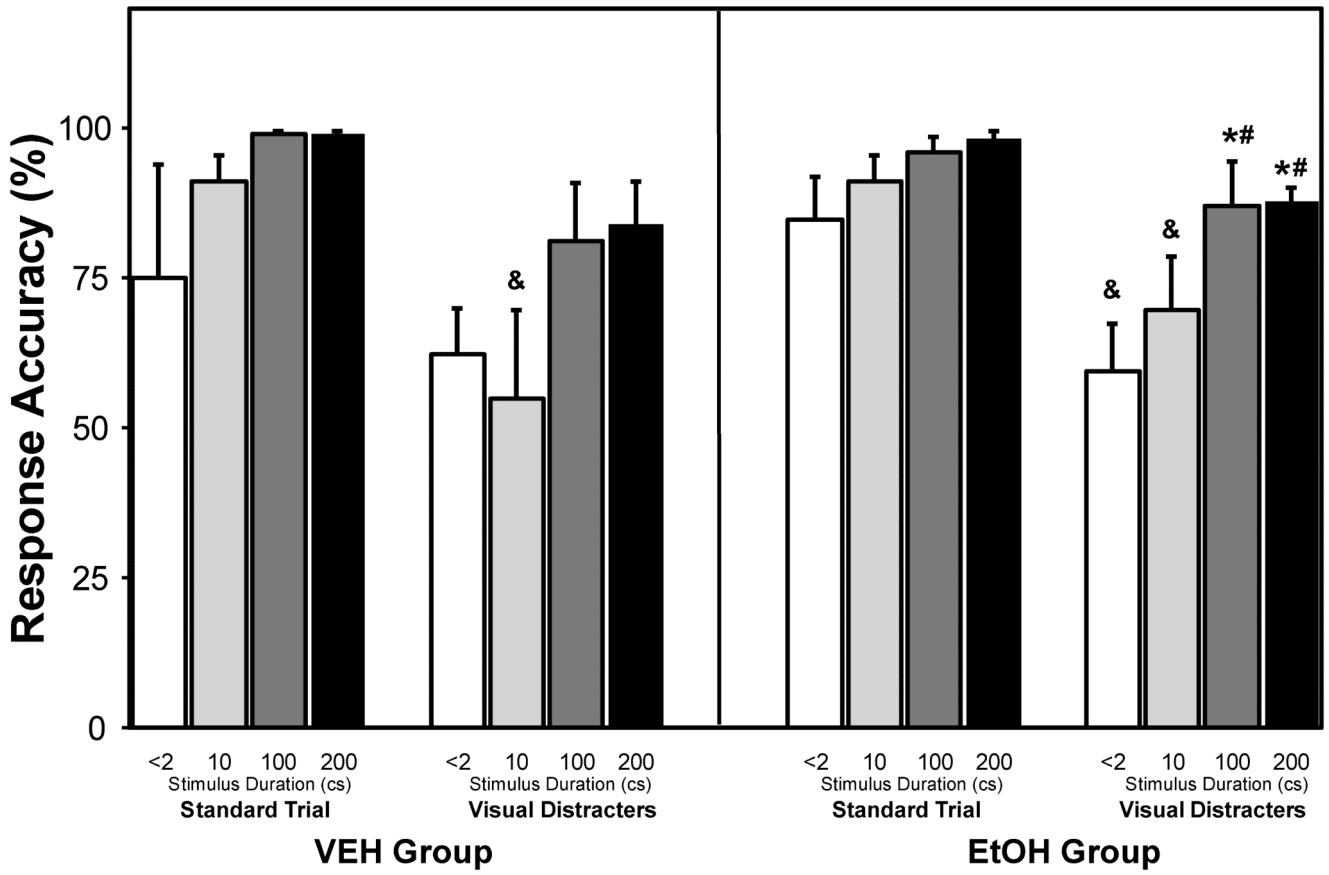

Figure 6.

5-Choice Serial Reaction Time: Mean (N = 5 per group; bars indicate SEM) response accuracy in the 5CSRT task is depicted for animals who had consumed vehicle (VEH) or alcohol (EtOH) for 10 months. Performance is grouped for trials in which only a target stimulus appeared (Standard Trial) and trials in which a non-target distracting stimulus was presented (Visual Distractors). Within each distraction condition, the stimuli appeared for varying durations of time, as indicated. A significant difference from trials when stimulus duration was <2cs is indicated by *, from 10 cs trials by # and a significant difference between standard and distractor trial performance (within a stimulus duration) is indicated by &.

Table 1

Individual Ranks For Group Assignment

Animals were divided into groups using their relative rankings on several behavioral and alcohol assessments. Behavioral measures included initial touch screen training (sessions to criterion; **TS Train**), 5-choice serial response time task (**5CSRT**: Latency to make observing response on task initiation **Obs Rs**; target response latency, **Tgt Rs**; and percent correct targets, **% Corr**), latency to retrieve 16 raisins in a bimanual motor skill task (**BMS**), and the number of reinforcers acquired under a progressive ratio schedule (**PR**). Spontaneous alcohol preference measures included dose consumed (**Alc Dose**) and rate of consumption (**Alc Rate**) within the 30-60 minute access sessions). Alcohol preference measures were assigned a double weighting to produce a final overall score. Alcohol group individuals are indicated with the *.

Monkey	TS Train	5CSRT Obs Rs	5CSRT Tgt Rs	5CSRT % Corr	BMS	PR	Alc Dose	Alc Rate	Weighted Score	Rank
702*	9	2	1	10	4	8	1	2	4.0	1
708	1	6	2	6	9	6	4	1	4.0	2
705	4	3	7	2	6	1	6	5	4.5	3
707*	2	5	6	7	8	4	3	4	4.6	4
704*	5	9	8	1	5	9	2	3	4.7	5
706	3	1	4	3	3	2	8	10	5.2	6
700*	8	10	3	8	7	7	5	3	5.9	7
709	10	4	5	5	2	5	7	9	6.3	8
701*	6	7	9	9	1	3	10	8	7.1	9
703	7	8	10	4	10	10	9	7	8.1	10