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Chronic periadolescent alcohol consumption produces persistent cognitive deficits in rhesus macaques

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ABSTRACT

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.

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). 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. 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 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.

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 et al., 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 premorbid 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

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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, 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, 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 (Johnston et al., 2012a, 2012b). 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 (*Macaca mulatta*; Primate Products, Inc., Immokalee, FL, USA); prior studies in these animals have been reported by Wright and colleagues (Wright et al., 2013a, 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 et al., 1978) and observation of brain growth tapering off at about 40–50 months of age (Knickmeyer et al., 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 h 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-h 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, 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 15 raisins in a bimanual dexterity task; the behavioral procedures followed those previously described (Weed et al.,