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Persistent negative effects of alcohol drinking on aspects of novelty-directed behavior in male rhesus macaques

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ABSTRACT

Humans with histories of prolonged heavy alcohol use exhibit poorer performance on cognitive tasks associated with problem solving, short-term memory, and visuospatial reasoning, even following the cessation of drinking, when compared with healthy controls. It is unclear, however, whether the cognitive problems are a consequence of alcohol exposure or a contributing factor to alcohol-use disorders. Here, we examined the relationship between performance on a novel object recognition (NOR) task and total alcohol consumption (TAC) in adult male rhesus macaques (n = 12; ETH group; trained to self-administer alcohol). NOR performance in this group was assessed prior to induction of alcohol drinking ("pre") and, again, after a 1-year abstinence period ("post") and was compared to the performance of a second group (n = 6; Control group), which was alcohol-naïve. In the NOR task, difficulty was manipulated across three phases by varying specific object features and/or by varying duration of access to objects. For each monkey, we measured aspects of novelty-related behavior including novelty detection, novelty reactivity, and perseverative behavior. TAC during induction and a "free" access period in which the monkey could choose between water and a 4% w/v ethanol solution also was determined. We found that performance deficits in the NOR task were a consequence of high total alcohol intake instead of a predictor of subsequent high intake. Poor NOR performance in drinkers with the highest intakes was characterized by increased perseverative behavior rather than an inability to detect or react to novelty. Finally, the observed deficits are long-lasting – persisting even after a year of abstinence. Given the prevalent and persistent nature of alcohol-induced cognitive deficits in patients in treatment settings, understanding the nature of the deficit and its neural basis could ultimately offer novel treatment approaches based on the reversal of alcohol-induced impairment.

Introduction

Alcohol-use disorders (AUDs) are characterized by progressive cognitive decline in multiple domains (Beatty, Tivis, Stott, Nixon, & Parsons, 2000; Noël, Bechara, Dan, Hanak, & Verbanck, 2007). It is generally accepted that the greatest deficits are observed at the initiation of abstinence. However, the extent to and rate at which these deficits recover with prolonged abstinence remains controversial (Davies et al., 2005; Pitel et al., 2009). It is likely that while some cognitive functions improve following several weeks of abstinence, other functions show more persistent deficits that subside over months, or even years, of abstinence (for review/meta-analysis see Oscar-Berman & Marinković, 2007; Stavro, Pelletier, & Potvin, 2013). Because decision-making, response inhibition, learning and/or retention of new information, and cognitive flexibility are related to positive treatment outcome, it seems

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reasonable that alcohol-induced impairments in some or all of these domains may contribute to continued heavy alcohol use, high relapse rates, and poor treatment prognosis upon abstinence (Penick et al., 2010; Trick, Kempton, Williams, & Duka, 2014; Worley, Tate, Granholm, & Brown, 2014).

While wide-ranging cognitive deficits are a clear consequence of alcohol use, some evidence suggests that pre-existing cognitive deficits may be predictive of, or a risk factor for, subsequent heavy alcohol use. For example, several studies conducted in military personnel show that lower cognitive ability as measured by standardized intelligence tests in early adulthood is associated with an increased risk in middle age of AUDs and, in some cases, other psychiatric disorders (e.g., depression, generalized anxiety disorder; Gale et al., 2008; Latvala, Kuja-Halkola, D'Onofrio, Larsson, & Lichtenstein, 2016). Many studies also show that nonalcoholic, family history-positive individuals who are at high risk for developing AUDs have impaired visuospatial and perception skills, increased impulsiveness, and decreased executive functioning in the absence of significant alcohol exposure compared to family history-negative individuals (Gierski et al., 2013; Lovallo et al., 2013; Penick et al., 2010; for review see; Cservenka, 2016). Cognitive problems are not a risk factor solely in adults, because adolescents with limited attentional abilities compared to control subjects also appear to have higher risk for developing problematic alcohol use (Tapert, Baratta, Abrantes, & Brown, 2002). Interestingly, pre-existing deficits in cognitive domains, including attention and impulsivity/behavioral inhibition, appear to be predictive of poor treatment outcome (Penick et al., 2010; Tapert et al., 2002).

The fact that cognitive ability and AUDs are so inter-related is not surprising, given that brain regions involved in key cognitive abilities are particularly vulnerable to alcohol-induced damage, and include the prefrontal cortex (Chanraud et al., 2007; Fowler et al., 2014) and areas of the temporal lobe, including the hippocampus and para-hippocampal cortical regions (Chanraud et al., 2007; Mechtcheriakov et al., 2007; Nagel, Schweinsburg, Phan, & Tapert, 2005; Taffe et al., 2010). The prefrontal cortex is integral to decision-making, attention, and other executive functions, whereas the hippocampus is a key region involved in learning and memory formation. The hippocampus also interacts with other brain structures (e.g., amygdala, nucleus accumbens) to mediate attention to memories that are highly relevant to the formation of drug-related memories, as well as to drug reinforcement itself (Robbins, Ersche, & Everitt, 2008; Sesack & Grace, 2010). Moreover, circuitry including the hippocampus and prefrontal cortex is critical for an individual's ability to extract relevant information from prior experiences to support goal-oriented behavior (e.g., alcohol seeking; Murty, Calabro, & Luna, 2016). Collectively, these findings suggest that damage to these areas could critically influence the persistence of drinking behavior as well as the failure to remain abstinent.

The present study investigates the relationship between performance on a novel object recognition (NOR) task and alcohol drinking in rhesus monkeys. Specifically, we asked the question whether poor NOR performance predicts increased drinking levels and/or whether poor NOR performance results from heavier drinking. The NOR task was chosen because it relies critically on the hippocampus and surrounding areas. Moreover, the NOR task is sensitive to disruption by alcohol. In rodents and monkeys, acute (Matthews, Simson, & Best, 1995; Popke, Allen, & Paule, 2000), chronic (Crean, Vandewater, Katner, Huitron-Resendiz, & Taffe, 2011; Wright & Taffe, 2014), and binge-like (Cippitelli et al., 2010; Golub et al., 2015) alcohol exposure have been shown to impair performance on novel object/novel place recognition and other discrimination-type tasks. Importantly, human alcoholics typically show deficits in visuospatial learning and memory that, in some cases, appear to be negatively correlated to the amount of ethanol consumed (Nicolás et al., 1993; Sullivan, Rosenbloom, & Pfefferbaum, 2000; Zhang, Begleiter, Porjesz, & Litke, 1997). Interestingly, in both humans and laboratory animals, deficits in these types of tasks tend to manifest as abnormal perseveration and decreased cognitive flexibility (Chanraud et al., 2007; Ramos, 2013; Sullivan, Fama, Rosenbloom, & Pfefferbaum, 2002; Trick et al., 2014).

Materials and methods

Subjects

Alcohol-naïve adult male rhesus monkeys (*Macaca mulatta*, n = 18; Sources: Caribbean Primate Research Center, Puerto Rico and Mannheimer Foundation, Florida) served as subjects. Monkeys ranged in age from 4 to 6 years (mean age: 5.3 years) at the start of the study and had weights ranging from 9.7 to 16.6 kg. Initial NOR testing in all subjects and alcohol self-administration in a subset of subjects was conducted at Harvard Medical School/New England Primate Research Center (Southborough, MA); NOR re-testing in all subjects occurred at the University of Mississippi Medical Center (Jackson, MS).

Regardless of facility, monkeys were housed individually in a colony room with a 12-h light/dark cycle. Environmental conditions were controlled for temperature and humidity. Monkeys received a diet of monkey chow (Harlan Teklad Monkey Diet; Harlan Teklad, Madison, WI), supplemented with fruit, and water was available *ad libitum*. All animals were maintained in accordance with the guidelines outlined in the Guide for Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources, National Research Council, Department of Health, Education and Welfare, Publication No. (NIH) 85-23, revised 2011. Research protocols were approved by the Harvard Medical School and the University of Mississippi Medical Center Institutional Animal Care and Use Committees.

Novel object recognition (NOR) task

A subgroup of monkeys (n = 12) was trained to self-administer alcohol (ETH group) as described below; the remaining monkeys (n = 6) remained alcohol-naïve and served as a control group. ETH monkeys were evaluated on the NOR task at two time points: 1) prior to alcohol induction and self-administration (i.e., while alcohol-naïve), and 2) following a 1-year period of abstinence. Control monkeys were tested at these same time points, though they lacked the intervening period of alcohol exposure. During all aspects of the study (including the abstinence period), all monkeys received daily enrichment according to the Environmental Enrichment and Psychological Well-Being program associated with the specific facility (i.e., HMS/NEPRC, UMMC). The NOR task was a variation of the task as described in Platt and Novak (1999). The task had three phases of difficulty (achieved by increasing the complexity of objects and/or reducing time to become familiar with objects). In the easy phase (week 1), monkeys were exposed 24 h/day to two identical objects hung on the cage front on days 1–4. In the moderate phase (week 2), monkeys were exposed 24 h/day to two different objects hung on the cage front on days 1–4. In the difficult phase (week 3), monkeys were exposed to two different objects hung on the cage front only during the 10 min of data collection on days 1–4. In every phase, on day 5 (test day), one familiar object was replaced with a novel object.

Observers, blinded to the monkeys' group assignment, recorded the occurrence of all contacts the monkeys made to each object for 10 min daily. “Contacting” was defined as any touching (with hands