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The influence of acute and chronic alcohol consumption on response time distribution in adolescent rhesus macaques

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ABSTRACT

Background: Analysis of the distribution of reaction times (RTs) in behavioral tasks can illustrate differences attributable to changes in attention, even when no change in mean RT is observed. Detrimental attentional effects of both acute and chronic exposure to alcohol may therefore be revealed by fitting RT data to an ex-Gaussian probability density function which identifies the proportion of long-RT responses.
Methods: Adolescent male rhesus macaques completed a 5-choice serial reaction time task (5CSRT) after acute alcohol consumption (up to 0.0, 1.0 and 1.5 g/kg). Monkeys were next divided into chronic alcohol ($N = 5$) and control groups ($N = 5$); the experimental group consumed 1.5–3.0 g/kg alcohol for 200 drinking sessions. Unintoxicated performance in the 5CSRT task was determined systematically across the study period and the effect of acute alcohol was redetermined after the 180th drinking session. The effect of extended abstinence from chronic alcohol was determined across 90 days.
Results: Acute alcohol exposure dose-dependently reduced the probability of longer RT responses without changing the mean or the standard deviation of the RT distribution. The RT distribution of control monkeys tightened across 10 months whereas that of the chronic alcohol group was unchanged. Discontinuation from chronic alcohol increased the probability of long RT responses with a difference from control animals observed after 30 days of discontinuation.
Conclusions: Alcohol consumption selectively affected attention as reflected in the probability of long RT responses. Acute alcohol consumption focused attention, chronic alcohol consumption impaired the maturation of attention across the study period and alcohol discontinuation impaired attention.

1. Introduction

Acute alcohol consumption typically increases response times in humans at relatively high (Baylor et al., 1989; Cameron et al., 2001; King, 1975; Krull et al., 1992; Lubin, 1977) and low doses (Friedman et al., 2011; Schweizer et al., 2006). In such tasks there is often evidence that these changes in response time may be more attributable to *cognitive* impairment than motor impairment (Breitmeier et al., 2007; Hernández et al., 2006, 2010, 2007). Likewise, functional magnetic resonance imaging experiments with humans indicate that alcohol doses that increase response times also reduce activity in brain areas known to regulate attention, error detection and executive function (Anderson et al., 2011; Marinkovic et al., 2012). Inhibitory effects of alcohol on response time are most commonly observed on the ascending limb of the blood-alcohol concentration (BAC) curve and acute tolerance is thought to restore response times to pre-exposure levels during the descending limb of the BAC curve (Schweizer and Vogel-Sprott, 2008). Similar to observations with humans, moderate and large doses of alcohol have been shown to slow response time in monkeys (Moody et al., 1980).

Despite evidence that alcohol increases response times under many conditions, there is also evidence that it can produce activating effects in some instances. Acute alcohol has been shown to decrease response times in humans performing choice reaction time tasks (McManus et al., 1983; Tiplady et al., 2001), moderate to low doses (0.35–2.8 μmol i.c.v.; 0.5 g/kg i.p.; 0.6–1.0 i.g.) of alcohol have been shown to increase operant response rates (Arizzi et al., 2003) and to stimulate locomotor behavior in rats (Pohorecky et al., 1989; Stodulka, 1991); similar locomotor effects have been shown in mice (Kamens and Phillips, 2008; Larsson et al., 2002). Taken together, these data do not support the "global-slowing" effect of alcohol advanced by some (Maylor and Rabbitt, 1993). Instead, the existing data support the conclusion that the behavioral pharmacology of

Abbreviations: 5CSRT, 5-Choice Serial Reaction Time; BAC, Blood-Alcohol Concentration; PDF, Probability Density Function; RT, Reaction Time.

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alcohol is complex, task-specific and that results can vary as methodology changes (Ryan et al., 1996).

While alcohol can produce both stimulant and depressant effects (Lewis and June, 1990), there are only a few examples of alcohol decreasing response times. The shape of the typical response time distribution may, however, obscure the activating effects of alcohol since response times are rarely distributed normally and are typically positively skewed (Heathcote et al., 1991). The unimodal shape of response time distributions is characterized by a large proportion of short response times, a mean value close to the lower limit of observed response times and a long right-handed tail that contains a few comparatively long response times (Lacouture and Cousineau, 2008), see Fig. 1A. When mean response times are near the lower limit, any further reduction in those already low values can be difficult to detect.

Changes in response time performance are also difficult to confirm with common parametric techniques, largely because the data sets do not conform to the assumptions of those analyses (Heathcote et al., 1991; Lacouture and Cousineau, 2008; Matzke and Wagenmakers, 2009). One approach to dealing with data sets that are not distributed normally is to analyze the logarithmic transform of those data. Unfortunately, this technique also ignores important details about response time performance, such as the frequency with which extreme response times are emitted (Heathcote et al., 1991; Van Zandt, 2000). As an alternative analysis, fitting RT data sets to an ex-Gaussian probability density function (PDF) can produce important insight into the behavioral pharmacology of alcohol. Fitting response time data to an ex-Gaussian PDF allows normally-distributed (Gaussian) components to be deconvolved from exponentially-distributed components (Luce, 1986). This analysis renders the mean value of Gaussian component (*sigma*), the standard deviation of the Gaussian component (*mu*) and the mean of the exponential component (*tau*). By separating response time distributions into these constituent components, additional information about response time performance can be determined (Heathcote et al., 1991). In particular, changes in the probability of unusually long response times, can be detected by changes in *tau* (Luce, 1986) These analytical techniques have recently been applied to show that acute exposure to a moderate dose of alcohol (*i.v.*) could increase the probability of long response times in adult monkeys (Jedema et al., 2011). The present study sought to determine effects of acute and chronic alcohol exposure on the RT performance of adolescent monkeys using a more naturalistic oral consumption model (Katner et al., 2004). As we have previously discussed, alcohol is a commonly used recreational drug (Crean et al., 2011; Katner et al., 2007; Wright et al., 2013) with high potential to cause acute and lasting cognitive impairment in addition to other consequences (Crean et al., 2011; Marcondes et al., 2008; Taffe et al., 2010). Animal models are necessary to determine the specific effects of controlled alcohol exposure and to distinguish affected from spared cognitive domains. In this work the focus was on attentional properties indexed by skew in the RT distribution.

2. Material and methods

2.1. Subjects

These experiments were conducted on adolescent male rhesus macaques (*Macaca mulatta*, Primate Products, Inc, Immokalee, FL, USA). At the onset of these studies, the median age of the monkeys was 48 months (range = 39–50 months) and 70% of the monkeys were born within 60 days of each other. The mean weight was 6.5 kg (range = 5.4–7.4 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 36–48 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 a start in the immediate peri-pubertal time point and then stretching into late adolescence, similar to the high school population of humans.

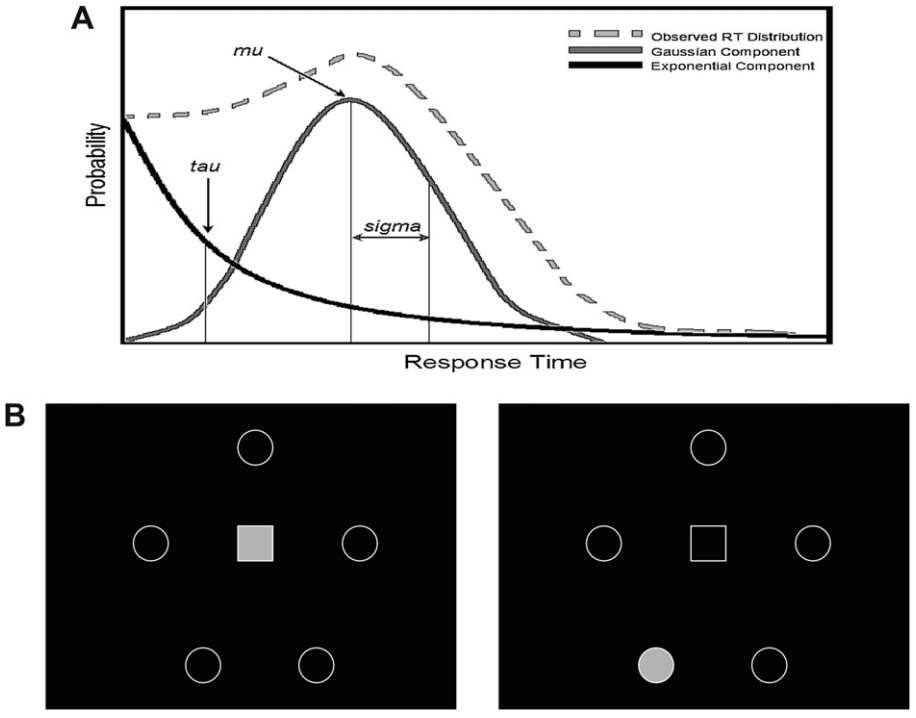

Fig. 1. (A) Illustration of response time probability density function (PDF). Response time PDF can be deconvolved to render estimates of *mu* (mean of Gaussian component), *sigma* (standard error of Gaussian component) and *tau* (mean of exponentially-distributed component). (B) Illustration of stimuli used in 5-choice serial reaction time task (5CSRT). Each 5CSRT trial began with an observing response on a centrally-located stimulus. To be successful, each observing response had to be maintained until a target stimulus was presented one of 5 possible target locations. Response time was defined as the latency to respond after the appearance of the target stimulus.