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# Nonhuman primate model of alcohol abuse: Effects of early experience, personality, and stress on alcohol consumption

(alcoholism/hypothalamic–pituitary–adrenocortical axis/rhesus monkey cerebrospinal fluid/monoamine metabolites)

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ABSTRACT **Twenty-two 50-month-old rhesus monkeys were provided concurrent free access to an aspartame-sweetened 7% ethanol solution and an aspartame-sweetened vehicle before, during, and after social separation. Subjects had been reared for their first 6 months of life either without access to adults but with constant access to age mates (peer reared), a condition producing reduced exploration and increased fear-related behaviors, or as controls with their mothers; thereafter, all subjects received identical treatment. During home-cage periods, for 1 hr each day, 4 days a week, when the ethanol solution and vehicle were freely available, peer-reared subjects consumed significantly more alcohol than mother-reared subjects. When stress was increased via social separation, mother-reared animals increased their alcohol consumption to a level nearly as high as that of peer-reared monkeys. Average individual differences in alcohol consumption were markedly stable over time. In addition, there were strong positive correlations between alcohol consumption and distress behaviors. Biological indices of increased stress, such as plasma cortisol and corticotropin, were higher in peer-reared subjects. Within the peer- and mother-reared groups, these indices were positively correlated with alcohol consumption. The results suggest that early rearing experiences that predispose monkeys to increased fear-related behaviors produce excessive alcohol consumption under normal living conditions. Furthermore, a major challenge such as social separation increases alcohol consumption to levels producing intoxication even in monkeys not particularly vulnerable to stress.**

Alcohol abuse is one of the most pervasive public health problems facing modern society. It has a complex etiology, which includes both environmental and genetic variables (1–4). Stress is widely held to produce increased alcohol consumption. This belief, however, has not been well documented. Indeed, a recent review by Cappell (p. 44 in ref. 5), one of the pioneers in this research area, stated: "It is not that there has been a failure to show that some stress manipulations may produce elevations in alcohol consumption . . . but that there is yet to emerge even a rudimentary understanding of the conditions under which various stress manipulations will or will not affect alcohol consumption in animals." Cappell and others note, however, that when variables such as the response required, the type and intensity of the stressor, and the timing of alcohol access are considered, stressful conditions do appear to increase alcohol consumption (5–8).

Studies on both animals (9–14) and humans (15–20) show that individuals vary systematically in reactivity along a continuum in their response to stimuli and that this variability in reactivity is associated with differential autonomic responsiveness (16–18). Differences in reactivity are a function of both experiential and genetic backgrounds (19), and excessive reactivity may be a risk factor in the development of certain anxiety disorders (20).

Anxiety and fearfulness appear to be risk factors for alcohol abuse. For example, studies on rodents indicate that strains that have a tendency to exhibit behaviors associated with fear show increased alcohol consumption (21–23). Not all studies have found, however, that reactive rats consume more alcohol (24). Sher (7) has noted that one possible reason for the apparently discrepant results across studies of stress-induced alcohol consumption is that stressors have not been applied to the reactive rats prior to alcohol availability. Furthermore, rearing conditions that increase or decrease fearfulness in rodents are positively related to increases or decreases in alcohol consumption (25, 26). Among humans, individuals with increased levels of anxiety are more likely to report that they expect alcohol to elevate their mood and to show a reduction in anxiety after its consumption (27, 28). There is also evidence that, relative to controls, individuals at high risk for developing alcoholism show more robust reductions in autonomic reactivity, as measured by responses of heart rate and muscle tension to stress, after consuming alcohol (29–31). Furthermore, studies on psychiatric patients indicate that anxiety or affective disorders may be risk factors for alcohol abuse (32, 33), with many patients reporting the use of alcohol to alleviate anxiety (34–36).

Severe or chronic anxiety cannot be ethically induced in humans to study stress-induced alcohol problems. Emerging evidence from a relatively small number of laboratories indicates, however, that when the drink is palatable and the ethanol concentration is below 15%, nonhuman primates sometimes voluntarily consume alcohol in sufficient quantities to produce intoxication (37–41). Furthermore, the amount of alcohol consumed increases in response to chronic stress (42, 43) or a major acute challenge such as social separation (44). Regardless of the level of stress, consumption varies widely among individual monkeys (37–41, 43–45). Preliminary evidence suggests that interindividual differences in alcohol consumption may be related to individual differences in anxiety or fearfulness and the predisposition to show despair in response to the stressor of social separation (43, 46), and it is clear that these differences in anxiety and fearfulness are at least in part related to early experience (10, 14). For example, relative to mother-reared monkeys, monkeys reared without adults but with age mates, a condition known as peer-rearing, demonstrate increased anxious-like

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Abbreviations: ACTH, corticotropin; CSF, cerebrospinal fluid; MHPG, 3-methoxy-4-hydroxyphenylglycol; 5-HIAA, 5-hydroxyindoleacetic acid; BAC, blood alcohol concentration.

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behaviors and fearfulness as indicated by increased clinging to each other, decreased play, increased self-directed behaviors, and increased plasma corticotropin (ACTH), cortisol, and cerebrospinal fluid (CSF) 3-methoxy-4-hydroxyphenylglycol (MHPG) and 5-hydroxyindoleacetic acid (5-HIAA) concentrations (10, 47, 48). Such animals provide a potentially relevant model to test the importance of developmental conditions and the role of early experience in interindividual variability in stress responsiveness and in stress-related alcohol consumption.

## MATERIALS AND METHODS

**Subject Description.** In two independent replications carried out over a 2-year period, 22 rhesus monkeys were tested for differences in voluntary alcohol consumption. The monkeys spent their first 6 months of life either without access to adults but with constant access to age mates in peer-reared social groups ($n = 4$ in each year), or with their mothers ($n = 8$ in the first year; $n = 6$ in the second year). Peer-reared subjects were randomly assigned by picking 4 females in each year who were due to conceive on or close to the same date and rearing their infants for the first 30 days in the neonatal nursery. Thereafter the infants were constantly kept together as a group of 4. They were fed Similac until they were 120 days old. The mother-reared monkeys remained with their mothers until they were 7 months old, an age when most infants are relatively independent of their mothers and the weaning process is largely completed (49). At this point, the mother-reared monkeys were removed from their mothers and placed with the peer-reared monkeys with whom they lived for the next 4 years. In other words, after the 7th month, the mother-reared monkeys and their peer-reared age mates were treated identically. Throughout the study period, the average weights of the peer-reared and the mother-reared monkeys were similar to each other [peer-reared, 4.6 ± 2.2; mother-reared, 4.9 ± 2.1 kg (means ± SD)].

**Procedures.** When the monkeys reached 50 months of age, they were provided access to red-colored aspartame-sweetened (30 mg per 100 ml of water), 7% (wt/vol) ethanol solution for 1 hr a day, 4 days a week, for a total of 8 consecutive weeks while they were either together as a group in their home cages (2.1 × 2.4 × 1.8 m) or during stress-producing social separations. During social separations, the monkeys were housed in single cages (300 × 300 × 400 cm) where they could hear but not see their cage mates. To control for the possibility that the monkeys were consuming the flavored alcohol for its gustatory value, during each of these sessions, the green-colored aspartame vehicle, sweetened similar to the ethanol solution, was available. The monkeys received their regular food (daily feeding at 0700) throughout the study. To preclude water satiation at the beginning of the session, cage water was turned off for 1 hr prior to dispensing the alcohol solution. Water was freely available at all other times, including the period when the alcohol solution was dispensed. At the beginning of the study, social rank within each group was determined by observing the frequency of physical displacements by each animal to all other animals in the social group. Rank-dependent differential access to the solutions was precluded by dividing the groups into high and low dominance groups each day and providing six clear Plexiglas chambers with an internal perch where subjects could enter and still see the other monkeys but sit and drink without harassment. The Plexiglas chambers hung on the front of the cage as 2 units (46 × 68 × 28 cm), each divided into three equal sized chambers (46 × 22 × 28 cm) in the upper and lower half of the cages. The subjects entered from the bottom and were surrounded on all sides by the clear Plexiglas. The alcohol was dispensed to each chamber by using gravity fed, self-zeroing burets, each connected via plastic tubing to a lick-initiated stainless steel nipple, identical to the nipple used to dispense water to the home cage. Analyses indicated no relationship between home cage alcohol consumption and dominance rank ($r = 0.08$ between dominance rank and amount of alcohol consumed).

After a 2-week home-cage preseparation baseline period, subjects were separated from their cage mates for four 4-day periods, each followed by 3 days of home-cage reunion. Alcohol was provided during each day of separation, except on days when CSF samples were obtained (see below). For descriptive purposes, the data for alcohol consumption were analyzed by dividing each of the separations into an initial acute phase (mean of the 1st day of separation) and a more long-term chronic phase (mean of the remaining 3 days). The separations were followed by 2 weeks of postseparation alcohol exposure. On the last day of the preseparation baseline phase, the postseparation recovery phase, and separations 1 and 4, monkeys were anesthetized and removed from their cages to obtain venous blood and cisternal CSF samples. CSF samples were assayed according to the procedure described by Scheinin et al. (50), and plasma cortisol and ACTH were assayed by Hazelton Biotechnologies using radioimmunoassays (51). Two additional blood samples were obtained by using a capture and restraint procedure on the 1st day of each separation 1 and 2 hr after the monkeys had been removed from their home cages. Alcohol was made available after the blood was drawn. On the remaining 3 days of separation, the animals were not disturbed prior to alcohol exposure. Systematic behavioral recordings were obtained by using hand-held portable computers for 5-min periods once daily during home-cage interactions and twice daily during the four social separations 5 days a week. Durations and frequencies of behaviors were obtained by using an objectively defined 14-category behavioral scoring system specifically designed to measure distress in the rhesus monkey (52). The five observers participating in the study were trained in the behavioral scoring system by a laboratory technician who had used the same system for over a decade with a criterion of $r = 0.95$ reliability across behaviors.

## RESULTS

**Alcohol Consumption Patterns.** The monkeys' daily alcohol consumption followed a predictable pattern. Over 60% of the alcohol was consumed quickly during the first 15 min, and the remainder was consumed in small amounts throughout the rest of the hour-long session [$F(3.60) = 54.8$; $P = 0.0001$]. While there were large individual differences, most monkeys consumed alcohol in sufficient quantities to reach blood alcohol concentrations (BACs) well in excess of the human legal limit of intoxication for motor vehicle operation in most states. On days of increased consumption, the monkeys demonstrated visible signs of intoxication with ataxia, sway, and vomiting as the most frequent behaviors. On three occasions, ataxia was severe enough that animals had to be placed in a small individual cage to prevent fall-related injuries. To obtain estimates of BACs without disturbing the monkeys' home-cage behavior, at the end of the experiment, nine of the monkeys from the 2nd year replication were intubated with the alcohol solution in an amount identical to the largest volume that they voluntarily consumed on any single day. As the subjects' daily voluntary average consumption was rapid, intubation probably reflects BACs similar to voluntary consumption; nevertheless, intubation may have produced somewhat higher BACs than voluntary consumption. To compensate for this, we sampled at 120 min, a time point beyond the peak of the mean BAC curve. Fig. 1 illustrates the BAC for these animals. On the day they were intubated with alcohol, one monkey vomited and two lost

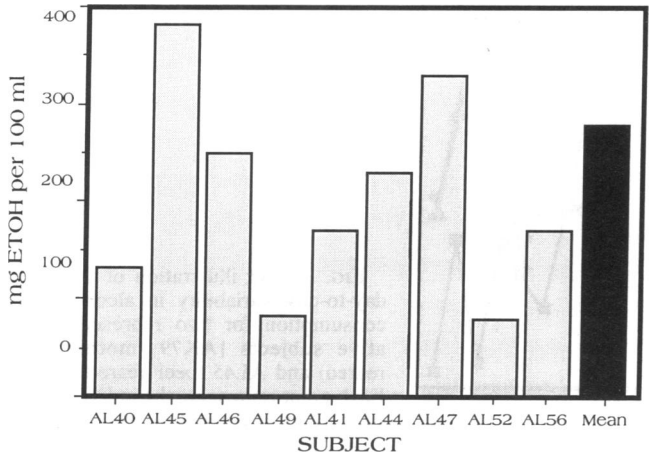


FIG. 1. An illustration of individual differences in BACs after intubation with the same volume of the 7% alcohol solution the monkeys had consumed on the day of their greatest intake of the alcohol solution. Blood samples for quantification of alcohol concentrations with head space gas chromatography were drawn 120 min after administration of the solution.

consciousness. The individual differences in BACs illustrated in Fig. 1 are representative of day-to-day individual differences in average alcohol consumption in the home cage ($r = 0.667$; $P < 0.05$).

**Effect of Early Rearing Experiences.** Differences in consumption were related in large part to early rearing experiences. A mixed design, two-way analysis of variance indicated that during the preseparation baseline and postseparation recovery phases the peer-reared monkeys consumed significantly more alcohol than the mother-reared controls; however, the mother-reared monkeys increased their alcohol consumption significantly during social separation [F(3.60) = 5.02; $P = 0.007$; see Fig. 2]. In rhesus monkeys, to reach a BAC of 0.10%, the limit of legal intoxication in most states, consumption of 1.4 g or more of alcohol per kg of body weight is required (53). While all animals consumed sufficient quantities of alcohol to produce pharmacological effects, in the home cage the peer-reared monkeys consumed >1.4 g of alcohol per kg of body weight significantly more frequently than the mother-reared monkeys [F(2.40) = 4.05; $P = 0.05$]. During the separations, the mother-reared monkeys increased their alcohol consumption to approach levels similar to the peer-reared monkeys' consumption (Fig. 2). Separate analysis of the peer-reared monkeys indicated an initial decline in consumption during the first separation when the peer-reared monkeys moved away from the observer by withdrawing to the rear of the separation cage and reducing their activity [F(7.56) = 3.14; $P = 0.01$]. During the last two separations, after adjusting to the novelty of the separation cages, the consumption patterns of the peer-reared monkeys returned to their previous level, except for the last two of the four separations. During the acute phase of the last two separations the peer-reared subjects' consumption pattern was the highest of any point of the study. Across the two replications the home-cage differences between peer-reared and mother-reared animals were stable and remained significantly different from each other in both years.

**Individual Differences.** As with studies on human alcoholics (54, 55), individual consumption varied markedly from day to day, with subjects showing consumption patterns well in excess of 1.4 g/kg on some days and minimal consumption on others (Fig. 3). However, independent of rearing conditions, as in other studies using monkeys (44), there was evidence that interindividual differences in alcohol consumption were very stable. The average weekly consumption rate

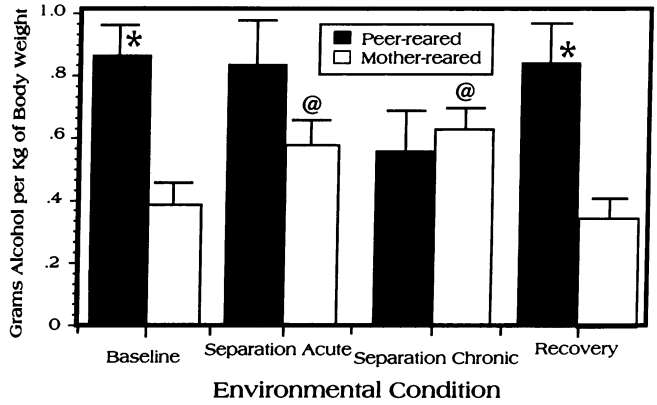


FIG. 2. An illustration of the effects of early rearing experiences and social separation on alcohol consumption [$n = 22$; F(3.60) = 5.02; $P = 0.007$]. Each bar represents the average and SD of alcohol consumption in g per kg of body weight for each group over experimental conditions; solid bar, peer-reared subjects; open bar, mother-reared subjects. The preseparation baseline period is the average of 10 days of alcohol consumption in the home cage. The average consumption for the four separations is divided into an overall acute phase (mean of 1st day of each of the four separations) and an overall chronic phase (mean of remaining 3 days of each separation). The postseparation recovery phase is the average of 10 days of alcohol consumption after the social separations. *, Significant difference between the peer-reared subjects and the mother-reared subjects within the same period, with the peer-reared subjects showing an increased consumption ($P < 0.05$). @, Significant increase in alcohol consumption for the mother-reared subjects during social separation relative to consumption in the home cage ($P < 0.05$). The apparent reduction in alcohol consumption by the peer-reared monkeys during the chronic phase of the social separations is not statistically significant ($T = 1.56$; $P > 0.10$).

during the 1st and 2nd weeks of pre- and postseparation correlated with each other ($r = 0.779$ and 0.636, respectively; $P < 0.001$). Individual differences in the rate of drinking across separations were also stable, with each subject's mean for the first 2 weeks correlating with the mean for the last 2 weeks ($r = 0.464$; $P < 0.05$). Furthermore, the average preseparation baseline and postseparation recovery alcohol consumption levels correlated strongly with each other as well ($r = 0.658$; $P < 0.01$).

**Behavioral and Physiological Correlates of Alcohol Consumption.** Behaviorally and physiologically the peer-reared monkeys exhibited more anxiety-like and fearful behaviors during their home-cage interactions. During baseline and postseparation recovery interactions, they demonstrated significantly more infant-like ventral contact [F(1,20) = 6.52; $P = 0.02$; means ± SD in sec per 5-min observation: peer-reared, 9.6 ± 23.0; mother-reared, 0.7 ± 2.9] and self-directed behaviors [F(1,20) = 5.34; $P = 0.05$; means ± SD in sec per 5-min observation: peer-reared, 46.0 ± 46.8; mother-reared, 29.0 ± 21.5]. As each separation progressed—i.e., during the last 3 days—the peer-reared monkeys showed increased distress behaviors [self-directed behaviors and huddling: F(1,20) = 4.90; $P = 0.04$; means ± SD in sec per 5-min observation: peer-reared, 80.7 ± 58.8; mother-reared, 41.5 ± 24.5]. After separation, during the postseparation recovery phase, levels of locomotion doubled relative to baseline and separation [F(1,20) = 9.61; $P = 0.006$; means ± SD in sec per 5-min observation: baseline, 32.5 ± 17.9; separation, 34.6 ± 16.4; recovery, 64.2 ± 38.7] and were strongly correlated with postseparation alcohol consumption ($r = 0.617$; $P = 0.01$). During the 2nd week of the preseparation baseline phase, which had been preceded by the stress of the first blood draw, the peer-reared monkeys had increased plasma cortisol; during the 1st week of the acute separation challenges, the peer-reared monkeys had in-

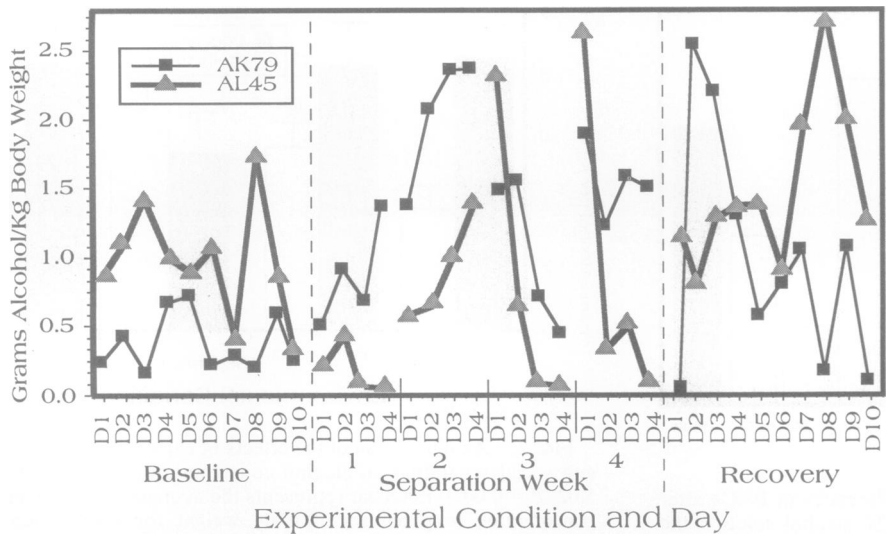


FIG. 3. An illustration of the day-to-day variability in alcohol consumption for two representative subjects [AK79 (mother reared) and AL45 (peer reared)]. Each point represents the individual alcohol consumption in g per kg of body weight for each subject over each day of all three experimental conditions. Squares, AK79; triangles, AL45.

creased plasma cortisol and ACTH concentrations compared to their mother-reared counterparts [cortisol: $F(7,140) = 2.53$; $P = 0.05$; means ± SD in μg/dl: peer-reared baseline, 24.9 ± 4.2; mother-reared baseline, 18.2 ± 6.5; peer-reared separation, 48.6 ± 8.3; mother-reared separation, 39.8 ± 6.0; ACTH: $F(6,120) = 2.96$; $P = 0.01$; separation means ± SD: peer-reared, 258.5 ± 316.4; mother-reared, 91.0 ± 109.8 pg/ml]. When the effects of rearing were statistically removed, self-directed behaviors across the chronic phase of the separation were positively correlated with alcohol consumption ($r = 0.434$; $P < 0.05$), and during separation the average peak plasma cortisol concentration was positively correlated with the overall average alcohol consumption ($r = 0.453$; $P < 0.05$). When the known positive correlation between body weight and MHPG concentration was statistically controlled, CSF MHPG concentrations during separation were negatively correlated with the average alcohol consumption ($r = -0.446$; $P < 0.05$).

## DISCUSSION

Our results are consistent with others who have investigated alcohol consumption in nonhuman primates (37–41, 44, 46, 53). As in previous studies, rhesus monkeys voluntarily consumed alcohol in sufficient quantities to produce pharmacological effects on a regular basis. Also consistent with other nonhuman primate studies of alcohol consumption, noradrenergic activity was negatively related to alcohol consumption (46, 56). This is to our knowledge, however, the only report in primates of early rearing experiences with known behavioral correlates apparently having a major effect on alcohol consumption. This report also directly links rearing-induced differences in behavior to stress-induced changes in alcohol consumption.

These findings indicate that early experiences that result in increased levels of anxious-like behaviors can have a major impact on alcohol consumption. Studies of human alcoholics have shown that for certain forms of alcoholism, early rearing experiences are important factors in determining alcohol abuse patterns (57). Adverse early rearing experiences are more likely to be reported in what Cloninger has labeled as type I alcoholism, a form of alcoholism characterized by personality traits of excessive harm and novelty avoidance. Similarly, at low levels of stress, peer-reared monkeys demonstrated chronically high levels of anxious-like behaviors, such as infant-like ventral clinging and self-directed behaviors. They showed increased pituitary adrenal activation upon separation, and they consumed alcohol at a rate double the mother-reared monkeys' rate. These findings also indicate a rearing condition–severity of stress interaction, which has a major impact on alcohol consumption. Independent of early rearing experiences, individual differences in anxiety and fearfulness contribute to stress-induced alcohol consumption, as individual differences in behavioral reactivity and physiological arousal were highly correlated with alcohol consumption. However, when a major stressor such as social separation was applied, even the less reactive mother-reared monkeys increased their consumption rates.

While the effects of peer-rearing on fearfulness and anxiety are clear in monkeys, the basis for the within-group differences in reactivity is less apparent. Studies indicate that when infants from mothers who have previously produced reactive infants are fostered to unrelated nurturant mothers, they are still more reactive behaviorally than would be expected by chance (10, 58), and their CSF MHPG and 5-HIAA concentrations are correlated with their biological mothers' but not their adoptive mothers' monoamine metabolite concentrations (10). When the infants are statistically grouped for comparison according to fathers (whom they have never seen), their plasma ACTH, cortisol, CSF 5-HIAA, and HVA concentrations are strongly influenced by sire (59), suggesting genetic effects on individual differences in behavioral reactivity and neurotransmitter functions. Thus, the individual differences in reactivity to stress and alcohol consumption may be at least partially genetically mediated.

It is unlikely that the major motivation for consuming the alcohol solution was based on a gustatory incentive. Some individuals consistently consumed sufficient quantities of the alcohol solution to produce symptoms of intoxication, even when they could have freely consumed the sweetened vehicle. Individual consumption patterns of the vehicle prior to the exposure to the alcohol solution were not correlated with individual alcohol consumption patterns. Our observations of the subjects indicated that as the burets were filled each day, monkeys waited in close proximity to the dispenser for the alcohol solution, but not the vehicle dispenser. While the majority of the vehicle was consumed independent of the alcohol solution, a frequent pattern of behavior was a protracted consumption of the alcohol solution, followed by a brief drink of the vehicle and a prolonged return to the alcohol solution followed again by a small drink of the vehicle. Nevertheless, the combination of these two consumption patterns resulted in a stronger preference for the vehicle relative to the alcohol solution. Across sessions, the monkeys consumed ≈2/3rd more vehicle than alcohol solution. As this model allows control for taste cues and incentive, subsequent studies can investigate what role, if any, gustatory factors play.

Our results provide a promising model to investigate antecedents of alcohol abuse. Because rhesus monkeys are genetically relatively closely related to humans and they have not been genetically selected for alcohol consumption over

many generations, the findings from studies with them may apply more readily to the human condition than studies in which other species were used. While our findings do not necessarily apply to all forms of alcohol abuse in humans, they provide a potentially important method to test etiological hypotheses and treatment modalities for anxiety-associated alcohol abuse using a nonhuman primate.

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