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Offspring of parents with an alcohol use disorder prefer higher levels of brain alcohol exposure in laboratory experiments involving computer-assisted self-infusion of ethanol (CASE)

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Abstract

Rationale: Acute alcohol effects may differ in social drinkers with a positive family history of alcohol use disorders (FHP) compared to FH negative (FHN) controls.

Objectives: To investigate whether FHP subjects prefer higher levels of brain alcohol exposure than do FHN controls.

Methods: 22 young healthy nondependent social drinkers participated in two identical experimental sessions. The 12 FHP (4 women) and 10 FHN (3 women) participants received a priming exposure, increasing arterial blood alcohol concentration (aBAC) to 30 mg% at 10 minutes and decreasing it to 15 mg% at 25 minutes. A 2-hour self-administration period followed, during which only the subjects could increase their aBAC by pressing a button connected to a computer controlling the infusion pump. Infusion rates were calculated instantaneously to increase aBAC by precisely 7.5 mg% within 2.5 minutes after each button press. Subjects were instructed to produce the same alcohol effects as they would do at a week-end party.

Results: The mean and maximum aBAC during the self-administration period and the number of alcohol requests (NOAR) were significantly higher in the FHP vs. FHN participants during the second, but not during the first session. All three outcome measures were significantly interrelated between days.

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Conclusions: This is the first laboratory experiment demonstrating higher alcohol self-administration in FHP compared to FHN subjects. This difference demonstrated significance on the second test day only, consistent with our previous experience that one practice day is needed in every participant before reliable data can be drawn from CASE experiments.

Keywords

Alcoholism; ethanol; self-administration; genetic risk; sensitivity; tolerance; Freibier; CASE

Introduction

Alcoholism runs in families, and biological offspring of alcoholics have a four- to eightfold increased risk to become dependent on alcohol. Adoption studies suggested that approximately 60% of this elevated risk can be explained by complex genetic factors (Prescott and Kendler 1999), (Heath et al. 1997), (Sigvardsson et al. 1996). Several mechanisms have been proposed to explain how genetic variation can modify the risk for alcoholism. Many of them refer to altered pharmacodynamic effects once alcohol is consumed. Respective findings with sons of alcoholics (SOA) were comprehensively reviewed by Newlin and Thompson (Newlin and Thomson 1990), who suggest a “newtonian differentiator model” claiming that SOA are more sensitive to the stimulatory and euphoric effects which occur while arterial blood alcohol concentration **(aBAC)** is rising. As a second factor, they postulate that SOA are quicker to develop acute tolerance against alcohol, which they think occurs as BAC begins to fall during the same drinking session, and which is associated with a negative hedonic value. Together, these two factors would drive SOA to keep BAC on the rise once a drinking session was initiated.

While this view refers to altered *quality* of alcohol effects, there is a literature reporting that subjects with a positive family history of alcoholism **(FHP)** experience some effects of ingested alcohol as being less pronounced, which refers to altered *quantity* of alcohol effects. For example, healthy young sons and daughters of alcoholics felt less intoxicated after ingesting a standard dose of alcohol, showed less motor impairment, and less endocrine perturbation after a high dosage compared to family history negative **(FHN)** controls (Schuckit et al. 1988;Schuckit 1994;Schuckit and Gold 1988). This low level of response was found to predict the development of alcohol problems later in life, which was true for both FHP and FHN subjects (Schuckit 1994). Tolerating alcohol better might thus be a second reason why offspring of alcoholics end up at higher aBACs compared to FHN subjects in social drinking situations.

If these differences are indeed relevant modulators of drinking behavior in offspring of alcoholics, it should be possible to demonstrate higher levels of alcohol self-administration in laboratory experiments with FHP subjects. In animal research, alcohol self-administration is a well-established tool to study effects of specific genetic variations (Crabbe et al. 2006). Some prior studies demonstrated that alcohol self-administration is also a valuable method in humans, showing that pretreatment with the opiate receptor antagonists naltrexone and nalmefene significantly reduced laboratory alcohol drinking in non-treatment-seeking

alcoholics (O'Malley et al. 2002), (Drobes et al. 2003), while nicotine pretreatment increased it in male social drinkers (Acheson et al. 2006).

Two previous studies provide data on how family history for alcoholism affects voluntary laboratory drinking. De Wit et al. (de Wit and McCracken 1990) conducted an experiment where 11 FHN and 11 FHP male social drinkers underwent several experimental sessions where they ingested color-coded capsules and drinks, but were blind to the fact that these could contain only either alcohol or placebo. The experiment always started with a priming drink containing either 0.1 g/kg ethanol or placebo. Thereafter, subjects were offered one more of these standard drinks every 15 minutes, which they could either consume or reject. The maximum observed number of ingested drinks over a 3-hours period was 11, equivalent to a cumulative dose of 1.1 g/kg body weight. The risk groups did not differ in the number of sessions on which they chose ethanol over placebo, based on the cup/capsule color. Contrary to the starting hypothesis, the number of drinks consumed during the alcohol sessions also did not differ between groups. The other study (Krishnan-Sarin et al. 2007) investigated 54 FHN and 38 FHP male and female non-treatment seeking alcohol-dependent volunteers in a one-session design. Subjects were pretreated with placebo or 50mg or 100 mg naltrexone per day during the week before a self-administration experiment, where they could consume or reject each of 4 alcoholic drinks offered in 2 consecutive one-hour periods. The number of drinks consumed was significantly influenced by a FHA × medication interaction effect, but no significant main effect of FHA status was detected. The same applied to the course of BAC over time, which was influenced by a FHA × medication × time effect, but not by a FHA main effect. Direct comparisons of only those 19 FHN vs. 12 FHP participants who were pretreated with placebo were not reported, but the figures depicting these subgroups indicate only marginally higher self-administration in FHP subjects, whose maximum BAC was 45 mg% compared to 30 mg% in the FHN group.

Several other studies of human alcohol self-administration could not substantiate various starting hypotheses (Young et al. 2005), (de Wit et al. 2003), (Petrakis et al. 2002), which leads us to infer that one reason for the two negative results concerning FHA main effects on laboratory drinking might be actually related to problems related to the oral route of experimental self-administration. Due to the idiosyncrasies of enteral alcohol absorption, the time-course of resulting aBAC and its maximum level varies up to threefold between subjects (Ramchandani et al. 2006), making it extremely difficult to gain experimental control over self-administration studies. We recently described the method of computer-assisted self-infusion of ethanol (CASE) and discussed why it might help to increase sensitivity of laboratory self-administration studies (Zimmermann et al. 2008). Here we report on a pilot study testing the hypothesis that non-dependent socially drinking FHP offspring of an alcohol-abusing or -dependent parent elect significantly greater voluntary brain exposure to alcohol than FHN controls when using the CASE setup instead of oral self-administration.

Methods

Subjects

All subjects were recruited from participants of the Mannheim Study of Risk Children (MARC), a longitudinal survey investigating mental development in a birth cohort of initially 384 firstborn children of the Rhine-Neckar region of Germany (Laucht et al. 2000). For the family history positive (FHP) group, the main inclusion criterion was having a biological parent with a history of alcohol abuse or -dependence. Lifetime diagnoses according to DSM-IV were determined using the substance abuse module of the Composite International Diagnostic Interview (Wittchen and Semler 1990), which had been performed with both parents at the children's age of 15 years. Additional cases of alcohol use disorders (AUDs) in biological parents not living with the family at the 15-year-assessment were identified by direct and indirect Structured Clinical Interviews for DSM-IV Disorders with the parents (Wittchen et al. 1997) conducted during a visit to the household of the family at the 3-month- to the 11-year-assessment. In case of absent fathers, the evaluation of paternal AUD relied on maternal information.

Other inclusion criteria were: at least one preceding episode of drunkenness with features of nausea, severe functional impairment, or a hangover; social drinking (i.e., drinking at least once a week throughout the preceding 2 months); being able to abstain from tobacco smoking for four hours without developing nicotine withdrawal; agreeing to abstain from any illegal drugs starting three weeks before the first experiment; agreeing to abstain from alcohol for two days before each experiment; effective contraception in women; and a body mass index (BMI) between 20 and 27 kg/m^2. Exclusion criteria were: any physical or mental disorder requiring current medical treatment or psychotherapy; current or prior alcohol or substance dependence; premenstrual dysphoric disorder; teetotalers; a history of epileptic seizures, liver or pancreatic disorders; known intolerance for ethanol; known pregnancy, breast-feeding, or positive urine pregnancy testing on any of the test days; a positive urine screen for illegal drugs; and any prior alcohol intake on the test day or on the day before.

In order to recruit 15 FHP subjects for the CASE study, 29 of the FHP MARC participants fulfilling the above criteria were invited to participate. Based on the prior assessments, their drinking histories and developmental psychiatric diagnoses, if any, were known and were used to select a same-size control group of FHN MARC participants which did not significantly differ in these measures. In the FHN group, both parents had never suffered from an AUD; otherwise, all the inclusion and exclusion criteria applied. After mailing an invitation letter, all potential participants for the current study were called and, if they were interested, a telephone screening interview was performed in order to pre-check inclusion and exclusion criteria. During that interview, subjects were informed about the experimental procedures. An overview of the recruitment process and numbers of evaluated participants is given in Table 1.

Experimental procedures

The methods of CASE were the same as described recently (Zimmermann et al. 2008). The general idea of the present protocol is that no work or payment is required to obtain alcohol;

therefore we call this application of CASE the “Freibier” paradigm, which is the German expression for “free beers”.

All subjects participated in 2 experimental sessions separated by at least one week. On the first day, they reported to the laboratory at 1300h. Written informed consent was obtained after full explanation of all study procedures. A medical and psychiatric history was obtained to confirm inclusion and exclusion criteria. A lifetime history of alcohol and substance use disorders was ruled out by asking the respective questions of the Composite Diagnostic Interview (CIDI) (Wittchen and Semler 1990) substance abuse section. Subjects completed a time-line follow-back interview (Sobell et al. 1996) to specify the number of drinks consumed on each day during the preceding 45 days. A urine sample was obtained to screen for cannabinoids, cocaine, amphetamines, opiates and benzodiazepines, and to perform a pregnancy test in women. All results were negative in all instances. Next, an 18G i.v. line was established in the antecubital fossa of the nondominant arm, followed by a 20-min break to provide a chance to relax and get familiar with the laboratory environment. At 1450 h the subjects were shown how to request a “drink” by pressing a button connected to the CASE computer, and how the CASE software would lead them through the experiment by displaying messages on a computer screen. Subjects were instructed to make use of the infusion in order to produce pleasant alcohol effects like they usually would when drinking at a week-end party where alcohol was available at no cost, but to avoid untoward alcohol effects.

At 1455h the experiment started with a priming period during which subjects were instructed to use the “drink” button four times in a row, prompted by the CASE software. Each request was followed by a linear increase of aBAC, from the value existing at the moment the drink button was pressed, by 7.5 mg% in 2.5 minutes, resulting in a priming alcohol exposure of 30 mg% after 10 minutes. For the next 15 minutes, no “drinks” could be requested. During this waiting period, aBAC fell by a linear descending limb slope (DLS) of −1 mg%/min, resulting in an aBAC of 15 mg% at 25 minutes in all participants, at which time the voluntary self-administration period was started by reactivating the “drink” button. Subjects were informed that during the next two hours they were free to request more alcohol, or to refrain from doing so, in order to achieve their preferred level of alcohol effect when drinking at a week-end party. Subjects completed the biphasic alcohol effects scale (BAES) (Martin et al. 1993) as translated by the authors at baseline and after 15 and 75 minutes. At 2:25 h, the experiment was terminated, the i.v. line was removed and subjects were offered a full meal. Subjects were free to leave the lab as soon as BAC had fallen to 20 mg%, or to take a taxi cab or be collected by a friend at a BAC of 45 mg%, provided they were not visibly impaired by alcohol. Before leaving, they were paid 60.

Subjects were rescheduled for the second session at the earliest possible date in the time frame between one week and one month after the first one. On the second day, a subject arrived at the lab at 1400 h. A brief history regarding the time since the last experiment was obtained, including questions for major life events and for side effects after the last experiment, when their last drinking occasion was, and how many drinks s/he had at that day. All experimental procedures were the same as on the first day. The experimenter was blind to the risk status of subjects until after the second experiment was finished. Before

leaving the lab, subjects were asked about alcohol problems in all their first- and second degree biological relatives in order to double-check their risk status. Thereafter they were paid 60. One month after the last experiment, a questionnaire concerning overall adverse effects was mailed to all participants. It included a time-line follow-back diary of daily alcohol intake throughout the four weeks after the last experiment.

Methods and equipment for ethanol infusion

The infusion solutions were prepared by mixing standard Ringer's solution with 95% ethanol (Alkohol Konzentrat 95% Braun, Melsungen, Germany) to give a final concentration of 6.0% (v/v). The infusion was warmed to body temperature and delivered by a dual infusion pump (Gemini PC2-TX, Cardinal Health, Dublin, OH). The CASE software controlled the pump via its RS 232 interface. Prior to an experiment, the subject's age, height, weight and gender were entered into the CASE software which transformed those measurements into the parameters of a physiologically-based pharmacokinetic (PBPK) model, thus tailored to the individual (Ramchandani et al. 1999), (Plawecki et al. 2004), (Han et al. 2006). Whenever the subject pressed the button, the MatLab Simulink® software solved the PBPK model equations to calculate the individualized infusion rate profile necessary to linearly increase BAC by 7.5 mg% within 2.5 minutes, and CASE software controlled the pump to deliver this infusion profile. After these 2.5 minutes the "drink" button was reactivated and the software controlled the pump in order to produce a steady decline of aBAC by a DLS of −1 mg%/min. This decline continued until either the subject ordered another "drink", or the infusion rate reached the keep-line-open rate (4 ml/h), or the experiment was over. An output of the simulated instantaneous aBAC values throughout the experiment was displayed to the technician, but not to the subject. Once a second in the background, the CASE software anticipated how high the next peak aBAC would be if the subject were to request a "drink" at that moment. If the anticipated peak was more than the preset safety limit of 120 mg%, the CASE software would display a message announcing to the subject that "the bar is temporarily closed", without providing an explanation until a new request was safe to administer. When a new drink would not cause aBAC to exceed the safety limit, the "drink" button was reactivated, and a message informed the subjects that they could resume requesting more alcohol. The delay required a maximum time interval of 7.5 minutes, since by that time aBAC decreased by 7.5 mg%, i.e., the increment following a new request.

Measurements of aBAC were obtained at least once every 20 minutes from breath alcohol samples using an Alcotest 7410 med breathalyzer (Draeger Sicherheitstechnik, Lübeck, Germany) applying the factor 210 to convert breath alcohol (mg/l air) to whole blood alcohol concentration (mg%).

The authors offer to provide all necessary software, except for MatLab® and Sinmulink®, for any new paradigm, and CASE equipment specifications to those colleagues who are interested in using the technology and who agree to keep technical details confidential. European investigators should contact Dr. Zimmermann at ulrich.zimmermann@uniklinikum-dresden.de; American investigators should contact Dr. O'Connor at oconnor1@iupui.edu.

Outcome measures

Outcome measures for self-infusion behavior were (i) the mean aBAC, defined as the arithmetic mean of all CASE-estimated aBAC values throughout the self-administration period; (ii) the maximum aBAC, defined as the maximum of all aBAC readings throughout the self-administration period and (iii) the number of requests made by the subject to obtain “drinks” throughout the experiment.

This study protocol complied with the Declaration of Helsinki and was approved by the University of Heidelberg ethical committee.

Results

Subject’s characteristics and drinking habits are given in Table 2. Affiliation with the FHP group was defined by the father (n=8) or mother (n=2) having a history of alcohol dependence, or by the father having a history of alcohol abuse (n=2). The number of second-degree relatives with an alcohol problem was 2 in one FHP, 1 in four FHP, and zero in all other participants. All subjects denied having ever used illegal drugs other than cannabinoids. Urine drug screens as well as pregnancy tests were negative in all instances. Psychiatric diagnoses according to ICD-10 (World Health Organization 1991), which had occurred earlier in life but were now in full remission were hyperkinetic disorders (F90, in 2 FHN and 2 FHP participants), conduct disorders (F91, in 3 FHN), emotional disorders with onset specific to childhood/ adjustment disorders (F93/ F43, 3 FHN and 1 FHP), and tic disorders (F95 in one FHN participant). DSM diagnoses could not be made with the diagnostic instruments previously used in this longitudinal survey.

All subjects except one FHN female made use of the opportunity to self-infuse alcohol, reaching considerable alcohol exposures. During first day, the safety limit (120mg%) was reached between 2 and 9 times in 7 out of the 22 sessions. Five of these sessions had tested FHP subjects. During the second day, the safety limit was reached once in 2 of the sessions testing FHP subjects, and never in the FHN participants. No adverse effects occurred during the experiments. Specifically, none of the subjects complained about nausea or vomited, and no experiment needed to be terminated prematurely. When arriving for the second session, all subjects reported that no side effects had occurred on the evening or the day after the first experiment, and all subjects specifically denied headache, nausea, excessive tiredness and hangovers following the first session. Fourteen subjects provided data of a second TLFB after study participation. In those, the mean number of drinks per month declined from 38.8 ± 28.6 before to 27.6 ± 22.8 after study participation (n.s.), while the mean number of drinks per drinking day declined from 3.9 ± 2.4 to 3.2 ± 1.6.

The mean and maximum aBAC and number of alcohol requests (NOAR) during the first and second test day in FHN and FHP groups are depicted in Figure 1a–c. T-tests comparing the outcome measures between risk groups revealed no significant differences during the respective first sessions. On the second test day, however, all outcome measures scored significantly higher in the FHP group ($t(20)= 2.34, 2.75$, and 2.46 for mean, maximum and NOAR; $p<0.05$, respectively).

All three measures were significantly interrelated between sessions (Pearson's r= 0.63, 0.70, and 0.71 for mean, maximum and NOAR, p<0.005, respectively, see Figure 2).

The biphasic alcohol effects scale (BAES) and its stimulant and sedative subscale scores did not change significantly between baseline and the end of the priming interval (i.e., at time 15 minutes, when aBAC was 25 mg%). The change scores of the BAES scale and both its sub-scales, calculated by subtracting the baseline score from that at time 15 minutes, were not different between risk groups. There was, however, a negative correlation between the BAES change score and all three outcome measures, which occurred during the first but not during the second session (Spearman's r= −0.64, −0.61, and −0.71 for mean, maximum and NOAR of 1st session; p<0.005, respectively). This correlation during the first day was entirely due to the inverse relation between the outcome measures and the BAES change score in the FHN group (r= −0.67, −0.65, and −0.82 for mean, maximum and NOAR; p<0.05, respectively), while no significant associations were found in the FHP group.

The mean and maximum aBAC during the second session correlated with some of the variables describing recent drinking history, such as total number of drinks during the last 45 days (Spearman's r= 0.45 and 0.44 for mean and maximum aBAC, p<0.05, respectively), bingeing days (r= 0.44, p< 0.05 for mean and r= 0.39, p= 0.072 for maximum aBAC), and the maximum number of drinks per occasion (r= 0.48 and r= 0.50 for mean and maximum aBAC, p< 0.05, respectively). Some correlations with drinking parameters were also found for data gathered during the first session. The maximum aBAC and the NOAR during the first session were positively related to the AUDIT score (r= 0.44 and r= 0.43, p< 0.05, respectively) and to the maximum number of drinks per occasion (r= 0.43 and r= 0.46, p< 0.05, respectively).

Discussion

The principal finding in this pilot study was that FHP subjects self-administered alcohol to achieve greater levels of aBAC, compared to FHN controls in the second CASE session. The difference is remarkable because the sample size was relatively small and the definition of FHP status was not particularly strict.

This study confirms our earlier results demonstrating that the CASE/ Freibier paradigm is a practical and safe method to study alcohol self-administration in socially drinking men and women. The absence of side-effects and hangovers is remarkable, given that the subjects achieved considerable aBACs. The statistically significant correlation of the outcome measures between both test days demonstrates good test-retest stability, suggesting that alcohol self-infusion behavior is stable over a period of two weeks and can be reliably measured using the CASE/ Freibier paradigm. Due to the relatively high safety limit of 120 mg%, the overall frequency of interruptions of the experiment due to aBAC approaching this limit appears low. This is especially true for the second session, ensuring that the results were not biased by a ceiling effect.

We substantiated our starting hypothesis by demonstrating that sons and daughters of a parent with an alcohol use disorder induced greater self-exposure to alcohol, compared

to family history negative controls. This difference was statistically significant on the second, but not on the first of two test days separated by a mean interval of near two weeks. That CASE was not sensitive enough to detect the risk group difference on the first day is compatible with our earlier results suggesting that one practice session is required before subjects are sufficiently confident to make unconstrained use of i.v. alcohol self-infusion. This interpretation is further supported by the negative correlation between the change of BAES scores during the priming period and aBAC during the subsequent self-administration, which occurred during the first but not the second session in the FHN subjects. That high BAES scores are associated with little self-administration suggests that during the first test, the FHN participants might have been particularly concerned about feeling the alcohol effects, which might have limited their self-infusion behavior. No indication of such apprehension could be seen during their second session, which is compatible with the notion that they felt more confident with the CASE/ Freibier setup when using it a second time. No relation of BAES during priming with subsequent alcohol exposure measures was noted in FHP subjects during either session, suggesting that their infusion behavior was not compromised by feeling an alcohol effect at the beginning of the experiment.

Two prior studies are inconsistent with our results, since they did not indicate increased oral self-administration in offspring of alcoholics (de Wit and McCracken 1990), (Krishnan-Sarin et al. 2007). De Wit and McCracken's study resembles ours with respect to the sample population of social drinkers, sample size, and the fact that there was more than one session. Methodological differences were that the subjects did not know whether they were receiving alcohol or any of a number of other drugs, and that they were not specifically encouraged to induce intoxication. Krishnan-Sarin et al. investigated a somewhat larger sample in their placebo group, but employed a different population compared to ours, i.e. non treatment-seeking alcoholics. They used only one session, and also did not specifically instruct subjects as to which alcohol effects they were to induce. They demonstrated a trend for more self-administration in the FHP compared to FHN participants. If our experience with CASE studies suggesting higher sensitivity during an identical second session also applies to oral self-administration, the small difference between FHA groups observed by Krishnan-Sarin et al. might possibly have developed into a significant difference, had the experiment been repeated a second time. Another possible reason for the lack of a FHA effect is that Krishnan-Sarin et al did not exclude the possibility that some of the FHN participants might still bear some genetic risk conveyed by 2nd degree alcoholic relatives.

One notable difference compared to our study is that the peak BAC was only half of that observed by us, although all participants were alcohol-dependent active drinkers as opposed to non-dependent social drinkers in our sample. Some putative reasons and their theoretical background were discussed earlier (Zimmermann et al. 2008) and convince us that the CASE/Freibier setup yields a more sensitive tool to detect factors modulating alcohol self-administration compared to oral self-administration. CASE/Freibier studies are also characterized by (i) a closer time contingency between the behavior (alcohol request) and its consequence (increase in brain alcohol exposure), (ii) achievement of identical increments in brain alcohol exposure per request in every subject, (iii) removing the variation caused by the influence of gustatory or olfactory cues or individual preferences

for specific alcoholic beverages, and (iv) eliminating all information about the amount of alcohol already consumed, requiring subjects to base their choices for or against more alcohol exclusively on what subjective alcohol effects they perceive.

Contrary to what would be expected in representative samples of subjects at high risk for developing alcoholism, our groups of FHN and FHP subjects did not differ in AUDIT scores, in parameters describing recent drinking history or smoking, or in the frequency of lifetime psychiatric diagnoses. This balance was achieved by selectively recruiting those FHN participants from the MARC study, who matched the FHP subjects in drinking history and psychiatric diagnoses when they were 15 years old. The FHP subjects' higher alcohol exposure during CASE sessions is therefore not attributable to altered drinking habits, acquired alcohol tolerance, or psychiatric morbidity, but rather appears to be caused by genetically determined factors specifically influencing alcohol intake.

Given the small sample size, we consider the FHA result to be preliminary, but suggest that the CASE method is sensitive enough to pick up subtle differences in human alcohol intake behavior. Being able to detect the hypothesized effect of familial risk in such a small sample improves the probability that CASE, in general, and the Freibier paradigm in particular may prove to be valuable new tools for alcohol research.

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This experiment fully compies with the current laws of the country in which it was performed; i.e., the Federal Republic of Germany.

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The authors have full control of all primary data and agree to allow the journal to review these data, if requested.

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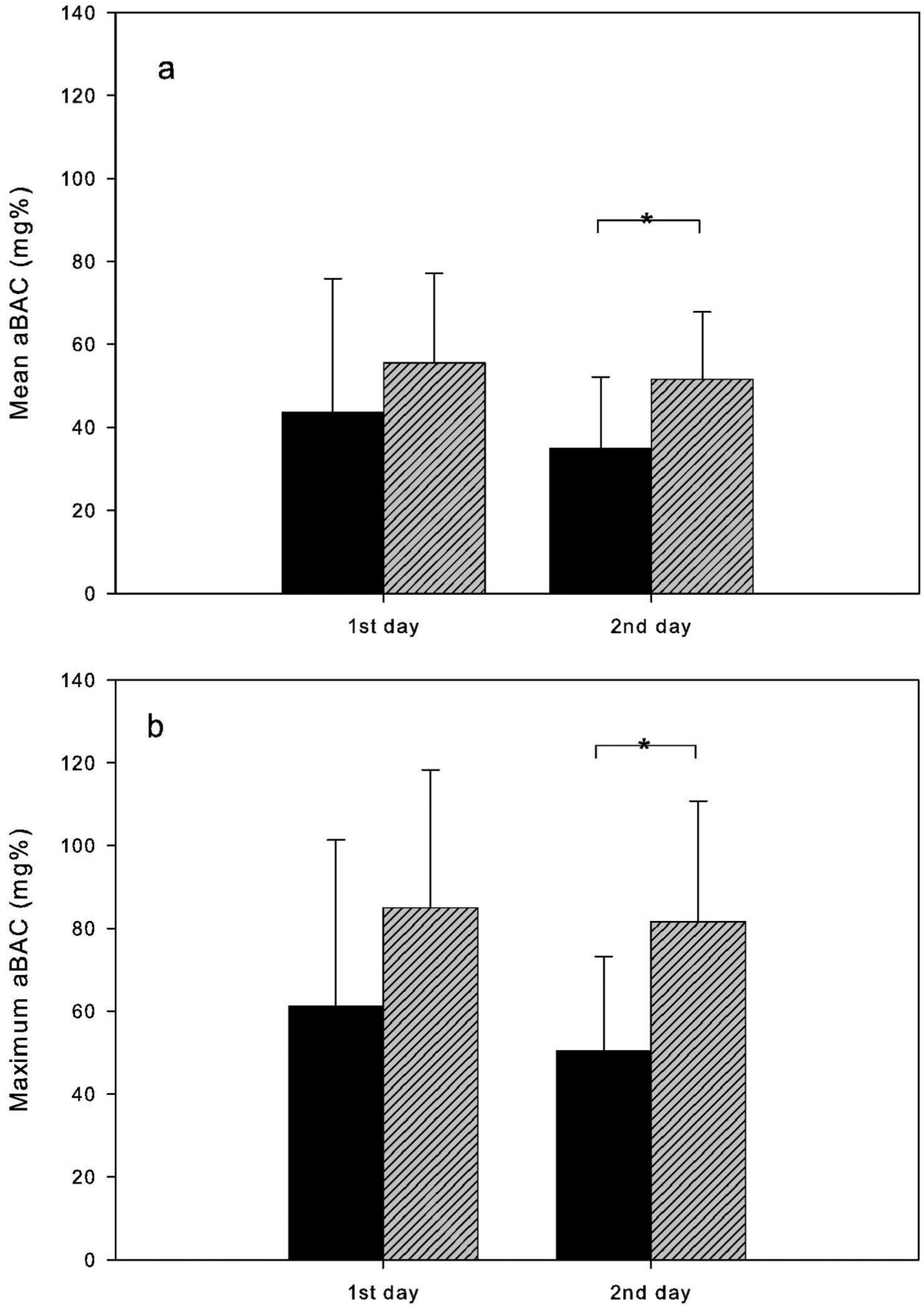

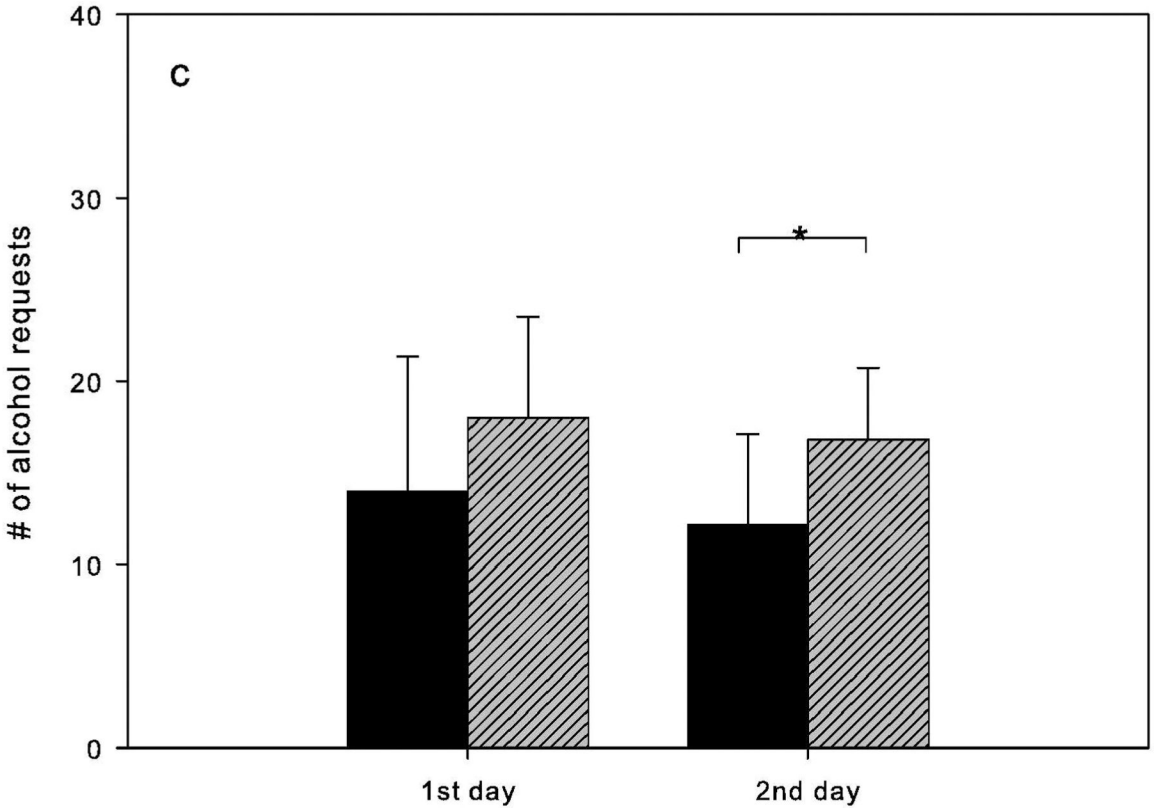

Figure 1a-c:
Mean and maximum arterial blood alcohol concentration and number of alcohol requests throughout the self-administration period. Black bars: FHN controls (n=10); hatched bars: FHP high-risk subjects (n=12).

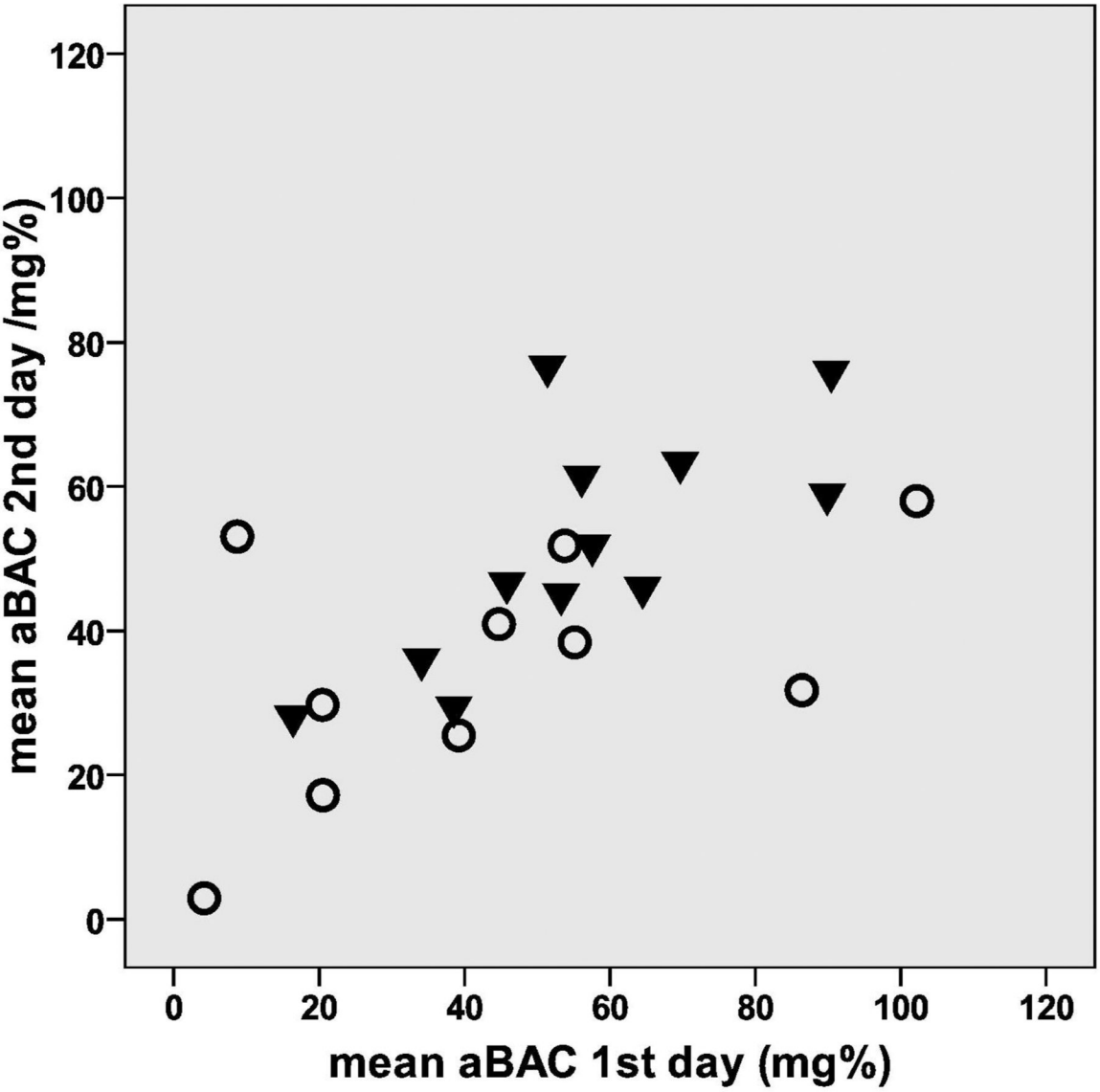

Figure 2:
Scatterplot of mean arterial blood alcohol concentration on the first vs. second test day. Open circles: FHN controls; triangles: FHP high-risk subjects.

Table 1:

Recruitment and reasons for exclusion or drop-out.

	FHN	FHP
selected from MARC study	29	29
declined participation before telephone interview	5	7
excluded during telephone interview due to: pregnancy (1), chronic methylphenidate treatment (1), never drunk before (1), drinking less frequently than once a week (13)	9	7
declined participation after telephone interview (including description of study procedures)	2	3
signed informed consent	13	12
no i.v. line obtained	1	0
withdrew consent after1st session	2	0
evaluated	10	12

MARC: Mannheim Study of Risk Children. FHN and FHP: family history negative and positive for alcohol use disorders.

Table 2:

Participant characteristics (mean ± SD, or numbers)

	FHN (n=10; 5 females)	FHP (n=12; 4 females)
having a 2nd degree relative with an "alcohol problem"	0	5 (42%)
age (year) *	20.9 ± 0.3	20.3 ± 0.5
BMI (kg/m^2)	24.1 ± 4.9	25.1 ± 5.5
days between sessions	13.3 ± 7.1	13.3 ± 6.6
Beck depression inventory	1.3 ± 1.6	1.4 ± 1.8
AUDIT score	5.2 ± 2.6	5.8 ± 2.2
total number of drinks[1]	47.7 ± 31.2	52.3 ± 32.9
total drinking days[1]	12.9 ± 8.9	14.8 ± 9.7
drinks per drinking day[1]	4.0 ± 2.7	4.4 ± 3.7
total bingeing days[1]	4.3 ± 3.5	5.2 ± 4.0
maximum drinks per drinking day[1]	7.7 ± 4.4	11.7 ± 10.2
daily smokers	5 (50%)	5 (42%)
FTND score (mean and SD of daily smokers only)	2.2 ± 1.9	2.0 ± 2.1
ever used cannabinoids[2]	1 (10%)	3 (25%)

[1] Drinking measures are from time-line follow-back interviews covering the last 45 days. Binge drinking refers to consuming 5/4 (male/ female) drinks or more on an occasion.

[2] use of illegal drugs other than cannabinoids was negated by all participants. FTND: Fagerstrom test of nicotine dependence.

* Significant group difference, $t(20)= 3.13$, $p< 0.01$