Recent Drinking History: Association with Family History of Alcoholism and the Acute Response to Alcohol during a 60 mg% Clamp*

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ABSTRACT. *Objective*: Family history of alcoholism (FHA) is associated with increased drinking history, which can be a confounding factor in studies of the influence of FHA on the acute response to alcohol. The objective of this analysis was to investigate the association between recent drinking history (RDH) and FHA in a sample of family history positive (FHP; n = 55, 28 women) and family history negative (FHN; n = 55, 29 women) subjects, and to explore the influence of RDH on the response to alcohol during a 60 mg% clamp. *Method*: RDH was measured using daily diary and timeline followback methods. The total number of drinks in the 4-week (TD28) and 1-week (TD07) intervals prior to the study were determined, as well as the number of drinking days in the same intervals. Dependent measures of brain function were obtained at baseline (B0), immediately after the target BrAC was achieved (B1) and 105 minutes later (B2). The alcohol response was quantified as an initial response (ira = B1-B0) and an adaptive response (ada = B2-B1). The association between RDH and the ira and ada measures was tested using multivariate regression. *Results*: The RDH measures showed a large variance across subjects, with no significant differences between FHP and FHN groups in the study sample. The initial responses for subjective perceptions of "high" and "intoxicated," Alcohol Sensation Scale scores and scores for the grooved pegboard task were significantly negatively associated with TD28. Acute tolerance to perceptions of "high" and "intoxication" was significantly negatively associated with TD28. *Conclusions*: Heavy drinking history is associated with a decreased initial response to alcohol and greater acute tolerance to alcohol, particularly for subjective measures. Although RDH was not associated with FHA in this study, it may be an important determinant of the response to alcohol. (*J. Stud. Alcohol* **63:** 734-744, 2002)

STUDIES INVESTIGATING the influence of family history of alcoholism (FHA) on the acute response to alcohol, both initial and adaptive, could be confounded by the drinking history of subjects. Previous studies have shown an increased drinking history in subjects with a family history of alcoholism. A review by Newlin and Thomson (1990) observed that most studies report higher alcohol consumption in high-risk (FHA positive) families than in control families. Studies in selectively bred rat lines demonstrate that high voluntary alcohol consumption is correlated with an enhanced capacity to develop and retain tolerance to the impairing effects of ethanol (Li et al., 1991).

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An additional consideration is the influence of recent drinking history as a possible independent determinant of the acute response to alcohol. Individuals with heavy drinking histories have been shown to demonstrate increased responses (Holdstock et al., 2000) as well as decreased responses (Hiltunen et al., 1997a,b, 2000; Portans et al., 1989) to acute alcohol challenges. It is not clear, however, if the alteration of the acute response to alcohol is due to chronic tolerance secondary to the drinking itself, or if the alteration in the response to alcohol becomes a determinant of increased drinking by the individual. Another important issue is the definition of "recent" drinking, as suggested by two studies in humans. One showed that acute tolerance to alcohol (in eye-hand coordination) developed only on Day 4 in a group receiving a moderate daily dose of alcohol for 5 days (Bennet et al., 1993). The other showed that peak self-reported intoxication levels were significantly lower for subjects who drank more in the last month (Portans et al., 1989).

Thus, drinking history may be a determinant of the acute response to alcohol and a potential confound of alcohol challenge studies that seek to illuminate associations between genetic influences on the response to alcohol and the risk for alcoholism. The overall objective of this project was to quantify the effect of family history of alcoholism (FHA) on the initial response and acute adaptation to alco-

hol, while the brain's exposure to alcohol was maintained at a constant level by clamping the breath alcohol concentration (BrAC) at 60 mg%. The objectives of this analysis were (1) to determine if there was an association between recent drinking history (RDH) and FHA and (2) to explore the influence of RDH on the acute response to alcohol while the BrAC was clamped at 60 mg%. Our hypothesis was that RDH would be associated with FHA: family history positive (FHP) subjects would have heavier drinking histories compared with family history negative (FHN) subjects, resulting in interactive effects of RDH and FHA on the acute response to alcohol during the 60 mg% clamp.

Method

Study design

This was a two-session, randomized, placebo-controlled study in young-adult, healthy, nondependent drinkers. Each subject underwent two testing sessions, an alcohol session at a target breath alcohol concentration (BrAC) of 60 mg% and a placebo session, on separate days. During each session, subjects undertook a battery of tests, including measures of subjective perceptions, neuropsychological measures of short-term memory and psychomotor performance, saccadic eye-movements and evoked potential tasks. The battery was completed three times during each session: at baseline, immediately following the establishment of the target BrAC (20 minutes after the start of the infusion) and starting precisely 105 minutes later, while the BrAC was maintained at the target level.

Subjects

Participants in the study (N = 110, 57 women) were recruited by local advertisement. They ranged in age from 21 to 38 years (median age = 26 years). Subjects were classified into two groups based on FHA. One group (n = 55, 28 women) was family history positive (FHP; two or more first- or second-degree relatives, other than the mother, affected with alcoholism). The other (control) group (n = 55, 29 women) was family history negative (FHN; no first- or second-degree relatives affected with alcoholism). Subjects were nondependent drinkers, as assessed by administration of the alcohol use section of the Semi-Structured Assessment of the Genetics of Alcohol (SSAGA) instrument (Bucholz et al., 1994). FHA status was assessed by administration of the family-history assessment module of the SSAGA instrument. Exclusion criteria were a clinically significant history of renal, hepatic, cardiovascular, pulmonary or gastrointestinal disease; any DSM-III-R Axis-1 illness, including substance dependence (American Psychiatric Association, 1987); history of seizure or loss of consciousness; mental illness requiring hospitalization; and current use of psychoactive medication. All women were studied in the first 14 days following cessation of menses. Smoking was not an exclusion criterion, although subjects were not allowed to smoke once they arrived at the laboratory for their study session. Subjects provided informed consent for the protocol approved by the Institutional Review Board of Indiana University School of Medicine.

Drinking history

Subjects completed daily diaries of drinking behavior during the 4-week interval that preceded the study sessions. In each diary, the type of drinks and number and time of consumption for each type were recorded by the subject on a daily basis. Subjects mailed the diaries in weekly.

In addition, subjects completed the Timeline Followback (TLFB) computerized questionnaire (Sobell et al., 1988) at the start of each study session. This questionnaire measures drinking history, by asking the subjects to fill in the number of drinks consumed each day of an interval (in this case, 4 weeks). To help subjects recall their drinking histories the calendar on the screen displayed important holidays and events that were entered by the subjects.

The following primary drinking measures were obtained separately from the diaries and from the TLFB: total number of drinks consumed in the 4-week interval (TD28) and number of drinking days (DD28). In addition, to explore the effect of the interval of collection of drinking history measures, the total number of drinks consumed in the 1-week interval (TD07) and number of drinking days (DD07) were also determined. The RDH measures from the diaries and TLFB were compared to determine the reliability between the two methods.

Study session procedures

Preparation for testing. Subjects were admitted to the General Clinical Research Center at Indiana University Hospital at 7:30 AM, having been instructed to abstain from alcohol for at least 24 hours and from food for at least 8 hours. Abstinence was assessed by examination of the diary and BrAC measurement. A negative urine beta-hCG test for pregnancy was obtained from female subjects prior to starting each session. An indwelling catheter was inserted into a vein in the antecubital fossa of each arm, the nondominant arm for the infusion and the dominant arm for blood sampling. At 8:00 AM, subjects ate a 350-calorie breakfast consisting of cereal, milk, toast and juice.

After breakfast, the subject was prepared for testing. This included placement of a 64-lead Electrocap (Electro-Cap International Inc., Eaton, OH) on the subject's head for measurement of evoked potentials (Ramchandani et al., 1999b). The subject was instructed in the use of the Alcosensor-IV BrAC meter (Intoximeters, Inc., St. Louis,

MO) and in the manner in which blood samples for offline assay of blood alcohol concentration (BAC) would be obtained. Following this, subjects underwent a practice trial of the battery of dependent measures of brain function (described below), in order to familiarize them with the devices and procedures and practice the tasks. The baseline block of the battery, B0, was then recorded.

Alcohol administration: *BrAC clamping*. During each session, subjects received, in randomized order, either an infusion of 6% v/v ethanol in Ringer's Lactate or Ringer's Lactate alone. The infusion was begun using a precomputed rate profile. The profile was derived by forcing a physiologically based model of the individual's alcohol pharmacokinetics to follow the desired time-course of BrAC as a function of time: a linear ascending limb reaching 60 ± 5 mg% at 20 minutes, then constant for 155 minutes (Ramchandani et al., 1999a,b). Based on serial BrAC measurements, small intermittent adjustments of the infusion rate were calculated to maintain the clamped BrAC within ±5 mg% of the target concentration. From the infusion rates, the alcohol elimination rate was estimated as the constant infusion rate necessary to maintain the BrAC at steady state (O'Connor et al., 1998; Ramchandani et al., 1999a).

After 155 minutes of clamping, the infusion was stopped, the IV-catheter was removed and the subject was provided with lunch. BrAC was tracked at 20-minute intervals until it fell below 20 mg%, at which time the subject was paid and discharged. The duration of a typical study session was 8 hours.

Dependent measures of brain function. The battery of dependent measures consisted of eight specific tasks and required 45 minutes of testing. In addition to the baseline block (B0), dependent measures were obtained twice during the clamped interval. The first block (B1) began 20 minutes after beginning the infusion (5 minutes after achieving the target BrAC for the alcohol session, or an equivalent amount of time for the placebo session) and the second block (B2) began 105 minutes later. Task order was the same within all three of the data collection blocks. Sampling of BrAC for clamping purposes was permitted only between tasks. Table 1 presents the tasks and a summary of the definitions for the primary variables used in this study. The tasks are described below.

Subjective perceptions. The Biphasic Alcohol Effects Scale (BAES; Martin et al., 1993) and the Alcohol Sensation Scale (SS; Maisto et al., 1980) are pencil and paper assessments of the subject's current perceptions about a variety of sensations that are often associated with alcohol but not specifically attributed to alcohol. In addition, a visual analog scale consisting of two items, "high" and "intoxicated," from the Subjective High Assessment Scale (SHAS; Schuckit, 1984), was used. Item scores were summed into several subscales for the BAES and SS. Stimulation and Sedation subscales were computed for the BAES (Martin et al., 1993). Five subscales were computed for the SS—Anesthetic, Warmth, Impairment, Peripheral Effects and Stimulation—as well as a total SS score (Maisto et al., 1980).

Neuropsychological measures. These included the Grooved Pegboard and Auditory Consonant Trigram tasks. The Grooved Pegboard is a test of motor speed and fine motor coordination, in which subjects retrieve, rotate and insert 25 small metal pegs into 25 slotted holes (Kløve, 1963). The dependent measure is the number of seconds to fill the board with the pegs, with dominant and nondominant hands tested separately. The Auditory Consonant Trigram task (Brown, 1958; Peterson and Peterson, 1959) is a test of short-term working memory. The test requires subjects to retain three nonsense letters while counting backwards from a specified number by 3 for randomized intervals of 0 (no distraction), 18 and 36 seconds. The dependent measures are the number of letter trigrams recalled after 18 and 36 seconds of distraction.

Saccadic eye movement tasks. These tests measure the high-velocity movements of the orbits that bring peripheral visual stimuli onto the fovea. Two tasks were performed. The first was a random-saccade task that measured the subject's ability to follow sudden deflections of a spot in the horizontal plane. Each trial provided a saccade to a random deflection and a semipredictable saccade to the known fixation point beginning at an unpredictable time. The second task was an antisaccade task and measured the subject's ability to inhibit the reflex to follow the visual target and instead to initiate an opposing volitional saccade. Subjects were instructed to look in the opposite direction, at an equal distance from the fixation point, as quickly as possible. Each task had 48 trials and required 4 minutes, including instructions, and was performed without interruption. Specific details of the experimental setup and analysis of the raw data have been published previously (Blekher et al., 1998; Ramchandani et al., 1999b). Dependent measures included the mean saccadic latency and velocity (model parameters) for random, predictable and antisaccades. The percentage of error-free volitional, reflexive (errors), omitted and corrected (reflexive, then volitional) saccades was counted for the antisaccade task.

Event-related potential (*ERP*) *tasks*. These tasks measure the temporal characteristics of neuroelectric brain activity reflected in stimulus-locked averages of electroencephalographic potentials recorded at 32 locations on the scalp. Two tasks were performed. The first, the Inhibition of Conditioned Response (ICR) ERP task, quantified the subject's ability to inhibit a learned response to auditory stimuli (Bauer et al., 1994). Three hundred binaural tones (600 Hz) were presented at precisely 1-second intervals and comprised 90% of the stimuli presented. The subject was instructed to press a button at every occurrence of this frequent tone with as little delay as possible, yielding a

conditioned response to the anticipation of the next stimulus. At pseudorandom intervals, 10% of the tones occurred at a higher frequency (1500 Hz) and the subject was instructed to withhold the response to these rare events. A large P300 component (evident in the rare nontarget ERP) occurred when the response was correctly suppressed, and the smaller N100 component was also well defined in the frequent target ERP.

The second ERP task, the Visual Oddball P3 paradigm (VP3; Porjesz et al., 1996), measured the subject's neuroelectric response to three kinds of visual stimuli. At pseudorandomized intervals (1.4-2.0 sec), 240 visual symbols were presented on a computer monitor placed in front of the subject. Most (75%) of the stimuli constituted the white outline of a square, and the subject was instructed to ignore these nontarget stimuli. A white "+" sign, of equal size and luminosity as the square and comprising 12.5% of all stimuli, was presented as the target, with instructions to push a button for each occurrence, balancing speed and accuracy of the response. The remaining 12.5% of the stimuli consisted of a set of brightly colored, novel patterns, and instructions were given to ignore these rare nontargets.

Specific details of the reduction and analysis of the raw data have been published previously (Ramchandani et al., 1999b). For the ICR task, dependent measures analyzed were the peak amplitude and latency of the P3 component of the rare nontarget and the N1 component of the frequent target ERPs. The number of rare nontargets for which a response was made (errors of commission), and the mean reaction time and standard deviation of the mean reaction time for frequent target responses, was also analyzed. For the VP3 task, dependent measures included the peak amplitude and latency of the N1 component of the frequent nontarget, and of the P3 component of the rare-target and novel nontarget ERPs.

Data analysis

Assessment of initial response and acute adaptation to alcohol. For each dependent measure, an index of the initial response (ira) was computed as the change in the value of the dependent measure from the baseline block (B0) to Block 1 (B1). The index of acute adaptation (ada) was computed as the change in the value of the dependent measure from Block 1 (B1) to Block 2 (B2). Ada was assigned a negative sign if the change represented a recovery of baseline function indicating acute, within-session tolerance and a positive sign if the change represented a progression away from baseline values indicative of acute sensitization. The indices were computed separately for the alcohol and placebo sessions.

Statistical analysis: *FHA and gender differences in RDH measures*. Nonparametric tests were used to evaluate the effect of FHA and gender on the RDH measures as a result of violations of assumptions of parametric tests. The Wilcoxon Rank Sum test was used to compare each RDH measure between FHP and FHN groups and between men and women.

Statistical analysis: *Association of RDH measures with alcohol elimination rate*. Multiple regression analysis was

TABLE 1. Battery of tests employed in the study

Task	Primary measures
Subjective perception scales	
Biphasic Alcohol Effects Scale (BAES)	• Stimulation and Sedation subscales
Alcohol Sensation Scale (SS)	• Total score • Anesthetic, warmth, impairment, and stimulation subscore
Visual Analog Scales	• High item score • Intoxicated item score
Neuropsychological tasks	
Grooved Pegboard	• Time to complete task for dominant hand • Time to complete task for nondominant hand
Auditory Consonant Trigram	• Total number of letters recalled
Saccadic eye movement tasks	
Random saccade task	• Mean latency for random and semipredictable saccades • Velocity for random and semipredictable saccades
Antisaccade task	• % of error-free volitional saccades and reflexive saccades • Mean latency for volitional and reflexive saccades • Velocity for volitional and reflexive saccades
Event-related potential tasks	
ICR (inhibition of conditioned response) task	• P300 latency and peak amplitude for rare nontargets • N100 latency and peak amplitude for frequent target
VP3 (visual P300 component) task	• P300 latency and peak amplitude for rare targets • N100 latency and peak amplitude for frequent nontargets

used to evaluate the effect of TD28 and DD28 on the alcohol elimination rate (AER). FHA, gender and body-weight were used as covariates, to determine if they had a significant effect on the relationship between drinking history and AER.

Statistical analysis: *Association of RDH measures with ira and ada indices*. Multivariate regression was used to test for the existence, magnitude and direction of the association between the primary drinking history measures (TD28 and DD28) and the ira and ada indices. This was done in two steps. (1) For each dependent measure, the index (ira or ada) was predicted by the full set of independent variables (TD28, DD28, gender, TD28 × Gender, DD × Gender). The corresponding index for the placebo session was used as a covariate. (2) Based on the sums of squared errors for each independent variable, a reduced model containing only those variables with significant contributions to the overall sums of squared errors was determined. This reduced model, which always included TD28 as an independent variable (as it was of primary interest), was then exercised to determine the significance level for each independent variable. In addition, the effect of the length of the interval for measurement of drinking history was examined by repeating the above regression analysis but using the 1-week interval measures (TD07, DD07).

The α level for significance was set at 0.05. As two statistical tests were performed for each dependent measure (one for initial response and one for adaptive response), the experiment-wise α level for significance was appropriately adjusted to 0.025. All statistical analyses were performed using SAS (Version 6.0, SAS Institute, Cary, NC).

TABLE 2. Subject demographics

	FHN	FHP
Number of women	29	28
Number of men	26	27
Median (range) age, years	26 (21-35)	27 (21-38)
Mean (SE) weight, kg	76.8 (2.3)	77.7 (2.4)
Mean (SE) height, cm	171 (1)	171 (1)
Number of smokers (M/F)	10 (4/6)	15 (8/7)

Results

Table 2 shows the characteristics of the 110 subjects. Complete drinking history data was obtained from all subjects. Pearson product-moment correlation analysis was used to determine the reliability between the diary and TLFB methods used for collecting drinking-history data. The correlation coefficients for the RDH measures TD28, TD07, DD28 and DD07 were 0.82, 0.74, 0.81 and 0.74, respectively (all p values < .0001), indicating a high degree of concordance between the data collected by the two methods. Figure 1 shows the scatterplots of the TD28 and DD28 measured by the two methods. All subsequent analyses were performed using data collected by the diary method.

Association of recent drinking history with family history of alcoholism and gender. Table 3 displays the summary statistics for the primary RDH measures, TD28 and

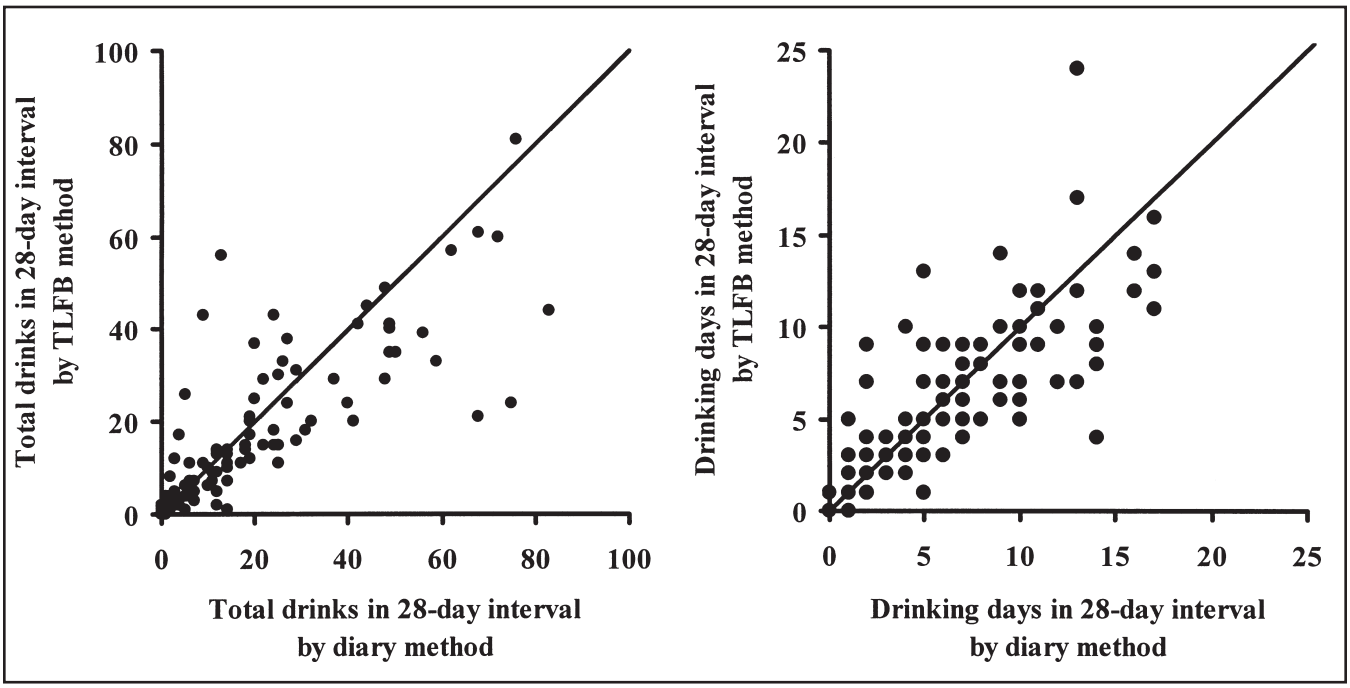

FIGURE 1. Correlation between diary and TLFB methods for assessing recent drinking history (the correlation for total drinks in the 28-day interval by the two methods [left panel] was 0.82, and the correlation for drinking days in the 28-day interval by the two methods [right panel] was 0.81; solid line is the Line of Identity)

TABLE 3. Recent drinking history measures, by family history of alcoholism and by gender

	FHN		FHP	
	Women (n = 29)	Men (n = 26)	Women (n = 28)	Men (n = 27)
Total drinks in 28-day interval				
Mean (SE)	18.0 (4.0)	27.3 (4.7)	13.0 (3.0)	17.6 (3.3)
Median (range)	12.0 (0-83)	18.5 (0-75)	10.0 (0-76)	13.0 (0-50)
Drinking days in 28-day interval				
Mean (SE)	5.9 (0.9)	8.3 (0.9)	4.7 (0.7)	5.6 (0.9)
Median (range)	4.0 (0-17)	8.5 (1-17)	4.0 (0-17)	5.0 (0-17)

DD28, by FHA and gender. There was substantial variability in RDH across all the subjects studied. Statistical analyses indicated no differences in the total drinks consumed over the 28-day interval by FHA or gender. FHN subjects had marginally significant higher drinking days in the 28-day interval (DD28) compared with FHP subjects (FHN vs FHP: Z = -2.006, p = .0448) and men had marginally significant higher drinking days in the same interval compared with women (men vs women: Z = 2.021, p = .0433). As RDH did not show any robust FHA-related differences, the influence of these two independent variables on the dependent measures of acute response to alcohol was studied separately. This article focuses on the association of recent drinking and response to alcohol. Results of the influence of FHA on the acute response to alcohol are published separately (Blekher et al., in press; Morzorati et al., 2002).

Association of recent drinking history with alcohol elimination rates. Regression analysis revealed the lack of a significant relationship between TD28 and the alcohol elimination rate (AER). Figure 2 shows the plot of TD28 versus AER. Inclusion of FHA, gender and/or body-weight into the regression analysis did not modify the result.

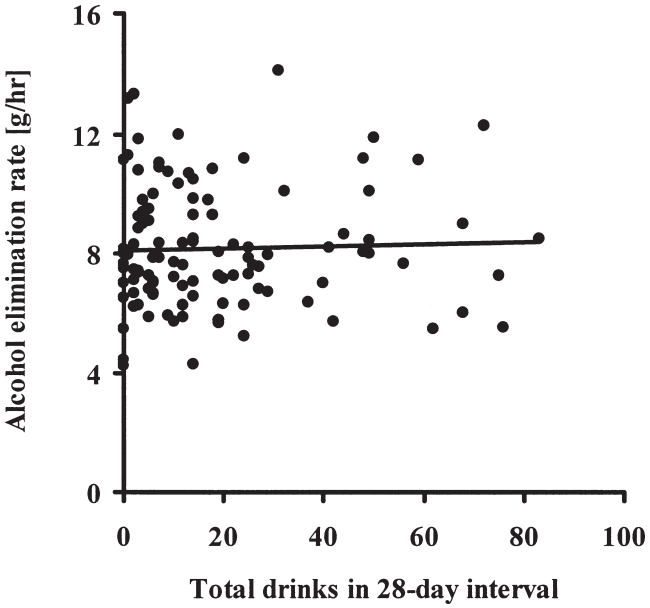

FIGURE 2. Alcohol Elimination Rate (AER) as a function of TD28 (there was no significant relationship between AER and the total drinks consumed in the 28-day interval)

Association of recent drinking history with the initial response to alcohol during clamping. Multiple regression analyses showed that the initial response to alcohol (ira) for the subjective measures were significantly associated with TD28. The initial response for the "high" (F = 28.743, 2/107 df, p = .0001) and "intoxicated" (F = 21.070, 2/107 df, p = .0001) items and the Sedation subscale of the BAES (F = 6.938, 1/108 df, p = .0097) were significantly related to TD28. For the SS, the total score (F = 11.156, 2/107 df, p = .0001), as well as the Anesthetic (F = 9.828, 2/107, p = .0001) and Stimulation (F = 12.545, 2/107 df, p = .0001) subscales, were found to be significantly associated with TD28.

Figure 3 shows scatterplots of four of the subjective measures plotted versus TD28. For all measures, the relationship had a negative slope, indicating that greater recent drinking history is associated with lower initial subjective responses to alcohol at 60 mg%. For all dependent measures of subjective perception, gender was not found to be a significant covariate of the relationship between RDH and the ira measures. The initial response during the placebo session was found to be a significant covariate for all subjective measures that were significantly associated with TD28, however. There was a high variability in the subjective responses across subjects, and the proportion of variance in the measure accounted for by the independent variables evaluated was usually low. All initial response measures that showed a significant association with TD28 also showed significant relationships for TD07 (albeit with less robust p values).

Analyses of the association between TD28 and the measures from the grooved pegboard task showed a significant association (Figure 4). The initial response for the time to complete the task, for both the dominant and nondominant hand, was significantly related to TD28 (dominant hand: F = 8.449, 1/80 df, p = .0047; nondominant hand: F = 6.733, 2/79 df, p = .002). Gender was not a significant covariate and the initial response during the placebo session was a significant covariate only for the nondominant hand score.

The grooved pegboard measures did not show a significant association with the 1-week interval measure, TD07.

The remaining neuropsychological, eye movement and ERP initial response measures did not reveal any consistent significant relationships with TD28 or DD28.

Association of recent drinking history with the adaptive response to alcohol during clamping. Multiple regression analyses of the subjective measures showed that the adaptive response measures (ada) for the "intoxicated" and "high" items were significantly associated with TD28 (intoxicated: $F = 5.722$, 1/108, $p = .0185$; high: $F = 3.920$, 1/108 df, $p = .05$). Neither FHA nor gender was found to be significant as covariates. Figure 5 shows the scatterplots for these measures plotted versus TD28. These plots indicate that greater drinking history is associated with a smaller change in response during the clamp (i.e., a smaller adaptive response, or less acute tolerance, to alcohol clamped at 60 mg%). The ada for the other subjective measures did not show significant associations with TD28 or DD28. Both adaptive response measures that showed a significant association with TD28 also showed significant relationships for TD07 (albeit with less robust p values).

Analyses of the association between TD28 and DD28 and each of the neuropsychological, eye movement and ERP adaptive response measures did not reveal any consistent significant relationships.

Discussion

The primary findings of this analysis were that RDH did not differ between FHP and FHN subjects in our sample, but that RDH was a significant determinant of the subjective and psychomotor response to alcohol during a 60 mg% clamp.

In this study, drinking history was assessed using the daily diary and the TLFB method. The correlation between

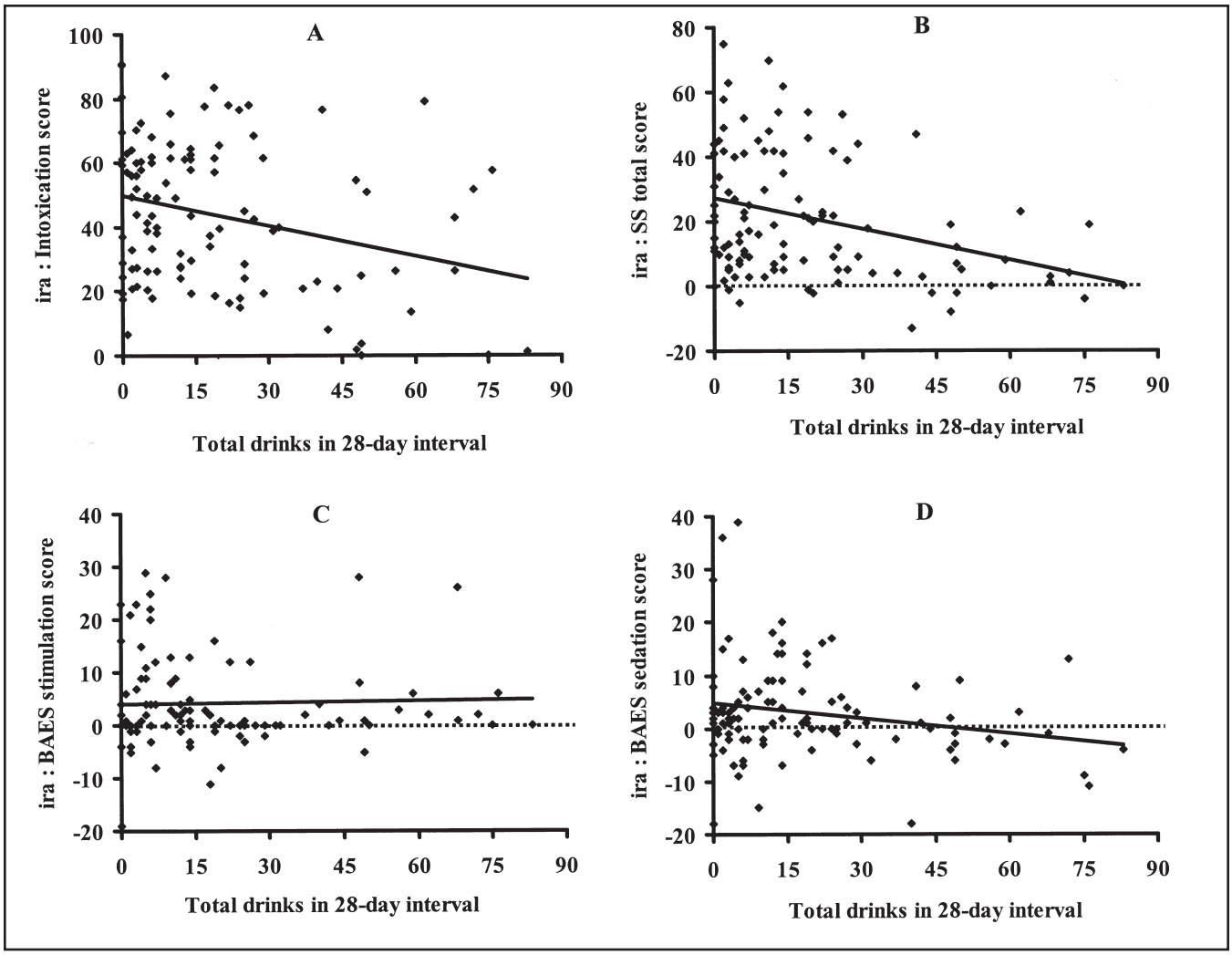

FIGURE 3. Initial response to alcohol (ira) for subjective measures versus TD28 (A = intoxication score, B = SS total score, C = BAES stimulation score, D = BAES sedation score)

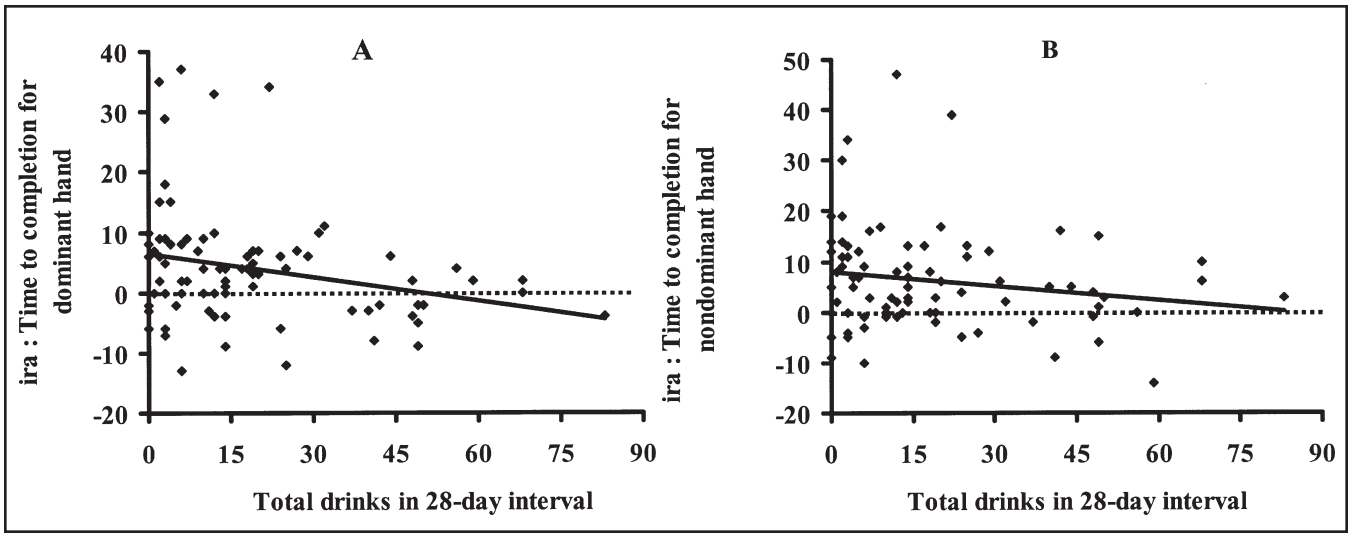

FIGURE 4. Initial response to alcohol (ira) for psychomotor performance measures versus TD28 (A = time to complete grooved pegboard task for dominant hand; B = time to complete grooved pegboard task for nondominant hand)

measures derived from the two methods reveals a high degree of concordance between the methods; this is consistent with other reports in the literature (Cohen and Vinson, 1995; Sobell et al., 1988). The data from the current study, as well as from previously published studies, do lend support to the reliability of the TLFB method for assessing drinking history.

The lack of significant differences in drinking history between FHP and FHN subjects may have been a consequence of excluding subjects with past or current history of alcohol dependence. Our hypothesis was that FHP subjects would show greater drinking histories and, therefore, RDH would be an important consideration and covariate in studies evaluating the influence of FHA on the response to alcohol. That did not happen in this study. As heavy drinking tends to be associated with problems related to alcohol abuse and dependence, subjects with heavier drinking histories may have been excluded from the sample, resulting in subjects with differing FHA having comparable histories of recent drinking when assessed over a 4-week interval prior to testing. There may be FHA-related differences in past or lifetime drinking history or age of onset of drinking (McGue et al., 2001), but these were not assessed in this study.

For several measures of subjective perceptions, there were negative associations between RDH and the initial response and positive associations between RDH and the adaptive response to alcohol. The initial subjective perceptions of both "high" and "intoxication," as well as the SS total score, decreased with an increase in RDH, and the adaptive response on these measures during the clamp also decreased with an increase in RDH. This indicates that the

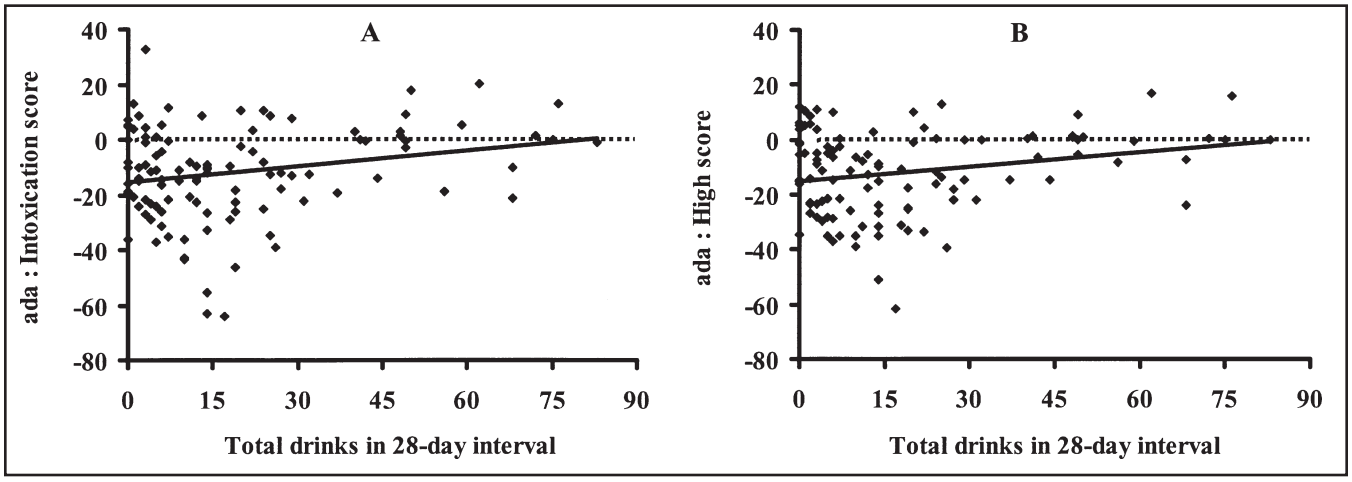

FIGURE 5. Adaptive response to alcohol (ada) for subjective measures versus TD28 (A = intoxicated score, B = high score)

heavier drinkers showed a lower initial subjective response to alcohol and also a lower magnitude of acute tolerance to alcohol while clamped at 60 mg%. There was also a negative association between RDH and the initial response on the grooved pegboard task. The increase in time to complete the task, which is a measure of fine-motor impairment, was lessened with an increase in RDH, indicating that heavier drinkers showed lower impairment in fine motor coordination following alcohol.

The lower initial response to alcohol in the heavier drinkers may be a consequence of chronic tolerance to the effects of alcohol, which would be expected to have developed in this group (Kalant, 1998). The lower magnitude of acute tolerance development may be secondary to a lower initial response to these subjective perceptions. This was suggested by Jellinek, who proposed that chronic heavy drinkers may show less acute tolerance (his so-called "short-term accommodation") than moderate drinkers, possibly due to a decrease in the initial effects of alcohol, related to chronic tolerance (Jellinek, 1960, p.148).

There are, however, few studies that have looked directly at the relationship between drinking history and the acute initial response and acute tolerance to the effects of alcohol. One study, conducted in both moderate and heavy drinkers, reported that acute tolerance to alcohol occurred independent of drinking history and chronic tolerance (Moskowitz et al., 1979). In another study, Portans et al. (1989) examined the development of acute tolerance to the subjective effects of alcohol, and found that peak self-reported perceptions of intoxication were significantly lower and occurred earlier for heavier drinkers. The authors suggested that this might be due to chronic tolerance to alcohol, which would be expected to have developed in the heavier drinkers. Studies by Hiltunen (1997a,b) demonstrated tolerance development to the effects of alcohol on subjective perceptions as well as cognitive performance, which appeared to be modulated by drinking history. In his studies, light and heavy drinkers were given two doses of alcohol; the light drinkers showed tolerance at both doses, whereas the heavier drinkers showed tolerance only at the high dose of alcohol administered. On the other hand, a study by Holdstock et al. (2000) has shown that moderate to heavy drinkers show greater stimulant-like and lower sedative-like effects than light social drinkers, following oral alcohol administration. The authors speculate that this pattern of response in heavy drinkers might increase their risk of developing alcohol-use disorders.

With regard to neuropsychological responses to alcohol, studies dating as far back as the 1940s (Goldberg, 1943) have shown that the magnitude of the response to alcohol on several objective tests, including tests of motor coordination, was inversely related to the amount of alcohol consumed by the subjects. More recent studies have shown differences in alcohol-induced psychomotor impairment between novice and experienced drinkers (Fillmore and Vogel-Sprott, 1995, 1996). In the present study, response to alcohol on measures of motor coordination did show an influence of drinking history, although the trigram test of memory did not show drinking history influences. Recent drinking history was also not significantly associated with the response to alcohol on other physiological measures (e.g., eye-movements and ERPs). There have been no studies evaluating the relationship between drinking history and the eye-movement or ERP response to alcohol. The lack of association for these measures indicates that they may not demonstrate the development of chronic tolerance following regular (or heavy) drinking, and therefore were not influenced by the range of drinking history observed in this study.

In this study, recent drinking history was assessed for a period of 4 weeks prior to the study. Studies that have explored the influence of drinking history have used a wide variety of time periods and methods to assess drinking history. Measures of drinking history also vary significantly between studies, ranging from measures of quantity, frequency, variability and combinations thereof. The results of this study indicate that drinking history assessed as the total drinks consumed over a 4-week interval is an adequate direct measure for examining the influence of RDH on the response to alcohol. A smaller interval may be less robust as it would be prone to larger inter- and intra-individual variability in drinking patterns. Measures of the frequency of drinking were also obtained in this study, but were not found to be associated with the initial or adaptive responses to alcohol.

There are several limitations to the interpretation of the findings of this study. First, the study did not account for the smoking history of the subjects, which may have an effect on the response to alcohol, as indicated by Madden et al. (1995, 1997). The study was open to smokers and resulted in the inclusion of 25 smokers, from a total of 110 subjects. Of these 25, 15 were FHP (8 men) and 10 were FHN (6 women). We believe that this number was too small, especially when categorized by gender and/or FHA, to conduct any meaningful analyses. In addition, the range of smoking history was fairly substantial across the smokers (anywhere from 1 to 800 cigarettes in the 28-day interval prior to the study).

Other limitations result from the use of the clamping method of administration of alcohol via the intravenous route. The intravenous route, although not employed by users of alcohol, provides exquisite control of the breath and, therefore, of the brain's exposure to alcohol. This minimizes the substantial (three- to fourfold) pharmacokinetic variability in alcohol concentrations that would have resulted following oral administration and would have confounded the interpretation of differences in response due to drinking history, family history, gender or any other deter-

minant. The use of the intravenous route of administration, however, may result in responses and findings that cannot be extrapolated to the oral route of administration, especially with regard to expectancies associated with alcohol and the influence of these expectancies on the response to alcohol. All the subjects in this study were nondependent drinkers who had never received intravenous alcohol but may have had alcohol-related expectancies, as implied by initial responses on their placebo sessions. The influence of route of administration on the response to alcohol, and the influence of such factors as drinking history and alcohol-related expectancies have not been previously studied, and are the subjects of current and future investigations.

In summary, we conclude that recent drinking history is associated with the initial response to alcohol on subjective and psychomotor measures, and associated with acute tolerance to alcohol for subjective measures. Recent drinking history was not associated with FHA in this study, but was found to be an independent determinant of the response to alcohol during a 60 mg% clamp.

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