The level of response to alcohol in daughters of alcoholics and controls

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Abstract

Background: The low level of response (LR) to alcohol is a genetically influenced characteristic related to the development of alcohol use disorders (AUDs). This phenotype is found in men with a family history (FH) of alcoholism, predicts future AUDs, and has heritabilities as high as 60%. However, despite evidence of genetic influences for AUDs in both sexes, the majority of studies evaluating differences in LR across high- and low-risk groups have been conducted on males, and it is unclear how generalizable these results are to women.
Methods: Twenty-five women who are family history positive (FHP) for alcohol dependence were matched with 25 women with no FH of alcoholism (FHN) on factors that may impact LR. Using an alcohol challenge paradigm, data on the reaction to a moderate dose of alcohol were gathered over a period of 3.5 h. Assessments included breath alcohol concentrations (BrACs), the Subjective High Assessment Scale (SHAS), as well as body sway or static ataxia.
Results: Family history positives reported lower subjective intoxication than FHNs. In addition, when body sway scores were corrected for skewness, FHPs had significantly lower scores on alcohol-related changes in lateral sway. These differences remained after considering the effects of drinking history and BrAC values.
Conclusions: This study evaluated the LR to alcohol in the largest sample of alcohol challenges in matched FHP and FHN women to date. Overall, the findings are consistent with most data from earlier investigations of smaller sized samples of FHP women. The results suggest that, similar to sons of alcoholics, a low LR to alcohol might also be characteristic of daughters of alcoholics.
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1. Introduction

Alcoholism is a complex, genetically influenced syndrome where multiple, heterogeneous genetic factors combine to account for approximately 60% of the vulnerability for an alcohol use disorder (AUD) (Enoch and Goldman, 2001; McGue, 1999; Schuckit, 2002; Zucker et al., 2000). These include the influence of alcohol-metabolizing enzymes, behavioral and neuronal disinhibition, a predisposition to other psychiatric disorders, such as manic-depressive disease and schizophrenia, as well as the low level of response (LR) to alcohol.

There are multiple lines of evidence supporting the importance of the LR to alcohol as a genetically influenced phenotype related to the alcoholism risk. First, most studies using alcohol challenges in children of alcoholics and controls reported that a low LR to alcohol was seen in individuals at higher risk for AUDs (Erblich and Earleywine, 1999; Pollock, 1992; Schuckit and Gold, 1988; Schuckit and Smith, 2000; Schuckit et al., 1996, 2000). Results from an investigation using rapidly infused i.v. ethanol also indicated differences between family history positives (FHPs) and family history negatives (FHNs), but noted a higher response for FHPs at rapidly rising blood alcohol concentrations (BACs) (Ramchandani et al., 2002). A similar finding was obtained by observation of very rapid drinking results in an oral alcohol

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challenge protocol, although at later time points with falling BACs, the FHP subjects tended to demonstrate lower LRs than the FHNs (Schuckit et al., 2002). Second, supporting the probable reliability and validity of a low LR are data from all four relevant longitudinal studies showing that this phenotype predicts future heavier drinking and alcohol-related problems, with data generated in the United States, Australia, and Denmark (Heath et al., 1999; Rodriguez et al., 1993; Schuckit and Smith, 1996, 2000; Volavka et al., 1996). When used as part of an alcohol challenge protocol, the LR measures appear reliable as the correlation between two different doses of alcohol over several weeks is as high at .70, with a test-retest correlation at the same dose as high as .60 (Schuckit and Gold, 1988; Schuckit, 1985; Viken et al., 2003). Third, a low LR to alcohol has been documented in several other groups at high risk for alcohol-related problems using a retrospective self-report measure of the usual number of drinks required for various effects, including studies of Native Americans and Koreans. (Ehlers et al., 1999; Garcia-Andrade et al., 1997; Luczak et al., 2002; Wall et al., 1992, 1999). At the same time, one group at relatively low future risk for alcoholism, Jewish subjects, demonstrated a significantly higher intensity of response to alcohol in an alcohol challenge (Monteiro et al., 1991). Data from most relevant animal studies also indicate a relationship between a lower intensity of response to alcohol and the consumption of higher doses of alcohol in experimental situations (Baldwin et al., 1991; Barr et al., 2004; Crabbe et al., 1996; Tecott and Heberlein, 1998). Further support for the importance of LR as a risk factor for heavier drinking, alcohol-related problems, and AUDs comes from the demonstration in both animal models and human studies of a heritability for LR estimated to be between .40 and .60. These include data from twin studies, the demonstration of significantly higher correlations for LR among first-degree relatives than unrelated pairs of subjects, as well as animal work (Heath et al., 1999; Heath and Martin, 1992; Neale and Martin, 1989; Schuckit et al., 2001, in press; Viken et al., 2003). Finally, regarding LR, low responses to alcohol appear to relate to cross-sectional risk factors, as well as predict future alcohol-related problems. These are found even among light drinkers at a relatively early age, are observed even when higher and lower risk groups have similar blood alcohol levels on alcohol challenges, and do not appear to be directly related to peripheral alcohol-metabolizing enzymes (Heath et al., 1999; Schuckit, 2002; Schuckit and Smith, 1996).

While multiple lines of evidence support the importance of the LR to alcohol as a risk factor for future heavier drinking and alcohol-related problems, not all studies agree (e.g., De Wit and McCracken, 1990; Lipscomb et al., 1979; McCaul et al., 1991; Nagoshi and Wilson, 1987; Newlin and Thomson, 1991; Vogel-Sprott and Chipperfield, 1987). Some level of disagreement regarding such a complex trait is not surprising. Both genetic and environmental factors contribute to the LR risk (Schuckit, 2002; Heath et al., 1999), and therefore, research protocols investigating LR must take all possible steps to control for the effects of recent drinking, age, other substance use, including smoking, the percent body water, and any other factors that might impact on either the metabolism of alcohol or the intensity of effects on the brain. In addition, the LR to alcohol may differ with different doses of the drug, and may be influenced by the rapidity of rise of BACs (Ramchandani et al., 2002; Schuckit and Gold, 1988; Schuckit et al., 2002). Furthermore, the LR to alcohol is only one of several genetically influenced vulnerabilities for AUDs, with the result that any FHP group is likely to be heterogeneous regarding risk factors, which, when combined with the modest level of heritability for any trait, means that only a minority of children of alcoholics are likely to carry any one genetically influenced characteristic. Thus, studies of small samples of subjects (e.g., less than at least 15 in high-risk groups and 15 in low-risk groups) might not have sufficient statistical power to appropriately test the importance of LR as a risk factor. These characteristics are likely to have contributed to the diversity of findings across even well designed investigations, as the results are likely to reflect aspects of how samples were selected and the testing protocols executed. Nonetheless, the findings regarding the low LR to alcohol as a vulnerability across several samples of children of alcoholics, the consistent results regarding additional AUD risk factors, such as Native American and Korean backgrounds, and the parallels between animal and human work, along with the ability of a low LR to predict future problems, all support the potential importance of this characteristic regarding the AUD risk.

The majority of investigations of the LR to alcohol in different groups have been carried out in males, although a few have examined this characteristic in female participants. The adequate evaluation of women for a genetically influenced characteristic is important because the heritability for AUDs in females is similar to that for men, but the rate of expression of AUDs is lower, possibly reflecting a higher rate of abstainers and related cultural factors for women (Heath, 1995; Heath et al., 1997; Prescott et al., 1999). A study of alcohol challenges in 18–25-year-old college students and their relatives included 92 FHP women and 67 FHP men, reporting that there were no consistent differences between sons and daughters of alcoholics regarding either subjective ratings of intoxication or alcohol-related changes in body sway (Schuckit et al., 2004). This is consistent with findings from an evaluation using 18–25-year-old, predominantly blue collar subjects from the Collaborative Study on the Genetics of Alcoholism (COGA), where the 38 FHP women and 75 FHP men demonstrated similar lower LRs compared to the 68 FHN male controls (Schuckit et al., 2000).

There have also been several small-scale comparisons of FHP and FHN female subjects. Results from an evaluation of six pairs of FHPs and FHNs matched on age, drinking history, and height–weight ratio indicated that the FHPs demonstrated fewer changes in body sway and incorrect Digit Symbol Substitutions Test (DSST) trials following alcohol than FHNs, but there were no differences on subjective intoxication scores

(Lex et al., 1988). In a subsequent report, that did not include matched participants, 7 FHPs rated themselves as feeling less "Drunk" and "High," as well as less intense "Alcohol Effects" than 10 FHNs following alcohol, but demonstrated greater impairment with longer visual search response times on the Divided Attention Task (Lex et al., 1994). Another study of six unmatched pairs of FHP and FHN women revealed no significant differentials on alcohol-related changes in mood state, perceived physiological sensations, or performance on a grooved-pegboard task, although the FHPs did consistently report lower scores on central stimulant effects and were less impaired on a finger-tapping task following ethanol (Savoie et al., 1988). An investigation of 38 FHP women, 75 FHP men, and 68 FHN males also presented pilot data on 11 FHN female controls (Schuckit et al., 2000). The results confirmed the similarity in LR for sons and daughter of alcoholics. In addition, the daughters of alcoholics had a trend for lower subjective ratings of intoxication and less alcohol-induced body sway than FHN women, however, reflecting the small number of FHNs, these group differences were not significant (Schuckit et al., 2000). Most recently, a larger scale evaluation of 16 pairs of FHP and FHN women matched on age, race, level of education, and current and lifetime patterns of drug use, found that the FHPs had significantly lower LRs to alcohol for the DSST, but were more impaired on immediate digit recall (Evans and Levin, 2003). The FHNs tended to be more impaired on observer ratings of intoxication and on a balance task, although these differences were not significant.

Thus, to date there are interesting data, primarily from small samples, that indicate that the difference in LR between sons of alcoholics and controls may also be seen when daughters of alcoholics are compared to women with no FH of alcoholism. However, significant differences were not obtained in all of the reports, and results were not consistent across measures or studies. In addition, few of the evaluations controlled for other factors that might also be related to the alcoholism risk, and no investigation adequately matched FH groups on variables that might impact LR, such as drinking and drug histories, and height–weight ratio. The current work evaluates whether a low LR to alcohol is seen in women with a FH of alcoholism compared to well-matched FHN controls.

2. Methods

2.1. Participants

The comparisons of 25 matched pairs of FHP and FHN women (50 subjects) incorporated data from three sources, each of which used materials and procedures approved by the relevant Human Subjects Protection Committees. First, as part of a larger study, 20 of the FHNs and 17 of the FHPs were selected from among yearly mailings to 18–29-year-old students randomly chosen from lists acquired from the Registrar's Offices at the University of California, San Diego (UCSD) and San Diego State University (SDSU)

(Wilhelmsen et al., 2003). The original questionnaire gathered demographic information (e.g., age, education, ethnicity, etc.), a brief medical history, and a list of all current medications. Subjects were asked to provide current and lifetime patterns of use of alcohol and illicit drugs, and to list associated problems. This screener also contained an abbreviated FH section focusing on substance use disorders in first-degree relatives. All personal and family data were subsequently corroborated during the structured personal interview session described below.

The eight remaining FHPs were selected from COGA families. These women were identified as drinking, but not alcohol dependent 18–29-year-old members of COGA from any of the six sites. All participants were interviewed using the Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA) described below, and parental diagnoses were established using the data from the parent's SSAGA.

Finally, five of the FHNs are daughters of original subjects from the ongoing San Diego Prospective Study of 453 families (Barnow et al., 2002; Preuss et al., 2002; Schuckit, 1998; Schuckit and Smith, 2000). In the 15-year follow-up of this investigation, 18–29-year-old offspring of the initial participants were contacted and recruited for alcohol challenges. Family history of these women was established with SSAGA-like interviews with the parents themselves.

When invited to participate, subjects were told that this was a study investigating differences in how people respond to alcohol. Individuals were considered to be FHP if their father or mother met criteria for alcohol dependence based on the third edition, revised, of the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM-III-R*; American Psychiatric Association, 1987). Regarding alcohol dependent mothers, participants were only chosen if there was no evidence of alcohol dependence in the mother prior to the birth of the alcohol challenge subject. Participants were included as FHNs if they did not have any first-degree relative who met *DSM-III-R* criteria for alcohol dependence or abuse. To minimize the potential impact of alcohol-metabolizing enzymes, none of the alcohol challenge subjects were Asian, African-American, or Jewish (Chen et al., 1999; Ehlers et al., 2001; Hasin et al., 2002a,b; Shea et al., 2001; Shen et al., 1997; Wall et al., 1997, 2003). To control for the possible influence of other genetically influenced characteristics relevant to the alcoholism risk, no participant had ever met criteria for dependence on alcohol or any other drug; had a history of bipolar disorder, schizophrenia, or ASPD; or had any first-degree relative with these disorders (Schuckit, 2002). The women were required to have had some experience with alcohol, and could not have any major medical disorder or be on a medication for which alcohol challenges might be contraindicated or difficult to interpret. An additional exclusion criterion was pregnancy, which was evaluated by a urinary pregnancy test carried out in the laboratory before participation in the experiment.

For these analyses, each FHN subject was matched with a FHP woman on age, ethnicity, height–weight ratio, quantity and frequency of alcohol intake in the prior six months, as

well as lifetime and current pattern of use of nicotine and illicit drugs.

2.2. Pre-session and alcohol challenge

Subjects participated in a two-session protocol, the first of which involved the face-to-face administration of the full adult SSAGA, if this had not already been obtained, and a review of her FH using the Family History Assessment Module (FHAM), described below. This first meeting was also used to introduce individuals to the alcohol challenge laboratory and to practice the different assessments that would be administered during testing. The second session was the alcohol challenge, in which the women arrived at the laboratory at 7:30 a.m., received a standard light breakfast of toast and juice, participated in baseline evaluations, and gave a breath alcohol concentration (BrAC) sample (AlcoSensor Model III, Intoximeters, Inc., St. Louis, MO), with the requirement that the value had to be zero. Bloods were drawn for a blood count and chemistry panel (CBC/SMAC), and urine samples were gathered to test for pregnancy. At approximately 9:00 a.m., the women were given 0.75 ml/kg of 95% ethanol as a 20% by volume solution in a room-temperature, decaffeinated, sugar-free, carbonated soda via an apparatus that disguised the taste and made it difficult to determine the number of drinks consumed (Mendelson et al., 1984). Subjects were told they might receive a small amount of alcohol to as much equivalent to four standard drinks. For the mean weight of the participants, 65 kg, the volume of alcohol was 49 ml mixed with 196 ml of soda. Subjects were requested to finish the beverage in as close to 8 min as possible, and to spread consumption throughout the entire period.

At baseline, immediately following beverage administration, 30 min, and every half-hour, thereafter, over a 3.5-h period, participants completed a series of tests to establish changes from baseline associated with alcohol. These included BrAC, subjective feelings of intoxication, and levels of standing steadiness or body sway.

2.3. Measures

2.3.1. Semi-Structured Assessment for the Genetics of Alcoholism

This instrument was developed by COGA and screens for 17 *DSM-III-R* Axis I diagnoses. Test-retest and across center reliabilities are high, with kappas of .60 to 1.00 (Bucholz et al., 1994, 1995). The validity of the SSAGA has also been evaluated as compared to the Schedule for Clinical Assessment in Neuropsychiatry (SCAN), with kappas for most diagnoses between .60 to .85 (Hesselbrock et al., 1999).

2.3.2. Family History Assessment Module

This brief COGA developed screener evaluates 6 *DSM-III-R* Axis I diagnoses among the respondent's first-degree relatives. Sensitivity is approximately 65%, specificity is ap-

proximately 88%, and agreement with direct interview data (from the relative's SSAGA) is approximately 73% (Rice et al., 1995).

2.3.3. Subjective High Assessment Scale (SHAS)

This analogue scale evaluates 13 subjective feelings of intoxication as changes from baseline. Each question is rated on a Likert-type scale from zero (no effect) to 36 (extreme effect) to assess both positive (e.g., Happy, Relaxed, High, Intoxicated, etc.) and negative (e.g., Nauseated, Clumsy, Confused, etc.) effects that can be associated with alcohol. The intersession reliability of the SHAS is approximately .80, and clearly higher and lower scores on this measure correlate at approximately .60 with a retrospective self-report measure of the usual number of drinks required for different effects (Schuckit et al., 1997a,b). The major analyses focus on the SHAS7, the average of seven items that have demonstrated the greatest sensitivity to the effects of alcohol, and which cluster together with an overall item-to-total correlation of .80 or higher and a Chronbach alpha of .96 (Schuckit et al., 2000). The SHAS7 includes three general items (Effects of Alcohol, Drunk, and High) and four specific aspects of the effects of alcohol (Clumsy, Confused, Dizzy, and Difficulty Concentrating).

2.3.4. Body sway

This was recorded using a harness attached to the participant at the level of the axilla, from which ropes extended to the front and side at an approximate 90 degree angle from one another (Lipscomb et al., 1979). Each rope passed over a pulley and anterior-posterior (AP) and lateral sway were recorded as the total number of centimeters of back and forth movement of the rope. Subjects completed three 1-min trials at each time point with eyes open, feet together, and hands at their sides, with scores recorded as the mean values of the three trials. This is the same approach that has been used in the San Diego laboratory since about 1980 (Schuckit, 1985; Schuckit and Gold, 1988). The level of increased sway in the upper body after consuming alcohol has long been recognized as a sensitive marker of the degree of intoxication (Lipscomb and Nathan, 1980; Lipscomb et al., 1979; Moskowitz et al., 1974). Historically, most studies have demonstrated higher levels of sway or lack of standing steadiness in offspring of alcoholics versus controls following alcohol administration (Heath and Martin, 1992; Hill and Steinhauer, 1993; Schuckit, 1984, 1985; Schuckit and Gold, 1988). While not as extensively evaluated as subjective feelings of intoxication, measures of impaired motor performance that reflect balance generally parallel subjective highs, and predict future alcohol-related problems (Lex et al., 1988; Rodriguez et al., 1993; Schuckit and Gold, 1988). At the same time, there are data to support the contention that separate, but perhaps overlapping, genes may contribute to the intensity of change in subjective feelings of intoxication and to body sway (Heath and Martin, 1992), indicating that there are benefits from measuring both domains in alcohol challenges.

2.4. Statistical analyses

The adequacy of FHP/FHN matching was evaluated using Student's *t* tests for continuous variables and chi-square tests for categorical data. Differences between the two FH groups after consuming alcohol were determined using FH-by-Time mixed design ANOVAs with time as a repeated measure. Significant effects were followed up with post hoc comparisons at 30 and 60 min after beverage consumption, as these are the time points that historically have demonstrated the greatest group differences in LR (Schuckit and Gold, 1988; Schuckit and Smith, 1996; Schuckit et al., 1996). Because the direction of the FH differences were predicted a priori, the Student's *t* tests are reported as one-tailed. Determination of effect size used the partial eta squared (η_p^2) statistic, with small effects regarded as zero to .05, medium effects as .06 to .14, and large values as .15 or higher.

3. Results

The 50 FHP and FHN women had a mean age of 21.0 (S.D. = 2.06) years and 86% were White, not of Hispanic origin, 12% White-Hispanic, and 2% were East Indian. The religious backgrounds included 56% who identified themselves as Protestant, 18% as Catholic, while 26% reported no religious preference. Eighty-four percent of the subjects drank regularly (use of at least one day a month over the prior six months) at a usual drinking frequency of 3.8 (S.D. = 3.28) days per month, and a usual quantity of 2.8 (S.D. = 1.33) drinks per drinking day (a drink was defined as approximately 12 g of ethanol, the amount in 12 ounces of beer, 4 ounces of wine, and a single shot of approximately 80 proof liquor). Among this group, 46% had some prior experience with tobacco products, with 18% reporting that they were regular smokers (*M* = 5.9, S.D. = 9.48 days per month and *M* = 2.8, S.D. = 2.28 cigarettes per day of use). Regarding

cannabis, 56% had tried this drug, and 4% had recent regular use (*M* = 1.0, S.D. = 0.00 days per month and *M* = 1.5, S.D. = 0.71 units per occasion). Twenty percent had some lifetime experience with other illicit substances, including 6% who had tried cocaine, 8% tried amphetamines, 2% had experience with sedative/hypnotics, 14% with hallucinogens, and 4% with opioids.

Table 1 describes demographic comparisons and substance use histories for the FHP and FHN women. The groups were similar on age, years of schooling, religion, and ethnicity. There were no differences on other variables used to match the pairs, such as drinking history, smoking, height, weight, and height–weight ratio. Consistent with an adequate match on recent use of alcohol, the values for two state markers of heavy drinking, mean corpuscular volume (MCV) and gamma-glutamyl transferase (GGT), were also equivalent, with both groups demonstrating values in the normal range (Irwin et al., 1988). For illicit drugs, the proportion of women who had ever used cannabis was similar, but FHP women were more likely to have ever tried a drug other than cannabis, with hallucinogens representing the only significant specific difference. Because of this difference between the groups on Drug Use, all major analyses were repeated using the variable as a covariate.

The mean BrACs by FH status for the alcohol challenge session are displayed in Fig. 1, demonstrating a peak for both groups at 60 min after beverage administration, followed by a decrease over the remainder of the session. When baseline scores were deleted (all were zero), there was a significant FH-by-Time interaction (*F* = 2.28, 6/288 d.f., *p* = .04, η_p^2 = .045) but no between-group difference (*F* = 0.62, 1/48 d.f., *p* = .43, η_p^2 = .013).

The SHAS7 scores are presented in Fig. 2, where both FHPs and FHNs peaked at 30 min post-ethanol. By definition, baseline SHAS values were zero, as subjects were asked to rate subjective feelings as differences from the period before they drank the beverage. There was an overall FH-by-
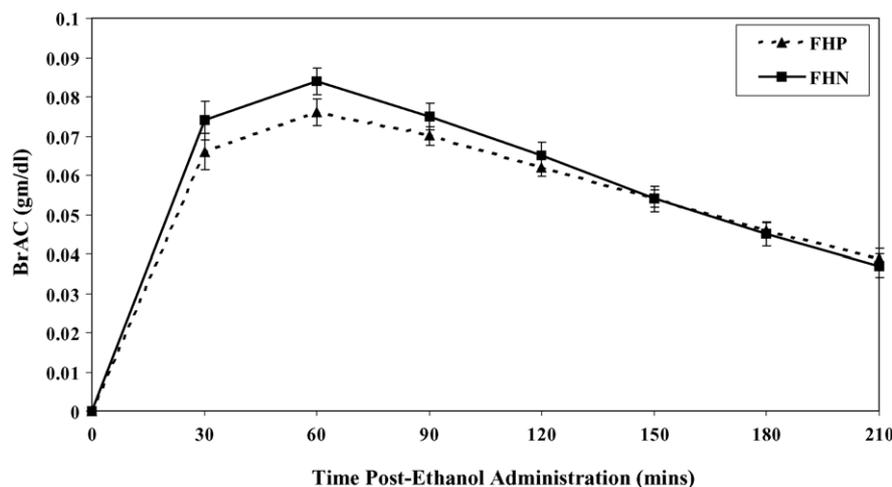

Fig. 1. Breath alcohol concentration (gm/dl) for 25 FHP versus 25 FHN women at eight time points over 210 min in the lab session. Vertical lines depict standard errors of the means.

Table 1
Comparisons of demography, state markers of heavy drinking, and Drug Use histories

Variable	FHP ($n = 25$)	FHN ($n = 25$)	t Value or χ^2
Age, years (S.D.)	21.2 (2.36)	20.8 (1.72)	0.62
Education, years (S.D.)	14.0 (1.65)	14.2 (1.50)	−0.36
Ethnicity			2.67
Caucasian	21 (84%)	22 (88%)	
Hispanic	4 (16%)	2 (8%)	
Other	0 (0%)	1 (4%)	
Religion			3.39
Catholic	7 (28%)	2 (8%)	
Protestant	12 (48%)	16 (64%)	
None	6 (24%)	7 (28%)	
Ht-Wt ratio (S.D.)	0.5 (0.06)	0.5 (0.07)	−0.45
MCV, fL (S.D.)	89.8 (3.51)	88.5 (3.50)	1.22
GGT, IU/L (S.D.)	13.7 (5.51)	12.9 (4.72)	0.49
Alcohol			
Use over prior six months			
At least one day per month	21 (84%)	21 (84%)	
Days per month (S.D.)	3.7 (3.51)	3.9 (3.11)	−0.23
Drinks per drinking day (S.D.)	2.8 (1.22)	2.9 (1.46)	−0.23
Tobacco			
Ever used	14 (56%)	9 (36%)	2.01
Use over prior six months			
At least one day per month	5 (20%)	4 (16%)	0.14
Days per month (S.D.)	3.0 (3.94)	9.5 (13.70)	−1.03
Cigarettes per day of use (S.D.)	2.0 (1.22)	3.8 (3.10)	−1.17
Cannabis			
Ever used	16 (64%)	12 (48%)	1.30
Use over prior six months			
At least one day per month	2 (8%)	0 (0%)	2.08
Days per month (S.D.)	1.9 (0.00)		
Joints per day of use (S.D.)	1.5 (0.71)		
Lifetime use of other drugs			
Any	8 (32%)	2 (8%)	4.50[*]
Cocaine	3 (12%)	0 (0%)	3.20
Amphetamine	3 (12%)	1 (4%)	1.09
Sedative/hypnotic	1 (4%)	0 (0%)	1.02
Hallucinogen	6 (24%)	1 (4%)	4.15[*]
Opioid	2 (8%)	0 (0%)	2.09

[*] $p < .05$.

Time effect ($F = 2.54$, 6/288 d.f., $p = .02$, $\eta_p^2 = .054$), but no significant FH effect ($F = 0.66$, 1/48 d.f., $p = .42$, $\eta_p^2 = .014$). When the analysis was repeated, including Drug Use as a covariate, the FH-by-Time interaction demonstrated a larger effect size ($F = 3.68$, 6/282 d.f., $p < .01$, $\eta_p^2 = .073$), however, the between-group difference remained non-significant ($F = 1.76$, 1/47 d.f., $p = .19$, $\eta_p^2 = .036$). The data in Fig. 2 were analyzed where SHAS7 scores were residualized onto usual drinking quantity and frequency, and BrAC values for each relevant time point. The results revealed a significant FH-by-Time effect ($F = 2.25$, 6/288 d.f., $p = .04$, $\eta_p^2 = .045$), but again, no FH effect ($F = 0.53$, 1/48 d.f., $p = .47$, $\eta_p^2 = .011$). Residualizing procedures were used in order to preserve degrees of freedom and, hence, power for this modest sized sample. When the data were analyzed using drinking history and BrAC at 60 min as covariates, the FH-by-Time effect was close to significant ($F = 2.10$, 6/270 d.f., $p = .05$, $\eta_p^2 = .045$), with no between-subjects effect ($F = 0.36$, 1/45 d.f., $p = .55$, $\eta_p^2 = .008$). An evaluation of individual time points using one-tailed post-hoc independent t tests revealed that FHPs had significantly lower scores at 30 min ($M = 51.6$, S.D. $= 41.62$ and $M = 75.4$, S.D. $= 57.03$ for FHPs and FHNs, respectively, $t = -1.68$, 48 d.f., $p < 0.05$, $\eta_p^2 = 0.056$), while the difference at 60 min ($M = 47.8$, S.D. $= 41.19$ and $M = 66.2$ SD $= 57.48$ for FHPs and FHNs, respectively, $t = -1.31$, 48 d.f., $p = 0.10$, $\eta_p^2 = 0.034$) was in the predicted direction, but non-significant. Repeating these analyses after covarying for BrAC at the 60 min time point and usual drinking quantity and frequency revealed similar results regarding the magnitude of group differences at 30 min ($t = -1.57$, 45 d.f., $p = .06$, $\eta_p^2 = .052$) and at 60 min ($t = -1.17$, 45 d.f., $p = .13$, $\eta_p^2 = .029$).
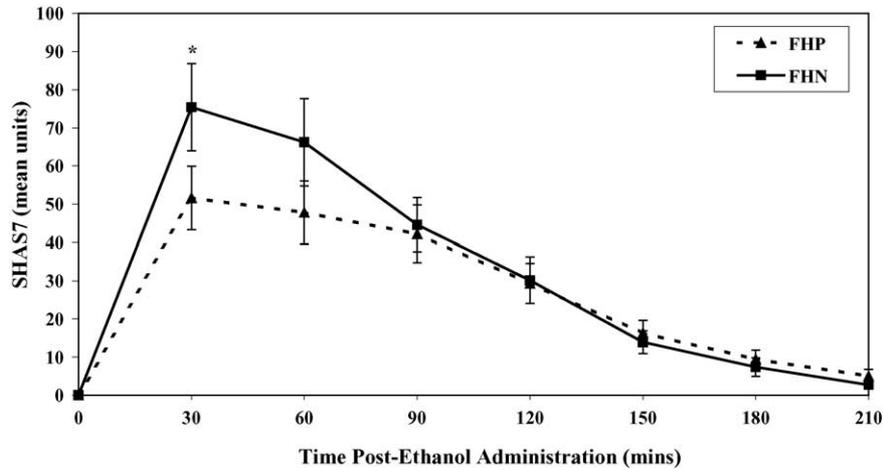
Fig. 2. Change from baseline in SHAS7 response (mean units) for 25 FHP versus 25 FHN women at eight time points over 210 min in the lab session. Vertical lines depict standard errors of the means. $^*p < .05$.

Data were also available on specific SHAS items. Focusing on two more general effects of alcohol, after residualizing the data onto drinking history variables and the BrAC values, FHP scores remained lower with the FH-by-Time effect significant for "Effects of Alcohol" ($F = 2.84$, 6/288 d.f., $p < .01$, $\eta_p^2 = .056$) and for feeling "Drunk" ($F = 2.26$, 6/288 d.f., $p = .04$, $\eta_p^2 = .045$). From the remaining items, the FH-by-Time effect was also significant for feeling "Clumsy" ($F = 2.69$, 6/288 d.f., $p = .02$, $\eta_p^2 = .053$) and for "Confused" ($F = 3.08$, 6/288 d.f., $p < .01$, $\eta_p^2 = .060$). While the FH-by-Time effects for the remaining items (Difficulty Concentrating, Dizzy, and High) were in the predicted direction, they were not significant.

Changes from baseline in lateral body sway for the two FH groups are illustrated in Fig. 3. At baseline, the mean scores on lateral body sway were 21.4 (S.D. = 7.19) and 21.6 (S.D. = 7.34) for FHPs and FHNs, respectively, a difference that was not significant ($t = -0.62$, 48 d.f., $p = .54$). For this measure, both groups peaked at 60 min,

after which values decreased. No significant FH ($F = 0.13$, 1/48 d.f., $p = .72$, $\eta_p^2 = .003$) or FH-by-Time ($F = 1.85$, 5/240 d.f., $p = .10$, $\eta_p^2 = .037$) effects were obtained for the raw data. Including Drug Use as a covariate generated a significant FH-by-Time effect ($F = 2.39$, 5/235 d.f., $p = .04$, $\eta_p^2 = .048$), but non-significant between-group difference ($F = 0.28$, 1/47 d.f., $p = .60$, $\eta_p^2 = .006$). While the independent one-tailed t tests at 30 and 60 min were both non-significant, because differences at the 30 min time point approached significance ($M = 8.3$, S.D. = 13.51 and $M = 13.2$, S.D. = 15.11 for FHPs and FHNs, respectively, $t = -1.21$, 48 d.f., $p = .12$, $\eta_p^2 = .030$), further analysis of the data was conducted to evaluate whether possible differences might have been obscured by violations of normality. Visual examination of the distributions of lateral body sway scores for each of the time points revealed that they were skewed to the right. Formal analysis of skewness indicated significant results at each of the time points (z-scores for skewness ranged from 2.58 to 6.00). Thus, log transformations of the scores were performed (Tabchnick and
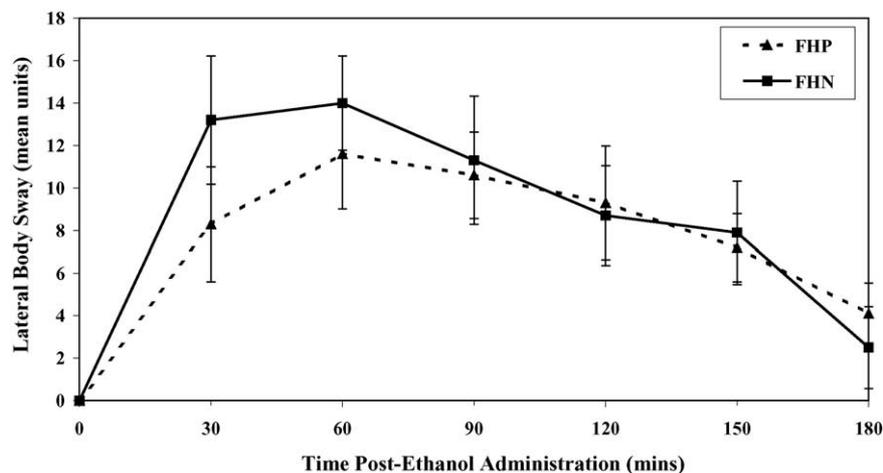

Fig. 3. Change from baseline in lateral body sway (mean units) for 25 FHP versus 25 FHN women at seven time points over 180 min in the lab session. Vertical lines depict standard errors of the means.

Fidell, 2000). A retest of the log transformed data revealed that no significant skewness remained at any of the time points except for 180 min (z-score for 180 min = 4.69, z-scores for all other time points ranged from -1.36 to 0.53). For the transformed data, a significant FH-by-Time interaction was seen ($F = 3.47$, 5/240 d.f., $p < .01$, $\eta_p^2 = .067$), but no FH effect ($F = 0.02$, 1/48 d.f., $p = .90$, $\eta_p^2 = .000$), and the independent t tests at 30 and 60 min were both non-significant. Similar to results reported for the SHAS, the transformed data for body sway were also reanalyzed with scores residualized onto drinking quantity and frequency, as well as BrAC values. The evaluation of lateral body sway was close to significant for the FH-by-Time effect if these residualized values were used ($F = 2.20$, 5/240 d.f., $p = .06$, $\eta_p^2 = .044$). The effect became significant when the raw data were analyzed using drinking history and BrAC at 60 min as covariates ($F = 3.06$, 5/225 d.f., $p = .01$, $\eta_p^2 = .064$). While not shown, none of the analyses regarding AP sway revealed significant results.

4. Discussion

The data reported here describe the largest sample of alcohol challenges in FHP and FHN matched women (50 subjects) to date. Overall, the results support the hypothesized lower LR to alcohol in women with an alcohol dependent parent. The findings are consistent with most previous data on daughters of alcoholics. These earlier investigations often involved small samples (e.g., Evans and Levin, 2003; Lex et al., 1988, 1994; Savoie et al., 1988; Schuckit et al., 2000), or evaluated the similarity between sons and daughters of alcoholics without directly comparing FHP and FHN women (e.g., Schuckit et al., 2004). While these studies indicated that a low LR was more likely to be observed in FHP compared to FHN women, this is the first investigation to support this conclusion where the women were carefully matched on variables that may affect LR (e.g., age, drinking history), while also minimizing the effect of other factors that are possibly related to the risk for AUDs (e.g., Asian background).

The current study revealed that daughters of alcoholics reported a clearly lower LR on the SHAS7, a subjective measure of response to alcohol. The data are consistent with Lex et al. (1994) who found that the FHP group had lower scores on the "High," and "Drunk" items, and noted less intense "Alcohol Effects" than the FHNs. Further support for differences in subjective ratings of LR between FHN and FHP women come from Savoie et al. (1988) who reported that FHP women appeared to have lower ratings of central stimulant effects of alcohol (i.e., Light Headed, Head Spinning, Dizzy, Ringing/Buzzing) at peak BAC than the FHN group. Finally, in an evaluation by Schuckit et al. (2000), a comparison of daughters of alcoholics and controls revealed possible lower SHAS7 scores for the FHP group. The differentials for these latter two studies, however, were not significant, most likely reflecting the small samples involved in the investigations.

The results were not as clear regarding a second measure of LR, body sway. The data in Fig. 3 revealed that FHPs appeared to demonstrate less alcohol-related lateral sway than FHNs at 30 and 60 min following beverage administration, but these differences were not significant unless the data were log transformed to correct the right skewness. Even less of a group differential was seen for AP body sway. The lack of clarity regarding body sway is consistent with the results of Lex et al. (1988) who found a non-significant trend for FHPs to have less lateral sway than FHNs at 30 and 180 min after alcohol, along with significant differences for AP sway at 60, 90, and 120 min, and for combined sway scores at 15, 30, 60, 90, and 120 min. In the Schuckit et al. (2000) study, group differences were in the predicted direction at 30 and 60 min for AP body sway (data on lateral sway were not reported), but, with only 11 FHNs and no group matching, the difference in scores was not significant.

Several factors might have contributed to the lack of a clear differential between FH groups on body sway. One possibility is that subjective ratings of intoxication and body sway measure different components of the LR to alcohol. A principal components analysis of the data from the Australian twin study revealed two orthogonal components, rather than a global, unidimensional factor of response to alcohol, and there were marked gender differences for which component body sway was most heavily loaded upon (Heath and Martin, 1992). The first component was related to alcohol consumption, subjective feelings of intoxication, ratings of willingness to drive, and for men only, body sway. The second component was associated with blood alcohol levels, psychomotor and hand–eye co-ordination, and in women, body sway. A multivariate genetic analysis indicated that these two components may be related to independent genetic factors, suggesting that body sway and self-rated intoxication might be influenced by the same factor in men, but not in women. Thus, it could be that the difference in findings presented here regarding body sway compared to prior studies involving male samples reflects a possible gender difference in the genetic factors associated with the LR to alcohol.

A second explanation might relate to the variability in body sway scores. It is possible that women demonstrate more variability in body sway than men, thereby obscuring any group differences. Support for this possibility comes from a prior report from the San Diego group in which the reported standard deviation for the average body sway scores across time for women was significantly higher than that for men ($M = 24.1$, S.D. = 8.42 and $M = 28.1$, S.D. = 11.42 for men and women, respectively, Levene's Test for Equality of Variances $F = 1.84$, $p = .03$) (Schuckit et al., 2000). Another possible factor is that body sway may not be as sensitive of a measure to alcohol-induced changes as the SHAS. In a comparison of a divided attention task, body sway, and subjective estimates of impairment, body sway was the least sensitive and most variable measure of the pharmacological effects of alcohol (Mills and Bisgrove, 1983). This

suggests that differences on the LR to alcohol between FHPs and FHNs may be more easily detected in moderate samples using subjective ratings of intoxication rather than body sway.

There are a number of strengths to the current work. First, the FHP and FHN women in this study were carefully matched on alcohol consumption, as recent drinking history has been shown to be associated with one's reaction to ethanol (Heath and Martin, 1992; Hiltunen, 1997a,b; Holdstock et al., 1988; Portans et al., 1989; Ramchandani et al., 2002; Schuckit and Klein, 1991; Viken et al., 2003). In the current investigation, there were no FH differences in the self-reported recent drinking histories, a conclusion supported by the similarities on GGT and MCV values. The FHP and FHN subjects were also well matched on height–weight ratio, as this correlates with percentage body fat (and thus, total body water). Finally, the participants were similar on age and race.

At the same time, several caveats must be recognized. First, placebo controls were not used, making it difficult to prove that the FH differences did not reflect different expectancies or learning effects. Second, the women were relatively well educated, the majority of whom were university students, and all but one subject was Caucasian or Latino. Therefore, the generalizability to other populations is not known. In addition, the subjects were not matched on phase of menstrual cycle, and it has been hypothesized that this might influence alcohol pharmacokinetics as a result of changes in levels of sex steroid hormones (Jones and Jones, 1976, 1984; Sutker et al., 1987a,b). However, the majority studies do not support a relationship between menstrual cycle and ethanol metabolism, and suggest that menstrual phase has little effect on subjective or behavioral reactions to alcohol (Correa and Oga, 2004; Freitag and Adesso, 1993; Gill, 1997; Holdstock and de Wit, 2000; Lammer et al., 1995; Mumenthaler et al., 1999, 2001). A third limitation is that the data are cross-sectional and do not provide information on how LR might be related to future AUDs in women or address the stability of LR over time. Also, none of the participants were alcohol-naïve, thus, we cannot determine the extent to which LR results were a consequence of differences in initial sensitivity to alcohol, or the effects of developing chronic tolerance. Finally, while the data presented here come from the largest sample of FHP and FHN women in the literature, the number of participants is smaller than that of alcohol challenge studies comparing men with and without a FH of AUDs (e.g., Schuckit, 1994, Schuckit and Gold, 1988).

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