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Blunted hypothalamic–pituitary–adrenocortical axis responsivity to stress in persons with a family history of alcoholism

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Abstract

Abstinent alcoholics show a blunted stress cortisol response that may be a consequence of drinking or a preexisting risk marker. We tested cortisol responses to psychological stress in 186 18–30 year-old, healthy social drinkers having no personal history of alcohol or drug dependence, 91 of whom had one or two alcoholic parents (FH+) and 95 having no family alcoholism for two generations (FH–). We predicted that, similar to alcoholic patients, the FH+ would have reduced stress cortisol responses that would be partially determined by their temperament characteristics, specifically antisocial tendencies as measured by the California Psychological Inventory. On a stress day, subjects performed continuous simulated public speaking and mental arithmetic tasks for 45 min, and on a control day they sat and rested for the same time period. The FH+ who were low in sociability had smaller cortisol responses than FH–, high-sociability persons ($t = 2.27, p = .02$). These two groups were not different in diurnal cortisol secretion patterns or affective responses to the stressors. Persons with a familial risk for alcoholism who have more antisocial tendencies may have altered central nervous system responses to emotionally relevant social challenges. Disrupted cortisol stress responses may serve as a risk marker for the development of substance use disorders.

Keywords

Hypothalamic–pituitary–adrenal (HPA) axis; Cortisol; Alcoholism; Family history; Stress; Oklahoma Family Health Patterns Project

1. Introduction

Having a family history of a substance use disorder increases a person's statistical risk for developing an alcohol or drug problem (Merikangas et al., 1998). One possible explanation for the increased risk is an inherited alteration in brain mechanisms that respond during emotional states. It would be desirable to identify physiological response markers sensitive to a person's risk for alcoholism and other substance use disorders. A candidate marker is the cortisol response to stress, reflecting activity in the hypothalamic–pituitary–adrenocortical axis (HPA). In healthy individuals, cortisol is secreted in a diurnal pattern exhibiting a morning

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peak and a nighttime nadir. Cortisol is also regulated in response to a range of stressors (Lovallo, 2005; Munck et al., 1984). Cortisol's response to psychological stress reflects the actions of extrahypothalamic regions of the brain, including the limbic system acting on the HPA. As a result, variations in cortisol's secretion to psychological stress may reflect individual differences in affective processes, including alterations in neurobiological mechanisms as well as differences in appraisal and coping processes.

Alcoholic patients show a persisting cortisol hyporeactivity to a wide range of stressors (Adinoff et al., 2005a,b), including insulin-induced hypoglycemia (Costa et al., 1996), as well as psychological stressors, including mental arithmetic plus a cold pressor test (Errico et al., 1993), mental arithmetic plus isometric handgrip in males (Bernardy et al., 1996), and simulated public speaking plus isometric handgrip in females (Bernardy, 1995). These findings raise the question of whether the HPA in alcoholics has been damaged by prolonged exposure to high levels of ethanol. However, later studies demonstrated that patient groups were hyporesponsive to combined mental arithmetic and public speaking stress, although they had a normal diurnal pattern of cortisol secretion (Lovallo et al., 2000). The normal diurnal pattern suggested intact HPA function, while the patients' stress cortisol hyporesponsiveness may have reflected a difference in stress-related neural inputs to the hypothalamus that are needed for a psychological stress reaction. In parallel with these HPA findings, we observed that the same patients had an attenuated heart rate response to public speaking stress, although their reflex heart rate and blood pressure changes to orthostatic stress were normal (Panknin et al., 2002). These HPA and cardiovascular findings are in agreement that the abstinent alcohol and polysubstance abusing patients had normal homeostatic regulation of visceral function, but that the neurological response to psychological stress was blunted. This led us to ask if these patients had a preexisting alteration in neural systems that regulate HPA responses to stress (Lovallo et al., 2000).

A family history (FH) of alcoholism also appears to be associated with autonomic and endocrine hyporesponsiveness to stress. In comparison to FH- controls, boys, 10 to 12 years of age, whose fathers had been diagnosed with alcohol and psychoactive substance use disorders were found to exhibit a lower level of salivary cortisol secretion when anticipating a novel stressor task (Dawes et al., 1999; Moss et al., 1995b) and when faced with an unfamiliar electroencephalographic study in a hospital laboratory (Moss et al., 1995a). During a 3–5 year follow-up, the boys most likely to have begun using tobacco and experimenting with drugs were those with the smallest cortisol responses, regardless of family history (Moss et al., 1999). Adult children of alcoholics also have been found to exhibit a significantly lower plasma cortisol levels to an alcohol challenge in comparison to controls, which is noteworthy because alcohol stimulates the HPA axis under normal circumstances (Croissant and Olbrich, 2004). Additionally, compared to FH- controls, nonalcoholic men with a high-density family history of alcoholism demonstrated smaller skin conductance responses to a tone signaling delivery of an electric shock (Finn et al., 1994). These results raise the question of whether the stress hyporesponsivity of FH+ may signify elevated risk of future substance use disorders.

Personality variables have been shown to distinguish between FH+ and FH- groups, suggesting that certain personality traits may serve as markers of a person's risk for development of a substance abuse problem (Elkins et al., 2004). Personality variables measuring behavioral disinhibition and negative emotionality are often associated with substance abuse (Sher et al., 1999). Studies of FH+ children show a clustering of temperamental, behavioral, and biochemical changes that are consistent with a hypothesis that genetic risk factors for alcoholism may be accompanied by altered functioning of the limbic system of the brain and that these alterations may be seen in emotionally or motivationally relevant situations (Blackson et al., 1996; Cloninger et al., 1981). Interestingly, antisocial behavior by adolescent

boys has been associated with low cortisol responses and this effect was larger in those whose fathers displayed antisocial characteristics (Vanyukov, 1993).

The goal of the Oklahoma Family Health Patterns project is to study healthy non-alcohol dependent FH+ and FH− individuals across three laboratory visits to identify markers of high risk in the domains of temperament, cognition and behavior, and psychophysiological function, with an emphasis on probes of emotional response systems. The purpose of this paper is to report on cortisol and autonomic responses to combined social and cognitive stressors in persons at risk of future alcoholism by virtue of a positive family history and their behavioral disinhibition characteristics. The primary hypothesis was that a family history of alcoholism would predict reduced salivary cortisol response to a psychological stressor, but that this reduction would be explained in whole or in part by the temperament characteristics of these persons.

2. Methods

2.1. Participants

The present sample consisted of 186 healthy young adults (91 FH+ and 95 FH−) recruited through community advertisement from the general population of Oklahoma City, OK. They were 86% European American, 8% African American, 2% Native American, 2% Hispanic American, and 2% other race and ethnicity. As shown in Table 1, participants averaged 24 years of age and had 15 years of education. All participants signed a consent form approved by the Institutional Review Board of the University of Oklahoma Health Sciences Center and the Veterans Affairs medical Center in Oklahoma City, OK and were paid for participating.

2.1.1. Inclusion and exclusion criteria—Prospective participants were excluded if they had any of the following: a history of alcohol or drug dependence; diagnosis of substance abuse within the past 2 months; current use of any abused drug (subjects were required to pass a urine drug screen and alcohol breath test on each day of testing); current Axis I disorder as defined by the Diagnostic and Statistical Manual of Mental disorders, 4th ed. (APA, 1994) and assessed by Diagnostic Interview Schedule (past history of an Axis I disorder not exclusionary unless it was for substance dependence or occurred 2 months prior to participation in study); Axis II disorders in clusters A or C assessed by Structured Clinical Interview for Diagnosis-II questionnaire and interview. All participants were required to be in good health as determined by self-report, have normal hearing assessed by audiologic exam, be taking no prescription medications at the time of testing, and to have no history of serious medical disorder, including neurological disorders, cardiovascular diseases, or diabetes. Women could not be pregnant based on self-report and negative urine test. Smoking and tobacco use were not exclusionary. Subjects completed the Fagerström Test for Nicotine Dependence (Fagerström and Schneider, 1989) to later estimate the effect of smoking on dependent variables.

2.2. Screening

An initial telephone screening to ensure general conformity with inclusion and exclusion criteria was followed by a screening at the laboratory conducted by a trained interviewer supervised by a licensed clinical psychologist.

2.2.1. Family history of alcoholism and other drug problems—Family history classification was established using the Family History Research Diagnostic Criteria (FH-RDC) (Andreasen et al., 1977). The FH-RDC has a high degree of inter-rater reliability (.95) for reports of substance use disorders (Andreasen et al., 1977; Zimmerman et al., 1988). Persons were considered FH+ if either biological parent met criteria for alcohol or substance use disorder by subject report. FH− were those reporting an absence of alcohol or substance use

disorders in their biological parents and grandparents. Confirmation of the FH-RDC report by the proband was obtained by parent interview in all possible cases (79% of the total sample), and by extrapolation, an estimated 91% of all subjects are accurately classified. Individuals were excluded if either they or a family collateral informant indicated possible fetal exposure to alcohol or other drugs.

2.2.2. Physical health, mental health, and other assessments—Physical health was assessed through a medical history and self-report of current good health. Psychological functioning was assessed using the computerized version of the Diagnostic Interview Schedule-IV (DIS-IV) conducted by a research assistant certified in its administration and through the Beck Depression Inventory II (Beck et al., 1996). Alcohol and drug use were assessed through the Cahalan Drinking Habits Questionnaire (Cahalan et al., 2004), the Alcohol Use Disorders Identification Test (Babor et al., 1992), and a Drug Use Questionnaire (Cognitive Studies Laboratory, 1994). Personality and temperament variables associated with behavioral undercontrol that may be relevant to alcohol and drug abuse risk were assessed through self-report measures. The Sociability scale of the California Personality Inventory (CPI-So) was administered to assess the degree of a person's conformity to social norms. This measure has a very high degree of agreement with clinical measures of antisocial personality and is useful in studies of offspring (Cooney et al., 1990; Kosson et al., 1994). Other measures of personality that were administered were the Tridimensional Personality Questionnaire (TPQ) (Cloninger et al., 1991), the Eysenck Personality Inventory (EPI) (Eysenck, 1964; Eysenck and Eysenck, 1968), and the Psychopathic Personality Inventory (PPI) (Lilienfeld and Andrews, 1996). SES was measured using the Hollingshead scale (Hollingshead, 1975) with updated occupational categories and was based on the primary occupation of the main breadwinner in the household in which the subject grew up.

2.3. Testing protocol

The study involved mental stress testing in Session 1 and a nonstressful, resting control period in Session 2. Both sessions were held at the same time of day for a given subject, and the stress day always occurred first to maximize its stressfulness with the control day being second to minimize its threat value. The stress day included: arrival at the lab, a standard meal, urine specimen, alcohol breath test, and audiologic test; an auditory startle paradigm (to be reported elsewhere); and the stress procedure including prestress baseline (20 min), mental stress testing (45 min), and recovery (20 min). The Session 2 control day included cognitive and behavioral tasks, such as the Stroop Color-Word Test (Smith and Jonides, 1999; Stroop, 1935) and the Iowa Gambling Task (Bechara et al., 1997; Bechara et al., 2001). The cognitive and behavioral tasks were completed in the same amount of time as the preparation and startle procedure in Session 1 (salivary cortisol was not measured during this period of time) and were followed by the rest period consisting of 80 min of rest corresponding to the baseline, stress, and recovery periods in Session 1 prior to dismissal.

2.3.1. Stress testing—Stress testing included simulated public speaking (Al'Absi et al., 1997) followed by mental arithmetic. The speech task (30 min) included three speeches prepared and delivered with no breaks. At the start of each speech, the subject was given a topic and told that they had 4 min to prepare a speech without making notes and 4-min to deliver it from memory. To increase the sense of realism, the speech was observed by a white-coated experimenter holding a clipboard and with a nearby video camera set to the record mode. The subject was told that his or her speech would be shown to the laboratory staff that would judge the subject's fluency of delivery and how convincing were their arguments. The order of speech topics was randomly assigned for each participant.

The mental arithmetic task included three 5-min periods and commenced after the speech period with no interruption other than brief instructions. In each period, the subject was given a three-digit number (e.g., 325) and told to add the digits (10) and to add that total to the original number (335), to recite the new number, and to proceed in that fashion for 5 min until told to stop. The task was monitored by the experimenter who corrected errors by telling the subject the answer was wrong and to start back at the previous correct answer.

2.3.2. Saliva sampling—Saliva was collected by the subject at 10 times on each day: at home upon awakening, immediately upon arrival at the lab, just prior to the startle or behavioral test protocol, at 10 min and 20 min during baseline to the stress period, after the second and third speeches, at the end of the mental arithmetic, and at the end of poststress recovery, and again at home at bedtime. Control day samples were taken at these same time points.

Saliva was collected using the commercially available Salivette device that consisted of an absorbent cellulose collector and storage tube (Salivette®, Sarstedt, Germany). Participants were instructed to place the cellulose collector in the mouth for 2 to 3 min until saturated with saliva, replaced in the storage tube, and capped. After each test session, the tubes were centrifuged, the collection device was discarded, and the sample was stored at -70°C until assay. The samples were then sent to Salimetrics (State College, PA, U.S.A.), a laboratory specializing in salivary assays, where the saliva free cortisol concentrations were quantified with a commercial radioimmunoassay kit.

2.3.3. Heart rate measurement—Heart rate was recorded using a Dinamap automated monitor (Critikon, Tallahassee FL, USA) during periodic measurements of blood pressure taken at 2-min interval throughout the stress and rest-day protocol.

2.4. Data analysis

Results and demographic variables were analyzed by Student's t test, by χ^2 and by analysis of variance (ANOVA) using SAS (SAS System for Windows, version 8.2; SAS Institute, Cary, NC). In cases of inhomogeneity of variance, t tests were done using corrected degrees of freedom based on Satterthwaite's approximation.

3. Results

3.1. Group demographics

Demographic variables are reported in Table 1. Fisher's Exact Test was used to examine differences in ethnic status given the small sample sizes with most of the ethnic categories. FH $-$ consisted of significantly more European Americans than the FH $+$ ($p=.009$). Although the SES scores were significantly different between FH groups, both FH groups fell within the same broad middle-class level (54–40; medium business, minor professional, technician). The FH $+$ group scored significantly higher on the AUDIT [$t(167)=-2.08$; $p=.04$] and the BDI-II [$t(173)=-2.76$; $p=.006$] than the FH $-$ group. However, neither group scored in the clinically significant range for problem drinking or depression.

3.2. Personality measures

Preliminary analyses revealed that the FH groups differed on relevant temperament variables. FH groups differed on PPI Factor II [$t(178)=2.28$, $p=.024$], EPI Neuroticism [$t(153)=-2.81$, $p=.006$], and CPI-So [$t(184)=5.67$, $p<.0001$]. Compared to the FH $-$ subjects, the FH $+$ group was lower on PPI Factor II (immunity to stress, social potency, and fearlessness) and they were higher on neuroticism and lower in sociability. The FH groups did not differ significantly on any other personality scales.

It is noteworthy that the FH groups had a pronounced difference in sociability scores [M FH +=28.76; M FH=32.87; $t(184)=5.67, p<.0001$]. This finding replicated our previous pilot study findings (Miranda et al., 2002). As is illustrated in Fig. 1, FH- individuals scored on average above 30 and FH+ averaged below 30 in both studies. Gough (1994) pointed out that the score of 30 forms an empirically established cut-off based on a large number of studies. High scores indicate a greater degree of conformity to social norms. Scores of 30–31 suggest normative social compliance. Scores ≥ 32 suggest above-average rectitude and conformity to social norms, and scores ≤ 29 suggest problems with social conformity. Other studies have found a similar pattern of scores when examining the relationship between FH of substance use and sociability scores. For example, (Searles and Alterman, 1994) found that sons of fathers showing one or two DSM-III symptoms of alcoholism had scores of 27, and sons of fathers with three or more symptoms scored 25. Alcoholics score 22 (Cooney et al., 1990; Gough, 1994). On the strength of these findings, we accepted a score of 30 as an empirically valid cut point in the score distribution, and we subdivided the FH groups at that point. Accordingly, the following analyses were based on four groups based on family history and CPI-So scores above 30 (HiSo) or below 30 (LoSo) to form four risk groups (FH-/ HiSo, FH+/HiSo, FH-/LoSo, and FH+/LoSo). Because of evidence on sociopathy and substance abuse risk reviewed above, we provisionally labeled the FH+/LoSo group as High Risk and the FH-/HiSo group as Low Risk, with the other groups considered intermediate in their level of risk.

3.3. Cortisol

3.3.1. Acute stress response—The response to the stressors was calculated as the increase in the mean cortisol level during the stress period on the stress day from the corresponding mean on the rest day, shown in Fig. 2. These difference scores across the four CPI-So groups did not differ to a significant degree [$F(3,182)=2.03, p=.11$]. We examined possible influences on the cortisol stress responses. Depression is often accompanied by changes in cortisol secretion, however among our subjects, the correlation between BDI-II score and cortisol stress reactivity scores was not significant [$r(168)=.06, p=.41$]. We also examined any effect of racial group on cortisol responses and found no significant differences between ethnic groups [$F(4,180)=.63, p=.64$]. There was a small, but significant, negative correlation between AUDIT scores and cortisol stress responses [$r(168)=-.16, p=.03$]. It is not known whether this correlation reflects a direct effect of heavier drinking on the cortisol response tendency or an effect of greater levels of risk on both drinking and cortisol.

Based on our suspected difference in risk for alcoholism and our original directional hypothesis that greater risk of alcoholism would be accompanied by lower levels of cortisol reactivity, we carried out a 1-tailed Student's t test comparing the High and Low Risk groups. In this comparison, the High Risk subjects had a significantly smaller cortisol increase to the stressors than did the Low Risk subjects [$t(116)=-2.27, p=.02$] (Fig. 2).

3.3.2. Diurnal cortisol patterns—One possible explanation for the hyporesponsiveness of our High Risk subjects is that they have a general HPA dysregulation. Fig. 3, presents the diurnal curves from the four CPI-So groups on the nonstress day. We found no significant differences between CPI-So risk groups [$F(3,172)=1.06, p=.37$] or secretion patterns across the day based on the groups by sample point interaction [Wilks $\lambda=.94, F(12,447)=.85, p=.60$]. By visual inspection, the High Risk group shows no tendency to differ in diurnal pattern from the other three subgroups, suggesting that all four groups had intact diurnal HPA regulation under nonstress conditions.

3.3.3. Stressor effectiveness—Another explanation for the findings could be that the relative sociopathic tendency of the High Risk subjects rendered public speaking to be an ineffective stressor. We accordingly examined the affective reports of the four groups. All four

CPI-So groups had significant changes in both negative and positive affect across baseline, stressor, and recovery periods [Negative Affect Wilks $\lambda=.69$, $F(2, 172)=39.5$, $p<.0001$; Positive Affect Wilks $\lambda=.78$, $F(2, 172)=23.9$, $p<.0001$]. The group by period interactions were not significant indicating that the groups had similar patterns of response [Negative Affect Wilks $\lambda=.99$, $F(6, 344)=.32$, $p=.93$; Positive Affect Wilks $\lambda=.98$, $F(6, 344)=.66$, $p=.68$], and they did not differ in their absolute levels of affect [Negative Affect $F(3, 173)=.71$, $p=.51$; Positive Affect $F(3, 173)=.67$, $p=.57$]. Cardiovascular responses, defined as change from baseline to stressor on stress day, also indicated that all four groups, including the High Risk subjects, showed significant heart rate and blood pressure elevations to the stressors ($ps<.0001$) suggesting that the psychological stressor effectively elicited a cardiovascular response.

3.3.4. Blunted heart rate response to stress—Mean heart rate response to stress paralleled the blunted cortisol findings among the FH+/LoSo group. Mean heart rate response to stress, defined as the change in baseline to stress on rest versus stress days, is depicted in Fig. 4. Based on our prior studies showing a blunted stress cortisol response in abstinent alcohol-dependent patients, we compared heart rate responses in the High and Low Risk groups. The heart rate responses differed significantly across the four groups [$F(3, 182)=3.28$, $p=.02$] with the largest difference seen between the Low Risk and High Risk groups [$t(116)=-3.0$; $p=.0025$].

4. Discussion

The present results are consistent with our primary hypothesis that a reduced cortisol stress response would be seen in persons with a family history of alcoholism who have a disinhibited behavioral style. The stress hyporesponsiveness of these subjects was also seen in their reduced heart rate response to the combined stressors. The response reduction was not attributable to an inability to experience the events as emotionally activating because all groups had robust increases in self-reports of affect, and all had significant rises in heart rate and blood pressure. This reduction in cortisol response to stress also was not due to a dysregulation of basal cortisol secretion since the High Risk subjects had apparently normal diurnal curves. The results allow us to rule out the possibility that the blunted stress cortisol responses we observed in patients with alcoholism or polysubstance use disorders were caused by those disorders. Instead it appears that the blunted reactivity is a preexisting element of risk.

It is noteworthy that a family history of alcoholism alone did not account for much of the reduction in the cortisol stress response. However, a family history is not a perfect indicator of an equivalent genetic inheritance or degree of expression in a given offspring. In accord with other work showing that externalizing tendencies (defiance, rule breaking, impulsivity) may mark higher levels of risk for substance use disorders, we had predicted that manifestations of behavioral disinhibition would add useful information to that provided by the family history groupings. Cloninger (Cloninger, 1987; Cloninger et al., 1981) proposed a neuropsychiatric model of brain function, temperament, and alcohol seeking tendencies that he suspected represented the pathways through which a presumed genetic risk would operate. Sher and colleagues characterized young adult offspring of alcoholics as behaviorally undercontrolled (Sher and Trull, 1994). A key component of behavioral undercontrol is a tendency toward antisocial behavior (rule breaking, poor adherence to norms, lack of behavioral inhibition) (Finn et al., 1990; Sher et al., 2004). Sociopathy is a frequent accompaniment of alcohol use disorders. In two earlier studies, we also found sociopathic tendencies to account for significant differences in psychophysiological reactivity to emotionally significant stimuli in offspring of alcoholics (Miranda et al., 2002) and in alcoholics (Miranda et al., 2003). Twin adoption studies indicate that risk for alcoholism has a high degree of coinheritance with antisocial personality disorder and may share a common mode of transmission (Langbehn et al., 2003).

One potential explanation for these findings is that the antisocial characteristics of the High Risk group might have reduced their stress appraisals of the situation, resulting in a reduced cortisol response. A normal response to a social stressor such as public speaking depends on an individual's appraisal of the situation and the related limbic system inputs to the HPA axis (Lovallo, 2005). An individual's appraisal of the situation involves the perception, interpretation, and evaluation of the stressor (Olff et al., 2005). Recently, Olff et al. (2005) proposed a stress-coping model that addresses specific appraisal and coping components involved in adult response to stressors that determine neuroendocrine responses to stress and most likely are influenced by personality variables. However, the High Risk group reported subjective evaluations of the situation and their own reactions in a manner consistent with the other groups we tested. Therefore, these subjects may have had a normal cognitive appraisal of the situation but failed to produce adequate outputs to hypothalamic and brainstem areas responsible for the peripheral response.

A stress cortisol response depends not only on the person's appraisals, but also on limbic system inputs to the paraventricular nucleus of the hypothalamus (Schulkin et al., 1994). In order for a stress cortisol response to occur the activation signals appear to involve the amygdala, outputs to the bed nuclei stria terminalis, and the response of the hypothalamus. A disruption in the signal at any one of these brain structures could result in a reduction in the hypothalamic outputs during stressful situations. It is noteworthy that the bed nuclei of the stria terminalis are located near two critical structures responsible for linkages between outputs of the limbic system and activity of the prefrontal cortex. The bed nuclei lie adjacent to the nucleus accumbens, a structure with many dopaminergic terminals and one where dopamine secretion occurs in response to acute administration of alcohol and all other drugs of abuse (Koob et al., 1994). It is also noteworthy that the bed nuclei and nucleus accumbens are in extensive two-way contact with the medial prefrontal cortex, and area where Damasio suggests visceral inputs are used to generate affective biases that allow us to make decisions under motivationally significant circumstances (Damasio, 1994). Inadequate visceral responses to social stimuli may also underlie a reduced ability to be able to understand how others feel in response to one's own actions (empathy) and to use such information to restrain one's behavior in society (abiding by rules and adhering to social norms) both sets of behaviors being typical of the subjects with low scores on the So scale. We speculate that inadequate neural communication at this frontal-limbic juncture may have implications for antisocial tendencies in these subjects and for their inadequate inputs to the paraventricular nucleus of the hypothalamus.

One limitation to this study was that the sample size prohibited us from examining gender differences in the pattern of stress responsivity across the four CPI-So risk groups. Future studies on larger samples are needed to examine the influence of other personality traits and gender on cortisol stress response across the four CPI-So risk groups. A second limitation was that our sample consisted only of individuals who did not meet DSM-IV criteria for alcohol or drug dependence. As a result we were unable to examine cortisol reactivity in persons at the highest levels of risk manifested by outright dependence. Including higher risk subjects and incorporating assessment of threat appraisal and coping in this population should be a focus of future studies. Finally, without conducting follow up studies on these volunteers, we will not know which ones will develop alcohol or drug dependencies in the future, and this too is a desired goal.

The primary hypothesis was supported that FH would predict a reduced cortisol response to stress, but that this reduction would be explained in whole or in part by the temperament characteristics of these persons. The reduced cortisol stress response seen in persons with one or two alcoholic parents and who were relatively less well socialized suggests that this element of temperament maybe a key to understanding which FH+ individuals have a higher risk for future addictions. These findings suggest that personality factors associated with sociability

and behavioral disinhibition influence stress response and may serve as risk markers for the development of substance use disorders. The findings reported here are speculative until further work is carried out assessing the predictive value of the attenuated stress cortisol response.

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Fig. 1. CPI Sociability scores by Family History of Alcoholism from a preliminary study (Miranda, Meyerson et al., 2002) and the current study.

Fig. 2.

Cortisol stress response defined as the increase in the mean cortisol level during the stress period on the stress day from the corresponding mean on the rest day.

Fig. 3.
Diurnal cortisol patterns for the four CPI-So groups on rest day.

Fig. 4.
Heart rate stress response defined as the change in baseline to stress on rest versus stress days.

Table 1

Subject characteristics

N	FH-95	FH+91	<i>p</i>
Demographics			
Men (%)	26	19	ns
Women (%)	25	30	ns
Caucasian (%)	92	79	.009
Age (yrs)	23 (.36)	24 (.38)	ns
SES	49 (1.35)	44 (1.41)	.007
Education (yrs)	15.7 (.22)	15.2 (.24)	ns
Shipley vocabulary	30.3 (.46)	29.6 (.42)	ns
Shipley abstraction	15.8 (.47)	17.2 (.62)	ns
Shipley mental age	14.3 (.15)	14.5 (.16)	ns
Self-report measures			
AUDIT	2.7 (.24)	3.5 (.32)	.04
Cahalan (oz./month)	38.8 (3.64)	47.3 (4.03)	ns
BDI-II	4.2 (.43)	6.1 (.54)	.006

Entries show mean (standard error). FH=Family history of alcoholism. SES=socioeconomic status by the Hollingshead scale. AUDIT=Alcohol Use Disorders Identification Test. BDI-II=Beck Depression Inventory, revised.