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Alcohol use, urinary cortisol, and heart rate variability in apparently healthy men: Evidence for impaired inhibitory control of the HPA axis in heavy drinkers

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Abstract

Alcoholism and heavy drinking are associated with a number of physiological, behavioral, affective, and cognitive problems. One such problem involves dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis, with alcoholics showing higher basal cortisol levels and reduced inhibitory feedback control. In addition, alcohol consumption is associated with decreased heart rate variability (HRV). In the present study we examined the relationships among alcohol consumption, cortisol excretion, and HRV in 542 apparently healthy men. Men in the top tertile of self-reported alcohol consumption had higher cortisol levels and lower HRV compared to men in the lower two tertiles of alcohol consumption. In addition, the inverse relationship between cortisol and HRV was greatly attenuated in the heavy drinking group even after accounting for a number of potential confounding factors. These results support prior research on the HPA axis dysregulation in alcoholics and suggest impaired inhibitory control of the HPA axis in heavy drinkers. The findings are consistent with the neurovisceral integration model, which links central and peripheral processes, and may provide a comprehensive framework for the future investigation of the complex mix of physiological, behavioral, affective, and cognitive factors which comprise the heavy drinking phenotype.

Keywords: Cortisol; Heart rate variability; Alcohol; Amygdala; Prefrontal cortex

Chronic alcohol use and alcoholism are associated with a diverse range of physiological, behavioral, affective, and cognitive problems. Therefore any comprehensive model of alcohol use and abuse must attempt to understand the common underlying mechanisms that might join these functions into the phenotype of the heavy drinker. We have recently applied such a comprehensive model to the understanding of alcohol use and craving (Ingjaldsson et al., 2003a,b,c). In the present study we sought to expand the scope of these investigations to include the regulation of the hypothalamic–pituitary–adrenal (HPA) axis across the spectrum of alcohol use in an apparently healthy, non-alcoholic population.

Numerous studies have found that alcohol use is associated with dysregulation of the HPA axis. Common findings include higher basal cortisol levels and blunted stress induced HPA axis activation in alcohol users compared to non-users (Wand and Dobs, 1991; Adinoff et al., 1998; Bernardy et al., 1996; Errico et al., 2002; Lovallo et al., 2000). HPA axis dysregulation has been found in children of alcoholics and abstinent alcoholics and thus does not appear to be entirely dependent upon the currently active pharmacological effects of alcohol (Adinoff et al., 1998; Bernardy et al., 1996; Croissant and Olbrich, 2004; Errico et al., 2002; Gerra et al., 1999; Lovallo et al., 2000).

Whereas the nature of the HPA axis dysregulation is complex one prominent idea is that heavy alcohol use leads to impaired inhibitory control of the HPA axis (Adinoff et al., 1998; Hundt et al., 2001). For example, studies using the dexamethasone (DEX) suppression test and more recently the combined DEX-suppression/corticotrophin-releasing hormone (CRH) stimulation test have found hypersecretion of cortisol in alcohol users and suggested that it is a function of reduced inhibitory feedback of the HPA system (Hundt et al., 2001). A

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similar lack of inhibitory feedback of the HPA system has been found in a number of disorders including depression, anxiety disorders, schizophrenia, chronic stress, and epilepsy to name a few (Drevets, 1999; Zobel et al., 2004). The commonalities among these disorders suggests a common neural circuitry for this lack of inhibitory control.

Numerous researchers have suggested sets of neural structures that are involved in the regulation of physiological, behavioral, affective, and cognitive responses (Benarroch, 1993, 1997; Davidson, 2000, 2002; Devinsky et al., 1995; Thayer and Brosschot, 2005; Thayer and Lane, 2000). One such model, termed the neurovisceral integration model, has identified a flexible neural network associated with self-regulation and adaptability that might provide a unifying framework within which to view the diversity of responses across domains (Thayer and Brosschot, 2005; Thayer and Friedman, 2004; Thayer and Lane, 2000). For the present study, the major components of this neural circuit include the amygdala, as a source of outputs that are associated with cortisol excretion, and the prefrontal cortex, as a source of inhibitory influences on amygdala outputs (Davidson, 2002; Thayer, in press). CRH neurons are heavily concentrated in the central nucleus of the amygdala and these are associated with the release of cortisol. Furthermore the amygdala is under tonic inhibitory control by the prefrontal cortex (Davidson, 2002; Drevets, 1999; Thayer and Brosschot, 2005; Thayer, in press) and this inhibitory control has been linked to the parasympathetic nervous system and heart rate variability (HRV) (Henry, 2002; Ruiz-Padial et al., 2003; Thayer and Brosschot, 2005; Thayer, in press). Numerous studies have found reduced HRV associated with both acute and chronic alcohol ingestion (Ingjaldsson et al., 2003a,b,c). Interestingly reduced HRV has also been found in many of the other disorders associated with a lack of inhibitory control of the HPA axis such as depression, anxiety disorders, schizophrenia, and chronic stress (Friedman and Thayer, 1998; Thayer and Friedman, 2004).

We have found HRV to be associated with the regulation of the amygdala as indexed by startle magnitude and emotion-modulated startle (Ruiz-Padial et al., 2003). Individuals with lower HRV had larger magnitude startle responses and poorer emotion-modulated startle, as indexed by potentiated startle responses in the presence of neutral foreground stimuli, compared to those with higher baseline levels of HRV. We have also reported an association between resting levels of HRV and cortisol responses to mild cognitive challenge (Johnsen et al., 2002). In this study we found that persons with low HRV showed larger salivary cortisol responses just after each and during the recovery from a series of mild cognitive challenges but did not differ in cortisol levels in the morning, during pre-task baseline, or in the evening in comparison to those with higher levels of HRV.

We have also shown that HRV is associated with activity of the prefrontal cortex (Ahern et al., 2001; Lane et al., 2001). Specifically both pharmacological blockade and neuroimaging studies suggest that greater HRV is linked to greater prefrontal inhibition of sympathoexcititory circuits involved in stress responses. Taken together these findings from diverse literatures lead us to several hypotheses. One, individuals with high levels of self-reported habitual alcohol consumption would show higher levels of cortisol and lower levels of HRV compared to those with lower levels of self-reported alcohol consumption. Two, self-reported habitual alcohol consumption would be positively related to overnight urinary cortisol levels. Three, HRV and cortisol levels would be inversely related. And four, these relationships among alcohol use, HRV, and cortisol would be dysregulated in persons with high levels of alcohol consumption. Specifically, the inverse relationship between cortisol and HRV would be reduced in heavy drinkers compared to lighter drinkers.

However to clearly investigate these hypotheses several potential confounding factors need to be considered. Heavy alcohol consumption is associated with a number of health related problems including hypertension, depression, smoking, and sleep disturbances (Adinoff et al., 1998). Heavy drinkers and alcoholics have been shown to having higher blood pressure, more depressive symptoms, greater tobacco use, and more sleep problems. These factors have all been associated with cortisol and HRV and thus need to be accounted for in any investigation of the relationships among alcohol use, cortisol, and HRV. In the present study these factors were investigated and entered into multivariate models to account for their effects. Thus the present study represents the first large study to investigate alcohol use, cortisol, and HRV after accounting for a wide range of potential confounding factors.

1. Methods

1.1. Participants

The study population comprised apparently healthy employees of an airplane manufacturing plant in Southern Germany. The sample spanned the entire age of the work force (18–63 years) and all levels of socioeconomic status (from the general manager to unskilled workers). The majority of the participants were engineers or highly skilled aircraft mechanics. The study was approved by the institutional review board of the Swiss Federal Institute of Technology. All participants gave written informed consent.

We excluded subjects from the analysis with recording failures of the ECG recorder ($n=10$), missing laboratory data ($n=7$), incomplete physical examination ($n=2$) and subjects who had missing items regarding demographics or medical history ($n=27$). This yielded a final sample of 542 men with complete datasets.

Prior to the heart rate recording a medical examination was performed. Blood pressure via sphygmomanometry was recorded from the dominant arm in the seated position after a standardized 20-min rest period. All participants were examined between 9 and 11 am on a typical work day. Heart rate was recorded as beat-to-beat intervals with a Mini-Vitaport ECG logger (Becker Medical Systems, Karlsruhe, Germany), sampling the three electrode ECG at a rate of 400 Hz. Beat-to-beat

intervals were calculated as the interval between two successive *R*-spikes. After instrumentation with the ambulatory ECG recorder, individuals proceeded with their daily work until 3:30 pm and then continued with their usual leisure and sleep activities. The next morning between 7:15 and 8:00 am fasting blood samples were collected from all individuals and the ECG monitors were disconnected.

Subjects were asked to complete an overnight urine collection from 9 pm on the night preceding the blood sample until and including the first voiding after awakening in the morning. Urine catecholamines were determined by HPLC and overnight urinary cortisol, standardized to gram excreted creatinine, used as our measure of HPA axis activity.

Blood samples were immediately transported to a commercial laboratory (Synlab, Augsburg, Germany), where they were analyzed within six hours of sample collection. Hematocrit and blood lipids were determined using routine laboratory analyzers (Hitachi 911, Roche Diagnostics).

Raw data for determination of heart rate variability were processed according to the Task Force Guidelines (Task Force Guidelines, 1996). Beat-to-beat intervals that corresponded to a heart rate below 30 or above 200 were excluded, as well as any intervals resulting in an increase or drop in heart rate by more than 30% between successive intervals. The root mean square of successive differences (RMSSD) was calculated from all valid adjacent beat-to-beat intervals during the entire recording period. The RMSSD is viewed as a time-domain based index corresponding to parasympathetic neural regulation of the heart and was used as our primary index of HRV. Calculations were carried out using SAS (version 8.2, SAS Inc, Cary, NC).

Participants completed a number of demographic and self-report questionnaires. Demographic variables included age and family income. Family income was measured as the average monthly disposable income in Euros after taxes, social security, health insurance, and pension contributions using a Likert scale (1=<1000; 2=1000–1500; 3=1500–2000; 4=2000–2500; 5=2500–3000; 6=3000–4000; 7=4000–5000; 8=>5000). Smoking was assessed as a dichotomous variable with 0 being never smoked and 1 being current or former smoker. Depressive symptoms were assessed with the HADS Depression scale and sleep quality was assessed with the Jenkins Sleep Questionnaire (Jenkins et al., 1988). Alcohol use was assessed as grams of alcohol consumed per day. Two groups were formed on the basis of their self-reported alcohol use: one group including those in the highest tertile of alcohol use (>20 g of alcohol per day: high use group) and the other being the lower two tertiles of alcohol use (<20 g of alcohol per day: low use group).

2. Results

2.1. Differences between alcohol use groups

Descriptive statistics for the total sample, the highest tertile of alcohol use, and the bottom two tertiles of alcohol use separately are presented in Table 1. The high alcohol use group had significantly greater age, income, SBP, DBP, sleep problems, urinary cortisol, and as expected alcohol use. The lower alcohol use group had significantly greater RMSSD. The alcohol use groups did not differ significantly on urinary norepinephrine, BMI, percentage of smokers, or depression.

Table 1
Sample characteristics

	High use grp	Low use grp	Total
n	196	346	542
Age (years)	45.46 (9.8)*	40.36 (11.2)	42.20 (11.0)
Smokers (*n*, %)	58 (28.6)	89 (24.7)	147 (27.1)
History of hypertension (*n*, %)	38 (18.9)	40 (11.2)	78 (14.4)
History of myocardial i nfarction (*n*, %)	0 (0)	5 (1.4)	5 (0.9)
Diabetes insulin dependent (*n*, %)	3 (1.5)	7 (1.9)	10 (1.8)
Family income (range 1–8)	5.08 (1.6)*	4.54 (1.7)	4.74 (1.7)
Systolic blood pressure (mm Hg)	126 (14)*	122 (15)	123 (14)
Diastolic blood pressure (mm Hg)	82 (10)*	80 (10)	81 (10)
Body-mass-index (kg/m^2)	26.8 (3.3)	26.4 (3.6)	26.5 (3.5)
Jenkins Sleep Questionnaire	5.89 (4.2)*	5.17 (3.9)	5.43 (4.0)
High-density lipoprotein (mg/dl)	56 (11.9)	51 (11.5)	53 (11.9)
Low-density lipoprotein (mg/dl)	140 (37.0)	130 (37.5)	134 (37.5)
Triglycerides (mg/dl)	151 (98)	160 (135)	157 (123)
HADS Depression	4.97 (3.3)	4.86 (3.1)	4.90 (3.2)
Alcohol (g/day)	35.7 (15.7)*	8.0 (5.8)	18.0 (17.0)
Urinary Cortisol (μg/g urinary creatinine)	43.9 (19.2)*	40.0 (18.3)	41.4 (18.7)
Urinary norepinephrine (μg/g urinary creatinine)	15.9 (6.4)	15.9 (9.6)	15.9 (8.6)
RMSSD (ms)	36.4 (12.9)*	40.5 (18.3)	38.9 (14.5)

Note: Values are means and standard deviations unless otherwise noted. *Indicates significant difference between high alcohol use and low alcohol use groups.

2.2. Relationships among alcohol use, cortisol, and HRV

2.2.1. Total sample analyses

In the total sample, urinary cortisol was positively correlated with daily alcohol use ($r=0.11$, $p=0.005$) and negatively correlated with RMSSD ($r=-0.16$, $p<0.001$). Importantly, RMSSD remained significantly negatively correlated with cortisol in multivariate models controlling for a wide range of covariates (see Table 2).

2.2.2. Low alcohol use analyses

In the lower alcohol use group, multivariate analyses revealed that urinary cortisol was marginally positively correlated with alcohol use (Model 1: $r=0.081$, $p=0.07$ one tailed; Model 2: $r=0.06$, $p=0.25$). Importantly, RMSSD was significantly negatively correlated with urinary cortisol after controlling for covariates (Model 1: $r=-0.14$, $p=0.01$; Model 2: $r=-0.13$, $p=0.02$).

2.2.3. High alcohol use analyses

In the higher alcohol use group, multivariate analyses showed that urinary cortisol was no longer correlated with alcohol use (Model 1: $r=0.001$, $p=0.99$; Model 2: $r=0.058$, $p=0.44$). Importantly, the negative relationship between RMSSD and urinary cortisol was greatly attenuated and no

Table 2
Correlations and partial correlations between cortisol and alcohol use and RMSSD

		Zero order	Model 1	Model 2
Total sample	Alcohol use	**0.11 (0.005)**	0.06 (0.17)	**0.09 (0.04)**
	RMSSD	**−0.16 (<0.001)**	**−0.11 (0.013)**	**−0.097 (0.026)**
High use group	Alcohol use	0.06 (0.2)	0.001 (0.99)	0.058 (0.44)
	RMSSD	−0.095 (0.093)	−0.05 (0.50)	−0.048 (0.52)
Low use group	Alcohol use	0.06 (0.13)	0.08 (0.14)	0.06 (0.25)
	RMSSD	**−0.18 (<0.001)**	**−0.14 (0.01)**	**−0.13 (0.02)**

Model 1: Partial correlations controlled for diagnosed hypertension, prior MI, diagnosed diabetes, number of smokers, systolic BP, diastolic BP, BMI, HDL, LDL, hematocrit, tryglycerides, and age.
Model 2: Partial correlations controlled for prior MI, diagnosed diabetes, number of smokers, Jenkins Sleep Questionnaire scores, family income, HADS Depression, urinary norepinephrine, systolic BP, diastolic BP, BMI, and age.
In models 1 and 2 the association between cortisol and RMSSD was also controlled for alcohol use. Significant associations are in bold.

longer significant (Model 1: $r=-0.05$, $p=0.50$; Model 2: $r=-0.048$, $p=0.52$).

3. Discussion

We found that apparently healthy adult men that drank more than twenty grams of alcohol per day had significantly higher levels of urinary cortisol as well as significantly lower levels of HRV than men that drank less than twenty grams of alcohol per day. The higher alcohol use group also had significantly higher blood pressure and more self-reported sleep problems compared to the lower alcohol use group. Urinary cortisol levels were positively correlated with alcohol use, and inversely associated with HRV even after controlling for a wide range of covariates and potential confounders. Importantly, these relationships among alcohol use, cortisol, and HRV were greatly altered in the high alcohol use group. Cortisol and alcohol use were no longer related in the high use group and the inverse relationship between cortisol and HRV was greatly attenuated and no longer significant. Thus, in the high alcohol use group evidence for HPA axis dysregulation was found.

The observed relationship between cortisol and HRV might suggest that the appropriate regulation of the HPA axis depends in part on the autonomic nervous system (ANS) and parasympathetic influences in particular. Thus the observed inverse relationship may suggest a negative feedback mechanism by which cortisol output is modulated by the autonomic nervous system. Clearly the HPA axis and the ANS are related as components of an internal regulation system (Benarroch, 1993, 1997; Thayer and Lane, 2000). However as cogently described by Benarroch this internal regulation system is regulated by a set of neural structures that he has termed the central autonomic network (CAN: Benarroch, 1993, 1997). The CAN includes a number of structures throughout the neuraxis including the prefrontal cortex and the amygdala. The overlap of the CAN with the network hypothesized to be involved in the inhibitory control of the HPA axis is therefore not surprising (Diorio et al., 1993; Zobel et al., 2004). Moreover given that peripheral measures such as cortisol and HRV are associated with activity of the amygdala and the prefrontal cortex, respectively, the observed inverse relationship between cortisol and HRV may reflect the inhibitory influence of the prefrontal cortex on the amygdala which has been reported in both animal and human studies (for reviews see Thayer and Brosschot, 2005, and Thayer, in press). Thus the present results are largely consistent with the neurovisceral integration model in which a set of neural structures that regulates physiological, behavioral, affective, and cognitive responses can be indexed via peripheral indices such as cortisol excretion, startle blink magnitude, inflammatory markers, and HRV (Thayer and Brosschot, 2005).

The attenuated negative association between cortisol and HRV found in the high drinking group may reflect a breakdown of the 'functional connectivity' between the PFC and the amygdala that has been reported in healthy subjects in two recent neuroimagaing studies of the serotonin transporter gene as well as the breakdown of such connectivity with certain polymorphisms (Heinz et al., 2005; Pezawas et al., 2005). Alcoholism has been associated with dysregulated serotonin function such that alcoholics have decreased levels of serotonin, and enhanced serotonin has been associated with decreased alcohol intake (Anthenelli et al., 2001; Manuck et al., 2005; McBride and Li, 1998). These findings become even more relevant when one notes that cortisol is associated with enhanced serotonin reuptake and thus lower levels of serotonin (Tafet et al., 2001a,b). Thus elevated levels of cortisol, whether induced by alcohol use, stress, or genetics, may act via altered serotonin levels to alter the functional connectivity between the PFC and the amygdala. That we may be able to index this by the use of peripheral measures is consistent with the neuroviseral integration model and may provide a framework for the integration of the complex mix of physiological, behavioral, affective, and cognitive problems that define the heavy drinking phenotype (Thayer and Lane, 2000).

Heavy alcohol intake is associated with a number of health related problems including hypertension, depression, tobacco use, and sleep problems (Wand and Dobs, 1991; Adinoff et al., 1998). In the present study adult males that reported drinking more than 20 g of alcohol had significantly higher blood pressure and reported more sleep problems than men that reported drinking less than 20 g of alcohol per day. However, the drinking groups in the present study did not differ on depressive symptoms or the percentage of smokers. Whereas HPA axis dysregulation has been associated with depressive symptoms and recently with smoking the present results appear not to be modulated by such factors (al' Absi et al., 2003; Drevets, 1999).However future research should certainly explore these factors as well as hypertension and sleep problems as their high co-morbidity with alcohol use suggests that they might also be amenable to investigation from the same theoretical perspective as applied here.

Heavy active alcohol intake is associated with increased cortisol secretion. Wand and Dobs (1991) reported that active alcoholics had two-fold greater 24-h urinary cortisol levels than did matched low drinking control subjects. In the present study the high alcohol intake group had significantly higher overnight urinary cortisol levels compared to the lower

drinking group. Interestingly, excess cortisol levels are also associated with high blood pressure, mood alterations including depression, smoking, and disturbed sleep among other problems (Adinoff et al., 1998; al' Absi et al., 2003). Therefore it is possible that the hypertension, depression, tobacco use, and sleep problems seen in alcoholics could be secondary to their excess cortisol excretion. The present findings are not inconsistent with this idea. However given the cross-sectional nature of these data causal inferences cannot be drawn. Importantly, the present findings with respect to the relationship between cortisol and HRV remained even when such potential confounding factors were accounted for.

Both acute and chronic alcohol ingestion are associated with decreased vagally mediated HRV (Ingjaldsson et al., 2003c). The results of the present study found that the high alcohol intake group had significantly lower HRV than the lower intake group. Therefore in terms of behavioral, cardiovascular, and HPA axis responses our data are consistent with a large body of literature on the effects of heavy alcohol consumption. Though the effects in the present study with respect to cortisol and HRV were smaller than those of other researchers (Ingjaldsson et al., 2003a,b,c; Wand and Dobs, 1991), our findings were derived from a group of high functioning, working drinkers with no known diagnosis of alcoholism. This suggests that a continuum of drinking exists with higher levels of alcohol intake associated with increased health risk even without a diagnosis of alcoholism. Moreover, given our rather limited self-report assessment of alcohol use it is possible that the present results underestimate the magnitude of the effects that might be found with a more extensive and objective alcohol assessment.

Whereas it is possible that some men in our high drinking group had an undiagnosed alcoholism the fact that they were working, did not report being absent from work more than the lower intake group, were otherwise apparently healthy, and did not present with an alcoholism diagnosis upon screening argues against such a possibility. Similarly, whereas it is possible that differences among the groups in potential confounding factors such as hypertension, depression, smoking, or sleep problems may have affected the results the fact that the groups did not differ on history of hypertension, myocardial infarction, diabetes, percentage of smokers, or depression argues against such an influence. In addition, these as well as other potential confounding factors such as norepinephrine excretion were statistically controlled in our analyses. Finally, the group as a whole was quite healthy with less than 100 individuals reporting a history of hypertension, MI, or diabetes, and with none of the mean values for other factors such as blood pressure, depression, or sleep problems being in the clinical range. Thus we feel confident that our results will generalize to other apparently healthy men.

The literature on HPA axis function in alcohol use is replete with reports not only of excess cortisol excretion but HPA axis dysregulation in heavy drinkers. In many studies this dysregulation takes the form of blunted cortisol responses to various stressors (Bernardy et al., 1996; Errico et al., 2002; Lovallo et al., 2000; Wand and Dobs, 1991; Adinoff et al., 1998). This dysregulation has been probed by the use of the combined DEX-suppression/CRH-stimulation test in alcoholics (Hundt et al., 2001). For example, these researchers reported that alcoholics showed elevated cortisol responses to CRH after pretreatment with dexamethasone. These results suggest a deficient inhibitory feedback system. Similar results are found in depressive patients and the nature of this deficient inhibition in alcoholism has been illuminated by studies in depressive patients. Furthermore, many studies suggest that chronic stress is also associated with reduced inhibitory feedback control of the HPA axis and it has been suggested that chronic high levels of alcohol intake might serve as such a chronic stressor on the HPA system (Hundt et al., 2001; Vanitallie, 2002).

Very recent studies in epilepsy have also found evidence for impaired inhibitory control of the HPA axis (Zobel et al., 2004). Moreover these authors provided a particularly informative analysis of the deficient inhibitory control. In particular they noted that the amygdala is a target region for control of the HPA axis due in part to the high concentration of CRH neurons in the extended amygdala. They further noted that the amygdala receives large inputs from the vagus nerve which might serve to modulate the CRH neurons and thus contribute to the feedback control of the HPA axis. In addition they and others (Davidson, 2000, 2002; Drevets, 1999; Thayer and Brosschot, 2005; Thayer, in press) have noted that the prefrontal cortex exerts inhibitory control on the amygdala and thus might be a site of relevance to the impaired inhibitory control seen in a wide range of disorders including epilepsy, depression, and alcohol abuse. This inhibitory control appears to be at least partly vagally mediated as well as a result of common central nervous system circuits and thus is consistent with the neurovisceral integration model which stresses the importance of the parasympathetic nervous system in providing negative feedback on sympathoexcitatory stress responses (Thayer, in press; Thayer and Brosschot, 2005).

It is also possible that the reduced 'functional connectivity' between the prefrontal cortex and the amygdala may be a predisposing factor for alcohol abuse as well as epilepsy, chronic stress, depression, and other addictive behaviors such as smoking. This would not be inconsistent with the data on at-risk populations for these disorders in which at-risk individuals are often found to share certain abnormal responses with persons with diagnosed disorders (Gerra et al., 1999). This idea is also not inconsistent with the research on serotonin regulation where certain polymorphisms have been associated with decreased functional connectivity (Heinz et al., 2005; Pezawas et al., 2005). Future research might fruitfully explore the effects of certain genetic polymorphisms on relationships within and among central and peripheral measures such as the relationship between cortisol and HRV investigated in the present study. For example, we have reported reduced HRV in persons with a polymorphism of the angiotensin-converting enzyme insertion/deletion gene (ACE I/D) that has also been associated with the risk for psychopathology (Thayer et al., 2003; Gard, 2002).

In summary, the present study replicated previous research that found that heavy drinking is associated with increased basal cortisol levels and decreased HRV. However the present

study extended such work by showing that the inhibitory control of the HPA axis is disrupted in heavy drinkers and that this was independent of a number of potential confounding factors including hypertension, depressive symptoms, smoking, and sleep problems. These results are consistent with the neurovisceral integration model and may provide a comprehensive framework for the investigation of the many complex factors that define the heavy drinking phenotype.

References

Adinoff, B., Iranmanesh, A., Veldhuis, J., Fisher, L., 1998. Disturbance of the stress response: the role of the HPA axis during alcohol withdrawal and abstinence. Alcohol Health Research World 22, 67–72.

Ahern, G.L., Sollers, J.J., Lane, R.D., Labiner, D.M., Herring, A.M., Weinand, M.E., Hutzler, R., Thayer, J.F., 2001. Heart rate and heart rate variability changes in the intracarotid sodium amobarbital (ISA) test. Epilepsia 42, 912–921.

al' Absi, M., Wittmers, L.E., Erickson, J., Hatsukami, D., Crouse, B., 2003. Attenuated adrenocortical blood pressure responses to psychological stress in ad libitum and abstinent smokers. Pharmacology, Biochemistry, and Behavior 74, 401–410.

Anthenelli, R.M., Maxwell, R.A., Geracioti, T.D., Hauger, R., 2001. Stress hormone dysregulation at rest and after serotonergic stimulation among alcohol-dependent men with extended abstinence and controls. Alcoholism: Clinical and Experimental Research 25, 692–703.

Benarroch, E.E., 1993. The central autonomic network: functional organization, dysfunction, and perspective. Mayo Clinic Proceedings 68, 988–1001.

Benarroch, E.E., 1997. The central autonomic network. In: Low, P.A. (Ed.), Clinical Autonomic Disorders, 2nd ed. Lippincott-Raven, Philadelphia, pp. 17–23.

Bernardy, N.C., King, A.C., Parsons, O.A., Lovallo, W.R., 1996. Altered cortisol response in sober alcoholics: an examination of contributing factors. Alcohol 13, 493–498.

Croissant, B., Olbrich, R., 2004. Stress response dampening indexed by cortisol in subjects at risk for alcoholism. Journal of Studies on Alcohol 65, 701–707.

Davidson, R.J., 2000. The functional neuroanatomy of affective style. In: Lane, R.D., Nadel, L. (Eds.), Cognitive Neuroscience of Emotion. Oxford University Press, New York, pp. 106–128.

Davidson, R.J., 2002. Anxiety and affective style: role of prefrontal cortex and amygdala. Biological Psychiatry 51, 68–80.

Devinsky, O., Morrell, M.J., Vogt, B.A., 1995. Contributions of anterior cingulate cortex to behavior. Brain 118, 279–306.

Diorio, D., Viau, V., Meaney, M.J., 1993. The role of the medial prefrontal cortex (cingulate gyrus) in the regulation of the hypothalamic–pituitary–aredenal response to stress. Journal of Neuroscience 13, 3839–3847.

Drevets, W.C., 1999. Prefrontal cortical–amygdalar metabolism in major depression. Annals of the New York Academy of Sciences 877, 614–637.

Errico, A.L., King, A.C., Lovallo, W.R., Parsons, O.A., 2002. Cortisol dysregulation and cognitive impairment in abstinent male alcoholics. Alcoholism: Clinical and Experimental Research 26, 1198–1204.

Friedman, B.H., Thayer, J.F., 1998. Autonomic balance revisited: panic anxiety and heart rate variability. Journal of Psychosomatic Research 44, 133–151.

Gard, P.R., 2002. The role of angiotensin II in cognition and behavior. European Journal of Pharmacology 438, 1–14.

Gerra, G., Zaimovic, A., Sartori, R., Raggi, M.A., Bocchi, C., Zambelli, U., Timpano, M., Zanichelli, V., Delsignore, R., Brambilla, F., 1999. Experimentally induced aggressiveness in adult children of alcoholics (ACOAs): preliminary behavioral and neuroendocrine findings. Journal of Studies on Alcohol 60, 776–783.

Heinz, A., et al., 2005. Amygdala–prefrontal coupling depends on a genetic variation of the serotonin transporter. Nature Neuroscience 8, 20–21.

Henry, T.R., 2002. Therapeutic mechanisms of vagus nerve stimulation. Neurology 59, S3–S14.

Hundt, W., Zimmermann, U., Pottig, M., Spring, K., Holsboer, F., 2001. The combined dexamethasone-suppression/CRH-stimulation test in alcoholics during and after acute withdrawal. Alcoholism: Clinical and Experimental Research 25, 687–691.

Ingjaldsson, J., Thayer, J.F., Laberg, J.C., 2003a. Pre-attentive processing of alcohol stimuli. Scandinavian Journal of Psychology 44, 161–165.

Ingjaldsson, J., Thayer, J.F., Laberg, J.C., 2003b. Craving for alcohol and pre-attentive processing of alcohol stimuli. International Journal of Psychophysiology 49, 29–39.

Ingjaldsson, J.T., Laberg, J.C., Thayer, J.F., 2003c. Reduced vagal tone in chronic alcohol abuse: relationship with negative mood, chronic thought suppression, and compulsive drinking. Biological Psychiatry 54, 1427–1436.

Jenkins, C.D., Stanton, B.A., Niemcryk, S.J., Rose, R.M., 1988. A scale for the estimation of sleep problems in clinical research. Journal of Clinical Epidemiology 41, 313–321.

Johnsen, B.H., Hansen, A.L., Sollers III, J.J., Murison, R., Thayer, J.F., 2002. Heart rate variability is inversely related to cortisol reactivity during cognitive stress. Psychosomatic Medicine 64, 148 (abstract).

Lane, R.D., Reiman, E.M., Ahern, G.L., Thayer, J.F., 2001. Activity in medial prefrontal cortex correlates with vagal component of heart rate variability during emotion. Brain and Cognition 47, 97–100.

Lovallo, W.R., Dickensheets, S.L., Myers, D.A., Nixon, S.J., 2000. Blunted stress cortisol response in abstinent alcoholic and polysubstance-abusing men. Alocoholism: Clinical and Experimental Research 24, 651–658.

Manuck, S.B., Kaplan, J.R., Lotrich, F.E., 2005. Brain serotonin and aggressive disposition in humans and non-human primates. In: Nelson, R.J. (Ed.), Handbook on the Biology of Aggression. Oxford University Press, New York, pp. 65–113.

McBride, W.J., Li, T.K., 1998. Animal models of alcoholism: neurobiology of high-alcohol-drinking behavior in rodents. Critical Reviews in Neurobiology 12, 339–369.

Pezawas, L., et al., 2005. 5-HTTLPR polymorphism impacts human cingulate–amygdala interactions: a genetic susceptibility mechanism for depression. Nature Neuroscience 8, 828–834.

Ruiz-Padial, E., Sollers III, J.J., Vila, J., Thayer, J.F., 2003. The rhythm of the heart in the blink of an eye: emotion-modulated startle magnitude covaries with heart rate variability. Psychophysiology 40, 306–313.

Tafet, G.E., Toister-Achituv, M., Shinitzky, M., 2001a. Enhancement of serotonin uptake by cortisol: a possible link between stress and depression. Cognitive, Affective, and Behavioral Neuroscience 1, 96–104.

Tafet, G.E., Idoyaga-Vargas, V.P., Abulafia, D.P., Calandria, J.M., Roffman, S.S., Chiovetta, A., Shinitzky, M., 2001b. Correlation between cortisol level and serotonin uptake in patients with chronic stress and depression. Cognitive, Affective, and Behavioral Neuroscience 1, 388–393.

Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996. Heart rate variability: standards of measurement, physiological interpretation and clinical use. Circulation 93, 1043–1065.

Thayer, J.F., in press. On the importance of inhibition: Central and peripheral manifestations of nonlinear inhibitory processes in neural systems. Nonlinearity in Biology,Toxicology, and Medicine.

Thayer, J.F., Brosschot, J.F., 2005. Psychosomatics and psychopathology: looking up and down from the brain. Psychoneuroendocrinology 30, 1050–1058.

Thayer, J.F., Friedman, B.H., 2004. A neurovisceral integration model of health disparities in aging. In: Anderson, N.B., Bulato, R.A., Cohen, B. (Eds.), Critical Perspectives on Racial and Ethnic Differences in Health in Late Life. The National Academies Press, Washington, DC, pp. 567–603.

Thayer, J.F., Lane, R.D., 2000. A model of neurovisceral integration in emotion regulation and dysregulation. Journal of Affective Disorders 61, 201–216.

Thayer, J.F., Merritt, M.M., Sollers III, J.J., Zonderman, A.B., Evans, M.K., Yie, S., Abernethy, D.R., 2003. Effect of angiotensin-converting enzyme insertion/deletion polymorphophism DD genotype on high-frequency heart rate variability in African Americans. American Journal of Cardiology 92, 1487–1490.

Vanitallie, T.B., 2002. Stress: a risk factor for serious illness. Metabolism 51, 40–45.

Wand, G.S., Dobs, A.S., 1991. Alterations in the hypothalamic–pituitary–adrenal axis in actively drinking alcoholics. Journal of Clinical Endocrinology and Metabolism 72, 1290–1295.

Zobel, A., Wellmer, J., Schulze-Rauschenbach, S., Pfeiffer, U., Schnell, S., Elger, C., Maier, W., 2004. Impairment of inhibitory control of the hypothalamic pituitary adrenocortical system in epilepsy. European Archives of Psychiatry and Clinical Neuroscience 254, 303–311.