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Blunted stress reactivity reveals vulnerability to early life adversity in young adults with a family history of alcoholism

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Abstract

Background and aims: Persons with blunted stress reactivity have poor impulse control and also show increased risk for alcoholism. Exposure to early life adversity (ELA) contributes to blunted reactivity, but individual differences in susceptibility to ELA are not well understood. This study aimed to determine whether exposure to ELA has a greater impact on stress reactivity in young adults with a family history of alcoholism (FH+) compared with young adults with no family history of alcoholism (FH–).

Design: Observational study using linear modelling.

Setting: Oklahoma, USA.

Participants: 709 young adults (398 females) recruited through community advertisement.

Measurements: We obtained heart rates and cortisol levels in subjects while undergoing public speaking and mental arithmetic stress compared with a resting control day (1418 test sessions). ELA was quantified as 0, 1, or > 1 adverse events experienced by age 15 yr. FH+ persons had 1 or 2 parents with an alcohol use disorder, and FH– controls had no such history for 2 generations.

Findings: Increasing levels of ELA predicted progressive blunting of cortisol and heart rate reactivity for the whole sample ($F = 4.6, p < .01$), but examination by FH status showed that the

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Author Contributions

W.R.L. designed the study and details of the protocol. A.J.C., and A.S.V. maintained the data set and analyzed the data. K.H.S. oversaw the assessment procedures and psychiatric interviews. A.A. participated in interpretation of the analysis and formulation of the interpretation. All authors contributed to writing the paper and approve of its content.

Declarations of interest
None

effect of ELA was significant only among FH+ ($F_s = 3.5$, $p < .05$) and absent in FH– ($p > .40$). This difference in ELA impact was not explained by the cortisol diurnal cycle or subjective evaluation of the stressors.

Conclusions: People with a family history of alcoholism appear to be vulnerable, in terms of changes to physiological stress response, to the impact of exposure to early life adversity (ELA) while people with no family history of alcoholism appear to be resilient. Blunted stress reactivity may reflect differential vulnerability to ELA in young adults with a family history of alcoholism.

Keywords

family history of alcoholism; lifetime adversity; stress reactivity; heart rate; cortisol

INTRODUCTION

Blunted reactivity to stress may contribute to risk for addictions. We have noted that patients in treatment for alcoholism have diminished cortisol and heart rate stress responses to a range of stressors (1–3). Although blunted responses may have reflected chronic alcohol exposure, we surmised that they may also represent a premorbid marker of elevated risk (4). Blunted stress reactivity is now seen as a predictive of alcoholism and disinhibitory psychopathology more generally (5, 6). Adults with blunted responses tend to encounter legal difficulties and have poor impulse control, along with elevated rates of alcohol and drug abuse (7–10). They have high rates of relapse after smoking cessation (11, 12) and are likely to consume alcohol following acute stress exposure (13). Adolescents with blunted cortisol responses in the laboratory are likely to engage in risky driving and to have arrests for driving under the influence of alcohol (9, 14) indicating a common propensity to risk-taking and abusive drinking.

Although blunted stress reactivity accompanies risk for alcoholism, the contributors to blunted reactivity remain poorly understood (15). Recent attention has focused on adverse childhood experiences on health outcomes, including alcoholism, in adulthood (16), and a growing literature points to early experience, and parental behavior in particular, to shape the stress axis in adulthood (17, 18). In the Family Health Patterns Project, we found that healthy young adults exposed to early life adversity (ELA) had blunted cortisol and heart rate responses to mental stress in the laboratory (19) in agreement with work by Carpenter and colleagues (20). The contribution of ELA to blunted reactivity and risk for alcoholism gains significance in light of disrupted family relationships often occurring in alcoholic households.

Alcoholic patients are likely to report having alcoholic parents (21), and offspring of alcoholic families (FH+) are at increased risk of alcoholism compared to persons with no parental history (FH–) (22). Twin-adoption studies yield a significant heritability estimate for alcoholism (23). Not surprisingly, FH+ offspring experience family disruption, maladaptive parenting, and life stress more frequently than FH– (24, 25). The prevalence of ELA in alcoholic families raises the question of whether FH+ may show a differential impact of such exposure relative to their FH– counterparts. We examined cortisol and heart

rate responses to mental stress in healthy FH+ and FH– young adults and predicted that exposure to ELA would have a greater impact on stress reactivity in FH+ persons.

METHODS

Overview.

The Family Health Patterns Project is a study of healthy FH+ and FH– young adults and risk for alcohol and other substance use disorders. The present analysis extends our prior report on ELA and stress reactivity (19), by allowing us to account for the impact of ELA within FH+ and FH– groups.

Subjects.

The present sample includes 709 persons (398 females) recruited through community advertisement. Each subject 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, USA (IRB no 2302), and received financial compensation for participating.

Inclusion and exclusion criteria.

Exclusion criteria were designed to identify healthy FH+ persons who would carry risk factors for alcoholism in the absence of changes associated with heavy alcohol and drug exposure. Prospective volunteers were excluded using DSM-IV criteria if they had: a personal history of alcohol or drug dependence; met criteria for current substance abuse within the past 2 months; failed a urine drug screen or breath-alcohol test on days of testing; had a history of any Axis I disorder, other than past depression or dysthymia (> 60 days previous), as defined by the Diagnostic and Statistical Manual of Mental disorders, 4th ed. (26). Women were required to have a negative urine pregnancy test on each day of testing and none were nursing. All participants were in good physical health, had a body mass index < 30, were not taking prescription medications, and had no reported history of serious medical disorder. Smoking and smokeless tobacco use were not exclusionary. Preliminary analyses showed no difference in cortisol reactivity between tobacco users and nonusers.

Subject background and psychological assessments

A preliminary telephone screening was followed by assessment of subject's family history of alcoholism using the Family History Research Diagnostic Criteria (FH-RDC) (27) and a personal psychiatric history using the computerized version of the Diagnostic Interview Schedule-IV (C-DIS-IV) (28), conducted by a trained assistant under the supervision of a licensed clinical psychologist.

FH and ELA assessment.

The FH-RDC calls for volunteers to answer questions matching C-DIS-IV items about their biological parents and grandparents. Volunteers were considered FH+ if either parent met 2 or more DSM-IV criteria for alcohol or other substance abuse or dependence. FH– reported no such problems in the parents or grandparents. Proband reports were crosschecked with

parents in 79% of all cases, with an initial confirmation in 91% of those. Reassignment of classification or dropping of cases resulted in 97% confirmed assignments in the sample reported here (29).

ELA was assessed using C-DIS-IV items closely similar to life events assessed retrospectively by Caspi (30, 31) as follows: Physical or Sexual Adversity (“Have you ever been mugged or threatened with a weapon or ever experienced a break-in or robbery?” “Have you ever been raped or sexually assaulted by a relative?” “Have you ever been raped or sexually assaulted by someone not related to you?”, yielding a possible 3 points) and Separation from Parents (“Before you were 15, was there a time when you did not live with your biological mother for at least 6 months?” “Before you were 15, was there a time when you did not live with your biological father for at least 6 months?”, for a possible 2 points). Each person was assigned a C-DIS-IV adversity score ranging from 0 (no events) to a maximum of 5. A subset of this study sample ($N = 261$) also completed the short form of the Childhood Trauma Questionnaire (CTQ-SF) (32). The C-DIS-IV scores (0–5) were significantly correlated with CTQ-SF total scores, $r = 0.616$, $p < .0001$. Due to a limited number of C-DIS-IV reports yielding scores ≥ 3 ($N = 35$), the scores were recoded for further analysis to form ELA groups representing 0, 1, or > 1 events.

Study design and procedure

Following screening, subjects visited the lab twice at the same time on both days, either in the morning at 0900h ($N = 349$) or in the afternoon at 1300h ($N = 360$). Percentages of subjects in morning and afternoon sessions were similar across the study subgroups (Table 1). To maximize stress responses, the first lab day involved the stress procedure, comparable to other single-day stress studies, and the second day was designated the resting control day (33). Subjects were briefed in advance of this test order and were told to expect to deliver short speeches and a mental arithmetic task on the stress day.

Stress protocol.

The protocol called forth significant effort to perform well in the presence of an experimenter engaging in social evaluation and providing corrections for errors, both of which threatened embarrassment for lapses in performance (34). The protocol (75 min) included a prestress baseline (30 min), during which the subject sat quietly and read general interest magazines, followed by mental stress (45 min) consisting of simulated public speaking (30 min) (35) and mental arithmetic (15 min) (34). A white-coated experimenter monitored performance taking notes on a clipboard and corrected errors during mental arithmetic.

Resting control day.

The protocol lasted 75 min, during which the subject sat and read general interest magazines or watched videotapes of nature programs lacking emotional content.

Subjective reports.

Subjects rated their moods at each saliva sample using 12 10-point visual-analogue scales adapted from Foresman (36) containing a Distress subscale (impatience, irritability, distress, pleasantness, and feelings of control) and an Activation subscale (effort, tension, concentration, interest, and stimulation) (34).

Saliva collection times and cortisol assay

Because cortisol secretion is dependent on the sleep-wake cycle (37), volunteers were required to have a normal work or school schedule and a nighttime sleep pattern. Also, because acute cortisol secretion is affected by prevailing blood glucose levels (38), all volunteers ate a standard meal at the lab before beginning the protocol. Saliva samples were collected using the Salivette device (Sarstedt, Newton, NC, USA) and were taken at 9 periods across both days: awakening, arrival at the lab, min 10 and 20 of the baseline period, min 15, 30, and 45 of the stress protocol or continued rest, and at 30 min post stress or rest, and at bedtime. Salivettes were centrifuged at 4200 RPM for 20 min, and the saliva was transferred to cryogenic storage tubes and stored at - 20° C until quantification. Saliva free cortisol assays were conducted by Salimetrics (State College, PA, USA) using a competitive enzymatic immunoassay (39) with a sensitivity of <.083 µg/dL and an interassay coefficient of variation of < 6.42%.

Heart rate

Heart rate was measured continuously during both protocol days from readings made every 2 min using an oscillometric monitor (Dinamap, V100, General Electric, USA). Heart rate data were unavailable for 4 subjects due to recording failures.

Data analysis

Dependent variables were cortisol and heart rate responses to stress along with self-reports. Cortisol data were log transformed to normalize the distribution. Cortisol reactivity was measured as the average change from rest day to stress day in saliva samples taken at minutes 30 and 45 of the stress period and at the same two times during the extended rest protocol. Heart rate reactivity was measured as the mean heart rate during speech preparation periods minus the heart rate at those times during the rest day protocol to avoid confounding by vocal activity during the speech delivery or mental arithmetic.

The analysis used a general linear model including ELA (scaled as 0, 1, or >1 adverse experiences), FH (FH+, FH-), and the ELA x FH interaction. Type III sums of squares were evaluated to ensure independence of significant effects. Model results are provided in Table S1 in the Supplemental Material. Preliminary tests of the model revealed that the interaction term was not significant. Inspection of Figure 1 indicates that ELA appears to have had no differential effect among the FH- subjects, and in contrast, that ELA was associated with diminishing reactivity scores among the FH+ subjects. The interaction term was dropped, and subsequent analyses were done on the main effects of FH and ELA (Table S1). On the basis of our *a priori* hypothesis, we tested the impact of 0, 1, and >1 levels of ELA within

the respective FH– and FH+ groups using independent *F* ratios (40). As a check for the influence of hormonal contraceptive use (41), we tested the results including and excluding data from women using this method of birth control and found no change in the results. Missing data were not replaced. Data were analyzed using SAS software, Ver. 9.2 for Windows. Copyright© 2012 SAS Institute Inc. SAS and all other SAS Institute Inc. product or service names are registered trademarks of SAS Institute Inc., Cary, NC, USA.

RESULTS

Demographics are shown in Table 1. FH groups did not differ in alcohol intake, consistent with the aim of limiting alcohol abuse to avoid confounding with FH status. Compared to FH–, FH+ reported more frequent ELA exposure ($X^2 = 127$, $p < .001$) and had lower SES scores ($X^2 = 19.7$, $p < .001$). ELA exposure was accompanied by less educational achievement in both FH groups ($F = 5.31$, $p < .005$).

Impact of ELA on stress reactivity in FH+.

Cortisol responses are shown in the top panels of Figure 1. FH+ subjects had smaller responses than FH–, $F(1, 707) = 4.15$, $p < .043$, and ELA led to progressively diminished cortisol responses to stress, $F(1, 689) = 4.57$, $p < .011$, in agreement with our previous report on a smaller sample (19). Tests on ELA groups stratified by FH status showed that exposure to increasing ELA led to progressively blunted cortisol responses in FH+ persons, $F(2, 260) = 3.19$, $p < .044$, partial $\eta^2 = .024$, with no such effect in the FH– group, $F(2, 422) = 0.75$, $p > .47$, partial $\eta^2 = .002$.

The same pattern of results occurred for heart rate reactivity, as shown in the bottom panels of Figure 1. The FH+ group had reduced heart rate reactivity compared to the FH– group, $F(2, 703) = 3.10$, $p < .079$, and responses were progressively smaller in persons exposed to greater degrees of ELA, $F(2, 689) = 4.70$, $p < .009$. However, the effect ELA was significant only among FH+ persons, $F(2, 260) = 3.53$, $p < .031$, partial $\eta^2 = .031$, and absent among the FH– group, $F(2, 422) = 0.75$, $p > .47$, partial $\eta^2 = .004$.

ELA and diurnal cortisol secretion.

We tested these results for the effects of diurnal cortisol secretion, use of hormonal contraceptives, time of day of testing, resting day values, and subjective states and found no effect on the above results, as shown in Figure S1, Supplementary Material.

Subjective responses to stress.

Reports of Activation and Distress are shown in Table S3a. These showed the predicted increases to the stress protocol, however these subjective responses did not affect the primary cortisol and heart rate responses to stress (Table S3b).

Type of ELA and altered reactivity.

The ELA scale included reports of separation from a parent and physical and sexual abuse (Table S4). We examined the type of reported ELA in relation to laboratory stress responses and found that, in this data set, cortisol reactivity was diminished in relation to separation

from a parent, $F(5, 686) = 3.75, p < .024$, but not by exposure to physical and sexual abuse, $F(5, 686) = 1.66, p > .17$. The same results held for heart rate reactivity, with smaller heart rate responses as a function of separation from a parent, $F(5, 682) = 5.31, p < .005$, and no effect for physical and sexual abuse, $F(5, 682) = 0.46, p > .71$.

DISCUSSION

Blunted stress reactivity is associated with disinhibition, maladaptive behavior, and risk for psychopathology, including alcohol and other substance use disorders (7). There is little information on the sources of blunted reactivity and on individual differences in susceptibility to these sources. We previously reported that exposure to ELA during childhood and adolescence contributes in a dose-response manner to blunting of stress axis reactivity in early adulthood (19). The present findings are based on an expanded study sample and show that FH+ persons are vulnerable to ELA while their FH- counterparts appear to be resilient. The impact of ELA on stress reactivity is consistent with observations by Miller and Chen that early life stress leaves a “biological residue” that affects stress reactivity and behavior (42). The differential vulnerability among FH+ persons is in agreement with Ellis and Boyce that some individuals show a biological “sensitivity to context” (43). The results provide insight into sources of blunted stress axis reactivity and their consequences for health behaviors, and they suggest directions for future work.

FH+ persons are at increased risk for alcoholism (22) with contributions from genes and environment (44, 45). The susceptibility of FH+ persons to ELA is consistent with earlier findings that genetic variation may render some individuals vulnerable to maltreatment, leaving others resilient (30, 31, 44). The differential impact of ELA on FH+ persons suggests that the search for genes conferring risk for alcoholism may profitably focus on intermediate phenotypes such as blunted stress reactivity and vulnerability to ELA. None of the present subjects met diagnostic criteria for posttraumatic stress disorder. In perspective, the lack of psychiatric comorbidities in this study sample suggests that nontraumatizing adversity may nonetheless alter physiology in otherwise healthy individuals. ELA and diminished endocrine and autonomic reactivity is similar to blunted responses in adolescents with antisocial tendencies, who also show low physiological activation, behavioral impulsivity, and risky decision-making (46). The presence of ELA in the present study sample also predicted higher levels of impulsivity, poorer working memory, faster discounting of delayed rewards, and elevated scores on the Eysenck Neuroticism Scale and the Beck Depression Inventory (47). A loss of risk aversion and reduced emotional stability following ELA exposure in FH+ persons may contribute to early initiation of drinking and ignoring negative consequences of excessive intake resulting in increased risk of alcohol and other substance use disorders (24, 47, 48).

These collective results point to a pervasive effect of ELA on physiological reactivity and behavior in a potentially vulnerable FH+ population. Consistent with this interpretation, neuroimaging studies show that persons exposed to adverse rearing conditions may have altered interactions between the ventromedial prefrontal cortex and the amygdala, resulting in modifications in how the stress axis is activated during periods of increased adaptive demands (49–51). These brain areas are highly sensitive to the environment, particularly to

early life experience (17, 52, 53), and they appear to be meaningful targets for study in relation to behavioral dispositions and alcohol and drug abuse potential (54). Neuroimaging of smaller subject samples from the Family Health Patterns project has shown that FH+ persons exposed to emotional faces had blunted amygdala responses that were associated with antisocial scores on a measure of socialization and disinhibition (55), and they also had exaggerated responses of the anterior cingulate gyrus and caudate nucleus while playing a risky game of chance (56), both findings being consistent with enhanced approach tendencies and diminished aversion. We also carried out anatomical brain scans in a small sample of volunteers from this study ($N = 55$) and younger subjects 10 to 14 years of age from an unrelated project ($N = 114$) (57). The FH+ subjects in both samples had impairments of white matter integrity (seen in low fractional anisotropy) in the anterior corona radiata. The relevance for alcoholism was that fractional anisotropy was reduced in proportion to the number of alcoholic relatives in both of the age groups (both $r_s = .40$). In the older subjects, reduced fractional anisotropy was associated with an earlier age at first drink ($r = 0.35$, $p < .01$, unpublished observation) which is a predictor of later problem drinking. Although the present study sample was not exposed to severe forms of child abuse, others have reported impaired myelination of white matter pathways in the frontal cortex of abused children (58). Mild impairments of communication between the prefrontal cortex and other brain regions, including the amygdala, are understood to accompany disinhibitory behavioral styles, antisocial behavior, and poor controls over alcohol use (59). In moving forward, studies of genetic polymorphisms in FH+ persons, who are commonly exposed to ELA, and development of relevant brain structures may provide insights into persons at greatest risk for addiction.

Strengths and limitations.

The present sample is large for a study of stress responses, thereby lending confidence to the findings. Nonetheless, the ELA questions were based on retrospective reports and covered broad categories of life events in childhood and adolescence. The data do not allow analysis of specific ages of exposure or the specific reasons for parental separations. The relationship between ELA and blunted stress reactivity in the FH+ represent small effect sizes. Longitudinal data will allow better resolution on the ages of greatest vulnerability and specifics of adverse events (60). Some perspective on the impact of ELA is gained by noting that none of our subjects met diagnostic criteria for posttraumatic stress disorder. These nontraumatizing levels of ELA nonetheless appear to modify the stress axis in early adulthood, pointing to the very significant impact that these relatively common life events can have in otherwise healthy persons. The greater prevalence of ELA in the FH+ group raises questions about gene-by-environment effects on the individual and conversely about gene effects on the household environment, as noted by others (61). Studies showing the negative impact of ELA also call attention to possible sources of resiliency provided by nurturing early environments (62).

The impact of ELA in the present study accords with findings from the Adverse Childhood Experiences Study that have documented a pervasive contribution of early life stress to poorer overall health in adulthood (63, 64). The correlational nature of this evidence calls for studies of biomarkers to fill the gaps between early experience and health consequences

(65). The present data call attention to FH+ as a marker of vulnerability to ELA and point to the stress axis, as focus of biological interest (7). A new effort to assess central nervous system involvement in substance use disorders is represented by the Adolescent Brain and Cognitive Development study recently launched by NIH. This will assess a national sample of subjects, ages 8–15 years, for development of brain structures and function in relation to FH status, ELA, and initiation of alcohol and drug use (<https://addictionresearch.nih.gov/abcd-study>, Accessed June 1, 2018).

Conclusion

ELA contributes to blunted stress axis reactivity in adulthood. The impact of ELA represents a form of environmental programming of physiological function, and this programming may have implications for adaptive behavior and health. ELA resulted in programming of the stress axis in the full study sample analyzed here, but this programming occurred to a greater degree in FH+ persons. The results suggest that stress axis biomarkers may be useful in probing how ELA affects behavior and health outcomes in persons with inherited vulnerability to alcohol and other substance use disorders. In contrast, the more robust stress responses in FH– persons call for parallel research efforts on stress resilience and positive health outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Cortisol responses (top panels) and heart rate responses (bottom panels) to a mental stress protocol. ELA refers to low, moderate, and higher levels of early life adversity (ELA = 0, 1, >1 forms of adversity experienced in childhood and adolescence). FH refers to a negative or positive family history of alcoholism (FH-, FH+). Left panels show data by FH- and FH+ groups. Middle panels show data by exposure to ELA. Right panels show data for FH x ELA groups.

Table 1:

Demographic and Biometric Characteristics

ELA	FH+			FH-		
	0	1	> 1	0	1	> 1
N = 709	77	104	90	293	117	28
ELA (%)	29	38	33	67	27	6 ^a
Females %	49	69	72	50	53	54 ^{b, c}
Age (yr)	23.9 [0.4]	23.1 [0.3]	24.6 [0.3]	23.4 [0.2]	23.9 [0.4]	23.9 [0.7]
Race (% White)	83	74	74	83	81	75
SES	45 [1.4]	45 [1.3]	41 [1.4]	50 [0.7]	47 [1.2]	48 [2.0] ^c
Education (yr)	15.7 [0.2]	15.2 [0.2]	15.1 [0.2]	16.1 [0.1]	15.6 [0.2]	15.3 [0.4] ^b
BMI (kg/m ²)	23.5 [0.4]	23.6 [0.3]	24.4 [0.4]	23.3 [0.2]	23.6 [0.3]	23.9 [0.8]
Smokers (%) (n)	11.9 (9)	10.6 (11)	12.2 (11)	6.5 (19)	3.4 (4)	10.7 (3)
AUDIT	4.5 [0.4]	4.2 [0.4]	3.5 [0.3]	3.9 [0.2]	3.7 [0.3]	3.7 [0.5]
Alcohol Use (oz/mo)	27.4 [3.7]	20.5 [3.4]	15.7 [3.0]	20.8 [2.0]	18.8 [2.6]	22.0 [5.8]
PM Test Time (%)	49	46	53	52	52	46

Note: Entries show M [SEM] unless noted otherwise. FH = family history of alcoholism, ELA = early life adversity, Par Sep = separation from one or both parents for 6 mos before age 15 yr. Phys, Sex = Report of physical abuse or sexual abuse occurring prior to the time of subject's interview. BMI = body mass index, SES = Hollingshead socioeconomic status index, AUDIT = Alcohol Use Disorders Identification Test. The sample size reflects the total number of persons with complete cortisol data (N = 694) plus those with complete heart rate data (N = 688).

^a ELA score by FH group: $\chi^2 = 25.71, p < .0001$

^b ELA group: F = 3.8, $p < .05$

^c FH group: F = 5.6, $p < .05$

Table 2.

Reports of Early Life Adverse Events

	FH-	FH+
Total events		
0	67 (293)	29 (77)
1	27 (117)	38 (104)
> 1	6 (28)	33 (90)
Separation from Parents		
0	82 (357)	41 (112)
1	16 (68)	42 (113)
> 1	3 (13)	17 (46)
Physical and Sexual Abuse		
0	81 (355)	66 (178)
1	17 (76)	28 (75)
> 1	2 (7)	6 (18)

Note: Entries show % (N) for ELA groups