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Early-Life Adversity Interacts with *FKBP5* Genotypes: Altered Working Memory and Cardiac Stress Reactivity in the Oklahoma Family Health Patterns Project

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Exposure to stress during critical periods of development can have adverse effects on adult health behaviors, and genetic vulnerabilities may enhance these stress effects. We carried out an exploratory examination of psychological, physiological, and behavioral characteristics of 252 healthy young adults for the impact of early-life adversity (ELA) in relation to the G-to-A single nucleotide polymorphism (SNP), rs9296158, of the *FKBP5* gene. *FKBP5* is a molecular cochaperone that contributes to the functional status of the glucocorticoid receptor (GR) and to the quality of corticosteroid signaling. *FKBP5* expression is upregulated by cortisol exposure during stressful episodes, with greater upregulation seen in A-allele carriers. As such, *FKBP5* expression and GR function may be environmentally sensitive in A-allele carriers and therefore suitable for the study of gene-by-environment (G × E) interactions. Compared with *FKBP5*, GG homozygotes ($N = 118$), A-allele carriers ($N = 132$) without psychiatric morbidity had progressively worse performance on the Stroop color-word task with increasing levels of ELA exposure (Genotype × ELA, $F = 5.14$, $P = 0.007$), indicating a G × E interaction on working memory in early adulthood. In addition, heart rate response to mental stress was diminished overall in AA/AG-allele carriers ($F = 5.15$, $P = 0.024$). Diminished working memory and attenuated autonomic responses to stress are both associated with risk for alcoholism and other substance use disorders. The present data suggest that *FKBP5* in the GR pathway may be a point of vulnerability to ELA, as seen in this group of non-traumatized young adults. *FKBP5* is accordingly a potential target for more extensive studies of the impact of ELA on health and health behaviors in adulthood.

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INTRODUCTION

Exposure to stress during critical periods of development has adverse effects on health and health behaviors in adulthood (Dube *et al*, 2003). There is suggestive evidence that specific genetic polymorphisms may constitute vulnerability pathways, by which early-life adversity (ELA) can contribute to maladaptive adult characteristics (Caspi *et al*, 2002, 2003). We have recently shown that persons with greater exposure to ELA have (a) diminished physiological stress reactivity (Lovallo *et al*, 2012a), (b) diminished cognitive performance (Lovallo *et al*, 2013), and (c) altered regulation of affect (Sorocco *et al*, 2015), and these phenotypic characteristics may contribute to increased risk-taking and vulnerability to alcohol and other substance use disorders. ELA is much more common in persons with a family history of alcoholism (Lovallo *et al*, 2013), suggesting the desirability of studies of gene-by-environment (G × E) interactions on phenotypic characteristics that contribute to substance abuse risk (Moffitt *et al*, 2006).

The corticosteroid receptor system is a target for such a G × E analysis. Glucocorticoid and mineralocorticoid receptors (GR and MR) are regulated by acute stress exposure, and their functional status is subject to epigenetic programming by early experience (Meaney, 2010; Meaney *et al*, 1985). The presence of GR and MR throughout the limbic system and prefrontal cortex (McEwen *et al*, 1969; Sanchez *et al*, 2000) suggests that modification of corticosteroid receptor pathways can influence behavioral dispositions, affective states, and cognitive function (Champagne and Meaney, 2001; Lupien *et al*, 2002; Meaney *et al*, 2013; Zaharia *et al*, 1996).

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The *FKBP5* protein is a molecular cochaperone that contributes to the functional status of the GR (Zannas and Binder, 2014), thereby influencing how cortisol (CORT) interacts with neurons of the central nervous system (CNS) (Davies *et al*, 2002). *FKPB5* acts together with heat-shock proteins to allow free GR in the cytosol to complex with CORT (Pratt and Toft, 1997) permitting translocation of CORT to the cell nucleus, where it then regulates gene expression (Baxter *et al*, 1972; Rousseau *et al*, 1975). CORT exerts at least two seemingly opposing effects on *FKPB5* expression and GR functionality: (1) CORT increases *FKBP5* expression (Hubler and Scammell, 2004; Jaaskelainen *et al*, 2011) by demethylating an intronic enhancer region of *FKPB5* (Lee *et al*, 2010) and (2) elevated expression of *FKBP5* interferes with the final conformation of the GR super-complex, diminishing its potential for nuclear translocation and impairing cellular responses to CORT (Binder, 2009). Accordingly, CORT elevation, increased *FKBP5* expression, and reduced functionality of the GR constitute a potential pathway through which the environment may exert long-term effects on GR and behavior (Zannas and Binder, 2014).

Modification of the GR pathway in the presence of CORT may occur more readily in persons carrying a specific A-to-G single-nucleotide polymorphism (SNP) of *FKBP5*, rs9296158, under study here. This SNP is in allelic identity and strong linkage disequilibrium with a functional SNP, rs1360780, located in an intronic enhancer of the *FKBP5* gene. The rs1360780 minor allele is more readily demethylated in the presence of CORT than is the major, G allele (Klengel *et al*, 2013). As such, the A allele of rs9296158 may display greater environmental control of the GR pathway with implications for behavior, as supported by several studies. Childhood abuse predicts increased symptoms of post-traumatic stress disorder in A-allele carriers (Binder *et al*, 2008). Minor allele carriers diagnosed with major depressive disorder have higher basal CORT output that is resistant to dexamethasone suppression (Binder, 2009; Binder *et al*, 2004). The rs1360780 minor allele predicts suicidal behavior in adults who were abused in childhood (Roy *et al*, 2010), and *FKBP5* genotypes have different levels of amygdala reactivity to emotional faces (White *et al*, 2012).

Given that minor-allele carriers of *FKBP5* rs1360780, and of the tightly linked rs9296158, may be differentially susceptible to ELA, and considering the presence of GR on structures of the limbic system and prefrontal cortex, the effects of ELA may reasonably include changes in temperament, cognitive function, and stress reactivity (Lovallo, 2013; Lovallo *et al*, 2012b, 2013; Sorocco *et al*, 2015). Accordingly, we employed a G × E analysis on data from the OFHP cohort to investigate the interactive effects of ELA and *FKBP5* rs9296158.

MATERIALS AND METHODS

Subjects

Subjects were healthy young adults participating in the OFHP project, a broad-based study of risk factors for alcoholism (Lovallo *et al*, 2013). The present analysis includes 252 volunteers who had been genotyped for *FKBP5* and had sufficient background data to compute ELA scores. Each subject signed an informed consent form approved by the Institutional Review Board of the University of Oklahoma Health Sciences Center and the VA Medical Center, Oklahoma City, Ok, USA, and was given financial compensation.

Inclusion and exclusion criteria. Subjects were 18- to 30-year-old men and women from the community who were in self-reported good health. Prospective volunteers were excluded if they had: a mental age score of <22 on the Shipley Institute of Living Scale (John and Rattan, 1992); a history of alcohol or drug dependence; substance abuse within the past 2 months; a positive urine screen for abused drugs (iCup, Instant Technologies, Norfolk, VA) or breath-alcohol test on days of testing; a history of Axis I disorder, other than past depression (>60 days), using the Diagnostic and Statistical Manual of Mental disorders, 4th ed. (American_Psychiatric_Association, 1994) based on the CDIS-4 interview (Blouin *et al*, 1988); had a body mass index of $>30\,kg/m^2$; needed prescription medications other than hormonal contraceptives; or had a current medical disorder. Women all had negative urine pregnancy tests at the time of testing. Smoking and smokeless tobacco use were not exclusionary.

ELA assessment. ELA was derived from C-DIS-IV items closely similar to adverse life events assessed retrospectively in studies by Caspi *et al* (2002, 2003) as follows: Physical or Sexual Adversity ('Have you ever been mugged or threatened with a weapon?' 'Have you 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?') and Emotional Adversity ('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?'). Each person was assigned to an ELA group based on 0 reported adverse event, 1 event, or >1 event.

Study Design and Procedure

Subjects passing an initial telephone contact were screened at the laboratory and then tested on 2 days. The laboratory screening was conducted by a trained interviewer supervised by a licensed clinical psychologist and included: the C-DIS-IV interview, assessment of family history of alcoholism using family history research diagnostic criteria (Andreasen *et al*, 1977; Lovallo *et al*, 2013), documentation of the subject's smoking, alcohol and drug use history including the Alcohol Use Disorders Identification Test (AUDIT) (Babor *et al*, 1992), and completion of a series of cognitive, personality, and temperament scales including: the California Personality Inventory Socialization Scale (CPI-So) (Gough, 1994), Beck Depression Inventory (Beck and Beamesderfer, 1974), Eysenck Personality Inventory (Eysenck and Eysenck, 1964), Tridimensional Personality Questionnaire (Cloninger *et al*, 1991), and the Shipley Institute of Living Scale, Revised (John and Rattan, 1992).

Subjects visited the laboratory twice more for behavioral and stress testing. The first test day involved a stress

procedure consisting of public speaking and mental arithmetic, and the second day was a resting control day, as described elsewhere (Sorocco *et al*, 2006). Laboratory testing on both days also involved cognitive testing and behavioral tasks (Lovallo *et al*, 2013).

Testing procedures

Stress procedure. Stress testing lasted 105 min, including a resting baseline in a seated position (30 min) followed by simulated public speaking (30 min) and mental arithmetic (15 min) and a 30-min resting recovery period as described elsewhere (Al'Absi *et al*, 1997; Lovallo *et al*, 2012a). The resting control day involved sitting for 105 min while reading and watching nature videos. Heart rate was monitored every 2 min along with blood pressure measurements taken on both days using an automated monitor (Critikon, Dinamap). Saliva samples for cortisol determination were collected using the Salivette device (Sarstedt, Newton, NC, USA) at 10 times across each test day, including: at home upon awakening and at bedtime, and 8 times in the lab, including twice during the stress protocol and twice during recovery (Lovallo *et al*, 2010a). Salivettes were centrifuged at 4200 r.p.m. for 20 min, and saliva was stored at −70 °C. Assays were conducted by Salimetrics (State College, PA, USA) where the saliva-free cortisol concentrations were quantified using a competitive enzymatic immunoassay (Salimetrics, 2015). The assay has a sensitivity of <.083 μg/dl and an interassay coefficient of variation of <6.42%. Stress responses were computed as the difference in respective values obtained during the stress day compared with the corresponding values on the resting control day and then averaged to provide a single reactivity score, as discussed previously (Al'Absi *et al*, 1997; Lovallo *et al*, 2010a).

Cognitive and behavioral tasks. The Stroop Color-Word Test, Dodrill's version, consists of 176 repetitions of the color words 'red, orange, green, and blue,' presented in a random order with each word printed in a discrepant ink color (eg, the word 'red' printed in blue ink). The subject recites the list aloud two times, first reading the printed words and next reporting the ink colors. Time is recorded during each reading, and an interference score is calculated as the difference between the time to read the ink colors and time to read the words (Salinsky *et al*, 2002; Stroop, 1935). The Tridimensional Personality Questionnaire (Cloninger, 1987) contains three subscales, Novelty Seeking, Harm Avoidance, and Reward Dependence, purported to assess temperament underlying motivations to obtain rewards and avoid punishments in relation to stimuli such as alcohol and recreational drugs (Cloninger *et al*, 1991).

Additional cognitive and behavioral tasks included: the Iowa Gambling Task (Bechara *et al*, 1994), the Balloon Analogue Response Task (Lejuez *et al*, 2002), a Go-NoGo reaction time task (Saunders *et al*, 2008), the ultimatum game (Sanfey *et al*, 2003), and a delay discounting task (Acheson *et al*, 2011).

Genotyping

Subjects provided a saliva sample by passive drool into an Oragene collection and preservation kit (DNA Genotek, Kanata, Ontario, Canada). DNA samples were genotyped with the Illumina OmniExpress array using standard protocols. Samples with call rates below 95% were excluded, and randomly selected samples showed an average reproducibility of 99.998%. The genotype completion rate was 0.993 (using a cutoff of 0.95 call rate). The OmniExpress array does not contain the rs1360780 SNP for *FKBP5*, although the linked tag SNP, rs9296158, is available and is in Hardy–Weinberg equilibrium, and so the latter was used in the present analysis. Of the 252 samples, we were able to impute 241 rs1360780 genotypes with an accuracy of 0.974 using IMPUTE2. Only three genotypes differed between rs1360780 and rs9296158; and therefore, the latter SNP was used in the present analysis because of the larger sample size.

Assessment of population stratification using ancestry informative markers (AIMS). A panel of 2491 SNPs from the Illumina OmniExpress array was selected as AIMS based on the following criteria: (1) large differences in the reference allele frequency of pairwise SNPs from the HapMap Project between African, Chinese, and European populations; (2) mapping on different chromosomes or in different regions of the same chromosome; and (3) shared by both Illumina Human Hap550v3 and HumanOmniExpress-12v1 array. Individual ethnic factor scores corresponding to geographical regions: Africa, Europe, Middle East, Central Asia, Far East Asia, Oceania, and America, were estimated using STRUCTURE v2.3 software and using a known set of 1051 subjects representing 51 worldwide populations (CEPH population) as a reference (http://www.cephb.fr/en/hgdp_panel.php). The data set was predominantly Caucasian. The mean (SD) and median European ancestry of the sample were 0.89 (0.19) and 0.95. Twenty participants had EU ancestry % <0.50, 16 of African ancestry, and 4 of Native American ancestry.

Data Analysis

In accordance with our previous findings on the impact of ELA, data analysis included the predictor variables, Genotype and ELA, and five functional families of dependent variables representing: (a) stress reactivity including CORT and heart rate (HR) change to stress, (b) cognition (Stroop Interference and Shipley Mental Age scores), (c) affect regulation and temperament (scores on the Eysenck neuroticism scale, Beck Depression Inventory, Tridimensional Personality Questionnaire, and CPI-So scale), (d) behavioral impulsivity (BART, Iowa Gambling Task, Go-NoGo reaction time task, ultimatum game, and delay discounting), and (e) substance use and dietary practice (drinking variables, drug experimentation, smoking, and BMI). The families of variables were organized by function in a heuristic model conceptualizing how ELA could have a differential impact on vulnerable persons, resulting in enhanced risk of alcohol and other substance use disorders (Lovallo, 2013).

Because of small sample sizes, we combined data from the AA homozygotes ($N=25$) with the AG heterozygotes ($N=116$) for the analyses. (Data are displayed for the AA, AG, and GG genotypes in Supplementary information.) The data were subjected to analyses of variance including: Genotype (AA/AG, GG), ELA (0, 1, >1), and the G × ELA interaction term. Type III sums of squares were used to

ensure independence of individual F ratios. In preliminary analyses we examined the impact of ancestry by comparing persons with Caucasian *vs* non-Caucasian AIMS in the analytic model, and we also included the separate European, African, Far East Asian, Oceanian, and American ancestry scores as covariates. These preliminary analyses did not change the results, and ancestry was not considered further. Tests were considered as statistically significant if $P<0.05$. Analyses were conducted using SAS software 9.2 (Copyright, SAS Institute, Cary, NC, USA).

RESULTS

Demographics and group descriptive data for the *FKBP5* Genotype (AA/AG, GG) × ELA (0, 1, >1) groups are shown in Table 1. No significant G × ELA interactions were found for age, SES, or years of education, although persons with higher ELA scores had lower SES and fewer years of education, and were more likely to be from a family with a history of alcoholism, as reported previously (Lovallo, 2013). Persons in the present sample are considered to be non-traumatized since selection criteria excluded persons meeting diagnostic criteria for post-traumatic stress disorder or current major depression.

G × ELA Analyses

Cognitive function. Interference scores on the Stroop task showed a significant ELA × Genotype interaction, $F=5.14$, $P=0.007$, partial $eta^2=0.04$, in which AA/AG carriers had progressively poorer performance with 0, 1, and >1 ELA events. No effect of ELA appeared in GG homozygotes (Figure 1, top). We also observed significant main effects of ELA, $F=3.45$, $P=0.03$, partial $eta^2=0.03$, and Genotype, $F=6.66$, $P=0.01$, partial $eta^2=0.026$, with poorer performance occurring with greater ELA exposure and in AA/AG carriers. No significant effects were seen in Shipley Institute of Living Scale mental age scores, as shown in Table 1.

Stress reactivity. As shown in Figure 1, middle panel, HR response to stress was significantly lower in persons carrying the minor *FKBP5* allele (AA/AG) relative to GG homozygotes, $F=5.15$, $P=0.024$, partial $eta^2=0.021$. Although the ELA × Genotype interaction was not significant, $F<1.0$, A-allele carriers appear to show a diminishing HR response as a function of greater ELA exposure. Cortisol data showed no ELA × Genotype effects for baseline values or stress responses, as shown in Table 1. These findings were not influenced by subjective responses to the stressors, as the AA/AG and GG genotypes did not differ in their reports of subjective activation and distress on the rest day or changes from rest to stress day.

Affect and temperament. We observed a modest main effect of Genotype on the TPQ Reward Dependence scores, $F=4.01$, $P=0.046$, partial $eta^2=0.016$, such that minor allele carriers had higher scores on this scale than G-allele homozygotes, as shown in Figure 1, bottom, and Table 1. No genotype differences were seen in any other variable in this category as shown in Table 1.

Behavioral impulsivity. None of the variables included in the behavioral impulsivity cluster showed a significant main effect of genotype, ELA, or a G × ELA interaction, and these are not described further.

DISCUSSION

We examined healthy young adults for a G × E relationship between ELA exposure and the rs9296158 SNP as a surrogate for the functional SNP, rs136078, on the *FKBP5* gene. *FKBP5* is a molecular cochaperone that has a role in the functional status of the GR. Its place in the GR pathway and its consequent interactions with CORT signaling and stress mechanisms make it a potential target for extensive study of environmental impacts on behavior. Because GR function is relatively disrupted in A-allele carriers, we predicted that behavioral and physiological functions associated with the GR system could be modified differentially by ELA in AA/AG relative to GG carriers. Earlier analyses of the OFHP study population have shown a significant overall impact of ELA on stress reactivity, cognitive function, temperament, and behavior (Lovallo, 2013; Lovallo *et al*, 2012a; Sorocco *et al*, 2015). The present analysis extends these findings by showing a differential vulnerability to ELA in *FKBP5* A-allele carriers that is lacking in GG homozygotes. Stroop task performance was progressively worse in A-allele carriers exposed to increasing amounts of ELA, with no such effect in GG homozygotes. This finding points to a possible G × E effect on working memory. We also observed significant *FKBP5* genotype main effects on HR response to stress and, to a more limited degree, on the temperament characteristic of reward dependence, both of which showed a greater impact of ELA among AA/AG carriers. These findings bear comparison to current research on G × E effects involving *FKBP5* alleles, and they suggest avenues for future study.

The importance of the GR pathway for behavioral regulation is consistent with the presence of GR in the limbic system and prefrontal cortex as seen in animal models (McEwen *et al*, 1968; Sanchez *et al*, 2000). Acute administration of hydrocortisone to human volunteers at rest leads to rapid changes in amygdala and hippocampal activation, seen using fMRI (Lovallo *et al*, 2010b). Hydrocortisone taken after exposure to emotional photographs aids in establishment of long-term declarative memories (Buchanan and Lovallo, 2001). Corticosteroids also have acute and long-term effects on working memory (Al'Absi *et al*, 2002; Oei *et al*, 2009; Terfehr *et al*, 2011b). Patients with CORT excess because of Cushing's syndrome and a deficit due to Addison's disease both show cognitive and emotional disturbances, involving disruption of GR-mediated functions of the prefrontal cortex and limbic systems (Anglin *et al*, 2006; Starkman *et al*, 1981, 1992; Tytherleigh *et al*, 2004), and these deficits resolve with successful treatment (Schultebraucks *et al*, 2015; Starkman *et al*, 1999). The importance of GR pathways in registering the effects of stress is seen in studies of psychiatric morbidity indicating that *FKBP5* A-allele carriers are vulnerable to a history of traumatic stress exposure that is associated with risk for depression (Binder *et al*, 2004) and anxiety disorders (Binder, 2009), including posttraumatic stress disorder (Binder *et al*, 2008). We have previously identified four

Table 1 Demographics and Outcome Variables for *FKBP5* and ELA Groups

Genotype	**AA/AG**			**GG**			***P*-value**
ELA	**0**	**1**	**>1**	**0**	**1**	**>1**	
***N* = 252**	**62**	**47**	**25**	**58**	**42**	**18**	
Demographics							
Age	23.6 (0.4)	23.1 (0.4)	23.3 (0.7)	23.5 (0.3)	24.0 (0.5)	24.7 (0.6)	
SES[a]	49 (2)	46 (2)	43 (3)	50 (2)	48 (2)	44 (3)	[a]
Education (years)[a]	16.0 (0.2)	15.3 (0.3)	15.0 (0.3)	16.0 (0.2)	15.4 (0.3)	15.7 (0.5)	[a]
AIMS (%)	89.4 (2.5)	88.2 (3.0)	90 (3.8)	94 (1.0)	93 (1.4)	81 (6.4)	
Cognition							
Shipley MA (years)	18.1 (0.2)	17.8 (0.1)	17.8 (0.2)	18.0 (0.2)	18.2 (0.1)	17.3 (0.3)	
Stress reactivity							
CORT	0.09 (0.01)	0.03 (0.01)	0.02 (0.01)	0.09 (0.02)	0.05 (0.01)	0.06 (0.03)	[a]
Affect and temperament							
Beck depression	4.4 (0.6)	3.3 (0.5)	4.8 (0.9)	3.9 (0.6)	4.3 (0.6)	6.0 (1.2)	
EPI neuroticism	5.2 (0.5)	5.2 (0.5)	6.6 (0.8)	5.8 (0.5)	5.5 (0.6)	6.0 (0.9)	
CPI-So	33.2 (0.6)	31.9 (0.6)	30.4 (0.9)	33.8 (0.5)	30.7 (0.7)	31.0 (0.9)	[a]
PPI-I	17.5 (0.3)	18.2 (0.5)	17.4 (.05)	17.6 (0.4)	16.4 (0.5)	17.2 (0.7)	
PPI-II	12.1 (0.3)	12.0 (0.3)	12.2 (0.4)	12.0 (0.3)	12.1 (0.3)	12.0 (0.6)	
TPQ RD	20.0 (0.5)	19.9 (0.6)	20.3 (0.8)	18.8 (0.6)	19.2 (0.7)	18.3 (1.3)	[b]
TPQ HA	9.1 (0.7)	8.8 (0.8)	11.0 (1.3)	9.2 (0.7)	11.3 (1.0)	9.8 (1.2)	
TPQ NS	15.6 (0.6)	15.0 (0.8)	15.8 (0.8)	14.1 (0.6)	15.0 (0.8)	13.7 (1.0)	
Substance use and BMI							
AUDIT	4.3 (0.4)	4.0 (0.4)	3.1 (0.6)	4.2 (0.4)	5.0 (0.7)	3.7 (0.7)	
FH+ (%)	26	51	33	29	50	72	[a]
Smokers, *N* (%)	2 (3)	3 (6)	3 (12)	6 (10)	3 (7)	1 (6)	[a]
BMI (kg/m^2)	23.5 (0.3)	24.2 (0.4)	23.4 (0.8)	23.6 (0.5)	23.4 (0.5)	24.1 (1.0)	

Abbreviations: AIMS, Ancestry Informative Markers (% with European ancestry markers); AUDIT, Alcohol Use Disorders Information Test; BMI, body mass index; CORT, cortisol response to stress; CPI-So, California Personality Inventory Socialization Scale; ELA, Early-Life Adverse experience; FH+, Positive parental history for alcohol use disorder; HA, Harm Avoidance; MA, Shipley mental age score; NS, novelty seeking; PPI, Psychopathic Personality Inventory (I = core psychopathy, II = disinhibition); RD, Reward Dependence; SES, socioeconomic status; TPO, Tridimensional Personality Questionnaire.
Entries show mean (±SEM) unless otherwise noted. No significant ELA × Genotype interactions were found for any listed variable.
[a]ELA, $P < 0.05$.
[b]Genotype, $P < 0.05$.

families of adult outcomes resulting from ELA exposure: cognitive function, stress reactivity, personality and temperament, and behavioral impulsivity, and have incorporated these into a heuristic model of ELA and risk for alcohol and other substance use disorders (Lovallo, 2013). The current results extend this analysis to show enhanced vulnerability to ELA in healthy, non-traumatized young adults who carry the *FKBP5* A allele.

The present Stroop performance data suggest that working memory processes are subject to a G × E interaction as a function ELA and *FKBP5* genotype. Stroop performance assesses working memory, executive processes in particular (Smith and Jonides, 1997, 1999), and these in turn are influenced by the functional status of the dorsolateral prefrontal cortex, the anterior cingulate gyrus (Friedman and Goldman-Rakic, 1994; Goldman-Rakic, 1998), and the temporoparietal association cortex (Acheson *et al*, 2014; Silveri *et al*, 2011). Given the distribution of GR in prefrontal cortex, modification of the GR pathway by the A allele of *FKBP5* is a particularly useful target for the study of G × E effects on behavior and psychological characteristics (Bogdan *et al*, 2015). Variants of the GR gene are associated with altered working memory performance (Kumsta *et al*, 2010). Healthy subjects carrying the rare variant allele of *FKBP5*, rs1360780, closely linked to the rs9296158 SNP used here, had greater attentional biasing and levels of hippocampal

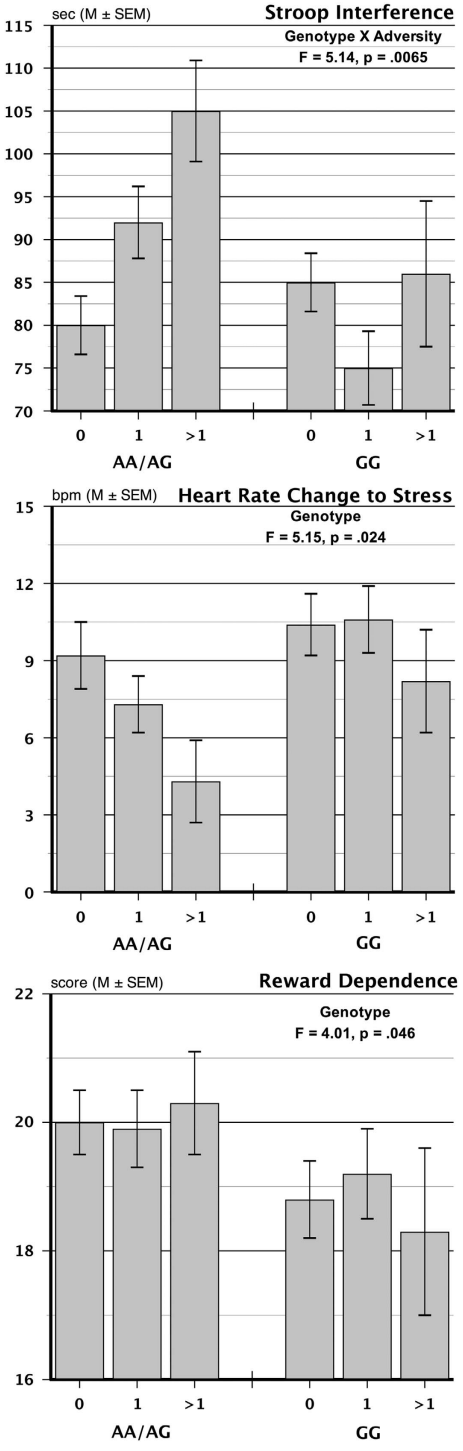

Figure 1 Effects of exposure to early-life adverse events in childhood and adolescence (0, 1, or >1 events) in persons carrying AA or AG alleles of the gene for the molecular cochaperone, *FKBP5 vs* GG carriers. Top panel: Interference scores on the Stroop color-word test. Middle panel: Increase in HR from rest during exposure to a combined mental arithmetic and public speaking stressor. Bottom panel: Scores on the Reward Dependence scale of the Tridimensional Personality Questionnaire.

activation to threat signals in a dot-probe task (Fani *et al*, 2013). *FKBP5* genotypes and ELA showed a G × E effect on amygdala responses to emotional faces in adults (Holz *et al*, 2015) and amygdala volumes in children (Pagliaccio *et al*, 2014), as reviewed elsewhere (Bogdan *et al*, 2015). Other research shows that reduced working memory capacity is associated with elevated risk for alcohol and other substance use disorders (Cservenka *et al*, 2012; Desmond *et al*, 2003; Finn *et al*, 2002; Lovallo *et al*, 2006). The present findings and work just cited suggest the value of more intensive study of working memory and its interactions with emotional responsivity in relation to ELA in *FKBP5* AA/AG carriers.

In examining physiological responses to behavioral stress, we observed a diminished HR response among *FKBP5* AA/AG allele carriers, but we saw no corresponding difference in CORT reactivity. The diminished HR response to our mental stress protocol among A-allele carriers was accompanied by a non-significant tendency toward progressively smaller responses as a function of increasing ELA. The HR data therefore support reduction in autonomic reactivity to stress in carriers of the A allele of *FKBP5*, but a more complete understanding of a differential vulnerability to ELA will require a larger sample size, as being currently acquired in the OFHP. Additional studies should also address whether the diminished HR reactivity observed here is associated with diminished limbic system outputs through the hypothalamus and brainstem pathways to the heart. Diminished HR responses to stress are seen in abstinent alcoholic patients (Panknin *et al*, 2002) and in persons at elevated risk for alcohol and other substance use disorders (Lovallo, 2013). These results, and the potential association of blunted stress reactivity with substance use disorders, suggest the value of studying a broader range of autonomically mediated stress responses in relation to *FKBP5* allele status and exposure to ELA.

In contrast to our HR findings, we observed no impact of *FKBP5* genotype on CORT levels or stress responses, although CORT reactivity was progressively diminished in response to ELA exposure levels (Lovallo *et al*, 2012a). Although CORT results might be expected to parallel HR findings, this is not a necessary outcome. If ELA acts by way of epigenetic changes to *FKBP5* expression, then these effects may vary according to both the person–environment interaction and the specific cell types found in different brain regions (see Klengel and Binder, 2015 for a review). For example, demethylation of the *FKBP5* enhancer region following dexamethasone occurs in hippocampal dentate gyrus but not in other hippocampal tissues (Yang *et al*, 2012). Other data suggest that the effects of *FKBP5* on CORT regulation may be confined to depressed patients (Binder, 2009; Menke *et al*, 2013), but not in healthy controls (Menke *et al*, 2013). Our cohort consists of healthy individuals whose affective responses to the environment may accordingly differ from persons with clinical depression. Similarly, while acute administration of hydrocortisone alters memory performance in healthy controls, it may not do so in patients with major depressive disorder (Terfehr *et al*, 2011a), and there are several non-*FKBP5* candidate mechanisms that may contribute to GR modifications specific to depression (Bet *et al*, 2009; Derijk and de Kloet, 2008; Kumsta *et al*, 2009; Pariante, 2004; van Rossum *et al*, 2006; van West *et al*, 2006).

In addition to the lack of cortisol effects, we also saw no effects of *FKBP5* on a range of cognitive, psychological, and behavioral measures under study here (Table 1) other than reward dependence. This lack of uniformity of G × E effects

across this range of tasks and self-report instruments may be attributable to differences in the sensitivity of the different measures, and ELA effects may not be reflected equally in all brain regions and on their associated functions. In this case, animal models can provide useful guides for interpreting human data, but predictions in the case of individual cognitive and behavioral tasks are premature at present.

The present findings are subject to several limitations. The sample of AA carriers is currently small ($N = 25$), limiting our analysis of potential gene-dose effects. The Stroop interference data represent a limited slice of possible working memory processes, and future work would benefit from intensive study of other tasks to probe-specific working memory components. The HR results presented here point to a possible ELA effect in A-allele carriers, although achieving a significant G × E interaction may require a larger sample size. Although we tested a number of dependent variables, we did not correct for multiple statistical tests. Our reasons were that: (1) we examined different families of phenotypic variables, (2) our earlier ELA findings supported the G × E approach used here, and (3) the lack of existing data in relation to the reasonable ELA-*FKBP5* call for exploratory analyses leading to more hypothesis-driven approaches in future studies. We therefore consider the present findings to be exploratory in nature.

Healthy young adult carriers of the *FKBP5* A allele showed progressively diminished working memory performance following greater levels of ELA, indicating vulnerability to environmental stress in carriers this genotype (Klengel *et al*, 2013). Under this mechanism, A-allele carriers, possibly being exposed to elevated CORT accompanying the stress of ELA, may have shown upregulation of *FKBP5* expression and reprogramming of GR pathways, leading to behavioral effects persisting into early adulthood. As our strongest finding involved working memory, we conclude that ELA may have affected the prefrontal cortex and, by extension, its interactions with the limbic system.

CONCLUSION

The long-term effects of stress during childhood and adolescent development may be reflected in the functional status of the GR pathway, and these effects may be exaggerated in persons inheriting the minor, rs9296158 allele of the molecular cochaperone, *FKBP5*. Early-life stress was reflected in A-allele carriers as diminished cognitive function and blunted stress reactivity. These functional changes may have clinical consequences as diminished working memory capacity and blunted cardiac responses to stress are associated with disinhibitory behavioral characteristics, delinquency, and risk for alcoholism (Gao *et al*, 2010; Lovallo, 2013; Panknin *et al*, 2002). Functional variants of *FKBP5* are a possible target for further study in relation to ELA and its contribution to poor health behaviors in adulthood, including risk for alcohol and other substance use disorders.

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