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Early life adversity and blunted stress reactivity as predictors of alcohol and drug use in persons with *COMT* (rs4680) Val158Met genotypes

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Abstract

Background: Risk for alcoholism may be enhanced by exposure to early life adversity (ELA) in persons with genetic vulnerabilities. We examined ELA in the presence of a common variant of the gene for the enzyme catechol-o-methyltransferase (*COMT*, Val158Met, rs4680) in relation to cortisol reactivity, the onset of early drinking, and experimentation with drugs.

Methods: Saliva cortisol reactivity to speech and mental arithmetic stress was measured in 480 healthy young adults (23.5 years of age, 50% females) who experienced either 0, 1, or 2 forms of ELA during childhood and adolescence, provided information on use of alcohol and recreational drugs, and were genotyped for the Val158Met polymorphism.

Results: ELA led to progressively smaller cortisol responses in the Met/Met and Val/Met allele groups but to progressively larger responses in Val homozygotes, $F = 3.29$, $p = .011$. ELA independently predicted earlier age at first drink, $F = 14.2$, $p < .0001$, with a larger effect in Met allele carriers, $F = 13.95$, $p < .00001$ and a smaller effect in Val homozygotes $F = 4.14$, $p = .02$. Similar effects were seen in recreational drug use. Cortisol reactivity was unrelated to drinking behavior or drug experimentation.

Conclusions: ELA leads to blunted stress reactivity and, independently, contributes to potentially risky drinking and drug-use behaviors in persons carrying one or two copies of the *COMT* 158Met allele. The results reinforce the impact of early experience on the stress axis and on risky behaviors, and they point to the 158Met allele as conveying a vulnerability to the early environment.

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Keywords

drinking behavior; cortisol; stress; early life adversity; dopamine; genotype; catechol-O-methyltransferase

Exposure to stress during childhood and adolescence modifies the stress axis in adulthood (Lovallo et al., 2012, Carpenter et al., 2007, Carpenter et al., 2013), illustrating a significant impact of the early environment that may contribute to adverse outcomes, including addictive behaviors (Miller et al., 2009). The degree and direction of this sensitivity to early life adversity (ELA) varies across individuals, determined in part by the actions of catecholamines in the central nervous system. The enzyme catechol-O-methyltransferase (COMT) is responsible for breakdown of catecholamines (Axelrod, 1957, Matsumoto et al., 2003), with particular functional importance in the brain's prefrontal cortex (Maier and Watkins, 2005, Aston-Jones and Cohen, 2005, Comings and Blum, 2000, Seamans and Yang, 2004, Kaenmaki et al., 2010) relative to other brain regions (Chen et al., 2004). Individual differences in COMT activity may therefore be sensitive to the early environment in ways that affect patterns of stress reactivity and adaptive behavior in adulthood (Lovallo et al., 2017).

A single nucleotide polymorphism of the gene for COMT (Val158Met; rs4680) (Chen et al., 2004, Lotta et al., 1995) is strongly conserved in humans and nonhuman primates. The Val allele results in COMT that is highly stable and more efficient at breakdown of norepinephrine and dopamine in the prefrontal cortex and reward systems (Lotta et al., 1995, Zhu et al., 2004). The greater persistence of dopamine and norepinephrine in Met-allele carriers may plausibly increase sensitivity to the environment relative to their Val/Val counterparts (Radley et al., 2008, Egan et al., 2001, Akil et al., 2003, Alexander et al., 2012). Accordingly, Met-allele carriers may perform better on tests of attention, working memory, and decision-making (Malhotra et al., 2002, Enoch et al., 2009, Schneider et al., 2015, Barnett et al., 2011, Schulz et al., 2012), although not all studies agree (Wardle et al., 2013). Despite cognitive advantages, Met/Met homozygotes are more anxious, sensitive to painful stimuli (Zubieta et al., 2003), reactive to emotional faces (Drabant et al., 2006, Enoch et al., 2008), and they have larger subjective and physiological responses to psychosocial stress (Hernaus et al., 2013, Bouma et al., 2012).

This evidence suggests that Val158- and Met158-allele carriers may also differ in long term consequences of a stressful early environment (Goldman et al., 2005). In the Family Health Patterns cohort, exposure to ELA diminished cortisol and heart rate reactivity to psychological stress and modifies psychological and behavioral characteristics in adulthood (Lovallo, 2013, Sorocco et al., 2015, Lovallo et al., 2012). A growing body of evidence suggests that both ELA and blunted stress reactivity may predict risky behaviors including alcohol and drug abuse (Dawes et al., 1999, Moss et al., 1999, Bibbey et al., 2015, al'Absi, 2006, Evans et al., 2013, Evans et al., 2016, Cook et al., 2012, Brody, 2002). The foregoing suggests further study of sensitivity to the early environment in Met158-allele carriers with potential modifications of the stress axis and an impact on alcohol and drug use. In a prior report on 252 healthy young adults we have shown that ELA resulted in blunted stress

reactivity with a strong effect in *COMT*(rs4680) Met158-allele carriers (Lovallo et al., 2017). We expanded this study sample to 480 persons, and examined ELA exposure, stress reactivity, and their impact on alcohol and drug experimentation.

Methods

Participants

Participants were 480 healthy young adults in the Family Health Patterns (FHP) project (Lovallo et al., 2013) who had been genotyped for the *COMT* Val158Met polymorphism along with ancestry informative markers (AIMS) and had sufficient background data to compute ELA scores. Each participant signed an informed consent form approved by the Institutional Review Boards of the: University of Oklahoma Health Sciences Center and VA Medical Center, Oklahoma City, OK, University of Texas Health Sciences Center San Antonio, TX, and University of Arkansas for Medical Sciences, Little Rock, AR, USA, and was provided financial compensation.

Study Design and Procedure

Participants passing an initial telephone screen underwent detailed assessments at the laboratory (Lovallo et al., 2010). The lab screening included a diagnostic interview using the computerized diagnostic interview system 4 (C-DIS-4) (Blouin et al., 1988) using Diagnostic and Statistical Manual IV criteria (American Psychiatric Association, 1994) that was conducted by a trained interviewer supervised by a clinical psychologist. Participants passing the lab screening then visited the lab twice more for a stress reactivity protocol including a day of public speaking and mental arithmetic challenges followed by a resting control day, as described elsewhere (Lovallo et al., 2013, Lovallo et al., 2010).

Inclusion and exclusion criteria—Participants were 18–30 yr-old men and women recruited from the community who were in self-reported good health, had no reported history of serious medical disorder, had a body mass index < 30, were not taking prescription medications other than hormonal contraceptives, as described earlier (Lovallo et al., 2017). Persons were excluded if they had: a personal history of alcohol or drug dependence; met criteria for current substance abuse within the past 60 days; had a history of any Axis I disorder, other than past depression or dysthymia (> 60 days previous), or if they failed a urine drug screen or breath-alcohol test on days of testing. Smoking and smokeless tobacco use were not exclusionary. Women taking hormonal contraceptives were excluded from the present analysis, if they took part in a morning test session, in light of findings showing significantly elevated cortisol baseline levels and an absence of stress responses during the morning hours in this group relative to women not using hormonal contraceptives (Carr et al., 1979, Kuhl et al., 1993, Lovallo et al., 2019).

ELA assessment—ELA was derived from psychiatric interview items that are closely similar to the adverse life events assessed retrospectively by Caspi and Moffitt (Caspi et al., 2003, Caspi et al., 2002) as follows: Physical or Sexual Adversity (“Have you ever been mugged or threatened with a weapon or 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, 1, or 2 reported forms of adversity they experienced. The levels of ELA were considered nontraumatic because selection criteria excluded persons meeting criteria for posttraumatic stress disorder or current major depression. In a subset of 261 persons, ELA (0–5) scores were significantly correlated with total scores on the Childhood Trauma Questionnaire-SF, $r = 0.601$, $p < .001$ (Bernstein et al., 2003).

Alcohol, tobacco, and recreational drug use—During screening, subjects reported on several measures of alcohol, tobacco, and drug use, including the following: the Alcohol Use Disorders Identification Test (Babor et al., 2001); a quantity-frequency index of recent drinking, yielding ounces of pure ethanol consumed in the past month (Babor et al., 1992); listing the age at which they first consumed a full drink of beer, wine or distilled spirits; if they ever began cigarette smoking; and they counted the number of recreational drugs they had “ever tried” one or more times, including: marijuana, hallucinogens, opiates, amphetamine and cocaine, tranquilizers and benzodiazepines, barbiturates, antidepressants, and inhalants.

Stress procedure. Lab sessions were held at either 9:00 am or 1:00 pm, with the time held constant for each subject. Stress testing lasted 105 min while subjects were seated, including a resting baseline (30 min) followed by simulated public speaking (30 min) and mental arithmetic (15 min) and a 30-min resting recovery period as described elsewhere (Lovallo et al., 2010, Al’Absi et al., 1997). The resting control day involved sitting for 105 min while reading general interest magazines and watching nature videos. Prior reports showed no effect of time of day, smoking, caffeine intake, or menstrual cycle stage on the pattern of cortisol reactivity or group differences (Lovallo et al., 2010). Participants reported their level of perceived activation and distress on a set of 10-point scales at the end of the baseline and stress periods (Lundberg and Frankenhaeuser, 1980).

Saliva samples for cortisol determination were collected using Salivettes at 9 times across each day as shown in Figure 1B. Saliva sampling time points are described in Figure 1B caption. Heart rate was monitored every 2 min along with blood pressure measurements using an automated monitor.

Cortisol

Salivettes were centrifuged at 4200 RPM (1500 x g) for 20 min. The saliva was transferred to cryogenic storage tubes and placed into a -70°C freezer until shipping. Saliva free cortisol was quantified by enzyme linked immunosorbent assay by Salimetrics (Carlsbad, CA, USA) (Salimetrics, 2015).

Genotyping

DNA was prepared from saliva collected by passive drool into an Oragene collection and preservation kit (DNA Genotek, Inc., Kanata, Ontario, Canada) and genotyped with the

Illumina Human OmniExpressExome-12v1 array. Samples with call rates below 95% were excluded and randomly selected samples showed an average reproducibility of 99.999%.

Assessment of population stratification using ancestry informative markers (AIMS).—Our dataset was predominantly of European origin, with mean (SD) and median European ancestry being 0.89 (0.19) and 0.95 in this sample. Twenty participants had European ancestry scores < 0.50. Of these, 16 were of African ancestry and 4 had Native American ancestry. Genotypes for the COMT Val158Met (rs4680) polymorphism were in Hardy Weinberg Equilibrium in the overall sample ($p = 0.57$).

Data Analysis

Cortisol responses to stress were calculated as the average of the three samples taken during the stress period on the stress day (STR1, STR2, STR3) minus the equivalent three samples taken on the rest day. Cortisol data were analyzed by a general linear model including: Genotype (Met/Met, Val/Met, Val/Val), ELA (0, 1, 2), and the G x ELA interaction term. The significant interaction was followed by simple effects tests to compare subgroups. The potential confounders, sex and European and African AIMS scores, were examined as covariates and did not influence the results, as documented elsewhere (Lovallo et al., 2017). The unadjusted F ratios are reported here. Type III sums of squares were used to ensure independence of individual F ratios. Tests were considered statistically significant if $p < 0.05$. Analyses were conducted using SAS software 9.2 (Copyright, SAS Institute Inc., Cary, NC, USA).

Results

Demographics for the COMT Val158Met genotypes are shown in Table 1. The proportions of Met/Met, Val/Met, and Val/Val genotypes in the present sample (24%, 51%, and 26%, respectively) match the allele distribution in European and Han Chinese populations (Wardle et al., 2013, Li et al., 1997).

Genotype x ELA and stress reactivity

Cortisol responses.—Cortisol data are shown in Figure 1. Since responses may be influenced by baseline levels, we examined the cortisol diurnal curves. As shown in Figure 1B, the genotype groups had nearly identical patterns of cortisol secretion across the rest day, indicating equivalent levels of intrinsic HPA axis activity. Cortisol responses during the stress protocol were smaller in the Val/Val homozygotes and larger in the Met carriers, $t_s > 2.25$, $p_s < .025$.

Stress responses differed in the ELA x Genotype groups, as shown in a significant interaction (Figure 1C), $F(4, 464) = 3.29$, $p = .011$, partial $\eta^2 = .028$, suggesting that the effect of ELA on cortisol stress responses in adulthood differed in the COMT genotype groups. The Met/Met genotype group showed a pronounced diminution of cortisol reactivity to both 1 and 2 levels of ELA exposure. A similar, less pronounced trend was seen in the Val/Met heterozygotes. In contrast the Val/Val group produced larger cortisol responses in relation to greater ELA exposure.

For visual comparison, Figure 1D shows the genotype data arranged as a function of ELA exposure. Under minimal reported levels of ELA (ELA = 0), the Met/Met group was more reactive than the Val/Val group. In contrast, under high levels of ELA (ELA = 2), the Val/Val carriers had the largest stress responses. The genotype groups reporting a moderate level of ELA (ELA = 1) were relatively similar in cortisol reactivity regardless of genotype.

Given the similar impact of ELA on the Met/Met and Val/Met genotype groups we formed a combined Met allele group as shown in Figure 1A. The graph and the significant interaction indicated clearly opposing effects of ELA exposure in the Val and Met genotype groups, $F(2, 464) = 4.38, p = .013$, partial $\eta^2 = .019$. Neither Genotype nor ELA main effects were significant, $F_s > 1.0, p_s > .70$. The cortisol data from our earlier report on COMT genotypes is provided elsewhere (Lovallo et al., 2017).

Heart rate responses.—HR response to stress (Table S1) was moderately lower in persons with greater levels of ELA exposure, consistent with a prior report (Lovallo et al., 2012), although the ELA effect did not achieve statistical significance in this data set, $F = .95, p = .39$. Similarly, HR response did not differ across the COMT genotype groups or for the Genotype x ELA interaction, $F_s < 1.0, p_s > .75$. The ELA effects of *COMT* alleles appear to be confined to the hypothalamic-pituitary-adrenocortical axis and may not affect the autonomic axis.

Subjective states.—As a check on the perceived impact of the stressors, we examined the changes from baseline to poststress in participants' reports of Activation and Distress as shown in Table S2. Activation and Distress reports for all subgroups increased from the baseline to poststress periods. Change scores did not differ across the ELA or COMT genotype groups ($F_s = 2.15, p_s = .117$) indicating similar experiences of the stress procedure in the respective groups.

Stress reactivity in relation to alcohol and drug use

ELA and COMT genotype effects on alcohol and drug use indicators.—ELA increases the risk for problem intake of alcohol and drugs (Carroll et al., 2017). We explored the relationship between ELA and alcohol and drug use in the COMT genotypes, as shown in Figure 2 and Table S3. Higher levels of ELA led to early use of alcohol and drug experimentation, $F_s = 14.20$ and $9.08, p_s < .0001$, respectively. No genotype effects were seen in AUDIT scores or the quantity-frequency index. Cigarette smoking in this population was minimal, and the data did not allow for meaningful comparison among the groups. Exploratory simple effects tests showed that ELA effects on early drinking and drug experimentation were numerically greater in Met/Met persons and smaller in the Val/Met or Val/Val groups as indicated in Figure 2 and shown in Tables S3 and S4.

Cortisol stress reactivity in relation to drinking and drug use.—Figure 1A indicates that the impact of ELA on cortisol response to stress is not linear; the Met-allele carriers had blunted cortisol responses following ELA while the opposite pattern held true for the Val homozygotes. We then inquired whether cortisol reactivity, would form a predictive bridge from ELA to drinking and drug use. In lieu of complex modeling, we

conducted Pearson correlations between cortisol stress responses and age at first drink and the number of drugs ever tried as shown in Table 2. In all cases, the correlations between the cortisol reactivity score and drinking and drug use were < 0.1 , accounting for $< 1\%$ of the variance. None of the correlations suggested a relationship that would be explained by using more complex models. The indication from these data is that cortisol reactivity and substance use are both affected by a history of ELA, but do not form a direct causal link.

Discussion

Stress exposure during critical periods of development can affect health behaviors in adulthood (Dube et al., 2003), and the impact may be greater in persons carrying specific genotypes as illustrated in early G x E studies (Caspi et al., 2002, Caspi et al., 2003). We and others have observed that stress reactivity is diminished in persons exposed to ELA in childhood and adolescence (Lovallo et al., 2012, Carpenter et al., 2007). Adverse childhood experiences and blunted stress reactivity may also signal risk for maladaptive health behaviors and adverse long-term outcomes (Carroll et al., 2017, Anda et al., 2002). ELA may not affect all individuals to the same degree, but instead may be greater in persons carrying specific genetic polymorphisms. We recently reported in a smaller sample of volunteers (N = 252) that the impact of ELA on the stress axis is partially dependent on the individual's COMT genotype (Lovallo et al., 2017). The present paper extends this finding to an enlarged sample of volunteers (N = 480) with an additional emphasis on alcohol and drug experimentation. These collective results suggest four observations of interest.

First, ELA led to greatly diminished cortisol responses in Met/Met homozygotes with less pronounced effects in Val/Met heterozygotes, consistent with a gene-dose effect of the Met158 allele on cortisol stress reactivity.

Second, homozygous carriers of the Val158 allele had a symmetrically opposite effect; ELA exposure led to increased cortisol responsivity, consistent with a G x E effect of ELA in COMT Val158Met genotypes. These findings bear comparison with a study of COMT genotype and concurrent life stress in children that found diminished cortisol reactivity in those undergoing greater daily stress exposure but with smaller responses in Val/Val carriers, although no G x E interaction was found (Armbruster et al., 2012). We found no effect of Genotype or any G x E effects in basal cortisol levels, heart rate reactivity or reports of subjective responses to the stressor, providing a specific focus on cortisol reactivity relative to ELA and the COMT genotypes.

Third, the individual's ELA history was related to an earlier age of experimentation with alcohol and a greater number of drugs, although these risky intake variables did not show an overall G x E interaction. Nonetheless, Met homozygotes experiencing 2 forms of ELA reported taking a first drink at 14.5 years of age in contrast to their 0- and 1-ELA counterparts, who began drinking 3 years later. A similar effect of ELA on the Met158 genotype occurred in experimentation with recreational drugs. Onset of alcohol consumption prior to age 15, is a significant predictor of future dependence. Sensitivity to the early environment appears to be greater in persons carrying the Met allele relative to their Val/Val

counterparts, and the present results suggest that this sensitivity may have implications addiction risk.

Fourth, cortisol reactivity was not directly correlated with either alcohol or drug use indicators. This finding may be useful in considering the mechanisms by which ELA exerts its effects on the stress axis on the one hand and on alcohol and drug use on the other hand. In this case, blunted cortisol reactivity may be a consequence of ELA but may not act as a direct contributor to substance abuse. This is a potentially important finding concerning the linkages between early experience, the stress axis, and health behaviors.

Although much attention has been focused on possible health effects of large stress responses, both exaggerated and diminished cortisol reactivity represent departures from normal homeostatic regulation (Lovallo et al., 2010), with possible consequences for long-term health and behavioral adaptation (Carroll et al., 2009). Given cortisol's role in regulating activity in the central nervous system, normal cortisol responses to stress are considered central to healthy behavioral adaptation relative to demands from the environment (McEwen, 2007, McEwen and Sapolsky, 1995). Several lines of evidence now point to ELA and diminished cortisol responses as being associated with behavioral disorders including disinhibitory behavioral characteristics and vulnerability to alcohol and other substance use disorders (Errico et al., 1993, Lovallo, 2013, Ehrensaft et al., 2004, Biederman et al., 2002, Eaves et al., 2010, Foley et al., 2004, Enoch, 2011). The present results largely agree with this conclusion but suggest that cortisol actions in the central nervous system are not causally related to substance abuse.

The present results and prior analyses of data from the FHP study suggest multiple effects of ELA in adulthood, irrespective of genotype. ELA contributes to globally diminished cortisol and HR reactivity to stress (Lovallo et al., 2012), altered decision-making and cognitive function (Lovallo et al., 2013), and unstable regulation of affect (Sorocco et al., 2015). We show here that the primary effects of ELA are qualified by genotype-driven sensitivities, some of which specifically implicate glucocorticoid mechanisms and some of which contribute to alcohol use and drug experimentation in adolescence. However, the present data do not point to a direct contribution of blunted cortisol responses to risky drinking and drug use in early adulthood. Instead, blunted cortisol reactivity and early adoption of alcohol and drug experimentation may be independent consequences of ELA in COMT Met-allele carriers.

Perspective and limitations

In designing the FHP study, a primary consideration was to avoid possible central nervous system toxicity associated with prolonged heavy use of alcohol and drugs. We therefore excluded persons with a history of substance dependence based on DSM-IV criteria. The strength and magnitude of relationships reported here should now be tested in persons with a wider range of intake history than in this study cohort. Similarly, the reports of ELA were derived from retrospective self-reports, and as such are subject to recall bias. The present findings, nonetheless provide a scaffolding for evaluating studies in persons with a more severe history of substance exposure.

The genotype effects documented here have small effect sizes. Although the present sample is relatively large for studies of this type, due to the modest effect size, we were unable to pursue potentially fruitful G X G interactions on health and behavior. For example, *COMT* genotypes may interact with other genetic polymorphisms affecting glucocorticoid regulation (Lovallo et al., 2016) or opioid receptor function (Lovallo et al., 2015). Serotonin receptor polymorphisms may cause variations in cortisol response to acute stress (Way et al., 2016), and a polymorphism in the promoter region of the serotonin transporter gene may modify regulation of affect and overt behavior (Lovallo et al., 2014), again having possible interactions with *COMT* Val158Met genotypes.

This study shares limitations with others of its type. The data set is small for a candidate G x E study and limited statistical power raises the possibility of a Type I error, as has been found in a number of such studies (Dick et al., 2015). This concern is mitigated to a degree by two considerations: (a) Existing evidence suggests a high prior probability that the present G x E finding may be true. (b) We followed the recommendations by Moffitt, Caspi, and Rutter in the G x E design and analysis (Moffitt et al., 2006). (c) Moreover, the G x E effect yielded a partial $\eta^2 = .045$, accounting for 4.5% of the variance, suggesting a small-to-medium effect size (Cohen, 1988), boosting confidence in this finding. (4) Finally, the larger sample size in the present analysis builds systematically on the smaller sample in our earlier paper. Nevertheless, we emphasize that the present result should be considered provisional prior to replication with independent datasets and in persons with a wider range of alcohol and drug intake. Due to the sample size, we were unable to test for the simultaneous effects of multiple confounders or pursue promising ELA effects in relation to G x G interactions. The sample was selected for an absence of current psychiatric disorders, and the results therefore apply only to otherwise healthy individuals.

Conclusion

Miller and Chen comment that early experience leaves a “biological residue” that persists into adulthood and may affect systems relevant for health and disease (Miller et al., 2009). A goal of the present analysis is to understand how stress in early life affects persons inheriting *COMT* Val158Met genotypes. ELA exposure leads to diminished cortisol reactivity in Met allele carriers but causes enhanced reactivity in Val/Val carriers. ELA independently contributes to earlier initiation of alcohol intake and greater drug experimentation. Alcohol and drug intake did not appear to depend on cortisol reactivity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1.

Cortisol saliva measurements at home and during visits to the laboratory. Panel A: Cortisol stress responses in ELA exposure groups (0, 1, 2) who were Met vs. Val/Val carriers of COMT rs4680 on a stress day referenced to a nonstress control day. Panel B: Cortisol values on a nonstress control day (dashed lines) and on a stress day (solid lines) for Met and Val/Val allele groups. Cortisol measurement time points are: AM, immediately upon awakening; Pre, upon arrival at the lab; BL1, BL2, 30 min and 15 min prior to the onset of the stress procedure or comparable time on the resting control day; STRS1, at the start of the stress protocol, STRS2, following speech presentations, and STRS3, the end of the stress protocol, or the comparable time points on the resting control day; Rec, 45 min after the end of the stress protocol or comparable time point on the resting control day; PM, at bedtime. Panel C: Cortisol stress responses for ELA groups x separate allele groups. Panel D: Data from Panel C rearranged to show the effect of Val158Met genotypes within ELA groups. Figure labels. 0, 1, 2 indicates the number of childhood adversities experienced in childhood and adolescence. Met and Val refer to single nucleotide polymorphisms of *COMT*.

Figure 2.

Drinking and drug use variables. Age at first drink and the number of recreational drugs the volunteers reported ever having tried. P-values refer to F ratios of stratified comparisons of ELA groups within genotype. Figure labels as in Figure 1.

Table 1.

Demographics for COMT genotypes

Genotype	MET/MET	VAL/MET	VAL/VAL	<i>p</i> -value
N = 480 (%)	114 (24%)	246 (51%)	120 (25%)	
Sex (% F)	52	50	50	0.93
Age	24.0 [0.28]	23.6 [0.22]	23.6 [0.28]	0.49
SES	48.5 [1.15]	46.4 [0.79]	47.5 [1.09]	0.28
Education (yr)	16.1 [0.19]	15.7 [0.13]	15.7 [0.19]	0.26
ELA (% 2)	11	16	16	0.16
FH+ (%)	37	34	33	.81
AIMS (% E)	91 [1]	83 [2]	74 [3]	<.0001

Note: Entries show Mean ($\pm$ SEM) unless otherwise noted. No significant ELA x Genotype interactions were found, and the *p*-values refer to genotype comparisons only. SES = Socioeconomic Status. ELA = Early Life Adversity. FH = Family History of alcoholism.

AIMS = Ancestry Informative Markers (% with European ancestry markers). *p*-values refer to *F*-ratio or Chi-squared comparison across genotype groups.

Table 2.

Cortisol reactivity and alcohol and drug use in COMT genotypes

	Age of first drink		Number of drugs tried	
	Pearson <i>r</i>	<i>p</i>	Pearson <i>r</i>	<i>p</i>
Overall	– 0.09	.04	0.04	.43
Mets	– 0.09	.09	0.03	.58
Val/Val	– 0.10	.26	0.05	.61