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ORIGINAL INVESTIGATION

History of childhood adversity is positively associated with ventral striatal dopamine responses to amphetamine

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Abstract
Rationale Childhood exposure to severe or chronic trauma is an important risk factor for the later development of adult mental health problems, such as substance abuse. Even in nonclinical samples of healthy adults, persons with a history of significant childhood adversity seem to experience greater psychological distress than those without this history. Evidence from rodent studies suggests that early life stress may impair dopamine function in ways that increase risks for drug abuse. However, the degree to which these findings translate to other species remains unclear.
Objectives This study was conducted to examine associations between childhood adversity and dopamine and subjective responses to amphetamine in humans.
Methods Following intake assessment, 28 healthy male and female adults, aged 18–29 years, underwent two consecutive 90-min positron emission tomography studies with high specific activity [^{11}C]raclopride. The first scan was preceded by intravenous saline; the second by amphetamine (AMPH 0.3 mg/kg).
Results Consistent with prior literature, findings showed positive associations between childhood trauma and current levels of perceived stress. Moreover, greater number of traumatic events and higher levels of perceived stress were each associated with higher ventral striatal dopamine responses to AMPH. Findings of mediation analyses further showed that a portion of the relationship between childhood trauma and dopamine release may be mediated by perceived stress.
Conclusions Overall, results are consistent with preclinical findings suggesting that early trauma may lead to enhanced sensitivity to psychostimulants and that this mechanism may underlie increased vulnerability for drug abuse.

Keywords Dopamine · Positron emission tomography (PET) · Human · Amphetamine · Childhood adversity · Stress

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Introduction

Childhood adversity can be defined as negative events occurring during childhood or adolescence which are (1) outside of the control of the child, (2) have the potential to alter normal development, and (3) may impair the child's physical and/or psychological well-being (Burgermeister 2007). In recent years, there has been increasing awareness that adverse childhood experiences (ACEs) may contribute to the development of a wide range of mental health problems in adulthood (Benjet et al. 2010; Cuijpers et al. 2011; Gordon 2002; Huang et al. 2011; Husted et al. 2012; Matheson et al. 2012; Nanni et al. 2012; Nelson et al. 2002; Weber et al. 2008). Greater severity, frequency, and duration of trauma are generally associated with greater likelihood of such problems and

with worse prognosis (D'Andrea et al. 2012; Edwards et al. 2003; Felitti et al. 1998; Finkelhor et al. 2007; Ford et al. 2010; Kessler et al. 2010). Moreover, it has been shown that even children who do not go on to develop adult psychopathology may suffer long-term consequences of childhood maltreatment. In nonclinical samples of adults, individuals with a history of ACEs often report greater psychological distress, emotional reactivity, and sensitivity to stress than those without this history (Chu et al. 2013; Edwards et al. 2003; Glaser et al. 2006; Hyman et al. 2007; Marx and Sloan 2003).

One potentially modifiable consequence of childhood adversity is elevated risks for substance abuse. Numerous studies have documented associations between childhood adversity and the development of substance use disorders in adults (Carswell et al. 2008; Kendler et al. 2000; Pilowsky et al. 2009; Rothman et al. 2008). Although no single pathway can be expected to entirely explain this complex relationship, findings showing that substance abusers with a history of ACEs report greater psychological distress than those without this history suggest that alcohol and/or drugs may be used as a form of self-medication by these groups (Medrano et al. 2002; Wang et al. 2010). There is also a large body of research showing that perceived stress and current daily hassles are also positively associated with substance use and related problems (Back et al. 2008; Cole et al. 1990; Corbin et al. 2013; Kaplan 2013; Nakajima and al'Absi 2012; Waldrop et al. 2007).

A large body of preclinical literature suggests that both acute and chronic stress may influence vulnerability for drug abuse by altering mesocorticolimbic dopamine (DA) neurotransmission (Belujon and Grace 2011; Kosten et al. 2003; Lu et al. 2003; Mangiavacchi et al. 2001; Marinelli and Piazza 2002; Miczek et al. 2011; Saal et al. 2003; Shimamoto et al. 2011; Yavich and Tiihonen 2000). Interestingly, there is also preclinical evidence showing that early life stress may lead to long-term derangements in DA neurotransmission that persist into adulthood. Rodents exposed to early life stress exhibit altered ventral striatal (VS) and nucleus accumbens (NAcc) DA responses to stress in later life (Brake et al. 2004; Chocyk et al. 2011; Fulford and Marsden 1998; Jahng et al. 2010; Meaney et al. 2002; Hall et al. 1999), as well as enhanced DA responses to psychostimulants (Hall et al. 1999; Kosten et al. 2005; Moffett et al. 2006) and increased alcohol/drug consumption (Kosten et al. 2005; Moffett et al. 2007; Zhang et al. 2005). These preclinical findings suggest that early life trauma has sustained effects on brain DA systems, which may lead to altered drug sensitivity and greater vulnerability for drug abuse in later life (Rodrigues et al. 2011).

Clinical studies examining the impact of childhood trauma on brain DA function and associated risks for drug abuse are sparse. In one functional magnetic resonance imaging (fMRI) study, Dillon et al. (2009) showed dysfunction in left basal ganglia reward pathways in adults who were abused as children. Mehta and colleagues (2010) similarly reported that adolescents who experienced severe global deprivation early in life exhibited hyporesponsivity of the VS and, to a lesser extent, the caudate nucleus during anticipation of monetary reward. Although it is likely that this hyporesponsiveness was related to altered DA activity, interpretation of the precise nature of the underlying dysfunction was limited by the lack of clear understanding about relationships between fMRI blood-oxygen-level dependent (BOLD) response and DA neural function. Using positron emission tomography (PET) imaging, Pruessner and colleagues (2004) found that persons who reported low maternal care had greater stress-induced changes in VS [^{11}C]raclopride binding potential (BP_{ND}) than individuals who reported high maternal care. In the present study, we selected intravenous (IV) amphetamine (AMPH) to interrogate mesolimbic DA function, conducting the first examination of relationships among childhood adversity, perceived stress, and DA and subjective drug responses in humans. Participants were healthy young adults who did not meet diagnostic criteria for a major DSM-IV psychiatric Axis I disorder (American Psychiatric Association 2000). The advantage of conducting the study in healthy adults without psychopathology was that it allowed us to rule out alternative explanations for hypothesized relationships between childhood trauma and DA functioning. Because of prior evidence that the NAcc plays a central role in the reinforcing effects of psychostimulants and in reward-based behaviors (Di Chiara et al. 2004; McGinty et al. 2013; Robison et al. 2013; Wise. 1996), the VS was our primary region of interest in this study. Our primary hypotheses were that childhood trauma would be positively associated with (1) VS AMPH-induced DA release, (2) pleasant drug effects, and (3) current levels of perceived stress.

Materials and methods

Participants

Twenty-eight healthy male (n=19) and female (n=9) participants, aged 18–29 years, were recruited from the Baltimore metropolitan area by newspaper advertisements, fliers, and internet postings. Respondents who appeared to qualify for the study on the basis of a brief telephone screen were invited to our research offices at the University of Maryland to complete an intake session. All volunteers provided written informed consent after being given a complete description of the study. The research was approved by the University of Maryland and the Johns Hopkins Medicine Institutional Review Boards.

Psychiatric diagnostic screening was conducted using the Structured Clinical Interview for DSM Disorders (SCID-I/NP) (First et al. 2002). Alcohol consumption and drug use were

further evaluated by 90-day time line follow back (Sobell and Sobell 1992). Additional screening measures included the Beck Depression Inventory (Beck et al. 1996), Shipley Institute of Living Scale-2 (Shipley et al. 2009), Fagerstrom Test for Nicotine Dependence (Heatherton et al. 1991), alcohol breathalyzer test, and urine toxicology. Participants also completed a medical evaluation that consisted of a history and physical examination, complete blood count, comprehensive metabolic panel (including renal and hepatic function tests), coagulation tests, pregnancy screen/progesterone levels (women), electrocardiogram, and urinalysis. The medical evaluation was conducted at the University of Maryland School of Medicine General Clinical Research Center (GCRC).

Exclusion criteria included (a) younger than 18 or older than 30 years; (b) lifetime history of a major DSM-IV psychiatric Axis I disorder, including attention deficit hyperactivity disorder (ADHD) or conduct disorder; (c) BDI score >18; (d) currently in need of psychiatric treatment; (e) illicit drug use during the past 30 days or lifetime stimulant use; (f) positive urine drug screen; (g) nicotine dependence or smokes >10 cigarettes weekly; (h) heavy alcohol consumption; (i) oral contraceptive use, pregnant, or lactating; (j) active medical conditions; (k) treatment (past 12 months) with antidepressants, neuroleptics, sedative/hypnotics, appetite suppressants, opiates, antihypertensives, dopamine or serotonergic agents, glucocorticoids, or propecia; (l) claustrophobia or fear of needles; (m) BMI <20 or >31; and (n) less than fifth grade reading level.

Qualified participants were scheduled to complete MRI and PET scans at the Johns Hopkins Hospital Department of Radiology. For women, PET scans were scheduled during the follicular phase of their menstrual cycle, confirmed by progesterone levels drawn on the day of the session. Women with progesterone levels <2 ng/ml were classified as being in the follicular phase of the menstrual cycle.

Baseline assessment measures

Self-report measures administered during the intake assessment to evaluate primary and secondary hypotheses of the study included the Perceived Stress Scale (Cohen 1994) and the Early Trauma Inventory Short Form (Bremner et al. 2007).

Perceived stress scale The PSS is a 10-item questionnaire that measures the degree to which situations are appraised as stressful. In contrast to life event measures, which assess objective life events, the PSS is a global measure designed to tap how unpredictable, uncontrollable, and overloaded respondents find their lives. Items are answered on a five-point scale from "never" to "very often", e.g., "In the last month, how often have you found that you could not cope with all the things that you had to do?" The PSS has shown adequate internal consistency and test–retest reliability (Cohen et al. 1983), as well as criterion-related and construct validity (Cohen 1994).

Early trauma inventory short form The 27-item ETISR-SF is a self-report measure that assesses traumatic events that occurred before the age of 18 years in each of four domains: general trauma (11 items), physical punishment (five items), emotional abuse (five items), and sexual abuse (six items). The ETI "total score" is derived by summing the number of items positively endorsed in each domain, which gives an index of the total extent of abuse. The ETI-SF was adapted from the earlier 62-item self-report version of the measure (ETI-SR) through factor analysis and other correlational methods and has been shown to have similarly acceptable psychometric properties of validity and internal consistency in healthy and clinical populations (Bremner et al. 2007; Plaza et al. 2011; Tonmyr et al. 2011; Wang et al. 2010).

MRI acquisition

A spoiled gradient (SPGR) sequence using the 3-T Siemens Trio MRI was obtained on each subject for anatomical identification of the structures of interest using the following parameters: repetition time, 35 ms; echo time, 6 ms; flip angle, 458°; slice thickness, 1.5 mm with no gap; field of view, 24×18 cm^2; and image acquisition matrix, 256×192, reformatted to 256×256.

PET experiments

General procedures

Participants were asked to arrive at our research office at Johns Hopkins at 08:30 on the day of the scans fasting, except for water. A brief medical evaluation, urine toxicology screen, alcohol breathalyzer test, hematocrit level, and serum pregnancy test (women) were conducted. Serum progesterone levels were also obtained for women. A caffeine-free, calorie-controlled breakfast and lunch were provided. PET data acquisition commenced at 13:00. Both scans were conducted on the same day as described below.

PET data acquisition

Upon arrival at the PET center, a venous catheter was placed in the antecubital vein for the radioligand injection and saline/AMPH administration. Subjects were positioned in the scanner with their heads restrained by a custom-made thermoplastic mask to reduce head motion. A 6-min transmission scan was acquired using a rotating Cs-137 source for attenuation correction. Each subject had two scans performed on the High Resolution Research Tomograph scanner (HRRT; CPS Innovations, Inc., Knoxville, TN, USA) with a high specific

activity IV bolus injection of [^{11}C]raclopride, an antagonist radioligand for dopamine D_2/D_3 receptors, following bolus IV injection of equal volumes of either saline or AMPH (0.3 mg/kg). Dynamic PET acquisition was performed in a three-dimensional list mode for 90 min following each injection of [^{11}C]raclopride. The [^{11}C]raclopride was prepared with minor changes in purification and formulation according to published procedure (Ehrin et al. 1985). Participants had approximately 45 min between the two scans to get up to stretch and void if needed. All participants were under continuous cardiovascular monitoring during the scans. Because of potential carry-over effects of AMPH, the order of drug administration is routinely fixed when both scans are completed on the same day; saline was administered during the first scan and AMPH during the second in all cases. One participant did not complete both scans on the same day due to equipment problems; however, the saline scan was done on one day and the AMPH scan on the following day. All participants were blind to the order of drug administration.

Reconstruction of PET data

Emission PET scans were reconstructed using the iterative ordered-subset expectation-maximization algorithm correcting for attenuation, scatter, and dead-time (Rahmim et al. 2005). The radioactivity was corrected for physical decay to the injection time and re-binned to 30 dynamic PET frames of 256 (left-to-right) by 256 (nasion-to-inion) by 207 (neck-to-cranium) voxels of 1.2188 mm cubic dimensions. The frame schedules were four 15-s, four 30-s, three 1-min, two 2-min, five 4-min, and twelve 5-min frames. The final spatial resolution is expected to be less than 2 mm full width at half-maximum in three directions (Rahmim et al. 2005).

Subjective assessments

Visual analog scales of subjective drug effects were administered at scheduled intervals following saline and AMPH administration as previously described (Oswald et al. 2005). The measure included five scales asking about pleasant drug effects (i.e., good effects, high, rush, liking, and desire for drug) and six asking about negative effects (i.e., bad effects, fidgety, anxious, dizziness, dry mouth, and distrust). Each effect was rated on a scale ranging from 0 "not at all" to 10 "extremely".

Cortisol assays

Measurements of baseline plasma cortisol levels were obtained prior to each scan (−25 and −5 min). Plasma concentrations were measured as previously described (Oswald et al. 2005).

PET data analysis

Volumes of interest (VOIs)

VOIs for putamen, caudate nucleus, and cerebellum were defined on MRI using the 3-D interactive-segmentation mode of a locally developed VOI defining tool (VOILand), as previously reported (Oswald et al. 2005). Striatal VOIs were subdivided into motor (posterior putamen), associative striatum (anterior putamen and anterior and posterior caudate nucleus), and limbic ventral striatum subdivisions using a semi-automated method that incorporated anatomical guidance based on post-mortem human materials (Baumann et al. 1999; Oswald et al. 2005). VOIs were transferred from MRI to PET space according to MRI-to-PET coregistration parameters obtained with the coregistration module SPM5 (The Statistical Parametric Mapping 5; The Wellcome Trust Centre for Neuroimaging; available at www.fil.ion.ac.uk/spm) (Ashburner and Friston 2003), and applied to PET frames to obtain regional time (radio-)activity curves. PET frames were aligned to the frame of the highest counts (decay-uncorrected) using the SPM coregistration module to correct head motion during the scan (Kumar et al. 2007; Montgomery 2006). VOIs of two sides were unified after confirming no side-to-side differences in PET outcome variables described below.

Derivation of PET outcome variables

Binding potential (BP_{ND}) (Innis et al. 2007) of [^{11}C]raclopride was obtained by the reference tissue graphical analysis (Logan et al. 1996) for striatum subdivisions. Then, intrasynaptic DA release, which represents the displacement of [^{11}C]raclopride by endogenous DA (DA_{Rel} in %) (Innis et al. 1992), was obtained using the following formula: $(BP_{ND}[S]-BP_{ND}[A])/BP_{ND}[S]\times 100$, where [S] and [A] stands for BP_{ND} of saline and AMPH scans.

Statistical analyses

Associations between participant characteristics and primary outcome variables were examined using Pearson Product Moment correlations for continuous variables and independent samples *t* tests for gender. Paired *t* tests were used to examine differences in [^{11}C]raclopride BP_{ND} and in subjective drug effects between the saline and AMPH sessions. Drug effect ratings were summarized as area under the time response curve (AUC), calculated by trapezoidal approximation from 3 to 85 min following drug administration. The AUC values for the five measures of pleasant effects were highly intercorrelated within each session, internal reliability was moderately high, and findings of factor analysis confirmed that one saline and one active session variable could be extracted (eigenvalues >1). Therefore, for purposes of data

reduction, we derived composite AMPH and saline session "pleasant effects" scores for each subject by averaging his/her AUC values on these five items. Findings of factor analysis did not support similar derivation of composite scores for the six scales measuring unpleasant drug effects. Because we were interested primarily in individual differences in pleasant subjective responses to AMPH and to avoid running multiple tests, no further analyses were conducted on unpleasant effects.

Evaluation of progesterone levels suggested that two of the female participants were not in the follicular phase of their menstrual cycle on the day of the scans (level >2 ng/ml). However, *t*-test findings indicated that VS DA release values for these two women did not differ from those of the other women who completed the scans. Therefore, data from all nine women were included in subsequent analyses.

Linear regression models were used to evaluate each of the primary hypotheses. The independent variable of interest in each regression was the ETI total score. Outcome variables for the three respective hypotheses were as follows: (1) VS DA release defined as the percent change in (saline-AMPH PET)/saline PET BP_{ND}, (2) AMPH scan composite pleasant drug effect ratings (saline scan ratings were used as a covariate for baseline adjustment), and (3) PSS scores. Regression models were also used to evaluate whether PSS scores predicted DA release or subjective drug responses. Measures of VS DA release or pleasant drug effects were treated as outcome variables; the primary independent variable was PSS scores. Although brain DA neurotransmission has previously been shown to vary as a function of age (Cervenka et al. 2008; Del Arco et al. 2001; Inoue et al. 2001; Tupala et al. 2003), we did not covary for age in the regression analyses since this variable was already controlled by the study design and findings of preliminary correlational analyses showed no relationships between age and any of the outcome variables. However, because of the lack of control for gender in the design and prior evidence of sex differences in DA and subjective responses to AMPH (Abi-Dargham et al. 2003; Evans 2007; Munro et al. 2006; White et al. 2002), perceived stress (Allen et al. 2011; Andreou et al. 2011), and responses to ACEs (Heffner et al. 2011; Kendler et al. 2002; Samplin et al. 2013), we did evaluate the relevance of gender by controlling for it and testing interactions with each of the primary independent variables of interest. When interactions were significant, we conducted post hoc analyses to examine the models separately in each gender. For parsimony, the interaction term was dropped if not significant. Saline scan [^{11}C]raclopride BP_{ND} was used as the outcome variable in parallel analyses that examined associations between VS D2 receptor availability and ETI or PSS scores. Although our primary region of interest was the VS, we conducted exploratory regression analyses of four additional striatal regions to evaluate the specificity of associations between VS DA release or BP_{ND} and ETI or PSS scores. The additional regions included anterior and posterior subdivisions of the caudate nucleus and the putamen as described in the "PET data analysis" section. Mean baseline cortisol levels were obtained by averaging the values of specimens obtained prior to the placebo and amphetamine scans. Relationships between mean baseline cortisol levels and DA release, ETI scores, and PSS scores were evaluated using gender-adjusted regression analyses.

Based on associations observed in the regression analyses, we also tested whether perceived stress may mediate the relationship between childhood trauma and DA release. Mediation analysis consisted of four steps, as discussed in the classical approach (Baron and Kenny 1986). First, we assessed associations between (1) ETI and PSS scores (a path), (2) PSS scores and VS DA release (b path), (3) ETI scores and VS DA release (c path), and (4) ETI scores and VS DA release (c′ path) controlling for PSS score. The mediation effect of perceived stress was examined with the following two regressions using the path model: (a) PSS on ETI scores and (b) VS DA release on PSS scores after controlling for the ETI scores. The mediation effect (indirect effect) was estimated by the product of estimates of parameters (a*b). Since Sobel test is underpowered in this data set, bias-corrected Bootstrapping method, which is especially effective for relatively small sample sizes and relaxes the normality assumption of the outcome variables (MacKinnon 2008; MacKinnon et al. 2002, 2004; Shrout and Bolger 2002), was used to estimate the significance of the indirect effect. The significance of the mediation effect was tested using the 95 % confidence interval. Since findings of secondary analyses showed that ETI scores were not significantly associated with DA release in other striatal regions, no mediation analyses were performed for other regions.

Results

Sample characteristics

Participants were between the ages of 18 and 29 years, predominantly male (67.9 %), and light to moderate drinkers, with the exception of two who reported no alcohol use. Twenty-six participants were non-smokers; two were non-dependent occasional smokers, and one reported <1 and the other <5 cigarettes/weekly. Demographic characteristics and mean scores on self-report measures are displayed in Table 1. Mean scores on the PSS were slightly lower than norms previously reported for this age group (Cohen et al. 1983). Mean ETI total and subscale scores were generally consistent with those reported by Bremner and colleagues in healthy adults without a history of psychiatric disorder (Bremner et al. 2007). Dopamine release, PSS, and ETI total scores were normally distributed in the sample. Although pleasant

Table 1 Subject characteristics[a]

	Total	Male n=19	Female n=9	p value
Race, no. (%)				
Asian	3 (10.7)	3 (100.0)	0 (0.0)	0.272[b]
Black	10 (35.7)	6 (60.0)	4 (40.0)	
White	14 (50.0)	10 (71.4)	4 (28.6)	
Other	1 (3.6)	0 (0.0)	1 (100.0)	
Age, years	22.5 (3.1)	22.8 (3.1)	21.8 (3.2)	0.430
BMI	24.1 (2.8)	24.1 (2.2)	24.2 (2.2)	0.869
Drinks per week	1.7 (3.0)	2.0 (3.6)	1.3 (1.7)	0.893[c]
Beck Depression Inventory (BDI)	2.3 (2.7)	2.4 (2.8)	2.1 (2.6)	0.707[c]
Perceived Stress Scale (PSS)	10.4 (4.8)	10.6 (4.7)	9.8 (5.3)	0.671
Early Trauma Inventory (ETI)-Total	3.9 (3.1)	4.6 (3.1)	2.6 (3.0)	0.114
General traumas	1.9 (1.8)	2.1 (1.6)	1.4 (2.1)	0.235[c]
Physical punishment	1.4 (1.5)	1.6 (1.6)	1.0 (1.1)	0.291
Emotional abuse	0.64 (0.91)	0.7 (0.9)	0.4 (1.0)	0.203[c]
Sexual events	0.07 (0.26)	0.1 (0.3)	0 (0.0)	0.321[c]

[a] Values represent means (SD) except where otherwise indicated. Gender differences were compared by t test except where otherwise indicated

[b] Fisher's exact test

[c] Wilcoxon–Mann–Whitney test

drug effect ratings were not, skewness was within an acceptable range and the boxplot showed no outliers. No associations were found between scores on outcome measures and demographic characteristics of age, BMI, drinking history, or gender. None of the participants were clinically depressed and no relationships were observed between BDI scores and DA release, BP_{ND}, or pleasant drug effects. However, BDI scores were positively associated with both perceived stress (r=0.540; p=0.003) and trauma ratings (r=0.578; p=0.001).

Associations with childhood trauma

DA release

A significant decrease in VS [^{11}C]raclopride BP_{ND} (p<0.001) was noted from the post-saline (M=3.06, SD=0.31) to the post-AMPH (M=2.64, SD=0.30) scan, indicating significant AMPH-induced DA release. A positive relationship was found between ETI scores and VS DA release in the sample as a whole (Table 2), suggesting that individuals who experience a greater number of adverse events in childhood have greater VS DA responses to AMPH. No significant interaction was observed between ETI scores and gender. The unadjusted relationship is shown in Fig. 1. Images of ΔBP_{ND} (saline minus AMPH scans) are displayed in Fig. 2 to further illustrate the relationship using subjects in the highest and lowest quartiles of ETI scores.

No significant relationships were observed between ETI scores and DA release in the other striatal regions (ACN, PCN, APU, and PPU) examined in exploratory analyses (Table 3).

D2 receptor availability

Findings indicated that associations between ETI scores and VS D2 receptor availability (BP_{ND}) differed in males and females. Gender-stratified post hoc analyses showed a positive relationship between ETI scores and VS BP_{ND} among males, but a marginally negative relationship among females (Table 2).

Interactions between ETI scores and gender were also significant in exploratory analyses of APU and ACN BP_{ND}, showing that males with higher ETI scores had higher VS D2 receptor availability (BP_{ND}). Although not significant, the direction of the relationships was negative in females, consistent with what was observed between ETI scores and BP_{ND} in the VS (Table 3).

Pleasant drug effects

Ratings on all five scales of pleasant drug effects were significantly higher during the AMPH than during the saline scan (≤0.001 in all cases). Mean scores on four of these measures are shown in Fig. 3. A significant interaction was observed between ETI scores and gender in the full model (Table 2). Although findings of subsequent gender-stratified post hoc analyses were not significant in either gender, the direction of the relationship between childhood trauma and pleasant drug effects was noted to be positive among males and negative among females.

Perceived stress

ETI scores were positively related to scores on the PSS in the sample as a whole (Table 2), suggesting that individuals who experience a greater number of ACEs also experience higher levels of perceived stress as adults. No significant interaction was found between ETI scores and gender. The unadjusted relationship between ETI and PSS is shown in Fig. 4.

Associations with perceived stress

DA release

A positive association was observed between PSS scores and VS DA release in the sample as a whole; higher perceived stress was associated with greater VS DA responses to AMPH (Table 4). The relationship between perceived stress and VS DA release did not differ in males and females.

Table 2 Effects of early trauma and gender on ventral striatal dopamine function, pleasant drug effects, and perceived stress

Outcomes	Models[a]			Females only	Males only
	ETI total b1 (*p* value)	Gender b2 (*p* value)	ETI-by-gender interaction b3 (*p* value)	ETI total b1 (*p* value)	ETI total b1 (*p* value)
DA release					
VS	0.79 (0.047)	0.59 (0.816)	–	–	–
Pleasant drug effects[b]					
Composite score	12.12 (0.254)	−31.73 (0.591)	−38.42 (0.048)	−27.24 (0.152)	12.18 (0.257)
Perceived stress					
PSS	0.70 (0.024)	0.56 (0.775)	–	–	–
Saline scan BP_{ND}					
VS	0.06 (0.015)	−0.06 (0.643)	−0.10 (0.017)	−0.05 (0.084)	0.06 (0.031)

ETI Early Trauma Inventory, *DA* dopamine, *VS* ventral striatum, *PSS* Perceived Stress Scale, BP_{ND} [11C]raclopride binding potential

[a] Full models included terms for ETI total scores, gender, and their interaction. If ETI-by-gender interaction was not significant, the reduced models included ETI total scores and gender only

[b] Models of pleasant drug effects also controlled for drug effects during saline scan

A positive relationship was observed between PSS scores and AMPH-induced DA release in the ACN in exploratory analyses (Table 5). Effects were not modified by gender. Scores on the PSS were not associated with DA release in any of the other striatal subdivisions.

D2 receptor availability

No relationships were observed between PSS scores and VS D2 receptor availability (BP_{ND}) in the primary analyses (Table 4).

A trend was observed in exploratory analyses, which suggested that levels of perceived stress are positively associated with ACN BP_{ND} in males and negatively associated with ACN BP_{ND} in females (Table 5).

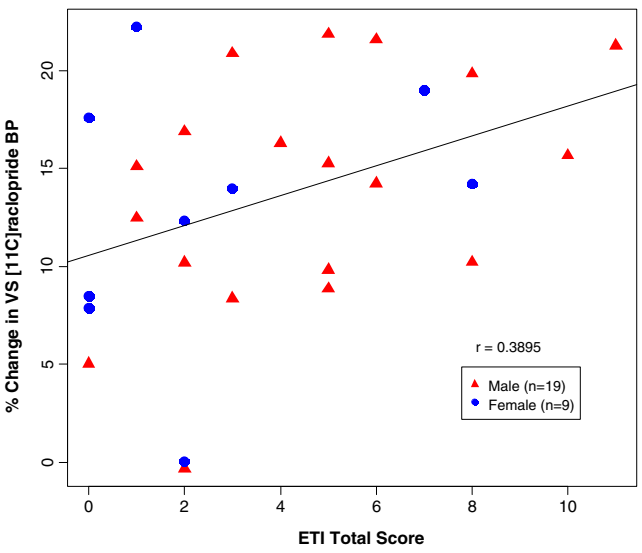

Fig. 1 Unadjusted relationship between amphetamine-induced ventral striatal (VS) dopamine release and total scores on the Early Trauma Inventory coded by gender. Dopamine release = percent change in [^{11}C]raclopride BP_{ND} from the placebo to the amphetamine scan

Pleasant drug effects

Examination of the relationship between PSS scores and pleasant subjective effects of AMPH revealed a significant interaction between PSS scores and gender (Table 4). Findings of gender-stratified analyses showed that PSS scores were positively related to pleasant drug effects among males, whereas no association was observed among females.

Associations with baseline cortisol

No associations were observed between baseline cortisol levels and DA release, total ETI scores, or PSS scores.

Mediation analysis

The first regression indicated that ETI scores were associated with PSS scores (path a in Fig. 5), which is consistent with the previous findings when controlling for gender. In the second regression, ETI scores were positively associated with VS DA release (path c). The third regression revealed that the effect of ETI scores on DA release was not significant after controlling for PSS scores, suggesting that the relationship between ETI and DA was mediated by PSS (path c′). The alternative bias-corrected bootstrap method confirmed the mediating role of PSS on the relationship between ETI and DA. The production of a*b (0.67*0.43) is 0.285. The 95 % bias-corrected bootstrapped confidence interval of this mediation effect was within the range of 0.008–0.856, indicating the presence of mediation.

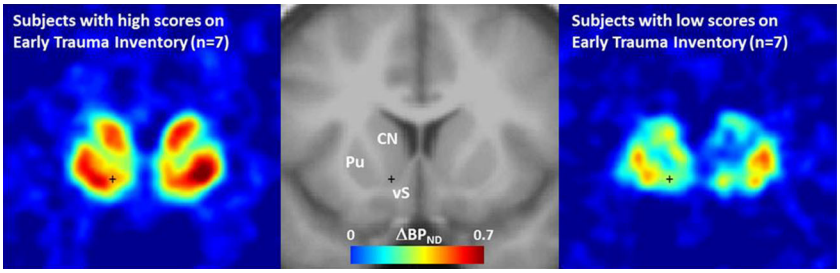

Fig. 2 Coronal images (10 mm anterior to the anterior commissure point) of ΔBP_{ND} images (saline−amphetamine), spatially normalized to a standard MRI (*middle panel*), smoothed, and averaged across subjects who showed high (>5; *left*) or low total scores (<2; *right*) on the Early Trauma Inventory. Regions are putamen (*Pu*), caudate nucleus (*CN*), and ventral striatum (*VS*). A point in VS was indicated by a *plus sign* (+) to mark equivalent positions across images. Note that subjects with high total scores showed slightly greater ΔBP_{ND} in the VS than subjects with low total scores

Discussion

A major gap that still remains in our knowledge about relationships between childhood adversity and the etiology of substance use disorders is lack of understanding about biological mechanisms that may underlie the relationship. To our knowledge, this study represents the first examination of relationships between childhood adversity and mesolimbic DA responses to AMPH in humans. Results indicated that the number of ACEs that participants experienced was positively associated with their DA responses to AMPH, as well as with levels of perceived stress that they experienced as adults. Current levels of perceived stress were also positively associated with DA responses to AMPH in the sample as a whole and partially mediated the relationship between childhood trauma and AMPH-induced DA release, suggesting that ACEs may have both direct and indirect effects on DA neurotransmission. Although associations between childhood trauma and DA release did not differ in males and females, relationships between childhood trauma and both D2 receptor availability and pleasant drug effects were significantly modified by gender. Childhood trauma was positively associated with D2 receptor availability and in males, whereas a trend for a negative relationship was observed in females. Although not significant, similar gender differences in directionality were observed in relationships between ACEs and pleasant drug effects (i.e., positive in males and negative in females). Perceived stress was also positively associated with pleasant drug effects in males, whereas no relationship was observed in females. No associations were found between perceived stress and D2 receptor availability. Overall, our results are consistent with notions that early life experiences may have an enduring influence on neural systems that mediate responses to stress and drugs of abuse in humans.

Findings from observational studies have provided compelling evidence that a history of childhood adversity may

Table 3 Effects of early trauma and gender on regional striatal dopamine function

Outcomes	Models[a]			Females only	Males only
	ETI total b1 (*p* value)	Gender b2 (*p* value)	ETI-by-gender interaction b3 (*p* value)	ETI total b1 (*p* value)	ETI total b1 (*p* value)
DA release					
APU	0.28 (0.471)	−2.17(0.392)	–	–	–
PPU	−0.38 (0.276)	−5.1 (0.032)	–	–	–
ACN	0.67 (0.123)	−0.84 (0.766)	–	–	–
PCN	0.35 (0.509)	−0.98 (0.778)	–	–	–
Saline scan BP_{ND}					
APU	0.064 (0.023)	−0.22 (0.153)	−0.13 (0.016)	−0.06 (0.118)	0.064 (0.034)
PPU	0.019 (0.503)	−0.13 (0.472)	–	–	–
ACN	0.077 (0.001)	−0.16 (0.217)	−0.13 (0.002)	−0.057 (0.161)	0.077 (0.001)
PCN	0.044 (0.148)	−0.045 (0.822)	–	–	–

ETI Early Trauma Inventory, *DA* dopamine, *APU* anterior putamen, *PPU* posterior putamen, *ACN* anterior caudate nucleus, *PCN* posterior caudate nucleus, BP_{ND} [11C]raclopride binding potential

[a] Full models included terms for ETI total scores, gender, and their interaction. If ETI-by-gender interaction was not significant, the reduced models included ETI total scores and gender only

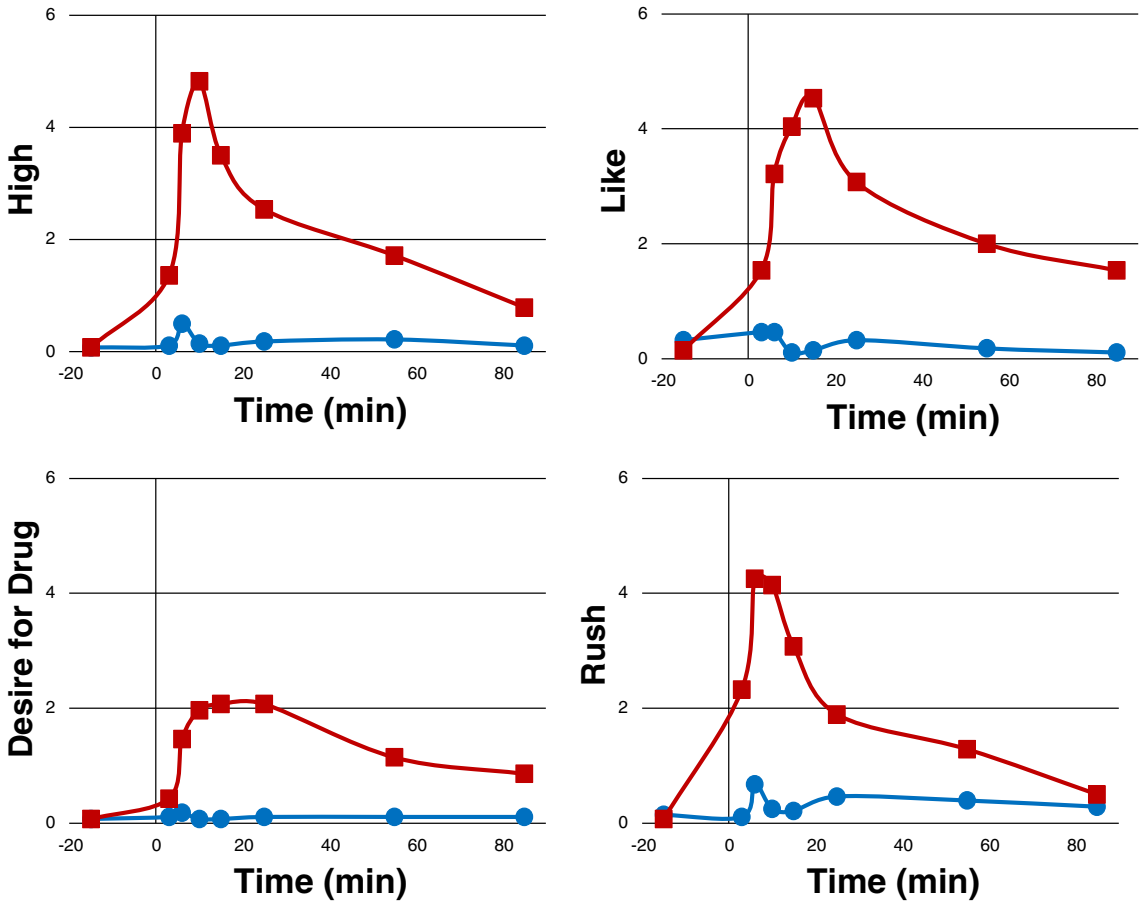

Fig. 3 Unadjusted means of subjective drug effects (i.e., High, Like, Desire for Drug, and Rush) during the saline (*circles*) and amphetamine (*squares*) scans

increase risks for substance abuse in both adolescents and adults (Carswell et al. 2008; Fishbein et al. 2011; Hamburger et al. 2008; Kerr et al. 2009; Rothman et al. 2008; Sansone et al. 2009; Shin et al. 2013; Simpson and Miller 2002; Strine et al. 2012). It is logical to speculate that one biological mechanism that may underlie this relationship is mesolimbic DA neurotransmission. First, a voluminous body of preclinical (Bonci et al. 2003; Doyon et al. 2003; Koob 2003; Wise 1998) and human neuroimaging (Drevets et al. 2001; Leyton et al. 2002; Martinez et al. 2003; Oswald et al. 2005; Urban et al. 2010; Volkow et al. 1999, 2002; Yoder et al. 2007) literature has established the importance of mesocorticolimbic DA pathways in reinforcement, reward, and addiction. Second, there is preclinical evidence that early life stress may lead to profound and long-lasting alterations in DA pathways in animals. During critical developmental periods when plasticity is heightened, the brain may be particularly sensitive to the destructive effects of adverse experiences on neural function (Rodrigues et al. 2011). In rodents, early life stress is associated with increased tissue levels and reduced rate of DA clearance in the striatum (Matthews et al. 2001; Womersley et al. 2011), as well as altered levels of D2 receptor expression, which vary as a function of D2 polymorphisms (Lovic et al. 2013). Several investigators have reported enhanced striatal DA responses to later stress in rodents exposed to early life adversity (Brake et al. 2004; Fulford and

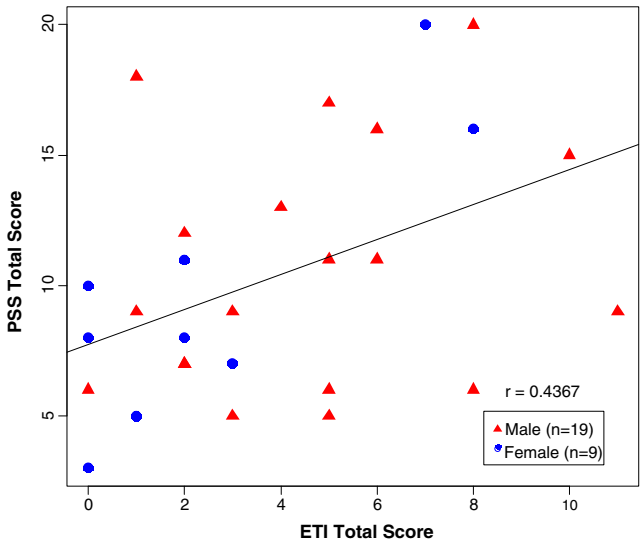

Fig. 4 Unadjusted relationship between total scores on the Early Trauma Inventory (ETI) and Perceived Stress Scale (PSS) coded by gender

Table 4 Effects of perceived stress and gender on ventral striatal dopamine function and pleasant drug effects

Outcomes	Models[a]			Females only	Males only
	PSS b1 (*p* value)	Gender b2 (*p* value)	PSS-by-gender interaction b3 (*p* value)	PSS b1 (*p* value)	PSS b1 (*p* value)
DA release					
VS	0.56 (0.023)	−0.54 (0.821)	–	–	–
Pleasant drug effects					
Composite score[b]	17.89 (0.012)	−12.55 (0.809)	−24.63 (0.027)	−6.84 (0.549)	17.91 (0.007)
Saline scan BP_{ND}					
VS	0.004 (0.75)	−0.03 (0.827)	–	–	–

ETI Early Trauma Inventory, *DA* dopamine, *VS* ventral striatum, *PSS* Perceived Stress Scale, BP_{ND} [11C]raclopride binding potential

[a] Full models included terms for ETI total scores, gender, and their interaction. If ETI-by-gender interaction was not significant, the reduced models included ETI total scores and gender only

[b] Models of pleasant drug effects also controlled for drug effects during saline scan

Marsden 1998; Meaney et al. 2002; Miura et al. 2002), although blunting of DA responses has also been found (Brake et al. 2004; Fulford and Marsden 1998; Jahng et al. 2010; Meaney et al. 2002; Miura et al. 2002). Enhanced DA responses to psychostimulants (Hall et al. 1999; Kosten et al. 2003) and increased propensity for drug self-administration have also been observed (Brake et al. 2004; Kosten et al. 2005, 2006; Meaney et al. 2002; Moffett et al. 2007; Ploj et al. 2003; Zhang et al. 2005).

Exposure to glucocorticoids during early life also has enduring effects on the organization and epigenetic control of midbrain DA systems (McArthur et al. 2007; Niwa et al. 2013), suggesting that the neurobiological mechanisms by which early life stress alters DA function may involve the hypothalamic–pituitary–adrenal axis. Elevated levels of glucocorticoids induced by environmental stress during adolescence were recently shown to be associated with augmented NAcc DA levels following methamphetamine challenge in a transgenic mouse model with a relevant genetic risk factor (Niwa et al. 2013). The enhancement in DA levels in that study was shown to be a consequence of cortisol-induced epigenetic methylation of the tyrosine hydroxylase gene whose gene product is an important enzyme in the biosynthesis of DA. Although no associations were observed between DA release and baseline cortisol levels in our sample, the lack of associations does not preclude the possibility that

Table 5 Effects of perceived stress and gender on regional striatal dopamine function and pleasant drug effects

Outcomes	Models[a]			Females only	Males only
	PSS b1 (*p* value)	Gender b2 (*p* value)	PSS-by-gender interaction b3 (*p* value)	PSS b1 (*p* value)	PSS b1 (*p* value)
DA release					
APU	0.40 (0.089)	−2.4 (0.302)	–	–	–
PPU	0.029 (0.894)	−4.3 (0.061)	–	–	–
ACN	0.63 (0.016)	−1.7 (0.510)	–	–	–
PCN	0.30 (0.356)	−1.4 (0.665)	–	–	–
Saline scan BP_{ND}					
APU	−0.005 (0.755)	−0.19 (0.252)	–	–	–
PPU	−0.0003 (0.988)	−0.17 (0.339)	–	–	–
ACN	0.03 (0.073)	−0.14 (0.285)	−0.069 (0.015)	−0.039 (0.077)	0.03 (0.089)
PCN	0.0046 (0.811)	−0.13 (0.512)	–	–	–

PSS Perceived Stress Scale, *DA* dopamine, *APU* anterior putamen, *PPU* posterior putamen, *ACN* anterior caudate nucleus, *PCN* posterior caudate nucleus, BP_{ND} [11C]raclopride binding potential

[a] Full models included terms for ETI total scores, gender, and their interaction. If ETI-by-gender interaction was not significant, the reduced models included ETI total scores and gender only

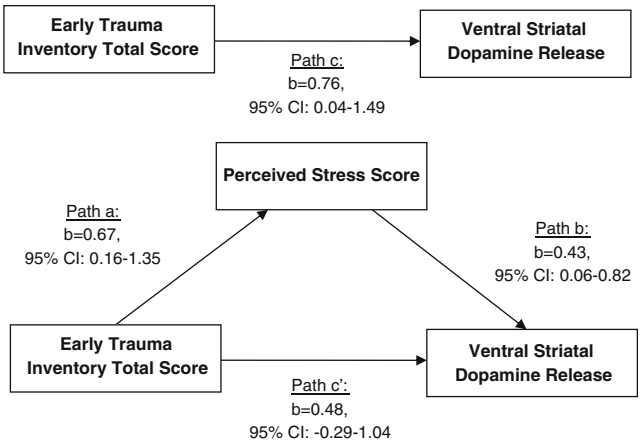

Fig. 5 Model depicting the direct and indirect effects of childhood trauma on amphetamine-induced ventral striatal (VS) dopamine release. Note: the indirect effect from childhood trauma to dopamine release (mediated by perceived stress) was significant ($a*b$=0.285, 95 % CI = 0.008–0.856)

prolonged elevations in glucocorticoid levels *during the period of trauma exposure* may lead to alterations in DA function that persist into adulthood. This assumption fits a body of literature showing crucial time windows in development where neuroplasticity can be altered (Rosa et al. 2013).

The first evidence that some of these findings may translate to humans was provided by Pruessner and colleagues (2004) in an [^{11}C]raclopride PET study. Acute psychosocial stress was associated with a significant increase in stress-induced DA release in subjects who reported low maternal care, but not in those who reported high maternal care. Low maternal care humans also had higher anxiety and lower self-esteem scores. In the current study, we extended this line of research by showing that ACEs are also associated with enhanced VS DA sensitivity to AMPH in humans. Our findings parallel those of preclinical studies showing that rodents exposed to early life stress have augmented VS DA responses to psychostimulants (Hall et al. 1999; Kosten et al. 2003). Findings of the exploratory analyses suggested that relationships between ETI scores and D2 receptor availability in the anterior putamen (APU) and anterior caudate (ACN) may be analogous to those observed with D2 receptor availability in the VS. Although it is well established that the NAcc region of the VS plays a key role in appetitive behaviors and in the reinforcing effects of drugs of abuse, there has been growing evidence in recent years that the dorsal striatum is fundamental in the transition from voluntary to habitual or compulsive drug-seeking (Everitt and Robbins 2013). Thus, concurrent subversion of DA function in both ventral and dorsal regions of the striatum by early life stress could be expected to have a significant impact on the broad-based integration of learning and motivational behaviors across the various phases of addiction.

Somewhat unexpectedly, relationships between ACEs and both baseline D2 receptor availability and pleasant drug effects were found to be significantly modified by gender. The underlying processes and clinical relevance of these sexual dimorphisms are not currently clear, but the findings are consistent with prior evidence that males may have greater cortisol reactivity to stress (Strine et al. 2012; Uhart et al. 2006) and greater DA and subjective responses to AMPH than females (Gabbay. 2005; Munro et al. 2006). Gender-specific differences in the function of brain monoamine systems early trauma have previously been reported in rodents exposed to early life stress (Chocyk et al. 2011; Festa et al. 2004; Matthews et al. 2001; Nazarian et al. 2009; Walker et al. 2006). Interestingly, maternal separation has been shown to be associated with ethanol consumption and preference in male, but not female rats (Gustafsson et al. 2005; Jaworski et al. 2005; Moffett et al. 2007; Roman et al. 2004). It is possible that our gender-related findings may have been different if the women were in the luteal phase of the menstrual cycle. Differences in D2 receptor availability have been reported in female cynomolgus monkeys as a function of menstrual cycle; levels were significantly higher in the luteal as compared to the follicular phase in both the caudate nucleus and putamen (Czoty et al. 2009). Nevertheless, the current findings related to gender should be interpreted cautiously since the sample included only nine females.

A positive correlation was found between childhood adversity and perceived stress in this study. Because each of these variables was measured at the same time, the findings might reflect a recall bias, i.e., people who feel less stressed may not report as many negative events as those who feel more stressed. However, the observed relationship between childhood adversity and perceived stress was analogous to findings of prior research showing associations between ACEs and psychological distress and/or reactivity to acute laboratory stressors in both healthy adults (Cagampang et al. 2011; Edwards et al. 2003; Glaser et al. 2006; Kendler et al. 2004; McFarlane et al. 2005; Pierrehumbert et al. 2009; Sesar et al. 2010; Tyrka et al. 2008) and substance abusers (Back et al. 2008; Medrano et al. 2002; Wang et al. 2010). A vast body of findings from preclinical, human laboratory, and clinical observational studies has shown that stress may contribute to the pathogenesis and progression of substance use disorders (Back et al. 2010; Breese et al. 2011; Erb et al. 1996; Karlsgodt et al. 2003; Kreek et al. 2005; Laudet et al. 2004; Lu et al. 2003; Sinha 2001; Soderpalm and de Wit 2002; Tidey and Miczek 1997). Recent preclinical findings indicate that both acute and chronic stress impact DA neurotransmission and that the DA system may be an important vulnerability substrate in the relationship between stress and drug abuse (Cuadra et al. 2001; Kosten and Ambrosio 2002; Piazza and Le Moal 1996; Rouge-Pont et al. 1993; Tidey and Miczek 1996; Tsukada et al. 2011; Yavich and Tiihonen 2000). Although results of the few human studies that have examined effects of acute psychological stress on brain DA levels have

been mixed (Lataster et al. 2011; Montgomery et al. 2006; Pruessner et al. 2004), our group and others have previously shown that cortisol responses to either psychosocial stress (TSST; Trier Social Stress Test) (Kirschbaum et al. 1993) or AMPH are positively associated with AMPH-induced DA release in humans (Pruessner et al. 2004; Oswald et al. 2005; Wand et al. 2007). Our current findings further revealed that levels of perceived stress (which may reflect stress reactivity) were also positively associated with DA release. Findings of the preliminary correlational analyses, which gave no evidence of associations between BDI scores and DA release or BP_{ND}, also support inferences that observed effects on DA neurotransmission were linked to stress as opposed to depression.

Results indicated that the relationship between childhood trauma and DA sensitivity to AMPH was partially mediated by perceived stress. Thus, exposure to childhood trauma may not directly influence DA function in some individuals unless it leads to elevated levels of psychological distress in adulthood. Choy et al. reported that a combination of maternal deprivation and later stress had added effects on disruption of prepulse inhibition by AMPH in young adult rats (Choy et al. 2009). Psychological distress, avoidant coping, and mood/anxiety disorders have also been shown to mediate the relationship between ACEs and adult alcohol or drug problems (DeWit et al. 1999; Douglas et al. 2010; Fishbein et al. 2011; Min et al. 2007; Simpson and Miller 2002; Strine et al. 2012; White and Widom 2008). Results from a study conducted by Douglas et al. (2010) indicated that effects of childhood trauma on risks for substance dependence are cumulative, based on the number of events experienced.

Our design has both strengths and limitations. None of the subjects met diagnostic criteria for a DSM-IV Axis I disorder and the number of ACEs reported were generally low. An important strength of this design is that the absence of comorbid depression or anxiety strengthens our supposition that associations with DA release were related to childhood trauma rather than to depression or anxiety. A limitation of the design is that effect sizes may be underestimated given the restricted range of adverse events that subjects reported. We suggest that our finding in this sample of healthy adults represents an underestimation of the true relationship, which may have emerged even stronger in a more clinically diverse group. However, this hypothesis remains to be examined. Prior evidence that DA signaling modulates brain function in an inverted U-shaped manner (Gjedde et al. 2010; Tian et al. 2013) leaves open the possibility that our findings may not generalize to persons with a psychiatric diagnosis. Another limitation of the study is related to the interpretation of findings. Although our findings indicate that childhood adversity is associated with enhanced DA responses to AMPH, the cross-sectional nature of the study and the fact that none of the subjects met diagnostic criteria for alcohol or drug abuse/dependence preclude definitive causal conclusions about the predictive relevance of the findings. The extent to which findings related to AMPH will generalize to alcohol and other drugs of abuse is also undetermined. Nevertheless, the vast body of preclinical literature showing close interactions between stress, mesocorticolimbic DA function, and drug reinforcement supports such extrapolation. One final caveat to consider is that not all children who have been exposed to ACEs go on to develop a substance use disorder. Individual differences in susceptibility to the effects of childhood trauma on DA-dependent processes and related psychopathology could be the result of variations in the duration or developmental stage of stress exposure, interactions of early stress with the genome, epigenetic programming effects of early life stress, or later environmental experiences, which were beyond the scope of this study to examine (Das et al. 2011; Enoch 2011; Kim-Cohen and Turkewitz 2012; Heim and Binder 2012; Tyrka et al. 2012; Lovic et al. 2013).

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