Development and Psychopathology (2023), **35**, 1497–1514
doi:10.1017/S0954579422000244

CAMBRIDGE UNIVERSITY PRESS

Regular Article

Dampened psychobiological responses to stress and substance use in adolescence

Danny Rahal[1], Elizabeth A. Shirtcliff[2], Andrew Fuligni[1,3], Katherine Kogut[4], Nancy Gonzales[5], Megan Johnson[4], Brenda Eskenazi[4] and Julianna Deardorff[4]

[1]Department of Psychology, University of California, Los Angeles, Los Angeles, CA, USA, [2]Center of Translational Neuroscience, University of Oregon, Eugene, OR, USA, [3]Department of Psychiatry and Biobehavioral Sciences, University of California, Los Angeles, Los Angeles, CA, USA, [4]Center for Environmental Research and Children's Health, Berkeley School of Public Health, University of California, Berkeley, CA, USA and [5]Psychology Department, Arizona State University, Tempe, AZ, USA

Abstract

Substance use increases throughout adolescence, and earlier substance use may increase risk for poorer health. However, limited research has examined whether stress responses relate to adolescent substance use, especially among adolescents from ethnic minority and high-adversity backgrounds. The present study assessed whether blunted emotional and cortisol responses to stress at age 14 related to substance use by ages 14 and 16, and whether associations varied by poverty status and sex. A sample of 277 Mexican-origin youth (53.19% female; 68.35% below the poverty line) completed a social-evaluative stress task, which was culturally adapted for this population, and provided saliva samples and rated their anger, sadness, and happiness throughout the task. They also reported whether they had ever used alcohol, marijuana, cigarettes, and vaping of nicotine at age 14 and again at age 16. Multilevel models suggested that blunted cortisol reactivity to stress was associated with alcohol use by age 14 and vaping nicotine by age 16 among youth above the poverty line. Also, blunted sadness and happiness reactivity to stress was associated with use of marijuana and alcohol among female adolescents. Blunted stress responses may be a risk factor for substance use among youth above the poverty line and female adolescents.

Keywords: adolescence; cortisol; emotion; stress response; substance use

(Received 17 February 2021; revised 28 January 2022; accepted 1 February 2022; First Published online 27 June 2022)

Substance use initiation greatly increases across adolescence (Johnston et al., 2019). Youth with greater internalizing and externalizing problems tend to show high risk for substance use, and differences in the activation of to two key stress response systems – hypothalamic pituitary adrenal (HPA) axis and emotion – have been related to both (e.g., Bai & Repetti, 2018; Hartman et al., 2013). However, limited research has examined whether differences in the biological and psychological responses to stress, with respect to changes in cortisol secretion and emotions following stressor onset and across a recovery period, relate to substance use among adolescents, especially those at heightened risk for substance use. The present study examined how differences in the stress response related to substance use in a sample of Mexican-origin youth growing up with high levels of adversity in a low-income region (Stein et al., 2016). Using a longitudinal study design, we tested whether differences (i.e., exaggerated and blunted) in HPA axis and emotion reactivity and recovery to stress at age 14 were associated with use of alcohol, marijuana, and cigarette use by age 14 (i.e., the substances most commonly used by adolescents); use of alcohol, marijuana, cigarettes, and vaping of nicotine by age 16; and onset of alcohol, marijuana, and cigarette use between ages 14 and 16. Finally, we tested whether associations between stress reactivity, stress, recovery, and substance use varied by poverty status and sex.

Corresponding author: Danny Rahal, email: danrahal@ucla.edu

Cite this article: Rahal, D., *et al.* (2023). Dampened psychobiological responses to stress and substance use in adolescence. *Development and Psychopathology* **35**: 1497–1514, https://doi.org/10.1017/S0954579422000244

Adolescent substance use and stress

Substance use greatly increases during adolescence, as the percentage of students who have used an illicit drug doubles from 8th to 10th grade, and nearly half of students report using at least one substance by 12th grade (Johnston et al., 2019). Although experimentation is common in adolescence, youth who use alcohol, tobacco, and marijuana earlier in adolescence are at higher risk for psychopathology and substance use disorders in adulthood (e.g., Andersen et al., 2003; Ellickson et al., 2003; Fergusson et al., 2002; Riala et al., 2004; Taylor et al., 2017). Previous research has also consistently found that use of alcohol and marijuana by ages 14 and 16 specifically are related to poorer adjustment and higher use later in adolescence and adulthood (e.g., Colell et al., 2014; DeWit et al., 2000; Duke, 2018; Grant & Dawson, 1997; Grant et al., 2006; Hingson et al., 2006; Strunin et al., 2017; Swift et al., 2008; Wagner et al., 2005). Risk is particularly high for Latinx adolescents, who show higher lifetime use of varied substances by 8th grade and by 12th grade compared to White and Black youth, and tend to begin using cigarettes, alcohol, and other drugs at earlier ages than other ethnic minorities (Johnston et al., 2019; Kann et al., 2018). Furthermore, prior research suggests that

Mexican American adolescents, specifically, are more likely to have initiated substance use by the eighth grade than non-Latinx and other Latinx youth (Delva et al., 2005).

Substance use and stress reactivity and recovery

People generally respond to stress by showing increased negative emotion, decreased positive emotion, and activation of the HPA axis, a biological system especially sensitive to social-evaluative stressors (Dickerson & Kemeny, 2004). Exaggerated emotion reactivity to stress has been related to poorer health (e.g., Uink et al., 2018). However, inability to mount a response or showing blunted reactivity to stress may suggest disengagement and has also been related to poorer well-being (Carroll et al., 2017). Dampened reactivity and recovery following stress (i.e., smaller or no changes in emotion and cortisol secretion following stress onset) have also been related to poorer health including depression and externalizing problems (e.g., Bylsma et al., 2008; Jones et al., 2009; Stadler et al., 2007).

Individuals can show blunted rather than exaggerated stress reactivity and recovery for many reasons (Shirtcliff et al., 2021). Individuals who experience chronic or repeated stress may initially show heightened emotional and biological stress reactivity and recovery, and these responses may habituate and show a blunted profile over time (Peters & McEwen, 2015). Therefore, whereas unpredictable, acute stressful life events may promote a profile of exaggerated reactivity to stress, living in adversity can serve as a chronic stressor and consequently can promote inflexibility of psychobiological systems over time, such that individuals are incapable of responding to acute stressors (Del Giudice et al., 2011; Shirtcliff et al., 2021). Indeed, youth and adults who experience more adversity generally show blunted rather than enhanced cortisol and heart rate reactivity to acute stress (Carpenter et al., 2007, 2011; Lovallo, 2011; Trickett et al., 2014), as well as reduced activation of neural regions involved in threat such as the amygdala (Ginty et al., 2013; Yang et al., 2015). It has been posited that individuals who experience high levels of adversity may be inclined to disengage from stressors, which can attenuate psychobiological reactivity and recovery (Carroll et al., 2017). Lastly, low reactivity may result from socialization from peers and parents (Chaplin et al., 2018; Guo et al., 2017). For instance, youth who experience adversity may interact with deviant peers or bullies who prompt them to be less responsive to stress and may be socialized by parents to be less affected by daily stressors (Calkins & Hill, 2007; Ouellet-Morin et al., 2011).

Just as heavy substance use can dysregulate HPA axis function (e.g., Koob & Kreek, 2007; Lovallo, 2006), dysregulation of the HPA axis may also contribute to substance use risk. Youth with blunted HPA axis reactivity to stress may lack physiological inhibitory control, such that they may be less inhibited by the social consequences of risk-taking compared to adolescents who show greater cortisol reactivity to stress (e.g., Salis et al., 2016; Wright et al., 2019). Alternatively, adolescents with chronic underarousal may be generally more inclined to pursue risky behaviors to promote physiological arousal (Brewer-Smyth et al., 2004; Ortiz & Raine, 2004; Platje et al., 2013). Youth may not show cortisol reactivity to a stressor because they are not sensitive to that stressor, or because their cortisol has already become elevated in anticipation of a stressor (i.e., anticipatory cortisol). That is, certain youth may be more responsive to the threat such that they already show elevated levels of cortisol prior to stress onset and consequently show no further elevation in cortisol thereafter. Both blunted cortisol reactivity and anticipatory cortisol have been associated with more frequent substance use later in adolescence, especially among youth with difficulties in emotion regulation (Evans et al., 2016; Kliewer et al., 2016; Poon et al., 2016). Dysregulation of HPA axis function may similarly promote risk for lifetime substance use during adolescence. Adolescents with higher basal cortisol had earlier onset of substance use, although cortisol was not assessed following stress (Huizink et al., 2006, 2009; Rao et al., 2009), and blunted cortisol secretion in anticipation of a laboratory task has been linked to greater substance use in pre-pubertal boys (Moss et al., 1999). Given the potential for bidirectional associations between HPA axis function and substance use, longitudinal studies are needed to disentangle whether HPA axis reactivity to and recovery from stress relate to risk for substance use onset during adolescence. Specifically, it is well-established that heavy substance use – as opposed to substance use initiation or less frequent substance use – can dysregulate physiology (Koob & Le Moal, 2008; Lovallo, 2006), so researchers may be best positioned to examine the role of biology on substance use risk during adolescence when youth are initiating substance use but have not yet engaged in heavy substance use.

In addition to cortisol reactivity, emotion reactivity to stress may relate to substance use. There are several emotion-related risk factors for substance use and substance use disorders in both adults and adolescents, including greater negative emotions, emotional lability, and emotional dysregulation (Hersh & Hussong, 2009; Shadur et al., 2015; Shomaker & Reina, 2015; Simons & Carey, 2002; Simons et al., 2009). Although it is well-established that emotions influence frequency of substance use among users, it remains unclear whether emotion reactivity to stress relate to adolescents' risk for substance use initiation. Emotion reactivity to stress often includes increases in negative emotions of both high arousal (e.g., anger) and low arousal (e.g., sadness) and decreases in positive emotion, and each form of emotional change can have unique implications for health (e.g., Young et al., 2019). Youth with exaggerated and dampened stress reactivity and recovery with respect to emotion may be particularly at risk for earlier onset of substance use, especially for Mexican-heritage adolescents, who experience culturally-specific stressors (e.g., discrimination, acculturation, immigration stressors; Eskenazi et al., 2019). Therefore, research is needed to determine whether emotion reactivity to stress and recovery from stress is related to substance use and the emergence of substance use among these youth.

Sex differences in substance use motivation

The impact of stress reactivity and recovery on substance use during adolescence may vary by sex. Adolescents' motivations for substance use differ by sex (Becker et al., 2012; Chaplin et al., 2018). Male youth tend to be more motivated to use substances for social enhancement whereas female adolescents are more motivated to use substances to cope with negative emotion and stress (Kuntsche et al., 2015; Pompili & Laghi, 2019). Further, female adolescents show higher comorbidity between substance use and depression relative to male adolescents, suggesting that emotion and stress may be particularly tied to female adolescents' substance use (Latimer et al., 2002). Therefore, although male adolescents tend to show earlier and more frequent substance use relative to female adolescents (Johnston et al., 2019), substance use may be particularly related to the stress response among female adolescents. Indeed, prior research regarding youth who have used substances by age 16 in

https://doi.org/10.1017/S0954579422000244 Published online by Cambridge University Press

this cohort of Mexican-origin adolescents has found that greater cortisol reactivity relates to earlier age of initiation of alcohol use for girls, whereas blunted cortisol reactivity was related to earlier initiation of marijuana use only for boys with less advanced pubertal status (Johnson et al., 2020). It is critical to disentangle whether differences in stress reactivity and recovery precede substance use across the sexes.

Poverty status differences in substance use motivation

Poverty status may also moderate associations between responses to stress and substance for two reasons. First, early life adversity including poverty status has been found to influence psychobiology such that youth who experience early life adversity, including youth below the poverty line, tend to show profiles of blunted cortisol responses to stress (e.g., Joos et al., 2019). Because these youth are already at heightened risk for blunted cortisol responses, the association between these responses and substance use may be stronger among these youth. Second, poverty status may influence adolescents' propensity for substance use. Youth below the poverty line may experience earlier exposure to substance use and substance-related crime, more targeted marketing of substances, and lower parental involvement (Biener & Siegel, 2000; Wills et al., 2004). They may also be more motivated to use substances for reasons beyond stress, such as due to boredom, sensation seeking, and pursuit of enhancing effects in order to compensate for a lack of pleasurable substance-free daily activities (Lee et al., 2018; Martz et al., 2018). Poverty status may similarly influence the types of substances that adolescents use. Whereas cigarette use is more common among youth with lower socioeconomic status, marijuana, alcohol, and vaping are generally more prevalent among more affluent youth, potentially due to differences in cost, availability, and social norms (Jones et al., 2016; Melotti et al., 2011; Patrick et al., 2012). As a result, associations between stress reactivity and recovery and certain substances (i.e., cigarettes, marijuana, alcohol, vaping) may differ by poverty status.

Present study

The present study investigated whether adolescents' HPA axis and emotion responses to the Trier Social Stress Test (TSST), a validated paradigm for eliciting social-evaluative threat, were related to the use of various substances among Mexican-origin youth growing up in a low-income, high-risk agricultural setting (Kirschbaum et al., 1993). Responses to a social stressor were selected because adolescents tend to be particularly responsive to social threats, compared to younger children and adults (Spear, 2009), and youth often use substances in peer contexts to reduce social stress or enhance social experiences. In line with prior research highlighting how people vary in the types of emotions they experience in response to stress (e.g., Duijndam et al., 2020; Habra et al., 2003), we examined changes in three emotions following stress: anger, sadness, and happiness. Discrete emotions have different functional purposes and have unique impacts on cognitions and judgments (e.g., Lench et al., 2011; Lerner & Keltner, 2001). Therefore, rather than aggregating across emotions, we assessed unique effects of each emotion. We tested whether stress reactivity and recovery related to substance use among adolescents at heightened risk for substance use, in line with previous studies that have examined substance use initiation in high-risk samples (e.g., Moss et al., 1999).

Most prior studies examining stress responses and substance use have been conducted in the context of adult substance users or with cross-sectional designs (see Moss et al., 1999 as an exception). Therefore, we employed a longitudinal design to disentangle whether dampened psychobiological stress reactivity and recovery at age 14 precede the emergence of substance use initiation by age 16. Models examined whether differences in adolescents' HPA axis and emotion reactivity and recovery to the TSST at age 14 were related to a) use of substances by age 14, b) use of substances by age 16, and c) emergence of substance use between ages 14 and 16, excluding youth who had already used by age 14. Given the high levels of adversity in this sample, dampened psychobiological stress reactivity and recovery were predicted to be associated with use of alcohol and marijuana among these youth, in line with previous research (Evans et al., 2012, 2013; van Leeuwen et al., 2011). Although not previously tested with use of cigarettes and vaping, we examined whether dampened psychobiological reactivity and recovery would similarly relate to these substances which are also commonly used in adolescence.

Finally, models examined whether associations between HPA axis and emotion stress reactivity and recovery and substance use differ by sex and poverty status. Given that female adolescents may be more inclined than male adolescents to use substances to reduce negative emotion (Chaplin et al., 2018), we predicted that associations between dampened stress reactivity and recovery and substance use would be stronger for female adolescents than male adolescents. Because poverty status can promote profiles of dampened reactivity and can influence the types of substances that youth use (e.g., Joos et al., 2019; Melotti et al., 2011), we tested whether associations differ by poverty status.

Method

Participants

Participants were recruited as part of the CHAMACOS study, a longitudinal birth cohort study (Eskenazi et al., 2003). The cohort is comprised of Mexican-origin adolescents and their primary caregivers living in the agricultural Salinas Valley in Monterey County, California. The study includes two cohorts: an initial cohort ("CHAM1") of participants followed from birth and a second cohort ("CHAM2") of 9-year-old children recruited part-way through the study.

At the time of CHAM1 enrollment in years 1999–2000, mothers of CHAM1 children were aged 18 or over and pregnant with the target child, under 20 weeks of gestation, eligible for California's low-income health insurance program (Medi-Cal), receiving prenatal care, and planning to deliver at the county hospital. These CHAM1 women were recruited at pregnancy clinics. Originally, 1130 women were eligible, 601 were recruited, and 531 remained in the study after childbirth. Of their children, 325 CHAM1 remained enrolled in the study until age 14, with the majority of attrition occurring by age 3. Attrition was highest from pregnancy to delivery and was considerably lower since the assessment at age 5 (Sagiv et al., 2015). A second cohort (CHAM2) of 300 9-year-old children were recruited between 2009 and 2011, and they and their mothers have completed the same or comparable data collection activities as CHAM1 families since age 9 (Sagiv et al., 2015). Like the children from CHAM1, the mothers of CHAM2 children were 18 or older when pregnant with the child, primarily Spanish or English-speaking, eligible for Medi-Cal, and received prenatal care in the Salinas Valley. Retention rates for both cohorts were high between ages 9 and 14 (95% for CHAM1, 94% for CHAM2). These adolescents were low-income

https://doi.org/10.1017/S0954579422000244 Published online by Cambridge University Press

and had high levels of social adversity. As described in detail in previous articles (Hyland et al., 2022; Johnson et al., 2020; Sagiv et al., 2015), roughly 40% of participants experienced an adverse life event between ages of 6 months and 5 years of age, over 60% of participants had a mother with depression at 1 or 3.5 years of age), over one in four adolescents had three or more adverse childhood experiences, and the sample generally reported high numbers of early life events ($M = 4.5$, $SD = 3.3$).

Funding was allocated for the experimental component of the study such that the TSST could only be administered to a subset of participants at age 14 data collection. Recruitment was primarily limited to a subset of CHAM1 participants, and few CHAM2 participants also completed the TSST. All adolescents needed to meet the following criteria to complete the TSST at age 14: completing the visit in-office (as opposed to the at-home visits conducted with families who had moved from the study area), IQ above 70 at age 12, no diagnosis of Autism Spectrum Disorder, no extreme atypical behaviors at past visits, less than three standard deviations above the mean for depressive scores for their age and sex, and no gang involvement in the previous year given the risk for violent responses to the TSST. No participants reported using anabolic steroids. Importantly, participants who completed the TSST at age 14 did not differ from adolescents who completed surveys at age 14 but did not complete the TSST with respect to sex, mother's education, poverty status, or substance use, $ps > .06$. Please see Figure S1 for a full schematic of attrition across the study.

In total, 277 adolescents (53.19% female; 68.35% below the poverty line; 94.15% from CHAM1 cohort) completed the TSST at age 14 ($M = 14.11$, $SD = 0.18$), when the majority of participants were in either 8th grade (59.57%) or 9th grade (34.30%). Two years later, 260 of these adolescents (93.86%) completed additional data collection at age 16 ($M = 16.45$, $SD = 0.27$). Participants who completed the study at age 16 did not differ from those who did not with respect to sex, mother's education, poverty status, and cigarette use at age 14, $ps > .15$. However, differences did emerge by substance use, such that participants who did not complete the survey at age 16 were more likely to have used alcohol and marijuana at age 14; $\chi2(1) = 6.71$, $p = .010$, $\chi2(1) = 4.86$, $p = .028$, respectively.

We examined poverty status as an indicator of relative socioeconomic status. Poverty status was determined using the poverty-income ratio (i.e., family income divided by the poverty line). About two-thirds of participants had family income below the poverty line for their family size (68.35% below the poverty line), and almost all of the remaining participants were below 200% of the poverty line. Household crowding, calculated by dividing the number of family members by the number of rooms in the household, was negatively correlated with poverty-income ratio, $r(267) = -.18$, $p = .0023$. Participants with a poverty-income ratio below 1 were coded as living below the poverty line ($M_{Below} = 0.90$, $SD = 0.50$), and those with a value above 1 were coded as living above the poverty line ($M_{Above} = 1.06$, $SD = 0.47$); a t-test indicated that individuals above the poverty line had significantly higher poverty-income ratio values compared to those below the poverty line. Adolescents who were in poverty also reported lower mother's education ($M_{Below} = 3.09$, $SD = 1.36$; $M_{Above} = 3.47$, $SD = 1.74$; $t(275) = 2.00$, $p = .047$), compared to adolescents who were not in poverty. There was no difference in poverty status between male and female adolescents, $p = .95$, or by grade at age 14, $p = .16$.

Procedure

At age 14, adolescents completed a study visit starting primarily between 3:00 p.m. and 8:00 p.m., in which they completed the TSST, a validated paradigm for eliciting social-evaluative threat (Dickerson & Kemeny, 2004; Kirschbaum et al., 1993). On average, most participants completed the session at 6:05 ($SD = \pm 2$ hr). Adolescents were in the lab space for 2 hr completing benign surveys and other measures, in order to attenuate arrival effects and ensure participants acclimated to the laboratory environment (Ruttle et al., 2011; Shirtcliff et al., 2014). They then rested for 10 min prior to the task and watched a 3 min soothing video of the sea before being instructed to prepare a speech regarding how they are a good friend. They had 3 min to prepare the speech and then presented the speech for 5 min to two confederate 'judges' who appeared to be slightly older than the participant and who were described as experts in evaluating task performance. Immediately afterward, participants completed a mental arithmetic task involving serial subtraction for an additional 5 min. The confederates were trained to maintain neutral emotion and provide no positive feedback, and adolescents were also obtrusively video recorded throughout the speech and math tasks. Participants were debriefed within 15 min of completing the task to minimize distress.

This protocol differed from the traditional protocol in the following ways for this population of Mexican-origin adolescents from high adversity backgrounds: confederates were from the local Salinas area and were from Latinx backgrounds; the difficulty of the math task was titrated such that participants would complete slightly easier math tasks if necessary to keep them consistently engaged with the task; participants were debriefed immediately after the TSST rather than after the full recovery period to avoid having participants feel sustained levels of distress; and gang-affiliated youth were excluded from the task due to both emotional outbursts and threats from at least one gang-affiliated youth and staff concerns about safety. An initial subsample of participants still showed a robust cortisol response, similar to that elicited by a traditional TSST, in spite of these modifications, before administering this protocol to the full sample (see Johnson et al., 2017 for a full description).

Measures

Cortisol

Adolescents provided four 1–2 mL saliva samples via passive drool throughout the task. They provided the first sample after spending over 2 hr in the laboratory environment, during which they completed benign surveys, and then resting in the lab for 10 min. The second sample was collected immediately after the TSST was completed, roughly 15 min after TSST onset. The third sample was collected 30 min after TSST onset, and the fourth and final sample was collected 60 min after TSST onset. This sampling procedure was similar to previous administrations of the TSST (e.g., Chiang et al., 2017; Gunnar et al., 2009; Hostinar et al., 2014; Natsuaki et al., 2009). By collecting samples immediately after and 30 min after TSST onset, we were able to collect saliva samples when cortisol levels were expected to increase post-TSST and increased our chances of capturing peak cortisol response in line with previous guidelines (Dickerson & Kemeny, 2004; Goodman et al., 2017). Samples were frozen at −80°C and later thawed and assayed in duplicate using commercially available enzyme immunoassays (Salimetrics, LLC) in the SPIT lab, with low

https://doi.org/10.1017/S0954579422000244 Published online by Cambridge University Press

mean inter- and intra-assay coefficients of variation (12.4% and 6.9%, respectively). Samples were assayed again if the optical-density intra-assay coefficient of variation was over 10%.

Emotion

Adolescents also provided emotion ratings throughout the session. They rated the degree to which they felt happy, sad, and angry at four times: at baseline immediately prior to task onset, and at 15, 30, and 60 min following task onset. Importantly, at 15 min following task onset, participants completed two reports: they reported how they felt during the TSST, as well as how they felt at that moment. Participants completed two reports at this time point in order to assess emotion felt during the TSST without interrupting the task itself, and because emotion would be expected to change most between baseline and during the task, as opposed to immediately afterward when participants may feel relieved that the task is finished. This resulted in a total of five emotion ratings, all of which were included in analyses. Adolescents reported each form of emotion on a scale from *1* (not at all) to *10* (extremely). Brief and single-item measures of emotion have been commonly used in assessment of emotion responses to stress tasks and throughout the day (e.g., Kelly et al., 2008; Moons et al., 2010; Steptoe et al., 2005).

Substance use

Adolescents also reported whether they had ever used alcohol, marijuana, and cigarettes in their lifetime at age 14 using items from the Monitoring the Future survey, with separate items for each substance (Johnston et al., 2019). Two years later at age 16, adolescents again reported whether they had ever used alcohol, marijuana, or cigarettes or vaped nicotine in their lifetime.

Analytic plan

Models tested the association between adolescents' stress reactivity and recovery at age 14 and substance use by age 14, substance use by age 16, and initiation of substance use between ages 14 and 16. Because participants provided multiple cortisol samples and emotion ratings throughout the protocol, we utilized a multilevel framework with observations (Level 1) nested within participants (Level 2). Specifically, saliva samples and emotion ratings were variables at Level 1 and substance use was measured at Level 2. Multilevel models allow for missing data at Level 1, such that participants could be missing data on a sampling occurrence (e.g., provide insufficient saliva for one time point) and still be included in analyses. Models included 905 total observations for cortisol, and 1299 total observations for emotion. Number of cortisol samples and emotion ratings did not vary by gender, grade, poverty status, reported substance use at age 14, and baseline levels of each emotion, all $ps > .05$. Multilevel models also allow for the number of observations and the specific timing of the collection of each saliva sample to vary across participants, so that the cortisol response to stress can be accurately modeled. This framework leveraged all data and enabled both stress reactivity and recovery to be modeled simultaneously. Participants reported substance use at ages 14 and 16, which enabled testing of whether stress reactivity and recovery at age 14 were related to substance use at age 14, substance use at age 16, and substance use initiation over 2 years among non-users.

Substance use was collected at the level of the participant (Level 2) and was therefore included as a predictor of stress reactivity and recovery (Level 1), and models tested whether differences in the magnitude of stress reactivity and recovery at age 14 related to whether adolescents had ever used each substance (i.e., alcohol, marijuana, cigarettes, vaping nicotine) by ages 14 and 16. It is important to note that we consistently model cortisol and emotion at age 14 as the outcome, even though differences in the stress response (i.e., reactivity and recovery) are thought to be a risk factor for substance use at age 16. This approach is necessary statistically, as other approaches are unable to simultaneously model stress reactivity and recovery with this number of time points. This modeling also allows for piecewise modeling. There are a total of four samples for cortisol and five reports of emotion, both of which allow for piecewise (i.e., non-linear) assessment. Although three time points are generally needed to predict a linear trend, this modeling of all time points allows for HPA axis recovery to be computed using only two time points and for emotion reactivity to be computed using two time points. Alternative approaches include creating another index (e.g., empirical Bayes estimate, change score, regression coefficient) to test as a predictor of substance use, but these indices generally involve exaggerated error terms or violate statistical assumptions by assuming no error for each value (e.g., Liu et al., 2021; Nebebe & Stroud, 1986). Conceptually this model is appropriate because, just as a correlation reflects a bidirectional association, this model tests the association between substance use and differences in stress reactivity and recovery, irrespective of which is the predictor versus outcome. A similar approach has been used in previous papers (e.g., Shirtcliff & Essex, 2008).

Adolescents' substance use was dummy-coded (0 = never used, 1 = had ever used). Separate models predicted cortisol, anger, sadness, and happiness as a function of adolescents' substance use. Prior research has highlighted that multilevel models are generally robust to violations of assumptions, including having skewed outcome variables (Schielzeth et al., 2020). Piecewise modeling was used so that reactivity and recovery could be modeled simultaneously within the same model, and reactivity and recovery were estimated separately by calculating separate time terms at Level 1 (e.g., Hastings & Kahle, 2019). Reactivity was calculated as the number of minutes before the sample's peak level, and all subsequent values were coded as 0. Recovery was calculated as the numbers of minutes following peak level, and all prior values were coded 0. To examine associations between stress reactivity and recovery with substance use, we included the substance use dummy-code, the reactivity time term, the recovery time term, and the cross-level Substance Use × Reactivity Time and Substance Use × Recovery Time interactions as predictors in the model. The reactivity time and recovery time variables were included as random effects. Models used the following equations:

$$L1: \widehat{CortisolorEmotion}_{ij} = \beta_{0j} + \beta_{1j}(Reactivity\ Time) + \beta_{2j}(Recovery\ Time)$$

$$L2: \beta_{0j} = \gamma_{00} + \gamma_{01}(Substance\ Use) + \gamma_{02}(Sex) + \gamma_{03}(Poverty\ Status) + \gamma_{04}(Mothers\ Education) + \gamma_{05}(Grade) + u_{0j}$$

$$\beta_{1j} = \gamma_{10} + \gamma_{11}(Substance\ Use) + u_{1j}$$

$$\beta_{2j} = \gamma_{20} + \gamma_{21}(Substance\ Use) + u_{2j}$$

Significant interactions were probed at the two levels of substance use (i.e., never used, had ever used). Because cortisol and emotion were assessed at different time points, the time variables were coded differently for each outcome, as described in the

https://doi.org/10.1017/S0954579422000244 Published online by Cambridge University Press

Results section. When interactions were significant, we also probed simple slopes to examined whether there were differences in baseline levels of cortisol and emotion by substance use. These analyses enabled assessment of whether associations were potentially driven by differences at baseline, and whether substance use may also relate to tonic differences in cortisol and emotion.

Next, analyses examined whether stress reactivity and recovery at 14 predicted lifetime use of alcohol, marijuana, cigarettes, and vaping nicotine by age 16. Finally, we repeated these models excluding adolescents who were already using each substance by age 14. This way, models examined whether stress reactivity and recovery were related to emergence of substance use over the next 2 years. Finally, three-way interaction terms were included in multilevel models predicting cortisol and emotion to test whether associations between substance use and both reactivity and recovery varied by sex (i.e., Substance Use × Reactivity Time × Sex and Substance Use × Recovery Time × Sex) and poverty status (i.e., Substance Use × Reactivity Time × Poverty Status and Substance Use × Recovery Time × Poverty Status). Significant interactions were probed using simple slopes at each level of sex (male, female) and poverty status (below poverty line, above poverty line). These models used the following equations:

$$L1: \widehat{Cortisol\ or\ Emotion}_{ij} = \&\beta_{0j} + \beta_{1j}(Reactivity\ Time) \\ \& + \beta_{2j}(Recovery\ Time)$$

$$L2: \beta_{0j} = \&\gamma_{00} + \gamma_{01}(Substance\ Use) + \gamma_{02}(Poverty\ Status) \\ \& + \gamma_{03}(Substance\ Use * Poverty\ Status) + \gamma_{04}(Sex) \\ \& + \gamma_{05}(Mother'\ Education) + \gamma_{06}(Grade) + u_{0j}$$

$$\beta_{1j} = \&\gamma_{10} + \gamma_{11}(Substance\ Use) + \gamma_{12}(Sex) \\ \& + \gamma_{13}(Substance\ Use * Sex) + u_{1j}$$

$$\beta_{2j} = \&\gamma_{20} + \gamma_{21}(Substance\ Use) + \gamma_{22}(Poverty\ Status) \\ \& + \gamma_{23}(Substance\ Use * Poverty\ Status) + u_{2j}$$

$$L1: \widehat{Cortisol\ or\ Emotion}_{ij} = \&\beta_{0j} + \beta_{1j}(Reactivity\ Time) \\ \& + \beta_{2j}(Recovery\ Time)$$

$$L2: \beta_{0j} = \&\gamma_{00} + \gamma_{01}(Substance\ Use) + \gamma_{02}(Sex) \\ \& + \gamma_{03}(Substance\ Use * Sex) + \gamma_{04}(Poverty\ Status) \\ \& + \gamma_{05}(Mother's\ Education) + \gamma_{06}(Grade) + u_{0j}$$

$$\beta_{1j} = \&\gamma_{10} + \gamma_{11}(SubstanceUse) + \gamma_{12}(Sex) \\ \& + \gamma_{13}(SubstanceUse * Sex) + u_{1j}$$

$$\beta_{2j} = \&\gamma_{20} + \gamma_{21}(Substance\ Use) + \gamma_{22}(Sex) \\ \& + \gamma_{23}(Substance\ Use * Sex) + u_{2j}$$

All models included the following covariates: sex (0 = male, 1 = female), poverty status at age 14 (below poverty line = 0, above poverty line = 1), parents' education (grand-mean centered), and grade at age 14 for substance use by age 14 (grand-mean centered, 0 = 8th grade) and grade at age 16 for analyses of substance use by age 16 (grand-mean centered, 0 = 10th grade). All associations were maintained in unadjusted models. Finally, due to concerns regarding skewness of emotion ratings and salivary cortisol, all analyses were repeated after natural log transforming values with extreme skewness (i.e., exceeding 1).

A statistical correction was incorporated for the number of effective tests. The study was designed to test whether (1) HPA axis reactivity and recovery and (2) emotional reactivity and recovery were related to use of different substances. Given that substances have different effects and results may not carryover across substances, analyses of HPA axis and emotional reactivity and recovery for each substance were treated as a separate family of analyses. Three related measures of emotion were administered. Because the emotion items showed a high factor loading using exploratory factor analysis both at baseline and across assessments (eigenvalue = .90), we completed separate analyses of each emotion and incorporated a correction for the degree to which emotion items were related to one another (i.e., the degree to which they were independent analyses; e.g., Purves et al., 2019). The high inter-relatedness of items suggests that analyses are largely non-independent, which resulted in a critical *p*-value of .046.

Results

Most participants had never used each substance by age 14, with 19.26% using alcohol, 17.21% using marijuana, and 7.32% using cigarettes by 14. Use of alcohol (40.24%), marijuana (31.30%), and cigarettes (11.38%) increased by age 16, and the number of youth who had used each substance significantly increased from ages 14 to 16, all McNemar's $\chi^2(1) > 4.5$, $ps < .05$.

Descriptive statistics and figures illustrating changes in cortisol and emotion over time are given in supplementary materials (Tables S1–S4, Figs. S2-S3). Repeated measures ANOVAs indicated that there was no mean-level change in cortisol levels across the sample, $F(3) = 0.86$, $p = .5$, suggesting that on average participants did not show robust changes in cortisol across the TSST. Repeated measures ANOVAs indicated robust changes in each form of emotion and significant quadratic effects, suggesting that participants on average displayed reactivity in the form of changes between baseline and immediately following the TSST and displayed recovery across the 60 min following task onset; $F(4) = 184.78$, $F_{quadratic}(4) = 307.95$ for happiness, $F(4) = 93.16$, $F_{quadratic}(4) = 125.10$ for sadness, $F(4) = 25.67$, $F_{quadratic}(4) = 33.85$ for anger, all $ps < .001$. Adolescents' happiness and anger returned to baseline levels by 60 min post-TSST onset, $ts < .6$, $p > .5$, and adolescents were significantly less sad at the end than at the start of the session, $t(249) = 4.23$, $p < .001$. HPA axis reactivity to and recovery from stress were generally not related to emotion reactivity and recovery, with the exception that greater cortisol recovery was related to blunted anger reactivity and recovery among adolescents above the poverty line (Table 1).

Cortisol and substance use associations

Piecewise multilevel models were used to examine whether substance use was related to differences in cortisol reactivity and recovery simultaneously. Time was centered at the second cortisol sample, 30 min post-task onset, because salivary cortisol tends to peak 20–30 min following stress onset. Separate time terms were calculated for reactivity and recovery (Hastings & Kahle, 2019). Reactivity time was coded as the number of minutes prior to the 30 min sample and was coded as 0 for samples following 30 min post-task onset, and recovery time was coded as the number of minutes following the 30 min sample and as 0 for samples before 30 min post-task onset. Coefficients for reactivity time and recovery time represent the change in cortisol per minute.

https://doi.org/10.1017/S0954579422000244 Published online by Cambridge University Press

Table 1. Correlations between emotion and cortisol reactivity and recovery

Group (sample size)		Happiness reactivity	Happiness recovery	Sadness reactivity	Sadness recovery	Anger reactivity	Anger recovery
Full sample (194–210)[a]	Cortisol reactivity	0.03	−0.07	−0.08	−0.02	0.15*	−0.14*
	Cortisol recovery	−0.07	0.09	0.01	0.07	−0.09	0.09
Below the poverty line (127–137)	Cortisol reactivity	0.09	−0.11	−0.07	−0.01	0.04	−0.05
	Cortisol recovery	−0.11	0.12	−0.04	0.09	−0.03	0.01
Above the poverty line (63–70)	Cortisol reactivity	−0.15	0.05	−0.09	−0.06	0.33**	−0.30*
	Cortisol recovery	0.02	0.03	0.08	0.09	−0.27	0.29
Female (116–119)	Cortisol reactivity	0.10	−0.14	−0.15	0.06	0.17*	−0.13*
	Cortisol recovery	−0.01	0.04	0.15	−0.04	−0.02	0.01
Male (78–91)	Cortisol reactivity	−0.01	0.00	−0.11	0.09	−0.12	0.02
	Cortisol recovery	−0.16	0.17	0.19	−0.14	0.16	−0.16

Note. Reactivity to stress was calculated as the number of standard deviations change in emotion from baseline to during the task and in cortisol from baseline to 30 min post-task onset, and emotion recovery was calculated as the number of standard deviations change in emotion from during the task to the end of recovery and in cortisol from 30 min post-task to 45 min post-task onset.

[a]Sample sizes are provided in parentheses for each group, and ranges are provided to account for participants varying in the number of cortisol samples and emotion ratings they completed

*$p < .05$.

**$p < .01$.

Models tested interactions between substance use and time variables as predictors of cortisol to determine whether the magnitude of cortisol reactivity and recovery differed between adolescents who had versus had never used each substance by age 14. Models were repeated with substance use at age 16, and interactions were probed to examine cortisol reactivity and recovery at age 14 for adolescents who had versus had never used each substance by age 16.

These models did not suggest that cortisol reactivity or recovery was related to use of alcohol, marijuana, cigarettes, or vaping nicotine use by ages 14 or 16 (Tables S5–S11). There was also consistently no main effect of poverty status on cortisol across all models, $ps > .05$.

Moderation of associations between cortisol reactivity and recovery and substance use

Models then examined moderation of associations by poverty status and sex by including three-way interactions (Tables S12–S18 for poverty status, Tables S19–S25 for sex). There was no significant moderation of associations between either cortisol reactivity or recovery and substance use by sex for any substance, all $ps > .05$. Poverty status significantly moderated associations between cortisol reactivity and alcohol use by age 14 ($B_{Reactivity} = -0.007$, $SE = 0.003$, $p = .010$; $B_{Recovery} = -0.005$, $SE = 0.003$, $p = .142$), alcohol use by age 16 ($B_{Reactivity} = -0.004$, $SE = 0.002$, $p = .042$; $B_{Recovery} = -0.001$, $SE = 0.003$, $p = .594$), and vaping of nicotine by age 16 ($B_{Reactivity} = -0.005$, $SE = 0.002$, $p = .040$; $B_{Recovery} = -0.003$, $SE = 0.003$, $p = .243$). Specifically, there was no association between cortisol reactivity and either use of alcohol by age 14 or vaping nicotine by age 16 for adolescents below the poverty line, $ps > .4$. Among adolescents above the poverty line, blunted cortisol reactivity to the TSST was associated with use of alcohol by 14 and vaping of nicotine by 16. Blunted cortisol reactivity to the TSST – as indicated by smaller increases in cortisol following the TSST at age 14 – were observed for adolescents who had used alcohol by 14 and those who proceeded to vape nicotine by 16 compared to those who did not (Figure 1). This difference appeared to be driven by elevated baseline cortisol among adolescents who used alcohol by 14 and those who proceeded to vape nicotine by 16. In contrast, cortisol reactivity was not related to use of alcohol by 14 or vaping nicotine by 16 among youth below the poverty line (Supplemental Fig. S4). Despite the significant interaction term for use of alcohol by age 16, associations between cortisol reactivity and alcohol use were non-significant when probing the association between blunted cortisol reactivity and use of alcohol by age 16 at different levels of poverty status.

We also tested whether substance use was related to differences in baseline cortisol. Simple slopes analyses indicated that adolescents who had used alcohol by age 14 had higher cortisol at baseline than adolescents who had not used alcohol by age 14 ($B = 0.19$, $SE = 0.06$, $p = .003$), but that there was no significant difference in baseline cortisol between youth who had and those who had never vaped nicotine by age 16 ($B = 0.09$, $SE = 0.05$, $p = .095$). Associations between cortisol reactivity and alcohol use by age 14 and vaping nicotine by age 16 remained significant when controlling for baseline salivary cortisol. When analyses were repeated covarying for TSST start time, all significant results remained significant. There were 10 cortisol values that were over four standard deviations above the mean and 22 cortisol values that were over three standard deviations above the mean for that time point. The same pattern of associations between cortisol reactivity and recovery and substance use was observed when using unadjusted values, when winsorizing these values to three and four standard deviations, and when excluding these values.

Emotion reactivity and recovery and substance use by age 14

Again, reactivity and recovery were modeled simultaneously within the same model using all five reports of emotion, and

https://doi.org/10.1017/S0954579422000244 Published online by Cambridge University Press

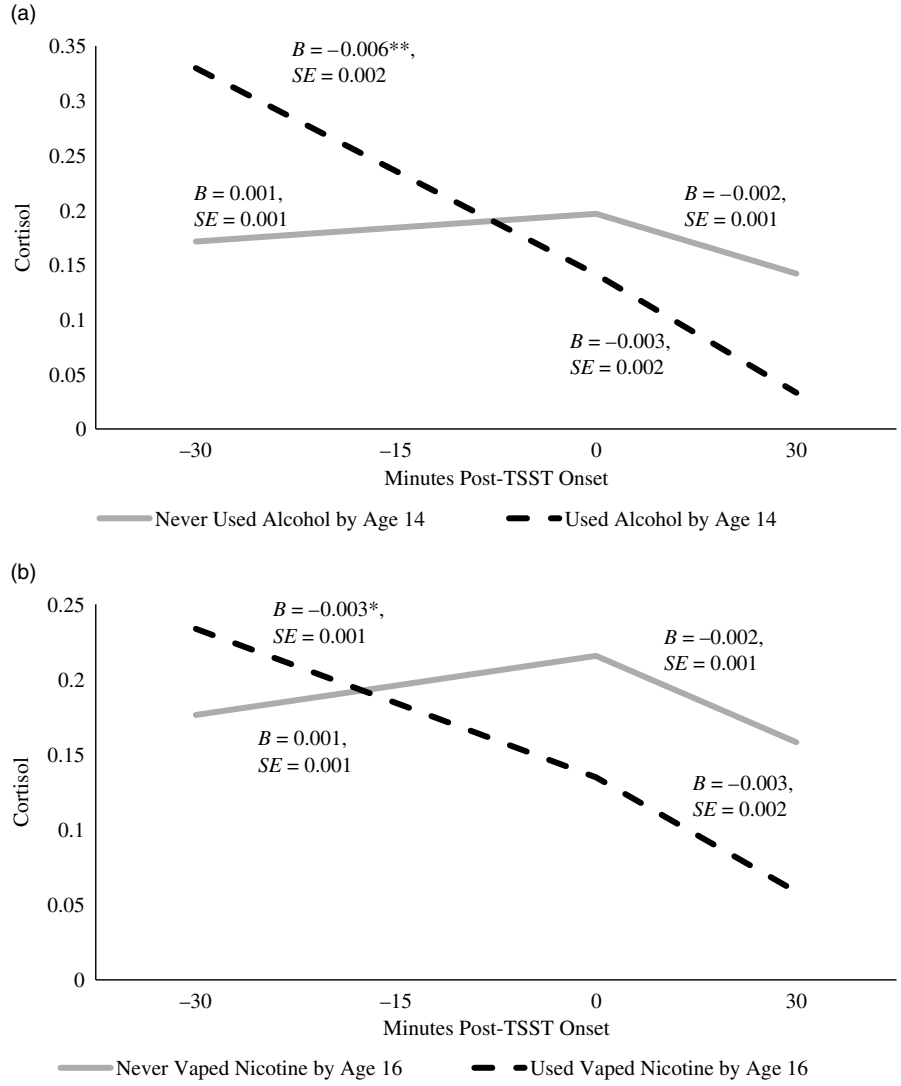

Figure 1. Cortisol responses to the TSST as a function of alcohol use by age 14 (a) and vaping of nicotine by age 16 (b) in youth above the poverty line. *Note*. *$p < .05$, **$p < .01$.

reactivity and recovery were estimated by calculating separate time terms (Hastings & Kahle, 2019). As expected, participants reported feeling the most extreme levels of emotion during the TSST using the retrospective report. This report was coded as how participants felt at the midpoint of the TSST, which lasted about 15 min in total, and each assessment was coded with respect to the number of minutes before or after the middle of the TSST. Therefore, the baseline report was 7.5 min before the middle of the TSST, and the reports following the TSST were 7.5, 22.5, and 52.5 min following the middle of the TSST.

For the reactivity time variable, baseline emotion was coded as -7.5 and all subsequent time points were coded as 0, so that this coefficient would only measure changes in emotion between prior to the TSST and during the TSST. Ideally, three or more time points would be used to estimate a linear trajectory. However, within this experimental context, it was not feasible to include another assessment of emotion that would improve estimation of emotion reactivity. For the recovery time variable, the ratings of emotion at baseline and during the TSST were coded as 0, and the subsequent three time points were coded with respect to the number of minutes following the middle of the TSST (i.e., 7.5, 22.5, and 52.5). Coefficients for the time variables represent the rate of change in emotion per minute.

First, models tested whether emotion reactivity to and recovery from the TSST at age 14 were related to whether adolescents had ever used substances by age 14 (Tables S5–S7). Neither changes in anger nor happiness were related to substance use, all $ps > .07$. Sadness reactivity to the TSST was related to marijuana use by age 14 ($B_{\text{Reactivity}} = -0.08$, $SE = 0.03$, $p = .023$; $B_{\text{Recovery}} = 0.005$, $SE = 0.004$, $p = .298$). Blunted reactivity (i.e., smaller increases) in sadness between pre- and immediately post-TSST was observed in adolescents who had used marijuana relative to adolescents who had not used marijuana by age 14.

Analyses then tested whether emotion reactivity and recovery at age 14 related to lifetime substance use by age 16 (Tables S8–S11). Again, anger reactivity and recovery were not related to substance use. Sadness reactivity to and recovery from the TSST at age 14 was related to adolescents' marijuana use by age 16 ($B_{\text{Reactivity}} = -0.07$, $SE = 0.03$, $p = .018$; $B_{\text{Recovery}} = 0.008$, $SE = 0.004$, $p = .044$).

https://doi.org/10.1017/S0954579422000244 Published online by Cambridge University Press

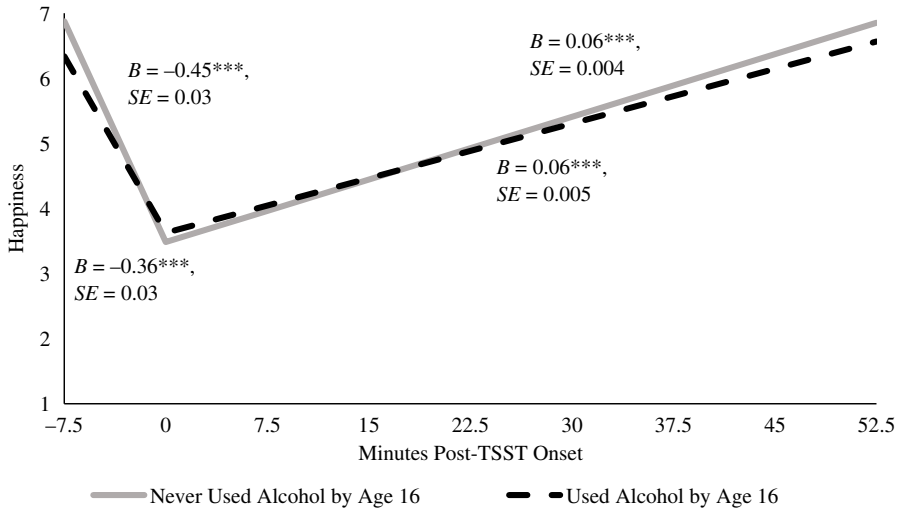

Figure 2. Happiness responses to the TSST as a function of alcohol use by age 16. Analyses included all participants, regardless of alcohol use by age 14. *Note*. ***$p < .001$.

Smaller increases in sadness immediately following the TSST at age 14 and smaller decreases across the recovery period were found in youth who had used marijuana by age 16 relative to those who had never used marijuana by age 16. However, results were non-significant when excluding individuals who had already used marijuana by age 14, suggesting that the association was driven by adolescents who had used marijuana by age 14 rather than youth who began using marijuana between ages 14 and 16.

Happiness reactivity to the TSST was also associated with adolescents' use of alcohol by age 16 ($B_{Reactivity} = 0.09$, $SE = 0.04$, $p = .042$; $B_{Recovery} = -0.01$, $SE = 0.01$, $p = .195$; Figure 2) and use of marijuana by age 16 ($B_{Reactivity} = 0.11$, $SE = 0.05$, $p = .022$; $B_{Recovery} = -0.004$, $SE = 0.007$, $p = .562$). Whereas decreases in happiness in response to the TSST were found for adolescents who did not use alcohol and marijuana by age 16, smaller changes in happiness between before and immediately after the TSST (i.e., blunted happiness reactivity) were found in adolescents who had used alcohol and marijuana by age 16. The association between happiness reactivity to the TSST at age 14 and use of alcohol by age 16 was no longer significant when limiting the sample to participants who had never used alcohol by age 14 ($B_{Reactivity} = 0.10$, $SE = 0.05$, $p = .055$; $B_{Recovery} = -0.008$, $SE = 0.007$, $p = .273$). However, the association between happiness reactivity to the TSST at age 14 and use of marijuana by age 16 was maintained when limiting the sample to participants who had never used marijuana by age 14 ($B_{Reactivity} = 0.14$, $SE = 0.06$, $p = .014$; $B_{Recovery} = -0.004$, $SE = 0.009$, $p = .675$) suggesting that this association was apparent in youth who initiated substance use between ages 14 and 16.

Moderation of emotion reactivity and recovery and substance use associations

Next, models tested whether associations between emotion reactivity and recovery and substance use varied by poverty status (Tables S12–S18) and by sex (Tables S19–S25). Poverty status moderated associations between sadness recovery and adolescents' use of marijuana by age 16 ($B_{Reactivity} = 0.09$, $SE = 0.06$, $p = .10$; $B_{Recovery} = -0.03$, $SE = 0.01$, $p = .035$) and between sadness reactivity, but not recovery, and use of alcohol by age 16 ($B_{Reactivity} = 0.13$, $SE = 0.06$, $p = .028$; $B_{Recovery} = -0.02$, $SE = 0.01$, $p = .058$). However, when probing simple slopes at different levels of poverty status, associations between sadness reactivity and recovery and alcohol and marijuana use were non-significant, $ps > .07$.

When examining moderation by sex, results suggested that emotion reactivity and recovery to the TSST were related to substance use primarily in female adolescents. First, sex differences emerged in the associations between anger and sadness reactivity and recovery to the TSST and marijuana use by age 14, such that associations were only apparent among female adolescents. Blunted anger reactivity (i.e., smaller increases in anger immediately following the TSST) and recovery (i.e., smaller decreases in anger across the recovery period) were associated with marijuana use by age 14 in female adolescents ($B_{Reactivity} = -0.21$, $SE = 0.10$, $p = .029$; $B_{Recovery} = 0.03$, $SE = 0.01$, $p = .028$; Figure 3a). Similarly, both blunted sadness reactivity and recovery were associated with marijuana use by age 14 in female adolescents ($B_{Reactivity} = -0.23$, $SE = 0.07$, $p < .001$; $B_{Recovery} = 0.02$, $SE = 0.01$, $p = .024$; Figure 3b). In contrast, male adolescents' emotion reactivity and recovery were consistently not related to marijuana use by age 14.

Associations between emotion reactivity and recovery to stress at age 14 and substance use by age 16 also emerged in female adolescents. We observed sex differences in associations between sadness reactivity to the TSST at age 14 and alcohol use by age 16 ($B_{Reactivity} = -0.12$, $SE = 0.05$, $p = .035$; $B_{Recovery} = 0.01$, $SE = 0.01$, $p = .148$) and between sadness recovery from the TSST at age 14 and marijuana use by age 16 ($B_{Reactivity} = -0.11$, $SE = 0.06$, $p = .056$; $B_{Recovery} = 0.02$, $SE = 0.01$, $p = .030$). Again, whereas sadness reactivity and recovery were not related to substance use in male adolescents, blunted sadness reactivity was associated with alcohol use by age 16 (Figure 4a) and blunted sadness recovery was associated with use of marijuana by age 16 in female adolescents (Figure 4b). However, neither associations was maintained after excluding adolescents who had used each substance by age 14; taken together, there was no evidence that sadness reactivity and recovery were related to the emergence of substance use between ages 14 and 16 among non-users.

Finally, among female adolescents, happiness reactivity to the TSST at age 14 was related to use of cigarettes ($B_{Reactivity} = 0.29$,

https://doi.org/10.1017/S0954579422000244 Published online by Cambridge University Press

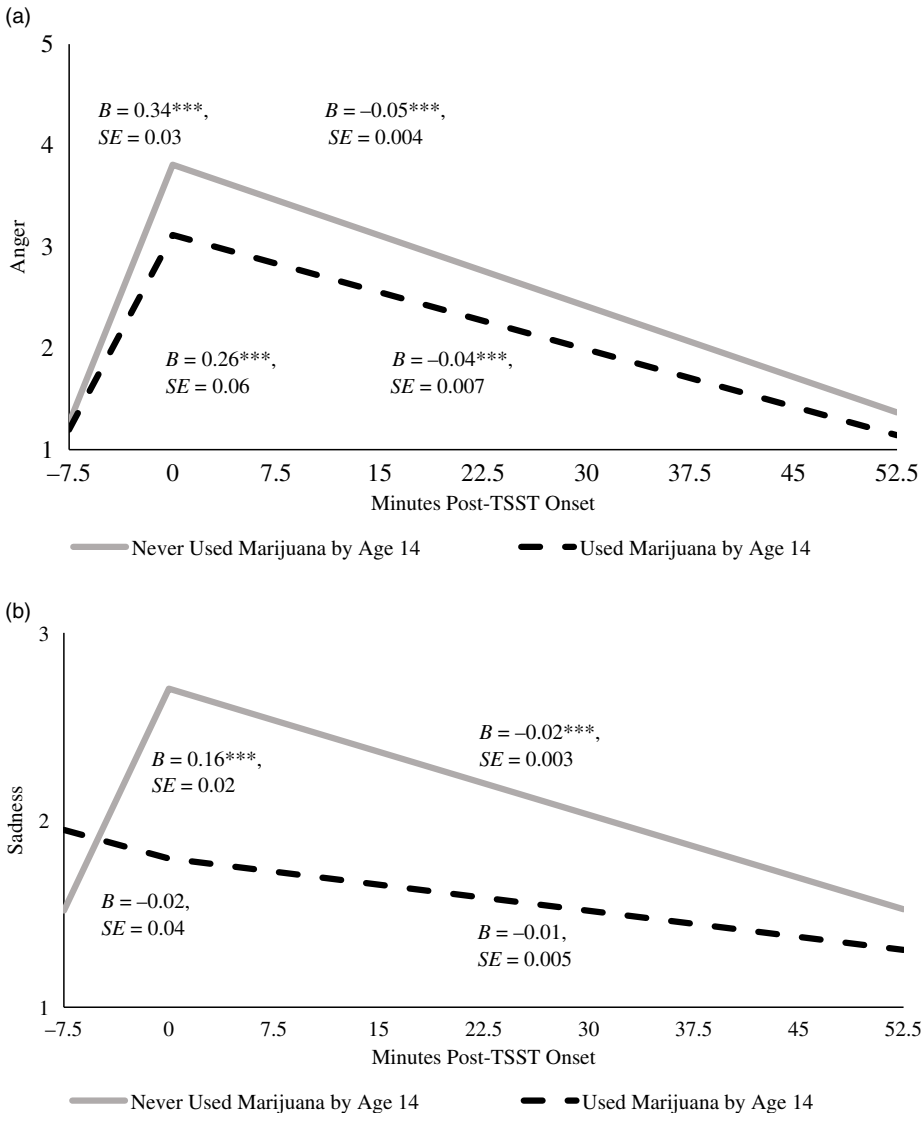

Figure 3. Anger responses (a) and sadness responses (b) to the TSST as a function of marijuana use by age 14 in female adolescents. *Note*. ***$p < .001$.

$SE = 0.14$, $p = .039$; $B_{Recovery} = -0.04$, $SE = 0.02$, $p = .071$) and marijuana by age 16 ($B_{Reactivity} = 0.26$, $SE = 0.09$, $p = .005$; $B_{Recovery} = -0.03$, $SE = 0.01$, $p = .050$). A similar pattern emerged, as blunted happiness reactivity was related to use of cigarettes and marijuana by age 16 among female but not male adolescents (Figure 5a,b). These associations remained significant when excluding adolescents who had used each substance by age 14, suggesting that blunted happiness reactivity was related to the emergence of cigarette use and marijuana use between ages 14 and 16 among female non-users. When probing simple slopes to examine differences in baseline emotion, we found that female adolescents who had used cigarettes by age 16 had significantly lower happiness at baseline compared to female adolescents who had never used cigarettes by age 16 ($B = -2.48$, $SE = 0.94$, $p = .008$). Similarly, female adolescents who had used marijuana by age 16 reported marginally lower happiness at baseline at age 14 compared to female adolescents who had never used marijuana by age 16 ($B = -1.11$, $SE = 0.55$, $p = .046$). We therefore re-tested models controlling for baseline happiness, and associations between happiness reactivity and cigarette and marijuana use by age 16 remained significant.

Variable transformation

Finally, as a robustness check, we re-tested all models after transforming distributions of outcome variables to account for skew. Cortisol values were positively skewed, as the majority of participants show low levels of salivary cortisol (skewness = 2.58). Happiness was not skewed (skewness = 0.00), but anger and sadness were positively skewed such that participants tended to report very low levels of each emotion (skewness = 2.38 for anger, 3.00 for sadness). Therefore, cortisol, anger, and sadness values were natural log transformed, although anger and sadness distributions remained skewed, albeit to a lower degree (skewness = 0.33 for cortisol, 1.51 for anger, 2.08 for sadness). All associations remained significant with one exception: anger reactivity was no longer significantly related to marijuana use by age 14 among female adolescents, $p = .107$.

Discussion

Although difficulties with stress regulation are related to more frequent substance use among users (e.g., Koob & Kreek, 2007), less is known regarding whether psychobiological responses to

https://doi.org/10.1017/S0954579422000244 Published online by Cambridge University Press

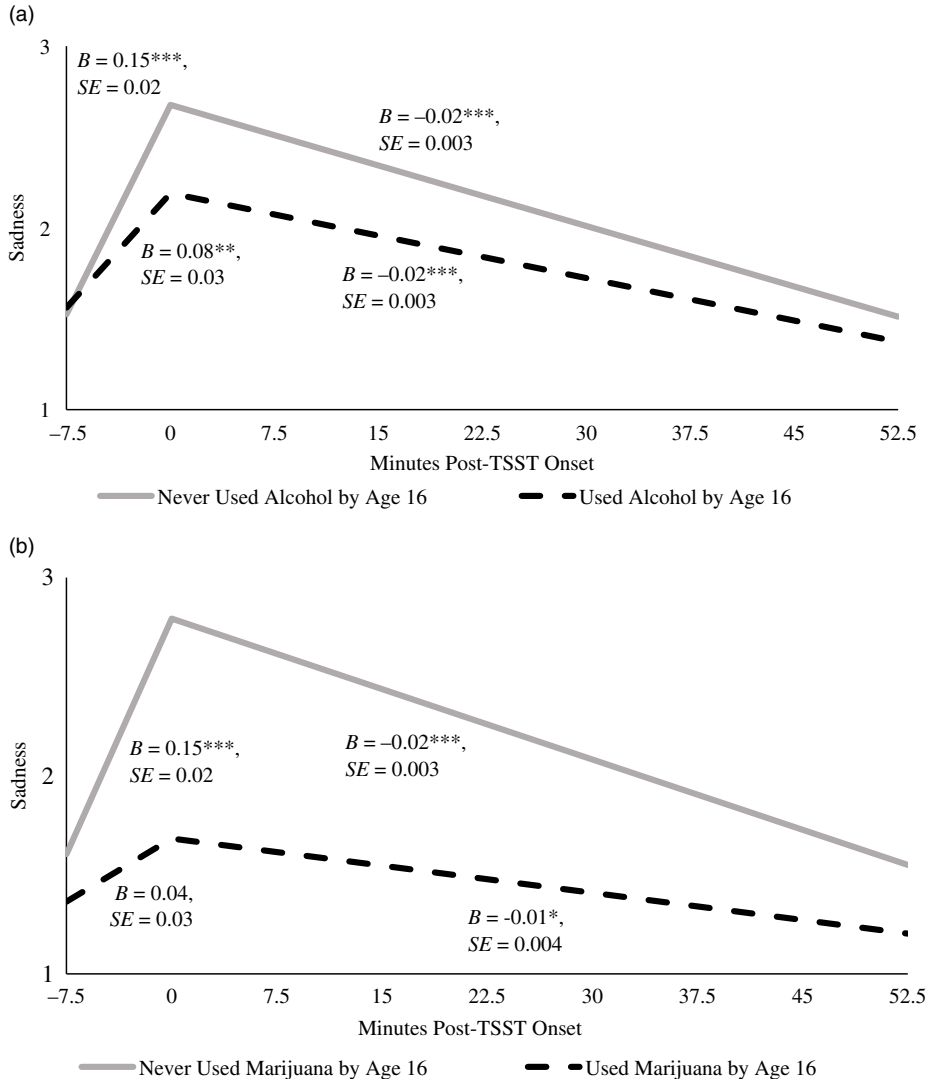

Figure 4. Sadness responses to the TSST as a function of alcohol use by age 16 (a) and marijuana use by age 16 (b) in female adolescents. Analyses included all participants, regardless of substance use by age 14. *Note*. *$p < .05$, **$p < .01$, ***$p < .001$.

stress relate to substance use and precede initiation of use in adolescence. Therefore, the present study investigated whether dampened HPA axis and emotion responses to stress were related to substance use in a sample of Mexican-origin adolescents who had experienced high levels of adversity. Findings suggested that differences in HPA axis and emotion responses to social-evaluative stress relate to – and in some cases temporally precede – substance use among these adolescents, although associations varied by poverty status and sex. Dampened cortisol reactivity to stress was related to use of alcohol by age 14 and vaping nicotine by age 16 among youth above the poverty line, although there was no evidence that cortisol reactivity to stress related to initiation of use of substances between ages 14 and 16. In turn, dampened emotion responses to stress were related to substance use primarily in female adolescents. Among female adolescents, blunted anger reactivity to stress was related to marijuana use by age 14, and blunted sadness reactivity and recovery to stress were related to use of alcohol by age 16 and use of marijuana by ages 14 and 16. Blunted happiness reactivity to stress was related to use of alcohol by age 16, regardless of sex, and to the emergence of use of marijuana and cigarettes between ages 14 and 16 among female adolescents who had not used these substances by age 14. Differences in associations between stress reactivity and recovery to stress and substance use by poverty status and sex may be due to differences in adolescents' access to substances or differences in motivation for substance use.

Cortisol responses to stress and substance use among youth above the poverty line

Dampened cortisol reactivity to stress was related to use of alcohol by age 14 and vaping of nicotine by age 16 for youth above, but not below, the poverty line. These findings align with prior work suggesting that blunted cortisol responses to stress relate to riskier substance use 4 years later among adolescents (Evans et al., 2016). Differences in stress physiology have been related to greater substance use among users (e.g., Sinha, 2001; Wemm & Sinha, 2019), as well as greater risk for substance use initiation among youth (Evans et al., 2016; Kliewer et al., 2016; Moss et al., 1999; Poon et al., 2016). Inability to elicit a cortisol response from a

https://doi.org/10.1017/S0954579422000244 Published online by Cambridge University Press

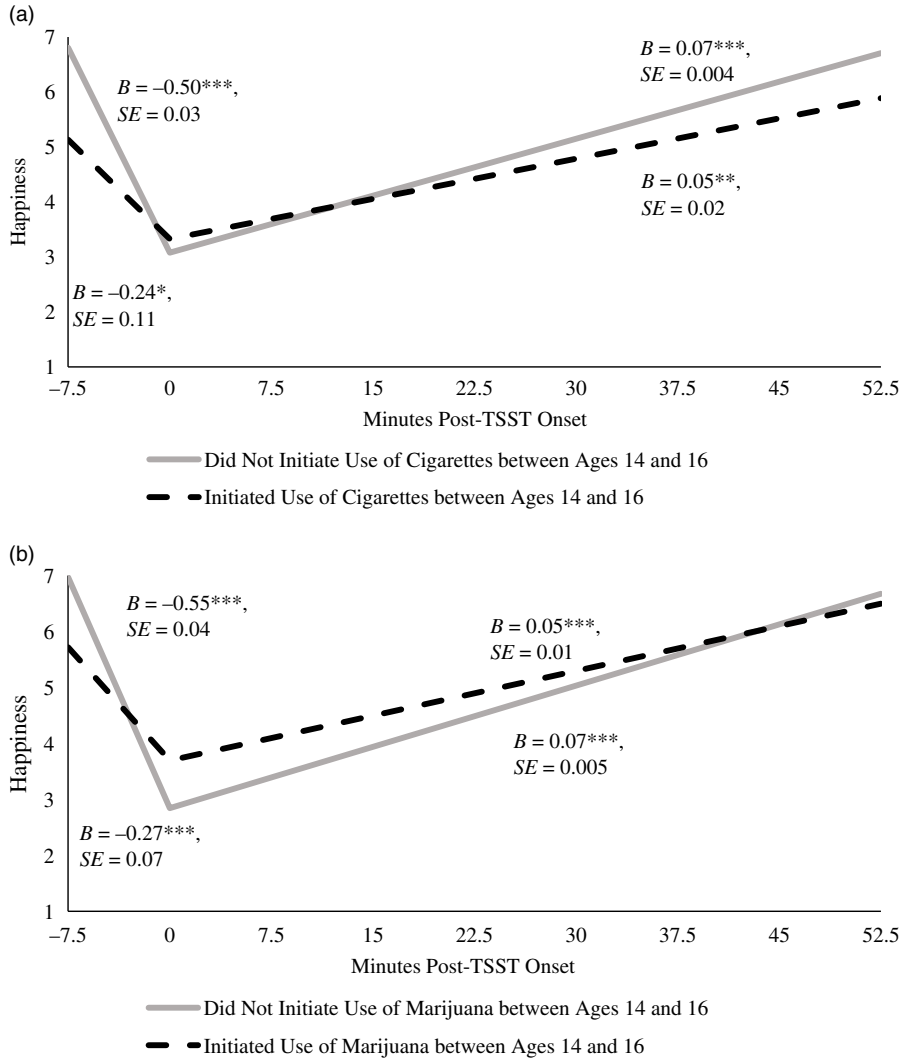

Figure 5. Happiness reactivity to and recovery from the TSST as a function of initiation of cigarettes between ages 14 and 16 (a) and initiation of marijuana between ages 14 and 16 (b) among female adolescents. Analyses excluded participants who used each substance by age 14. *Note*. $^{*}p < .05$, $^{**}p < .01$, $^{***}p < .001$.

stressor may suggest inflexibility of the HPA axis, such that people are unable to mobilize biological resources in the context of stress. Dampened cortisol reactivity to stress may be indicative of difficulties with regulating stress, as strategies for emotion regulation have been linked with psychobiological responses to stress (e.g., Lam et al., 2009). For instance, prior studies have found that adolescents and adults with poorer emotion regulation show blunted cortisol reactivity to stress, often characterized by consistently high levels of cortisol (Ayer et al., 2013; Kliewer et al., 2016; Krkovic et al., 2018). Furthermore, moderate cortisol responses to stress can promote executive function including emotion processing and behavioral inhibition during stress (Peters et al., 2016; Shields et al., 2015). Stress responses may be particularly tied to emotion regulation during adolescence, when youth are particularly sensitive to social threat and are still developing strategies for emotion regulation (Spear, 2009; Zimmermann & Iwanski, 2014). Although associations with alcohol use at age 14 were cross-sectional, most evidence regarding the effect of substance use on HPA axis function has been observed among heavy users (Koob & Le Moal, 2008; Lovallo, 2006), and we do not have heavy use in this sample given participants' age. Therefore, a more likely pathway is that differences in the stress response confer risk for substance use.

Interestingly, youth above the poverty line who used alcohol by age 14 had higher levels of baseline salivary cortisol compared to youth who had never used alcohol by age 14. Although adolescents had 2 hr in the laboratory environment to acclimate to space and to rule out an arrival effect (Shirtcliff et al., 2014), there is a chance that adolescents who showed higher levels of salivary cortisol at baseline may have been stressed in anticipation of the TSST, in line with previous findings that adolescents with anticipatory reactivity to stress may be at higher risk for substance use (Evans et al., 2016; Moss et al., 1999). An alternative possibility is that these youth tend to show chronically higher levels of cortisol output as well as dampened reactivity to the task, although this possibility seems somewhat unlikely given that there were no differences in cortisol across the recovery period.

Associations between dampened cortisol responses and substance use only emerged for youth above the poverty line. This finding was particularly interesting given that this sample of adolescents was very low-income overall (per the selection criteria into the parent study). We assessed differences by poverty status because youth living in poverty often experience additional stressors that can influence their risk for substance use. However, it is important to note that this sample is still low-income overall,

https://doi.org/10.1017/S0954579422000244 Published online by Cambridge University Press

such that results may not generalize to differences in socioeconomic status among wealthier (e.g., middle and upper class) adolescents. First, youth who experience relatively more adversity or more challenging home environments are more likely to show blunted cortisol responses to stress (e.g., Joos et al., 2019; Peckins et al., 2016). Therefore, blunted cortisol reactivity to stress may be more consistently related to substance use among youth above the poverty line, whereas blunted responses relate to environmental factors among youth below the poverty line.

Second, associations emerged only for alcohol and vaping nicotine, which tend to be more commonly used among youth with higher family income (Jones et al., 2016; Melotti et al., 2011; Patrick et al., 2012). In this study, adolescents above the poverty line may have been more exposed to alcohol and vaping, specifically, compared to youth below the poverty line. Importantly, irrespective of family poverty status, adolescents may still be able to access substances that they find at home. Third, poverty status may influence adolescents' motivations for substance use; stress may relate to substance use for youth above the poverty line, whereas youth below the poverty line may turn to less costly means of stress relief or may also use substances for alternative reasons. For instance, adolescents with lower parental education engage in fewer pleasurable substance-free activities, and may aim to use substances to amplify positive emotions (Andrabi et al., 2017; Lee et al., 2018). High basal cortisol or dampened cortisol reactivity to stress may be indicative of difficulties with emotion regulation (Krkovic et al., 2018), and difficulties with emotion regulation may more strongly relate to substance use for youth above the poverty line. Associations between stress responses and substance use may differ by levels of socioeconomic status, and it is important to note that the poverty rate was much higher in the present sample than in the county due to the inclusion criteria of the parent study. Therefore, findings may generalize to families who are lower on the distribution of income, but not to more affluent families. Future research is needed to examine whether adolescents' access to and motivation for substances can explain why associations between dampened cortisol reactivity to stress and alcohol use by age 14 and vaping by age 16 differ by poverty status, and whether similar associations are observed among affluent youth.

Emotion responses to stress and substance use among female adolescents

In addition to HPA axis responses to stress, we found that dampened emotion reactivity to social-evaluative stress was related to alcohol, marijuana, and cigarette use, particularly among female adolescents. Substance use may have been related to dampened rather than exaggerated emotion responses to the TSST because of the nature of this laboratory stressor. Although modified to avoid eliciting undue distress for this population (Johnson et al., 2017), the TSST can be a particularly taxing stressor. This may have caused youth to disengage rather than actively cope with the task and thereby manifested in dampened stress reactivity (Carroll et al., 2017). Engagement in strategies such as distraction has been related to emotional and behavioral difficulties specifically for youth who show blunted cortisol responses to social stress (Bendezú et al., 2021). Additionally, these youth have backgrounds of high adversity and life stress which may have contributed to dampened emotion responses. Previous research has indicated that youth who experience adversity show reductions in activation of neural regions related to threat and emotion processing (Ginty et al., 2013; Yang et al., 2015).

Several associations between dampened emotion responses and substance use were unique to female adolescents, potentially related to sex differences in adolescents' motivations for substance use (e.g., Chaplin et al., 2018). It is important to note that although emotion responses to stress were more related to substance use in female than in male adolescents, male adolescents tend to be at higher risk for earlier substance use (Johnston et al., 2019). Our results suggest that stress responses may be particularly related to substance use and substance use initiation among female adolescents, although male adolescents may have different motivations that place them at higher risk for substance use more generally. Prior research has found that female adolescents are more motivated to use substances to reduce stress and negative emotion, whereas male adolescents are more motivated to use substances for social benefits (Kuntsche & Müller, 2012; Kuntsche et al., 2015; Pompili & Laghi, 2019), and that stress is more strongly related to substance use in female than in male adolescents (Chaplin et al., 2018; Jun et al., 2015). Future research should investigate the factors that contribute to male adolescents' risk for substance use.

Alcohol and marijuana use may have been more consistently related to emotion responses than cigarettes or vaping because alcohol and marijuana are the most commonly used substances during adolescence and are often used to reduce stress (Cooper et al., 2016). Cigarette use may have only related to happiness reactivity to stress but not sadness or anger reactivity because of the low prevalence of use in this sample, as cigarettes have declined in popularity over time especially among Latinx youth (Miech et al., 2020; Rolle et al., 2015). Emotion reactivity to stress may not have been related to vaping of nicotine because vaping is more frequently used for experimentation and taste rather than to influence stress and emotion (Evans-Polce et al., 2018; Jones et al., 2016; Temple et al., 2017). Further information on adolescents' motivation for use may provide insight regarding the mechanisms relating substance use and emotion responses to stress.

Finally, sadness and happiness reactivity to stress were more consistently related to substance use than anger reactivity. Anger reactivity to stress was only related to marijuana use by age 14 among female adolescents, and this association was not maintained after transforming the data to account for skew. Studies that examine whether anger reactivity to and recovery from stress relate to substance use can consider other paradigms or forms of stress that elicit a more robust change in anger. Substances are commonly used to reduce sadness and stress and to increase positive emotion (e.g., Cooper et al., 2016), which may explain why associations emerged between sadness and happiness reactivity to stress, but not anger reactivity, and substance use. Although prior research has emphasized the role of negative emotions in motivation for substance use (e.g., Gould et al., 2012), dampened happiness reactivity to stress was uniquely related to initiation of cigarette and marijuana use between ages 14 and 16 among female adolescents. We also found that female adolescents who used marijuana and cigarettes by age 16 reported lower levels of happiness at baseline than female adolescents who never used these substances by age 16, but no differences in other emotions. It is possible that these youth use substances to promote positive emotion, or that lower happiness reactivity may indicate lower reactivity to other positive daily activities and greater inclination to use substances. Positive emotion has received relatively less attention in the context of stress responses, but the present findings suggest that future studies incorporating social-evaluative threat would be well-positioned to examine how

https://doi.org/10.1017/S0954579422000244 Published online by Cambridge University Press

happiness and different dimensions of positive emotion relate to substance use in the context of stress. Further research is needed to understand how dampened positive emotion reactivity to stress may confer risk for substance use in adolescence.

Limitations

Findings must be interpreted within the context of the study design. Results at age 14 may suggest that substance use can influence adolescents' stress reactivity and ability to self-regulate within the context of stress. In turn, stress reactivity at age 14 may relate to substance use at age 16 through various mechanisms, such as through greater inclination to use substances to relieve stress, greater risk-taking, or greater susceptibility to peer pressure, which should be explored in future studies. There were limitations in cortisol assessment. The present study lacked data regarding current use of anxiolytics and antidepressants, both of which could influence cortisol responses. Estimates of cortisol recovery may be affected because participants were debriefed shortly after completing the TSST. Whereas other protocols collect all saliva samples prior to debriefing, the TSST was highly distressing for many participants in this sample, and debriefing occurred earlier to ensure adolescents were not distressed for longer than necessary (detailed in Johnson et al., 2017). This decision may have resulted in higher levels of recovery than would have been experienced otherwise. Although we utilized a social stressor given the high salience of social threats during adolescence, future studies can assess whether similar results are assessed with respect to nonsocial stressors (e.g., physical stressors, stressful film clips or photographs). Also, due to the low number of assessments, we needed to anchor responses at the sample peak rather than at each participant's peak. We could not use analytic techniques such as Landmark registration because we would be unable to assess recovery for a subset of participants who peaked at the fourth time point. Future studies should include multiple assessments of salivary cortisol throughout the recovery period so that this technique can be used.

The present study was limited by the assessment of substance use and emotion. Because adolescents reported whether they had ever used each substance at age 14 and again at age 16, items may assess experimentation, and it is possible that adolescents may have only used a substance once and never again (Kuntsche et al., 2016). Frequency of use over the past month or past year may be a better indicator of adolescents' substance use and risk for problems with substance use in adulthood, although these outcomes had limited variability in the current sample at these ages. Future studies with greater variability in frequency or with slightly older samples should examine how frequency of use is related to differences in the stress response. Furthermore, without items regarding the context of daily use, it is difficult to determine the mechanisms by which differences in stress reactivity relates to substance use. Another important limitation of the present study is that stress responses were measured only at age 14, such that we cannot assess the stability of responses at age 14 and age 16 and cannot determine whether stress responses at age 14 confer risk for substance use at age 16 over and above current stress responses at age 16.

Additionally, only three discrete emotions were measured, and participants were not able to report how they felt at that moment during the TSST. Potentially by using a different stress paradigm or passive assessment tools, participants could report their emotion as they experienced the stressor rather than immediately afterward in order to limit bias due to retrospective report and maintain consistency across ratings. We also had multiple ratings of emotion across the recovery period, but only one measure of emotion prior to the TSST. Future studies should employ experimental paradigms that allow for incorporation of more assessments of emotion during the stress task and therefore enable better estimation of emotion reactivity to stress. Results could also potentially vary by analytic approach, and other approaches such as longitudinal structural equation modeling can be used. Given the design of this study, multilevel models allowed for all available data to be included, while allowing for timing of individual assessments to vary across participants and allowing for random intercepts and random slopes of reactivity and recovery.

Finally, analyses were tested in a primarily Mexican-origin sample of adolescents with high levels of adversity and poverty, who may be at heightened long-term risk for substance use. We studied youth with high substance use risk because of our interest in how stress responses relate to substance use initiation, as has been done in previous studies (Evans et al., 2016; Moss et al., 1999). We anticipated that the stress responses may be more related to substance use among youth who experience more major negative life events and chronic daily stressors, as these youth may be more inclined to use substances as a means of decreasing negative emotion as opposed to other purposes such as increasing positive emotion compared to other populations (Stein et al., 2016). Therefore, although our results suggest dampened stress responses may predict substance use in this sample, effects may be weaker in other adolescent samples with less adversity. This study was embedded within a larger longitudinal birth-cohort study and therefore limited by attrition. It is possible that mothers who chose to participate in the study and to continue for multiple assessments may have differed from those who did not, although retention since age 9 was around 95%. Given limitations, results should be replicated among diverse populations, as well as other samples of Mexican-origin youth. Lastly, the study was limited to youth who had no gang involvement because of risk for violent responses to the TSST. This criterion may have attenuated associations, as gang members often show greater substance use (Sanders, 2012).

Conclusions

Dampened HPA axis and emotion responses to stress were related to adolescents' substance use for certain groups (i.e., adolescents above the poverty line, female adolescents). These results suggest that dampened stress responses can be a risk factor for adolescent substance use, and may indicate difficulties with responding to stress. Specifically, dampened cortisol reactivity to stress was related to use of alcohol by age 14 and vaping of nicotine by age 16 among adolescents above the poverty line, and dampened happiness reactivity to stress specifically was found to temporally precede initiation of use of cigarettes and marijuana among female adolescents. Poverty status differences may have emerged because early adversity and poverty status can influence HPA axis function, whereas differences by sex may have emerged because female adolescents may be particularly motivated to use substances to relieve stress and influence emotion. Taken together, these findings illustrate how adolescents' capacity for responding to stress can influence substance use and potentially position these adolescents for poorer mental health and long-term outcomes in adulthood.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0954579422000244

Acknowledgements. The authors thank the parents and adolescents who participated in the Center for the Health Assessment of Mothers and Children of Salinas (CHAMACOS) study.

Funding statement. The study was funded by the National Institute of Drug Abuse Grant R01 DA035300, the United States Environmental Protection Agency Grant RD83451301, and the National Institute of Environmental Health Sciences Grants P01 ES009605 and R01 ES017054. Danny Rahal was supported by National Institute of Drug Abuse grant 1 F31 DA051181-01A1.

Conflicts of interest. None.

References

Andersen, A., Due, P., Holstein, B. E., & Iversen, L. (2003). Tracking drinking behaviour from age 15-19 years. *Addiction*, *98*(11), 1505–1511. https://doi.org/10.1046/j.1360-0443.2003.00496.x

Andrabi, N., Khoddam, R., & Leventhal, A. M. (2017). Socioeconomic disparities in adolescent substance use: Role of enjoyable alternative substance-free activities. *Social Science & Medicine*, *176*, 175–182. https://doi.org/10.1016/j.socscimed.2016.12.032

Ayer, L., Greaves-Lord, K., Althoff, R. R., Hudziak, J. J., Dieleman, G. C., Verhulst, F. C., & van der Ende, J. (2013). Blunted HPA axis response to stress is related to a persistent Dysregulation Profile in youth. *Biological Psychology*, *93*(3), 343–351. https://doi.org/10.1016/j.biopsycho.2013.04.002

Bai, S., & Repetti, R. L. (2018). Negative and positive emotion responses to daily school problems: Links to internalizing and externalizing symptoms. *Journal of Abnormal Child Psychology*, *46*(3), 423–435. https://doi.org/10.1007/s10802-017-0311-8

Becker, J. B., Perry, A. N., & Westenbroek, C. (2012). Sex differences in the neural mechanisms mediating addiction: A new synthesis and hypothesis. *Biology of Sex Differences*, *3*(1), 1–35. https://doi.org/10.1186/2042-6410-3-14

Bendezú, J. J., Howland, M., Thai, M., Marceau, K., Shirtcliff, E. A., Hastings, P. D., & Klimes-Dougan, B. (2021). Adolescent cortisol and DHEA responses to stress as prospective predictors of emotional and behavioral difficulties: A person-centered approach. *Psychoneuroendocrinology*, *132*, 105365. https://doi.org/10.1016/j.psyneuen.2021.105365

Biener, L., & Siegel, M. (2000). Tobacco marketing and adolescent smoking: More support for a causal inference. *American Journal of Public Health*, *90*(3), 407. https://doi.org/10.2105/AJPH.90.3.407

Brewer-Smyth, K., Burgess, A. W., & Shults, J. (2004). Physical and sexual abuse, salivary cortisol, and neurologic correlates of violent criminal behavior in female prison inmates. *Biological Psychiatry*, *55*(1), 21–31. https://doi.org/10.1016/S0006-3223(03)00705-4

Bylsma, L. M., Morris, B. H., & Rottenberg, J. (2008). A meta-analysis of emotional reactivity in major depressive disorder. *Clinical Psychology Review*, *28*(4), 676–691. https://doi.org/10.1016/j.cpr.2007.10.001

Calkins, S. D., & Hill, A. (2007). Caregiver influences on emerging emotion regulation: Biological and environmental transactions in early development. In J. J. Gross (Ed.), *Handbook of emotion regulation* (pp. 229–248). The Guilford Press.

Carpenter, L. L., Carvalho, J. P., Tyrka, A. R., Wier, L. M., Mello, A. F., Mello, M. F., & Price, L. H. (2007). Decreased adrenocorticotropic hormone and cortisol responses to stress in healthy adults reporting significant childhood maltreatment. *Biological Psychiatry*, *62*(10), 1080–1087. https://doi.org/10.1016/j.biopsych.2007.05.002

Carpenter, L. L., Shattuck, T. T., Tyrka, A. R., Geracioti, T. D., & Price, L. H. (2011). Effect of childhood physical abuse on cortisol stress response. *Psychopharmacology*, *214*(1), 367–375. https://doi.org/10.1007/s00213-010-2007-4

Carroll, D., Ginty, A. T., Whittaker, A. C., Lovallo, W. R., & De Rooij, S. R. (2017). The behavioural, cognitive, and neural corollaries of blunted cardiovascular and cortisol reactions to acute psychological stress. *Neuroscience & Biobehavioral Reviews*, *77*, 74–86. https://doi.org/10.1016/j.neubiorev.2017.02.025

Chaplin, T. M., Niehaus, C., & Gonçalves, S. F. (2018). Stress reactivity and the developmental psychopathology of adolescent substance use. *Neurobiology of Stress*, *9*, 133–139. https://doi.org/10.1016/j.psyneuen.2005.02.010

Chiang, J. J., Bower, J. E., Irwin, M. R., Taylor, S. E., & Fuligni, A. J. (2017). Adiposity moderates links from early adversity and depressive symptoms to inflammatory reactivity to acute stress during late adolescence. *Brain, Behavior, & Immunity*, *66*, 146–155. https://doi.org/10.1016/j.bbi.2017.06.015

Colell, E., Bell, S., & Britton, A. (2014). The relationship between labour market categories and alcohol use trajectories in midlife. *Journal of Epidemiology and Community Health*, *68*(11), 1050–1056. https://doi.org/10.1136/jech-2014-204164

Cooper, M. L., Kuntsche, E., Levitt, A., Barber, L. L., & Wolf, S. (2016). Motivational models of substance use: A review of theory and research on motives for using alcohol, marijuana, and tobacco. In K. J. Sher (Eds.), *Oxford library of psychology. The Oxford handbook of substance use and substance use disorders* (pp. 375–421). Oxford University Press.

Del Giudice, M., Ellis, B. J., & Shirtcliff, E. A. (2011). The adaptive calibration model of stress responsivity. *Neuroscience & Biobehavioral Reviews*, *35*(7), 1562–1592. https://doi.org/10.1016/j.neubiorev.2010.11.007

Delva, J., Wallace, J. M., Jr., O'Malley, P. M., Bachman, J. G., Johnston, L. D., & Schulenberg, J. E. (2005). The epidemiology of alcohol, marijuana, and cocaine use among Mexican American, Puerto Rican, Cuban American, and other Latin American eighth-grade students in the United States: 1991-2002. *American Journal of Public Health*, *95*(4), 696–702. https://doi.org/10.2105/AJPH.2003.037051

DeWit, D. J., Adlaf, E. M., Offord, D. R., & Ogborne, A. C. (2000). Age at first alcohol use: A risk factor for the development of alcohol disorders. *American Journal of Psychiatry*, *157*(5), 745–750. https://doi.org/10.1176/appi.ajp.157.5.745

Dickerson, S. S., & Kemeny, M. E. (2004). Acute stressors and cortisol responses: A theoretical integration and synthesis of laboratory research. *Psychological Bulletin*, *130*(3), 355. https://doi.org/10.1037/0033-2909.130.3.355

Duijndam, S., Karreman, A., Denollet, J., & Kupper, N. (2020). Emotion regulation in social interaction: Physiological and emotional responses associated with social inhibition. *International Journal of Psychophysiology*, *158*, 62–72. https://doi.org/10.1016/j.ijpsycho.2020.09.013

Duke, N. N. (2018). Adolescent adversity and concurrent tobacco, alcohol, and marijuana use. *American Journal of Health Behavior*, *42*(5), 85–99. https://doi.org/10.5993/AJHB.42.5.8

Ellickson, P. L., Tucker, J. S., & Klein, D. J. (2003). Ten-year prospective study of public health problems associated with early drinking. *Pediatrics*, *111*(5), 949–955. https://doi.org/10.1542/peds.111.5.949

Eskenazi, B., Bradman, A., Gladstone, E. A., Jaramillo, S., Birch, K., & Holland, N. (2003). CHAMACOS, a longitudinal birth cohort study: Lessons from the fields. *Journal of Children's Health*, *1*(1), 3–27. https://doi.org/10.3109/713610244

Eskenazi, B., Fahey, C. A., Kogut, K., Gunier, R., Torres, J., Gonzales, N. A., & Deardorff, J. (2019). Association of perceived immigration policy vulnerability with mental and physical health among US-born Latino adolescents in California. *JAMA Pediatrics*, *173*(8), 744–753. https://doi.org/10.1001/jamapediatrics.2019.1475

Evans, B. E., Greaves-Lord, K., Euser, A. S., Thissen, S., Tulen, J. H., Franken, I. H., & Huizink, A. C. (2016). Stress reactivity as a prospective predictor of risky substance use during adolescence. *Journal of Studies on Alcohol and Drugs*, *77*(2), 208–219. https://doi.org/10.15288/jsad.2016.77.208

Evans, B. E., Greaves-Lord, K., Euser, A. S., Tulen, J. H., Franken, I. H., & Huizink, A. C. (2012). Alcohol and tobacco use and heart rate reactivity to a psychosocial stressor in an adolescent population. *Drug and Alcohol Dependence*, *126*(3), 296–303. https://doi.org/10.1016/j.drugalcdep.2012.05.031

Evans, B. E., Greaves-Lord, K., Euser, A. S., Tulen, J. H., Franken, I. H., & Huizink, A. C. (2013). Determinants of physiological and perceived physiological stress reactivity in children and adolescents. *PloS One*, *8*(4), e61724. https://doi.org/10.1371/journal.pone.0061724

Evans-Polce, R. J., Patrick, M. E., Lanza, S. T., Miech, R. A., O'Malley, P. M., & Johnston, L. D. (2018). Reasons for vaping among US 12th graders. *Journal of Adolescent Health*, *62*(4), 457–462. https://doi.org/10.1016/j.jadohealth.2017.10.009

Fergusson, D. M., Horwood, L. J., & Swain-Campbell, N. (2002). Cannabis use and psychosocial adjustment in adolescence and young adulthood. *Addiction*, *97*(9), 1123–1135. https://doi.org/10.1046/j.1360-0443.2002.00103.x

Ginty, A. T., Gianaros, P. J., Derbyshire, S. W., Phillips, A. C., & Carroll, D. (2013). Blunted cardiac stress reactivity relates to neural hypoactivation. *Psychophysiology*, *50*(3), 219–229. https://doi.org/10.1111/psyp.12017

Goodman, W. K., Janson, J., & Wolf, J. M. (2017). Meta-analytical assessment of the effects of protocol variations on cortisol responses to the Trier Social Stress Test. *Psychoneuroendocrinology*, *80*, 26–35. https://doi.org/10.1016/j.psyneuen.2017.02.030

Gould, L. F., Hussong, A. M., & Hersh, M. A. (2012). Emotional distress may increase risk for self-medication and lower risk for mood-related drinking consequences in adolescents. *International Journal of Emotional Education*, *4*(1), 6.

Grant, B. F., & Dawson, D. A. (1997). Age at onset of alcohol use and its association with DSM-IV alcohol abuse and dependence: results from the National Longitudinal Alcohol Epidemiologic Survey. *Journal of Substance Abuse*, *9*, 103–110. https://doi.org/10.1016/S0899-3289(97)90009-2

Grant, J. D., Scherrer, J. F., Lynskey, M. T., Lyons, M. J., Eisen, S. A., Tsuang, M. T., & Bucholz, K. K. (2006). Adolescent alcohol use is a risk factor for adult alcohol and drug dependence: Evidence from a twin design. *Psychological Medicine*, *36*(1), 109–118. https://doi.org/10.1017/S0033291705006045

Gunnar, M. R., Frenn, K., Wewerka, S. S., & Van Ryzin, M. J. (2009). Moderate versus severe early life stress: Associations with stress reactivity and regulation in 10-12-year-old children. *Psychoneuroendocrinology*, *34*(1), 62–75. https://doi.org/10.1016/j.psyneuen.2008.08.013

Guo, J., Mrug, S., & Knight, D. C. (2017). Emotion socialization as a predictor of physiological and psychological responses to stress. *Physiology & Behavior*, *175*, 119–129. https://doi.org/10.1016/j.physbeh.2017.03.046

Habra, M. E., Linden, W., Anderson, J. C., & Weinberg, J. (2003). Type D personality is related to cardiovascular and neuroendocrine reactivity to acute stress. *Journal of Psychosomatic Research*, *55*(3), 235–245. https://doi.org/10.1016/S0022-3999(02)00553-6

Hartman, C. A., Hermanns, V. W., de Jong, P. J., & Ormel, J. (2013). Self-or parent report of (co-occurring) internalizing and externalizing problems, and basal or reactivity measures of HPA-axis functioning: A systematic evaluation of the internalizing-hyperresponsivity versus externalizing-hyporesponsivity HPA-axis hypothesis. *Biological Psychology*, *94*(1), 175–184. https://doi.org/10.1016/j.biopsycho.2013.05.009

Hastings, P. D., & Kahle, S. (2019). Get bent into shape: The non-linear, multi-system, contextually-embedded psychophysiology of emotional development. In *Handbook of emotional development* (pp. 27–55). Springer. https://doi.org/10.1007/978-3-030-17332-6_3

Hersh, M. A., & Hussong, A. M. (2009). The association between observed parental emotion socialization and adolescent self-medication. *Journal of Abnormal Child Psychology*, *37*(4), 493–506. https://doi.org/10.1007/s10802-008-9291-z

Hingson, R. W., Heeren, T., & Winter, M. R. (2006). Age at drinking onset and alcohol dependence: Age at onset, duration, and severity. *Archives of Pediatrics & Adolescent Medicine*, *160*(7), 739–746. https://doi.org/10.1001/archpedi.160.7.739

Hostinar, C. E., McQuillan, M. T., Mirous, H. J., Grant, K. E., & Adam, E. K. (2014). Cortisol responses to a group public speaking task for adolescents: Variations by age, gender, and race. *Psychoneuroendocrinology*, *50*, 155–166. https://doi.org/10.1016/j.psyneuen.2014.08.015

Huizink, A. C., Ferdinand, R. F., Ormel, J., & Verhulst, F. C. (2006). Hypothalamic-pituitary–adrenal axis activity and early onset of cannabis use. *Addiction*, *101*(11), 1581–1588. https://doi.org/10.1111/j.1360-0443.2006.01570.x

Huizink, A. C., Greaves-Lord, K., Oldehinkel, A. J., Ormel, J., & Verhulst, F. C. (2009). Hypothalamic-pituitary–adrenal axis and smoking and drinking onset among adolescents: the longitudinal cohort TRacking Adolescents' Individual Lives Survey (TRAILS). *Addiction*, *104*(11), 1927–1936. https://doi.org/10.1111/j.1360-0443.2009.02685.x

Hyland, C., Bradshaw, P., Deardorff, J., Gunier, R. B., Mora, A. M., Kogut, K., & Eskenazi, B. (2022). Interactions of agricultural pesticide use near home during pregnancy and adverse childhood experiences on adolescent neurobehavioral development in the CHAMACOS study. *Environmental Research*, *204*, 111908. https://doi.org/10.1016/j.envres.2021.111908

Johnson, M. M., Deardorff, J., Parra, K., Alkon, A., Eskenazi, B., & Shirtcliff, E. (2017). A modified Trier Social Stress Test for vulnerable Mexican American adolescents. *JoVE (Journal of Visualized Experiments)*, *125*, e55393. https://doi.org/10.3791/55393

Johnson, M. M., Shirtcliff, E. A., van Dammen, L., Dahl, R. E., Gonzales, N., Harley, K. G., & Deardorff, J. (2020). Earlier age of sex and substance use initiation is associated with unique hormone profiles during social evaluative threat in Mexican American adolescents. *Psychoneuroendocrinology*, *121*, https://doi.org/10.1016/j.psyneuen.2020.104828

Johnston, L. D., Miech, R. A., O'Malley, P. M., Bachman, J. G., Schulenberg, J. E., & Patrick, M. E. (2019). Monitoring the future national survey results on drug use, 1975-2018: Overview, key findings on adolescent drug use. *Institute for Social Research*, https://doi.org/10.3998/2027.42/150621

Jones, A. P., Laurens, K. R., Herba, C. M., Barker, G. J., & Viding, E. (2009). Amygdala hypoactivity to fearful faces in boys with conduct problems and callous-unemotional traits. *American Journal of Psychiatry*, *166*(1), 95–102. https://doi.org/10.1176/appi.ajp.2008.07071050

Jones, C. B., Hill, M. L., Pardini, D. A., & Meier, M. H. (2016). Prevalence and correlates of vaping cannabis in a sample of young adults. *Psychology of Addictive Behaviors*, *30*(8), 915. https://doi.org/10.1037/adb0000217

Joos, C. M., McDonald, A., & Wadsworth, M. E. (2019). Extending the toxic stress model into adolescence: Profiles of cortisol reactivity. *Psychoneuroendocrinology*, *107*, 46–58. https://doi.org/10.1016/j.psyneuen.2019.05.002

Jun, H. J., Sacco, P., Bright, C. L., & Camlin, E. A. (2015). Relations among internalizing and externalizing symptoms and drinking frequency during adolescence. *Substance Use & Misuse*, *50*(14), 1814–1825. https://doi.org/10.3109/10826084.2015.1058826

Kann, L., McManus, T., Harris, W. A., Shanklin, S. L., Flint, K. H., Queen, B., & Lim, C. (2018). Youth risk behavior surveillance—United States. *2017 MMWR Surveillance Summaries*, *67*(8), 1. https://doi.org/10.15585/mmwr.ss6708a1

Kelly, M. M., Tyrka, A. R., Anderson, G. M., Price, L. H., & Carpenter, L. L. (2008). Sex differences in emotional and physiological responses to the Trier Social Stress Test. *Journal of Behavior Therapy & Experimental Psychiatry*, *39*(1), 87–98. https://doi.org/10.1016/j.jbtep.2007.02.003

Kirschbaum, C., Pirke, K. M., & Hellhammer, D. H. (1993). The 'Trier Social Stress Test'–a tool for investigating psychobiological stress responses in a laboratory setting. *Neuropsychobiology*, *28*(1-2), 76–81. https://doi.org/10.1159/000119004

Kliewer, W., Riley, T., Zaharakis, N., Borre, A., Drazdowski, T. K., & Jäggi, L. (2016). Emotion dysregulation, anticipatory cortisol, and substance use in urban adolescents. *Personality and Individual Differences*, *99*, 200–205. https://doi.org/10.1016/j.paid.2016.05.011

Koob, G., & Kreek, M. J. (2007). Stress, dysregulation of drug reward pathways, and the transition to drug dependence. *American Journal of Psychiatry*, *164*(8), 1149–1159. https://doi.org/10.1176/appi.ajp.2007.05030503

Koob, G. F., & Le Moal, M. (2008). Addiction and the brain antireward system. *Annual Review of Psychology*, *59*, 29–53. https://doi.org/10.1146/annurev.psych.59.103006.093548

Krkovic, K., Clamor, A., & Lincoln, T. M. (2018). Emotion regulation as a predictor of the endocrine, autonomic, affective, and symptomatic stress response and recovery. *Psychoneuroendocrinology*, *94*, 112–120. https://doi.org/10.1016/j.psyneuen.2018.04.028

Kuntsche, E., & Müller, S. (2012). Why do young people start drinking? Motives for first-time alcohol consumption and links to risky drinking in early adolescence. *European addiction research*, *18*(1), 34–39. https://doi.org/10.1159/000333036

Kuntsche, E., Rossow, I., Engels, R., & Kuntsche, S. (2016). Is 'age at first drink' a useful concept in alcohol research and prevention? We doubt that. *Addiction*, *111*(6), 957–965. https://doi.org/10.1111/add.12980

Kuntsche, E., Wicki, M., Windlin, B., Roberts, C., Gabhainn, S. N., Van Der Sluijs, W., & Demetrovics, Z. (2015). Drinking motives mediate cultural differences but not gender differences in adolescent alcohol use.

https://doi.org/10.1017/S0954579422000244 Published online by Cambridge University Press

Journal of Adolescent Health, *56*(3), 323–329. https://doi.org/10.1016/j.jadohealth.2014.10.267

Lam, S., Dickerson, S. S., Zoccola, P. M., & Zaldivar, F. (2009). Emotion regulation and cortisol reactivity to a social-evaluative speech task. *Psychoneuroendocrinology*, *34*(9), 1355–1362. https://doi.org/10.1016/j.psyneuen.2009.04.006

Latimer, W. W., Stone, A. L., Voight, A., Winters, K. C., & August, G. J. (2002). Gender differences in psychiatric comorbidity among adolescents with substance use disorders. *Experimental & Clinical Psychopharmacology*, *10*(3), 310. https://doi.org/10.1037/1064-1297.10.3.310

Lee, J. O., Cho, J., Yoon, Y., Bello, M. S., Khoddam, R., & Leventhal, A. M. (2018). Developmental pathways from parental socioeconomic status to adolescent substance use: Alternative and complementary reinforcement. *Journal of Youth & Adolescence*, *47*(2), 334–348. https://doi.org/10.1007/s10964-017-0790-5

Lench, H. C., Flores, S. A., & Bench, S. W. (2011). Discrete emotions predict changes in cognition, judgment, experience, behavior, and physiology: A meta-analysis of experimental emotion elicitations. *Psychological Bulletin*, *137*(5), 834–855. https://doi.org/10.1037/a0024244

Lerner, J. S., & Keltner, D. (2001). Fear, anger, and risk. *Journal of Personality and Social Psychology*, *81*(1), 146–159. https://doi.org/10.1037/0022-3514.81.1.146

Liu, S., Kuppens, P., & Bringmann, L. (2021). On the use of empirical bayes estimates as measures of individual traits. *Assessment*, *28*(3), 845–857. https://doi.org/10.1177/1073191119885019

Lovallo, W. R. (2006). Cortisol secretion patterns in addiction and addiction risk. *International Journal of Psychophysiology*, *59*(3), 195–202. https://doi.org/10.1016/j.ijpsycho.2005.10.007

Lovallo, W. R. (2011). Do low levels of stress reactivity signal poor states of health? *Biological Psychology*, *86*(2), 121–128. https://doi.org/10.1016/j.biopsycho.2010.01.006

Martz, M. E., Schulenberg, J. E., & Patrick, M. E. (2018). Passing on pot: high school seniors' reasons for not using marijuana as predictors of future use. *Journal of Studies on Alcohol & Drugs*, *79*(5), 761–769. https://doi.org/10.15288/jsad.2018.79.761

Melotti, R., Heron, J., Hickman, M., Macleod, J., Araya, R., & Lewis, G. (2011). Adolescent alcohol and tobacco use and early socioeconomic position: The ALSPAC birth cohort. *Pediatrics*, *127*(4), e948–e955. https://doi.org/10.1542/peds.2009-3450

Miech, R., Keyes, K. M., O'Malley, P. M., & Johnston, L. D. (2020). The great decline in adolescent cigarette smoking since 2000: Consequences for drug use among US adolescents. *Tobacco Control*, https://doi.org/10.1136/tobaccocontrol-2019-055052

Moons, W. G., Eisenberger, N. I., & Taylor, S. E. (2010). Anger and fear responses to stress have different biological profiles. *Brain, Behavior, & Immunity*, *24*(2), 215–219. https://doi.org/10.1016/j.bbi.2009.08.009

Moss, H. B., Vanyukov, M., Yao, J. K., & Kirillova, G. P. (1999). Salivary cortisol responses in prepubertal boys: the effects of parental substance abuse and association with drug use behavior during adolescence. *Biological Psychiatry*, *45*(10), 1293–1299. https://doi.org/10.1016/S0006-3223(98)00216-9

Natsuaki, M. N., Klimes-Dougan, B., Ge, X., Shirtcliff, E. A., Hastings, P. D., & Zahn-Waxler, C. (2009). Early pubertal maturation and internalizing problems in adolescence: Sex differences in the role of cortisol reactivity to interpersonal stress. *Journal of Clinical Child & Adolescent Psychology*, *38*(4), 513–524. https://doi.org/10.1080/15374410902976320

Nebebe, F., & Stroud, T. W. F. (1986). Bayes and empirical Bayes shrinkage estimation of regression coefficients. *Canadian Journal of Statistics*, *14*(4), 267–280. https://doi.org/10.2307/3315184

Ortiz, J., & Raine, A. (2004). Heart rate level and antisocial behavior in children and adolescents: A meta-analysis. *Journal of the American Academy of Child & Adolescent Psychiatry*, *43*(2), 154–162. https://doi.org/10.1097/00004583-200402000-00010

Ouellet-Morin, I., Odgers, C. L., Danese, A., Bowes, L., Shakoor, S., Papadopoulos, A. S., & Arseneault, L. (2011). Blunted cortisol responses to stress signal social and behavioral problems among maltreated/bullied 12-year-old children. *Biological Psychiatry*, *70*(11), 1016–1023. https://doi.org/10.1016/j.biopsych.2011.06.017

Patrick, M. E., Wightman, P., Schoeni, R. F., & Schulenberg, J. E. (2012). Socioeconomic status and substance use among young adults: A comparison across constructs and drugs. *Journal of Studies on Alcohol and Drugs*, *73*(5), 772–782. https://doi.org/10.15288/jsad.2012.73.772

Peckins, M. K., Susman, E. J., Negriff, S., Noll, J. G., & Trickett, P. K. (2016). Cortisol profiles: A test for adaptive calibration of the stress response system in maltreated and nonmaltreated youth. *Development & Psychopathology*, *28*(4), 1563–1564. https://doi.org/10.1017/S0954579415000875

Peters, A., & McEwen, B. S. (2015). Stress habituation, body shape and cardiovascular mortality. *Neuroscience & Biobehavioral Reviews*, *56*, 139–150. https://doi.org/10.1016/j.neubiorev.2015.07.001

Peters, A. T., Van Meter, A., Pruitt, P. J., Briceño, E. M., Ryan, K. A., Hagan, M., & McInnis, M. (2016). Acute cortisol reactivity attenuates engagement of fronto-parietal and striatal regions during emotion processing in negative mood disorders. *Psychoneuroendocrinology*, *73*, 67–78. https://doi.org/10.1016/j.psyneuen.2016.07.215

Platje, E., Vermeiren, R. R. J. M., Raine, A., Doreleijers, T. A., Keijsers, L. G. M. T., Branje, S. J. T., & Jansen, L. M. C. (2013). A longitudinal biosocial study of cortisol and peer influence on the development of adolescent antisocial behavior. *Psychoneuroendocrinology*, *38*(11), 2770–2779. https://doi.org/10.1016/j.psyneuen.2013.07.006

Pompili, S., & Laghi, F. (2019). Binge eating and binge drinking among adolescents: The role of drinking and eating motives. *Journal of health psychology*, *24*(11), 1505–1516. https://doi.org/10.1177/1359105317713359

Poon, J. A., Turpyn, C. C., Hansen, A., Jacangelo, J., & Chaplin, T. M. (2016). Adolescent substance use & psychopathology: Interactive effects of cortisol reactivity and emotion regulation. *Cognitive Therapy & Research*, *40*(3), 368–380. https://doi.org/10.1007/s10608-015-9729-x

Purves, K. L., Constantinou, E., McGregor, T., Lester, K. J., Barry, T. J., Treanor, M., & Eley, T. C. (2019). Validating the use of a smartphone app for remote administration of a fear conditioning paradigm. *Behaviour Research & Therapy*, *123*, 103475. https://doi.org/10.1016/j.brat.2019.103475

Rao, U., Hammen, C. L., & Poland, R. E. (2009). Mechanisms underlying the comorbidity between depressive and addictive disorders in adolescents: Interactions between stress and HPA activity. *American Journal of Psychiatry*, *166*(3), 361–369. https://doi.org/10.1176/appi.ajp.2008.08030412

Riala, K., Hakko, H., Isohanni, M., Järvelin, M. R., & Räsänen, P. (2004). Teenage smoking and substance use as predictors of severe alcohol problems in late adolescence and in young adulthood. *Journal of Adolescent Health*, *35*(3), 245–254. https://doi.org/10.1016/S1054-139X(03)00350-1

Rolle, I. V., Kennedy, S. M., Agaku, I., Jones, S. E., Bunnell, R., Caraballo, R., & McAfee, T. (2015). Cigarette, cigar, and marijuana use among high school students—United States, 1997-2013. *Morbidity and Mortality Weekly Report*, *64*(40), 1136–1141. https://doi.org/10.15585/mmwr.mm6440a2

Ruttle, P. L., Serbin, L. A., Stack, D. M., Schwartzman, A. E., & Shirtcliff, E. A. (2011). Adrenocortical attunement in mother-child dyads: Importance of situational and behavioral characteristics. *Biological Psychology*, https://doi.org/10.1016/j.biopsycho.2011.06.014

Sagiv, S. K., Kogut, K., Gaspar, F. W., Gunier, R. B., Harley, K. G., Parra, K., & Eskenazi, B. (2015). Prenatal and childhood polybrominated diphenyl ether (PBDE) exposure and attention and executive function at 9-12 years of age. *Neurotoxicology & Teratology*, *52*, 151–161. https://doi.org/10.1016/j.ntt.2015.08.001

Salis, K. L., Bernard, K., Black, S. R., Dougherty, L. R., & Klein, D. (2016). Examining the concurrent and longitudinal relationship between diurnal cortisol rhythms and conduct problems during childhood. *Psychoneuroendocrinology*, *71*, 147–154. https://doi.org/10.1016/j.psyneuen.2016.05.021

Sanders, B. (2012). Gang youth, substance use patterns, and drug normalization. *Journal of Youth Studies*, *15*(8), 978–994. https://doi.org/10.1080/13676261.2012.685707

Schielzeth, H., Dingemanse, N. J., Nakagawa, S., Westneat, D. F., Allegue, H., Teplitsky, C., & Araya-Ajoy, Y. G. (2020). Robustness of linear mixed-effects models to violations of distributional assumptions. *Methods in*

Ecology and Evolution, *11*(9), 1141–1152. https://doi.org/10.1111/2041-210X.13434

Shadur, J. M., Hussong, A. M., & Haroon, M. (2015). Negative affect variability and adolescent self-medication: The role of the peer context. *Drug and Alcohol Review*, *34*(6), 571–580. https://doi.org/10.1111/dar.12260

Shields, G. S., Bonner, J. C., & Moons, W. G. (2015). Does cortisol influence core executive functions? A meta-analysis of acute cortisol administration effects on working memory, inhibition, and set-shifting. *Psychoneuroendocrinology*, *58*, 91–103. https://doi.org/10.1016/j.psyneuen.2015.04.017

Shirtcliff, E. A., & Essex, M. J. (2008). Concurrent and longitudinal associations of basal and diurnal cortisol with mental health symptoms in early adolescence. *Developmental Psychobiology*, *50*(7), 690–703. https://doi.org/10.1002/dev.20336

Shirtcliff, E. A., Hanson, J. L., Phan, J. M., Ruttle, P. L., & Pollak, S. D. (2021). Hyper-and hypo-cortisol functioning in post-institutionalized adolescents: The role of severity of neglect and context. *Psychoneuroendocrinology*, *124*, 105067. https://doi.org/10.1016/j.psyneuen.2020.105067

Shirtcliff, E. A., Peres, J. C., Dismukes, A. R., Lee, Y., & Phan, J. M. (2014). Hormones: Commentary: Riding the physiological roller coaster: Adaptive significance of cortisol stress reactivity to social contexts. *Journal of Personality Disorders*, *28*(1), 40–51. https://doi.org/10.1521/pedi.2014.28.1.40

Shomaker, L. B., & Reina, S. A. (2015). Intraindividual variability in mood experience and mood regulation in childhood and adolescence. In *Handbook of intraindividual variability across the life span* (pp. 103–122). Routledge.

Simons, J. S., & Carey, K. B. (2002). Risk and vulnerability for marijuana use problems: The role of affect dysregulation. *Psychology of Addictive Behaviors*, *16*(1), 72. https://doi.org/10.1037/0893-164X.16.1.72

Simons, J. S., Carey, K. B., & Wills, T. A. (2009). Alcohol abuse and dependence symptoms: A multidimensional model of common and specific etiology. *Psychology of Addictive Behaviors*, *23*(3), 415. https://doi.org/10.1037/a0016003

Sinha, R. (2001). How does stress increase risk of drug abuse and relapse? *Psychopharmacology*, *158*(4), 343–359. https://doi.org/10.1007/s002130100917

Spear, L. P. (2009). Heightened stress responsivity and emotional reactivity during pubertal maturation: Implications for psychopathology. *Development & Psychopathology*, *21*(1), 87. https://doi.org/10.1017/S0954579409000066

Stadler, C., Sterzer, P., Schmeck, K., Krebs, A., Kleinschmidt, A., & Poustka, F. (2007). Reduced anterior cingulate activation in aggressive children and adolescents during affective stimulation: Association with temperament traits. *Journal of psychiatric Research*, *41*(5), 410–417. https://doi.org/10.1016/j.jpsychires.2006.01.006

Stein, L. J., Gunier, R. B., Harley, K., Kogut, K., Bradman, A., & Eskenazi, B. (2016). Early childhood adversity potentiates the adverse association between prenatal organophosphate pesticide exposure and child IQ: The CHAMACOS cohort. *Neurotoxicology*, *56*, 180–187. https://doi.org/10.1016/j.neuro.2016.07.010

Steptoe, A., Wardle, J., & Marmot, M. (2005). Positive affect and health-related neuroendocrine, cardiovascular, and inflammatory processes. *Proceedings of the National Academy of Sciences*, *102*(18), 6508–6512. https://doi.org/10.1073/pnas.0409174102

Strunin, L., Díaz-Martínez, A., Díaz-Martínez, L. R., Heeren, T., Chen, C., Winter, M., & Solís-Torres, C. (2017). Age of onset, current use of alcohol, tobacco or marijuana and current polysubstance use among male and female Mexican students. *Alcohol & Alcoholism*, *52*(5), 564–571. https://doi.org/10.1093/alcalc/agx027

Swift, W., Coffey, C., Carlin, J. B., Degenhardt, L., & Patton, G. C. (2008). Adolescent cannabis users at 24 years: Trajectories to regular weekly use and dependence in young adulthood. *Addiction*, *103*(8), 1361–1370. https://doi.org/10.1111/j.1360-0443.2008.02246.x

Taylor, M., Collin, S. M., Munafò, M. R., MacLeod, J., Hickman, M., & Heron, J. (2017). Patterns of cannabis use during adolescence and their association with harmful substance use behaviour: Findings from a UK birth cohort. *Journal of Epidemiology & Community Health*, *71*(8), 764–770. https://doi.org/10.1136/jech-2016-208503

Temple, J. R., Shorey, R. C., Lu, Y., Torres, E., Stuart, G. L., & Le, V. D. (2017). E-cigarette use of young adults motivations and associations with combustible cigarette alcohol, marijuana, and other illicit drugs. *The American Journal on Addictions*, *26*(4), 343–348. https://doi.org/10.1111/ajad.12530

Trickett, P. K., Gordis, E., Peckins, M. K., & Susman, E. J. (2014). Stress reactivity in maltreated and comparison male and female young adolescents. *Child Maltreatment*, *19*(1), 27–37. https://doi.org/10.1177/1077559513520466

Uink, B., Modecki, K. L., Barber, B. L., & Correia, H. M. (2018). Socioeconomically disadvantaged adolescents with elevated externalizing symptoms show heightened emotion reactivity to daily stress: An experience sampling study. *Child Psychiatry & Human Development*, *49*(5), 741–756. https://doi.org/10.1007/s10578-018-0784-x

van Leeuwen, A. P., Creemers, H. E., Greaves-Lord, K., Verhulst, F. C., Ormel, J., & Huizink, A. C. (2011). Hypothalamic-pituitary–adrenal axis reactivity to social stress and adolescent cannabis use: The TRAILS study. *Addiction*, *106*(8), 1484–1492. https://doi.org/10.1111/j.1360-0443.2011.03448.x

Wagner, F. A., Velasco-Mondragón, H. E., Herrera-Vazquez, M., Borges, G., & Lazcano-Ponce, E. (2005). Early alcohol or tobacco onset and transition to other drug use among students in the state of Morelos. *Mexico Drug & Alcohol Dependence*, *77*(1), 93–96. https://doi.org/10.1016/j.drugalcdep.2004.06.009

Wemm, S. E., & Sinha, R. (2019). Drug-induced stress responses and addiction risk and relapse. *Neurobiology of Stress*, *10*, 100148. https://doi.org/10.1016/j.ynstr.2019.100148

Wills, T. A., Resko, J. A., Ainette, M. G., & Mendoza, D. (2004). Role of parent support and peer support in adolescent substance use: A test of mediated effects. *Psychology of Addictive Behaviors*, *18*(2), 122. https://doi.org/10.1037/0893-164X.18.2.122

Wright, N., Hill, J., Pickles, A., & Sharp, H. (2019). Callous-unemotional traits, low cortisol reactivity and physical aggression in children: Findings from the Wirral Child Health and Development Study. *Translational Psychiatry*, *9*(1), 79. https://doi.org/10.1038/s41398-019-0406-9

Yang, H., Spence, J. S., Briggs, R. W., Rao, U., North, C., Devous Sr, M. D., & Adinoff, B. (2015). Interaction between early life stress and alcohol dependence on neural stress reactivity. *Addiction Biology*, *20*(3), 523–533. https://doi.org/10.1111/adb.12135

Young, K. S., Sandman, C. F., & Craske, M. G. (2019). Positive and negative emotion regulation in adolescence: Links to anxiety and depression. *Brain Sciences*, *9*(4), 76. https://doi.org/10.3390/brainsci9040076

Zimmermann, P., & Iwanski, A. (2014). Emotion regulation from early adolescence to emerging adulthood and middle adulthood: Age differences, gender differences, and emotion-specific developmental variations. *International Journal of Behavioral Development*, *38*(2), 182–194. https://doi.org/10.1177/0165025413515405