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Dampened Autonomic Nervous System Responses to Stress and Substance Use in Adolescence

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Abstract

We investigated whether parasympathetic and sympathetic nervous system responses to social-evaluative threat at age 14 were related to the number of substances used between ages 14 and 16 among Mexican-origin adolescents (*N*=243; 70.4% had never used substances by 14). Participants completed the Trier Social Stress Test, while cardiac measures of parasympathetic and sympathetic nervous system activity were measured continuously using respiratory sinus arrhythmia (RSA) and pre-ejection period (PEP), respectively. Participants reported whether they had ever used alcohol, marijuana, and cigarettes, and had ever vaped nicotine in their lifetime at ages 14 and 16. Multilevel models were used to test associations between RSA and PEP responses at age 14 and substance use at 16. Among youth who had not used substances by 14, dampened RSA and PEP responses, and profiles of greater coinhibition and lower reciprocal SNS activation between RSA and PEP, at age 14 were associated with using substances by 16. Among youth who used by 14, exaggerated PEP responses were associated with using more substances by age 16. Taken together, dampened autonomic responses to social-evaluative threat predicted initiation of substance use over two years, and difficulties with coordination of physiological responses may confer risk for substance use in adolescence.*Keywords*: sympathetic nervous system, parasympathetic nervous system, substance use, adolescent, stress

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Substance use greatly increases across adolescence. Hispanic youth are at heightened risk for substance use in the 8[th] grade relative to White youth and youth with other ethnicities in the United States (Johnston et al., 2019), and risk may be particularly high for Mexican-

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origin youth (Delva et al., 2005; Kann et al., 2018). Both early use and poly-substance use have been related to heightened risk of substance use-related problems and disorders in adulthood (Latimer & Zur, 2010; Zapert et al., 2002). Studies have shown that Mexican-origin adolescents with both internalizing and externalizing problems are more likely to initiate and escalate substance use (Gonzales et al., 2017), and dampened autonomic responses to stress have been related to greater internalizing and externalizing problems in children (Graziano & Derefinko, 2013). Yet, limited research has examined whether stress physiology may also relate to adolescent substance use.

Dampened cardiovascular reactivity to stress has been consistently related to poorer mental health and greater substance use (e.g., Bibbey et al., 2016; Chaplin et al., 2018; Evans et al., 2016). These dampened responses may suggest conscious and unconscious disengagement with stress (Carroll et al., 2017), heightened risk for depressive symptoms over time (Gentzler et al., 2009), and difficulties with emotion regulation (Phillips et al., 2013), all of which are risk factors for elevated substance use (Wills et al., 1999). Autonomic nervous system (ANS) responses can alert the body to threat, including social threats such as risky circumstances and peer pressure. Dampened ANS responses may decrease youths' abilities to self-regulate and increase their inclination to engage with deviant peers and to use substances as a means of coping with stressors. Yet, few studies have tested associations during adolescence, when substance use emerges, especially among youth at heightened risk.

The two branches of the ANS—the sympathetic nervous system (SNS) and parasympathetic nervous system (PNS)—are physiological stress-response systems that may be particularly tied to adolescents' substance use (e.g., Hinnant et al., 2015, 2021). Dampened PNS and SNS responses to stress may indicate impaired ability to regulate one's emotions following stress and consequently may signal risk for use of more substances. According to the neurovisceral integration model (Thayer & Lane, 2009), higher PNS activity has been related to greater activation of prefrontal cortical regions involved in emotion regulation. Resting PNS activity has therefore been considered a marker of greater emotion regulatory capacity (Beauchaine, 2015). Indeed, higher resting PNS activity has been related to fewer difficulties with emotion regulation (Visted et al., 2017; Williams et al., 2015), more effective use of emotion regulation strategies in the laboratory (Gillie et al., 2013) and greater engagement in daily emotion regulation processes (Geisler et al., 2010).

These effects are likely because higher resting PNS activity suggests greater cardiac control (i.e., ability to modulate PNS activity in response to stimuli, such as showing vagal withdrawal with stress onset), such that individuals can elicit activation of prefrontal cortical regions in response to environmental stimuli. Another index of cardiac control is the degree to which people show vagal withdrawal to a stressor, such that individuals who show greater reactivity may more adaptively modulate neural and physiological resources to respond to a stressor (Porges, 2007). Both resting PNS activity and PNS reactivity to stress have been assessed as potential measures of emotion regulatory ability (Beauchaine, 2015; Hinnant et al., 2018). Greater PNS reactivity to stress, specifically, has been found to consistently buffer the effects of environmental and family stress on youths' mental health (El-Sheikh & Erath, 2011; Hinnant et al., 2015), whereas dampened PNS reactivity to a sad film was related to greater depressive symptoms in adolescents (Yaroslavsky et al., 2016). In turn, dampened parasympathetic responses are associated with poorer mental health, including internalizing and externalizing problems (Graziano & Derefinko, 2013). SNS reactivity has been related to amygdala reactivity as well as poorer executive function during stress, such that blunted SNS responses may hamper adolescents' ability to deal with peer pressure regarding substance use (Alexander et al., 2007; Hurlemann et al., 2010; Ramos & Arnsten, 2007; van Stegeren et al., 2005). Similar to findings for PNS reactivity, blunted SNS reactivity is also consistently related to psychopathology, including externalizing problems such as aggression and rule-breaking (Fung et al., 2005; Lorber, 2004), depressive symptoms (Schwerdtfeger & Rosenkaimer, 2011), and poorer mental health for adolescents living in risky home environments (Erath et al., 2009, 2011; Hinnant et al., 2015).

Furthermore, substance use may relate to profiles of PNS and SNS reactivity. According to the autonomic space model (Figure 1), autonomic responses at a given moment can be measured on two dimensions: reciprocity and overall activation (Berntson et al., 1994, 2008). The SNS and PNS can show reciprocal activation in the form of reciprocal SNS dominance, which is generally regarded as a classic response to stress and is characterized by increased SNS activity and vagal withdrawal (i.e., decreases in PNS activity), or reciprocal PNS dominance, characterized by decreased SNS activity and vagal augmentation (i.e., increases in PNS activity). The degree of reciprocal activation is measured in terms of cardiac autonomic balance (CAB), operationalized as the difference between SNS and PNS activity. Extreme values would indicate dominance of either system, whereas values near zero would suggest a lack of reciprocal activation (Berntson et al., 1994, 2008). There are also non-reciprocal profiles in the forms of coactivation (i.e., both SNS and PNS activity increase) or coinhibition (i.e., SNS and PNS activity decrease), and the degree of coactivation is measured as cardiac autonomic regulation (CAR). CAR is operationalized as the sum of SNS and PNS activity, with low values indicating a lack of overall activity and high values indicating high overall activity (Berntson et al., 1994, 2008). Non-reciprocal patterns of reactivity suggest lower cross-system coordination. Lower SNS reciprocity and greater coinhibition, or lower activity across systems, suggest that bodily systems are not mobilized to appropriately respond to stress. Indeed, these profiles generally relate to poorer mental health in children and adolescents (e.g., Boyce et al., 2001; Quigley & Moore, 2018). However, few studies measure both SNS and PNS activity and examine minute-by-minute variations in physiology across a task.

Although SNS and PNS activity dynamically develop in early childhood, they stabilize during late childhood and may have predictive utility for adolescents comparable to that for adults (Gatzke-Kopp & Ram, 2018; Hinnant et al., 2018). Only one study has utilized SNS and PNS activity to predict substance use; in children ages 8–12, dampened SNS reactivity to reward was related to greater alcohol use the next year (Brenner & Beauchaine, 2011). Given that substances are often used to reduce stress and to enhance emotion (Kuntsche et al., 2015), SNS and PNS reactivity to stress may also be predictive markers of substance use during adolescence.

Present Study

The present study examined whether physiological responses to social-evaluative stress were related to the number of substances ever used (i.e., substance use count) in a sample of Mexican-origin adolescents. Substance use count was used as a measure because of research suggesting youth who use more substances are at higher risk of experimentation and problematic substance use in adulthood (Moss et al., 2014). Although frequency of use is often a particularly predictive measure of problems with substance use, variability in substance use frequency was limited in this sample given the age of these youth. Additionally, research has suggested that substance use at younger ages is problematic because neurobiological changes during adolescence cause youth to be particularly vulnerable to addiction during this period, and youth who use alcohol and marijuana by age 16 tend to show more frequent subsequent use compared to youth who do not (Grant et al., 2006; Hingson et al., 2006; Moss et al., 2014; Swift et al., 2008). Adolescents are particularly sensitive to social threats (Forbes & Dahl, 2010), and youth are often motivated to use substances to cope with social stress and due to peer pressure. Therefore, we specifically assessed responses to social-evaluative threat, rather than nonsocial or physical stress.

A sample of Mexican-origin adolescents from high-adversity, low-income backgrounds completed a stress task at age 14 and reported whether they had ever used various substances at age 14 and again two years later at age 16. Given this longitudinal design, we examined how autonomic stress responses at age 14 related to the emergence of substance use by age 16. Because earlier substance use is related to patterns of more frequent and riskier substance use (e.g., Kendler et al., 2008; Richmond-Rakerd et al., 2017), analyses were tested separately among adolescents who had never used any substances by age 14, in order to assess substance use initiation between ages 14 and 16, and among youth who had used substances by age 14, in order to assess escalation of substance use between ages 14 and 16. Social situations involving peers and substance use can be stressful for adolescents, and youth with dampened ANS responses to stress may be more inclined to use substances either as a means to conform with peers or to cope with stress. Therefore, adolescents with dampened SNS and PNS responses to stress at age 14 were hypothesized to use more substances by age 16. Physiological responses may differ in response to social versus nonsocial stressors, and youth with blunted responses to social-evaluative stress (i.e., speech and math tasks) were predicted to initiate substance use between ages 14 and 16. Further, adolescents with greater cross-system dysregulation (i.e., lower reciprocity and greater coinhibition) were predicted to use more substances by age 16.

Because our primary interest was in the initiation of substance use, we first tested all associations among youth who had never used substances by age 14. Then, using the full sample, we tested whether the strength of associations between ANS responses to social-evaluative stress at age 14 and substance use at age 16 differ between youth who have and have not used by age 14. If significant associations emerged, we then conducted secondary analyses among youth who had used by age 14. Assessment of differences in the strength of associations by prior use of substances by age 14 was exploratory, and we did not have *a priori* hypotheses regarding whether associations would emerge in youth who had used substances by age 14.

Method

Participants.

Participants were adolescents from the CHAMACOS study, a longitudinal birth cohort study of over 500 Mexican-origin adolescents living in the agricultural Salinas Valley community (Eskenazi et al., 2003). Mothers were initially eligible to enroll in the study in 1999–2000 if they were age 18 or older and under 20 weeks of gestation, eligible for California's low-income health insurance program, receiving prenatal care, and planning to deliver at a county hospital. For this cohort, there were 1,130 women eligible for the study, of whom 601 were recruited, 531 remained in the study after childbirth, 350 remained in the study at age 5, and 325 remained in the study at age 14. Rates of attrition were highest from pregnancy to delivery and were very low following the age 5 assessment (Eskenazi et al., 2003). A second cohort of 300 9-year-old children were also recruited in 2009, and they and their mothers completed data collection comparable to the original cohort (Sagiv et al., 2015). Retention rates for both cohorts were high between ages 9 and 14 (95% for CHAM1, 94% for CHAM2). The two cohorts did not differ in age at the age 14 and 16 assessments, ps > .05. Due to funding constraints, most youth who completed the stress task in the present study were from the original cohort (94.15%).

To participate in the stress task at age 14, adolescents needed to meet the following criteria: IQ above 70 at age 12, no diagnosis of autism spectrum disorder, no extreme atypical behaviors at past visits, within three standard deviations of the mean for depressive scores for their age and sex, still living in the Salinas Valley, and no gang involvement in the previous year. In total, 277 adolescents completed the stress task (59.57% in 8^{th} grade, 67.15% below the poverty line; 45.85% female). This sample size was smaller for the TSST versus the surveys at age 14 because participants who moved out of the Salinas Valley but still lived in California or Arizona completed the survey but not the TSST. All of the participants were asked to participate in the ANS data collection but some participants who completed the TSST refused the application of electrodes or did not have clean, scoreable SNS or PNS data due to equipment failures or noise. Therefore, of these adolescents, PNS responses were recorded in 243 adolescents, and SNS responses were recorded in 229 adolescents during the laboratory visit at age 14. Almost all adolescents completed additional data collection at age 16 (97.12%). Participants whose PNS and SNS responses were recorded did not differ in terms of demographics from both the larger cohorts of participants who had completed assessments at any age ($N = 849$) and the sample of adolescents who completed an assessment at age 14 but not the stress task ($N = 604$) with respect to mother's education, sex, poverty status, and substance use count at ages 14 and 16, all ps > .10.

Separate analyses were tested among youth who had never used substances by age 14 ($n = 171$; 50.88% female, 65.29% below poverty line, 54.97% in 8th grade at age 14) and youth who had used substances by age 14 ($n = 72$; 54.17% female, 68.57% below poverty line, 63.89% in 8th grade at age 14). Analyses among youth who had never used substances by age 14 tested whether ANS responses were related to substance use initiation between ages 14 and 16, whereas analyses among youth who had used substances by age 14 tested whether ANS responses were related to escalation of substance use. Participants who had used substances by age 14 did not differ from those who did not with respect to mother's education, family income-to-needs ratio, grade at age 14, or grade at age 16, all *p*s > .232. Participants who used substances by age 14 reported higher substance use count by age 16 ($M = 2.25$, $SD = 1.23$) than participants who had not used substances by age 14 ($M = 0.69$, $SD = 0.99$), $t(232) = 10.09$, $p < .001$.

Procedure.

Adolescents completed the Trier Social Stress Test (TSST), a validated social-evaluative stress paradigm, during the study visit at age 14 (Kirschbaum et al., 1993). The protocol was modified for this population to invoke an appropriate level of distress and challenge (detailed in Johnson et al., 2017). Adolescents rested for 10 min. to acclimate to the space and then watched a 3 min. video as a neutral baseline. Participants stood up and counted to 100 for 2 min. before receiving the instructions regarding the speech and math tasks. Participants then had 3 min. to prepare a speech on how they are a good friend. They then presented the speech for 5 min. to two confederate judges, who were of similar age and ethnicity to participants and were introduced as experts in evaluating the task. After the speech task, youth completed a mental arithmetic task for an additional 5 min. Confederates were trained to maintain neutral affect and provide no positive feedback, and adolescents were obtrusively video recorded during the tasks. Participants were then debriefed within 15 min. after task completion to minimize distress.

Throughout the task, electrocardiogram (ECG) and impedance measures were continuously monitored. Participants had three spot electrodes on their chest in a lead II configuration to acquire ECG waveforms. Placement of electrodes, data recording, and data reduction followed conventions and published guidelines (Berntson et al., 1997). Impedance was measured using four spot electrodes on the neck and trunk. Impedance cardiography, measured as vascular resistance in the thoracic cavity, was measured using four spot electrodes on the neck, back, and chest (e.g., Paunović et al., 2014). Interbeat intervals (IBIs) were calculated from ECG. IBIs were checked and edited for artifacts using statistical detection algorithms (e.g., Berntson et al., 1990) and visually inspected. The high-frequency variability of IBIs was calculated as a frequency-domain index of respiratory sinus arrhythmia (RSA), controlling for respiration rate. Impedance was calculated from the ECG and impedance waveforms. Pre-ejection period (PEP) was measured as the time between the onset of ventricular depolarization (Q point on the ECG wave) and the onset of left ventricular ejection (B point on the impedance waveform) in milliseconds. Data were processed in one-minute epochs using ensemble averaging (Kelsey & Guethlein, 1990) using Mindware software (mindwaretech.org). The RSA index measures PNS withdrawal with lower RSA indices, and the PEP in milliseconds measures SNS activity, with lower PEP values indicating SNS activation. Both low RSA (withdrawal) and low PEP (activation) increase heart rate.

Finally, at the 14-year visit, adolescents completed items from the Monitoring the Future Survey regarding whether they had used alcohol, marijuana, or cigarettes in their lifetime using a computer-based survey (Johnston et al., 2019). At the 16-year visit, adolescents reported whether they had ever used cigarettes, marijuana, alcohol, or a vape in their lifetime. For each adolescent, we calculated the number (count) of substances that they had ever used, with a maximum of 3 at age 14 (i.e., use of cigarettes, marijuana, and alcohol in their lifetime) and a maximum of 4 at age 16 (i.e., use of cigarettes, marijuana, alcohol, and vaping nicotine in their lifetime).

Analytic Plan

RSA and PEP responses were modeled using three-level multilevel models with time nested within task segment, nested within adolescents. The TSST comprised five task segments (i.e., baseline, preparation, speech, math, and debriefing), each lasting about 5 min. RSA and PEP were also recorded as participants counted aloud to 100 and received instructions prior to the TSST, each lasting approximately 2 min. These segments were too short to reliably assess associations between physiology and substance use, and reactivity is best examined by comparing segments of similar duration, especially given the rapid habituation of the SNS and PNS. Therefore, RSA and PEP during the counting task and instructions were included in models but were not of primary interest. All variables are described in Table S1.

First, changes in RSA and PEP for the entire sample were modeled across the task (Eq. 1). Task minute and segment were included in descriptive models, with random effects for minute at Level 1 and each segment (i.e., baseline, preparation, speech, math, and debriefing) at Level 2. Each minute of the segment was coded at Level 1 (i.e., the first minute of a segment would be coded as 0) to account for habituation of physiological responses within a segment. Each segment was dummy-coded at Level 2, with baseline as the reference group. Sex (dummy-coded; 0=male, 1=female), poverty status (dummy-coded; 0=below poverty line, 1=above poverty line), and grade at either age 14 for concurrent models (centered at 8th grade) or age 16 for prospective models (centered at 10th grade) were included as control variables at Level 3 in this and all subsequent models (variable coding is summarized in Table S1).

$$
\begin{aligned}
&L1: \widehat{RSA}_{tij} \;\; or \;\; \widehat{PEP}_{tij} = \pi_{0ij} + \pi_{1ij}(Minute)\\
&L2: \;\; \pi_{0ij} = \beta_{00j} + \beta_{01j}(Task \;\; Preparation) + \beta_{02j}(Speech) + \beta_{03j}(Math) + \beta_{04j}(Debrief) + \beta_{05j}\\
&(Counting \;\; Task) + \beta_{06j}(Instructions)\\
&\pi_{1ij} = \beta_{10j}\\
&L3: \;\; \beta_{00j} = \gamma_{000} + \gamma_{001}(Sex) + \gamma_{002}(Poverty \;\; Status) + \gamma_{003}(Grade) + u_{00j}\\
&\beta_{01j} = \gamma_{010} + u_{01j}\\
&\beta_{02j} = \gamma_{020} + u_{02j}\\
&\beta_{03j} = \gamma_{030} + u_{03j}\\
&\beta_{04j} = \gamma_{040} + u_{04j}\\
&\beta_{05j} = \gamma_{050} + u_{05j}\\
&\beta_{06j} = \gamma_{060} + u_{06j}\\
&\beta_{10j} = \gamma_{100} + u_{10j}
\end{aligned}
$$

Equation 1

Next, models examined whether substance use count by age 16 related to adolescents' ANS responses to the task at age 14 among participants who had never used substances (i.e., substance use count = 0 at age 14), so that we could test whether ANS responses related to initiation of substance use over two years. Models predicted RSA and PEP from the task segments, adolescents’ substance use count, and interaction terms between the dummy-coded task segments and the number of substances each adolescent had ever used in order to identify whether changes in RSA and PEP across task segments varied by adolescents’ substance use count. These models do not make assumptions about the distributions of predictor variables, such that having substance use as a count variable does not invalidate model assumptions. Although stress responses may theoretically influence substance use count, we consistently modeled substance use count as the predictor and stress responses as the outcome because of the structure of the data (i.e., RSA and PEP values summarized at the level of minutes nested within participants, and substance use count at the level of participants), as has been done in previous research (e.g., Shirtcliff & Essex, 2008). In contrast to other approaches, this statistical technique enabled all minutes of the stress response to be modeled and for assessment of whether the stress response at age 14 systematically differed by adolescents’ substance use count. Contrasts between all task segments enabled assessments of changes from baseline to social-evaluative stress (i.e., speech and math tasks) versus nonsocial stress (i.e., task preparation), such that we could differentiate the type of stressor from the autonomic response. By testing all contrasts within the same model, models accounted for unique associations between each task segment with substance use and accounted for error across all contrasts.

We also conducted models in which segments were dummy-coded with task preparation as the reference group to represent non-evaluative stress. With this coding, the baseline and debriefing coefficients represented the difference between non-stressful segments (i.e., baseline and debriefing) and nonsocial evaluative stress (i.e., task preparation). The speech and math coefficients represented the difference between social-evaluative stress and non-evaluative stress and therefore reflect the unique effect of social-evaluation on the stress response.

Cross-level interactions between adolescents’ substance use count at age 16 at Level 3 and segments at Level 2 tested whether changes in RSA and PEP across the task varied by number of substances used (Eq. 2). Significant interactions between task segments and lifetime substance use count were probed at different levels of substance use count (i.e., 0, 1, 2, 3, or 4 substances used).

$$
\begin{aligned}
&L1: \quad \widehat{RSA}_{tij} \quad or \quad \widehat{PEP}_{tij} = \pi_{0ij} + \pi_{1ij}(Minute) \\
&L2: \quad \pi_{0ij} = \beta_{00j} + \beta_{01j}(Task \quad Preparation) + \beta_{02j}(Speech) + \beta_{03j}(Math) + \beta_{04j}(Debrief) + \beta_{05j} \\
&(Counting \quad Task) + \beta_{06j}(Instructions) \\
&\pi_{1ij} = \beta_{10j} \\
&L3: \quad \beta_{00j} = \gamma_{000} + \gamma_{001}(Sex) + \gamma_{002}(Poverty \quad Status) + \gamma_{003}(Grade) + \gamma_{004}(Substance \quad Use) + u_{00j} \\
&\beta_{01j} = \gamma_{010} + \gamma_{011}(Substance \quad Use \quad Count) + u_{01j} \\
&\beta_{02j} = \gamma_{020} + \gamma_{021}(Substance \quad Use \quad Count) + u_{02j} \\
&\beta_{03j} = \gamma_{030} + \gamma_{031}(Substance \quad Use \quad Count) + u_{03j} \\
&\beta_{04j} = \gamma_{040} + \gamma_{041}(Substance \quad Use \quad Count) + u_{04j} \\
&\beta_{05j} = \gamma_{030} + u_{03j} \\
&\beta_{06j} = \gamma_{040} + u_{04j} \\
&\beta_{10j} = \gamma_{100} + u_{10j}
\end{aligned}
$$

Equation 2

Next, models were conducted to examine whether coordination between RSA and PEP at age 14 differed by adolescents' substance use count by age 16. The ANS profile of reciprocal SNS activation and PNS withdrawal—generally considered a classic response to stress—is characterized by low RSA and PEP values (i.e., reduced PNS and increased SNS activity, respectively). To determine the specific profiles of ANS activity involved, we calculated CAB (i.e., level of reciprocal activation) and CAR (i.e., level of coactivation) as defined by Berntson and colleagues (1997, 2008). Minute-by-minute RSA and PEP values were *z*-transformed within each individual. CAB was calculated as the difference between RSA and PEP and indicated the degree of reciprocal activation, with more positive values suggesting greater PNS dominance and more negative values suggesting greater SNS dominance. In turn, CAR was calculated as the sum of RSA and PEP and indicated the degree of coactivation, with more positive values suggesting coactivation and more negative values suggesting coinhibition. Three-level multilevel models examined whether interactions between substance use count at age 16 and task segments predicted CAB and CAR (Eq. 3). Significant interactions would suggest that the profile of ANS responses during that task segment varied with the number of substances adolescents had ever used by age 16. Baseline was consistently used as the reference group, such that coefficients indicate the degree to which CAB and CAR values change from baseline to each task segment.

$$
\begin{aligned}
&L1:\ \widehat{RSA+PEP}_{tij}\ \ or\ \ \widehat{RSA-PEP}_{tij} = \pi_{0ij} + \pi_{1ij}(Minute)\\
&L2:\ \pi_{0ij} = \beta_{00j} + \beta_{01j}(Task\ \ Preparation) + \beta_{02j}(Speech) + \beta_{03j}(Math) + \beta_{04j}(Debrief) + \beta_{05j}\\
&(Counting\ \ Task) + \beta_{06j}(Instructions)\\
&\pi_{0ij} = \beta_{10j}\\
&L3:\ \beta_{00j} = \gamma_{000} + \gamma_{001}(Sex) + \gamma_{002}(Poverty\ \ Status) + \gamma_{003}(Grade) + \gamma_{004}(Substance\ \ Use\ \ Count) + u_{00j}\\
&\beta_{01j} = \gamma_{010} + \gamma_{011}(Substance\ \ Use\ \ Count) + u_{01j}\\
&\beta_{02j} = \gamma_{020} + \gamma_{021}(Substance\ \ Use\ \ Count) + u_{02j}\\
&\beta_{03j} = \gamma_{030} + \gamma_{031}(Substance\ \ Use\ \ Count) + u_{03j}\\
&\beta_{04j} = \gamma_{040} + \gamma_{041}(Substance\ \ Use\ \ Count) + u_{04j}\\
&\beta_{05j} = \gamma_{030} + u_{03j}\\
&\beta_{06j} = \gamma_{040} + u_{04j}\\
&\beta_{10j} = \gamma_{100} + u_{10j}
\end{aligned}
$$

Equation 3

Finally, we repeated analyses to determine whether associations between ANS responses and substance use count were also apparent in youth who had used substances by age 14. An identical pattern of results emerged when testing models in the full sample first and then testing interactions for differences by whether youth had used substances by age 14. First, we included use by age 14 (0 = no substances by age 14, 1 = at least one substance by age 14) as a moderator of associations between substance use count at 16 and RSA, PEP, CAR, and CAB responses in order to determine whether associations differed between adolescents who had and had not used by age 14. If interactions were significant, associations between substance use count by age 16 and RSA, PEP, CAR, and CAB reactivity were tested for youth who had used substances by age 14. Significant interactions between task segments and substance use count were again probed at different levels of substance use count (i.e., 0, 1, 2, 3, or 4 substances used).

Results

The majority of adolescents (72.1%) did not use substances by age 14, although 15.2% reported using one substance, 9.4% reported using two substances, and 3.3% reporting using all three substances at some point in their lifetime by age 14. Lifetime use of alcohol, marijuana, and cigarettes increased by age 16, $t(219) = 6.89$, $p < .001$. At age 16, 46.3% of youth had never used alcohol, marijuana, or cigarettes and had never vaped nicotine, and 19.1%, 15. 5%, 14.2% and 4.9% reported using one, two, three, and all four substances, respectively, by age 16.

RSA and PEP Responses to Stress

First, multilevel models were used to model RSA and PEP responses to the different segments of the TSST (i.e., baseline, task preparation, speech, math, debriefing; Fig. 2; Table S2). As expected, participants' RSA was highest at baseline. Youth showed vagal withdrawal, such that RSA was relatively lower during task preparation, $B = -0.99$, $SE = 0.05$, $p < .001$, the speech task, $B = -0.70$, $SE = 0.05$ $p < .001$, and the math task, $B = -0.99$, $SE = 0.05$ $p < .001$. RSA increased during debriefing, although it was still lower than at baseline, $B = -0.27$, $SE = 0.05$, $p < .001$. Participants showed lower PEP from baseline to task preparation, $B = -0.85$, $SE = 0.38$, $p = .025$, and from baseline to the speech task, $B = -1.24$, $SE = 0.42$, $p = .003$. PEP during the math task did not differ from baseline, $B = -0.28$, $SE = 0.44$, $p = .5$, and participants showed higher PEP during debriefing than at baseline, $B = 1.16$, $SE = 0.43$, $p = .007$.

Responses for adolescents who had and had not used substances by age 14 are presented in in Figure S1. Using data from the entire sample, we tested whether PNS and SNS reactivity were related cross-sectionally to substance use at age 14, with substance use assessed as both a continuous count variable and as a dichotomous variable (i.e., used versus never used by age 14). Results suggested that SNS reactivity was not related to concurrent substance use, all ps > .05. However, use of substances by age 14 was related to PNS responses to the math task ($B = 0.19$, $SE = 0.09$, $p = .039$). Although on average adolescents showed significant declines in PNS activity from baseline to the math task (i.e., vagal withdrawal), youth who had never used substances by age 14 ($B = -1.06$, $SE = 0.05$, $p < .001$) showed a significantly larger degree of vagal withdrawal during the math task relative to youth who had used substances by age 14 ($B = -0.88$, $SE = 0.08$, $p < .001$). See full results in Supplemental Tables S3-S4.

RSA and PEP Responses to Stress and Initiation of Substance Use by Age 16

Models then tested differences in RSA and PEP responses at age 14 by adolescents' substance use count by age 16 by including interactions between task segments and substance use count (Table S5-S6). Models initially tested associations between ANS responses to social-evaluative stress at age 14 and substance use initiation at age 16 among youth who had never used by age 14, the primary subsample of interest. Among youth who had never used a substance by age 14, models indicated that greater declines in RSA (i.e., vagal withdrawal) from baseline to task preparation at age 14 were associated with greater substance use count at age 16, $B = -0.10$, $SE = 0.05$, $p = .049$. Specifically, although all youth showed a significant decline in RSA, this decline was smaller for youth who used no substance by age 16, *B* = −0.91, *SE* = 0.07, $p < .001$, relative to youth who went on to use all four substances by age 16, *B* = −1.32, *SE* = 0.18, $p < .001$ (Fig. 3).

RSA and PEP responses to the speech and math portions (i.e., the social-evaluative components) of the TSST at age 14 were also associated with adolescents' substance use count by age 16 among youth who had never used a substance by age 14. Youth who showed greater increases in RSA (i.e., dampened vagal withdrawal) from task preparation to both the speech task and the math task used significantly more substances by age 16, *B* = 0.14, *SE* = 0.04, $p = .001$ for speech, *B* = 0.14, *SE* = 0.04, $p = .002$ for math (Fig. 3). Although participants generally showed increases in RSA from task preparation to the speech task, this increase was smaller for youth who used no substance by age 16, *B* = 0.19, *SE* = 0.06, $p = .001$, than for youth who used four substances by age 16, *B* = 0.76, *SE* = 0.15, $p < .001$. In turn, youth who used no substance by age 16 showed significant declines in RSA from task preparation to the math task, *B* = −0.16, *SE* = 0.06, $p = .007$, whereas youth who initiated use of one or two substances showed no significant change in RSA, *p*s = .777 and .107, and youth who initiated use of three or four substances showed increases in RSA from task preparation to the math task, *B* = 0.27, *SE* = 0.12, $p = .020$ for three substances, *B* = 0.41, *SE* = 0.16, $p = .009$ for four substances. Changes in RSA between baseline and debriefing were not associated with substance use count at age 16, *p*s > .1.

Changes in PEP from baseline to the speech task, *B* = 1.42, *SE* = 0.41, $p < .001$, and the math task, *B* = 1.58, *SE* = 0.46, $p = .001$, were associated with substance use by age 16 (Fig. 4a). Specifically, an increase in SNS activity (lower PEP) from baseline to the speech task was observed for youth who abstained from substance use by age 16, *B* = −1.80, *SE* = 0.55, $p = .001$. In contrast, no significant change in SNS activity was observed for 14 year olds who initiated use of one or two substances by age 14, *p*s = .444 and .150, and a significant decrease in SNS activity (i.e., increase in PEP) was observed for youth who initiated three or four substances; *B* = 2.46, *SE* = 1.06, $p = .020$ for three, *B* = 3.88, *SE* = 1.44, $p = .007$ for four. Regarding changes from baseline to the math task, a significant increase in SNS activity was observed for youth who used no substances by age 16, *B* = 1.40, *SE* = 0.61, $p = .021$, no change in SNS activity was observed for youth who used one substance by age 16, $p = .744$, and decreases in SNS activity were associated with initiation of two, three, or four substances; *B* = 1.76, *SE* = 0.80, $p = .029$ for two, *B* = 3.34, *SE* = 1.19, $p = .005$ for three, *B* = 4.92, *SE* = 1.62, $p = .002$ for four substances. Neither changes in RSA between baseline and task preparation nor between task preparation and debriefing were associated with substance use count at age 16, *p*s > .07.

Profiles of RSA and PEP Responses to Stress and Initiation of Substance Use

To identify the specific profiles that may contribute to this association, models tested whether CAB and CAR—indicators of the degree of reciprocity and coactivation, respectively— throughout the task were related to substance use count. As before, three-level models predicted CAB and CAR from interactions between task segments and substance use count by ages 14 and 16. Substance use count by age 14 was not related to either CAB or CAR (Tables S7-S8). Models also tested differences in CAB and CAR between youth who had used substances and youth who had never used substances by age 14, and use by age 14 was related to differences in CAB during task preparation; $B = -0.43$, $SE = 0.17$, $p = .011$. Although youth on average showed a significant decline in CAB (i.e., greater reciprocal SNS activation) from baseline to task preparation, youth who had used substances by age 14 ($B = -1.67$, $SE = 0.16$, $p < .001$) had significantly lower CAB at task preparation compared to youth who had not used by age 14 ($B = -1.25$, $SE = 0.11$, $p < .001$).

Changes in both CAB and CAR were related to substance use count by age 16 (Table S9). Blunted declines in CAB (i.e., reduced reciprocal sympathetic activation) from baseline to the speech task, $B = 0.35$, $SE = 0.09$, $p < .001$, and from baseline to the math task, $B = 0.37$, $SE = 0.10$, $p < .001$, were related to substance use count. Specifically, greater declines in CAB from baseline to the speech task, $B = -1.10$, $SE = 0.12$, $p < .001$, and from baseline to the math task, $B = -1.40$, $SE = 0.13$, $p < .001$, were associated with abstaining from substance use by age 16, whereas no significant changes in CAB were associated with use of three or four substances between ages 14 and 16, *p*s = .227 and .851. Changes in CAB reflect the degree of reciprocal SNS dominance, or the degree to which greater SNS activity is accompanied by PNS withdrawal. Therefore, this result suggested that greater reciprocal SNS activation during the math task at age 14 was associated with abstaining from substances by age 16, and a lower degree of reciprocal SNS activation during the math task was associated with use of more substances by age 16 (Fig. S2).

We also found that greater declines in CAR (i.e., greater coinhibition) from baseline to task preparation, $B = -0.29$, $SE = 0.10$, $p = .004$, from baseline to the speech task, $B = -0.22$, $SE = 0.09$, $p = .020$, and from baseline to the math task, $B = -0.21$, $SE = 0.10$, $p = .028$, were related to greater substance use count by age 16. Probing of simple slopes indicated that smaller declines in CAR from baseline to task preparation, the speech task, and the math task were associated with abstaining from substance use by age 16, and larger declines in CAR were associated with initiation of four substances between ages 14 and 16. More negative values of CAR reflect coinhibition, or lower overall SNS and PNS activity, such that greater coinhibition during stress was related to use of more substances by age 16 (Fig. S3).

RSA and PEP Responses to Stress and Escalation of Substance Use between Ages 14 and 16

Finally, moderation models tested whether the strength of associations differed between youth who had and had not previously used substances by age 14. If there was a significant degree of moderation, simple slopes were tested among youth who had used substances by age 14. We tested whether associations between substance use count at age 16 and ANS responses differed by adolescents' use of substances by age 14 by including a three-way Substance Use Count by 16 × Segment × Ever Used by 14 interaction. There were no differences in associations for RSA, all *p*s > .15. Rather, the three-way interactions indicated significant differences in associations between substance use count by 16 and PEP during the speech task, $B = -2.21$, $SE = 0.84$, $p = .008$, and the math task, $B = -2.52$, $SE = 0.98$, $p = .008$. We probed simple slopes to examine associations between PEP responses and substance use by 16 among adolescents who had used substances by age 14. Whereas decreased SNS reactivity (i.e., blunted declines in PEP) from baseline to the speech and math tasks were related to greater substance use count by age 16 for youth who had never used substances by age 14, results suggested that greater SNS reactivity (i.e., greater declines in PEP) from baseline to the speech task, $B = -1.16$, $SE = 0.51$, $p = .022$, and math task, $B = -1.30$, $SE = 0.55$, $p = .018$, were related to greater substance use count by age 16 among adolescents who had used substances by age 14 (Fig. 4b).

Results also indicated differences in the degree to which substance use by age 16 was related to changes in CAB from baseline to the speech task, $B = -0.51$, $SE = 0.15$, $p = .001$, and to the math task, $B = -0.60$, $SE = 0.16$, $p < .001$, as well as to changes in CAR from baseline to the speech task, $B = 0.34$, $SE = 0.16$, $p = .033$, and to the math task, $B = 0.35$, $SE = 0.16$, $p = .031$. Although greater declines in CAB and blunted declines in CAR were related to substance use for youth who had not initiated use of substances by age 14, probing of simple slopes indicated that neither changes in CAB nor CAB from baseline to the speech and math tasks were related to substance use among youth who used substances by age 14, all *p*s > .20.

Discussion

The present study investigated whether dysregulation of ANS responses to social-evaluative stress at age 14 were related to substance use count at age 16. Previous work has found that dampened and anticipatory cortisol responses precede substance use initiation among adolescents (e.g., Evans et al., 2016; Moss et al., 1999), but few studies have empirically tested temporal associations between ANS responses and substance use outcomes. Results suggested that dampened SNS and PNS reactivity to social-evaluative threat at age 14, and both lower reciprocity between the SNS and PNS and greater coinhibition (i.e., lower activity in both systems) were associated with initiation of use of more substances by age 16 among youth who have never used by age 14. Peer interactions can be stressful, particularly when substances are involved, and adolescents with dampened ANS responses to social-evaluative stress and profiles of greater coinhibition and reduced reciprocal SNS activation and PNS withdrawal may be at higher risk for initiating substance use in these circumstances. Interestingly, greater PEP reactivity was also related to greater substance use between ages 14 and 16 among youth who had used substances by age 14.

Dampened PNS responses and SNS responses at age 14 were related to initiation of substance use by age 16 among youth who had not used by age 14. Similarly, youth who used substances by age 14 showed attenuated PNS reactivity to the math task. Findings align with prior work suggesting that blunted SNS and PNS reactivity is related to poorer mental health including greater depressive symptoms, internalizing problems, and externalizing problems (Erath et al., 2009, 2011; Graziano & Derefinko, 2013; Hinnant et al., 2015; Hamilton & Alloy, 2016; Schwerdtfeger & Rosenkaimer, 2011; Yaroslavsky et al., 2016), which can confer substance use risk for Latino adolescents (Gonzales et al., 2017). It is possible that dampened PNS and SNS reactivity may indicate difficulties with stress regulation, which may be particularly important for youth in this sample who experienced high levels of adversity (Sagiv et al., 2015) as well as cultural stressors including discrimination and acculturation (Stein et al., 2012). Youth with these responses may be at heightened risk for using substances to cope with stress (e.g., academic, interpersonal, cultural), or to conform in socially-evaluative circumstances (e.g., social gatherings, parties).

Seemingly at odds with our results that attenuated RSA reactivity to the social-evaluative components of the task were related to use of more substances, greater (rather than attenuated) declines in RSA from baseline to task preparation were associated with use of more substances by age 16. This finding highlights the importance of social-evaluative versus nonsocial stress during adolescence. Adolescents are more responsive to social than nonsocial stressors due to neurobiological changes during this period (Forbes & Dahl, 2010). Peer pressure is one social stressor which confers risk for substance use. It is possible that youth who are more responsive to nonsocial threats may be more motivated to use substances to cope, whereas those who are less responsive to social threats may be more susceptible to following deviant peers and conforming to peer pressure. This finding also is particularly important for reconciling discrepancies in results across studies given that other studies may use nonsocial stressors, which may result in a different pattern of results.

Given that adolescents show heightened sensitivity to peer influence and social status concerns (Blakemore, 2008), it is possible that ANS responses to social-evaluative stress may influence adolescent substance use through peer processes. For example, Latino adolescents with higher family risk (e.g., poorer family relationship quality and conflict) reported associating with more deviant peers, which in turn predicted substance use and risky behavior over time (Gonzales et al., 2017). A previous study found that the consequences of associating with deviant peers on adolescents' own substance use may differ by physiological vulnerability, as adolescents who engaged with deviant peers showed greater substance use if they also showed blunted SNS responses to challenge (Hinnant et al., 2016). Adolescents tend to show heightened reward-sensitivity and to engage in greater risk-taking when being evaluated by peers, such that peers can greatly impact adolescents' inclination to use substances (Chein et al., 2011). Interactions with deviant peers may be stressful for youth (i.e., pressure to conform), and dampened ANS responses to social-evaluative stress may impair adolescents' recruitment of neural regions involved in cognition and decision-making (Weissman et al., 2018). Inability to respond to these situations may heighten adolescents' risk for succumbing to peer influence and initiating substance use, as adolescents who are more easily influenced by peers show greater substance use (Allen et al., 2006).

Adolescents who had ever used more substances by age 16 also showed greater coinhibition and lower reciprocal SNS activation during the speech and math tasks. In line with previous research suggesting that blunted ANS responses are related to poorer mental health (Graziano & Derefinko, 2013), blunted cardiovascular responses have been posited to indicate unconscious disengagement from a stressor such that individuals are less responsive to their social environment (e.g., Carroll et al., 2017). In contrast, adolescents with a greater degree of reciprocal SNS activation may have been more alert to the math task and attentive to the confederates' cues and thereby been better able to emotionally regulate during social-evaluative stress. Indeed, greater reciprocal sympathetic activation following stress has been found to buffer the negative impacts of conflict on mental health, particularly internalizing and externalizing problems (e.g., Gordis et al., 2010; McKernan & Lucas-Thompson, 2018). Lower reciprocal activation may also indicate impaired ability to regulate social-evaluative stress and therefore greater substance use risk. Importantly, synchrony between the SNS and PNS responses to social-evaluative stress may change throughout development and during adolescence specifically (Gatzke-Kopp & Ram, 2018). Further work should examine stability of SNS-PNS synchrony during adolescence and whether reciprocal ANS responses are similarly relate throughout early and late adolescence.

Interestingly, analyses indicated that youth who had used a substance by age 14 showed a greater degree of reciprocal SNS dominance during task preparation relative to youth who had not used substances by age 14, and that profiles of ANS responses at age 14 were not related to substance use count by age 16 among youth who had used a substance by age 14. Further, whereas dampened SNS responses were related to greater substance use count among youth who had not initiated use by 14, the opposite pattern was observed such that greater SNS reactivity was related to higher substance use count by age 16 among youth who had used a substance by age 14. These results highlight how a combination of biological and environmental factors can influence psychological outcomes, supporting the differential susceptibility hypothesis (Belsky, 2016); greater SNS reactivity may not be uniformly associated with substance use for all youth, but may be protective for some youth and a risk factor for substance use for others.

Differences in associations between SNS reactivity to social-evaluative stress and substance use by age 14 may emerge for multiple reasons. First, prior research has consistently highlighted the importance of substance use by age 14 as a risk factor for problems with substance use in adulthood (e.g., DeWit et al., 2000; Strunin et al., 2017). Alcohol, nicotine, and cannabis use are highly correlated early in adolescence such that users tend to use multiple substances and non-users tend to fully abstain, and these correlations weaken later in adolescence (Kendler et al., 2008). Therefore, youth who use by age 14 may constitute a high-risk population relative to youth who have not used by age 14, and earlier use may position these youth for trajectories of more frequent or poly-substance use irrespective of physiological responses during stressful conditions. Indeed, earlier use of alcohol, tobacco, and cannabis are associated with greater initial frequency of use of other substances (Richmond-Rakerd et al., 2017), and youth who initiate use at an earlier age tend to use substances alone and engage in riskier use whereas late initiators tend to use at social gatherings (Kingston et al., 2017). Although dampened reactivity is often a risk factor for poorer mental health, exaggerated SNS reactivity has been previously found in adolescents who experience clinical trauma relative to healthy controls (Schuurmans et al., 2021), and it is possible that exaggerated reactivity may be observed for at-risk youth.

Second, youth who use by age 14 may differ from those who abstain with respect to their access to substances and their motivation for subsequent substance use. Use of one substance by age 14 may relate to use of other substances because of social and familial environmental factors that increase risk of substance use broadly (Kendler et al., 2008). Youth who use a substance by age 14 may live in a community with increased substance use exposure or may befriend deviant peers who are also using at a younger age and thereby develop greater access to and dependence on substances relative to youth who do not use by age 14. Regarding substance use motivation, it has been posited that blunted reactivity may indicate lower sensitivity to social-evaluative stress and thus greater risk for using substances to promote positive emotion or sociability (Chaplin et al., 2018). In contrast, greater SNS reactivity may suggest greater sensitivity to social-evaluative stress and may reflect greater risk for using substances to cope with negative emotion or conforming to peer pressure.

Given that ANS responses to social-evaluative stress may precede substance use, ANS activity may be targeted in interventions for reducing substance use. ANS activity has been posited to play a role in substance use treatment given its ties to neural regions involved in emotional regulation and processing (Eddie et al., 2015). For instance, in adults recovering from substance use disorders, daily heart rate variability biofeedback was related to reduced cravings for alcohol (Eddie et al., 2014). Examining profiles of SNS and PNS responses or addressing biofeedback in the context of stressful situations may help to develop effective treatment for adolescent substance users.

Findings must be interpreted within the context of the study design. The sample was limited to CHAMACOS participants who remained in the Salinas Valley at age 14 and therefore could complete the TSST in our field office. Another limitation of the present study was the low variability in substance use frequency, therefore substance use count was included but not substance use frequency. Although study results provide temporal precedence for the association between ANS responses and substance use, further research is needed to determine whether ANS responses to social-evaluative stress are causally related to substance use risk. It is possible that both dampened ANS responses and substance use risk may emerge due to aspects of adolescents' home environments, such as adversity (e.g., Dube et al., 2003; McLaughlin et al., 2014). The majority of youth lived in poverty and experienced high levels of adversity (described in Sagiv et al., 2015), which are risk factors for earlier substance use initiation and psychopathology (e.g., Dube et al., 2003; Johnston et al., 2019). As a result, ANS responses to social-evaluative stress may not be related to substance use among other populations of youth who experience lower levels of adversity. In turn, other pathways, such as using substances to increase positive emotion, may be more prevalent among other populations of youth. Also, although the analytic strategy has been previously used (e.g., Shirtcliff & Essex, 2008), this method has limitations including temporal inconsistency (i.e., analytically predicting ANS responses at age 14 from substance use at age 16). These models are still able to test associations between variables but do not necessarily allow for causal inference. Finally, the present study assessed responses to social-evaluative stress which may differ from responses to nonsocial stress (e.g., cold presser, startling film clips), and future studies should assess whether SNS and PNS responses to nonsocial stressors similarly relate to the emergence of substance use during adolescence.

Conclusions

Substance use greatly increases during adolescence, and use of multiple substances has been related to greater risk of substance use disorders in adulthood (Latimer & Zur, 2010; Zapert et al., 2002). The longitudinal design of this study in high-risk youth enabled us to identify that adolescents with dampened PNS and SNS responses, as well as profiles of coinhibition and lower reciprocal SNS activation, to social-evaluative stress at age 14 initiated use of more substances by age 16, among youth who never used substances previously. These physiological responses may suggest difficulties in emotion regulation following social-evaluative stress. Among youth who had used substances by age 14, exaggerated SNS reactivity to social-evaluative stress was related to greater substance use by age 16. Further research is needed to examine how ANS responses to stress impart risk for substance use during adolescence, whether these responses relate to substance use by influencing peer processes and susceptibility to peer pressure, and the potential utility of targeting ANS responses in substance use treatments (e.g., biofeedback).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

Alexander JK, Hillier A, Smith RM, Tivarus ME, & Beversdorf DQ (2007). Beta-adrenergic modulation of cognitive flexibility during stress. Journal of Cognitive Neuroscience, 19(3), 468–478. 10.1162/jocn.2007.19.3.468 [PubMed: 17335395]

Allen JP, Porter MR, & McFarland FC (2006). Leaders and followers in adolescent close friendships: Susceptibility to peer influence as a predictor of risky behavior, friendship instability, and depression. Development & Psychopathology, 18(1), 155. 10.1017/S0954579406060093 [PubMed: 16478557]

Beauchaine TP (2015). Respiratory sinus arrhythmia: A transdiagnostic biomarker of emotion dysregulation and psychopathology. Current Opinion in Psychology, 3, 43–47. 10.1016/j.copsyc.2015.01.017 [PubMed: 25866835]

Belsky J (2016). The differential susceptibility hypothesis: sensitivity to the environment for better and for worse. JAMA pediatrics, 170(4), 321–322. 10.1001/jamapediatrics.2015.4263 [PubMed: 26831915]

Berntson GG, Cacioppo JT, Quigley KS, & Fabro VT (1994). Autonomic space and psychophysiological response. Psychophysiology, 31(1), 44–61. 10.1111/j.1469-8986.1994.tb01024.x [PubMed: 8146254]

Berntson GG, Norman GJ, Hawkley LC, & Cacioppo JT (2008). Cardiac autonomic balance versus cardiac regulatory capacity. Psychophysiology, 45(4), 643–652. 10.1111/j.1469-8986.2008.00652.x [PubMed: 18282204]

Berntson GG, Quigley KS, Jang JF, & Boysen ST (1990). An approach to artifact identification: Application to heart period data. Psychophysiology, 27(5), 586–598. 10.1111/j.1469-8986.1990.tb01982.x [PubMed: 2274622]

Berntson GG, Thomas Bigger J Jr., Eckberg DL, Grossman P, Kaufmann PG, Malik M, … & van der Molen MW (1997). Heart rate variability: Origins, methods, and interpretive caveats. Psychophysiology, 34(6), 623–648. [PubMed: 9401419]

Bibbey A, Ginty AT, Brindle RC, Phillips AC, & Carroll D (2016). Blunted cardiac stress reactors exhibit relatively high levels of behavioural impulsivity. Physiology & Behavior, 159, 40–44. 10.1016/j.physbeh.2016.03.011 [PubMed: 26988282]

Blakemore SJ (2008). The social brain in adolescence. Nature Reviews Neuroscience, 9(4), 267–277. 10.1038/nrn2353 [PubMed: 18354399]

Boyce WT, Quas J, Alkon A, Smider NA, Essex MJ, & Kupfer DJ (2001). Autonomic reactivity and psychopathology in middle childhood. British Journal of Psychiatry, 179(2), 144–150. 10.1192/bjp.179.2.144

Brenner S, & Beauchaine T (2011). Pre-ejection period reactivity and psychiatric comorbidity prospectively predict substance use initiation among middle-schoolers: A pilot study. Psychophysiology, 48(11), 1588–1596. 10.1111/j.1469-8986.2011.01230.x [PubMed: 21729103]

Carroll D, Ginty AT, Whittaker AC, Lovallo WR, & De Rooij SR (2017). The behavioural, cognitive, and neural corollaries of blunted cardiovascular and cortisol reactions to acute psychological stress. Neuroscience & Biobehavioral Reviews, 77, 74–86. 10.1016/j.neubiorev.2017.02.025 [PubMed: 28254428]

Chaplin TM, Niehaus C, & Gonçalves SF (2018). Stress reactivity and the developmental psychopathology of adolescent substance use. Neurobiology of Stress, 9, 133–139. 10.1016/j.ynstr.2018.09.002 [PubMed: 30450379]

Chein J, Albert D, O'Brien L, Uckert K, & Steinberg L (2011). Peers increase adolescent risk taking by enhancing activity in the brain's reward circuitry. Developmental Science, 14(2), F1–F11. 10.1111/j.1467-7687.2010.01035.x [PubMed: 21499511]

Delva J, Wallace JM Jr., O'Malley PM, Bachman JG, Johnston LD, & Schulenberg JE (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. 10.2105/AJPH.2003.037051 [PubMed: 15798132]

DeWit DJ, Adlaf EM, Offord DR, & Ogborne AC (2000). Age at first alcohol use: a risk factor for the development of alcohol disorders. American Journal of Psychiatry, 157(5), 745–750. 10.1176/appi.ajp.157.5.745 [PubMed: 10784467]

Dube SR, Felitti VJ, Dong M, Chapman DP, Giles WH, & Anda RF (2003). Childhood abuse, neglect, and household dysfunction and the risk of illicit drug use: the adverse childhood experiences study. Pediatrics, 111(3), 564–572. [PubMed: 12612237]

Eddie D, Kim C, Lehrer P, Deneke E, & Bates ME (2014). A pilot study of brief heart rate variability biofeedback to reduce craving in young adult men receiving inpatient treatment for substance use disorders. Applied Psychophysiology & Biofeedback, 39(3–4), 181–192. 10.1007/s10484-014-9251-z [PubMed: 25179673]

Eddie D, Vaschillo E, Vaschillo B, & Lehrer P (2015). Heart rate variability biofeedback: Theoretical basis, delivery, and its potential for the treatment of substance use disorders. Addiction Research & Theory, 23(4), 266–272. 10.3109/16066359.2015.1011625 [PubMed: 28077937]

El-Sheikh M, & Erath SA (2011). Family conflict, autonomic nervous system functioning, and child adaptation: State of the science and future directions. Development & Psychopathology, 23(2), 703–721. 10.1017/S0954579411000034 [PubMed: 23786705]

Erath SA, El-Sheikh M, & Mark Cummings E (2009). Harsh parenting and child externalizing behavior: Skin conductance level reactivity as a moderator. Child Development, 80(2), 578–592. 10.1111/j.1467-8624.2009.01280.x [PubMed: 19467012]

Erath SA, El-Sheikh M, Hinnant JB, & Cummings EM (2011). Skin conductance level reactivity moderates the association between harsh parenting and growth in child externalizing behavior. Developmental Psychology, 47(3), 693–706. 10.1037/a0021909 [PubMed: 21142369]

Eskenazi B, Bradman A, Gladstone EA, 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. 10.3109/713610244

Evans BE, Greaves-Lord K, Euser AS, Thissen S, Tulen JHM, Franken IHA, & Huizink AC (2016). Stress reactivity as a prospective predictor of risky substance use during adolescence. Journal of Studies on Alcohol and Drugs, 77(2), 208–219. 10.15288/jsad.2016.77.208 [PubMed: 26997179]

Forbes EE, & Dahl RE (2010). Pubertal development and behavior: hormonal activation of social and motivational tendencies. Brain & Cognition, 72(1), 66–72. 10.1016/j.bandc.2009.10.007 [PubMed: 19942334]

Fung MT, Raine A, Loeber R, Lynam DR, Steinhauer SR, & Stouthamer-Loeber M (2005). Reduced electrodermal activity in psychopathy-prone adolescents. Journal of Abnormal Psychology, 114(2), 187–196. 10.1037/0021-843X.114.2.187 [PubMed: 15869350]

Gatzke-Kopp L, & Ram N (2018). Developmental dynamics of autonomic function in childhood. Psychophysiology, 55(11), e13218. 10.1111/psyp.13218 [PubMed: 30059155]

Gentzler AL, Santucci AK, Kovacs M, & Fox NA (2009). Respiratory sinus arrhythmia reactivity predicts emotion regulation and depressive symptoms in at-risk and control children. Biological Psychology, 82(2), 156–163. 10.1016/j.biopsycho.2009.07.002 [PubMed: 19596044]

Gonzales NA, Liu Y, Jensen M, Tein JY, White RM, & Deardorff J (2017). Externalizing and internalizing pathways to Mexican American adolescents’ risk taking. Development & Psychopathology, 29(4), 1371–1390. 10.1017/S0954579417000323 [PubMed: 28367763]

Gordis EB, Feres N, Olezeski CL, Rabkin AN, & Trickett PK (2010). Skin conductance reactivity and respiratory sinus arrhythmia among maltreated and comparison youth: Relations with aggressive behavior. Journal of Pediatric Psychology, 35(5), 547–558. 10.1093/jpepsy/jsp113 [PubMed: 19995866]

Grant JD, Scherrer JF, Lynskey MT, Lyons MJ, Eisen SA, Tsuang MT, … & Bucholz KK. (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. 10.1017/S0033291705006045 [PubMed: 16194286]

Graziano P, & Derefinko K (2013). Cardiac vagal control and children’s adaptive functioning. Biological psychology, 94(1), 22–37. 10.1016/j.biopsycho.2013.04.011 [PubMed: 23648264]

Hamilton JL, & Alloy LB (2016). Atypical reactivity of heart rate variability to stress and depression across development: Systematic review of the literature and directions for future research. Clinical Psychology Review, 50, 67–79. 10.1016/j.cpr.2016.09.003 [PubMed: 27697746]

Hingson RW, Heeren T, & Winter MR (2006). Age at drinking onset and alcohol dependence: age at onset, duration, and severity. Archives of Pediatrics & Adolescent Medicine, 160(7), 739–746. 10.1001/archpedi.160.7.739 [PubMed: 16818840]

Hinnant JB, Erath SA, & El-Sheikh M (2015). Harsh parenting, parasympathetic activity, and development of delinquency and substance use. Journal of Abnormal Psychology, 124(1), 137. 10.1037/abn0000026 [PubMed: 25688440]

Hinnant JB, Erath SA, Tu KM, & El-Sheikh M (2016). Permissive parenting, deviant peer affiliations, and delinquent behavior in adolescence: The moderating role of sympathetic nervous system reactivity. Journal of Abnormal Child Psychology, 44(6), 1071–1081. 10.1007/s10802-015-0114-8 [PubMed: 26667026]

Hinnant JB, Gillis BT, Erath SA, & El-Sheikh M (2021). Onset of substance use: Deviant peer, sex, and sympathetic nervous system predictors. Development & Psychopathology, 1–10. 10.1017/S0954579421000158

Hinnant JB, Philbrook LE, Erath SA, & El-Sheikh M (2018). Approaches to modeling the development of physiological stress responsivity. Psychophysiology, 55(5), e13027. 10.1111/psyp.13027 [PubMed: 29086432]

Hurlemann R, Walter H, Rehme AK, Kukolja J, Santoro SC, Schmidt C, … & Onur OA. (2010). Human amygdala reactivity is diminished by the β-noradrenergic antagonist propranolol. Psychological Medicine, 40(11), 1839–1848. 10.1017/S0033291709992376 [PubMed: 20102667]

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

Johnston LD, Miech RA, O’Malley PM, Bachman JG, Schulenberg JE, & Patrick ME (2019). Monitoring the Future national survey results on drug use, 1975–2018: Overview, key findings on adolescent drug use. Institute for Social Research 10.3998/2027.42/150621

Kann L, McManus T, Harris WA, Shanklin SL, Flint KH, Queen B, … & Lim C. (2018). Youth risk behavior surveillance—United States, 2017. MMWR Surveillance Summaries, 67(8), 1. 10.15585/mmwr.ss6708a1

Kelsey RM, & Guethlein W (1990). An evaluation of the ensemble averaged impedance cardiogram. Psychophysiology, 27(1), 24–33. 10.1111/j.1469-8986.1990.tb02173.x [PubMed: 2339185]

Kendler KS, Schmitt E, Aggen SH, & Prescott CA (2008). Genetic and environmental influences on alcohol, caffeine, cannabis, and nicotine use from early adolescence to middle adulthood. Archives of General Psychiatry, 65(6), 674–682. 10.1001/archpsyc.65.6.674 [PubMed: 18519825]

Kingston S, Rose M, Cohen-Serrins J, & Knight E (2017). A qualitative study of the context of child and adolescent substance use initiation and patterns of use in the first year for early and later initiators. PLoS one, 12(1), e0170794. 10.1371/journal.pone.0170794 [PubMed: 28122018]

Kirschbaum C, Pirke K-M, & Hellhammer DH (1993). The 'Trier Social Stress Test' – A tool for investigating psychobiological stress responses in a laboratory setting. Neuropsychobiology, 28(1–2), 76–81. 10.1159/000119004 [PubMed: 8255414]

Kuntsche E, Wicki M, Windlin B, Roberts C, Gabhainn SN, van der Sluijs W, … & Demetrovics Z. (2015). Drinking motives mediate cultural differences but not gender differences in adolescent alcohol use. Journal of Adolescent Health, 56(3), 323–329. 10.1016/j.jadohealth.2014.10.267

Latimer W, & Zur J (2010). Epidemiologic trends of adolescent use of alcohol, tobacco, and other drugs. Child & Adolescent Psychiatric Clinics, 19(3), 451–464. 10.1016/j.chc.2010.03.002

Lorber MF (2004). Psychophysiology of aggression, psychopathy, and conduct problems: A meta-analysis. Psychological Bulletin, 130(4), 531. 10.1037/0033-2909.130.4.531 [PubMed: 15250812]

McKernan CJ, & Lucas-Thompson RG (2018). Autonomic nervous system coordination moderates links of negative interparental conflict with adolescent externalizing behaviors. Developmental psychology, 54(9), 1697. 10.1037/dev0000498 [PubMed: 30148397]

McLaughlin KA, Alves S, & Sheridan MA (2014). Vagal regulation and internalizing psychopathology among adolescents exposed to childhood adversity. Developmental Psychobiology, 56(5), 1036–1051. 10.1002/dev.21187 [PubMed: 24338154]

Moss HB, Chen CM, & Yi HY (2014). Early adolescent patterns of alcohol, cigarettes, and marijuana polysubstance use and young adult substance use outcomes in a nationally representative sample. Drug & Alcohol Dependence, 136, 51–62. 10.1016/j.drugalcdep.2013.12.011 [PubMed: 24434016]

Moss HB, Vanyukov M, Yao JK, & Kirillova GP (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. 10.1016/S0006-3223(98)00216-9 [PubMed: 10349035]

Paunović K, Stojanov V, Jakovljević B, & Belojević G (2014). Thoracic bioelectrical impedance assessment of the hemodynamic reactions to recorded road-traffic noise in young adults. Environmental Research, 129, 52–58. 10.1016/j.envres.2014.01.001 [PubMed: 24529003]

Phillips AC, Ginty AT, & Hughes BM (2013). The other side of the coin: Blunted cardiovascular and cortisol reactivity are associated with negative health outcomes. International Journal of Psychophysiology, 90(1), 1–7. 10.1016/j.ijpsycho.2013.02.002 [PubMed: 23454029]

Porges SW (2007). The polyvagal perspective. Biological Psychology, 74(2), 116–143. 10.1016/j.biopsycho.2006.06.009 [PubMed: 17049418]

Quigley KM, & Moore GA (2018). Development of cardiac autonomic balance in infancy and early childhood: A possible pathway to mental and physical health outcomes. Developmental Review, 49, 41–61. 10.1016/j.dr.2018.06.004

Ramos BP, & Arnsten AF (2007). Adrenergic pharmacology and cognition: focus on the prefrontal cortex. Pharmacology & Therapeutics, 113(3), 523–536. 10.1016/j.pharmthera.2006.11.006 [PubMed: 17303246]

Richmond-Rakerd LS, Slutske WS, & Wood PK (2017). Age of initiation and substance use progression: A multivariate latent growth analysis. Psychology of Addictive Behaviors, 31(6), 664. 10.1037/adb0000304 [PubMed: 28805408]

Sagiv SK, Kogut K, Gaspar FW, Gunier RB, Harley KG, 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. 10.1016/j.ntt.2015.08.001 [PubMed: 26271888]

Salomon K, Matthews KA, & Allen MT (2000). Patterns of sympathetic and parasympathetic reactivity in a sample of children and adolescents. Psychophsyiology, 37(6), 842–849. 10.1111/1469-8986.3760842

Schuurmans AA, Nijhof KS, Cima M, Scholte R, Popma A, & Otten R (2021). Alterations of autonomic nervous system and HPA axis basal activity and reactivity to acute stress: a comparison of traumatized adolescents and healthy controls. Stress, 1–12. 10.1080/10253890.2021.1900108

Schwerdtfeger A, & Rosenkaimer AK (2011). Depressive symptoms and attenuated physiological reactivity to laboratory stressors. Biological Psychology, 87(3), 430–438. 10.1016/j.biopsycho.2011.05.009 [PubMed: 21679744]

Shirtcliff EA, & Essex MJ (2008). Concurrent and longitudinal associations of basal and diurnal cortisol with mental health symptoms in early adolescence. Developmental Psychobiology, 50(7), 690–703. 10.1002/dev.20336 [PubMed: 18726897]

Stein GL, Gonzalez LM, & Huq N (2012). Cultural stressors and the hopelessness model of depressive symptoms in Latino adolescents. Journal of Youth & Adolescence, 41(10), 1339–1349. 10.1007/s10964-012-9765-8 [PubMed: 22528371]

Strunin L, Díaz-Martínez A, Díaz-Martínez LR, 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. 10.1093/alcalc/agx027 [PubMed: 28481972]

Swift W, Coffey C, Carlin JB, Degenhardt L, & Patton GC (2008). Adolescent cannabis users at 24 years: trajectories to regular weekly use and dependence in young adulthood. Addiction, 103(8), 1361–1370. 10.1111/j.1360-0443.2008.02246.x [PubMed: 18855826]

Thayer JF, & Lane RD (2009). Claude Bernard and the heart–brain connection: Further elaboration of a model of neurovisceral integration. Neuroscience & Biobehavioral Reviews, 33(2), 81–88. 10.1016/j.neubiorev.2008.08.004 [PubMed: 18771686]

Van Stegeren AH, Goekoop R, Everaerd W, Scheltens P, Barkhof F, Kuijer JP, & Rombouts SA (2005). Noradrenaline mediates amygdala activation in men and women during encoding of emotional material. Neuroimage, 24(3), 898–909. 10.1016/j.neuroimage.2004.09.011 [PubMed: 15652324]

Weissman DG, Guyer AE, Ferrer E, Robins RW, & Hastings PD (2018). Adolescents' brain-autonomic coupling during emotion processing. NeuroImage, 183, 818–827. 10.1016/j.neuroimage.2018.08.069 [PubMed: 30189339]

Wills TA, Sandy JM, Shinar O, & Yaeger A (1999). Contributions of positive and negative affect to adolescent substance use: Test of a bidimensional model in a longitudinal study. Psychology of Addictive Behaviors, 13(4), 327. 10.1037/0893-164X.13.4.327

Yaroslavsky I, Rottenberg J, Bylsma LM, Jennings JR, George C, Baji I, … & Kovacs M. (2016). Parasympathetic nervous system activity predicts mood repair use and its effectiveness among adolescents with and without histories of major depression. Journal of Abnormal Psychology, 125(3), 323. [PubMed: 26950752]

Zapert K, Snow DL, & Tebes JK (2002). Patterns of substance use in early through late adolescence. American Journal of Community Psychology, 30(6), 835–852. 10.1023/A:1020257103376 [PubMed: 12385485]

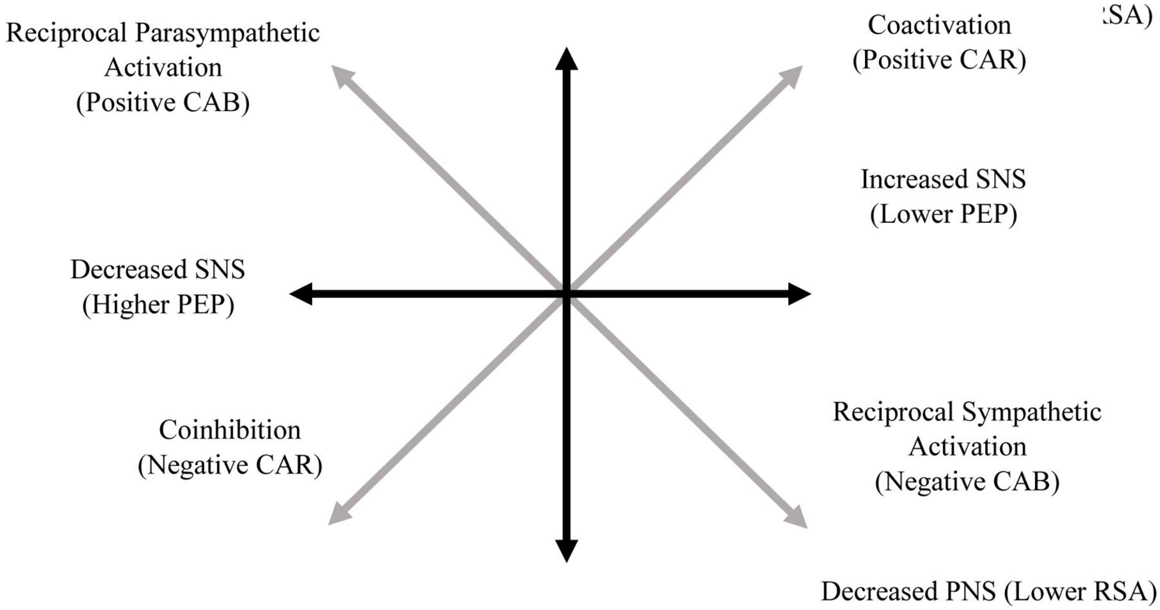

Figure 1. Representation of the autonomic space model (adapted from Berntson et al., 2008, using definitions from Berntson et al., 1991). Associations between parasympathetic activity, as measured by RSA values, and sympathetic nervous system activity, as measured by PEP values are bivariate. Profiles are presented in each quadrant. Associations between the degree of reciprocity, as measured by cardiac autonomic balance, and coactivation, as measured by cardiac autonomic regulation, are also bivariate.

Note: PNS = Parasympathetic Nervous System, SNS = Sympathetic Nervous System, RSA = Respiratory Sinus Arrhythmia, PEP = Pre-Ejection Period, CAB = Cardiac Autonomic Balance, CAR = Cardiac Autonomic Regulation.

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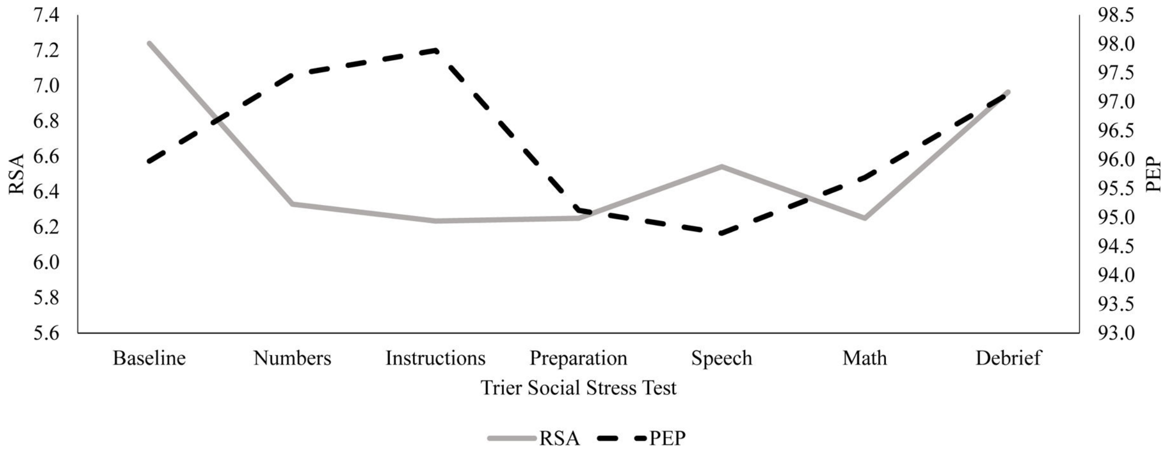

Figure 2. Adolescents' minute-by-minute RSA and PEP responses to the Trier Social Stress Test across the task protocol.

Note: RSA = Respiratory sinus arrhythmia, PEP = Pre-Ejection Period.

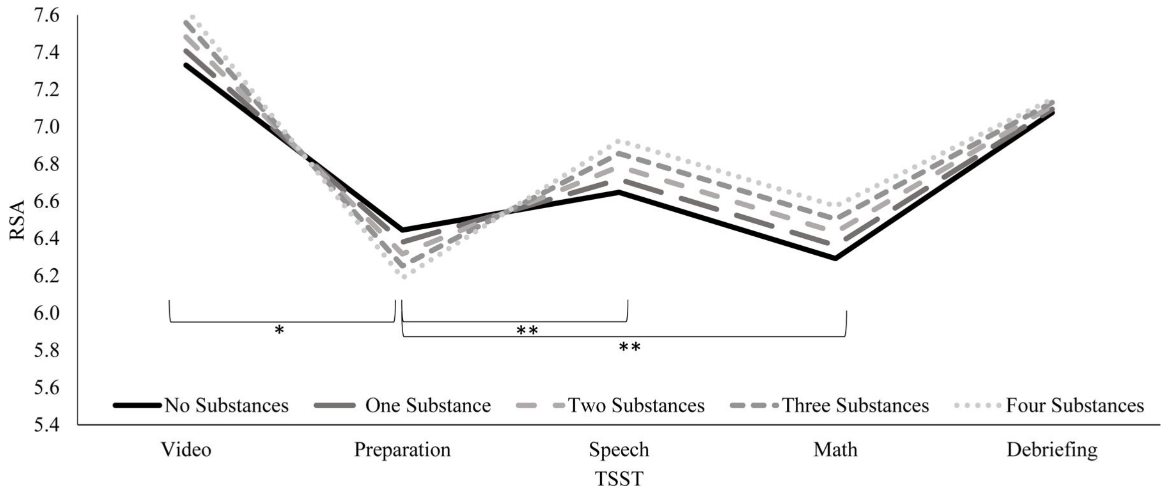

Figure 3. Adolescents' minute-by-minute RSA responses to the Trier Social Stress Test as a function of their substance use count by age 16 among youth who had never used any substances by age 14. Adolescents who used more substances by age 16 showed significantly greater decreases in RSA from baseline to task preparation and significant greater increases in RSA from task preparation to the speech task and the math task (indicated by brackets).

Note: RSA = Respiratory sinus arrhythmia, *p<.05 **p<.01.

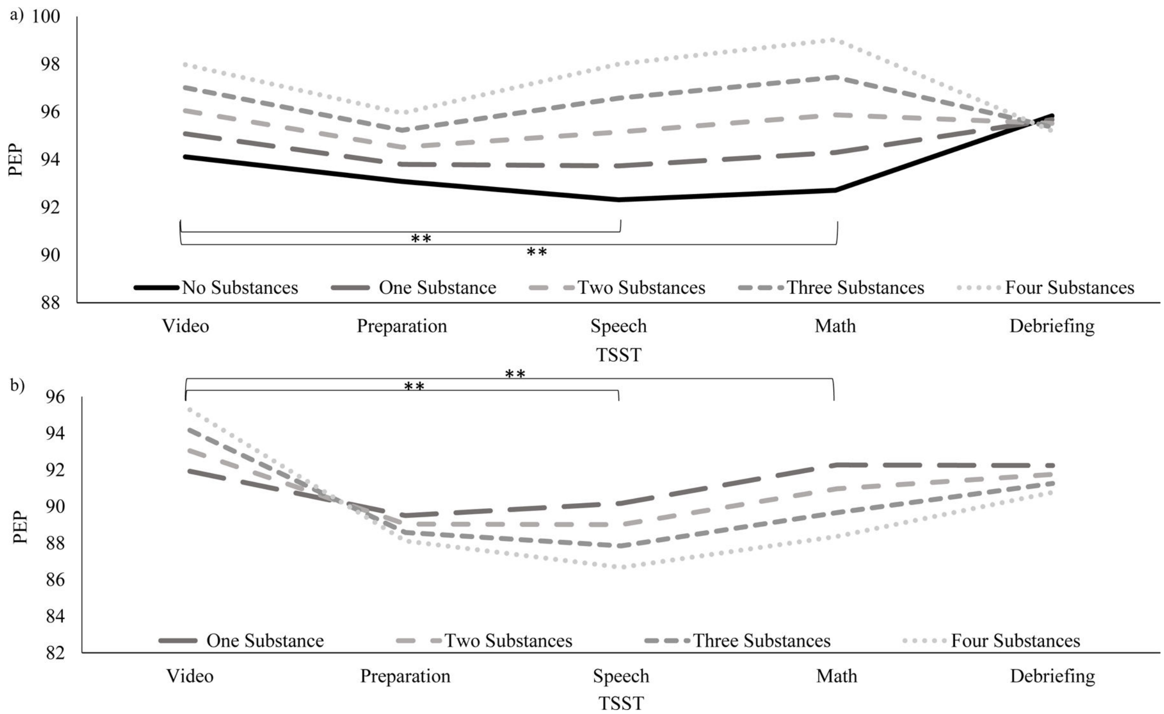

Figure 4. Adolescents' minute-by-minute PEP responses to the Trier Social Stress Test as a function of their substance use count by age 16, among youth who had never used any substances by age 14 (a) and adolescents who had used substances by age 14 (b). Among youth who had never used any substances by age 14, adolescents who used more substances by age 16 showed significantly greater increases in PEP from baseline to the speech and math tasks (indicated by brackets). Among youth who had used substances by age 14, adolescents who used more substances by age 16 showed significantly greater decreases in PEP from baseline to the speech and math tasks.

Note: RSA = Respiratory sinus arrhythmia, $^{**}p<.01$.