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Pre-ejection period reactivity and psychiatric comorbidity prospectively predict substance use initiation among middle-schoolers: A pilot study

SHARON L. BRENNER[a] AND THEODORE P. BEAUCHAINE[b]

[a]Department of Psychiatry and Behavioral Sciences, Duke University School of Medicine, Durham, North Carolina, USA
[b]Department of Psychology, Washington State University, Pullman, Washington, USA

Abstract

Youth with conduct problems (CPs) or depression are at high risk for early initiation of substance use, and for future substance use disorders (SUDs). Comorbid CPs and depression increase risk even further, yet understanding how these conditions interact remains elusive. One hypothesis is that altered mesolimbic dopamine function contributes to symptoms of CPs, depression, and SUDs. Cardiac pre-ejection period (PEP) reactivity to incentives is linked theoretically and functionally to central dopamine responding. We evaluated PEP reactivity to reward as a prospective biomarker of substance use in a study of 206 youth with depression, CPs, CPs and depression, or no psychiatric condition. Children were 8–12 years old at the first of three annual assessments. Reduced PEP reactivity was associated with increased likelihood of future alcohol use, and CPs interacted with anxiety and depression to double risk for marijuana and other substance use.

Descriptors: Substance use, Cardiac pre-ejection period, Conduct problems, Depression, Children

Experimentation with alcohol and drugs remains exceedingly prevalent among youth. In 2005, about 34% of 8th graders and 57% of 10th graders reported alcohol use in the past year, and up to 15% of 8th graders and 30% of 10th graders reported use of an illicit drug (Johnston, O'Malley, Bachman, & Schulenberg, 2006). These data indicate that experimentation with substances of abuse is common for adolescents, yet for a sizable minority excessive use adversely affects school achievement, promotes delinquency, potentiates mood disorders, and increases risk of suicide (Vida et al., 2009; Windle & Davies, 1999).

Given that only some who experiment with substances go on to experience problematic use, we are faced with unique challenges in our efforts to determine risk for future substance use disorders (SUDs). How do we identify those individuals who are at greatest risk? Addressing this question is of utmost importance because early enrollment in prevention programs is less costly than treating established SUDs, and more effective in addressing negative sequelae of use, including crime and incarceration (Conrod, Castellanos, & Mackie, 2007; Conrod, Stewart, Comeau, & Maclean, 2006). Thus, determining early behavioral and biomarkers of vulnerability confers advantages for prevention. In this study, we examine prospective prediction of risk for future initiation of alcohol and other substance use by psychiatric comorbidity and sympathetic nervous system (SNS)-linked cardiac reactivity to incentives among middle-schoolers.

Psychiatric Morbidity and Risk for Substance Use and Abuse

For many adolescents, psychiatric diagnoses including anxiety, depression, and conduct problems (CPs) predict elevated risk for early initiation of substance use (e.g., Grilo, Becker, Fehon, Edell, & McGlashan, 1996; Sartor, Lynskey, Heath, Jacob, & True, 2007). Estimates of substance use problems among depressed adolescents are around 20%–25% (Fleming & Offord, 1990; Lewinsohn, Rohde, Seeley, & Hops, 1991). Rates of substance use problems among youth with conduct disorder (CD) are higher still, with most estimates falling around 35% (Grilo et al., 1996; Lewinsohn et al., 1991). Thus, one likely fruitful approach to identifying prospective risk for SUDs is to follow children who experience internalizing (e.g., anxiety, depression) and/or externalizing (e.g., CD, oppositional defiant disorder [ODD]) psychopathology. Consistent with this perspective, longitudinal studies indicate that childhood CD predicts alcohol use and abuse prospectively in adolescence and young adulthood (Clark, Vanyukov, & Cornelius, 2002; Kumpulainen, 2000; Pardini,

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Address correspondence to: Sharon L. Brenner, Department of Psychiatry and Behavioral Sciences, Duke University School of Medicine, Box 3454 DUMC, Durham, NC 27710. E-mail: sharon.brenner@duke.edu

PSYCHOPHYSIOLOGY

White, & Stouthamer-Loeber, 2007). Similarly, although substance use problems sometimes precede mood disorders, in other cases depression places youth at later risk for early initiation and escalation of use (e.g., Diego, Field, & Sanders, 2003; Kumpulainen, 2000). In turn, substance use places depressed youth at heightened risk of mortality, in part as a result of attempted and completed suicide attempts (Zeitlin, 1999).[1]

Though experiencing either depression *or* early-onset CPs confers significant risk for later SUDs, comorbid CPs *and* depression increase vulnerability even further, placing youth at especially high risk of suicide and suicide attempts (Zeitlin, 1999). This is troubling because comorbid CPs and depression are common in childhood and adolescence (Angold & Costello, 1993). Traditionally, it has been assumed that heterotypic disorders arise from distinct etiologies. However, recent behavioral genetics studies indicate considerable shared heritable variance for internalizing and externalizing behaviors (Krueger & Markon, 2006; Krueger, Markon, Patrick, Benning, & Kramer, 2007). Furthermore, neuroimaging studies have identified mesolimbic dopamine (DA) dysfunction as a neural substrate of CPs, depression, *and* vulnerability to SUDs (e.g., Forbes, Shaw, & Dahl, 2007; Gatzke-Kopp et al., 2009; Wise, 2009).

Central Dopamine Functioning and Vulnerability to Substance Use

A comprehensive review of the neurobiology of alcohol and drug use is beyond the scope of this paper. However, modulation of substance use by dopaminergic reward circuits is particularly relevant for any discussion of vulnerability to SUDs. Much of the literature on the neurobiology of drugs of abuse has focused on increases in cellular and extracellular DA in the mesolimbic and mesocortical DA systems (Wise, 2009). In fact, both appetitive motivation and substance dependence have been linked with mesolimbic DA responding (see, e.g., Ashby, Isen, & Turken, 1999; Davidson et al., 2002; Robinson & Berridge, 1993). Tonic changes in extracellular (nonsynaptic) DA mediate motivational states, both appetitive and aversive, including cravings for drugs of abuse (Di Chiara, 1995; Volkow, Fowler, & Wang, 2004). Individual differences in both tonic and phasic DA functioning within these brain regions may explain why some are more vulnerable to becoming addicted than others.

Psychophysiological Assessment of Central Dopamine Responding

Recently, cardiac pre-ejection period (PEP) has been used as a peripheral marker of individual differences in central DA reactivity specifically to incentives (Beauchaine, Katkin, Strassberg, & Snarr, 2001; Brenner, Beauchaine, & Sylvers, 2005; Crowell et al., 2006; Richter & Gendolla, 2009)[2]. Pre-ejection period is determined exclusively by the SNS, which is advantageous because central DA reactivity to reward appears to be expressed peripherally through the SNS (Beauchaine, 2002; Brenner et al., 2005). This assertion is derived from both functional and phylogenetic relations between cardiac output and approach behaviors. First, behavioral approach requires expenditures of energy, and the functional role of the SNS has been viewed traditionally as one of mobilizing resources to deal with environmental demands. Second, increases in cardiac output, which are required for behavioral approach, are facilitated by SNS-mediated changes in the contractile force of the left ventricle (Sherwood, Allen, Obrist, & Langer, 1986; Sherwood et al., 1990). Third, infusions of DA agonists directly into the ventral tegmental area, a core structure within the mesolimbic reward pathway, induce SNS-mediated increases in blood pressure and cardiac output (van den Buuse, 1998). Finally, studies of autonomic responding across conditions of reward, punishment, and emotion-induction indicate that PEP reactivity is specific to reward trials, whereas respiratory sinus arrhythmia (RSA), a marker of peripheral nervous system activation, responds not only to reward, but to all other stimulus conditions as well (Brenner et al., 2005). Thus, although increases in cardiac output are effected through both autonomic branches, only SNS-responding is specific to reward in well controlled experiments.

Studies of preschoolers, middle-schoolers, and adolescents with CD and/or hyperactive-impulsive attention-deficit/hyperactivity disorder (ADHD) indicate either no response or lengthened PEP during monetary incentive tasks (Beauchaine et al., 2001; Beauchaine, Gatzke-Kopp, & Mead, 2007; Beauchaine, Hong, & Marsh, 2008; Crowell et al., 2006). In contrast, most control participants exhibit PEP shortening to incentives. These findings suggest impaired DA responding among externalizers, consistent with results from neuroimaging studies conducted in our lab and others demonstrating reduced DA reactivity in mesolimbic structures during conditions of reward among similar groups (for discussions, see Gatzke-Kopp et al., 2009; Shannon, Sauder, Beauchaine, & Gatzke-Kopp, 2009). However, evaluating PEP reactivity offers advantages over neuroimaging because it can be assessed for little expense and can be used with very young children.

Following from the above discussion, our primary goals in conducting this study were to determine whether (a) psychiatric comorbidity and/or (b) cardiac PEP responding to incentives predict later substance use among at risk middle-school children.

Method

Participants

All study procedures were approved by a University of Washington institutional review board. Children were accompanied by a biological parent (the mother in all but four cases). Parental

1. There is debate in the literature over the premise that depression predicts risk for substance use and SUDs, over and above the effects of CD. Some authors have reported no association between symptoms of depression and substance use when comorbid CD is controlled for statistically (Costello, 2007). Pardini et al. (2007) found that depression in adolescence predicted alcohol use problems by young adulthood only among boys with concurrent conduct problems. Importantly, however, their study did not include girls, who may have different motives for use (e.g., Conrod et al., 2000), and different use trajectories (e.g., Dierker, Vesel, Sledjeski, Costello, & Perrine, 2007). Furthermore, it may make little sense to covary symptoms of depression from symptoms of CD given evidence of shared neural vulnerability across disorders, as we discuss elsewhere and in later sections (see Beauchaine, Hinshaw, & Pang, 2010; Miller & Chapman, 2001).

2. We are not suggesting that PEP reactivity invariably marks central DA responding. Other active coping tasks, such as public speaking and mental arithmetic, also induce PEP shortening (e.g., Kelsey, Soderlund, & Arthur, 2004). However, these stimulus conditions induce different motivational states including but not limited to fear and anxiety. As a result, β-adrenergic cardiac reactivity, the peripheral mechanism of PEP change (see Sherwood et al., 1986), is likely effected through other brain systems (see, e.g., Pribram & McGuinness, 1975). Thus, stimulus conditions must be considered carefully when designing active coping tasks if one wishes to interpret the neural origin(s) of PEP responding.

consent and child assent were obtained at each visit. Data were from a longitudinal study examining the development of CPs and depression in middle childhood. At the time of their first visit, the sample consisted of 134 boys and 72 girls between ages 8 and 12 years (mean = 9.9, $SD = 1.5$). The sample was 12.1% African American, 6.3% Asian, 61.7% Caucasian, 10.2% Latino, 1.5% Native American, 2.4% Hawaiian or other Pacific Islander, and 5.8% mixed/unspecified heritage. Participants were recruited from predominantly lower socioeconomic status neighborhoods in Seattle through bus and newspaper advertisements, community publications, direct mailings, radio advertisements, and flyers placed in community centers. Advertisements targeted children who were "well adjusted," "down or depressed," or "experiencing behavior problems." Each advertisement stated that parents and their children could earn up to $175 by participating in a study about child adjustment. Median family income was $40,000, which is well below the population median of $69,795 for Seattle (United States Census Bureau, 2005).

Participants who responded to the advertisements completed a 20- to 30-min phone screen that included the anxious/depressed, aggression, inattention, and delinquency subscales of the Child Behavior Checklist (CBCL; Achenbach, 1991), as well as the ADHD (inattentive and hyperactive), oppositional defiant disorder (ODD), CD, major depressive disorder (MDD), and dysthymia (DYS) subscales of the Child Symptom Inventory (CSI; Gadow & Sprafkin, 1994). Parents were invited to the lab for a more detailed assessment if their child met inclusion criteria and failed to meet exclusion criteria (see below).

Although all participants are combined for the current analyses, four groups of children were recruited. In the CPs group ($n = 28$), children were required to meet Diagnostic and Statistical Manual of Mental Disorders, 4th edition (American Psychiatric Association, 2000) criteria for ODD and/or CD on the CSI, with age of onset at or before age 10 years, and to score $\geq$ the 98th percentile ($T \geq 70$) on the CBCL aggression subscale. To be included in the depression/dysthymia group ($n = 27$), children were required to meet DSM-IV criteria for depression and/or dysthymia on the CSI and to score $\geq$ the 85th percentile ($T \geq 60$) on the CBCL anxious/depressed subscale. Children who met criteria for both CPs and depression were placed in the comorbid group ($n = 81$). Children in the control group ($n = 70$) could not meet criteria for any CSI disorder, and had to score < 60th percentile on all CBCL scales. Children with symptoms of autism, mental retardation, and/or psychosis were excluded.

Lab Visits

At Year 1, the child and his or her biological parent completed extensive lifetime diagnostic interviews and self-report measures. Children returned 1–2 weeks later for a psychophysiological assessment. At Years 2 and 3, children and parents were administered abbreviated interviews and self-report measures assessing their behaviors during the past year.

Parent measures. At Years 1, 2, and 3, parents completed subscales of the CBCL and CSI regarding their child, in addition to self-report measures of psychopathology that are not reported in this study (for further details, see Kopp & Beauchaine, 2007; Shannon, Beauchaine, Brenner, Neuhaus, & Gatzke-Kopp, 2007).

Child measures. At Years 1, 2, and 3, children completed the Customary Drinking and Drug Use Record (CDDR; Brown, Myers, Lippke, Tapert, & Stewart, 1998), in addition to other measures not reported in this study (for descriptions, see Beauchaine, Hong, & Marsh, 2008; Shannon et al., 2007). The CDDR is a measure of adolescent and adult lifetime and past year substance use for tobacco, alcohol, marijuana, and six other drug classes including cocaine, hallucinogens, barbiturates, and opiates. The measure yields good internal consistency coefficients in both abusing and community samples of adolescents (αs = .72–.89; Brown et al., 1998).

Psychophysiological assessments. At Year 1, psychophysiological assessments were conducted during a monetary-incentive task that has been used extensively to evaluate children's autonomic reactivity to reward (e.g., Beauchaine et al., 2001, 2007; Iaboni, Douglas, & Ditto, 1997). The specific incentive task, described below, was chosen because it and similar tasks elicit both SNS-linked cardiac reactivity (Brenner et al., 2005; Richter & Gendolla, 2009) and neural activation within mesolimbic brain regions (e.g., nucleus accumbens, caudate) implicated in addiction (e.g., Gatzke-Kopp et al., 2009; Shannon et al., 2009).

Assessments were conducted with children seated alone in a sound-attenuated room monitored by a video camera and microphone. Physiological signals were collected during a 5-min baseline, and during the computerized repetitive response task, which included conditions of reward and non-reward. In brief, large, single-digit odd numbers (1, 3, 5, 7, or 9) were presented in random order on a video screen projected just above eye level. Participants were required to press the matching number on a 10-key pad mounted on a platform in front of them, and then press the enter key to initiate presentation of the next stimulus. Thus, the task required only small movements of participants' dominant hand. After 2 min of practice, the task was performed across six 2-min blocks, each separated by a 2.5-min intertrial baseline. The first three blocks were reward conditions in which signal tones and 6¢ incentives accompanied all correct responses. A running total of money earned was presented continuously in the upper right portion of the screen. Signal tones and incentives were omitted for incorrect responses, and the amount of money earned remained the same until the participant entered a correct response. The fourth block included 30 s of reward and 90 s of nonreward, during which monetary incentives and signal tones were omitted. The fifth block was completely reward, with signal tones and incentives reinstated. The sixth block included 90 s of nonreward followed by 30 s of reward. Participants were told that they could earn more money the faster they played, that most children earn about $25, and that they needed to continue responding during periods of nonreward in order to advance to the next reward condition.

Sympathetic (β-adrenergic) influences on the heart were assessed by measuring PEP—the interval between the onset of left ventricular depolarization and ejection of blood into the aorta. Shorter intervals represent greater sympathetic effects (Sherwood et al., 1986, 1990). Electro- and impedance-cardiographic signals were obtained using a HIC 2000 impedance cardiograph (Chapel Hill, NC). Both waveforms were sampled at 1 kHz using the spot electrode configuration described by Qu, Zhang, Webster, and Tompkins (1986). Pre-ejection period values were extracted by ensemble-averaging data in 30-s epochs (see Kelsey & Guethlein, 1990) using Bio-Impedance Technology's CopWin software system, version 5.06 (Chapel Hill, NC).

All ensemble-averaged waveforms were inspected visually by trained research assistants to correctly locate the dZ/dt B-wave in cases where the computer algorithm failed to do so.

Data Analyses

Data reduction. A single resting baseline score was computed for each participant by extracting the ensemble-averaged PEP value from the final 30-s epoch of the initial 5-min resting baseline. This ensured that participants were at a true resting state (see Jennings, Kamarck, Stewart, Eddy, & Johnson, 1992). Pre-ejection period reactivity was assessed by (a) calculating an intertrial baseline score for the last 30 s of rest preceding each block; (b) computing a single PEP reactivity score for each block by averaging PEP reactivity across epochs within each block; and (c) computing change scores between the intertrial baseline and the averaged PEP reactivity values for each block. This yielded six PEP reactivity scores (one for each reward block). For purposes of this study, these were averaged into a single PEP reactivity score, which was required for our multilevel models, described below. Data from extinction trials were omitted.

Substance use was represented by creating "yes" (1) or "no" (0) dummy-coded vectors for each substance based on CDDR responses at Years 1, 2, and 3. Thus, all substance use criterion variables were dichotomous. Creating these scores was necessary given the limited number of participants who began using substances by the end of the study (see below). Psychopathology severity was indexed using continuous *T* scores (CBCL) and symptom counts (CSI), providing improved power over group-based coding (see MacCallum, Zhang, Preacher, & Rucker, 2002).

Analyses exploring changes in outcome variables over time were conducted by constructing two-level multilevel models (MLMs) in HLM 6.06 (Raudenbush, Bryk, Cheong, & Congdon, 2004). Given dichotomous substance use outcomes, all models were specified using Bernoulli distributions. Repeated observations were nested within persons by age at each assessment at Level 1. Predictors that were measured across all time points were included as Level 1 time-varying covariates. Outcomes are represented as changes in the log odds of each variable. Accordingly, increases in slopes indicate increased likelihood of substance use. Restricted maximum likelihood models followed the general form presented below, which includes change in PEP during reward as Level 2 predictor of slopes in alcohol use:

Level 1:

$$p(\text{alcohol use in the past year} = 1|\pi) = \varphi$$
$$\text{Log}\,[\varphi/(1-\varphi)] = \eta$$
$$\eta = \pi_0 + \pi_1(\text{age})$$

Level 2:

$$\pi_0 = \beta_{00} + r_0$$
$$\pi 1 = \beta_{10} + \beta_{11}(\Delta\text{PEP}) + r_1$$

Level 1 variance = $1/[\pi/(1-\pi)]$

Moderation effects were tested using binary logistic regression models to examine the interaction between predictors (e.g., depression, CPs) and the likelihood of alcohol, marijuana, or any substance use. Interaction terms were calculated by multiplying predictor variables together. To support a moderational interpretation, the interaction term must be significant when entered with main effects into the regression equation (West, Aiken, & Krull, 1996).

Results

The total number of participants using cigarettes, alcohol, marijuana, or any substance were 10 in Year 1 (4.9 % of $n = 206$), 14 in Year 2 (7.4% of $n = 188$), and 16 in Year 3 (9.7% of $n = 165$). Thus, although use rates were relatively low given the young age of participants, experimentation with substances increased steadily from Year 1 to Year 3. Alcohol (6.0%) and marijuana (4.8%) were used more frequently than all other drugs combined (3.6%). Given the limited use rates in the sample, we constructed a composite variable indicating use of any substance for later analyses (see below). In addition, given the limited amount of cigarette and nonmarijuana drug use reported, analyses were conducted only with (a) alcohol use, (b) marijuana use, and (c) the combined index of all drug use.

To maximize power, groups were pooled for the correlational and MLM analyses, described below. Nevertheless, we report descriptive statistics by group for the parent-report measures of psychopathology, baseline PEP, and PEP reactivity in Table 1. As expected given the recruitment strategy, large group differences were found on all measures of psychopathology, all

Table 1. *Descriptive Statistics*

Variable	Group						
	CPs ($n = 28$)	Dep ($n = 27$)	CPs/Dep ($n = 81$)	Control ($n = 70$)	F(df)	p	η_p^2
Age	9.6 (1.6)	10.1 (1.5)	10.0 (1.5)	9.9 (1.5)	0.7 (3,202)	.57	.01
CBCL delinquency *T* score	64.8 (8.7)	56.2 (6.1)	66.3 (7.9)	53.5 (5.8)	42.7 (3,191)	< .001	.40
CBCL anxious/depressed *T* score	66.7 (8.6)	74.4 (7.4)	81.6 (8.5)	52.8 (3.6)	217.7 (3,202)	< .001	.76
CSI CD score	7.0 (5.1)	1.4 (1.5)	7.4 (4.7)	0.7 (1.1)	55.4 (3,202)	< .001	.45
CSI ODD score	16.3 (4.1)	7.4 (3.4)	17.0 (4.6)	4.0 (3.0)	164.1 (3,202)	< .001	.71
CSI MDD score	2.8 (2.8)	6.6 (3.4)	10.2 (4.9)	0.7 (1.0)	97.5 (3,202)	< .001	.59
CSI dysthymia score	2.9 (1.9)	7.0 (2.3)	9.7 (4.0)	0.9 (1.1)	131.6 (3,202)	< .001	.66
PEP at baseline (ms)	97.5 (16.4)	101.5 (17.0)	99.7 (19.3)	106.2 (16.8)	2.1 (3,181)	.10	.03
PEP change (ms)	− 0.6 (2.5)	− 0.3 (3.4)	0.2 (3.6)	− 0.1 (3.7)	0.4 (3,189)	.74	.01

Notes. All entries are expressed as mean (*SD*). CPs = conduct problems; Dep = depression; CPs/Dep = comorbid conduct problems and depression; CBCL = Child Behavior Checklist (Achenbach, 1991); CSI = Child Symptom Inventory (Gadow & Sprafkin, 1997); PEP = pre-ejection period. Baseline PEP values are from the initial resting baseline. PEP change values represent averages across all reward epochs.

Table 2. *Bivariate Correlations Among Substance Use Outcomes, Predictor Variables, and Psychophysiological Responding at Year 1*

Variable	*n* = 165 1	*n* = 165 2	*n* = 166 3	*n* = 163 4	*n* = 155 5	*n* = 165 6	*n* = 161 7	*n* = 165 8	*n* = 165 9	*n* = 165 10	*n* = 165 11	*n* = 162 12	*n* = 156 13
1. Used alcohol in past year	–	.45**	.78**	.10	.08	−.01	−.04	.12	.02	.00	−.02	−.01	−.04
2. Used marijuana in past year		–	.64**	.27**	.20**	.02	−.05	.32**	.10	.05	.02	.05	.02
3. Used any substance in past year			–	.14	.12	.02	−.06	.14	.05	.02	−.01	−.01	−.03
4. CBCL-delinquency				–	.79**	.47**	.51**	.82**	.70**	.54**	.49**	−.15	.20*
5. CBCL-externalizing					–	.67**	.70**	.76**	.83**	.64**	.60**	−.15	.34**
6. CBCL-anxious/depressed						–	.88**	.45**	.62**	.73**	.73**	−.14	.30**
7. CBCL-internalizing							–	.46**	.63**	.75**	.76**	−.08	.25**
8. CSI CD score								–	.76**	.54**	.50**	−.18*	.22**
9. CSI ODD score									–	.64**	.57**	−.15	.21**
10. CSI MDD score										–	.94**	−.10	.08
11. CSI dysthymia score											–	−.11	.12
12. Baseline PEP												–	−.03
13. PEP change during reward													–

Notes. CBCL = Child Behavior Checklist (Achenbach, 1991); CSI = Child Symptom Inventory (Gadow & Sprafkin, 1997); PEP = pre-ejection period. Baseline PEP values are from the initial resting baseline. PEP change values represent averages across all reward epochs.
*$p < .05$, **$p < .01$.

Fs $\geq$ 42.7, all ps $< .001$, all η_p^2s $\geq .40$. In contrast, group differences in baseline PEP and PEP reactivity were not significant, both Fs $\leq$ 2.1, both ps $\geq .10$, both η_p^2s $\leq .03$. The PEP findings were somewhat unexpected given our previous work demonstrating group differences between control children and those with ADHD, ODD, and CD on PEP reactivity to incentives (Beauchaine, 2002; Beauchaine et al., 2001; Crowell et al., 2006). Despite this finding, we performed the correlational and MLM analyses as planned given that group-based analyses are of low statistical power, and can obscure dimensional relations among variables in larger samples (MacCallum et al., 2002).

Correlations between (a) Year 3 alcohol, marijuana, and any substance use, (b) parent and self-reports of psychopathology, and (c) PEP at baseline and during reward appear in Table 2. Pre-ejection period reactivity to reward was correlated with all measures of externalizing behavior, and with the CBCL measures of internalizing behavior (see Table 2). Given that PEP reactivity is represented by shortened intervals (i.e., negative numbers), these correlations indicate less PEP reactivity among those scoring high on psychopathology. Correlations between PEP and substance use were not significant. Nevertheless, we tested the hypothesized statistical models outlined above, since several of our hypotheses specified longitudinal effects, which could not be addressed with correlations.

In the first set of MLMs, we examined whether substance use increased as a function of age. As shown in Figure 1, the likelihood of both alcohol, $\beta = 0.7$, $SE = 0.2$, $p < .001$, and marijuana use, $\beta = 0.7$, $SE = 0.2$, $p < .01$, increased with age, as did the likelihood of any substance use, $\beta = 0.6$, $SE = 0.1$, $p < .001$. Consequently, subsequent multilevel analyses were conducted with age included as a Level 1 time-varying covariate.

Pre-ejection period reactivity scores were entered into a MLM as a Level 2 predictor with alcohol, marijuana, and any substance use as outcomes. As expected, PEP reactivity to reward was associated with greater alcohol use, $\beta = 0.07$, $SE = 0.03$, $p < .05$. Consistent with the literature reviewed above, less PEP reactivity —indicating less sympathetic nervous system activation—was associated with increased likelihood of use (see Figure 2).

Next, CBCL T scores for both internalizing (anxious/depressed, withdrawn/depressed, and internalizing composite) and externalizing (aggression, delinquency, and externalizing composite) variables were entered at Level 1. Alcohol, marijuana, and any substance use were entered as dichotomous outcomes. Analyses revealed significant associations between CBCL delinquency T scores and likelihood of using alcohol, $\beta = 0.07$, $SE = 0.03$, $p < .01$, marijuana, $\beta = 0.12$, $SE = 0.04$, $p < .001$, and any substance, $\beta = 0.08$, $SE = 0.02$, $p < .001$. Broadband CBCL externalizing T scores were also associated with alcohol use, $\beta = 0.04$, $SE = 0.02$, $p < .05$, and any substance use, $\beta = 0.06$, $SE = 0.02$, $p < .01$. None of the CBCL internalizing T scores were associated with alcohol, marijuana, or any substance use, all βs $\leq .03$, all ps $\geq .11$.

To examine the effects of comorbidity on substance use, a CBCL internalizing and externalizing interaction vector was computed and entered at Level 1. In these equations, anxiety/depression and delinquency T scores interacted to predict marijuana use, $\beta = 0.01$, $SE = 0.002$, $p < .001$, and any substance use, $\beta = .0005$, $SE = 0.0002$, $p < .05$, across Years 1 to 3 of the study (see Figure 3). Thus, concurrently elevated scores on the anxious/depressed and delinquency subscales were associated with the highest likelihood of use for all ages for both marijuana and any substance use. Concurrently low scores on both were associated with the least use. An elevated score on either anxious/depressed or delinquency alone resulted in a likelihood of use that fell between high and low scorers on both CBCL measures for any substance use.

Discussion

Estimated rates of substance use among high school students range from 30%–50% (Johnston et al., 2006). Although such

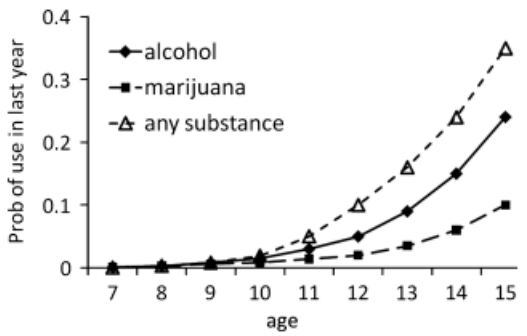

Figure 1. Probabilities of alcohol, marijuana, and any substance use by age.

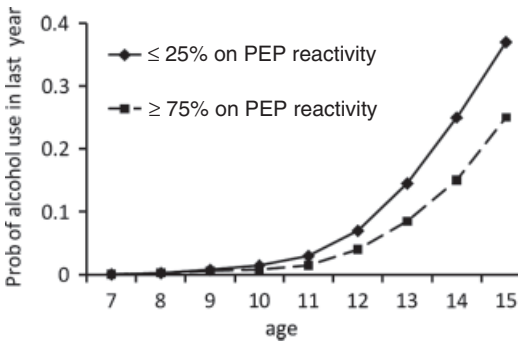

Figure 2. Association between age and probability of alcohol use in the past year for participants scoring below the 25th percentile and above the 75th percentile on PEP reactivity to incentives. Note that greater SNS responding is marked by PEP shortening. Thus, those scoring below the 25th percentile exhibited less PEP shortening than those scoring above the 75th percentile.

figures indicate that experimentation with substances is common, a sizable minority of adolescents exhibit earlier onset and higher rates of initial use than their peers, and quickly escalate in their quantity and frequency of use (e.g., Herting, Eggert, & Thompson, 1996). In efforts to identify such adolescents early, most studies have examined either concurrent or retrospective reports of psychiatric vulnerabilities and/or environmental risk factors. We sought to extend this research by examining

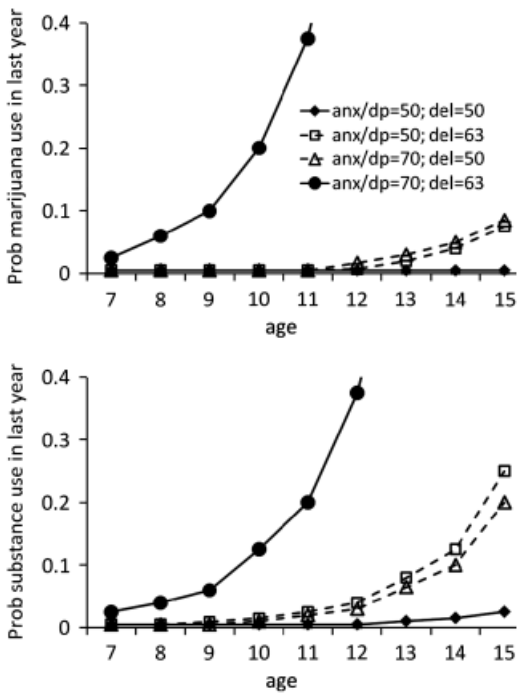

Figure 3. Associations between CBCL anxious/depressed (anx/dp) and delinquency (del) *T* scores and marijuana use (top panel) and any substance use (bottom panel). Each line represents use levels at 1.5 *SD* above and/or below the sample mean. For example, closed circles indicate use rates of children who scored 1.5 *SD* above the sample mean on both the anxious/depressed ($T = 70$) and delinquency ($T = 63$) subscales of the CBCL. In contrast, closed diamonds indicate use rates of children who scored 1.5 *SD* below the sample mean on both the anxious/depressed ($T = 50$) and delinquency ($T = 50$) subscales of the CBCL.

psychiatric risk (CPs, depression) and biological vulnerability (PEP reactivity to reward) as prospective predictors of substance use in a high-risk sample. Following from prior research, we hypothesized that psychopathology would be associated with increased use, particularly among those who were heterotypically comorbid. We also hypothesized that SNS-linked reward insensitivity, accessed via diminished PEP responding to incentives, would predict increased use during a developmental period in which risk for SUDs escalates markedly. As predicted, low PEP reactivity to monetary incentives prospectively predicted increases in alcohol use across three annual assessments. This is consistent with previous research indicating that (a) attenuated PEP responding to incentives marks trait-disinhibition among adolescents (e.g., Beauchaine et al., 2001); and (b) trait disinhibition predicts future alcohol use (e.g., Conrod, Pihl, Stewart, & Dongier, 2000; Iacono, Carlson, Taylor, Elkins, & McGue, 1999). Our study is the first of which we are aware to examine the correspondence between an established biomarker of reward insensitivity and emergence of later substance use. Assuming as we have argued that PEP reactivity to incentives marks central DA responding (e.g., Beauchaine et al., 2007; Brenner et al., 2005), our findings add to considerable evidence for a central role of compromised DA neurotransmission in the development of substance use problems (see e.g., Robinson & Berridge, 1993; Wise, 2009).

Confirming our hypotheses did not depend on group differences in PEP reactivity to incentives. Nevertheless, it is somewhat surprising given our previous work that the CPs group in particular did not display less PEP reactivity than one or more of the other groups. The most likely explanation for this may be the difference in severity of CPs between participants in this study compared with those in our previous studies of adolescents (e.g., Beauchaine et al., 2001). The present sample was recruited based on high risk for developing delinquency and CD. Thus, participants were not required to meet criteria for either condition on the CBCL and CSI, respectively. Rather, they were required to meet criteria for less serious conditions that predispose to CD (aggression, ODD). In our previous studies of adolescents, participants were required to meet full criteria for both delinquency and CD. Alternatively, including girls in the sample may have obscured group differences that would have emerged among boys only. Sex differences in PEP responding to incentives have been reported in high-risk samples (Beauchaine, Hong, & Marsh, 2008).

As predicted, higher CBCL delinquency scores were also associated with increased use of alcohol, marijuana, and all substances combined. This association was specific to delinquency, which is not entirely surprising given that the CBCL delinquency scale is associated most strongly with CD (Verhulst, Koot, & Van der Ende, 1994). We also predicted that internalizing scores would predict increased use. However, internalizing symptoms alone did not do so in this sample. Similar findings have been reported by others (Costello, 2007; Pardini et al., 2007). One possibility is that our sample was still a bit young to uncover internalizing-substance use relations. Finally, comorbid CPs and depression were hypothesized to confer the greatest risk for substance use, which was confirmed for marijuana use and use of all substances combined.

Despite findings confirming our primary hypotheses, fewer youth than expected reported substance use by Year 3 of the study. Even though use increased steadily with age, the sample was quite young, with an approximate mean age of 12 years at

termination. Even so, use rates were low compared to national averages. One possibility is that youth underreported their use. Adolescents must feel certain that confidentiality will be maintained to report use rates accurately (Brown, 2004). Although confidentiality was assured during assent at every visit, and before children completed questionnaires at Year 3, it remains possible that some underreported.

Regardless of the reason for the low use rate, we consider findings from this study to be preliminary. Although our hypotheses were generally supported, nonsignificant findings for some substances should not be interpreted as conclusive, since power was low. This is an especially important consideration for the moderational analyses, since interactions require large sample sizes for sufficient power to detect effects (e.g., Beauchaine & Mead, 2008).

A second limitation concerns low power to assess sex differences in the primary outcomes. This is not a trivial point given that prior research indicates differences between boys and girls in links between CPs and PEP reactivity to incentives (Beauchaine, Hong, & Marsh, 2008). In addition, although age predicted substance use, researchers are beginning to examine the association of developmental and pubertal status with early substance use, and how more specific maturational processes influence risk factors such as peer use (e.g., Windle et al., 2008). Pubertal status in particular should be assessed in future studies given that SNS control of cardiovascular function increases after puberty (e.g., Allen & Matthews, 1997; Tanaka et al., 2000). However, pubertal development likely does not explain the pattern results observed in this study. In order for differences in pubertal maturation to explain observed links between PEP reactivity and substance use, one would have to assume that children without conduct problems (who were less likely to use) entered puberty before children with conduct problems (who were more likely to use), and therefore had stronger SNS responses to reward, resulting in the observed pattern of results. However, numerous studies have documented quite the opposite: that delinquent children enter puberty sooner than nondelinquent children (e.g., Felson & Haynie, 2002). Given this, it is unlikely that differences in pubertal maturation explain our findings. Quite the contrary, such differences may have reduced power to detect predicted effects. Future research examining biological vulnerabilities and environment risk factors for substance use should include measures of puberty and other maturational processes, and larger samples, which would provide for assessment of sex differences within a broader developmental framework.

Limitations aside, prospective identification of risk for substance use is important for several reasons. Perhaps foremost among these, prevention is generally more effective among younger versus older individuals (Conrod et al., 2006, 2007). This is likely in part because the central nervous system is more plastic in young childhood (see, e.g., Dawson, 2008). As we have noted elsewhere (Beauchaine, Neuhaus, Brenner, & Gatzke-Kopp, 2008), considering neural plasticity may be especially important for developing mesolimbic and mesocortical DA systems, which subserve motivation and executive functions, and are exquisitely susceptible to long-term down-regulation through exposure to DA agonists (for a review, see Beauchaine, Neuhaus, Zalewski, Crowell, & Potapova, in press). Repeated elevations of DA neural firing in the nucleus accumbens induced by alcohol, stimulants, and certain forms of stress among rodents and nonhuman primates (a) down-regulate tonic DA activity (Scafidi et al., 1996); (b) sensitize phasic DA neural firing to drugs of abuse for impressively long time periods (Berger, Barros, Sarchi, Tarazi, & Antonelli, 2002; Jones, Marsden, & Robbins, 1990; Kippin, Szumlinski, Kapasova, Rezner, & See, 2008); and (c) suppress the strength of developing functional connections between mesolimbic structures and the prefrontal cortex (Thomas, Beurrier, Bonci, & Malenka, 2001), compromising top-down executive control over behavior (Everitt & Robbins, 2005; Kalivas & Volkow, 2005). Prospective identification of risk offers the possibility of intervening before this cascade of compromised brain development and self-regulation begins.

Finally, assuming that the theorized link between β-adrenergic cardiac reactivity and mesolimbic DA responding to incentives is correct, our study may provide evidence that compromised neural functioning predates substance use. In neuroimaging research with substance abusing humans, almost all studies demonstrating compromised mesolimbic responding have been conducted after significant exposure to drugs of abuse (e.g., Kilts, Gross, Ely, & Drexler, 2004). As noted above, most drugs of abuse down-regulate both tonic and phasic neural firing within mesolimbic structures, which makes it difficult if not impossible to determine which came first—compromised neural function or exposure to substances. Our findings may offer evidence, albeit indirect, that compromised neural function is a predisposing vulnerability to SUDs. However, this possibility is qualified by the fact that about half of the children who reported substance use had already begun using by the first annual assessment. Unfortunately, we did not have adequate statistical power to perform separate analyses for those who reported using substances at Year 1 versus those who began later. Thus, additional studies are needed before firm conclusions can be offered regarding the predictive value of low PEP reactivity to incentives—and by inference compromised neural reactivity in mesolimbic structures—and vulnerability to use among only substance naïve individuals. Fortunately, assessing PEP reactivity to incentives provides a means of evaluating reward sensitivity among children who are difficult to neuroimage given their age, making prospective studies among even younger children possible.

Based on our findings and those of others (e.g., Zeitlin, 1999), efforts to identify vulnerable children early should also focus on youth with psychiatric disorders including ODD, CD, and depression—particularly those who are heterotypically comorbid. Integrating what is known about neurobiological and psychiatric vulnerabilities to substance use will likely result in a clearer understanding of etiology, which is often a prerequisite for improved interventions (Preskorn & Baker, 2002).

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