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Behavioral and Neural Inhibitory Control Moderates the Effects of Reward Sensitivity on Adolescent Substance Use

Jungmeen Kim-Spoon^{a,*}, Kirby Deater-Deckard^b, Christopher Holmes^c, Jacob Lee^d, Pearl Chiu^{a,d}, and Brooks King-Casas^{a,d}

^aDepartment of Psychology, Virginia Tech

^bDepartment of Psychological and Brain Sciences, University of Massachusetts, Amherst

^cCenter for Family Research, University of Georgia, Athens, GA

^dVirginia Tech Carilion Research Institute

Abstract

The developmental period of adolescence is characterized by increasing incidence of health risk behaviors, including experimenting with drugs and alcohol. We examined how inhibitory control interacts with reward and punishment sensitivity to predict substance use severity and age of onset among early adolescents. The sample was comprised of 157 early adolescents (13-14 years of age, 52% male). Composite scores for behavioral activation system (BAS), behavioral inhibition system (BIS), and substance use severity and onset were computed using adolescents' questionnaire data, and inhibitory control was assessed based on adolescents' behavioral performance and brain imaging during the Multiple Source Interference Task (MSIT). Structural equation modeling analyses indicated that for both behavioral performance and neural activity indicators of inhibitory control, high levels of BAS predicted earlier onset of substance use among adolescents with low inhibitory control—but not among adolescents with high inhibitory control. BIS was not related to substance use severity and onset among adolescents. The results support the theoretically hypothesized moderating role of inhibitory control and its associated frontal cortex functioning, and offer new insights into the identification of adolescents with neurobehavioral vulnerabilities to developing maladaptive substance use behaviors.

Keywords

Adolescent Substance Use; Inhibitory Control; Reward Sensitivity; Regulation; Brain Imaging

Adolescence is a key period for the initiation of substance use and its consequences. National surveys indicate that 75% of U.S. high school students have used addictive substances including alcohol, tobacco, or marijuana (with 20% of those students meeting the

*Correspondence to: Jungmeen Kim-Spoon, Ph. D., Department of Psychology (MC 0436), Virginia Polytechnic Institute and State University, Blacksburg, Virginia, 24061, U.S.A. Phone: +1.540.231.0951; Fax: +1.540.231.3652; jungmeen@vt.edu. .

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medical criteria for addiction), and the average age when adolescents begin using substances is between 13 and 14 years (CDC, 2014; National Center on Addiction and Substance Abuse, 2011). The brain is actively developing throughout adolescence, and addictive substances can physically impair neural structure and function, contributing to inability of an individual to discontinue substance use (Goldstein & Volkow, 2002). Therefore, the younger the adolescent initiates substance use, the greater the probability of progressing from drug experimentation to drug addiction. As such, substance use behavior represents a pernicious—and preventable—risk that has profound consequences for health, economic, and social outcomes throughout the lifespan (Insel, 2014).

Our conceptual model focuses on two main systems of adolescent risk taking: a reactivity system represented by reward and punishment sensitivity and a regulation system represented by inhibitory control that involves frontal cortex functioning. We propose that the key to understanding individual differences in adolescent substance use lies in understanding how the regulation system *modulates* the operation of the reactivity system in the service of goal directed behavior (Carver, Johnson, & Joormann, 2009). Specifically, we propose that inhibitory control may not be an independent, direct predictor, but rather serves as a “regulator” that moderates the link between reward and punishment sensitivity and substance use.

In the current study, we measure inhibitory control at both behavioral and neural levels to examine how it interacts with reward and punishment sensitivity to statistically predict substance use among early adolescents. Inhibitory control is thought of as the ability to voluntarily suppress task-irrelevant, prepotent responses in favor of goal-directed responses (Luna, Padmanabhan, & O’Hearn, 2010). Our operationalization of inhibitory control focuses on behavioral responses and neural activation needed to overcome conflict and to perform effectively (Kerns et al., 2004). The ability to detect and respond to behavioral errors is a critical component of inhibitory control and is supported by a network of regions, including the prefrontal cortex and anterior cingulate cortex (Bush, Luu, & Posner, 2000; Luna et al., 2010). Indeed, research has demonstrated that reduced activity in inhibitory control related brain regions, such as bilateral anterior cingulate cortices, is correlated with greater risk-taking performance in adolescents, and adolescents show less activity in these regions than adults when making risky selections (Eshel, Nelson, Blair, Pine, & Ernst, 2007).

Within research on substance use, it has been theorized that deficits in executive functioning contribute to substance use problems as a result of poor cognitive regulation of behavior (Giancola & Mezzich, 2003). The majority of previous studies examining the associations between executive functioning and substance use focused on inhibitory control (Nigg et al., 2006; Peeters et al., 2015; Squeglia, Jacobus, Nguyen-Louie, & Tapert, 2014; also see Luna, Paulsen, Padmanabhan, & Geier, 2013 for a review). However, evidence for the direct association between inhibitory control and adolescent substance use in nonclinical populations is scant, and the effect sizes are often notably small. For example, in a large sample of high-risk adolescents from families with alcoholism, the effects of poor inhibitory control explained only about 1% of the variance in substance use disorder (Nigg et al., 2006). In a community sample of adolescents and young adults, Pharo and colleagues (2011)

reported a significant, yet weak, concurrent association between a composite of executive functioning (including inhibitory control) and a composite of risk-taking behaviors (including cigarette smoking and other drug use). Further, a longitudinal study involving a community sample of adolescents reported that adolescents who later transitioned into alcohol and marijuana users were not different on inhibitory control performance compared to those who remained substance-naïve (Squeglia et al, 2014).

According to Gray's (1987) reinforcement sensitivity theory, the behavioral approach system (BAS) is sensitive to conditioned reward stimuli and responds with appetitive motivation, whereas the behavioral inhibition system (BIS) responds with aversive motivation to conditioned cues signaling punishment. From this theory, risk-taking behaviors such as substance use can be viewed as resulting not only from sensitivity to reward but also from an inability to inhibit behaviors that will likely result in punishment. In animal models of development, enhanced sensitivity to the rewarding properties of drugs and attenuated sensitivity to the aversive consequences of drugs are consistently found in adolescents relative to adults (Doremus-Fitzwater, Varlinskaya, & Spear, 2010). Among humans, adolescents report greater reward sensitivity than do adults (Urošević, Collins, Muetzel, Lim, & Luciana, 2012), and self-report measures of BAS are associated with substance use behaviors in adolescents and young adults (Braddock et al., 2011; van Leeuwen, Creemers, Verhulst, Ormel, & Huizink, 2011). In contrast, the findings on BIS are mixed. Some researchers have reported that high BIS is related to low substance use (van Leeuwen et al., 2011), whereas other researchers have found non-significant associations (Colder et al., 2013) among adolescents. A recent study using a young adult sample demonstrated that attention control moderated the effects of punishment sensitivity, but not the effects of reward sensitivity, in predicting high alcohol use (Jonker, Ostafin, Glashouwer, van Hemel-Ruiter, & de Jong, 2014). Yet, possible moderating roles of inhibitory control in linking BIS/BAS with substance use initiation and progression among adolescents have not been studied.

In parallel with behavioral research, the neurobiological model of adolescent development (Ernst & Fudge, 2009; Somerville & Casey, 2010) proposes that heightened risk taking in adolescence may be explained by the imbalance among three neural systems: a network underlying responses to reward (centered on the striatum), a network underlying responses to punishment (centered on the amygdala), and a network exerting control over the pursuit or avoidance of risky options (centered on the prefrontal cortex). In particular, the dual systems model of adolescent risk taking emphasizes the imbalance in neural development, involving rapid development of subcortical functioning in conjunction with slow development of prefrontal functioning (Casey, Getz, & Galvan, 2008; Steinberg, 2008). Work in animal models has highlighted a computational role for dopamine in the updating of value expectations, and it is hypothesized that dopaminergic signaling undergoes a developmental transition during adolescence that can dramatically alter the values that adolescents attach to rewarding stimuli in their environment (Wahlstrom, White, & Luciana, 2010). Human neuroimaging work also provides evidence that adolescents are hyper-responsive to rewards, as shown in greater activation in ventral striatum compared to adults, particularly in response to reward receipt (Galvan, 2013).

In theory, neural correlates of inhibitory control have been posited to interact with neural mechanisms of valuation to contribute to impulse control difficulties in adolescence (Luna et al., 2013). This inhibitory control network includes regions of the frontal cortex that undergo maturation, including increased myelination and experience-dependent synaptogenesis and pruning, throughout adolescence and into early adulthood (Paus, 2005). However, current theories regarding the neurobiology of the adolescent brain are based largely on data from neuroimaging studies that compare adolescents to children and adults. To date, it is not known whether individual differences in the three neural systems additively and interactively predict adolescents' risky behaviors such as substance use.

In the current study, we investigated whether inhibitory control serves as a “regulator” that moderates the link between reward and punishment sensitivity and substance use behaviors among early adolescents. We measured inhibitory control using both behavioral performance and neural activity indicators and hypothesized that the link between self-reported BIS/BAS and substance use severity and onset would be significantly stronger for adolescents with weaker inhibitory control. Early adolescence is a particularly vulnerable developmental period characterized by marked increases in many psychopathological conditions including substance use disorders (Windle et al., 2008). Furthermore, early onset of substance use (i.e., 13 years or younger) is a significant predictor of lifetime substance use disorders (SAMSHA, 2009; Swendsen et al., 2012). Therefore, consideration of individual differences in regulatory strength of the control system is crucial to identifying those adolescents who are at greatest risk for substance use initiation and its associated deleterious health consequences.

METHOD

Participants

Participants were 157 adolescents (52% male) aged 13 to 14 years ($M = 14.13$, $SD = 0.54$). About 82% were White, 12% were African American, and 6% were in other racial groups. The median of family annual income ranged from \$35,000 to \$49,999. The sample was representative of the region of the state for household income and race/ethnicity. The exclusion criteria were as follows: claustrophobia, history of head injury resulting in loss of consciousness for more than 10 minutes, orthodontia impairing image acquisition, and contraindications to magnetic resonance imaging.

Procedure

Participants were recruited by diverse advertisement methods including flyers, recruitment letters, and e-mail distributions. Research assistants described the nature of the study to interested individuals over the telephone and invited them to participate. Data collection took place at the university's offices where adolescents and their primary caregivers were interviewed by trained research assistants. All adolescent participants provided written assent and their parents provided written consent for a protocol approved by the university's institutional review board, and they received monetary compensation for participation.

Measures

Substance Use Behaviors (CDC, 2006; Wills, Ainette, Stoolmiller, Gibbons, & Shinar, 2008)—Adolescents were asked to indicate typical frequency (1 = *never used* to 6 = *usually use every day*) and age of initiation (1 = *never used* to 7 = *17 years or older*) separately for cigarette, alcohol, and marijuana use. We recoded the age of initiation scores so that those who had started earlier had higher scores, which also represented having more years of use (1 = *never used*, 2 = *13-14 years*, 3 = *11-12 years*, 4 = *9-10 years*, and 5 = *8 years or younger*). Given the relatively low frequency of substance use in community samples of early adolescents and the significant intercorrelations among substance use behaviors for cigarette, alcohol, and marijuana (Wills et al., 2008), we used the maximum frequency (range = 1 to 5 for cigarette and 1 to 4 for alcohol and marijuana; $r = .48$ to $.53$, $p < .001$) and the earliest onset (range = 1 to 5 for cigarette, alcohol and marijuana; $r = .23$ to $.62$, $p < .01$) to best capture meaningful variation in substance use severity and early onset among our participants of 13-14 years. Our additional analyses confirmed that using average scores of frequency and onset yielded virtually identical results to using maximum frequency and earliest onset scores.

Behavioral Inhibition System and the Behavioral Approach System (BIS/BAS: Carver & White, 1994)—To measure self-reported punishment sensitivity, we used adolescents' reports on the BIS subscale that includes 7 items assessing reactions to the anticipation of punishment ($\alpha = .76$). To measure self-reported reward sensitivity, we used the mean of the Fun Seeking subscale reflecting a tendency to seek out novel, potentially rewarding experiences (4 items) and the Drive subscale reflecting strong pursuit of appetitive goals (4 items) scores of BAS ($\alpha = .76$; $r = .52$, $p < .001$). We did not include the Reward Responsiveness subscale of BAS because a recent meta-analysis study showed that while the Fun Seeking and Drive subscales load on a latent factor indicative of sensation seeking, the Reward Responsiveness failed to load on this factor (Sharma, Markon, & Clark, 2014). Adolescents' responses ranged from 1 = *very true for me* to 4 = *very false for me*.

Inhibitory Control—We measured detection and response to conflict associated with both flanker and spatial interference using the Multi-Source Interference Task (MSIT; Bush, Shin, Holmes, Rosen, & Vogt, 2003). The MSIT requires participants to indicate which of three numbers is different from the other two. In neutral conditions, target numbers were congruent with the numbers' presented locations. In interference conditions, target numbers were incongruent with the target locations (e.g., 2 was in the third position). Consistent with previous reports (Bush et al., 2003), we found a significant MSIT interference effect (i.e., main effect of congruency) in both measures of task performance: in accuracy, $t(155) = -13.29$, $p < .001$, and in reaction time, $t(155) = 68.65$, $p < .001$. Following MacDonald, Karlsson, Rieckmann, Nyberg, and Bäckman (2012), we used intraindividual variability in reaction time which was indexed as intraindividual standard deviations (ISDs) across correct response latency trials of interference conditions.

Imaging acquisition and analysis—We assessed hemodynamic correlates of cognitive conflict using the MSIT. Functional images were acquired using a 3.0T Siemens Tim Trio with the following parameters: echo-planar imaging, gradient recalled echo; repetition time

(TR) = 2 s; echo time (TE) = 30 ms; flip angle = 90°; 34 axial slices, 4.0 mm slice thickness, 220×220 mm field of view (FOV), 64×64 grid, and hyperangulated slices acquired at 30 degrees from anterior-posterior commissure. The structural scan was acquired using a high-resolution magnetization prepared rapid acquisition gradient echo sequence (TR = 1200 ms, TE = 2.66 ms, FoV = 245×245 mm, 1 mm slice thickness, 192 slices with spatial resolution of 1×1×1 mm). Data were processed and analyzed using SPM8 (Wellcome Department of Imaging Neuroscience, London, UK). Functional images were corrected for head motion using a six-parameter rigid-body transformation, realigned, and normalized to template space before smoothing. Images were then realigned and normalized to the Montreal Neurological Institute (MNI) template using parameters derived from a segmented anatomical image coregistered to the mean EPI and were spatially smoothed using an 8 mm full-width at half-maximum Gaussian kernel. As described below, general linear models were specified for each participant and subsequent second level random effects analyses were conducted.

For each participant, individual-level regions-of-interest (ROI) values were extracted at coordinates corresponding to peak activations in the interference minus neutral second-level contrast, as given in Table 1. Specifically, the first eigenvariate values of the contrast images were extracted using spherical masks of 5 mm surrounding MNI coordinates, thresholded at $p < .001$, family-wise error corrected. Among these extracted ROI values in Table 1, variables representing (1) regions known to be engaged by inhibitory control related to interference- and error-processing (Fitzgerald et al, 2010; Koechlin, Ody, & Kouneliher, 2003; Roberts & Hall, 2008) and (2) regions significantly correlated with behavioral performance (i.e., absolute magnitude of correlation $> .2$ with the behavioral performance factor score) were chosen as manifest indicators of the neural inhibitory control factor. These ROIs included left posterior-medial frontal cortex, right inferior frontal gyrus, left and right inferior parietal lobules, right insula, right superior frontal gyrus, and left middle frontal gyrus. Figure 1b illustrates activation in one of the prominent regions related to interference processing, medial frontal cortex.

RESULTS

For inhibitory control behavioral and neural variables, we created factor scores based on confirmatory factor analyses. One participant's behavioral and imaging MSIT data were excluded from the analyses due to extremely low accuracy ($< 16\%$), leaving 156 participants for the main analyses. Additionally, one participant's MSIT accuracy difference score was winsorized due to the extremely low value (i.e., 5 SD below the mean) by changing it to the next lowest value (which was not an outlier). There were 18 participants whose MSIT imaging data were not usable primarily due to excessive movement during image acquisition. For these participants, missing data for the neural variables were imputed by regression imputation using AMOS (Arbuckle, 2014). The structural equation modeling results were consistent between using only $N = 138$ (those who had both behavioral and neural MSIT data) and using $N = 156$ (missing data imputed for neural MSIT data); therefore, $N = 156$ were used.

In evaluating the overall goodness of fit of the structural equation models, we report the chi-square goodness-of-fit statistic (χ^2), degrees of freedom (df), and corresponding p value; the CFI, and the Root Mean Square Error of Approximation (RMSEA). CFI values greater than .90 and RMSEA values of .08 or lower are indicative of good-fitting models (Hu & Bentler, 1999). For testing the adequacy of equality constraints, we report the chi-square difference test results: χ^2 , df , and $p(d)$.

For the inhibitory control behavioral factor, confirmatory factor analysis was performed to produce a factor score using standardized scores of accuracy difference scores (i.e., interference condition minus neutral condition) and reverse coded ISDs of reaction time. In this fully saturated model ($\chi^2 = 0$, $df = 0$, CFI = 1.00), both factor loadings were significant (.73, $p < .001$). For the inhibitory control neural factor, confirmatory factor analysis testing a single factor model based on the 7 ROI variables indicated a good fit ($\chi^2 = 12.05$, $df = 11$, $p = .36$, CFI = 1.00, and RMSEA = .03). All factor loadings were significant ($p < .001$) ranging from .61 to .86. In this model, based on modification indices, three covariances between residuals were estimated: between left and right inferior parietal lobules, between right inferior frontal gyrus and left middle frontal gyrus, and between left posterior-medial frontal cortex and right insula. Higher factor scores of neural inhibitory control were negatively correlated with lower factor scores of behavioral inhibitory control: $r = -.29$ ($p < .001$). This result indicates that adolescents who were more challenged by the interference condition exhibited greater differentiation in hemodynamic activity between the interference and neutral conditions. In contrast, those that had lower differentiation between the conditions were more efficient in interference conditions. Thus, higher neural scores indicated poorer inhibitory control.

Table 2 presents descriptive statistics and correlations for all study variables. Multivariate general linear modeling (GLM) analyses revealed no significant effects of demographic characteristics on the outcome variables, including gender ($p = .44$), ethnicity ($p = .84$; contrasting White vs. Non-White), and family income ($p = .42$). We used two-group structural equation models, based on maximum likelihood estimation, to test our hypothesis regarding the moderating effects of inhibitory control in the link between reward and punishment sensitivity and substance use. There were no variables that deviated from assumptions of normality (skewness greater than 3 and kurtosis 10; Kline, 2011).

We formed high inhibitory control (above mean) vs. low inhibitory control (below mean) groups using the MSIT scores (separately for the behavioral and neural factor scores). We then tested whether the relationship between BIS/BAS and substance use severity and onset was moderated by MSIT (grouping variable) by examining whether the BIS/BAS and substance use association was significantly stronger for the low inhibitory control group compared to the high inhibitory control group. To test the statistical significance of the difference between high vs. low inhibitory control groups, we compared four nested models to the Configural Invariance model in which all parameters were freely estimated across the two groups. In the four nested models, we imposed an equality constraint to test numeric invariance between the low and high inhibitory control groups with respect to the effects of BIS/BAS on substance use severity and onset. If the strength of the particular path

significantly differed between the two groups, model fit was expected to become significantly worse by imposing the equality constraint.

As shown in Table 3, the results for nested model comparisons were consistent between behavioral and neural MSIT factor scores. We first fit the Configural Invariance model (a fully saturated model) and the equality constraint was added on one path at a time beginning with the path from BAS to SU onset. The chi-square difference test indicated that Equal BAS Effect on SU Onset model yielded a significantly worse fit compared to the Configural Invariance model. This finding suggested that the low and high inhibitory control groups showed significantly different magnitudes for the effect of BAS on substance use onset. Therefore, this particular path was freely estimated between the two groups in subsequent models. Next, adding an equality constraint on the effect of BAS on substance use severity between the two groups (Equal BAS Effect on SU Severity model) did not degrade significantly the overall model fit, indicating no significant moderation effect of inhibitory control in the link between BAS and substance use severity. Similarly, adding equality constraints on the effects of BIS on substance use onset (Equal BIS Effect on SU Onset model) and substance use severity (Equal BIS Effect on SU Severity model) did not degrade the model fits significantly. Therefore, the best-fitting models (Equal BIS Effect on SU Severity models in Table 3) included the path for the effect of BAS on substance use onset freely estimated while imposing equality constraints on all other regression paths. Thus, for both behavioral and neural moderation models, the findings indicated that the effects of BAS on substance use onset differed significantly between the two groups, whereas the effects of BAS on substance use severity and the effects of BIS on substance use severity and onset were comparable between the groups. We note that, in Figure 2 and 3, the standardized estimates of the regression paths with equality constraints do not necessarily show the same values due to the differences in standard errors between the groups.

For the moderation effects of behavioral inhibitory control (see Figure 2), higher BAS was predictive of earlier onset of substance use for the low inhibitory control group ($b = .57$, $SE = .22$, $p = .01$), but not for the high inhibitory control group ($b = .13$, $SE = .17$, $p = .45$). For both low and high inhibitory control groups, higher BAS predicted greater substance use severity ($b = .27$, $SE = .12$, $p = .03$) but BIS was not related to substance use onset ($b = .02$, $SE = .13$, $p = .87$) or severity ($b = -.01$, $SE = .10$, $p = .93$). Furthermore, to evaluate whether the link between BAS and substance use onset was strongest for adolescents with the weakest behavioral inhibitory control, we probed changes in simple slopes at various cut-points below the sample mean of behavioral inhibitory control. Indeed, the results indicated that the effect sizes of BAS $\rightarrow$ substance use onset increased as inhibitory control level decreased, with $b^* = .38$ at $-1\ SD$ and $b^* = .62$ at $-2\ SD$ below the mean (all $ps = .001$).

Results for the moderation effects of neural inhibitory control (see Figure 3) were highly consistent with those for behavioral inhibitory control. Higher BAS was predictive of earlier onset of substance use for the low inhibitory control group ($b = .57$, $SE = .20$, $p = .004$), but not for the high inhibitory control group ($b = .07$, $SE = .17$, $p = .69$). For both low and high inhibitory control groups, higher BAS was related to greater substance use severity ($b = .27$, $SE = .11$, $p = .01$), but BIS was not related to substance use onset ($b = .03$, $SE = .13$, $p = .80$) or severity ($b = .01$, $SE = .09$, $p = .90$). To evaluate whether the link between BAS and

substance use onset was strongest for adolescents showing the weakest neural inhibitory control, we probed simple slopes at various cut-points below the sample mean of neural inhibitory control. Consistent with the behavioral inhibitory results, the effect sizes of BAS → substance use onset increased as inhibitory control level decreased, with $b^* = .28$ at $-1 SD$ and $b^* = .37$ at $-2 SD$ below the mean (all p s < .05).

DISCUSSION

Based on a theoretical model emphasizing the moderating role of the regulation system over the reactivity system (Carver et al., 2009), we used behavioral, neural, and self-report measures to illustrate how inhibitory control interacts with reward and punishment sensitivity to produce differential vulnerability to substance use among early adolescents. To our knowledge, the current study presents the first evidence of the moderating role of inhibitory control (specifically, interference control) in the link between reward sensitivity and substance use onset, suggesting that inhibitory control regulates reactivity toward incentives that may ultimately determine substance use behaviors. Specifically, higher levels of reward sensitivity were significantly related to earlier onset of substance use among adolescents with low inhibitory control, but not among adolescents with high inhibitory control. In addition, the magnitude of the effect of reward sensitivity on substance use onset increased toward the low end of the inhibitory control continuum. Thus, reward sensitivity may be particularly important to substance use initiation among those adolescents with the most extreme levels of low inhibitory control.

Although prior research has shown that substance-dependent individuals exhibit deficits in executive functioning (Giancola & Mezzich, 2003), the role of executive functioning in the development of substance use behaviors among typically developing adolescents has not been clearly understood. Some available findings suggest that inhibitory control is not significantly associated with adolescents' risky decision-making (Hooper, Luciana, Conklin, & Yarger, 2004) or has significant yet weak effects on adolescent substance use severity and problems (Nigg et al., 2006; Squeglia et al., 2014). Furthermore, a large population-based longitudinal study of Dutch adolescents reported no significant associations between patterns of alcohol use (non-drinker, light drinker, infrequent drinker, increasing heavy drinker, decreasing heavy drinker, and chronic drinker) and differences in maturation of inhibitory control from age 11 to 19 years (Boelema et al., 2015).

Our findings support the theoretical views that consider cognitive control, governed by prefrontal functioning, as superordinate to reinforcement sensitivity (e.g., Carver et al., 2009; Ernst & Fudge, 2009) and provide a potential account for the weak association between inhibitory control and substance use previously found in studies focused on main effects. Our findings highlight a crucial role of inhibitory control in regulating reward sensitivity to determine substance use initiation among early adolescents. For 13-14 year olds with weak inhibitory control, indicated by poor performance and heightened prefrontal activity during an interference control task, those with high reward sensitivity are likely to initiate substance use at an early age. Yet, reward sensitivity does not seem to promote substance use among early adolescents with strong inhibitory control. A recent survival analysis reported that poor response inhibition itself is predictive of the likelihood of

adolescents' initiating drinking between the ages of 12 and 17 years (Peeters et al., 2015). However, the generalizability of this finding is limited due to the fact that the majority of the sample consisted of males (70%) and adolescents with high levels of externalizing behaviors (70%). Furthermore, from a prevention perspective, identifying predictors of early onset of use is more critical than predicting abstinence over adolescence, given that age of onset is a consistent predictor of lifetime substance use disorders (e.g., Donovan, 2014).

The current results are consistent with past research highlighting the significant role of prefrontal activation during anticipating and receiving rewards in predicting alcohol misuse in a large population-based longitudinal sample of Dutch adolescents (Whelan et al., 2014). Our findings also parallel longitudinal research suggesting a significant moderating effect of attention control, showing that increased anger reactivity between 9 and 11 years was related to increased risk-taking behaviors between 11 and 15 years, only for adolescents with low attention control (Kim-Spoon, Holmes, & Deater-Deckard, 2015). However, this previous study had limitations in that all study constructs were solely based on questionnaire items and the majority of items used for measuring attention control assessed problems with sustained attention—only one aspect of broader regulation skills. In the present study, we represented individual differences in inhibitory control by both behavioral performance and brain activation indicators using task-based laboratory measurements of interference control. Consistent results emerged from different levels of analysis—across behavioral and neural indicators—enabling us to make powerful inferences that we might have not been able to make otherwise. Ideally, future researchers should consider multiple levels of assessment simultaneously (e.g., behavior in laboratory paradigms, behavior in naturalistic contexts, brain imaging, and informant and self-reports) for comprehensive evaluation of individual differences in overall inhibitory control.

Unlike substance use onset, no significant moderation effect of inhibitory control for substance use severity was found. Our data showed that high levels of reward sensitivity were related to high levels of substance use severity among early adolescents, regardless of the level of inhibitory control. This finding is consistent with a previous study by Jonker and colleagues (2014) that demonstrated significant main effects of reward sensitivity and non-significant interaction effects between reward sensitivity and attention control on young adults' heavy alcohol use. However, in their study, significant interaction effects between punishment sensitivity and attention control indicated that low punishment sensitivity was related to heavy alcohol use only among young adults with weak attention control. The discrepancy in the findings regarding the interaction between punishment sensitivity and inhibitory/attention control between the current study and Jonker et al.'s study may reflect differences in the role of reward sensitivity vs. punishment sensitivity related to the developmental progression of substance use behaviors. Mid-adolescents (around ages 14 to 16 years) show heightened reward sensitivity relative to adults (Ernst et al., 2015; Geier, Terwilliger, Teslovich, Velanova, & Luna, 2010; Van Lijenhorst et al., 2010). During early to mid-adolescence, regulating effects of inhibitory control on reward sensitivity may be particularly important for delaying initiation of substance use. In contrast, regulating effects of inhibitory control on punishment sensitivity may be particularly important for demoting progression to heavy substance use among young adults. Future research should consider possible differential pathways by which reward and punishment sensitivity may interface

with inhibitory control to contribute to the *development*—onset, course, and trajectory—of adolescent substance use.

Current theories of neurobiological influences on adolescent risk taking focus on the imbalance between distinct developmental trajectories associated with the neural systems sensitive to reward and punishment and the neural systems associated with cognitive control (Ernst & Fudge, 2009; Somerville, Jones, & Casey, 2010; Steinberg, 2008). Although such developmental imbalance describes ontogenetic trajectories of brain development, it does not explain why only a subset of adolescents is prone to engage in serious risky behaviors that confer negative health consequences, thus highlighting the significance of individual differences in brain development related to adolescent substance use (e.g., Bjork & Pardini, 2015). While prior neuroimaging research has focused heavily on age-dependent differences in reward-related or inhibitory control-related hemodynamic activity and their independent contributions to adolescent risk taking, our findings imply that consideration of individual differences in these two systems and their interaction is crucial to identifying subgroups of adolescents most vulnerable to developing maladaptive substance use behaviors.

In the neuroscience literature, some researchers have studied the interactions between reward-related and control-related processes by introducing incentives to inhibitory control scales to examine how the control system may be affected by the reward system. For instance, prior research using an incentive based modified antisaccade functional magnetic resonance imaging task demonstrated that adolescents showed greater activation not only in striatal regions but also in inhibitory regions during preparation for reward-related inhibition relative to adults (Luna et al, 2013). In contrast, other studies utilizing reward-reinforced inhibitory control tasks failed to find significant differences in the influence of reward on inhibitory responses between adolescents and adults in neural activity (Strang & Pollak, 2014) or behavioral performance (Hardin, Schroth, Pine, & Ernst, 2007; Jazbec et al., 2006; Strang & Pollak, 2014). Compared to such studies using incentivized inhibitory control tasks, our methodological approach has clear advantages: First, considering ranges of reward sensitivity on a continuum better reflects individual differences in reward sensitivity than comparing reactions to discrete levels of incentives (e.g., such as money gain, money loss, and no money incentive conditions). Second, evaluating the statistical interaction between reward sensitivity and inhibitory control enhances our ability to understand why subgroups of adolescents are vulnerable to developing maladaptive substance use behaviors. For example, some adolescents may be vulnerable due to their extremely strong reward sensitivity, whereas others may be vulnerable due to their extremely weak inhibitory control.

Findings from the current study should be interpreted in the context of study limitations. First, the cross-sectional design and analyses do not allow us to infer causality in the identified relationships, and such inferences should be examined in future longitudinal studies. Furthermore, it will be important for future longitudinal research to examine the possibility that moderation effects of inhibitory control among adolescents with lower inhibitory control compared to those with higher inhibitory control may become stronger across development because high risk-takers tend to exhibit early onset of risk-taking behaviors that further impair the development of inhibitory control. Second, we primarily focused on examining whether interactions between reactivity and regulation predict

substance use behaviors. We acknowledge, however, that there are other important biological and environmental-social relationship factors (e.g., genetic, parenting, and peer influences) that contribute to the development of substance use. Finally, although the ranges of substance use behaviors were not restricted, the mean levels of substance use behaviors were relatively low in our sample, though typical of what is seen in community samples of young adolescents (e.g., Swendsen et al., 2012). Replications using adolescents with differing risk levels (e.g., referred or clinical samples) will be helpful to evaluate the generalizability of the current findings.

In conclusion, our findings provide evidence for the moderation effects of inhibitory control, measured at both neural and behavioral levels, potentially accounting for the weak relationship previously found between inhibitory control and substance use in studies focused on main effects. Importantly, the current findings demonstrate how individual differences in two systems theorized to influence the development of risk taking—valuation and control—interact to make joint contributions to substance use behaviors among early adolescents. Adolescent substance use may result from heightened reward seeking. However, if enough inhibitory control capacity is available, such reward seeking can be regulated, resulting in delayed substance initiation during adolescence. In addition to supporting the theoretically hypothesized moderating role of inhibitory control and its associated frontal cortex functioning, our results offer new insights into the identification of adolescents with neurobehavioral vulnerabilities to developing maladaptive substance use behaviors.

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Highlights

- We study two main systems of adolescent risk taking: a reactivity system represented by reward and punishment sensitivity and a cognitive regulation system represented by inhibitory control that involves frontal cortex functioning.
- Our structural equation modeling analyses suggest that inhibitory control, measured by behavioral and neural indicators, moderates the link between reward sensitivity and substance use onset among early adolescents.
- High behavioral activation system (BAS) is related to early onset among adolescents with low cognitive control but not adolescents with high cognitive control.
- Our findings imply that substance use may result from heightened reward sensitivity in adolescence; yet, inhibitory control may be targeted for early prevention strategies for regulating reward sensitivity, resulting in a delay in substance use initiation.

Figure 1.

a) In the multi-source interference task (MSIT), adolescents were asked to identify the digit that differed from two other concurrently presented digits, ignoring its position in the sequence. b) Adolescents exhibited greater medial frontal cortex activation for interference relative to neutral conditions, $t(137) = 20.43$, $p(\text{FWE}) < .001$; displayed at a $p(\text{FWE}) < .001$.

Figure 2.

Summarized modeling fitting results of the path model of relations among behavioral activation system (BAS), behavioral inhibition system (BIS) and substance use onset and severity moderated by behavioral inhibitory control. For each path, standardized coefficients are listed for low inhibitory control/high inhibitory control groups. Significant coefficients are in boldface. * $p < .05$.

Figure 3.

Summarized modeling fitting results of the path model of relations among behavioral activation system (BAS), behavioral inhibition system (BIS) and substance use onset and severity moderated by neural inhibitory control. For each path, standardized coefficients are listed for low inhibitory control/high inhibitory control groups. Significant coefficients are in boldface. * $p < .05$.

Table 1

Areas of significant activation for the contrast of Interference minus Neutral blocks of the Multi-Source Interference Task

Cluster		Peak	MNI Coordinates			Region
<i>k</i>	<i>p</i> (<i>FWE</i>)	<i>t</i>	<i>x</i>	<i>y</i>	<i>z</i>	
759	< .001	21.84	-42	-37	49	L postcentral gyrus
		19.61	-24	-64	49	L superior parietal lobule
		18.07	-30	-55	52	L inferior parietal lobule
265	< .001	20.43	-3	14	49	L posterior-medial frontal
506	< .001	20.42	-39	-85	-2	L inferior occipital gyrus
		20.15	-30	-91	-2	L inferior occipital gyrus
		19.05	-39	-73	-8	L fusiform gyrus
654	< .001	19.21	42	-64	-8	R fusiform gyrus
		19.17	42	-82	-2	R inferior occipital gyrus
		18.46	33	-91	1	R inferior occipital gyrus
		15.78	39	-67	-23	R cerebellum (crus 1)
		15.24	33	-49	-26	R cerebellum (VI)
245	< .001	19.06	-24	-4	55	L middle frontal gyrus
431	< .001	18.12	30	-58	52	R inferior parietal lobule
		18.11	45	-31	49	R postcentral gyrus
		16.52	30	-64	40	R superior occipital gyrus
140	< .001	17.38	27	-4	55	R superior frontal gyrus
94	< .001	16.89	-45	2	34	L inferior frontal gyrus (pars opercularis)
46	< .001	15.01	-9	-19	10	L thalamus
24	< .001	14.50	33	20	7	R insula lobe
7	< .001	13.47	6	-73	-20	Cerebellar vermis (7)
13	< .001	13.32	48	8	31	R inferior frontal gyrus (pars opercularis)
12	< .001	13.31	-30	17	10	L insula lobe
5	< .001	12.73	9	-19	10	R thalamus
9	< .001	12.66	-27	-55	-23	L cerebellum (VI)
		12.60	-27	-64	-23	L cerebellum (VI)

Note. Voxel-wise thresholded at $t = 12$, equivalent to $p = 2.00 \times 10^{-23}$ uncorrected. *k* = the number of voxels in each significant cluster; *FWE* = family-wise error corrected; *t* = peak activation level in each cluster; *x*, *y*, *z* = MNI coordinates; L = left; R = right.

Descriptive Statistics and Bivariate Correlations among Reward and Punishment Sensitivity, Inhibitory Control, and Adolescent Substance Use

Table 2

	1	2	3	4	5	M	SD
1. Behavioral Activation System (BAS)	–					2.80	.50
2. Behavioral Inhibition System (BIS)	–.04	–				2.86	.56
3. MSIT behavioral factor score	–.10	.09	–			.00	.84
4. MSIT neural factor score	–.07	.07	–.29**	–		.00	.27
5. Substance use severity	.20*	–.01	–.02	.08		1.47	.75
6. Substance use onset	.18*	.00	–.10	.06	.70**	1.50	.95

Note. MSIT = Multiple Source Interference Task.

* $p < .05$;
** $p < .01$

Comparisons of Two-Group Structural Equation Models for Reward and Punishment Sensitivity, Inhibitory Control, and Adolescent Substance Use

Table 3

Model Label	χ^2	df	p(exact)	CFI	RMSEA	p(close)	Comparison	χ^2	df	p(d)
<i>High vs. low groups by MSIT behavioral factor scores</i>										
1-a. Configural Invariance	0	0	-	1.00	-	-				
1-b. Equal BAS on SU Onset Effects	5.65	1	.02	.96	.17	.04	a vs. b	5.65	1	.02
1-c. Equal BAS on SU Severity Effects	2.47	1	.12	.99	.10	.19	a vs. c	2.47	1	.12
1-d. Equal BIS on SU Onset Effects	2.52	2	.28	1.00	.04	.41	c vs. d	0.05	1	.83
1-e. Equal BIS on SU Severity Effects	3.28	3	.35	1.00	.03	.51	d vs. e	0.76	1	.38
<i>High vs. low groups by MSIT neural factor scores</i>										
1-a. Configural Invariance	0	0	-	1.00	-	-				
1-b. Equal BAS on SU Onset Effects	4.98	1	.03	.96	.16	.06	a vs. b	5.00	1	.03
1-c. Equal BAS on SU Severity Effects	0.65	1	.42	1.00	.00	.50	a vs. c	0.65	1	.42
1-d. Equal BIS on SU Onset Effects	1.32	2	.52	1.00	.00	.63	c vs. d	0.67	1	.41
1-e. Equal BIS on SU Severity Effects	1.55	3	.67	1.00	.00	.78	d vs. e	.23	1	.63

Note. BAS = Behavioral Activation System; BIS = Behavioral Inhibition System; SU = Substance Use; $p(\text{exact})$ = probability of an exact fit to the data; CFI = comparative fit index; RMSEA = root mean square error of approximation; $p(\text{close})$ = probability of a close fit to the data; χ^2 = difference in likelihood ratio tests; df = difference in df ; $p(d)$ = probability of the difference tests. Best-fitting model is in bold face