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Reward activation in childhood predicts adolescent substance use initiation in a high-risk sample*

Lora M. Cope[a], **Meghan E. Martz**[a], **Jillian E. Hardee**[a], **Robert A. Zucker**[a], and **Mary M. Heitzeg**[a]

[a]Department of Psychiatry and Addiction Center, University of Michigan, 4250 Plymouth Road, Ann Arbor, MI, USA

Abstract

Background—Substance use at an early age conveys substantial risk for later substance-related problems. A better understanding of early risk factors could result in more timely and effective intervention. This study investigated the predictive utility of the brain's response to reward anticipation as a risk factor for early substance use initiation.

Methods—Participants were 34 children (25 male) at high risk for alcohol and other substance use disorders from a longitudinal functional magnetic resonance imaging study, scanned at a mean age of 10.5 years (*SD* = 1.2) when participants were substance-naïve. We used a monetary incentive delay task to examine the hemodynamic response of the nucleus accumbens to gain and loss anticipation. Logistic regression was used to test the hypothesis that these brain response patterns would have predictive utility over and above early externalizing behaviors and family history of substance use disorder, two key risk factors for substance use problems, in differentiating those who initiated substance use before age 16 (n = 18) and those who did not (n = 16).

Results—Greater nucleus accumbens activation during monetary gain anticipation in childhood increased the likelihood of initiating substance use during early adolescence (p = .023). The model that comprised neural data in addition to early externalizing behaviors and family history showed significantly better fit than the model without neural data (χ^2_2 = 7.38, p = .025).

Conclusions—Heightened gain anticipation activation in the nucleus accumbens may predispose individuals to early substance use, beyond the risk conveyed by other known factors.

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Correspondence: Mary M. Heitzeg, Department of Psychiatry and Addiction Center, University of Michigan, 4250 Plymouth Road, Ann Arbor, MI 48109, USA, mheitzeg@med.umich.edu.

Contributors

RAZ and MMH conceived of the study. MMH and LMC conceived of the analyses. LMC analyzed the data and drafted the manuscript, with help from MEM, JEH, RAZ, and MMH. All authors critically revised the manuscript and approved of the final version.

Conflict of Interest

The authors have no conflicts of interest.

Keywords

Monetary Incentive Delay (MID); Nucleus Accumbens (NAcc); functional Magnetic Resonance Imaging (fMRI); Externalizing; Family History; Logistic Regression

1. Introduction

Adolescence is marked by heightened risk for maladaptive behaviors including experimentation with drugs and alcohol. Despite its prevalence (Miech et al., 2018), adolescent substance use is associated with negative outcomes, including problematic use and substance use disorder (SUD) (Dawson et al., 2008; Grant and Dawson, 1997, 1998; King and Chassin, 2007). Animal work suggests that adolescent substance use may have neurotoxic effects on the brain, leading to long-term, harmful alterations in brain function (O'Shea et al., 2004; Taffe et al., 2010). Attempts to ameliorate the negative consequences of early substance use initiation may be aided by a better understanding of risk factors that contribute to such use, particularly those operating at the neural level.

Reward system functioning, mediated by the mesolimbic dopaminergic reward pathway, has been identified as a likely neurobiological risk marker for problem substance use (McBride and Li, 1998; Piazza et al., 1991; Volkow and Morales, 2015; Volkow et al., 2002) due to its critical role in incentive processing (Schultz, 1998) and the reinforcing properties of drugs of abuse (Robinson and Berridge, 2000). Drugs of abuse activate the mesolimbic dopamine reward pathway, as do natural rewards such as food and conditioned rewards such as money. Developmental changes in reward system functioning beginning in preadolescence are proposed to contribute to the risk-taking and impulsivity characteristic of this age group (see Casey and Jones, 2010 for a review). As youth transition into adolescence, "developmental mismatch" or "dual systems" models posit that subcortical reward system structures such as the ventral striatum (VS)—including nucleus accumbens (NAcc)—mature earlier and operate with a different trajectory relative to prefrontal control systems (Chambers et al., 2003; Galvan et al., 2006; Shulman et al., 2016; Somerville et al., 2011; Somerville et al., 2010). In addition, compared with both childhood and adulthood, D1 and D2 dopamine receptor density in the striatum is highest in early adolescence (Tarazi and Baldessarini, 2000). Whereas these developmental changes may underlie adolescent-typical behaviors that contribute to substance use risk, not all youth engage in impulsive, sensation-seeking, and risk-taking behaviors such as substance use. Individual variability in reward system functioning assessed before exposure to drugs and alcohol is likely to be informative in determining who is at the highest risk for substance use in adolescence.

Recent evidence suggests that mesolimbic dopamine is specifically related to the anticipatory rather than consummatory component of motivated behavior (Salamone and Correa, 2012; Schott et al., 2008). The monetary incentive delay (MID) task (Knutson et al., 2000) in conjunction with functional magnetic resonance imaging (fMRI) has been used to characterize the neural correlates of this anticipatory component: Anticipation of monetary gain and loss during this task robustly induces activation of the VS (including NAcc (Carter et al., 2009)), one of the central components of the reward pathway. Importantly, this fMRI

signal has been found to reflect phasic dopamine activity (Knutson and Gibbs, 2007). Note that herein we use the term *reward anticipation* more broadly than *gain anticipation*. That is, the former reflects the response of the reward system to the anticipation of both positive and negative incentives (Carter et al., 2009), whereas the latter refers specifically to the anticipation of winning money in the context of the MID or similar task.

There are opposing positions, however, regarding the association between pre-morbid reward functioning and risk for problem substance use. One theory asserts that a hyper-responsive reward system is indicative of reward-seeking tendencies, including increased substance use (Hariri et al., 2006; McClure et al., 2004), whereas others propose that a hypo-responsive reward system motivates the desire for drugs and alcohol to normalize low baseline dopamine levels (Blum et al., 2000). Most prior work on reward anticipation processing in addiction has been done in adults with SUDs. For instance, two studies found evidence for hypo-responsive reward system functioning during the anticipation of monetary gains and losses in individuals who had detoxified from alcohol relative to healthy controls (Beck et al., 2009; Wrase et al., 2007). In contrast, other studies have found no differences in VS activation to anticipatory gains and losses between substance users and healthy controls (Bjork et al., 2008b; Jia et al., 2011). Prospective studies involving younger participants have also examined associations between reward circuitry functioning and later problem substance use. For instance, one study of children, adolescents, and young adults found that elevated NAcc activation during MID task gain anticipation was positively correlated with later alcohol problems (Heitzeg et al., 2014).

Studies have also examined the impact of family history of SUD (FH) on reward anticipation due to substantial evidence of higher rates of substance-related problems in the offspring of individuals with a SUD (Russell et al., 1990; Schuckit and Smith, 1996; Sher et al., 1991). For instance, one study (Yau et al., 2012) found a drinking × FH interaction whereby light-drinking FH+ individuals had less NAcc activity during the anticipation of both monetary gains and losses compared to heavy-drinking FH+ and FH-individuals. NAcc activation during gain and loss anticipation positively correlated with drinking in FH+ individuals only. In contrast, (Muller et al., 2015) found no VS activation differences between FH+ and FH-adolescents with low levels of substance use during the anticipation of monetary gains. Finally, Bjork and colleagues (Bjork et al., 2008a) also found no differences between FH+ individuals and controls on VS activation during monetary gain versus non-gain anticipation, but importantly, they did find a significant correlation between self-reported sensation seeking and gain anticipation-induced VS activity, highlighting the potential link between heightened mesolimbic gain anticipation activation and conscious behaviors associated with substance use risk.

These prior studies were conducted in samples which were not substance-naïve (Beck et al., 2009; Bjork et al., 2008b; Heitzeg et al., 2014; Jia et al., 2011; Muller et al., 2015; Wrase et al., 2007; Yau et al., 2012), or the authors did not report level of substance use (Bjork et al., 2008a). Therefore, it is unclear whether the effects were a cause or a consequence of substance use. Indeed, little is known about reward responsivity differences in youth *before* they initiate substance use. There is mounting evidence that substance use alters reward responsivity—particularly to non-drug rewards such as money (Bechara et al., 2002; Filbey

et al., 2016; Martz et al., 2016; Nestor et al., 2010)—suggesting that previous work on past and/or current substance users are ill-equipped to speak specifically to risk. What is needed is the characterization of reward circuitry before drug and alcohol use is initiated. To our knowledge, there are no studies in substance-naïve individuals investigating reward responsivity as a marker for differentiating youth who do and do not go on to use substances.

To address this gap, we used a modified MID task during fMRI scanning to investigate the neural correlates of reward anticipation in youth before the initiation of substance use. Participants were recruited from the Michigan Longitudinal Study (MLS), a prospective community study of families enriched for alcohol and other SUDs (Zucker et al., 1996; Zucker et al., 2000). Children were scanned at a mean age of 10.5 years and tracked annually to determine if and when they initiated drug and/or alcohol use. Anatomically defined NAcc activity and logistic regression were used to differentiate the initiation and comparison groups. Specifically, we sought to determine whether, among substance-naïve children, those who go on to initiate substance use at an early age would show hypo- or hyper-active reward responding to incentive cues. Here we define *early substance initiation* as more than a sip of alcohol or any use of other substances before the age of 16. Based on developmental changes in dopaminergic reward systems and the studies addressing substance use risk (rather than past/current substance use) reviewed above, we hypothesized that hyper-active reward responding would be associated with early substance use initiation. An additional goal was to quantify the predictive utility of neural functioning during reward anticipation in children as an objective marker of early substance use initiation, over and above the risk conveyed by two other major risk factors, FH, and early externalizing behaviors.

2. Material and Methods

2.1 Participants

Participants were 34 youth (25 male) from the MLS (Zucker et al., 1996; Zucker et al., 2000), aged 8.2–12.9 at the time of the fMRI scan ($M = 10.5$, $SD = 1.2$). The MLS is a multi-wave, community-recruited study of families with and without parental alcohol use disorder (AUD). As part of the MLS, assessments were conducted every three years starting when the children were aged 3–5; adolescents and young adults were also assessed every year from age 11–26. Families were excluded if the target child displayed evidence of fetal alcohol effects or the mother reported drinking during pregnancy. The majority of participants in the present analyses (82.4%) were FH+ for SUD, making this a high-risk sample. (Although the original recruitment strategy of the MLS involved accessing a community-based sample of parents with AUD, their high other drug comorbidity meant that their offspring would be at elevated risk for both alcohol and other drug use. The MLS has historically focused on understanding these other risk patterns as well [Martel et al., 2009; Martz et al., 2016; Nigg et al., 2006]) Full details on MLS assessment and data collection can be found elsewhere (Zucker et al., 2000).

For the present imaging study, participants were excluded if they had any neurological, acute, uncorrected, or chronic medical illness; current or recent (within 6 months) treatment with centrally active medications; MRI contraindications such as metal implants or

claustrophobia; IQ < 70; history of psychosis in self or first-degree relatives; or current, active Axis I disorder according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) (American Psychiatric Association, 1994) criteria. However, disorders that are often comorbid with substance use were *not* part of the exclusion criteria (so as not to bias the sample against our construct of interest): current or past anxiety, conduct or attention deficit hyperactivity (ADHD) disorder, or past mood disorder. Participants who were taking medication for ADHD were asked to abstain at least 48 hours before the MRI scan. Parents/guardians of participants provided written informed consent and participants provided written informed assent. Study materials and procedures were approved by the University of Michigan Medical School Institutional Review Board.

2.2 Measures

2.2.1 Substance use—Drinking and drug use histories were obtained from each participant by trained research staff as part of the regular MLS assessment schedule. Beginning at age 6 and occurring at three-year intervals thereafter, a health and daily living questionnaire was used to assess the use of alcohol (more than a sip), cigarettes, marijuana, and other drugs. If applicable, the age at which use occurred and the quantity/frequency of use was also recorded. At annual assessments beginning at age 11, the Drinking and Drug History Form for Children (Zucker and Fitzgerald, 1994) was used to assess the quantity and frequency of alcohol, nicotine, and illicit drug (i.e., marijuana and 17 other drugs, including inhalants and prescription drugs used non-medically) use. Problems associated with alcohol and drug use, respectively (e.g., missed school because of drinking, had trouble getting along with friends because of drug use), were also assessed.

Previous research has shown that substance use initiation before the age of 16 confers a higher risk for later problems than does initiation in young adulthood (Clapper et al., 1995; Gruber et al., 2012; Strashny, 2013). Therefore, we used age 16 as the threshold for increased risk and selected participants from the ongoing longitudinal study for whom we had follow-up substance use data at age 16 or older (ensuring that all comparison participants were beyond the highest-risk window). Participants also had to have a fMRI scan prior to any substance use in order to be included in the present analyses. Of the 34 participants who met these criteria, 18 eventually initiated substance use (11 male; *initiation group*), whereas 16 did not (14 male; *comparison group*). On average, those in the comparison group were 17.9 years old (*SD* 1.5) at the most recent substance use assessment, whereas those in the initiation group were 13.4 years old (*SD* 1.5) at substance use initiation.

2.2.2 Other measures—The Wechsler Intelligence Scale for Children (WISC-III) (Wechsler, 1991) was used to assess full-scale IQ. Early externalizing behaviors ($M = 7.4$ years old, $SD = 1.0$) were assessed via parent-report with T-scores from the Child Behavior Checklist (CBCL) (Achenbach, 1991). For ADHD, conduct disorder, depression, and anxiety diagnoses (i.e., disorders that were not exclusionary during screening), the computerized Diagnostic Interview Schedule for Children (C-DISC) (Shaffer et al., 2000) was given, and diagnoses were tallied based on DSM-IV (American Psychiatric Association, 1994) criteria. Finally, FH was defined as the number of parents (0, 1, or 2) with a lifetime diagnosis of drug or alcohol abuse or dependence, according to DSM-IV criteria.

2.3 Stimuli and Task

A modified MID task (Knutson et al., 2000) was used to probe the brain's response to the anticipation of monetary incentive (i.e., gain and loss). Each trial was 6-s long and consisted of 4 stimuli, presented consecutively: 1) 2000-ms incentive cue ("Win $5.00," "Win $0.20," "Don't Lose $5.00," "Don't Lose $0.20," or "No Money at Stake"), 2) 2000-ms anticipation fixation cross, 3) variable-duration response target (i.e., a solid black shape cuing a button press), and 4) variable-duration feedback (e.g., "Correct Response. You earn $5.00!"). There was no inter-trial interval. Participants were instructed to press the button to the target; responding while the target was on the screen signified a successful trial (i.e., hit). Response target duration was calculated based on each participant's reaction time during a practice session prior to scanning and recalibrated after the first run for an overall success rate of approximately 60%. Participants were also instructed to respond to neutral targets (i.e., "No Money at Stake") despite no incentive value. Trials were presented in pseudorandom order in two 5-minute runs of 20 gain trials, 20 loss trials, and 10-neutral trials per run. Participants were paid money won during the task.

2.4 fMRI Data Acquisition

Whole-brain BOLD, functional images were acquired on a 3.0T GE MR750 scanner (Milwaukee, WI) using T2*-weighted single-shot combined spiral in/out sequences (Glover and Law, 2001) (TR 2000 ms, TE 30 ms, flip angle 90 degrees, field-of-view 200 mm, matrix size 64 × 64, slice thickness 4 mm, in-plane resolution 3.12 × 3.12 mm, 29 slices). High-resolution anatomical T1 scans were also obtained for spatial normalization (TR 12.2 ms, TE 5.2 ms, flip angle 15 degrees, field-of-view 26 mm, matrix size 256 × 192, slice thickness 1.2 mm, in-plane resolution 1.02 × 1.08 mm, 124 slices). Motion was minimized with foam padding around the head and instructing participants on the importance of keeping still.

2.5 Data processing and analytic strategy

2.5.1 Preprocessing—Functional images were reconstructed using an iterative algorithm (Noll et al., 2005; Sutton et al., 2003) and motion corrected using FSL v5.0.2.2 (FMRIB, Oxford, UK). Runs exceeding 3 mm translation or 3° rotation were excluded. The difference between initiation and comparison groups on the number of runs excluded was not significant: initiation = 16.7%, comparison = 15.6%, $t(32) = 0.13$, $p = .901$. Image preprocessing was completed using Statistical Parametric Mapping (SPM8; Wellcome Institute of Cognitive Neurology, Oxford, UK). Functional images were slice-time corrected, spatially normalized to the Montreal Neurological Institute (MNI) template using SPM8 defaults, and smoothed with a 6-mm full-width at half-maximum (FWHM) smoothing kernel. Low-frequency noise was removed with a high-pass filter (128 sec).

2.5.2 Individual-level analyses—Image processing was done in SPM8, and individual-level analyses were carried out using the general linear model. Two general events were modeled: 1) incentive cue + anticipation fixation, and 2) response target + feedback. The incentive cue + anticipation fixation event was modeled separately for each cue type: large gain, small gain, large loss, small loss, and neutral. The response + feedback

event was modeled separately for each cue (except neutral) and feedback type: positive (i.e., hit) and negative (i.e., miss) for each of large gain, small gain, large loss, and small loss. These were convolved with the standard hemodynamic response function, along with six realignment parameters and white matter signal intensity as nuisance variables. Owing to our focus in this study on NAcc activation during the anticipation of gaining and losing money, NAcc spherical anatomical masks of 5 mm in diameter and centered on the Montreal Neurological Institute coordinates of [$x = -10$, $y = 13$, $z = -8$] and [$x = 10$, $y = 13$, $z = -8$] (Bjork et al., 2008b) were used to extract mean parameter estimates with MarsBaR (Brett et al., 2002) for two contrasts of interest: large gain anticipation vs. neutral anticipation (i.e., Win $5.00 vs. No Money at Stake) and large loss anticipation vs. neutral anticipation (i.e., Don't Lose $5.00 vs. No Money at Stake). This task was originally developed with different incentive values so that the parametric effect of different monetary amounts could be investigated. Our interest here was in the function of reward processing overall rather than the difference between large and small incentives, and previous work has found that large incentives elicit a more robust signal than do small incentives (Bjork et al., 2008a). Thus, we focused on large gain and loss for the present analyses. After extraction, comparisons of the left and right NAcc using paired samples *t*-tests (large gain: $t(33)=0.94$, $p=.353$; large loss: $t(33)=0.09$, $p=.928$) and correlational analyses (large gain: $r=.84$, $p<.001$; large loss: $r=.73$, $p<.001$) indicated that a single averaged left/right NAcc variable for each of the two contrasts of interest could be used.

2.5.3 Prediction of substance use initiation using logistic regression—

Hierarchical logistic regression was used to test the predictive utility of substance use risk factors on the initiation of substance use by age 16. Group membership (initiation or comparison) was the dependent variable. Phenotypic variables (externalizing behaviors [continuous variable] and FH [i.e., 0, 1, or 2 parents]) were entered as predictors in the first block (restricted model). NAcc variables (large gain anticipation and large loss anticipation [continuous variables]) were added in the second block (full model). No other covariates were included in either block. Model comparison was performed using a likelihood ratio test to determine whether the full model (i.e., phenotypic and NAcc variables) showed a significantly better fit than the restricted model (i.e., phenotypic variables alone). In addition, beta coefficients were individually tested for significance. Alpha was set at .05 for both of these analyses.

2.5.4 Demographic, Psychometric, and Task Performance Measures—

Independent samples *t*-tests or Fisher's exact tests were used to evaluate differences between initiation and comparison groups on demographic, psychometric, and task performance measures.

3. Results

3.1 Demographic variables and participant characteristics

There were no significant differences (i.e., all ps > .05) between groups on sex, age at fMRI scan, IQ, or FH. There were also no significant differences in early externalizing behaviors

or lifetime conduct disorder, ADHD, anxiety, or depression diagnoses. No participants met criteria for SUD at follow-up. See Table 1 for statistics.

3.2 Task performance

There were no significant differences between initiation and comparison groups on task performance measures (i.e., success rate and reaction time). See Table 2 for statistics.

3.3 Brain imaging

To confirm that the MID task elicited the expected NAcc activations, we computed one-sample *t*-tests in the whole sample ($N = 34$) for each contrast of interest. See Supplemental Material[1] for these task main effects (Table S1 and Figure S1) as well as for analyses demonstrating our measurement of reward anticipation (and not general response anticipation) and our disentangling of the effects of anticipation from those of feedback.

3.3.1 Prediction of substance use initiation—The restricted model (i.e., comprising externalizing behaviors and FH) did not significantly predict group membership ($\chi^2_2 = 4.41$, $p = .110$) and had an overall classification accuracy of 61.8%. The full model (i.e., comprising NAcc variables in addition to externalizing behaviors and FH) significantly predicted group membership ($\chi^2_4 = 11.80$, $p = .019$). The full model was also a significantly better predictor of group membership than the restricted model ($\chi^2_2 = 7.38$, $p = .025$) according to a log likelihood test. The overall classification accuracy of the full model was 73.5%, and the area under the curve was .826. Of the four predictors, only anticipation of large gain was significant ($B = 1.76$, $p = .023$). The odds ratio for large gain anticipation was 5.81, indicating the increase in the odds of initiating substance use for a one-unit increase in the predictor, holding externalizing behaviors, FH, and large loss anticipation constant. See Table 3 for statistics.

4. Discussion

An aim of this prospective study was to determine whether activation during reward anticipation in substance-naïve children can predict who will go on to use substances in adolescence, above and beyond other risk factors. Results revealed that greater NAcc activity during the anticipation of winning money was associated with subsequent substance initiation, controlling for early externalizing behaviors and parental SUD. This finding is in line with the hypothesis that hyperactivation of reward circuitry may be a risk factor for later substance use problems.

The NAcc is one of the central structures in the mesolimbic dopaminergic pathway, receiving projections from the ventral tegmental area. Together these regions are critically involved in motivated behavior, including reward seeking and SUD. Convergent evidence has demonstrated that all drugs of abuse increase synaptic dopamine in the NAcc (e.g., (Dichiara and Imperato, 1988; Johnson and North, 1992)). The NAcc is also implicated in non-drug reward (e.g., (Beck et al., 2009; Ernst et al., 2005; Knutson et al., 2001)). The

[1]Supplementary material can be found by accessing the online version of this paper at http://dx.doi.org and by entering doi:

present study adds to the extant literature by demonstrating that (a) substance-naïve children who express greater NAcc activation during the processing of non-drug (i.e., monetary) gain anticipation are more likely to use substances in adolescence, and (b) neural circuitry regulating a specific aspect of reward processing (i.e., gain anticipation) appears to play at least as strong a role as do previously identified phenotypic measures.

Adolescence is a developmental period marked by heightened risk-taking (Spear, 2000), including substance use. Heightened sensitivity to reward has been identified as a possible mechanism (e.g., (Casey and Jones, 2010)). In support of this, increased magnitude of gain-related NAcc activation has been found in adolescents relative to adults (Galvan et al., 2006; Heitzeg et al., 2014). Not all adolescents engage in risky behavior, however, and here we found that differences during childhood in NAcc activation to the anticipation of winning money predicted who would go on to use drugs and/or alcohol at an early age. This finding is consistent with prior work by Galvan and colleagues (Galvan et al., 2007) that found the likelihood of engaging in risky behavior was significantly positively correlated with NAcc activity to large vs. small monetary gain. Associations between VS activity and risky decisions have also been found in adults (Kuhnen and Knutson, 2005; Matthews et al., 2004). The present findings are consistent with these adult and adolescent studies and extend the potential association between VS activity and risk-taking behavior, such as early substance use, to children.

As described previously, the MID task is characterized by an incentive cue followed by an anticipatory phase, a response target, and then feedback. The present study focused on the anticipation of large gains and large losses compared to neutral anticipation (i.e., no money at stake). Some reports indicate that activation of the VS to the anticipation of both monetary gains and losses supports the role of motivational salience in addiction risk (Robinson and Berridge, 2008; Yau et al., 2012). Other research suggests that two different systems underlie brain activation to the anticipation of gains and losses. According to this latter view, the anticipation of gain elicits a dopaminergic response from the mesolimbic reward pathway, whereas loss anticipation is thought to be associated to a greater extent with serotonergic responding as a function of behavioral inhibition and risk aversion (Beck et al., 2009; Daw et al., 2002). Although it was not possible in the present study to test the biochemical processes associated with brain activation, our findings demonstrating a significant positive effect of NAcc activation to monetary gain and a negative effect trending towards significance for NAcc activation to monetary loss point to the possibility of different neural mechanisms involved in gain versus loss in terms of substance use outcomes.

A number of strengths of this study are worth noting. First, we scanned subjects at a very early age (i.e., 8.2–12.9 years), ensuring that we would be able to characterize the neural correlates of reward anticipation *before* any experimentation with drugs or alcohol took place. This is particularly important given evidence that substance use may have diffuse effects on reward processing and extend to other types of rewards (e.g., (Nestor et al., 2010)). Second, because the initiation of alcohol (Clapper et al., 1995), marijuana (Gruber et al., 2012), or substance use in general (Strashny, 2013) before the age of 16 conveys greater risk for later social, emotional, and physical problems, we only included subjects for whom we had substance use data after the age of 16 in order to ensure that they had aged out of the

window of highest risk for these problems. Finally, we controlled for other common predictors of substance use initiation, namely FH and externalizing behaviors. These constructs have been shown to convey a significant risk for later SUDs and problems (Chassin et al., 1999; Hussong et al., 2012; Merikangas et al., 1998). For instance, one study found that family history conferred an 8-fold risk for SUD (Merikangas et al., 1998). Another study found significantly increased odds of regular alcohol, nicotine, and cannabis use at age 14 among those with high externalizing at age 11 (King et al., 2004). Based on these previous observations, it was important to account for the influence of both FH and externalizing when determining the extent to which brain activity predicts substance use.

Interestingly, in this sample, neither FH nor externalizing behaviors were significantly different between the initiation and comparison groups when tested is isolation with independent samples *t*-tests. In addition, neither variable was a significant predictor of substance use initiation. With regard to FH, one explanation for the nonsignificant finding could be due to the manner in which it was measured (i.e., number of parents with a SUD). Future work should consider including second-degree relatives and/or family density scores in the measurement of FH in order to provide a more fine-grained measure of the predictive power of this variable. It is possible that externalizing behaviors did not emerge as significantly different between groups because of reduced variance as a product of participants' relatively young age as well as the fact that none of them had started using alcohol or drugs at the time of the scan. Finally, as this was a high-risk sample with only 6 FH-participants, externalizing and FH may not have been predictive due to reduced variance in these variables. FH and externalizing behaviors may be predictive of substance use initiation in a healthy, community sample.

Several points are important to keep in mind when interpreting these results in the context of the broader literature on reward anticipation and substance use. Those who initiated substance use in the present study did not reach the threshold for a SUD, indicating that the contrast is between adolescents who try drugs and alcohol at a relatively early age and those who do not. Thus, the differences in brain function are related to substance use *initiation* rather than something more serious such as dependence. At the same time, adolescents who initiate alcohol use at age 15 have nearly four times the risk for later alcohol dependence compared to those who start at 21 or older (Grant and Dawson, 1997). Similarly, the risk for later drug dependence is almost twice as high in those who start using at age 15 relative to those who start at 21 or older (Grant and Dawson, 1998). Additionally, over 94% of the initiation group from the present sample reported using more than one substance, indicating a substantially increased risk for problem use later in life (Moss et al., 2014). It will be important to continue following these youth into late adolescence and young adulthood in order to track their substance use trajectories as a function of the neurobiological differences observed here. In addition, some limitations should be noted. First, we were not able to investigate sex differences in reward responsivity, owing to the sample being primarily male and to the modest sample size due to the practical constraints of scanning a high-risk sample of substance-naïve youth and following them annually. Second, this sample included children with conduct disorder, ADHD, and anxiety and depressive disorder diagnoses within their lifetime. That is, they display the variations in level of psychopathology that would be anticipated from a community sample whose families are elevated on substance

use and related comorbidities (e.g., antisocial behavior, depression). Thus, these results may not generalize to children at different levels of risk, such as samples with higher rates of disruptive behavior disorders (who would be expected to have an even greater risk) and those without any lifetime DSM diagnoses (who would be expected to have a lower risk). Finally, we did not have data on pubertal status, which may be important when the participant age range covers late childhood and early adolescence, as it did here. These issues should be considered in future studies.

4.1 Conclusions

To our knowledge, this is the first study to investigate reward anticipation processing in substance-naïve children as a predictor of adolescent substance use initiation. This work is important in order to differentiate the risk factors from the consequences of substance use. Given how malleable the brain is at this age, these results highlight the feasibility and importance of assessing youth quite early and focusing treatment efforts on neurobiological deficits that are directly related to risk *before* they transition to more problematic use in adulthood. Heightened responsivity to gain anticipation in the NAcc may predispose individuals to early substance use, beyond the risk conveyed by other factors. Despite the difficulty in scanning subjects at a young age and following them over a period of several years in order to characterize their substance use patterns, it will be critical to conduct further studies of this sort. Indeed, the National Institutes of Health's Adolescent Brain Cognitive Development study is currently underway and will undoubtedly produce other important information about substance abuse risk.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Substance-naïve children scanned with fMRI during a monetary incentive delay task
- Childhood nucleus accumbens activity predicted adolescent substance use initiation
- The model with neural variables performed better than the model without them

Table 1.

Participant Characteristics

	Initiation Group (*n* = 18)	Comparison Group (*n* = 16)	Statistic	Significance
% Female	38.9%	12.5%	—	$p = .125^{a}$
Age at fMRI Scan	10.7 (1.2)	10.2 (1.1)	$t(32) = 1.26$	$p = .216^{b}$
Age at First Substance Use	13.4 (1.5)	n/a	—	—
Full-Scale IQ *	106.8 (15.0)	107.3 (12.4)	$t(31) = 0.11$	$p = .910^{b}$
Phenotypic Variables				
Family History of SUD (*n*; 0/1/2 parents)	2/5/11	4/7/5	—	$p = .233^{a}$
Early Externalizing Behaviors **	51.1 (10.2)	46.0 (10.3)	$t(32) = 1.46$	$p = .155^{b}$
Nucleus Accumbens Variables				
Large Gain Anticipation vs. Neutral Anticipation	1.26 (0.78)	0.87 (0.83)	$t(32) = 1.40$	$p = .170$
Large Loss Anticipation vs. Neutral Anticipation	0.17 (0.60)	0.41 (0.67)	$t(32) = 1.11$	$p = .274$
Substance Use at Most Recent Follow-up				
Used Alcohol (*n*)	17	0	—	$\mathbf{p < .001}^{c}$
Used Cannabis (*n*)	15	0	—	$\mathbf{p < .001}^{c}$
Used Nicotine (*n*)	8	0	—	$\mathbf{p = .003}^{c}$
Used Other Drugs (*n*)	12	0	—	$\mathbf{p = .020}^{c}$
Used Multiple Substances (*n*)	17	0	—	$\mathbf{p < .001}^{c}$
Alcoholic Drinks Per Year ***	75.90 (78.66)	0	$t(17) = 3.88$	$\mathbf{p < .001}^{d}$
Occasions of Cannabis Use Per Year ***	47.90 (86.70)	0	$t(17) = 2.10$	$\mathbf{p = .026}^{d}$
Days of Nicotine Use Per Year ***	136.74 (134.24)	0	$t(16) = 2.34$	$\mathbf{p = .016}^{d}$
Number of Other Drugs Used Per Year ***	1.24 (0.39)	0	$t(17) = 5.16$	$\mathbf{p < .001}^{d}$
Lifetime Diagnosis (*n*; present/absent) ****				
Conduct Disorder	2/15	0/15	—	$p = .486^{a}$
ADHD	2/15	3/12	—	$p = .645^{a}$

	Initiation Group (*n* = 18)	Comparison Group (*n* = 16)	Statistic	Significance
Generalized Anxiety Disorder	1/16	0/15	—	$p > .999^{a}$
Depressive Disorder	2/15	0/15	—	$p = .486^{a}$

Note. fMRI, functional magnetic resonance imaging; SUD, substance use disorder; ADHD, attention deficit hyperactivity disorder. Numbers represent means, with standard deviations in parentheses, unless otherwise noted.

[a]Two-tailed Fisher's exact test.

[b]Two-tailed independent samples *t*-test.

[c]One-tailed Fisher's exact test.

[d]One-tailed independent samples *t*-test. Degrees of freedom reduction reflects equal variances not assumed.

*One participant in the initiation group was missing an IQ score.

**Early externalizing data are T-scores from the Child Behavior Checklist – Parent Report.

***Calculated only for those who reported using the indicated substance, beginning with the age of initiation of that substance.

****One participant in each group was missing diagnostic information.

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Table 2.

Monetary Incentive Delay Task Performance by Group

	Initiation Group	Comparison Group	Statistic	Significance
Hit Rate (%)				
Large Gain	64.7 (25.0)	62.5 (18.3)	$t(32) = 0.29$	$p = .772$
Neutral	42.2 (20.7)	45.6 (21.4)	$t(32) = 0.47$	$p = .642$
Large Loss	56.1 (23.4)	64.4 (14.4)	$t(29) = 1.26$[a]	$p = .220$
Hit Reaction Time (ms)				
Large Gain	203.5 (46.4)	226.0 (40.5)	$t(32) = 1.50$	$p = .144$
Neutral	202.8 (45.9)	216.5 (66.6)	$t(32) = 0.70$	$p = .488$
Large Loss	202.6 (52.1)	234.9 (43.4)	$t(32) = 1.95$	$p = .060$

Note. ms, milliseconds. For *Initiation* and *Comparison* columns, the numbers given are means, with standard deviations in parentheses. *Statistic* and *significance* columns refer to two-tailed independent samples *t*-tests.

[a]Degrees of freedom reduction reflects equal variances not assumed.

Table 3.

Prediction of Group Membership with Logistic Regression

	Model χ^2	Sig	Nagelkerke R^2	Classification Accuracy (overall, sensitivity, specificity)	*B*	*SE*	Sig	OR	95% CI for the OR
Restricted Model	4.41	.110	.16	61.8%, 66.7%, 56.3%					
Early Externalizing Behaviors					0.04	0.04	.244	1.05	0.97 – 1.13
Family History of SUD					0.74	0.51	.149	2.09	0.77 – 5.68
Constant					−3.01	1.95	.123	0.05	
Full Model	11.80	.019	.39	73.5%, 72.2%, 75.0%					
Early Externalizing Behaviors					0.06	0.04	.156	1.06	0.98 – 1.15
Family History of SUD					0.54	0.61	.377	1.71	0.52 – 5.67
NAcc: Large Gain Anticipation vs. Neutral Anticipation					**1.76**	**0.77**	**.023**	**5.81**	**1.28 – 26.42**
NAcc: Large Loss Anticipation vs. Neutral Anticipation					−1.93	1.04	.063	0.15	0.02 – 1.11
Constant					−4.66	2.28	.041	0.01	

Note. SUD, substance use disorder; NAcc, nucleus accumbens; Sig, significance; *B*, beta coefficient; *SE*, standard error; OR, odds ratio; CI, confidence interval

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