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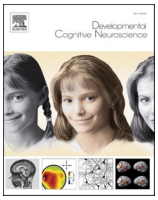

Neural activation to loss and reward among alcohol naive adolescents who later initiate alcohol use

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ABSTRACT

Adolescent alcohol use is associated with adverse psychosocial outcomes, including an increased risk of alcohol use disorder in adulthood. It is therefore important to identify risk factors of alcohol initiation in adolescence. Research to date has shown that altered neural activation to reward is associated with alcohol use in adolescence; however, few studies have focused on neural activation to loss and alcohol use. The current study examined neural activation to loss and reward among 64 alcohol naive 12–14 year olds that did (n = 20) and did not initiate alcohol use by a three year follow-up period. Results showed that compared to adolescents that did not initiate alcohol use, adolescents that did initiate alcohol use by the three year follow-up period had increased activation to loss in the left striatum (i.e., putamen), right precuneus, and the brainstem/pons when they were alcohol naive at baseline. By contrast, alcohol initiation was not associated with neural activation to winning a reward. These results suggest that increased activation in brain regions implicated in salience, error detection/self-referential processing, and sensorimotor function, especially to negative outcomes, may represent an initial vulnerability factor for alcohol use in adolescence.

1. Introduction

Alcohol use during adolescence is associated with adverse psychosocial outcomes (i.e., suicide, health risk behavior; Bonomo et al., 2001; Boden & Fergusson, 2011; Schilling et al., 2009) and later alcohol use disorder in adulthood (e.g., Rohde et al., 2001). For these reasons, it is imperative that we identify risk factors of adolescent alcohol use. Altered neural processing of reward and loss is one risk factor implicated in adolescent alcohol use that has garnered empirical attention. Most of this research has focused on examining neural response to reward outcomes (e.g., Cope et al., 2019; Swartz et al., 2020). However, much less work has examined neural responding to loss. Moreover, most of the literature is focused on adolescents that are already drinking alcohol. The disadvantage of this is that even minimal amounts of alcohol can alter brain function (e.g., Erewardg et al., 2014). Thus, it is unclear whether findings from studies on alcohol using (i.e., non-abstinent) adolescents represent an initial vulnerability factor for alcohol use or is a consequence of alcohol use.

1.1. Altered loss and reward neural processing and alcohol use

Extant theory has suggested that altered neural response to reward may be implicated in the development of alcohol use. Studies have shown that altered neural responding to anticipation and receipt of monetary win in the nucleus accumbens, anterior insula, and anterior cingulate cortex—regions implicated in salience processing (Menon, 2015) and cognitive control/executive function (Ptak, 2012)– are associated with greater alcohol use, with some studies finding increased neural response to reward and some finding decreased neural response to reward. This has been found in adults (e.g., Yau et al., 2012) and adolescents (Aloi et al., 2019; Baker et al., 2019; Braams et al., 2016; Cope et al., 2019; Swartz et al., 2020). Importantly, neural response to loss may *also* be associated with alcohol use (Bjork et al., 2008; Yau et al., 2012).

1.1.1. Theory on loss and alcohol use

Similar to research on neural response to reward receipt and

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anticipation, some research suggests that alcohol use may be associated with altered neural response to loss in several brain regions, including the nucleus accumbens, insula, and orbitofrontal cortex—regions implicated in salience (Menon, 2015) and cognitive control/attention (e.g., Ptak, 2012). There are two possible reasons for this. First, it may be that certain individuals experience heightened negative emotion from losing and drink alcohol to downregulate this negative emotion. This is consistent with research linking increased neural activation in emotion processing regions—amygdala, insula, and anterior cingulate cortex—to increased substance use in adolescents (Chaplin et al., 2019; Spechler et al., 2015) and young adults (Nikolova et al., 2016; Ray et al., 2010). Alternatively, individuals may experience "numbness" or blunted emotion in response to loss that may cause them to upregulate by drinking alcohol (Heitzeg et al., 2008; Yip et al., 2016). Second, certain individuals may have altered learning of stimulus-outcome associations. In other words, certain individuals may be less likely to learn that alcohol use is associated with negative consequences, making them less likely to abstain from drinking. This is bolstered by research demonstrating increased striatal activity to loss among adolescents with conduct disorder (see Blair et al., 2018 for a review).

1.1.2. Empirical studies on loss and alcohol use

To our knowledge, only two research studies have examined neural responding to loss and associations with alcohol use in adult samples. In one study of 18−22 year old adults, Yau et al. (2012) found that increased activation in the nucleus accumbens to anticipated monetary loss was associated with high risk drinking behavior among adults with a family history of alcohol use disorder (but not for adults without that family history). A second study examined neural activation to loss and alcohol use and found that, relative to healthy controls, 22−48 year old adults with alcohol use disorder had increased activation in the anterior insula when experiencing monetary loss outcomes (Bjork et al., 2008). Other studies on loss have found both increased activation in the inferior frontal gyrus (Balodis et al., 2012), superior temporal gyrus (Balodis et al., 2012), midbrain/parahippocampal gyrus (Gradin et al., 2014), and nucleus accumbens (Yip et al., 2014) to loss and decreased activation in the insula (Patel et al., 2013; Worhunsky et al., 2014), nucleus accumbens (Worhunsky et al., 2014), and orbitofrontal cortex (Filbey et al., 2013) to loss among adults with substance use disorder. Thus, some studies show increased and some studies show decreased neural activation to loss in regions implicated in cognitive control/executive and salience processing. Given that most of these studies examined individuals with problematic substance use, it is difficult to disentangle what is a vulnerability factor and what is a consequence of chronic substance use.

Only two studies have examined neural response to loss associated with substance use in adolescents. In the only study examining alcohol use and monetary loss in adolescence, Aloi et al. (2019) found that increased activation in the cuneus to loss (and loss of reward) was associated with increased alcohol use among 14−18 year old adolescents. The cuneus is involved in visual processing (e.g., Vanni et al., 2001) and may indicate increased attention to punishing cues in adolescents that drink more alcohol. In addition to this study, Ivanov et al. (2019) found that 8−13 year old children with attention deficit hyperactivity disorder (ADHD) and a family history of substance use disorders, compared to those with ADHD and no family-based risk for substance use disorders, showed heightened response in the bilateral putamen, bilateral insula, and right anterior cingulate cortex—salience regions—when unexpectedly not receiving a reward (unexpected nonreward versus expecting a nonreward) (Ivanov et al., 2019). Overall, both studies indicate that increased engagement of visual and salience regions among adolescents is associated with alcohol use and with risk for substance use in response to loss.

1.2. Factors implicated in reward and loss neural processing and alcohol use

There are several factors that may be implicated in the link between neural processing of reward and loss and alcohol use. Some research suggests that neural responding to reward and loss may vary depending on history of alcohol use (e.g., low risk drinking, high risk drinking, nondrinking; e.g., Yau et al., 2012). This is based on work demonstrating that drinking, even small amounts, may alter brain function over time (e.g., Wetherill et al., 2013; Squeglia & Gray, 2016; Erewardg et al., 2014). It is therefore challenging to identify whether findings from the literature indicate an initial vulnerability factor for alcohol use or a consequence of alcohol use. This is especially the case since most research in this area is conducted on high risk drinking (e.g., alcohol use disorder) samples, with very little research conducted on alcohol abstinent samples. Thus, it is critical that more research is conducted on alcohol naive samples to identify initial vulnerability factors that predict problematic alcohol use and alcohol use disorder later on.

It is also important that research on reward and loss neural processing and alcohol use examines the adolescent developmental period. This is because regions implicated in reward processing change across adolescence, fully maturing only in adulthood (Casey & Jones, 2010). The implication of this is that adolescents are biased towards engaging in reward seeking behavior (e.g., alcohol use) and are less able to modulate this reward seeking behavior to promote health and well-being (Casey & Jones, 2010; Duell et al., 2018; Faden, 2006; Geier, 2013; Shulman et al., 2016). It is therefore critical to examine neural responding to loss and reward and alcohol use among adolescents, preferably prior to their first drinks.

1.3. Current study

The current study compares neural activation to loss (i.e., losing money) and reward (i.e., winning money) on a card guessing task at baseline in 12−14 year old alcohol naive adolescents that do and do not initiate alcohol by a three year follow-up period. We hypothesized that prior to their first drink, those who later initiate alcohol will have altered (heightened or blunted) neural activation to loss and reward in regions implicated in reward processing compared to alcohol non-initiators. Based on the two adolescent studies on substance use and loss, we tentatively hypothesized that increased activation in sensorimotor and salience regions to loss would be associated with alcohol initiation by the three year follow-up period. In addition, the current study examines average whole brain activation to monetary loss and reward in the whole sample.

2. Method

2.1. Participants

Participants were 64 12−14 year old (M = 12.48; SD = .59; 30 females) adolescents that were drawn from a larger study on adolescent psychopathology and substance use. The sample of participants is representative of the communities from which it was recruited, with most participants being White (78.1 %; 1.60 % Black, 7.80 % Asian, 4.70 % Biracial, 7.80 % did not answer), non-Hispanic (90 %; 10 % Hispanic), and 79.70 % having household incomes greater than $100,000 (9.40 % between $75,000–100,000; 6.30 % between $60,000–74,999; 1.60 % between $45,000–59,999; 1.60 % <$45,000).

The larger study recruited participants using mailings to households in two metropolitan areas in the Northeastern or Mid-Atlantic US. Inclusion criteria included adolescent being 12−14 years old at time of recruitment, adolescent having an IQ greater than or equal to 80 (as assessed by the Wechsler Abbreviated Scale of Intelligence), and both adolescent and caregiver having adequate English proficiency to complete questionnaires in English. Exclusion criteria included prenatal

substance use exposure or psychotic disorder. A subset of participants from the larger study were given the opportunity to participate in an MRI scan if they met further MRI safety criteria (e.g., no metal in body, no pregnancy, no neurological conditions). Of the 81 participants that were scanned, two had neurological disorders, 11 were not alcohol naive at baseline, and four did not complete the three year follow-up. These adolescents were excluded for this paper because of our interest in examining prediction of alcohol initiation, resulting in a final sample of 64 adolescents. The final sample was not significantly different from the original 81 sample on demographic characteristics (i.e., race, age, gender).

The final sample was divided into two groups: one that initiated alcohol use by the three year follow-up ($n = 20$) and one that remained abstinent from alcohol use by the three year follow-up ($n = 44$). See Table 1 for group differences on baseline demographics, cognitive functioning, psychopathology, and alcohol use. The two groups were not significantly different in age, sex, household income, psychotropic medication use, depressive symptoms (i.e., Children's Depressive Inventory; Kovacs & Staff, 2003), oppositional defiant symptoms (Child Symptom Inventory – ODD subscale; Gadow & Sprafkin, 2002), conduct symptoms (Child Symptom Inventory – CD subscale; Gadow & Sprafkin, 2002), or attention deficit symptoms (Child Symptom Inventory – ADHD combined symptoms subscale; Gadow & Sprafkin, 2002). Alcohol initiators had reduced cognitive functioning (Weschler Abbreviated Scale of Intelligence; Wechsler, 1999) and were more likely to be White; all alcohol initiators were non-Hispanic.

2.2. Procedure

All study procedures were approved by the University's Institutional Review Board. Participants completed six sessions: a Baseline session, a fMRI session two weeks following the Baseline session, and six month, one year, two year, and three year follow-up sessions. For the Baseline and follow-up sessions, participants completed behavioral tasks, interviews, and self-report questionnaires, including questionnaires on alcohol use. Parents and adolescents provided consent and assent, respectively. Participants were monetarily compensated for all study sessions.

2.2.1. MRI session

Upon arrival to the MRI facility, adolescents were rescreened for MRI safety by an MRI technologist. Next, adolescents completed practice items for the card guessing task outside of the scanner. All adolescents confirmed abstinence from substance use the day of the scan.

Adolescents completed a T1-weighted structural scan and several functional scans, including the card guessing task. This paper will only examine data from the card guessing task. For the scan, adolescents were padded around the head with foam inserts to reduce motion and were given ear buds and headphones to reduce noise and increase comfort. Visual stimuli was projected to the head of the bore and was viewed using a mirror mounted on the head coil.

2.2.1.1. Card guessing task. Adolescents completed the card guessing task (similar to a monetary incentive delay task) developed by Forbes et al. (2009). Studies have shown that this task reliably recruits the striatum, particularly the nucleus accumbens, in adolescent samples (e.g., Forbes et al., 2009; Poon et al., 2019). This task is a single run, event-related design card. There are 24 trials, including 12 potential reward trials (i.e., win $1) and 12 potential loss trials (i.e., lose $.50); half of the trials have neutral outcomes (i.e., no winning money, no losing money). Participants are told that the trial outcomes are random, although in actuality the trial outcomes are predetermined. In addition, participants are told that their performance on the task determines how much monetary compensation they will receive. Trial order is pseudorandomized. Each trial is 20 s. A trial begins with a question mark where participants have 4 s to guess whether the next card is greater than or less than five. Participants use the response button pad to guess. Next, a six second image of shuffling cards appears that indicates the trial type (i.e., win $1, lose $.50, or neither win or lose). This is followed by a 500 ms image of the actual card number and then a 500 ms image of the outcome (i.e., win $1, lose $.50, or neither reward or lose). The trial ends with a 9 s crosshair.

2.2.1.2. MRI image acquisition. Functional and structural images were acquired on a Siemens 3 T Allegra MR scanner. T1-weighted MPRAGE anatomical images (TR/TE = 2,300/3 ms; FOV =260 mm; matrix size = 256 × 256; 160 1-mm-thick slices) were collected. For the card guessing task, images of the blood oxygen level-dependent (BOLD) responses were collected using T2*weighted gradient-echo echo planar images (EPI) [TR/TE: 2,250/30 ms; flip = 70°; field of view (FOV): 192 mm; matrix size: 64 × 64; 40 axial 3 mm thick/1 mm gap slices].

2.3. Measures

2.3.1. Alcohol use

Adolescent's lifetime alcohol use was assessed at the three year follow-up using a combination of self-report and physiological measures of alcohol use. For self-report, adolescents completed one item (i.e., "during your life, on how many days have you had at least one drink of alcohol?") from the Youth Risk Behavior Survey 2011 National Version

Table 1
Demographic, psychopathology, and alcohol use information.

	Alcohol Initiators ($n = 20$)	Non-Initiators ($n = 44$)	Group Difference
Sex: % boys	35 %	61 %	χ 2 (1) = 3.84
Race: % White	100 %	68 %	χ 2 (1) = 5.39*
Ethnicity: % Hispanic	0 %	14 %	χ 2 (1) = 3.01
Household income: % >100,000	85 %	79 %	χ 2 (1) = .311
Age: mean (*SD*)	12.50 (.61)	12.48 (.59)	$t(62) = .142$
IQ: mean (*SD*)	104.11 (9.81)	111.23 (10.57)	$t(56) = -2.42$*
Depressive disorder symptoms: mean (*SD*)[1]	6.25 (8.20)	4.02 (3.73)	$t(60) = 1.52$
Oppositional defiant disorder symptoms: mean (*SD*)[2]	12.65 (3.60)	13.44 (4.07)	$t(61) = -.745$
Conduct disorder symptoms: mean (*SD*)[2]	16.90 (2.83)	18.74 (4.77)	$t(57.22) = -1.92$
Attention deficit/hyperactivity disorder symptoms: mean (*SD*)[2]	26.18 (4.73)	31.24 (11.17)	$t(33.69) = -1.94$
Psychotropic medicine: % yes	5 %	14 %	χ 2 (1) = 1.05
Lifetime Alcohol Use: mean (*SD*)	1.65 (1.04)	0 (0)	$t(19) = 7.10$***[3]

Note. *p < .05, **p < .01, ***p < .001.

[1] Score derived from Children's Depressive Inventory (Kovacs and Staff, 2003), a self-report measure of depressive symptoms. A cut-off score of 19 or 20 is recommended to differentiate youth with or without depressive disorders in a non-clinical sample.

[2] Scores derived from the Child Symptom Inventory (Gadow and Sprafkin, 2002), a parent-report measure of DSM childhood disorders. T-tests for conduct disorder and attention deficit/hyperactivity disorder were conducted assuming unequal variances.

[3] T-test for lifetime alcohol use was conducted assuming unequal variances.

(YRBS; Brener et al., 2004). For physiology, adolescents completed a breath screen using the Alcosensor III Intoximeter. Adolescents were considered positive for alcohol use if they self-reported at least one day of alcohol use or obtained a positive (i.e., non-zero) breath screen at the three year follow-up. This data was used to create a dichotomous variable of lifetime use (positive) versus nonuse (negative). In total, 20 adolescents (31 % of sample) were positive for lifetime alcohol use. These adolescents reported drinking between 1–39 days in their lifetime (n = 13, 1–2 days; n = 3, 3–9 days; n = 2, 10–19 days; n = 2, 20–39 days).

2.4. Data analysis

2.4.1. MRI preprocessing and preliminary analyses

Data was analyzed using FMRIB's Software Library version 5.0 (FSL; Jenkinson et al., 2012). Data was motion corrected, B0 unwarped, and slice time corrected. Data was inspected for motion outliers—specifically, motion spikes greater than 6 mm in any direction for any repetition time (TR) or motion spikes greater than 1.5 mm for 80 % of the TRs. No participants had motion outliers and thus all were included in analyses. Data was then coregistered to each participant's mean MPRAGE and then to the Montreal Neurological Institute (MNI) template.

First-level analyses were run using FSL's fMRI Expert Analysis Tool (FEAT). For each adolescent, blood-oxygen-level-dependent (BOLD) signal at each voxel was modeled using generalized least squares with a voxel-wise, temporally and spatially regularized autocorrelation model, drift fit with Gaussian-weighted running line smoother (96 s FWHM). These models included regressors for onset and duration of events of interest, which were convolved with double gamma functions to create explanatory variables (i.e., monetary reward cue followed by monetary reward outcome, monetary reward cue followed by neutral outcome, monetary loss cue followed by monetary loss outcome, and monetary loss cue followed by neutral outcome). Motion correction parameters were also added to the model as nuisance regressors. In addition, data was smoothed with a 6 mm full width half maximum (FWHM) Gaussian kernel. These models created coefficient of parameter estimate (COPE) values for each explanatory value that were used to create our contrasts of interest: monetary loss outcome versus neutral outcome and monetary reward outcome versus neutral outcome.

2.4.2. Functional whole brain analysis

First, we examined whole brain activation to the task in the full sample of adolescents using FSL's Local Analysis of Mixed Effects (FLAME). Specifically, a one-sample t-test of the group level average in loss > neutral and reward > neutral contrasts was performed. Decreased activation in these contrasts was also examined (i.e., increased activation in neutral > loss and neutral > reward contrasts).

In order to test the hypothesis that adolescent neural responses to loss and reward would be associated with alcohol initiation three years later, we compared whole brain activation in alcohol initiators versus non-initiators for the loss and reward contrasts. Analyses were once again conducted using FLAME. In analyses, the predictor was alcohol initiation (coded as one for initiator by three year follow-up or zero if not initiator by three year follow-up) and this was associated with increased and decreased whole brain activation in the loss > neutral and reward > neutral contrasts (i.e., two-sample unpaired t test). A voxel-based threshold of $p < .001$ and a cluster-based correction of $p < 0.05$ were set for all analyses.

We considered including key demographic variables as covariates in these analyses. Since IQ was significantly associated with alcohol initiation at the three year follow-up, we included IQ as a covariate in follow-up analyses. No other demographic variables (e.g., age, gender, attention deficit symptoms etc.) were associated with alcohol initiation and thus not considered as potential covariates. Seven adolescents were on psychotropic medication (e.g., stimulants, antidepressants etc.). Although psychotropic medication can affect brain activity (e.g., Uftring et al., 2001), adolescents on psychotropic medications were not excluded from the sample because these adolescents are typically higher risk and more likely to engage in early alcohol drinking (Greene et al., 2016). Interestingly, in this sample, a greater proportion of non-drinking adolescents were on psychotropic medication compared to the alcohol-initiating adolescents. These adolescents were still kept in the sample as excluding those adolescents would result in a reduced sample size. Analyses were conducted first without IQ and psychotropic medication (yes/no) use as covariates and then rerun with both IQ and psychotropic medication use (yes/no) as covariates. Additional analyses examined psychotropic medication use alone as a covariate.

3. Results

3.1. Monetary loss outcome contrast

3.1.1. Main effects

To begin, average whole brain activation to the loss > neutral monetary outcome contrast in the whole sample was examined. There were no brain regions that showed increased activation to the loss > neutral monetary outcome contrast; this is in contrast to research demonstrating increased recruitment of regions such as the anterior cingulate cortex, anterior insula and putamen to loss (see Dugré et al., 2018). Adolescents showed *decreased* activation in two clusters comprising the left and right occipital fusiform gyrus, respectively. In addition, adolescents showed decreased activation in a cluster comprising the left precuneus and extending into the left cuneus and left superior lateral occipital cortex. In separate analyses covarying for psychotropic medication use alone, left precuneus was no longer a significant cluster. MNI coordinates for cluster peaks of activation are shown in Table 2 and visualized in Fig. 1.

3.1.2. Comparing alcohol initiators and noninitiators

Functional whole brain analyses were conducted to examine the primary hypothesis that brain activation to the loss > neutral monetary outcome contrast at baseline would be associated with alcohol use initiation (initiated/did not initiate) by the three year follow-up. Results indicated that increased activation in the left putamen (extending into the caudate nucleus and nucleus accumbens), brainstem/pons, and right precuneus (extending into the right lateral occipital cortex and cuneus) at baseline was associated with initiating alcohol by the three year follow-up. Alcohol initiation was not associated with decreased whole brain activation in the loss > neutral monetary outcome contrast. All results remained when covarying for psychotropic medication use except for the right precuneus cluster. The right precuneus cluster was no longer significant when covarying for psychotropic medication use alone. However, including both psychotropic medication and IQ as covariates resulted in this cluster being significant once again. Moreover, when covarying for both psychotropic medication use and IQ, additional clusters emerged in the left postcentral gyrus and left precuneus. MNI coordinates for cluster peaks of activation are shown in Table 3 and visualized in Fig. 2.

3.2. Monetary reward outcome contrast

3.2.1. Main effects

Average whole brain functional activation in the whole sample was also examined for the reward > neutral monetary outcome contrast. Adolescents showed increased activation to the reward > neutral monetary outcome contrast in a cluster comprising the left nucleus accumbens and extending into the caudate nucleus. Similarly, adolescents showed increased activation in a cluster comprising the left paracingulate gyrus and extending into the left frontal medial cortex. Adolescents showed *decreased* activation in a cluster comprising the right intracalcarine cortex and extending into the right precuneus to the reward > neutral monetary outcome contrast. In separate analyses

Table 2
Whole Sample Brain Activation to the Monetary Win and Loss Contrasts.

Region	Includes	Z_{max}	N voxels	Peak MNI coordinates (mm)		
				X	Y	Z
Win > Neutral						
L nucleus accumbens (+)	L caudate nucleus, L orbitofrontal cortex, L putamen, R nucleus accumbens, R caudate nucleus	5.32	648	−10	16	−6
L paracingulate gyrus (+)	L frontal medial cortex, L frontal pole, L anterior cingulate gyrus, R anterior cingulate cortex	4.62	492	−10	46	−8
R intracalcarine cortex (-)*	R lingual gyrus, R supracalcarine cortex, R precuneus, R lingual gyrus, R cuneus, R intracalcarine cortex, R occipital fusiform gyrus	4.01	358	20	−64	6
Loss > Neutral						
L occipital fusiform gyrus (-)	L inferior lateral occipital cortex, L lingual gyrus, L occipital pole, L inferior temporal gyrus	4.26	589	−26	−84	−20
R occipital fusiform gyrus (-)	R lingual gyrus, R inferior lateral occipital cortex	4.76	370	16	−82	−20
L precuneus (-)*	L cuneus, L superior lateral occipital cortex, L supracalcarine cortex, R precuneus, R cuneus, R supracalcarine cortex, R superior lateral occipital cortex	4.04	235	−2	−72	36

Note. L, left; R, right; +, increased activation; -, decreased activation; MNI, Montreal Neurological Institute. Voxel-based threshold set to $p < .001$ and cluster-based correction set to $p < .05$.

* Region did not survive when covarying for medication use alone.

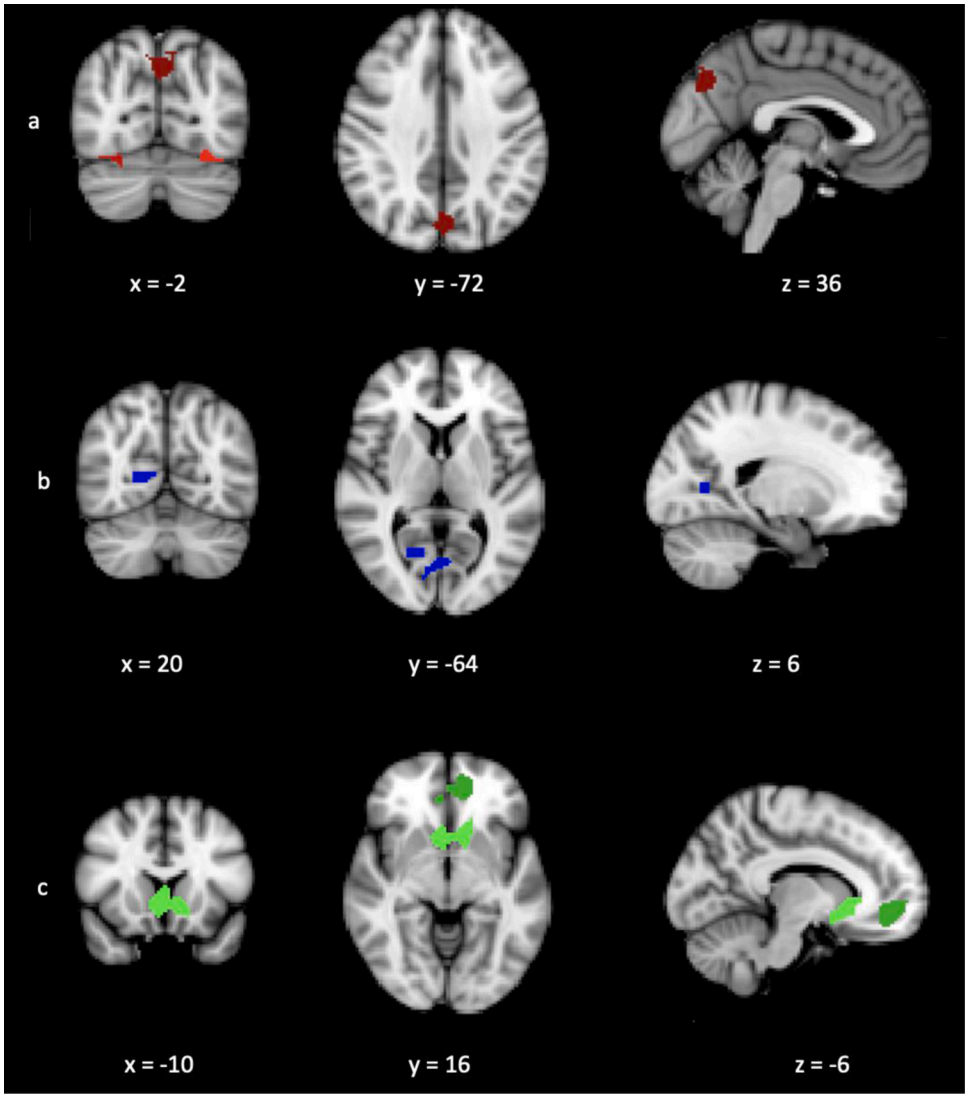

Fig. 1. Whole Sample Brain Activation to the Monetary Win and Loss Contrasts.
Note. (a) Clusters with decreased activation to the monetary loss outcome > neutral outcome contrast. (b) Clusters with decreased activation to the monetary win outcome > neutral outcome contrast. (c) Clusters with increased activation to the monetary win outcome > neutral outcome contrast. Voxel-based threshold set to $p < .001$ and cluster-based correction set to $p < .05$.

Table 3
Brain Activation to Monetary Loss in Alcohol Initiating Adolescents Versus Non-Initiating Adolescents.

Region	Includes	Z_{max}	N voxels	Peak MNI coordinates (mm)		
				X	Y	Z
Win > Neutral						
No significant clusters						
Loss > Neutral						
L putamen (+)	L pallidum, L caudate nucleus and L nucleus accumbens	4.61	405	−16	8	2
Brainstem (+)	Pons	4.60	308	8	−22	−44
R precuneus (+)*	R lateral occipital cortex, R superior parietal lobule, R cuneus	3.99	206	12	−66	42

Note. L, left; R, right; +, increased activation; -, decreased activation; MNI, Montreal Neurological Institute. Voxel-based threshold set to $p < .001$ and cluster-based correction set to $p < .05$.

* Region did not survive when covarying for medication use alone. Region did survive when covarying for both medication use and IQ.

covarying for psychotropic medication use alone, right intracalcarine cortex was no longer a significant cluster. These results are consistent with findings from other studies examining main effects of reward > neutral contrasts (e.g., Cao et al., 2019; Oldham et al., 2018; Bjork et al., 2010). MNI coordinates for cluster peaks of activation are shown in Table 2 and visualized in Fig. 1.

3.2.2. *Comparing alcohol initiators and noninitiators*

In line with the primary hypothesis that brain activation to the reward > neutral outcome contrast at baseline would be associated with alcohol initiation at the three year follow-up, functional whole brain analyses were conducted. Alcohol initiation was not associated with significant clusters of increased or decreased activation in the reward > neutral contrast. This was also the case when covarying for psychotropic medication use and IQ.

4. Discussion

There is a paucity of research investigating the neural correlates of alcohol use in adolescence, particularly in the context of loss. Indeed, only one study has examined the link between neural activation to loss and alcohol use in adolescents (Aloi et al., 2019). Moreover, this study (as well as most of the existing literature in this area) have used adolescent samples that are already using alcohol or other substances. This is problematic given studies demonstrating that minimal amounts of drinking can change brain function (e.g., Erewardg et al., 2014). Thus,

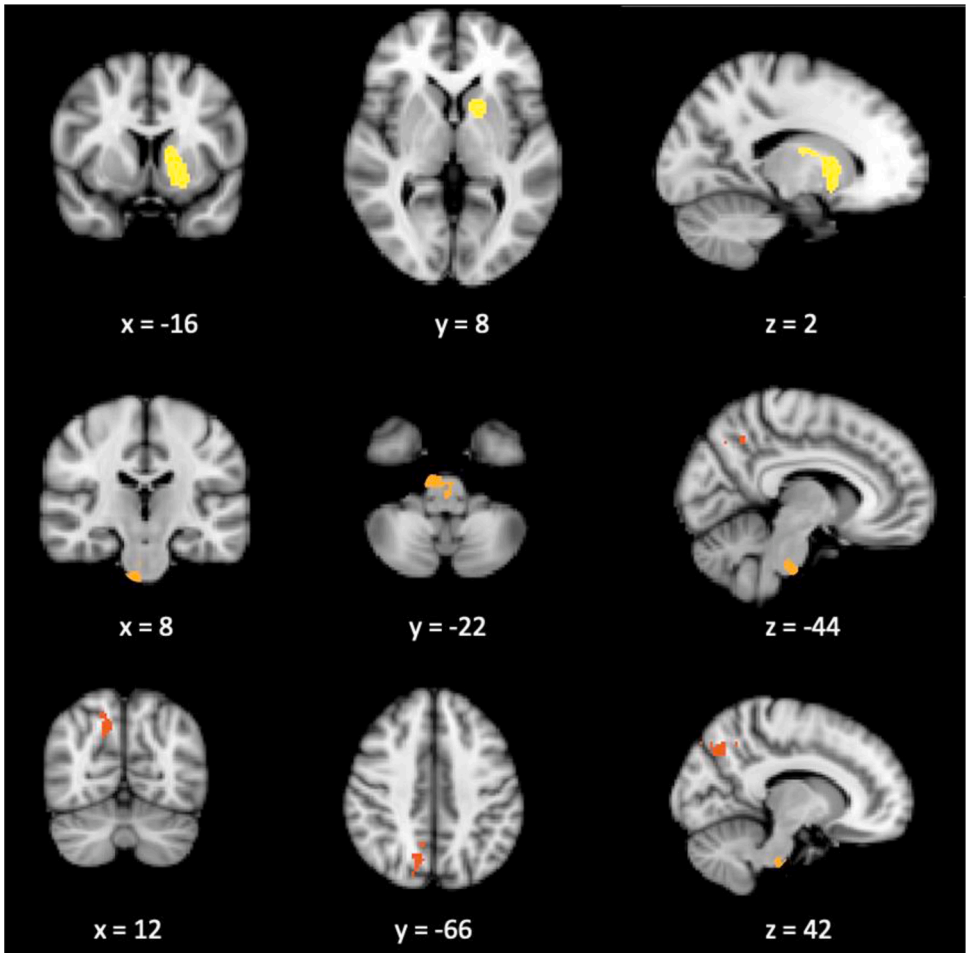

Fig. 2. Brain Activation to Monetary Loss in Alcohol Initiating Adolescents Versus Non-Initiating Adolescents.
Note. Clusters with increased activation to the monetary loss outcome > neutral outcome contrast in alcohol initiating adolescents versus non-initiating adolescents prior to the first drink. Voxel-based threshold set to $p < .001$ and cluster-based correction set to $p < .05$.

the primary purpose of the present study was to examine neural activation to loss and reward among alcohol naive adolescents that do and do not initiate drinking by a three year follow-up period.

4.1. Neural activation to monetary loss

When examining adolescents' overall activation to the monetary loss outcome contrast, there were no significant clusters in regions that we hypothesized. However, when looking at association with alcohol use initiation, clusters in the left putamen/nucleus accumbens, right precuneus, and brainstem/pons were associated with alcohol use. When covarying for IQ and psychotropic medication use, additional clusters in the left postcentral gyrus and left precuneus were associated with alcohol use initiation.

4.1.1. Putamen/Caudate nucleus and nucleus accumbens

Increased activation to monetary loss in a cluster in the left putamen/caudate nucleus extending into the nucleus accumbens was associated with alcohol initiation by the three year follow-up. Although both the putamen and nucleus accumbens are involved in reward processing, the putamen is specifically focused on learning stimulus-outcome associations, while the nucleus accumbens is focused on predicting future reward (Delgado, 2007; Mannella et al., 2013). Thus, this finding may suggest that prior to ever having had a drink, alcohol initiating adolescents, compared to non-alcohol initiating adolescents, are overvaluing the impact of loss, which may lead to increased negative emotion related to losing. Particularly in adolescents with still-developing emotion regulation skills (e.g., Theurel & Gentaz, 2018), this heightened negative emotionality to losing and perhaps negative stimuli overall may lead adolescents to engage in drinking to down-regulate their negative emotion over time. This aligns well with self-medication theories of alcohol use (e.g., Swendsen et al., 2000). Alternatively, this finding can more broadly suggest that loss, as well as win, is more salient among alcohol initiating adolescents, compared to non-alcohol initiating adolescents. It may be the case that alcohol initiating adolescents find loss outcomes more unexpected compared to non-alcohol initiating adolescents, reflecting disrupted salience/learning processes (see Blair et al., 2018). This theory would require more formal testing using learning paradigms to confirm.

Critically, this finding is consistent with other work on brain activation to monetary loss and alcohol use (as well as other substance use more generally) in adults. Yau et al. (2012) similarly linked increased activation in the nucleus accumbens to monetary loss (anticipated loss, not loss outcome) and increased alcohol use in young adults, in a sample with a family history of substance use disorder. Another study also showed increased activation in the nucleus accumbens to monetary loss outcome in young adults with cannabis use disorder compared to healthy controls (Yip et al., 2014). Of course, Yau et al. (2012) and Yip et al. (2014) examined non-abstinent young adults which may make it difficult to ascertain whether increased activation in the nucleus accumbens was an initial vulnerability factor or a consequence of alcohol use/substance use. Given that we found a similar result in an initially alcohol abstinent adolescent sample, it is more likely that increased activation in the putamen and nucleus accumbens and surrounding regions represents an initial vulnerability factor for alcohol use. This is consistent with a recent meta-analysis that linked heightened activation in the striatum, particularly the putamen, to vulnerability to substance use disorder among adolescents (Tervo-Clemmens et al., 2020).

Of note, this finding is in opposition with some of the literature on brain activation to monetary loss and substance use. Aloi et al. (2019) found that increased putamen activation to loss was associated with *reduced* cannabis use among adolescents. This study did not find associations between putamen or nucleus accumbens responses to loss and alcohol use, however. It is unclear what may be driving these discrepant findings. One possibility is that neural risk for cannabis use and alcohol use are distinct. Future research should re-examine the link between loss, putamen activation, and substance use risk.

4.1.2. Precuneus and Brainstem/Pons

We also found that increased activation of the right precuneus (also left precuneus when covarying for IQ and psychotropic medication use) and brainstem/pons to monetary loss was associated with alcohol initiation by the three year follow-up in initially abstinent adolescents. To our knowledge, no previous study has linked alcohol or substance use and precuneus activation to monetary loss. Previous studies have shown that increased activation of the precuneus has been observed during error processing in response inhibition tasks (e.g., Menon et al., 2001; Chikara et al., 2018), suggesting that the precuneus may have a role in error detection. Many studies have also implicated the precuneus in self-referential processing (Cavanna & Trimble, 2006), which raises the possibility, in our study, that adolescents that go on to initiate alcohol may be attributing losses to their selves more than their peers. This increased attention to the self may indicate that these adolescents are more emotionally reactive to negative stimuli and subsequently respond by engaging in behaviors (i.e., drinking) that down-regulate these emotions. Of note, this precuneus cluster extended into the lingual gyrus and cuneus, regions in the visual cortex implicated in the sensory-based visuospatial attention (e.g., Hahn et al., 2006). This is consistent with Aloi et al. (2019) who found increased activation in the cuneus to loss as being associated with increased alcohol use in adolescents.

Regarding our pons finding, although the upper portion of the pons (e.g., pedunculopontine nucleus and the raphe nucleus) is involved in reward processing (Haber & Knutson, 2009), the cluster we found to be associated with alcohol initiation appeared in the lower portion of the pons. The lower portion (e.g., abducens nucleus) is involved in eye movement (Linzenbold et al., 2011). Although it is unclear how this pons activation may be linked to monetary loss and related associations with alcohol initiation, it may signal increased attention to monetary loss outcome cues among alcohol initiators. As aforementioned, this may indicate increased negative emotion to monetary loss and other negative stimuli more generally that leads to alcohol initiation. It is important to note that historically there has been minimal attention paid to functional activation of the brainstem in regards to substance use and reward.

In addition, increased activation in the left postcentral gyrus extending into the supramarginal gyrus was associated with alcohol initiation by 3 Year follow-up *only* when holding psychotropic medication use and IQ constant. Although this finding is unexpected, it may indicate that alcohol-initiating adolescents are more strongly engaging somatosensory processes (Corkin et al., 1970) than non-alcohol drinking adolescents when losing monetary outcomes. The postcentral gyrus has been similarly recruited in clinical samples during reward processing involving visual stimuli (García-García et al., 2014). Notably, this finding is mostly driven by IQ, as this cluster did not emerge as significant when covarying for psychotropic medication alone. This suggests that cognitive functioning may confound performance on the card guessing task (e.g., understanding that their guesses are directly related to the outcome) and that controlling for cognitive functioning may increase power to detect group differences in neural-related loss processing.

4.2. Neural activation to monetary reward

For the whole sample, there was activation to the monetary reward contrast in several clusters involved in reward processing including the left nucleus accumbens, left parahippocampal gyrus, and right intracalcarine cortex. However, neural activation to monetary reward was *not* associated with alcohol initiation by a three year follow-up. This is in opposition with most of the literature that finds that altered activation (i.e., heightened or blunted activation) of salience network regions, particularly the nucleus accumbens, predicts increased engagement of

alcohol and substance use in adults and adolescents (Aloi et al., 2019; Baker et al., 2019; Braams et al., 2016; Cope et al., 2019; Swartz et al., 2020). Most likely, reward activation was not meaningfully associated with prospective alcohol initiation, perhaps because it is more predictive of concurrent risk behaviors. This is especially likely because we demonstrated that across all adolescents, there was significant activation in the monetary reward outcome contrast and not in the monetary loss outcome contrast (which was associated with prospective alcohol initiation). In addition, it may be the case that the association between reward activation and alcohol use is dependent on moderating factors (e.g., impulsivity) that are not captured using group level analyses. Alternatively, neural activation to reward may be a consequence of alcohol use versus a vulnerability factor for alcohol use.

4.3. Implications for neurodevelopmental models

The current findings provide partial support for current neurodevelopmental models (Shulman et al., 2016). These models propose that adolescence is characterized by exaggerated activation of the reward system in the brain, particularly the striatum, and blunted activation of systems controlling cognitive control, including regions of the prefrontal and parietal cortex (Shulman et al., 2016). This disequilibrium in these systems is then responsible for increased risk-taking in adolescence. Consistent with this, we found that increased activation in the striatum to monetary loss was associated with alcohol initiation. However, we did not find that alcohol-initiating adolescents had increased activation to monetary *reward* compared to non-initiating adolescents. We additionally found support for increased activation of regions that have been implicated in cognitive control, including posterior parietal regions (i.e., precuneus, superior parietal lobule, supramarginal gyrus), to monetary loss and alcohol initiation. Because these regions have diverse functions (e.g., self-referential processing) and the employed card guessing task does not explicitly tap cognitive control, it is less clear whether and how these findings fit into current neurodevelopmental models. More research is needed to examine the neural development of loss and reward processing, as well cognitive control, particularly as it relates to alcohol initiation.

4.4. Strengths, limitations, and future directions

The current study has several strengths that will add substantially to the literature. Unlike most studies in this area, our study employed a longitudinal design using an adolescent sample that was alcohol naive at the fMRI session. This enabled us to better elucidate if the detected results represented an initial vulnerability factor or a consequence of alcohol use. Future research should continue to employ these longitudinal designs in order to improve identification of neural risk factors of alcohol use. This approach moving forward may address some of the mixed findings in the literature stemming from varying alcohol use effects on the brain. In this study, we also concomitantly examined loss and reward neural processing. Most of the extant research is focused on reward processing which precludes an understanding of how loss processing may be a critical risk factor for alcohol use. Given that most monetary incentive delay tasks include both reward and loss contrasts and there is growing support of the role of neural processing of loss and alcohol use, analyses of both contrasts should be considered in future studies on alcohol use.

Despite the many strengths of this study, there are a few limitations that can be addressed in subsequent studies. One, although our sample is larger than that seen in many neuroimaging studies, our sample size may still be inadequate to detect all of the neural correlates of reward and loss that are associated with alcohol initiation. Two, our sample is fairly homogenous in terms of race, ethnicity, and socioeconomic status. This means that our results may not replicate in a non-White lower socioeconomic status sample of adolescents. This is especially important given research supporting demographic differences in alcohol use across the adolescent developmental period (Chen & Jacobson, 2012). Future attempts to diversify research samples is well indicated. Third, because we recruited a community sample, alcohol use rates were not high enough to conduct more complex analyses. For example, we were unable to examine whether neural activation to loss and reward differed between minimal drinking adolescents and adolescents with alcohol use disorder. We were limited to examining lifetime alcohol use more generally. Also, most of the alcohol initiators in this sample were low level drinkers, consuming at most 39 drinks in their lifetimes. Although consistent with community samples (Chen et al., 2012), it is still unclear whether low-level drinking is as meaningful of a predictor of future alcohol use disorder as binge drinking in adolescence. In other words, it is not at all certain what percentage of drinking adolescents in this study will go on to engage in problematic alcohol use or develop alcohol use disorder. Future studies can oversample for adolescents with greater likelihood to engage in problematic drinking (e.g., family history of alcohol use disorder), which would increase confidence that findings are identifying markers of vulnerability to problematic alcohol use and not just normative alcohol use.

4.5. Conclusion

Given the devastating impacts of alcohol use disorder and the fact that most adults with alcohol use disorder begin drinking as adolescents (Rohde et al., 2001), it is imperative that we identify risk factors of alcohol initiation in adolescence. The current study is the first, to our knowledge, to identify increased functional activation to monetary loss in sensorimotor (i.e., brainstem), error detection/self-referential (i.e., precuneus), and salience (i.e., putamen and nucleus accumbens) brain regions as a risk factor for alcohol initiation in adolescence. Following further research, these risk factors can be used to identify at-risk adolescents that could benefit from various prevention efforts.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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