

# Reward-Related Brain Activity Prospectively Predicts Increases in Alcohol Use in Adolescents

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**Objective:** Altered activity within reward-related neural regions, including the ventral striatum (VS) and medial prefrontal cortex (mPFC), is associated with concurrent problematic substance use. The aims of the present study were (a) to identify patterns of reward-related neural activity that prospectively predicted changes in alcohol use 2 years after magnetic resonance imaging in a sample of adolescents, and (b) to examine whether these patterns differed by sex. We also tested whether depression symptoms or impulsivity mediated associations between neural activity and future alcohol use.

**Method:** Participants were 262 adolescents (129 male and 133 female) of Mexican origin who completed the Monetary Incentive Delay task during a functional magnetic resonance imaging scan at age 16. Participants reported on their alcohol use at ages 16 and 18.

**Results:** Results indicated that different patterns of reward-related neural activity predicted future increases in alcohol use for male and female adolescents. In boys, higher VS activity during reward anticipation and average ventral mPFC activity during reward feedback predicted increases in alcohol use from age 16 to 18 years; in girls, higher dorsal mPFC activity and blunted VS activity during reward anticipation predicted increases in alcohol use from age 16 to 18 years. Depression symptoms or impulsivity did not mediate these associations.

**Conclusion:** The results suggest that different pathways of risk may lead to problematic alcohol use for adolescent boys and girls. These sex differences in neural risk pathways have important implications for prevention and intervention approaches targeting Mexican-origin youth.

**Key words:** fMRI, reward, alcohol, adolescence, sex

J Am Acad Child Adolesc Psychiatry 2020;59(3):391–400.  

**B**y the time they reach 18 years of age, most American adolescents will have tried alcohol and a quarter will have engaged in binge drinking.<sup>1–3</sup> Identifying patterns of neural activity that predict increases in alcohol use during this period will provide an important foundation for identifying adolescents at risk for alcohol use problems and for designing targeted preventions and interventions informed by neurobiological pathways of risk. Moreover, focusing on adolescents will provide critical information about the patterns of neural activity associated with the early stages of alcohol use. The goal of the present study is to identify patterns of neural activity that prospectively predict increases in alcohol use during late adolescence in a sample of adolescents of Mexican origin, a population that generally evidences earlier onset of alcohol use relative to other racial/ethnic groups.<sup>3</sup>

Individual differences in ventral striatum (VS) and medial prefrontal cortex (mPFC) response to reward have been linked to problematic alcohol use in prior research.<sup>4–7</sup> The VS, which includes the nucleus accumbens, is involved

in processing reward anticipation and receipt.<sup>8,9</sup> The VS is functionally connected to the mPFC, which is involved in evaluating reward cues and regulating responses to reward.<sup>8</sup> Reward-related neural activity has been examined in relation to many different subprocesses; two of the most commonly examined in this context are reward anticipation (ie, neural activity to cues signifying potential for reward) and reward feedback (ie, neural activity to cues indicating receipt of reward, such as money), although some task designs (eg, blocked) do not allow for the separation of blood oxygen-level–dependent (BOLD) signal between the reward anticipation and feedback stages.

Altered reward processing within the VS and mPFC has been associated with alcohol use problems,<sup>6,10–14</sup> and findings from neuroimaging and behavioral studies have suggested two potential routes to problematic alcohol use.<sup>15</sup> One potential pathway involves a relatively high VS response while receiving rewards and when response to anticipating and receiving rewards is assessed together (eg, as with a blocked task paradigm).<sup>4,6,12</sup> According to the

impulsivity theory of addiction,<sup>7</sup> higher VS response to reward cues may lead to problematic alcohol use through a pathway of higher sensation seeking and impulsivity.<sup>14,16,17</sup> A related factor is that blunted mPFC response during reward anticipation and reward feedback has been associated with more problematic alcohol use,<sup>4,5,10</sup> which may reflect reduced prefrontal regulation of reward processing. Thus, a relatively heightened VS response to reward or a blunted mPFC response to reward could lead to more problematic alcohol use through increased impulsivity and reduced regulation of reward-related behavior, although notably these effects do not always replicate.<sup>18</sup>

The second potential neural pathway is a blunted VS response when anticipating rewards or, again, when response to anticipating and receiving rewards is measured together.<sup>6,7,10</sup> In line with the reward deficiency syndrome theory,<sup>7,19</sup> individuals with a blunted VS response to reward may consume substances as a means of compensating for this blunted response to ordinary rewards such as money.<sup>6,11,20</sup> Because a blunted VS response to reward cues is observed in individuals who are depressed and is associated with anhedonia,<sup>21-24</sup> this pattern of brain activity may also predict using alcohol to cope with internalizing symptoms.<sup>11,15</sup> Importantly, although the majority of this research has been cross-sectional, some studies have shown that these patterns of brain activity prospectively predict future alcohol use at longitudinal assessments.<sup>6,14,25</sup>

There are two potential, not mutually exclusive, explanations for these distinct patterns of VS and mPFC activity observed in association with problematic alcohol use. First, these patterns may depend on whether neural activity was measured during anticipation or feedback of reward. For example, a meta-analysis suggested that individuals with substance use disorders evidence a blunted VS response during reward anticipation but heightened VS response during reward outcome.<sup>7</sup> In contrast, research examining mPFC activity suggests that effects are similar for the reward anticipation and feedback phases.<sup>4,5,7</sup> In other studies, reward paradigms use designs that place both stages of reward processing within blocks,<sup>6,10-12</sup> precluding the ability to examine responses to anticipation and feedback separately. Thus, there is a need to examine VS and mPFC activity separately during the reward anticipation and feedback phases.

The second potential explanation is that these patterns may reflect different pathways of risk in different individuals. For example, one study of a large sample of college students found two separate patterns of brain activity associated with alcohol use problems in different individuals: heightened VS activity to reward and blunted amygdala activity to threat in one group, and blunted VS

activity to reward and heightened amygdala activity to threat in a second group.<sup>6</sup> The authors suggested that the former group may exhibit more problematic alcohol use due to an impulsive/sensation-seeking risk pathway, whereas the latter group may exhibit problematic alcohol use due to an internalizing pathway.

The explanations offered above may further depend on the sex of the participants, given that there are sex differences in the prevalence of problematic alcohol use. Specifically, although sex differences in alcohol use disorders tend to be small during adolescence, they begin to emerge in late adolescence and young adulthood, with alcohol use disorders becoming more prevalent in men.<sup>3,26,27</sup> There are also sex differences in motives for alcohol use. Male adolescents are more likely to endorse enhancement motives (ie, drinking for fun and sensation seeking) compared to female adolescents.<sup>28</sup> Moreover, there are stronger associations between depressive symptoms, coping motives (ie, drinking to cope with negative emotions), and heavy alcohol use in female participants compared to male participants.<sup>29</sup> A related factor is that rates of depression are higher in female adolescents compared to male adolescents,<sup>30,31</sup> possibly rendering female adolescents more likely to follow an internalizing risk pathway. Sex differences have also been observed in the development of reward-related brain structure and function across adolescence,<sup>32</sup> including in the developmental timing of striatal volume changes in humans<sup>33</sup> and in neuronal pruning of the mPFC in rats postpuberty.<sup>34</sup> Thus, there may be sex differences in the patterns of reward-related neural activity that prospectively predict future increases in alcohol use during late adolescence.

In the present study, we tested whether reward-related neural activity measured at age 16 years prospectively predicted increases in alcohol use from age 16 to 18 years. Of importance, all participants were adolescents from Mexican-origin families, a growing US demographic underrepresented in neuroscience-based research who experience high levels of substance use problems.<sup>3,35,36</sup> We hypothesized that two potential patterns of brain activity would predict future increases in alcohol use: (1) heightened VS response or blunted mPFC response during reward anticipation and feedback (consistent with an impulsive, sensation-seeking pathway to alcohol use), or (2) blunted VS response during reward anticipation (consistent with an anhedonic pathway to alcohol use). In addition, based on sex differences in drinking motives and internalizing disorder prevalence, we predicted that the heightened VS/blunted mPFC (sensation-seeking/impulsive) pattern would be more predictive of future alcohol use in male adolescents, whereas the blunted VS (anhedonic/internalizing) pattern

would be more predictive of future alcohol use in female adolescents. We also tested these proposed pathways by examining whether impulsivity or depression symptoms mediated the association between neural activity and increases in alcohol use.

## METHOD

### Participants

Participants included a subsample drawn from a 10-year longitudinal parent study of 674 Mexican-origin families.<sup>35,37</sup> The first assessment occurred when the participants were in fifth grade (mean age = 10.8 years); subsequent follow-up assessments were conducted annually. When participants were between 15 to 17 years old, they were selected for two neuroimaging substudies (one focused on substance use and one focused on depression risk) that both included completing the Monetary Incentive Delay task during a functional magnetic resonance imaging (fMRI) scan. (See Supplement 1, available online, for further participant selection details.) Neuroimaging data from these participants has been published in previous research.<sup>36,38,39</sup> All procedures were approved by the University of California, Davis Institutional Review Board; Parents provided informed consent and adolescent participants provided informed assent before beginning study procedures. Participants received monetary compensation for their study participation. The final sample reported on in this article includes 197 participants from the depression substudy and 89 participants from the substance use substudy, yielding 286

participants. After excluding 24 participants for not meeting quality control criteria (see Supplement 1, available online), valid fMRI data were available for 262 participants (51% female and 49% male) (Table 1).

### Monetary Incentive Delay Task

The Monetary Incentive Delay (MID) task<sup>9</sup> has been used extensively in prior research on adolescent samples.<sup>40-42</sup> The MID was presented with E-Prime computer software (PST, Inc, Pittsburgh, PA). The version of the MID used in this study consisted of two runs (10.44 minutes each) of 70 contiguous 6-second trials. Participants viewed a cue indicating potential gain or loss of one of three magnitudes of money, or no change in outcome (a neutral condition). Participants then had to press a button in response to a target as quickly as possible to gain money on gain trials or to avoid losing money on loss trials. (See Supplement 1, available online, for further details.)

### BOLD fMRI Data Acquisition, Preprocessing, and Analysis

Participants underwent scanning on a research-dedicated 3T Siemens Tim Trio whole-body MRI system (Siemens Medical Solutions, Erlangen, Germany) with a 32-channel head coil. (See Supplement 1, available online, for details regarding pre-processing, first-level models, group-level analysis, and definitions of regions of interest.) The regions of interest (ROIs) included the left and right ventral striatum and the medial PFC. Functional clusters that were

**TABLE 1** Sample Characteristics for 262 Participants With Valid Functional Magnetic Resonance Imaging Data (fMRI)

	Male Participants (n = 129)			Female Participants (n = 133)			Group Difference
	Mean	SD	Min–Max	Mean	SD	Min–Max	
Age at fMRI scan, y	16.88	0.60	15.37–17.98	16.85	.58	15.47–17.97	t(260) = 0.44, p = .66
Frequency of alcohol use at age 16 y	0.53	1.33	0–8	0.51	1.01	0–5	t(260) = 0.11, p = .91
Frequency of alcohol use at age 18 y	0.87	1.58	0–7	0.86	1.45	0–8	t(255) = 0.08, p = .93
Any alcohol use at age 16 y (%)	20.2			26.3			$\chi^2(1) = 1.39, p = .24$
Any alcohol use at age 18 y (%)	34.4			38.6			$\chi^2(1) = 0.50, p = .48$
Depression symptoms at age 16 y	2.31	2.78	0–14	4.52	4.05	0–17	t(260) = -5.14, p < .001
Depression symptoms at age 17 y	2.05	2.60	0–12	3.96	3.58	0–17	t(259) = -4.91, p = .001
Impulsivity at age 16 y	2.45	0.62	1.13–4.13	2.26	0.67	1.00–4.00	t(260) = 2.37, p = .019
Impulsivity at age 18 y	2.09	0.62	1.00–4.00	1.99	0.65	1.00–4.75	t(255) = 1.19, p = .24
Reaction time for MID (ms)	124.60	24.91	44.28–189.24	123.11	29.42	13.63–177.59	t(260) = 0.44, p = .66
Accuracy for MID (%)	62.81	9.76	39–87	61.91	9.92	24–89	t(260) = 0.74, p = .46

**Note:** Frequency of alcohol use was determined based on responses on the Alcohol, Tobacco, and Other Drugs survey. Depression symptoms were assessed with the National Institute of Mental Health Diagnostic Interview Schedule for Children Version 4. Impulsivity was assessed with the Weinberger Adjustment Inventory. Five participants were missing data on alcohol use at age 18; 1 participant was missing data on depression symptoms at age 17 years; 5 participants were missing data on impulsivity at 1 year of age. Reaction time and accuracy for the MID are reported for all trials (gain, loss, and neutral). MID = Monetary Incentive Delay task performed during fMRI scanning.

significantly activated by each contrast were identified at a small-volume familywise error-corrected  $p < .05$  threshold. Next, mean contrast values were extracted from these functional clusters for use in further statistical analyses. Because contrast values for the left and right VS were highly correlated ( $r = 0.94$ ,  $p < .001$  for reward anticipation and  $r = 0.90$ ,  $p < .001$  for reward feedback), these were averaged to obtain mean measures of VS activity during reward anticipation and reward feedback. Outliers for VS and mPFC activity were winsorized to within 3 SD of the mean.

### Self-Report of Alcohol Use

Participants reported their history of substance use on the Alcohol, Tobacco, and Other Drugs (ATOD)<sup>43</sup> survey at each wave of the study. This survey included questions asking participants how often they had used or tried beer, wine, and hard liquor in the past 3 months. The questions on beer and wine use specified “more than just a few sips.” The response options were: never (0), less than once per week (1), about once per week (2), two to three times per week (3), and almost every day (4). Frequency of alcohol use at each age was determined by summing these scores for the three types of alcohol, resulting in a total frequency score ranging from 0 to 12. Alcohol use at age 18 years was missing for 5 participants.

### Covariates

Covariates included the number of years since initiation of substance use, mean life stress between age 10 and 16 years, alcohol use at age 16, and age at the fMRI scan (see Supplement 1, available online). Following the recommendations of Keller,<sup>44</sup> we tested predictor by covariate interactions for each predictor (VS activity, mPFC activity, sex) and covariate in the models one at a time. We retained interactions that were significant in the final model.

### Mediators of the Association Between Reward-Related Brain Function and Alcohol Use

To test our hypotheses that different patterns of brain activity predict future alcohol use through an impulsive/sensation-seeking pathway (for boys) and an internalizing/depression pathway (for girls), we examined two variables available in the dataset as potential mediators of this association. For the sensation-seeking/impulsive pathway, we used scores on the Impulsivity subscale of the Weinberger Adjustment Inventory.<sup>45</sup> This scale contains 8 items, with response options ranging from 1 (“not at all true”) to 5 (“very true”). The items were averaged to obtain a mean measure of impulsivity. For the internalizing/depression pathway, depression symptoms were assessed using the

Major Depression/Dysthymic Disorder module of the National Institute of Mental Health Diagnostic Interview Schedule for Children Version 4 (DISC-IV).<sup>46</sup> For this measure, participants reported on depression symptoms experienced in the past year with a yes/no response. Responses were summed to obtain a continuous measure of symptoms. Outliers were winsorized to within 3 SD of the mean for both mediators.

### Statistical Analysis

After extracting contrast values for VS and mPFC activity during reward anticipation and feedback, all self-report data and contrast values were imported into Mplus v7 software for further statistical analysis and were mean centered. To test our hypotheses that differences in reward-related brain function would be associated with future alcohol use, we created two separate models. In the first, we modeled paths from VS and mPFC activity during reward anticipation (measured at age 16 years) as a predictor of alcohol use measured at age 18. We also included predictors for sex, sex by VS, and sex by mPFC interactions, as well as quadratic terms for VS and mPFC activity and interactions with sex. Quadratic terms were included for the brain variables given evidence for potential quadratic effects from prior research (eg, both blunted and heightened VS activity to reward predict problematic alcohol use).<sup>4, 6,7,10,12</sup> Because the alcohol use variable had a zero-inflated count distribution, we used a zero-inflated Poisson regression model. This method uses a logit model to examine predictors of binary alcohol use (0 = no, 1 = yes) and a Poisson regression to examine predictors of the frequency count of alcohol use. We entered the same predictors for each part of the model. As described above, we also tested predictor by covariate interactions and included these when significant. In the second model, we conducted a similar zero-inflated Poisson regression using the same regressors and covariates, but used VS and mPFC contrast values for the reward feedback contrast.

To test the proposed mediators, we examined with linear regression whether VS and mPFC activity (at age 16 years) predicted depression symptoms (at age 17) or impulsivity (at age 18), controlling for age 16 depression symptoms or impulsivity, respectively (assessing the mediators at age 17 years is ideal for establishing the temporal order of effects, but impulsivity was not assessed at age 17, so we used the age 18 measure). In the final regression, we used zero-inflated Poisson regression to test whether depression symptoms (age 17) or impulsivity (age 18) predicted alcohol use (age 18), and modeled interactions with sex. Because only brain activity for the reward anticipation contrasts showed any associations with the

mediators, we controlled only for these contrasts in this final regression.

Overall, we conducted 48 statistical tests examining neural predictors of alcohol use, impulsivity, and depression, so we used the Benjamini–Hochberg false-discovery rate approach<sup>47</sup> to control for multiple comparisons. All statistical tests were two-tailed and were conducted with MPlus v7 software using full information maximum likelihood (FIML) estimation with robust standard errors.

## RESULTS

### Main Effects of Reward Anticipation in the VS and mPFC

As illustrated in Figure 1, the contrast of gain > neutral cues resulted in significant activation within the left VS:  $t(262) = 9.47$  (average),  $p$ -corrected < .05, peak coordinates = (−16, 4, −14), and the right VS:  $t(262) = 9.54$  (average),  $p$ -corrected < .05, peak coordinates = (18, 6, −12). There was also significant activation to gain > neutral cues within the dorsal mPFC (dmPFC):  $t(262) = 4.95$  (average),  $p$ -corrected < .05, peak coordinates = (2, 16, 42). Mean contrast values were extracted from these functionally activated clusters, and contrast values for the left and right VS were averaged. This resulted in two

variables for the reward anticipation phase: bilateral VS activity and dmPFC activity. Table S1, available online, displays bivariate correlations between brain activity and other key variables.

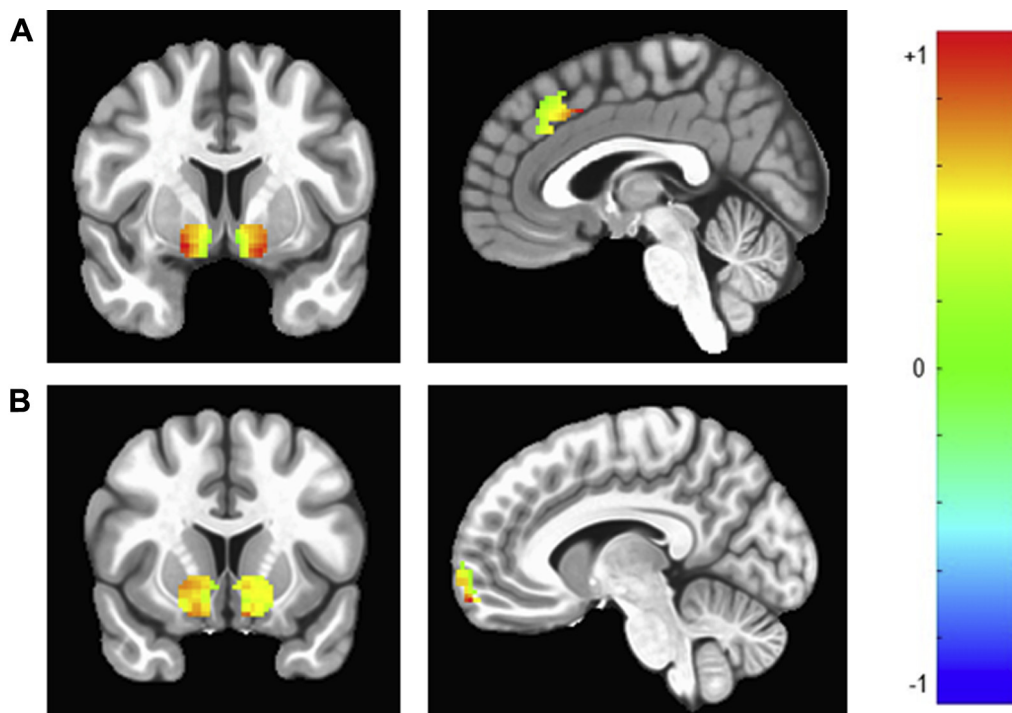
### Main Effects of Reward Feedback in the VS and mPFC

The contrast of gain > neutral feedback elicited significant activation in the left VS:  $t(261) = 3.20$  (average),  $p$ -corrected < .05, peak coordinates = (−12, 8, −18) and the right VS:  $t(261) = 3.19$  (average),  $p$ -corrected < .05, peak coordinates = (8, 8, −18) (Figure 1). Significant activation occurred in one ventral cluster of the mPFC (vmPFC):  $t(261) = 3.29$  (average),  $p$ -corrected < .05, peak coordinates = (8, 64, −14). Contrast values for the left and right VS were averaged to create a single bilateral VS variable, resulting in two variables for the reward feedback contrast: bilateral VS activity and vmPFC activity.

### Brain Activity Related to Reward Anticipation and Future Alcohol Use

We next examined whether VS or dmPFC response to gain > neutral cues at age 16 years predicted future alcohol use

**FIGURE 1** Main Effects of the Task



**Note:** (A) Bilateral ventral striatum (VS) and dorsal medial prefrontal cortex (mPFC) activity for the contrast of gain cues > neutral cues, minimum threshold  $t = 2.575$ ,  $p < .05$  corrected for each search region. (B) Bilateral VS and ventral mPFC activity for the contrast of gain feedback > neutral feedback, minimum threshold  $t = 2.575$ ,  $p < .05$  corrected for each search region. Please note color figures are available online.

approximately 2 years later, at age 18, controlling for age 16 alcohol use. Two interactions were significant for the Poisson model (see Table S2, available online). First, there was a significant interaction between dmPFC activity and sex ( $B = 3.80$ ,  $SE = 0.80$ ,  $p < .001$ ). This interaction was driven by a (nonsignificant) negative association between dmPFC activity and future alcohol use in boys ( $B = -0.65$ ,  $SE = 0.75$ ,  $p = .384$ ) but a positive association between dmPFC activity and future alcohol use in girls ( $B = 4.43$ ,  $SE = 0.76$ ,  $p < .001$ ) (Figure 2). The quadratic term for dmPFC activity was not significant. Second, there was a significant interaction between the quadratic VS term and sex ( $B = 4.69$ ,  $SE = 1.56$ ,  $p = .003$ ). This was driven by a negative quadratic effect of VS activity on future alcohol use in boys ( $B = -1.72$ ,  $SE = 0.79$ ,  $p = .029$ ) but a positive quadratic effect of VS activity on future alcohol use in girls ( $B = 2.53$ ,  $SE = 1.13$ ,  $p = .025$ ) (Figure 3). In boys, the negative quadratic effect suggests that lower levels of VS activity are associated with lower alcohol use frequency, but this effect plateaus at higher levels of VS activity and turns slightly downward. In girls, the positive quadratic effect of VS activity suggests that there is a sharper increase in alcohol use frequency at lower levels of VS activity, but this effect plateaus until higher positive values of VS activity, when the pattern turns slightly upward.

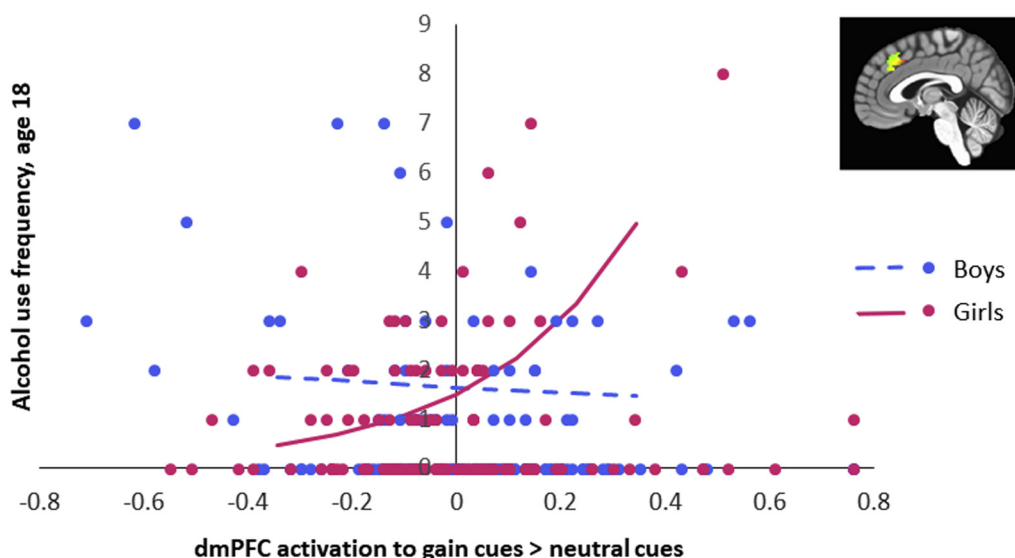
The interaction of VS activity and sex ( $B = -2.10$ ,  $SE = 0.84$ ,  $p = .012$ ), was significant at an uncorrected

threshold, but was not significant when applying an FDR threshold. There was also a significant interaction of dmPFC activity by stress ( $B = -0.29$ ,  $SE = 0.13$ ,  $p = .026$ ), but as this was intended as a covariate and not a predictor of interest, this was not included in the FDR correction and not explored further. Likewise, for the logit model, there was a significant interaction of dmPFC activity by stress ( $B = -0.93$ ,  $SE = 0.34$ ,  $p = .006$ ), but we did not include this in the FDR correction or explore it further. No other effects were significant for the logit model.

### Brain Activity Related to Reward Feedback and Future Alcohol Use

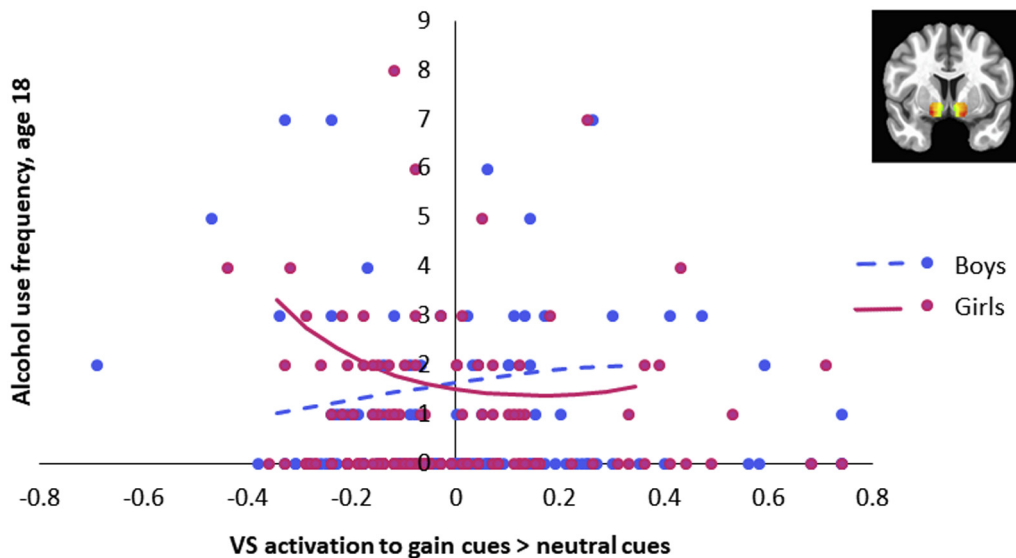
We used a similar approach to examine whether VS or vmPFC response to gain > neutral feedback at age 16 years predicted future alcohol use at age 18. In the Poisson model, there were two significant effects meeting the false discovery rate (FDR)-corrected  $p$  threshold: a quadratic effect of vmPFC activity ( $B = -2.72$ ,  $SE = 0.84$ ,  $p = .001$ ) and an interaction between the quadratic vmPFC effect and sex ( $B = 2.99$ ,  $SE = 1.02$ ,  $p = .003$ ) (see Table S3, available online). As shown in Figure 4, this was due to a significant negative quadratic effect of vmPFC activity in boys ( $B = -2.86$ ,  $SE = 1.24$ ,  $p = .021$ ) and a (nonsignificant) positive quadratic effect in girls ( $B = 0.68$ ,  $SE = 0.48$ ,  $p = .158$ ). The negative quadratic effect in boys suggests that average vmPFC activity during reward feedback is associated with higher alcohol use, but that this

**FIGURE 2** Association Between Dorsal Medial Prefrontal Cortex (dmPFC) Activation to Gain Cues > Neutral Cues and Future Alcohol Use in Male and Female Adolescents



**Note:** Lines are plotted for dorsal mPFC activity (mean-centered) from 1.5 SD below the mean to 1.5 SD above the mean using coefficients from the Poisson model (see Table S2, available online). Points on the y-axis represent alcohol use at 18 years (see Methods for description of how alcohol use was calculated). Please note color figures are available online.



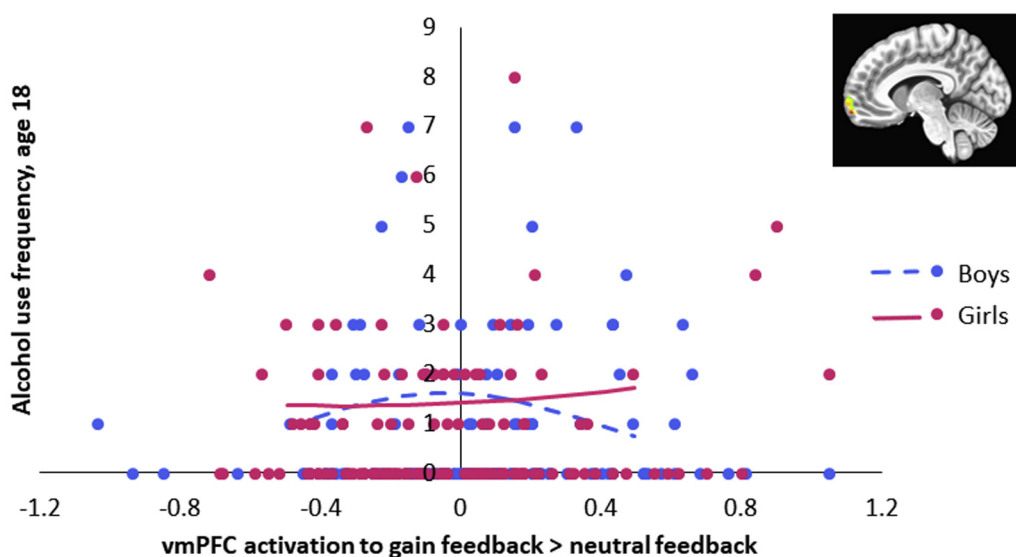
**FIGURE 3** Association Between Bilateral Ventral Striatum (VS) Activation to Gain Cues > Neutral Cues and Future Alcohol Use in Male and Female Adolescents

**Note:** Lines are plotted for VS activity (mean-centered) from 1.5 SD below the mean to 1.5 SD above the mean using coefficients from the Poisson model (see Table S2, available online). Points on the y-axis represent alcohol use at age 18 years. Please note color figures are available online.

effect turns downward at low or high levels of vmPFC activity. There was also an effect of VS activity on future alcohol use ( $B = -3.15$ ,  $SE = 1.39$ ,  $p = .024$ ), although it did not survive correction for multiple comparisons. For the logit model, no effects were significant even at an uncorrected  $p$  threshold.

#### Mediators of the Association Between Reward-Related Brain Function and Alcohol Use

We first tested whether neural activity predicted depression at age 17 years or impulsivity at age 18. There was a quadratic association between VS activity during reward anticipation and depression symptoms ( $B = 4.17$ ,  $SE = 1.64$ ,  $p = .011$ )

**FIGURE 4** Association Between Ventral Medial Prefrontal Cortex (vmPFC) Activation to Gain Feedback > Neutral Feedback and Future Alcohol Use in Male and Female Adolescents

**Note:** Lines are plotted for ventral mPFC activity (mean-centered) from 1.5 SD below the mean to 1.5 SD above the mean using coefficients from the Poisson model (see Table S3, available online). Points on the y-axis represent alcohol use at age 18 years. Please note color figures are available online.

(see Table S4, available online), although this did not survive correction for multiple comparisons. No other effects of brain activity on depression symptoms or impulsivity were significant (see Tables S4–S7, available online). Finally, we examined whether depression or impulsivity predicted alcohol use at age 18 years. In the Poisson model, there was a significant association between impulsivity at age 18 and alcohol use at age 18 ( $B = 0.58$ ,  $SE = 0.26$ ,  $p = .026$ ) (see Table S8, available online).

## DISCUSSION

The aim of the present study was to examine whether reward-related neural activity at age 16 years prospectively predicted alcohol use at age 18, controlling for age 16 alcohol use, in a sample of Mexican-origin adolescents, and to test two proposed mediating pathways. We found that the patterns of neural activity predictive of future alcohol use were different for male and female adolescents. For boys, higher VS activity during reward anticipation and average vmPFC activity during reward feedback predicted greater increases in alcohol use from age 16 to 18 years. For girls, blunted VS activity and higher dmPFC activity during reward anticipation predicted greater increases in alcohol use from age 16 to 18 years. These results indicate that different neural risk pathways are associated with increased alcohol use for male and female adolescents. However, neither impulsivity nor depression symptoms mediated these effects.

In boys, the pattern of higher VS activity during reward anticipation could indicate a sensation-seeking/impulsive pathway to alcohol use. Higher VS activity during reward anticipation may reflect a motivated drive toward rewarding stimuli. The quadratic effect of vmPFC activity on future alcohol use was not hypothesized and should be interpreted with caution until replicated. It is possible that high and low levels of vmPFC activity may indicate different psychological processes that may reduce risk through different mediating pathways, and this possibility should be tested in future research; we suggest some potential mediators below.

In contrast, in girls, a pattern of higher dmPFC activity and blunted VS activity during reward anticipation predicted future increases in alcohol use. Blunted VS activity during reward anticipation has previously been associated with problematic alcohol use, and is consistent with an internalizing/anhedonic pathway to alcohol use. It is possible that this blunted VS response while anticipating potential reward in girls reflects low levels of motivated behavior for obtaining ordinary rewards such as money, which could lead to alcohol use as a means to compensate for a blunted response to ordinary reward cues. In addition, in girls, the positive quadratic effect indicates that although

there was a steeper association between blunted VS activity and increased frequency of alcohol use, there was also a modest association between higher VS activity and alcohol use, suggesting that an average level of VS activity may be associated with the lowest risk for increased alcohol use. Although we did not directly hypothesize that higher dmPFC activity during reward anticipation would predict increased alcohol use in girls, this pattern of brain activity has been associated with higher depression symptoms in other samples,<sup>48,49</sup> and could be consistent with an internalizing pathway of risk. However, in this sample, the bivariate correlations (see Table S1, available online) suggest that higher dmPFC activity is associated with higher impulsivity in girls, which was counter to our predictions. Thus, further research is needed to identify the psychological processes underlying this effect. Overall, the separate patterns of results observed for male and female adolescents and the two contrasts suggest that differences in prior research findings may reflect the stage of reward processing examined as well as different risk processes across individuals.

Another key finding is that reward-related brain activity predicted increased alcohol use at age 18 years in the Poisson model (count outcome) testing increases in the frequency of alcohol use. However, these markers do not predict the initiation of new alcohol use (the binary outcome) during this time span. This indicates that different psychological mechanisms and different indices of brain function may be useful for differentiating risk for the onset of substance use versus the acceleration of substance use, with the current indices of brain function predicting the latter.

It is important to note, however, that despite our theoretical framework for the two proposed risk pathways mediated by depression and impulsivity, these mediators were generally not supported in the present analyses, although impulsivity was associated with frequency of alcohol use at age 18 years. It is perhaps surprising that impulsivity predicted the frequency but not the onset of alcohol use, but this may be because we measured these processes in late adolescence. Impulsivity may predict the onset of alcohol use earlier in adolescence and, as we observed, increases in frequency of alcohol use later in adolescence. In addition, these may not have been the ideal measures for the proposed mediators. For example, a specific measure of drinking motives may have been a stronger predictor of alcohol use than depression symptoms.<sup>29</sup> Alternatively, there may be mediators different from the ones proposed in the theoretical framework. Identifying the psychological and behavioral mechanisms that explain these associations will be an important direction for future research. This can be accomplished both by using imaging



paradigms that can better parse or constrain the psychological processes engaged during reward processing, as well as measuring additional mediators (eg, drinking motives, sensation seeking, delay discounting) that may link these patterns of brain activity to alcohol use.

The current study has some limitations. First, data on neural function were not collected before age 16 years, precluding our ability to determine whether alcohol use prior to age 16 preceded development of these patterns of brain activity. However, we controlled for years since initiation of substance use in our analyses to control for potential effects of prior substance use. Second, the MID task may not have been ideal for measuring the reward feedback stage of processing because, although difficulty level was set to result in ~66% accuracy, participants varied somewhat in their accuracy levels during the task, which led to a variable number of reward feedback trials available for each participant. Third, further research is necessary to establish the reliability of neural activity measured with the MID. Research conducted to date has generally focused on adults and suggests variable test–retest reliability for this or similar tasks, with intraclass correlation coefficients ranging between 0.43 and 0.81.<sup>50,51</sup> It will be critical for future research to establish the reliability of this measure in adolescents before applying it clinically. Fourth, not all participants in the study had initiated alcohol use by age 18 years, resulting in a zero-inflated count distribution. As a result, we used a zero-inflated Poisson regression to test hypotheses. Thus, the frequency count portion of the model was effectively limited to the participants who reported some amount of alcohol use at age 18. Fifth, the alcohol use measure used in these analyses asked about the frequency of alcohol use in the past 3 months but did not assess differences in the quantity of alcohol use. Sixth, although we had a strong rationale for modeling quadratic effects of VS activity and the effects survived a conservative Bonferroni correction, it is important to acknowledge that some of the quadratic effects may reflect overfitting of the data (particularly the unexpected quadratic effect of the vmPFC in boys). Seventh, this sample was selected based on risk for either substance use or depression. Although this approach helped to ensure observable variability in both potential pathways of risk (impulsive and internalizing), the

generalizability of these results may be limited to adolescents who are already exhibiting risk for either substance use or internalizing problems. Finally, because the sample was composed entirely of Mexican-origin adolescents, it is unknown whether these results would generalize to other populations.

Despite these limitations, several strengths of our study allowed us to extend prior research findings. Notably, our sample was large, comprising both boys and girls, and consisted of a population (Mexican-origin adolescents) underrepresented in prior clinical neuroscience research but with high risk for substance use. Our study also used a prospective longitudinal design to predict change in later markers of risk at age 18 years from imaging assessments collected at age 16. Replication of the current findings could aid in tailoring interventions designed to reduce adolescent alcohol use based on factors such as sex. Further research of this type holds promise for delineating the neural pathways associated with the development of future psychopathology, which could inform the prevention and treatment of substance use problems.

Accepted May 17, 2019.

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This research was supported by the National Institutes of Health grants R01MH098370 (A.E.G., P.D.H.) and R01DA017902 (R.W.R.), a William T. Grant Foundation Scholars Award 180021 (A.E.G.), a William T. Grant Foundation Mentoring Award 182606 (A.E.G.), and the University of California, Davis—Imaging Research Center Pilot Program (A.E.G.). J.R.S. was supported by Prop. 63, the Mental Health Services Act and the Behavioral Health Center of Excellence at UC Davis.

Data from this paper were presented as an oral presentation at the Association for Psychological Science 30<sup>th</sup> Annual Convention; May 24–27, 2018; San Francisco, CA.

Dr. Ferrer served as the statistical expert for this research.

Disclosure: Drs. Swartz, Weissman, Ferrer, Fassbender, Robins, Hastings, and Guyer and Ms. Beard have reported no biomedical financial interests or potential conflicts of interest.

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0890-8567/\$36.00/©2019 American Academy of Child and Adolescent Psychiatry

<https://doi.org/10.1016/j.jaac.2019.05.022>

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