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# Association of Marijuana Use With Blunted Nucleus Accumbens Response to Reward Anticipation

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**IMPORTANCE** Marijuana use may alter ventral striatal response to reward, which might heighten susceptibility to substance use disorder. Longitudinal research is needed to determine the effects of marijuana use on neural function involved in reward response.

**OBJECTIVE** To determine whether marijuana use among young adults prospectively affects nucleus accumbens (NAcc) activation during reward anticipation.

**DESIGN, SETTING, AND PARTICIPANTS** One hundred eight young adults were recruited from the Michigan Longitudinal Study, an ongoing study of youth at high risk for substance use disorder and a contrast sample of control families. Participants underwent 3 consecutive functional magnetic resonance imaging scans at approximate ages of 20 (time 1), 22 (time 2), and 24 (time 3) years. Self-report data on marijuana and other drug use occasions were collected annually since age 11 years.

**MAIN OUTCOMES AND MEASURES** Cross-lagged models were used to test the association of marijuana use with neural response in the NAcc to reward anticipation during a monetary incentive delay task controlling for sex, age, other substance use, and family history of substance use disorder.

**RESULTS** Of 108 participants, 39 (36.1%) were female and mean (SD) age at baseline was 20.1 (1.4) years. Greater marijuana use was associated with later blunted activation in the NAcc during reward anticipation (time 1 to time 2: β = −0.26, $P$ = .04; time 2 to time 3: β = −0.25, $P$ = .01). When the cross-lagged model was tested with the inclusion of previous and concurrent cigarette use, the effect of marijuana use from time 2 to time 3 remained significant (β = −0.29; $P$ = .005) and the effect of cigarette use was nonsignificant.

**CONCLUSIONS AND RELEVANCE** The findings of this study indicate that marijuana use is associated with decreased neural response in the NAcc during the anticipation of nondrug rewards. Over time, marijuana use may alter anticipatory reward processing in the NAcc, which may increase the risk for continued drug use and later addiction.

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Marijuana is the most commonly used illicit substance in the United States and is especially prevalent among young adults.[1] Marijuana use typically emerges during adolescence, peaking in the early 20s, with 35% of 21- and 22- year-old individuals reporting past year use.[2] This pervasiveness may be due to low perceptions of harm,[2] despite the short- and long-term negative consequences[3] of marijuana use. Short-term consequences include acute anxiety, paranoia, and altered perception,[4] as well as impaired motor coordination while driving.[5] Deficits in academic achievement[6] and disrupted brain structure and function[7-10] suggest long-term negative consequences of marijuana use. Of particular relevance to the present study is evidence that earlier onset of marijuana use leads to a faster transition to marijuana dependence[11] and increases the risk of developing other substance use disorders (SUDs).[12]

Marijuana's psychoactive properties are due largely to $\Delta^9$-tetrahydrocannabinol, which binds to CB1 cannabinoid neural receptors and stimulates the transmission of dopamine from the ventral tegmental area to the nucleus accumbens (NAcc) in the ventral striatum. The ventral striatum is a region involved in reward-driven behavior, including substance use.[13-15] A recent positron emission tomography study[16] demonstrated reduced reactivity of this system in long-term mari-

juana users during extracellular dopamine stimulation, which was correlated with greater addiction severity and craving. This finding is consistent with theories positing that, with long-term use, the incentive salience of cues that predict receipt of the drug strengthens, likely at the expense of rewards not associated with that drug. Such an effect is believed to contribute to the development and maintenance of SUD.[17-19] Thus, marijuana use may cause a perturbation of the dopaminergic reward system, thereby increasing risk for developing SUDs.

A number of cross-sectional studies[20-22] have investigated the effect of marijuana use on nondrug reward response during functional magnetic resonance imaging (fMRI) with the monetary incentive delay task. Monetary reward anticipation during the monetary incentive delay task reliably and robustly activates the ventral striatum, including the NAcc. Some studies[23,24] report that marijuana users show increased activation of the ventral striatum to monetary reward anticipation versus nonusers, whereas other investigations[25-27] have found no differences. However, cross-sectional studies may be unable to disentangle differences in activation due to preexisting neural susceptibilities compared with altered neural function as a result of marijuana use. Increased NAcc activation to reward anticipation has been linked to behavioral traits associated with substance use risk[22,28-30] and prospectively associated with later substance use problems.[21] Thus, longitudinal studies that account for preexisting susceptibilities are needed to more clearly identify the cumulative effect of marijuana use on neural mechanisms underlying reward responsivity.

To address this gap, the present study examined cross-lagged prospective associations between marijuana use and NAcc activation to monetary reward anticipation. Longitudinal fMRI during the monetary incentive delay task was conducted in young adults at the approximate ages of 20, 22, and 24 years, coinciding with the normative peak age of marijuana use.[2] Consistent with prior evidence supporting attenuated dopamine release in the ventral striatum among heavy marijuana users[16] and reduced incentive salience for nondrug rewards in long-term substance users,[17,18] we hypothesized that greater marijuana use would be associated with later decreases in NAcc activation to monetary reward anticipation beyond possible cofounding influences.

### Key Points

**Question** Does marijuana use alter nucleus accumbens (NAcc) responsivity to monetary reward anticipation?

**Findings** In this longitudinal study that included 108 young adults, cross-lagged analyses indicated an association between marijuana use and decreased neural response in the NAcc during anticipation of monetary rewards.

**Meaning** Over time, marijuana use may blunt the responsivity of the reward system to nondrug incentives; this may be a factor underlying continued drug use and addiction.

## Methods

### Participants

Participants were 108 young adults recruited from the Michigan Longitudinal Study, an ongoing prospective study of youth from families with high levels of SUD and a contrast sample of families without SUD.[31] A total of 84 participants (77.8%) were categorized as high risk based on parental history of SUD, which was ascertained by a clinical psychologist using the Diagnostic Interview Schedule-Version 4.[32] Exclusion criteria are presented in the eMethods in the Supplement. No minimum levels of marijuana use were required for inclusion in the present study. All eligible participants were assessed for psychosocial functioning at 3-year intervals and substance use and problems beginning annually at age 11 years. Additional details on Michigan Longitudinal Study assessment and data collection protocol are provided elsewhere.[31,33] Participants completed 3 consecutive fMRI scans at approximately 2-year intervals. The present study was reviewed and approved by the University of Michigan Medical School Institutional Review Board, and all participants provided written informed consent and received financial compensation. The **Table** displays participant characteristics, including race/ethnicity and sex.

### Substance Use Assessment

Substance use was assessed annually with the Drinking and Drug History questionnaire.[34] Past-year marijuana use was measured by the number of days during the past year that participants reported using marijuana or hashish. Past-year binge drinking was measured by the number of days during the past year that participants reported drinking 5 or more standard alcoholic drinks. Past-year cigarette use was measured by the number of days participants reported smoking cigarettes during the past year. For each substance, previous use was the number of days of use from age 11 through the year before time 1. Substance use data are reported in the Table.

### fMRI Paradigm

To assess neural response during anticipation of monetary reward, participants performed a modified version of the monetary incentive delay task.[20-22] Each trial began with an incentive cue indicating whether they could win or lose a small ($0.20) or large ($5.00) monetary reward or whether no money was at stake (cue). A fixation cross then appeared (anticipation) and was followed by a variable-duration target. Pressing the button while the target was on the screen signified a correct response. After each trial, participants were shown feedback indicating whether they pressed the button quickly enough (outcome). Additional details are provided in the eMethods in the Supplement.

### fMRI Data Acquisition and Analysis

Whole-brain blood oxygen level–dependent images were acquired on a 3-T scanner (Signa; GE Healthcare) using a T2*-weighted single-shot combined spiral in/out sequence[35] (repetition time [TR], 2000 milliseconds; echo time [TE], 30 milliseconds; flip angle, 90°; field of view [FOV], 200 mm; 64 × 64 matrix; in-plane resolution, 3.12 × 3.12 mm; section thickness, 4 mm).[34] In addition, a high-resolution, anatomic,

Table. Participant Characteristics

| Characteristic | Value |
|---|---|
| No. of participants | 108 |
| **Baseline** | |
| White race, No. (%)[a] | 104 (96.3) |
| Female sex, No. (%) | 39 (36.1) |
| Age, mean (SD), y | |
| Time 1 | 20.1 (1.4) |
| Time 2 | 22.1 (1.5) |
| Time 3 | 23.8 (1.7) |
| Family history of SUD, No. (%)[b] | 84 (77.8) |
| Lifetime diagnosis, No. (%) | |
| Conduct disorder | 18 (16.7) |
| ADHD | 5 (4.6) |
| Alcohol and drug use, mean (SD) | |
| Marijuana use by age 16 y, d | 15.4 (53.9) |
| Previous marijuana use[c] | 125.2 (320.3) |
| Previous binge drinking, d[c] | 47.8 (102.5) |
| Previous cigarette use, d | 284.9 (546.8) |
| **Time 1** | |
| Past year, mean (SD), d | |
| Marijuana use | 17.5 (58.1) |
| Binge drinking | 37.8 (61.6) |
| Cigarette smoking | 85.7 (129.1) |
| Diagnosis, No. (%) | |
| MUD | 5 (4.6) |
| AUD | 8 (7.4) |
| NUD | 7 (6.5) |
| **Time 2** | |
| Past year, mean (SD), d | |
| Marijuana use | 30.4 (87.6) |
| Binge drinking | 36.7 (59.7) |
| Cigarette smoking | 74.5 (122.0) |
| Diagnosis, No. (%) | |
| MUD | 5 (4.6) |
| AUD | 8 (7.4) |
| NUD | 6 (5.6) |
| **Time 3** | |
| Past year, mean (SD), d | |
| Marijuana use | 31.8 (89.9) |
| Binge drinking | 31.9 (46.5) |
| Cigarette smoking | 61.5 (122.2) |
| Diagnosis, No. (%) | |
| MUD | 4 (3.7) |
| AUD | 11 (10.2) |
| NUD | 6 (5.6) |

Abbreviations: AUD, alcohol use disorder; MUD, marijuana use disorder; NUD, nicotine use disorder; SUD, substance use disorder.

[a] Race/ethnicity was measured through self-reported categorical response options defined by the investigator and assessed to examine the representativeness of the study population.

[b] Family history of SUD was defined as having a biological father and/or mother with a lifetime diagnosis of any AUD or drug use disorder.

[c] Previous use was measured by use days from age 11 years through the year before time 1.

T1-weighted scan was obtained (TR, 25 milliseconds; minimum TE; FOV, 25 cm; 256 × 256 matrix; section thickness, 1.4 mm). Image processing and individual-level analyses are described in the eMethods in the Supplement.

The present report focuses on the contrast between anticipation during monetary gain trials and neutral trials (ie, reward anticipation). Contrasts for small and large gains were estimated separately. Given the problems associated with the circularity of statistical inference when defining volumes of interest based on observed contrast activation[36] and considering the present study's a priori interest in the NAcc, anatomic masks of the left and right NAcc were created as described previously[22,28] using the Build ROI function in MarsBaR[37] (eFigure 1 in the Supplement). Contrasts for small and large gains were then linearly combined with the mean determined across hemispheres. Associations between incentive amount and hemisphere in NAcc volume are described in the eMethods in the Supplement. Acceptable reliability of NAcc activation across sessions has been reported.[21]

## Cross-Lagged Model Analysis

To examine longitudinal associations between marijuana use and NAcc activation during monetary reward anticipation, cross-lagged analyses were conducted using robust maximum likelihood estimation in Mplus, version 7.2.[38] Log transformations were performed to improve the normality of the marijuana use variable (transformed variable skewness: time 1, 1.56; time 2, 1.62; and time 3, 1.83; and transformed variable kurtosis: time 1, 1.42; time 2, 1.30; and time 3, 1.82). Cross-lagged analyses included across-time stability coefficients for marijuana use and NAcc activation, within-time associations between marijuana use and NAcc activation, and across-time cross-lagged paths between marijuana use and NAcc activation.

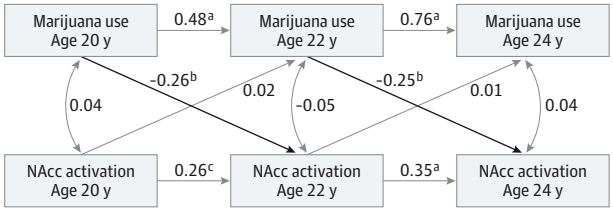
Covariates were sex, age at time 1, parental history of SUD, previous marijuana use and binge drinking, and past-year binge drinking. Age at time 1 was included to control for the range in ages (18-24 years) at the initial scan. Parental history of SUD was included to control for heightened risk of substance use.[39] Because of evidence[3,7] suggesting an effect of onset and duration of marijuana use on brain structure and function, we accounted for previous marijuana use. We also accounted for previous and past-year binge drinking, given the high comorbidity between marijuana and alcohol use.[40-42] Because marijuana use is also frequently seen with cigarette smoking[41] and some studies[43,44] suggest that nicotine use may reduce the influence of $\Delta^9$-tetrahydrocannabinol on NAcc response to nondrug reward anticipation, we tested an additional analytic model that included previous and past-year cigarette use as covariates. The following parameters determined adequate model fit: nonsignificant $\chi^2$, root mean square error of approximation below 0.06, and a comparative fit index and Tucker-Lewis Index of 0.95 or higher.[45] Significant pathways were established based on $\alpha = .05$. To allow comparison with earlier cross-sectional studies,[23-25,27] we also investigated associations between time 1 NAcc activation and previous marijuana use and age at first use with partial correlations, controlling for previous binge drinking and cigarette use.

## Results

### Task Performance

Reaction times and accuracy data are provided in the eResults and eTable 1 in the Supplement. Partial correlations were conducted to test associations between marijuana use and task performance, controlling for sex, age at time 1, parental history of SUD, previous marijuana use and binge drinking, and concurrent past-year binge drinking. No significant (α = .05) partial correlations were found between marijuana use and task performance (eTable 2 in the Supplement). Participants showed robust ventral striatum activation at each time during reward anticipation (eFigure 2 in the Supplement).

**Figure 1. Longitudinal Cross-lagged Associations Between Marijuana Use and Nucleus Accumbens (NAcc) Activation During Reward Anticipation**



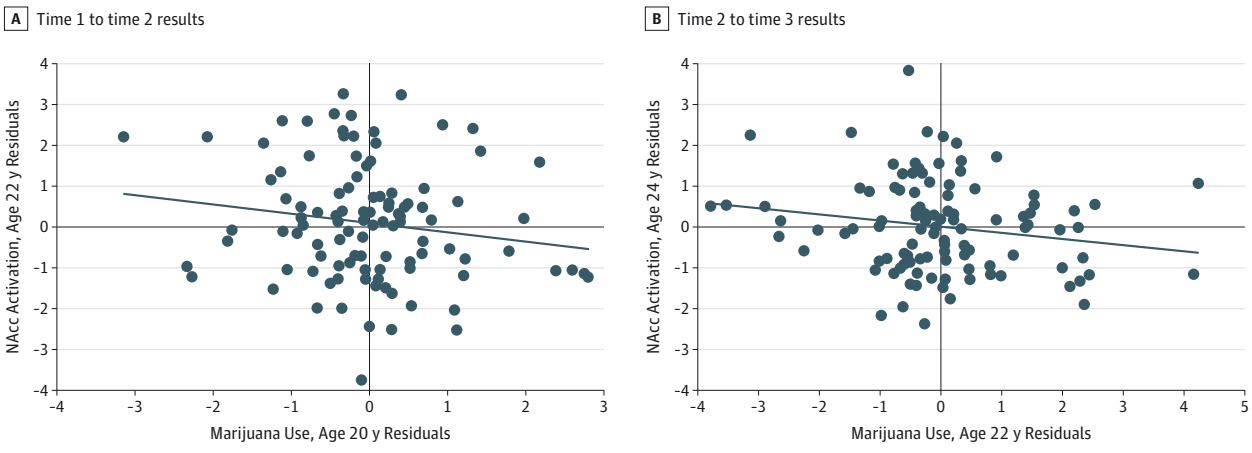

Results are shown from cross-lagged analysis of past-year marijuana use at each scan date and NAcc activation during reward anticipation. The coefficients indicated are standardized path coefficients with covariates of sex, age at time 1, parental history of substance use disorder, previous marijuana use and binge drinking up to 12 months before time 1, and past-year binge drinking corresponding to each time (covariances of exogenous variables are not depicted). Straight arrows represent causal paths; curved arrows, covariances. Indices of model fit are $\chi^2 = 8.94$; $P = .35$; root mean square error of approximation, 0.03; comparative fit index, 0.99; and Tucker-Lewis Index, 0.97.
[a]$P < .001$.
[b]$P < .05$.
[c]$P < .01$.

### Marijuana-NAcc Cross-Lagged Associations

Partial correlations found no association between NAcc activation at time 1 and previous marijuana use ($r = 0.10$; $P = .48$) and a marginally significant negative correlation between age of first marijuana use and NAcc activation at time 1 ($r = -0.23$; $P = .07$). The cross-lagged model showed excellent model fit and significant cross-lagged paths between marijuana use and blunted NAcc activation during monetary reward anticipation (**Figure 1**). Past-year marijuana use at time 1 was negatively associated with NAcc activation at time 2 (β = −0.26; $P = .04$), with no covariates reaching significance. Past-year marijuana use at time 2 was negatively associated with NAcc activation at time 3 (β = −0.25; $P = .01$), with significant covariates of previous marijuana use (β = 0.31; $P = .007$) and previous binge drinking (β = −0.17; $P = .01$). Stability coefficients were significant for past-year marijuana use (time 1-2: β = 0.48, $P < .001$; time 2-3: β = 0.76, $P < .001$) and for NAcc activation (time 1-2: β = 0.26, $P = .003$; time 2-3: β = 0.35, $P < .001$). A graphical representation of cross-lagged results is shown in **Figure 2**. Testing positive for marijuana use but reporting abstinence within 48 hours before each scan did not greatly affect the findings (eResults in the Supplement).

A cross-lagged model including previous and past-year cigarette use also fit well ($\chi^2 = 14.53$; $P = .27$; root mean square error of approximation, 0.04; comparative fit index, 0.99; Tucker-Lewis Index, 0.94). Stability coefficients were significant for past-year marijuana use (time 1-2: β = 0.44, $P = .003$; time 2-3: β = 0.73, $P < .001$) and NAcc activation (time 1-2: β = 0.27, $P = .002$; time 2-3: β = 0.36, $P < .001$). The negative association between time 2 marijuana use and time 3 NAcc activation remained significant (β = −0.29; $P = .005$) with significant covariates of previous marijuana use (β = 0.42; $P = .001$) and previous binge drinking (β = −0.17; $P = .008$); however, the association between time 1 marijuana use and time 2 NAcc activation was only marginally significant (β = −0.24; $P = .07$), with no covariates reaching signifi-

**Figure 2. Prospective Associations Between Marijuana Use and Nucleus Accumbens (NAcc) Activation During Reward Anticipation**




A, Past-year marijuana use at age 20 years (time 1) and NAcc activation during reward anticipation at 22 years (time 2). B, Past-year marijuana use at 22 years (time 2) and NAcc activation during reward anticipation at 24 years (time 3). Both partial regression plots controlled for all covariates included in cross-lagged analyses. Circles indicate data points for each participant; horizontal line, coefficient line.

cance. Pearson correlation coefficients were examined between marijuana use and other substances of interest included in cross-lagged analyses (eTable 3 in the Supplement).

## Discussion

To our knowledge, the present study is the first to report longitudinal associations between marijuana use and NAcc activation during a nondrug reward anticipation task. We found a significant prospective association between marijuana use and decreased NAcc activation to monetary reward anticipation. Our findings indicate that continued marijuana use may result in a blunted NAcc response to nondrug rewards, even when controlling for previous and concurrent substance use. The model also controlled for potential risk factors, such as familial risk for SUD and baseline differences in NAcc activation. This work provides robust evidence that marijuana use has long-term associations with anticipatory reward processing.

Although previous studies have shown increased NAcc activation to monetary reward anticipation among marijuana users[23,24] or no significant differences from controls,[25-27] we found decreased NAcc activation over time. Prior cross-sectional studies[23-27] may not have been able to account for preexisting differences in NAcc activation that predisposed certain individuals toward engaging in reward-seeking behavior, such as substance use. At time 1, we found a marginal association between greater NAcc activation and earlier age at onset of marijuana use, but no association with the amount, supporting the view that heightened reward system activation represents a risk factor for use rather than a consequence. Using prospective, cross-lagged analyses, we isolated the association between marijuana use and later NAcc function more directly while accounting for baseline NAcc activation at time 1. These findings indicate that continued marijuana use affects anticipatory reward processing, whereas preexisting differences in NAcc function were not associated with later marijuana use. Given that the baseline measurement in this study was conducted during young adulthood, future prospective studies at earlier ages may more clearly detect preexisting striatal risk associated with marijuana use.

Finding a prospective association between marijuana use and decreased NAcc activation to monetary reward supports a mechanism through which marijuana use may lead to enhanced vulnerability to SUD. Although early substance use involves voluntary decisions, our findings support the view that continued consumption produces long-term alterations in neural circuits involved in reward processing, which may in turn contribute to drug-seeking behavior and compulsive use.[19] One possible mechanism is that the effects of long-term marijuana use on these neural systems results in a general blunting of reward response. This blunting may lead to further drug use in an attempt to counteract insufficient reward responsivity, which is consistent with the reward deficiency theory of addiction.[46] We did not observe an association between NAcc response to monetary reward and later marijuana use. Although a direct robust association may not exist between these factors, repeated use may result in a bias toward marijuana and marijuana-associated cues relative to unrelated cues. Continued stimulation of mesolimbic neural circuits during marijuana use may sensitize this circuitry to attribute greater salience to stimuli paired with marijuana use.[47] This bias toward marijuana cues may contribute to long-term use of the substance and an increased risk for addiction. To test this theory, it will be necessary for future studies to prospectively examine neural response to both marijuana-associated and nondrug reward cues over time.

An alternative hypothesis is that blunted reward system response in marijuana users is associated with general anhedonia, which may maintain substance use. This association may be more specific to marijuana, given that endogenous cannabinoids have been shown[48] to be involved in regulating emotional responses, and animal work[49,50] has demonstrated a link between exposure to exogenous cannabinoids and depressive phenotypes. Marijuana may be used to cope with dysregulated mood, and continued use may alter neural systems involved in mood and emotion (eg, dopaminergic reward system). Attenuated striatal reactivity to dopamine stimulation in long-term marijuana users has been shown[16] to correlate with negative emotionality. This is also supported by prior work[51] demonstrating a prospective association between marijuana use and greater negative emotionality.

Given the high incidence of polysubstance use[41] and the fact that all drugs of abuse affect dopamine levels in the NAcc,[13-15] we accounted for potentially confounding substance use. For example, there is evidence[52,53] that heavy alcohol use may blunt NAcc activation to reward anticipation. We found an effect of long-term marijuana use on anticipatory reward processing when controlling for potential effects of previous and concurrent binge drinking. Thus, marijuana use may have a specific influence on NAcc response beyond that of heavy alcohol use. Cumulative marijuana use and binge drinking before time 1 had a significant effect on NAcc activation at time 3 but not at time 2. This finding was likely due to the more proximal influence of marijuana use at time 1 accounting for a large degree of the variance of time 2 NAcc activation, resulting in less unexplained variance to be accounted for by previous marijuana use and binge drinking. In contrast, there may have been more unexplained variance to be accounted for by previous marijuana use and binge drinking at time 2 given the weaker correlation (eTable 3 in the Supplement).

Owing to earlier work[43,44] showing blunted NAcc during monetary reward anticipation among marijuana users who also smoke cigarettes, we tested a cross-lagged model that included both variables. The association between marijuana use at time 1 and later NAcc activation was reduced to marginal significance, whereas the association between marijuana use at time 2 and later NAcc activation remained significant. This difference in the influence of cigarette use on the model over time is likely due to a higher correlation between marijuana and cigarette use at time 1 than at time 2 ($r$ = 0.42 and $r$ = 0.25, respectively) (eTable 3 in the Supplement). However, no significant effects of previous or concurrent cigarette use on NAcc activation were observed at any time. Our findings suggest that reduced NAcc activation was not being driven by nicotine effects on endocannabinoid modulation of the NAcc.[43] More specific cross-lagged group comparisons between marijuana,

cigarette, and combined marijuana and cigarette users may further disentangle the association between marijuana and nicotine on anticipatory reward processing.

One limitation of our study is that the binge drinking threshold was 5 or more standard alcoholic drinks for both men and women, which is greater than the typical cutoff of 4 or more drinks for women.[54] Our findings also may have limited generalizability, given that the sample consisted predominately of white and high-risk (defined by family history of SUD) young adults. However, in many ways this was an appropriate sample, given that both white youth[2] and youth with a family history of SUD[39] tend to show high levels of substance use. Finally, early vs late onset of marijuana use could be an important moderator, but we did not have an adequate number of early-onset users to test for such differences. Future studies with larger sample sizes should examine whether these associations differ across the age of onset of marijuana use.

## Conclusions

The present study provides evidence for the longitudinal effect of marijuana use on NAcc functioning during monetary reward anticipation. Because of the rise in marijuana use rates coupled with decreasing perceptions of harm,[2] this study provides important and what we believe to be novel information pertaining to the long-term influence of marijuana use on brain mechanisms underlying addiction. Educating youth about the influence of marijuana on this neural circuitry and its potential downstream consequences on addiction vulnerability may help improve efforts to prevent the initiation and escalation of marijuana use. Such efforts may dispel the notion that marijuana use produces no lasting neural influences and may elucidate the potential harms associated with this substance.

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**Author Contributions:** Dr Heitzeg had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
*Study concept and design:* Martz, Jester, Zucker, Heitzeg.
*Acquisition, analysis, or interpretation of data:* All authors.
*Drafting of the manuscript:* Martz, Cope, Hardee, Heitzeg.
*Critical revision of the manuscript for important intellectual content:* All authors.
*Statistical analysis:* Martz, Trucco, Cope, Hardee, Jester.
*Obtained funding:* Zucker, Heitzeg.
*Administrative, technical, or material support:* Cope, Zucker.
*Study supervision:* Cope, Heitzeg.

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