Running head:

ANTECEDENTS AND OUTCOMES OF ALCOHOL CUE-REACTIVITY

Antecedences and outcomes of neural reactivity towards alcohol cues in adolescence.

Allison M. Londerée[1], Dylan D. Wagner[1], Christopher R. Browning[2], Bethany Boettner[3], Baldwin M. Way[1]

1. Department of Psychology, The Ohio State University, Columbus, OH, USA

2. Department of Sociology, The Ohio State University, Columbus, OH, USA

3. Institute for Population Research, The Ohio State University, Columbus, OH, USA

Number of pages:

Number of figures:

Number of tables:

Number of multimedia:

Abstract word count:

Main text word count:

Figure captions word count:

Total word count:

*Corresponding author:

Dylan D. Wagner

Department of Psychology

The Ohio State University

1827 Neil Avenue

Telephone: (614) 688-1738

Fax: (614) 292-5601

E-mail: wagner.1174@osu.edu

Abstract

Introduction

Alcohol is the most widely used substance in the United States; over 80% of individuals aged 12 and over report that they have consumed alcohol at sometime in their life ("Section 2 PE Tables – Results from the 2018 National Survey on Drug Use and Health: Detailed Tables, Sections 1 - 3, SAMHSA, CBHSQ," n.d.). One feature shown to be important to alcohol-related outcomes is neural reward reactivity (Schacht, Anton, & Myrick, 2013). Alcohol-related activity in the ventral striatum (VS), anterior cingulate (Acc), and orbital frontal cortex (OFC) is positively associated with more drinking behavior (Courtney, Rapuano, Sargent, Heatherton, & Kelley, 2018; Tapert et al., 2003), as well as likelihood of transitioning from moderate to heavy alcohol use (Dager et al., 2014). In those with alcohol use disorder, greater neural alcohol-related activity is predictive of greater craving in adults (Myrick et al., 2004, 2008), desire in teens (Tapert et al., 2003), and greater severity of additiction (Claus, Ewing, Filbey, Sabbineni, & Hutchison, 2011). Additionally, having lower neural alcohol reactivity reduces the likelihood of post-treatment relapse (Grüsser et al., 2004; Reinhard et al., 2015).

Alcohol use and abuse in aldolecents is particularly high with 59% of school-aged teens reporting some use in their lifetime, and 9.4% self-reporting being drunk in the last 30 days (Johnston et al., 2020). This is perhaps related to the cascade of changes in brain development that occurs during adolescence, in particular, reward and self-control processing (Somerville & Casey, 2010; van Duijvenvoorde, Peters, Braams, & Crone, 2016; Velanova, Wheeler, & Luna, 2008). Adolecents display greater neural reward activity than adults in limbic and striatal regions (Silverman, Jedd, & Luciana, 2015). These increases in reward sensitivity are adaptive. For example, adolencents show enhanced reinforcement learning relative to adults (Davidow,

Foerde, Galván, & Shohamy, 2016) and striatum activity peaks at same time as learning performance (Peters & Crone, 2017). Still, this enhanced learning may also lead to increases susceptibility to appetitive environmental cues, even prior to drug experimentation (Londerée et al., 2018).

Developing a reward response to a novel environmental cue is a learned process. For example, conditioning a stimulus with the receipt of a reward leads to cue-reactivity and craving in response to this stimulus (Van Gucht, Vansteenwegen, Van den Bergh, & Beckers, 2008). Psychological and physiological responses to alcohol cues has been found to increase with greater experiance with alcohol (Curtin, Barnett, Colby, Rohsenow, & Monti, 2005; White & Staiger, 1991). Still, how neural reward activity towards alcohol is developed over time with experience is not well understood. Studies of neural alcohol cue-reactivity primarily focus on populations who have already developed a strong reward response to alcohol cues (drinking adults, or aldolecents that have engaged in prior alcohol use or those who have alcohol use disorder). Fewer studies have examined neural reward processing precursors to alcohol use in adolecents; however, these studies have either focused on domain general reward responses (Whelan et al., 2014), or environmental and social factors related to cue-reactivity (i.e. family history, early dating Nguyen-Louie et al., 2018) rather than previous experience with alcohol. Still, improving understanding of how alcohol cues develop a neural reward response is crucial, given that alcohol is used by over half of adolecents (Johnston et al., 2020), and the severity of alcohol use is related to earlier drinking behavior (Hingson, Heeren, & Winter, 2006). In addition, how these in-development neural responses are related to future intended behavior has not been examined, but key to understanding alcohol use, and abuse over time.

In the current study, we used an alcohol cue-reactivity paradigm in conjunction with longitudinal interview data to determine how past alcohol behaviors shape neural cue-reactivity towards alcohol and how these responses in turn predict future behavior. We predicted that the magnitidue of neural cue-reactivity towards alcohol cues in two primary reward regions (the lOFC and lNAcc) would be predicted by adolecents' past experiences with alcohol. In addition, we expected that this relationship would be stronger for those who have a longer period of alcohol use, and greater use during that period. In addition, we predicted that those with greater neural cue-reactivity will in turn report greater intentions and willingness to engage in drinking behavior in the future.

Materials and Methods

Data

Our sample consists of a subset of the 2014-2019 waves of the Adolescent Health and Development in Context (AHDC) study (N=1400). This study contains a representative sample of households with adolescents ages 11-17 residing in Franklin County, Ohio. The study aims to provide a longitudinal multimodal approach to understanding adolescent development, including information about social, psychological, and biological processes collected through a combination of in-home interviews, surveys, ecological momentary assessment, geolocation data, biological markers, and magnetic resonance imaging (MRI). The present examination utilizes a subset of these data collected at wave 1, 2 and 3, of this dataset, from survey, at-home interviews, and MRI sessions.

Participants

Two-hundred and seventy-four individuals participated in the wave 3 scanning session. A total of 57 participants were excluded from analyses: 17 participants were excluded from analyses due to missing or impartial functional imaging task data, and 40 subjects were excluded due to excessive head motion during scanning (i.e. several instances of >2 mm head motion). This proportion of loss of data due to head motion (16%) is consistent with other large datasets sampling adolescent individuals. In addition, approximately XX% of the sample were missing behavioral data from one or more waves. A listwise deletion method was used to remove subjects with missing data or skipped data for a particular analysis. All participants gave informed consent or assent; guardian provided consent for participants under 18.

Measures

Alcohol Use History

(insert interview procedure here)

Behavioral Questionnaires

At the in-lab experimental session (wave 3), participants completed a series of questionnaires assessing alcohol-related topics, as a part of a larger assessment battery. First, participants reported if they had ever before experimented with alcohol using the following item "*Have you ever tried or experimented with an alcoholic beverage, even one or two sips?*" with response options "*Yes*", "*No*", "*I don't know*", "*Skip*". Then, intentions to use alcohol and

flavored alcohol in the next year was assessed using two questions; "*Do you intend to use an [flavored] alcoholic beverage [(e.g., apple, chocolate, coca-cola, peach)] sometime in the next year?*" on a scale from (1) "*Definitely no*", to (7) "*Definitely yes"*. Next, following the same protocol as Gibbons et al., (2003), participants' willingness to drink alcohol was assessed by presenting risk-conducive scenarios, and then asking participants how willing they would be to engage in drinking behavior under those circumstances. The scenarios describe hanging out with a group of friends in the next few months, one friend is drinking alcohol, and offers the participant a sip. In the first scenario, the flavor of the alcoholic beverage is unspecified. In the second scenario, the flavor of the alcoholic beverage was specified to be "*flavored with something you like (e.g., apple, chocolate, coca-cola, peach)*". Participants were then asked to report their willingness to consume a sip and more than one sip on a 7-point scale ranging from (1) "*Not at all willing*" to (7) "*Very willing*". A summary of the average correlation between experimentation, intentions and willingness across all subjects is provided in Table X.

Cue Reactivity Task

While undergoing functional magnetic resonance imaging (fMRI), participants viewed a series of alcoholic beverages, food, flavored e-cigarettes, marijuana, and outdoor scenes across 2 runs. This task used a block design with image trials consisting of a single image displayed for 2.5 seconds within a 10 second block (1s TR). In addition, rest blocks consisting of a black fixation cross on a grey background were used. The presentation was optimized prior to scanning and then static across participants. To ensure attention to the images, participants were asked to respond to the question "Do you like this image?" by responding "Yes" or "No" with the index

and middle fingers of their right hand on image trials. The question was not presented on the screen. All stimuli were presented using Eprime.

Image acquisition

Magnetic resonance imaging was collected with a Siemens Prisma 3.0 Tesla MRI scanner using a 32-channel phased array coil. Structural images were acquired using a T_1 – weighted (208 sagittal slices, time repetitions [TR]: 2500ms; time echo [TE] 2.45; flip angle: 8°; 1mm isotropic voxels). Functional images were acquired using a T_2 – weighted echo-planar sequence (TR: 1000ms; TE: 28ms; flip angle: 60°). For each participant, 2 functional runs of 340 whole-brain volumes were collected (45 axial slices per whole brain volume; 3mm thickness; 3x3 in-plane resolution; multi-band acceleration factor of 3).

Image preprocessing

fMRI data were analyzed using the general linear model (GLM) for block designs in SPM12 in conjunction with a set of in-house tools for pre-processing and analysis (SPM12w, available at https://github.com/wagner-lab/spm12w). For each functional run, data were preprocessed to remove sources of noise and artifact. Images were corrected for differences in acquisition time between slices, realigned within and across runs, and then unwarped to reduce residual movement-related distortions. Data were normalized into a standard stereotaxic space (3mm isotropic voxels) based on the SPM12 EPI template that conforms to the International Consortium for Brain Mapping 152 brain template space. Normalized images were spatially smoothed with an 8-mm full-width-at-half-maximum Gaussian kernel. Volumes were then

inspected for scanner- and motion-related artifacts based on the realignment parameters and temporal SNR profiles for each run.

Region-of-interest selection

For each participant, a GLM containing task effects and covariates of non-interest (a session mean, a linear trend to account for low-frequency drift, and six movement parameters) was constructed to investigate reward-related brain activity to each condition. The GLMs were then convolved with a canonical hemodynamic response function (HRF). Contrast images comparing all (alcoholic beverages, food, flavored e-cigarettes, marijuana) > outdoor scene trials were created and entered into a second-level repeated measures analysis of variance (ANOVA) with subject effects explicitly modeled to account for between-subject differences in mean response. Consistent with prior studies, viewing alcohol images was associated with increased activity in the lOFC (for a review see, Schacht et al., 2013). This analysis revealed a functionally defined a lOFC cluster (57 voxels, $p < 0.001$ family-wise error rate corrected at the cluster level) centered at -27, 33, -15 ($f(648) = 63.61$, $p < 0.001$ at the voxel level). A 6mm sphere was constructed around this peak activation that was then used as a functional region-of-interest (ROI) to extract for all subsequent analyses (Fig. X).

Statistical Analysis

Analyses of behavioral data were conducted using the R statistical language using the stats package (R Core Team, 2020) and the lmerTest package (Kuznetsova, Brockhoff, & Christensen, 2017). Confidence intervals for each fixed effect parameter were estimated using

the confint function of the Lme4 package using a bootstrapping method (Bates, Mächler, Bolker, & Walker, 2015). A measure of time since first drink was constructed using interview data from waves 1, 2, and 3. The date at first use from interview waves 2 and 3 was combined with the age in years at first use from wave 1, taking the value from the earlier wave when more than one existed. These dates were then subtracted from the date of the MRI scan to create the time since first drink measure. Regression analyses were then conducted to test whether time since first drink was related to neural activity towards alcohol in the lOFC ROI. Follow-up analyses were conducted to determine if neural activity towards a different reward category, food, within the same ROI, was predicted by time since first drink. Additional regression analyses were constructed to examine if neural activity toward alcohol is associated with alcohol experimentation, and intentions and willingness to use alcohol in the future. Due to skewedness in the intentions and willingness measures, a log transform was applied before model construction.

For all regression-based analyses, the primary association of interest was examined as well as a model containing demographic covariates, including age in months at the time of scan, sex, household income, and race and ethnicity. Household income was measured using 4 primary categories (XXX) and treated as an ordinal variable in all analyses. Race was binned into 3 categories (Black n= 103, White n=71 , Other n=38) due to a small number of participants identifying with Hispanic (n=8), Asian (n=2), Native American (n=2), and multirace (n =26) groups.

Results

Descriptive Statistics.

Participants' age at the time of scanning averaged XX years old. XX% were female, and XX% were Black. At the time of the scan, XX% had reported having experimented with alcohol. For those who reported past alcohol use, the average time since first drink was XX (XX sd). Table X provides further descriptive statistics.

fMRI Results.

Time since first drink and neural alcohol reactivity.

We investigated whether alcohol-related cue reactivity was predicted by time since first drink of alcohol in those who had previously engaged in drinking alcohol (see Figure X). This analysis revealed a significant relationship between magnitude of alcohol cue reactivity in the lOFC and length of time since a participant's first drink of alcohol ($\beta = 0.0446$, SE = 0.016, 95% CI = [0.0112, 0.0776], $p = 0.009$). This relationship remained in a model containing demographic covariates ($\beta = 0.0517$, SE = 0.017, 95% CI = [0.0183, 0.0852], $p = 0.003$). In addition, age was also a significant predictor of alcohol cue-reactivity ($\beta = -0.0043$, SE = 0.001, 95% CI = [-0.0082, -0.0005], $p = 0.028$), such that older participants had lower alcohol cue-reactivity in the lOFC. No other covariates (sex, race, household income) were significant.

The above analysis provides evidence that the amount of time since first experimenting with alcohol is predictive of reward reactivity towards alcohol cues. Still, it is possible that this is be due to a domain-general reactivity to rewarding stimuli. To test this possibility, a model was

constructed predicting neural cue-reactivity towards food from time since first drink of alcohol. The results of this analysis showed no significant relationship between food cue-reactivity in the lOFC and time since first alcoholic drink (β = 0.009, SE = 0.019, 95% CI = [-0.0284, 0.0465], p = 0.631). In a model containing demographic covariates, this relationship was not significant (β = 0.0106, SE = 0.020, 95% CI = [-0.0296, 0.0510], p = 0.596), and no covariates were significant. This finding provides strong evidence that the relationship between alcohol reactivity and length of time since first alcoholic drink is not driven by individual differences in cue-reactivity, as there is a strong correlation between neural reactivity in the lOFC towards alcohol and food (r=0.46, p < 0.001).

Neural alcohol reactivity and intentions to drink alcohol.

A model investigating whether reward activation towards alcohol cues is predictive of intentions to drink revealed that lOFC alcohol reactivity was predictive of both intentions to drink alcohol (flavor unspecified; β = 0.3348, SE = 0.162, 95% CI = [0.0139, 0.6557], p = 0.041), and flavored alcohol (β = 0.4198, SE = 0.155, 95% CI = [0.1141, 0.7254], p = 0.007) in the next 12 months, such that greater alcohol reactivity was associated with greater intentions to drink. Additionally, when controlling for age, sex, race, and household income, this relationship remains for both alcohol (β = 0.3362, SE = 0.146, 95% CI = [0.0489, 0.6234], p = 0.022) and flavored alcohol (β = 0.4030, SE = 0.148, 95% CI = [0.1091, 0.6968], p = 0.007). Age was also a significant predictor in these models such that older individuals had greater intentions to drink alcohol (β = 0.0128, SE = 0.002, 95% CI = [0.0089, 0.0166], p < 0.001) and flavored alcohol (β = 0.0106, SE = 0.002, 95% CI = [0.0065, 0.0146], p < 0.001). No other demographic covariates were significant (all p > 0.08).

Neural alcohol reactivity and willingness to sip alcohol.

We then examined how alcohol reactivity is related to willingness to drink alcohol in the future under conducive circumstances. This analysis revealed that those with greater alcohol related activity in the lOFC were marginally more willing to drink a sip (β = 0.3303, SE = 0.169, 95% CI = [-0.0024, 0.6631], $p = 0.051$) or more than one sip of alcohol (β = 0.2920, SE = 0.169, 95% CI = [-0.0422, 0.6263], $p = 0.086$). In a model with covariates of interest, this relationship becomes significant for willingness to sip (β = 0.3224, SE = 0.153, 95% CI = [0.0201, 0.6246], $p = 0.038$), but not willingness to have more than one sip of alcohol (β = 0.2458, SE = 0.156, 95% CI = [-0.0614, 0.5530], $p = 0.116$). Age was also a significant predictor in both models (sip: β = 0.0119, SE = 0.002, 95% CI = [0.0079, 0.0160], $p < 0.001$, more than one sip: β = 0.0118, SE = 0.002, 95% CI = [0.0077, 0.0159], $p < 0.001$).

These relationships were also examined for flavored alcohol. The same pattern of results was revealed, such that greater lOFC alcohol reactivity was related to greater willingness to sip (β = 0.3981, SE = 0.164, 95% CI = [0.0751, 0.7211], $p = 0.016$) and have more than one sip (β = 0.3795, SE = 0.158, 95% CI = [0.0674, 0.6915], $p = 0.017$) of flavored alcohol. In models including covariates, these relationships remained (sip: β = 0.3775, SE = 0.153, 95% CI = [0.0755, 0.6795], $p = 0.015$, more than one sip: β = 0.3604, SE = 0.151, 95% CI = [0.0616, 0.6591], $p = 0.018$). Age was also a significant predictor of willingness to sip (β = 0.0113, SE = 0.002, 95% CI = [0.0073, 0.0154], $p < 0.001$) and have more than one sip of flavored alcohol (β = 0.0099, SE = 0.002, 95% CI = [0.0059, 0.0139], $p < 0.001$), such that that older individuals were more likely to report greater willingness to engage in drinking flavored alcohol.

Discussion

Author's Note

Allison M. Londerée, Dylan D. Wagner, Baldwin M. Way, Department of Psychology, The Ohio State University, Columbus OH. Christopher R. Browning, Department of Sociology, The Ohio State University, Columbus OH. Bethany Boettner, Department of Psychology, Institute for Population Research, The Ohio State University, Columbus OH.

This research was supported by grant number The study was funded by the National Institute on Drug Abuse (Way, R01DA042080 and Browning, R01DA032371); the Eunice Kennedy Shriver National Institute on Child Health and Human Development (Calder, R01HD088545 and Casterline, the Ohio State University Institute for Population Research, P2CHD058484); and the WT Grant Foundation. Correspondence concerning this article should be addressed to Dylan D. Wagner, Department of Psychology, 1827 Neil Avenue, The Ohio State University, Columbus, OH, 43202.

References

Bates, D., Mächler, M., Bolker, B., & Walker, S. (2015). Fitting Linear Mixed-Effects Models Using lme4. *Journal of Statistical Software*, *67*(1), 1–48. https://doi.org/10.18637/jss.v067.i01

Claus, E. D., Ewing, S. W. F., Filbey, F. M., Sabbineni, A., & Hutchison, K. E. (2011). Identifying neurobiological phenotypes associated with alcohol use disorder severity. *Neuropsychopharmacology*, *36*(10), 2086–2096. https://doi.org/10.1038/npp.2011.99

Courtney, A. L., Rapuano, K. M., Sargent, J. D., Heatherton, T. F., & Kelley, W. M. (2018). Reward System Activation in Response to Alcohol Advertisements Predicts College Drinking. *Journal of Studies on Alcohol and Drugs*, *79*(1), 29–38. https://doi.org/10.15288/jsad.2018.79.29

Curtin, J. J., Barnett, N. P., Colby, S. M., Rohsenow, D. J., & Monti, P. M. (2005). *Cue Reactivity in Adolescents: Measurement of Separate Approach and Avoidance Reactions**. *JOURNAL OF STUDIES ON ALCOHOL* (Vol. 66).

Dager, A. D., Anderson, B. M., Rosen, R., Khadka, S., Sawyer, B., Jiantonio-Kelly, R. E., … Pearlson, G. D. (2014). Functional magnetic resonance imaging (fMRI) response to alcohol pictures predicts subsequent transition to heavy drinking in college students. *Addiction*, *109*(4), 585–595. https://doi.org/10.1111/add.12437

Davidow, J. Y., Foerde, K., Galván, A., & Shohamy, D. (2016). An Upside to Reward Sensitivity: The Hippocampus Supports Enhanced Reinforcement Learning in Adolescence. *Neuron*, *92*(1), 93–99. https://doi.org/10.1016/j.neuron.2016.08.031

Gibbons, F. X., Gerrard, M., & Lane, D. J. (2003). A social reaction model of adolescent health risk. In *Social psychological foundations of health and illness.* (pp. 107–136). Retrieved from https://books.google.com/books?hl=en&lr=&id=NcBNnQhiBOgC&oi=fnd&pg=PA107&dq=Gibbons,+F.X.,+Gerrard,+M.,+%26+Lane,+D.J.+(2003).+A+social-reaction+model+of+adolescent+health+risk.+In+J.M.+Suls+%26+K.A.+Wallston+(Eds.),&ots=23dgocz-VE&sig=XaJMMaCDFtsdkI3ZmxE

Grüsser, S. M., Wrase, J., Klein, S., Hermann, D., Smolka, M. N., Ruf, M., … Heinz, A. (2004). Cue-induced activation of the striatum and medial prefrontal cortex is associated with subsequent relapse in abstinent alcoholics. *Psychopharmacology*, *175*(3), 296–302. https://doi.org/10.1007/s00213-004-1828-4

Hingson, R. W., Heeren, T., & Winter, M. R. (2006). Age at drinking onset and alcohol dependence: Age at onset, duration, and severity. *Archives of Pediatrics and Adolescent Medicine*, *160*(7), 739–746. https://doi.org/10.1001/archpedi.160.7.739

Johnston, L. L. D., Miech, R. R. A., Research, P. O.-… for S., 2020, U., O'Malley, P. M., Bachman, J. E., & Patrick, M. E. (2020). Monitoring the Future National Survey Results on Drug Use, 1975-2019: Overview, Key Findings on Adolescent Drug Use. *Institute for Social Research*. Retrieved from https://eric.ed.gov/?id=ED604018

Londerée, A. M., Roberts, M. E., Wewers, M. E., Peters, E., Ferketich, A. K., & Wagner, D. D. (2018). Adolescent Attentional Bias toward Real-world Flavored E-cigarette Marketing. *Tobacco Regulatory Science*, *4*(6), 57–65. https://doi.org/10.18001/trs.4.6.6

Myrick, H., Anton, R. F., Li, X., Henderson, S., Drobes, D., Voronin, K., & George, M. S.

(2004). Differential Brain Activity in Alcoholics and Social Drinkers to Alcohol Cues: Relationship to Craving. *Neuropsychopharmacology*, *29*(2), 393–402. https://doi.org/10.1038/sj.npp.1300295

Myrick, H., Anton, R. F., Li, X., Henderson, S., Randall, P. K., & Voronin, K. (2008). Effect of naltrexone and ondansetron on alcohol cue-induced activation of the ventral striatum in alcohol-dependent people. *Archives of General Psychiatry*, *65*(4), 466–475. https://doi.org/10.1001/archpsyc.65.4.466

Nguyen-Louie, T. T., Courtney, K. E., Squeglia, L. M., Bagot, K., Eberson, S., Migliorini, R., … Pulido, C. (2018). Prospective changes in neural alcohol cue reactivity in at-risk adolescents. *Brain Imaging and Behavior*, *12*(4), 931–941. https://doi.org/10.1007/s11682-017-9757-0

Peters, S., & Crone, E. A. (2017). Increased striatal activity in adolescence benefits learning. *Nature Communications*, *8*(1), 1–9. https://doi.org/10.1038/s41467-017-02174-z

R Core Team. (2020). R: A Language and Environment for Statistical Computing. Vienna, Austria. Retrieved from https://www.r-project.org/

Reinhard, I., Leménager, T., Fauth-Bühler, M., Hermann, D., Hoffmann, S., Heinz, A., … Vollstädt-Klein, S. (2015). A comparison of region-of-interest measures for extracting whole brain data using survival analysis in alcoholism as an example. *Journal of Neuroscience Methods*, *242*, 58–64. https://doi.org/10.1016/j.jneumeth.2015.01.001

Schacht, J. P., Anton, R. F., & Myrick, H. (2013, January 1). Functional neuroimaging studies of alcohol cue reactivity: A quantitative meta-analysis and systematic review. *Addiction Biology*. John Wiley & Sons, Ltd. https://doi.org/10.1111/j.1369-1600.2012.00464.x

Section 2 PE Tables – Results from the 2018 National Survey on Drug Use and Health: Detailed Tables, Sections 1 - 3, SAMHSA, CBHSQ. (n.d.). Retrieved October 29, 2020, from https://www.samhsa.gov/data/sites/default/files/cbhsq-reports/NSDUHDetailedTabs2018R2/NSDUHDetTabsSect2pe2018.htm#tab2-1b

Silverman, M. H., Jedd, K., & Luciana, M. (2015). Neural networks involved in adolescent reward processing: An activation likelihood estimation meta-analysis of functional neuroimaging studies. *NeuroImage*, *122*, 427–439. https://doi.org/10.1016/j.neuroimage.2015.07.083

Somerville, L. H., & Casey, B. J. (2010, April). Developmental neurobiology of cognitive control and motivational systems. *Current Opinion in Neurobiology*. https://doi.org/10.1016/j.conb.2010.01.006

Tapert, S. F., Cheung, E. H., Brown, G. G., Frank, L. R., Paulus, M. P., Schweinsburg, A. D., … Brown, S. A. (2003). Neural response to alcohol stimuli in adolescents with alcohol use disorder. *Archives of General Psychiatry*, *60*(7), 727–735. https://doi.org/10.1001/archpsyc.60.7.727

van Duijvenvoorde, A. C. K., Peters, S., Braams, B. R., & Crone, E. A. (2016, November 1). What motivates adolescents? Neural responses to rewards and their influence on adolescents' risk taking, learning, and cognitive control. *Neuroscience and Biobehavioral Reviews*. Elsevier Ltd. https://doi.org/10.1016/j.neubiorev.2016.06.037

Van Gucht, D., Vansteenwegen, D., Van den Bergh, O., & Beckers, T. (2008). Conditioned craving cues elicit an automatic approach tendency. *Behaviour Research and Therapy*, *46*(10), 1160–1169. https://doi.org/10.1016/j.brat.2008.05.010

Velanova, K., Wheeler, M. E., & Luna, B. (2008). Maturational changes in anterior cingulate and frontoparietal recruitment support the development of error processing and inhibitory control. *Cerebral Cortex*, *18*(11), 2505–2522. https://doi.org/10.1093/cercor/bhn012

Whelan, R., Watts, R., Orr, C. A., Althoff, R. R., Artiges, E., Banaschewski, T., … Garavan, H. (2014). Neuropsychosocial profiles of current and future adolescent alcohol misusers. *Nature*, *512*(7513), 185–189. https://doi.org/10.1038/nature13402

White, J. M., & Staiger, P. K. (1991). Response to alcohol cues as a function of consumption level. *Drug and Alcohol Dependence*, *27*(2), 191–195. https://doi.org/10.1016/0376-8716(91)90039-2

Citations

- Eprime
- SPM12
- SPM12w
- MATLAB

Figure Captions

Figure X. Example MRI stimuli with alcohol, food, and outdoor scenes.

Tables

Table X.

Study Sample Demographics (mean or %).

	Total (n=46)
Demographics	
Gender	
Female	%
Male	%
Mean Age	()
Mean Body Mass Index	()
Race	
Non-Hispanic white	%
African American	%
Hispanic	%
Asian	%
Native Hawaiian or Pacific Islander	%
Mixed Race	%
Socioeconomic Status (% middle class)	%
Alcohol Use	%

Note: Standard deviations for Mean Age and Mean Body Mass Index are in parentheses.

Table X.

Brain Regions Demonstrating Greater Activity in Response to Alcohol Than in Response to Outdoor Scenes Across All Participants.

				Coordinates of peak activation		
Brain Region	**Side**	**BA**	***t*(30)**	***x***	***y***	***z***

Note: The table reports the locations of peak voxels for significant clusters ($p < .05$, corrected). Coordinates are in Montreal Neurological Institute stereotaxic space. BA = Brodmann's area (approximate).