Archival Report

Reward-Related Ventral Striatum Activity Links Polygenic Risk for Attention-Deficit/ Hyperactivity Disorder to Problematic Alcohol Use in Young Adulthood

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ABSTRACT

BACKGROUND: Problematic alcohol use in adolescence and adulthood is a common and often debilitating correlate of childhood attention-deficit/hyperactivity disorder (ADHD). Converging evidence suggests that ADHD and problematic alcohol use share a common additive genetic basis, which may be mechanistically related to reward-related brain function. In the current study, we examined whether polygenic risk for childhood ADHD is linked to problematic alcohol use in young adulthood through alterations in reward-related activity of the ventral striatum, a neural hub supporting appetitive behaviors and reinforcement learning.

METHODS: Genomic, neuroimaging, and self-report data were available for 404 non-Hispanic European American participants who completed the ongoing Duke Neurogenetics Study. Polygenic risk scores for childhood ADHD were calculated based on a genome-wide association study meta-analysis conducted by the Psychiatric Genomics Consortium and tested for association with reward-related ventral striatum activity, measured using a number-guessing functional magnetic resonance imaging paradigm, and self-reported problematic alcohol use. A mediational model tested whether ventral striatum activity indirectly links polygenic risk for ADHD to problematic alcohol use.

RESULTS: Despite having no main effect on problematic alcohol use, polygenic risk for childhood ADHD was indirectly associated with problematic alcohol use through increased reward-related ventral striatum activity.

CONCLUSIONS: Individual differences in reward-related brain function may, at least in part, mechanistically link polygenic risk for childhood ADHD to problematic alcohol use.

Keywords: ADHD, Alcohol, fMRI, Polygenic, Reward, Ventral striatum

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Attention-deficit/hyperactivity disorder (ADHD) is characterized by persistent hyperactivity-impulsivity and/or inattention and is among the most common childhood psychiatric disorders, affecting approximately 5% of children worldwide (1). In addition to deficits in cognitive (2), academic (3), and socioemotional (4) domains during childhood, evidence suggests a continued pattern of impairment extending to adolescence and adulthood (5). Problematic alcohol use, typically conceptualized as levels of use associated with significant socioemotional, academic, or workplace impairment, is especially prevalent among these individuals, with prospective studies demonstrating that children with ADHD are at substantially increased (1.35–1.72) odds of developing alcohol use disorder (AUD) as adults (6,7). Supportive of a common etiology (8), twin studies have shown that shared additive genetic factors primarily account for this association (e.g., 91–99.8% of phenotypic covariance) (9,10). However, what neural mechanisms, if any, may mediate the effects of this shared genetic liability remain largely unexplored. Identifying such mechanisms is important not only for better understanding the etiology of ADHD, but also for informing the development of novel strategies for preventing comorbid dysfunction by providing target intermediate neural phenotypes that can serve as risk biomarkers.

Differences in neural response to reward may be one way through which shared genetic risk for ADHD and problematic alcohol use manifests. For example, emotional and motivational facets of impulsivity (i.e., positive and negative urgency) prospectively mediate the association between childhood ADHD and adult problematic alcohol use (11). At the neural level, ADHD (12,13), trait impulsivity (13,14), and problematic alcohol use (15,16) have each been associated with variability in reward-related brain function, particularly within the ventral striatum (VS), a region critical to generating and orchestrating motivated behavior including reward sensitivity and reinforcement learning (17). Moreover, a recent study identified transcripts associated with impulsive behavior within a mouse model and then showed that variation in the sequence of the genes coding for these transcripts in humans was associated with impulsivity, VS reactivity to reward, and problematic

alcohol use during adolescence (18). Collectively, this evidence suggests that genetically influenced individual differences in reward-related brain function may contribute to shared risk between childhood ADHD and later problematic alcohol use.

Though prior studies of comorbidity have relied on twin and family designs enriched for clinical cases (9,10,19), recent advances in statistical genetics allow for quantitation of genetic risk in healthy individuals without knowledge of family history. Building off of the idea that psychiatric disorders represent extremes of continuous phenotypes normally distributed throughout the population (20), it follows that those with a greater number of common risk variants for a particular disorder will be at heightened risk for diagnosis. Indices of genome-wide genetic risk, commonly referred to as polygenic risk scores (PRSs) (21), can be calculated based on the number of disorder risk alleles an individual possesses. The increasing availability of genome-wide association study (GWAS) summary statistics, made possible through collaborative efforts such as the Psychiatric Genomics Consortium (PGC) (http://www.med.unc.edu/pgc/), has facilitated the exploration of mechanisms of genetic risk for psychiatric disorders in independent nonclinical samples (22–24), which typically benefit from larger sample sizes and are generally without the confounds of clinical symptom expression and medication.

In the current study, we investigated whether alterations in reward-related VS activity mediate links between polygenic risk for childhood ADHD and problematic alcohol use among 404 non-Hispanic European American young adults. VS activity to reward was measured using blood oxygen level–dependent functional magnetic resonance imaging, and defined as relative activity to positive versus negative feedback associated with monetary reward (25). ADHD PRSs were calculated based on a PGC meta-analysis of childhood ADHD (26). Based on prior work, we hypothesized that both polygenic risk for childhood ADHD and self-reported problematic alcohol use would be associated with individual differences in reward-related VS activity, and that variability in VS activity would mediate the association between polygenic risk and problematic alcohol use during young adulthood.

METHODS AND MATERIALS

Participants

Self-report, neuroimaging, and genomic data were available from 438 non-Hispanic European American 18–22-year-old undergraduate students who completed the ongoing Duke Neurogenetics Study (25) by April 4, 2015. Ancestry was determined by self-report and confirmed using multidimensional scaling (i.e., no individuals were ±6 SDs from the mean on the top 10 components) (27). Participants provided informed written consent prior to the Duke Neurogenetics Study protocol, which was approved by the Duke University Medical Center Institutional Review Board. Study exclusion criteria were as follows: 1) medical diagnosis of cancer, stroke, diabetes requiring insulin treatment, chronic kidney or liver disease, or, importantly, lifetime psychotic symptoms; 2) use of psychotropic, glucocorticoid, or hypolipidemic medication;

and 3) conditions affecting cerebral blood flow and metabolism (e.g., hypertension). DSM-IV Axis I and select Axis II (borderline and antisocial personality) disorders were assessed with the electronic Mini International Neuropsychiatric Interview (28) and Structured Clinical Interview for the DSM-IV Axis II (29). Following exclusions during quality control procedures (Supplemental Table S1), a final sample of 404 participants (mean age = 19.785 ± 1.249 years; 213 women; 94 with a DSM-IV Axis I disorder; Supplemental Table S2) were included in analyses.

Genotyping and PRSs

DNA was isolated from saliva derived from Oragene DNA self-collection kits (DNA Genotek, Ottawa, Canada) customized for 23andMe (www.23andme.com). DNA extraction and genotyping were performed by the National Genetics Institute, a Clinical Laboratory Improvement Amendments–certified clinical laboratory and subsidiary of Laboratory Corporation of America. One of two different Illumina arrays with additional custom content, the HumanOmniExpress or HumanOmniExpress-24 (30), was used to provide genome-wide single nucleotide polymorphism (SNP) data. Genotype imputation was run separately for participants typed on each array using the prephasing/imputation stepwise approach implemented in SHAPEIT (31) and IMPUTE2 (32) using only biallelic SNPs and the default value for effective size of the population (20,000), and chunk sizes of 3Mb and 5Mb for the respective arrays. Within each array batch, genotyped SNPs used for imputation were required to have missingness <0.02, Hardy-Weinberg equilibrium $p > 10^{-6}$, and minor allele frequency >0.01. The imputation reference set consisted of 2,504 phased haplotypes from the full 1000 Genomes Project Phase 3 dataset (May 2013, over 70 million variants, release v5a). Imputed SNPs were retained if they had high imputation quality (information content [INFO] score >0.9), low missingness (<5%), and minor allele frequency >0.01.

PRSs were derived from GWAS summary statistics for the ADHD subset of the PGC's cross-disorder meta-analysis, which included 1947 trio cases, 1947 trio pseudocontrols, 840 cases, and 688 controls (http://www.med.unc.edu/pgc/downloads) (26). Because the original meta-analysis did not assess predictive utility of PRSs in additional case-control samples and thus did not identify an ideal threshold for the inclusion of variants, PRSs were constructed for p value thresholds .0001, .001, .01, .05, .1, .2, .3, .4, .5, and 1.0, to be consistent with the PRS analyses conducted in the PGC cross-disorder paper (26). SNPs were required to have minor allele frequency >0.02, genotyping rates >0.98, and Hardy-Weinberg equilibrium p values $> 10^{-6}$. SNPs within the major histocompatibility complex region (chr6: 25000000:35000000) were excluded because of their complex patterns of linkage disequilibrium. All remaining SNPs were pruned using p value–informed clumping (i.e., grouping linked SNPs; $R^2 = .10$, 500-kb window), leaving 95,423 SNPs for inclusion in PRS calculations. For each p value threshold, using the –score method in PLINK (v.1.07) (27), the log odds ratio for ADHD for each component SNP (i.e., those in the original meta-analysis with p values below the cutoff threshold) was multiplied by the number of reference alleles for that SNP

before being summed and divided by the total number of contributing SNPs to produce a single metric for each participant representing cumulative genome-wide risk for childhood ADHD. To assess the specificity of ADHD polygenic risk relative to risk for neurodevelopmental disorders more generally, PRSs were generated for autism spectrum disorders in the same manner based on summary statistics from a meta-analysis conducted by the PGC Autism Spectrum Disorders Workgroup (5305 cases, 5305 pseudocontrols; http://www.med.unc.edu/pgc/results-and-downloads) (33). ADHD and autism spectrum disorders PRSs were normally distributed (Supplemental Figure S1).

Neuroimaging

A number-guessing paradigm (25), consisting of a pseudorandom presentation of three blocks each of predominantly positive (80% correct guess) or negative (20% correct guess) feedback, interleaved with three control blocks, was used to probe VS activity associated with positive and negative feedback linked to monetary gains and losses. Participants were unaware of the fixed outcome probabilities associated with each block and were led to believe that their performance would determine their monetary gain at the end of the scanning sessions. However, all participants received $10 in winnings regardless of performance. During each trial, participants saw the back of a card and were given 3000 ms to guess whether the card was greater than or less than 5 (face cards excluded). After a choice was made, the value of the card was displayed for 500 ms, followed by appropriate feedback for 500 ms and then a crosshair for 3000 ms. Correct versus incorrect feedback was indicated by a green upward-facing arrow or a red downward-facing arrow, respectively. In the control condition, participants saw an X for 3000 ms, during which they were instructed to push a button, which was followed by an asterisk for 500 ms and then a yellow circle for 500 ms. Participants were scanned using one of two identical research-dedicated GE MR750 3T scanners equipped with high-power high-duty-cycle 50-mT/m gradients at 200 T/m/s slew rate, and an eight-channel head coil for parallel imaging at high bandwidth up to 1 MHz at the Duke-UNC Brain Imaging and Analysis Center. Details regarding specific acquisition parameters, preprocessing procedures, and primary analytic techniques may be found in the Supplement.

Consistent with prior studies (14,25,34), we focused on VS activity resulting from the contrast of all positive feedback blocks relative to negative feedback blocks (positive feedback > negative feedback) as an index of bilateral ventral striatal reactivity during blocks of monetary gains versus losses. Left and right VS regions of interest (ROIs) were defined using a 10-mm sphere based on the maximum voxels from a prior study (14). A voxel-level statistical threshold of $p < .05$, familywise error corrected for multiple comparisons across the ROIs, and a cluster-level extent threshold of 10 contiguous voxels were applied to these analyses. In line with our prior work (25) and recent recommendations (35), we extracted parameter estimates from functional clusters within these ROIs, which were then used for all statistical analyses. To maintain variability but constrain the influence of extreme outliers, prior to analyses all imaging variables were Winsorized (i.e., following data quality control procedures, outliers more than mean $\pm$ 3 SDs [$n = 5$ for left VS, $n = 3$ for right VS] were set at ±3 SDs from the mean).

Problematic Alcohol Use

Problematic alcohol use was assessed using the 10-item Alcohol Use Disorders Identification Test (AUDIT) (36). Although the AUDIT was originally designed to assess past-year hazardous and harmful patterns of alcohol consumption in primary-care settings, it has reasonable psychometric properties in college students (37) and showed good internal reliability in this sample ($\alpha = .818$). Of the 404 individuals included in analyses, a substantial majority reported having drunk alcohol in the past 12 months ($n = 354$; $mean_{AUDIT} = 6.590 \pm 4.200$); as such, nondrinkers ($n = 50$) were excluded from analyses involving AUDIT scores. AUDIT scores were then log transformed to reduce positive skew (Supplemental Figure S2).

Statistical Analyses

Ordinary least squares regression was used to test the association between each thresholded ADHD PRS and left and right VS reactivity, as well as direct associations with AUDIT scores. To address multiple testing, we implemented a label-swapping permutation procedure to assess whether the overall pattern of association across thresholds differed from that expected by chance. This procedure yielded an empirical p value, p_{PRS}, calculated as the proportion of times the number of nominally significant (i.e., $p < .05$) associations across p value thresholds across 10,000 permutations equaled or exceeded that of the original analysis (see the Supplement for details). We adopted this approach because of the nested structure of PRS scores across p value thresholds (i.e., each threshold contains all SNPs in more stringent p value thresholds).

To examine links from genes to brain to behavior, a mediational model was tested in MPlus (v.7.11) (38) with ADHD PRSs as the predictor, VS activity as the mediating variable, and AUDIT scores as the dependent variable. Because such a model is dependent on associations between ADHD PRSs and VS activity, we conducted these analyses at the p value threshold most strongly associated with VS activity (i.e., $p < .30$). Unstandardized indirect effects were computed for each of 5000 bootstrapped samples, consistent with the recommendations of Hayes (39). Full-information maximum likelihood estimation was used, and model goodness of fit was assessed using root mean square error of approximation (<.05), standardized root mean square residual (<.05), and the comparative fit index (>.90) (40).

Biological sex and the top two ancestry-informative multi-dimensional scaling components (27), selected for occurring prior to the point of inflection on the scree plot (Supplemental Figure S3), were entered as covariates for all analyses to control for possible confounding effects of sex and occult population stratification (38). For analyses involving alcohol phenotypes, being of legal drinking age in the United States (i.e., at least 21) was also included as a covariate of no interest ($n_{legal} = 132$, $n_{underage} = 222$).

RESULTS

Consistent with prior work, the contrast of interest (i.e., positive feedback > negative needback) yielded robust bilateral VS activity (Figure 1A). ADHD PRSs were significantly associated with bilateral VS activity (left VS: significant at 6 of 10 p value thresholds; most significant at $p < .3$: $\beta = .132$, $\Delta R^2 = .017$, $p = .008$; right VS: significant at 6 of 10 p value thresholds; most significant at $p < .3$: $\beta = .124$, $\Delta R^2 = .015$, $p = .013$; Figure 1B; Supplemental Table S3). Permutation analyses revealed that the overall bilateral pattern of associations across thresholds significantly deviated from that expected by chance ($p_{PRS} = .013$). Our negative control, autism spectrum disorder PRSs, were not associated with VS activity at any threshold (all $p > .15$; Supplemental Figure S4). ADHD PRSs failed to predict problematic alcohol use across thresholds (significant only at $p < .01$: $\beta = .103$, $\Delta R^2 = .010$, $p = .050$; $p_{PRS} = .223$; Supplemental Table S3). However, bilateral VS activity was significantly associated with problematic alcohol use (left VS: $\beta = .172$, $\Delta R^2 = .029$, $p < .001$; right VS: $\beta = .149$, $\Delta R^2 = .022$, $p = .004$). Repetition of analyses with raw (i.e., non-Winsorized) data did not alter results. Owing to the consistency in results across hemispheres, a combined bilateral ROI was used for structural equation modeling.

The path model of polygenic risk to VS activity to problematic alcohol use overall demonstrated good fit (root mean square error of approximation <.001, standardized root mean square residual = .001, comparative fit index = 1.00; Figure 2A). Within the full model, polygenic risk positively predicted VS activity ($\beta_{PRS} = .132$, 95% confidence interval [0.025–0.244], $p = .019$; Figure 2B), which, in turn, positively predicted problematic alcohol use ($\beta_{VS} = .162$, 95% confidence interval [0.068–0.259], $p < .001$; Figure 2C). The indirect pathway from ADHD PRSs to problematic alcohol use through VS activity was significant ($\beta_{IND} = .021$, 95%

confidence interval [0.005–0.051], $p < .01$). Follow-up mediation analyses conducted at the five additional p value thresholds associated with VS activation revealed consistently significant indirect effects.

DISCUSSION

Twin and family studies have shown that shared genetic factors account for the majority of phenotypic variance between childhood ADHD and problematic alcohol use during adolescence and adulthood (9,10,19). Here, we extend this work by providing initial evidence that polygenic risk for childhood ADHD predicts heightened reward-related VS activity, which, in turn, is associated with problematic alcohol use in young adulthood (Figure 2). Alongside evidence that elevated neural responsivity to reward is found among adolescents with ADHD and their unaffected siblings (12), and that such reactivity is associated with alcohol use initiation and escalation (41,42), these results suggest that elevated VS reactivity to reward may be a genetically influenced neural mechanism mediating the link between polygenic risk for childhood ADHD and later problematic alcohol use.

Childhood ADHD and Later Problematic Alcohol Use

Despite compelling prior epidemiological evidence of associations between childhood ADHD diagnosis and later problematic alcohol use (6,7), as well as previous twin and family studies demonstrating substantial genetic overlap between the two (9,10,19), we observed no direct association between polygenic risk for childhood ADHD and problematic alcohol use. Of note, though not significant across p value thresholds, the directionality of associations was consistent with the epidemiological literature (i.e., higher childhood ADHD polygenic risk leading to greater reported problem drinking).
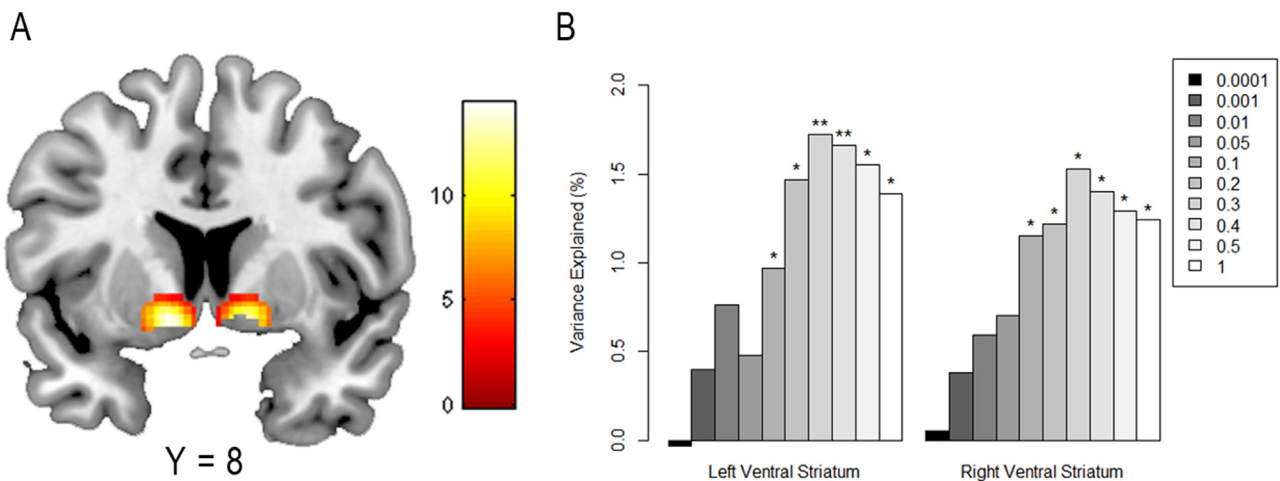

Figure 1. Main effects of functional magnetic resonance imaging task and attention-deficit/hyperactivity disorder (ADHD) polygenic risk on reward-related activity in the ventral striatum (VS). **(A)** Bilateral VS reactivity to reward (positive feedback > negative feedback) across all participants. Right hemisphere: Montreal Neurological Institute coordinates = 12, 10, and −8 ($t_{1050} = 13.287$, $p < .05$ familywise error), cluster size = 239 voxels. Left hemisphere: Montreal Neurological Institute coordinates = −12, 8, and −8 ($t_{1050} = 14.394$, $p < .05$ familywise error), cluster size = 293 voxels. **(B)** ADHD polygenic risk scores (PRSs) and bilateral ventral striatal reactivity to reward. The y axis is the percent of variation in VS reactivity explained by ADHD PRSs. Positive values indicate a positive association between ADHD PRSs and VS reactivity. Negative values are for display purposes only and indicate a negative association between ADHD PRSs and VS reactivity. Shades of gray in legend indicate the p value threshold at which the risk score was calculated. $*p < .05$, $**p < .01$.
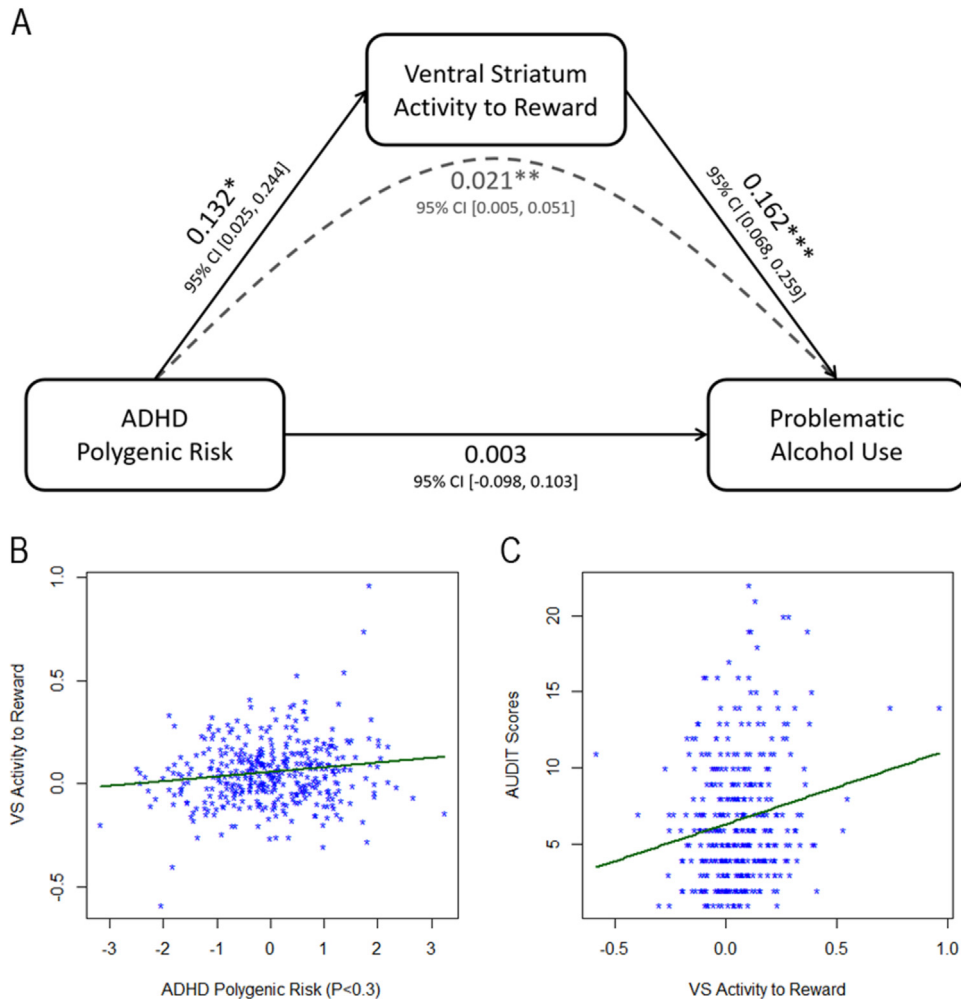
Figure 2. Structural equation model demonstrating the effect of attention-deficit/hyperactivity disorder (ADHD) polygenic risk on problematic alcohol use through bilateral ventral striatum (VS) activity to reward. The overall model is depicted in panel **(A)**, with raw data plots of the significant *a* and *b* pathways shown in panels **(B)** and **(C)**, respectively. The dashed line in panel **(A)** represents the indirect effect of ADHD polygenic risk scores on problematic alcohol use through bilateral VS activity to reward. Sex and the top two ancestry-informative multidimensional scaling components were included as covariates of no interest for all paths in the full model. Being of legal drinking age in the United States (i.e., 21+ years old) was included as a covariate in paths involving alcohol use outcomes (i.e., *b* and *c'*). *$p < .05$, **$p < .01$, ***$p < .001$. AUDIT, Alcohol Use Disorders Identification Test; CI, confidence interval.

Although it is possible that an absence of a statistically significant direct association is an artifact of our likely underpowered sample (i.e., 80% power to detect an R^2 of .023, when variance explained by PRSs in population-based studies is generally 1% or less) (22–24), we see a similar lack of association in a larger (*n* = 2573) sample ascertained for substance use disorders, including alcohol dependence (43). It is possible that the association between polygenic risk for ADHD and problematic alcohol use occurs indirectly through altered neural mechanisms of reward sensitivity and reinforcement learning and/or that a direct association would require a larger sample to detect.

ADHD and Associations With Reward-Related VS Activation

Although neural and behavioral research on ADHD has traditionally focused on deficits in executive functioning (2,44,45), more recent theoretical models of the disorder have proposed a key role for dysfunctional motivation and reward-related processes (46,47). For example, in healthy adults, individual differences in VS activity during both reward anticipation and

outcome are positively associated with behavioral and self-reported indices of impulsivity and reward responsiveness (13,14,48). ADHD symptoms and diagnosis, in contrast, have been predominantly characterized by lower VS responsiveness to reward-predicting cues [see (13) for meta-analysis and review, but see also (12) and subsequent commentary in (49) and (50)]. Neural activation to reward outcome has been less systematically studied in ADHD, with some evidence of relative hyperresponsiveness [see (12), (51), and (52), but see also (53) and (54)]. This discrepancy in relative VS activation to reward anticipation versus outcome may reflect impaired reward learning (51), consistent with evidence of impaired behavioral modification based on prior reinforcement history in ADHD (55). Given the design of our functional paradigm in which we compared mean VS activation across positive versus negative feedback blocks (with non–valence-specific cues), our results may more appropriately reflect emergent data linking ADHD to increased VS response to reward outcomes. Notably, our findings of elevated VS activity to positive versus negative feedback among young adults at higher polygenic risk for childhood ADHD complement those of a prior family study (12) in suggesting that heightened neural

responsiveness to reward may be a heritable neural mechanism through which ADHD expression manifests.

Reward-Related VS Activation and Risk for Problematic Alcohol Use

As with ADHD, addiction has been contextualized as a disorder of altered reward sensitivity and abnormal reinforcement learning. Influential theories of addiction emphasize the importance of conceptualizing the disorder within stages, whereby substance use initiation and initial problematic use are related to the positively reinforcing aspects of a substance, whereas later compulsive use is driven by negative reinforcement and diminished cognitive control resulting from chronic use-induced changes in neural plasticity and a revised homeostasis that includes the presence of the substance (56–60). Heightened VS activity to reward may characterize the initial stages (i.e., initiation and escalation) of substance use, causing at-risk individuals to be more likely to engage in initiation and also be more sensitive to the positively reinforcing aspects of the substance (16). Repeated use of substances, in contrast, may result in overstimulation and consequent downregulation of reinforcement mechanisms (57,61), thus decreasing VS activity to natural reward and increasing the threshold required to reach prior levels of responsiveness (16). Consistent with this model, increased striatum activity to reward in adolescence prospectively predicts substance use initiation (62) and problem drinking (41), and is retrospectively related to age-of-first-drink across both individuals with AUD and healthy volunteers (42). In contrast, the vast majority of studies among individuals with AUD have reported decreased VS reactivity to monetary reward cues (15,16) but hyperresponsive to alcohol cues relative to controls (63), indicating a shift in reward responsiveness from more generally salient stimuli (e.g., money) to the conditioned substance of choice as the disorder progresses.

Our data, showing that elevated VS activation during reward processing indirectly links polygenic risk for ADHD to problematic alcohol use among young adult college students, are therefore consistent with a heightened reward sensitivity model of substance initiation/escalation conferred by childhood ADHD polygenic risk. Owing to our relatively healthy sample, however, our findings cannot exclude the possibility that childhood ADHD polygenic risk impacts later stages of substance use disorders (e.g., transition to and maintenance of dependence) either through the VS or through alternative neural pathways (e.g., the cognitive control circuit) (64,65). Additional studies of genetic risk, in concert with longitudinal studies, are needed to better elucidate the temporal associations between reward-related VS reactivity and ADHD and AUD.

Limitations

Several limitations are important to consider when interpreting the results of our study. First, despite being large for a neuroimaging study ($n = 404$), our sample was small for genetic association analyses, which, as in other imaging genetics studies, may increase the risk of false negative and false positive findings and result in imprecise effect estimates (66). Correspondingly, the childhood ADHD GWAS meta-analysis used to generate PRSs in our study is small relative to more recent meta-analytic efforts (e.g., schizophrenia: n_{case} = 36,989, $n_{control}$ = 113,075) (67) and perhaps because of its resultant lack of power did not yield any genome-wide significant loci. As a result, it will be important for our observed association to be replicated and extended once larger ADHD GWAS meta-analyses and additional neurogenetics samples become available.

Second, because ADHD diagnosis and symptomatology were not assessed in the Duke Neurogenetics Study, it is not possible to rule out whether disorder expression is a mediating factor between polygenic risk and reward-related VS activity. One possible explanation for our results is that higher polygenic risk leads to ADHD and that the disorder itself is then associated with increased VS activity to reward. Correspondingly, we were unable to validate whether our childhood ADHD PRSs were indeed predictive of retrospective diagnosis in the current sample. However, a prior population-based study demonstrated that ADHD PRSs derived from the same meta-analysis used for this study were predictive of childhood but, intriguingly, not adult ADHD, thus indicating the utility and, somewhat surprisingly, childhood specificity of these scores (68).

Third, our study is cross sectional, making it impossible to establish temporal order for the association between VS activity and problematic alcohol use. As a result, we cannot rule out that alcohol misuse may have preceded increases in VS activity. However, longitudinal studies of the effect of VS activity on future alcohol use are consistent with our model (41). Furthermore, within our subsample of baseline nondrinkers who also had follow-up AUDIT data ($n = 29$), VS activity predicted future initiation of drinking, providing some preliminary evidence for temporality (Supplement).

Fourth, the blocked design of the functional neuroimaging paradigm used in our study (25) does not allow for the examination of distinct components of reward processing. Our results thus cannot be directly compared with prior studies of reward-related VS activity in ADHD and AUD, which have generally examined reward anticipation and outcome separately (13,15).

Lastly, the indirect association between polygenic risk and problematic alcohol use is a small effect that is not currently informative on an individual level. Nonetheless, the effect size is consistent with those reported in prior studies using PRSs (22–24), and these findings identify a promising neural mechanism that provides etiologic insight into associations between childhood ADHD and problematic alcohol use and is worthy of future study.

Conclusions

Limitations notwithstanding, our study provides initial evidence that relatively heightened reward-related VS activity mediates associations between polygenic risk for childhood ADHD and problematic alcohol use in young adulthood. Future studies may wish to interrogate dissociations between reward anticipation and receipt as they relate to genetic risk for ADHD and problematic alcohol use, and to extend these findings to additional substance use and externalizing disorders. Furthermore, as imaging and genetics sample sizes increase, pathway enrichment analyses [e.g., (69)] and functional annotation [e.g., (70)] may allow for the discovery of specific molecular pathways that underlie genetic associations among ADHD, neural reward activity, and problematic alcohol use.

Overall, our findings suggest that elevated VS response to reward is a promising neural mechanism through which ADHD polygenic risk and problematic drinking may manifest.

ARTICLE INFORMATION

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