Title: Caffeinated soda intake in children is associated with neurocognitive vulnerabilities of substance misuse and is predictive of a higher risk of alcohol sipping after 12 months

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ABSTRACT

Background and Aims Caffeinated soda contains two addictive substances, sugar and caffeine, and is the most preferred means of caffeine consumption among children. However, it remains unexplored if habitual caffeinated soda intake in childhood is associated with a higher risk of alcohol misuse in the future. Here, we investigated the neurocognitive correlates of caffeinated soda consumption and examined whether caffeinated soda intake is associated with a higher risk of alcohol initiation in children. **Methods** Using the Adolescent Brain Cognitive Development Study, we first investigated the relationships between frequent caffeinated soda intake and well-known risk factors of substance misuse: impaired working memory, high impulsivity, and blunted reward processing. We next examined whether caffeinated soda intake predicts more alcohol sipping after 12 months, and whether caffeinated soda intake mediates the link between neurocognitive risk factors and future alcohol sipping. **Results** Frequent consumption of caffeinated soda was associated with neurocognitive risk factors for substance misuse. Daily soda intake was associated with hyperactivity in the striatal and parietal regions and hypoactivity in the inferior frontal gyrus (IFG) during the emotional N-Back Task. In addition, the striatum, IFG, and anterior cingulate cortex (ACC) showed aberrant activity during the stop signal task, and the medial prefrontal cortex and the ACC exhibited increased and decreased activity, respectively, during the monetary incentive delay task. Furthermore, caffeinated soda intake predicted greater alcohol sipping after 12 months, and mediated the relationship between impulsivity and future alcohol sipping. **Conclusions** This study addresses the question that many parents are asking: "Is frequent caffeinated soda intake in childhood associated with a higher risk of substance misuse in the future?" We showed that caffeinated soda consumption in childhood was associated with impaired neurocognitive functioning and may predict future alcohol intake, which has significant public health implications.

INTRODUCTION

Soft drinks are commonly consumed even by children, and a vast majority of sodas contain caffeine [1–3]. Caffeinated soda refers to soft drinks containing caffeine as well as sweeteners and artificial flavorings. Thus, caffeinated soda combines the addictive substances of sugar and caffeine, both of which affect neurocognitive function and cause physical side effects, although the concept of sugar addiction remains controversial [4–6]. Not surprisingly, the consequences of excessive consumption of both sugar and caffeine have been well documented [7], including a strong association between caffeinated beverage consumption in adolescents and future substance use [8–13]. In prospective studies tracking the effects of substance use, the percentage of regular energy drink users who became alcohol or marijuana users after 1–2 years was approximately five times higher than that of non-energy drink users [9,12,13]. Others have shown that coffee or energy drink consumption in children significantly predicts future substance use, such as tobacco and alcohol use [8,10,12].

Previous studies examining the association between caffeine consumption and later substance use have focused more on adolescents who drink multiple caffeinated beverages on a daily basis, partially because the consumption level of coffee and energy drinks is extremely low in children (0.4% for coffee and < 0.1% for energy drinks in 9–10-year-old children) [14]. However, caffeinated soda is the most preferred and accessible mode of caffeine intake in children [1,4,15]. Moreover, it is well known that adolescence is the most common period for initiating substance use, and an earlier onset of substance use predicts greater addiction severity [16–19]. Therefore, there is a critical need to investigate the association between caffeinated soda intake during preadolescent childhood and the risk of substance use disorders (SUDs) in the future, including vulnerabilities, such as associated neurocognitive deficits or early exposure to substances of abuse. Environmental factors, particularly the role of family, should be examined together, considering the previous studies that suggested a critical role of parental interventions in youth soft drink consumption and substance use [20–26]. Few studies have directly examined the effects of frequent caffeinated soda consumption in adolescents and children, and they either

targeted only behavioral aspects using surveys or self-reports without obtaining neural data, or targeted only adolescents and not children [9,27–29].

Here, we addressed the unanswered question of whether frequent consumption of caffeinated soda in children indicates a higher risk of later substance misuse, using the Adolescent Brain Cognitive Development (ABCD) Study. First, we examined the relationship between caffeinated soda intake and three well-known neurocognitive risk factors for SUDs in children: impaired working memory (WM), high impulsivity, and altered reward processing [30]. These are the three main risk factors targeted in the ABCD study due to their significant implications for addiction (see [30] for more detail). We used psychological, behavioral, and neurological indices related to each risk factor, from the baseline data of the ABCD study (**Figure 1**). We applied a machine learning approach to the indices so that we could identify multivariate risk factors for SUDs associated with caffeinated soda intake [31]. We next examined whether caffeinated soda intake could predict future alcohol sipping, as (1) alcohol sipping has been reported to predict future alcohol abuse [32–34], and (2) alcohol sipping is the most common gateway behavior toward other substances of abuse [19,35]. Lastly, we examined mediation models explaining how the interaction between daily caffeinated soda intake and the SUD risk factors leads to future alcohol sipping behavior. Based on the previous literature suggesting that caffeinated beverage consumption predicts future substance use [8–10,12,13], we hypothesized that caffeinated soda intake would mediate the relationship between neurocognitive risk factors and future alcohol sipping (**Figure 1A**). We also evaluated family risk factors as mediators of this relationship, based on the literature that family risk factors, including family substance use or family support, are risk factors for substance use in adolescents [24–26]. Taken together, we aimed to elucidate the potential underlying risks of frequent caffeinated soda intake during childhood.

METHODS

Participants

We included 4,529 participants without any missing data pertaining to soda intake, risk factors for SUDs, alcohol sipping, and all the confounding variables. The participants were divided into four groups based on their caffeinated soda consumption: the non-drinking group (*N*=1,945), monthly drinking group (*N*=1,941), weekly drinking group (*N*=484), and daily drinking group (*N*=159) [36]. See **Supplementary Materials** for more details on the measures and participants.

Analysis

Caffeinated soda intake and risk factors for SUDs

To identify a multivariate profile of risk factors for caffeinated soda consumption, we performed a least absolute shrinkage and selection operator (LASSO) regression analysis [37], a machine learning algorithm, to distinguish the daily drinking group (*N*=159) from the non-drinking group (*N*=1,945). We focused on these two extreme groups to ensure adequate separation between habitual drinkers (daily drinking group) and non-drinkers (non-drinking group). We used all of the risk factors and confounding variables as input (i.e., predictors) in the LASSO-based prediction model to classify each individual into the daily drinking group (coded as "1") or non-drinking group (coded as "0). More specifically, candidate predictors included every measure for the three cognitive factors as well as other control variables. See **Supplementary Materials** for more details on the predictors and LASSO regression.

Caffeinated soda intake and future alcohol sipping

To rigorously examine the association between caffeinated soda intake and future alcohol sipping, we used univariate (hierarchical regression) and multivariate (machine learning) approaches. Hierarchical logistic regression analysis was used to test whether caffeinated soda intake at baseline can predict alcohol sipping after 12 months. To ensure that the main predictor

accounted for more variance than the confounding variables, we set a three-level hierarchical model (**Table 1**). See **Supplementary Materials** for more details on the hierarchical regression.

We also performed multivariate LASSO regression analysis to confirm the association between caffeinated soda intake and alcohol sipping. We used all possible variables, including the three neurocognitive risk factors (WM, impulsivity, and reward processing) and the confounding variables as candidate predictors collected at baseline. Using these inputs (i.e., predictors) and the LASSO-based model, we aimed to classify individuals who reported alcohol sipping after 12 months (coded as "1") and those who reported no alcohol sipping (coded as "0). All of the procedures, except for the predictors and dependent variables, are identical to those in the former analysis (see **METHODS - *Caffeinated soda intake and risk factors for SUDs*).**

Caffeinated soda intake, alcohol sipping, and risk factors for SUDs

We performed the mediation analysis to provide a more integrated insight into how the interactions between caffeinated soda intake and the SUD risk factors lead to future alcohol sipping in children. We fit three mediation models for each SUD risk factor, with a mediation design involving the following four elements: an independent variable (one neurocognitive risk factor for one model - WM, impulsivity, and reward processing), two mediators (caffeinated soda intake and family risk factors; covariance of these two mediators was included in the model), and a dependent variable (alcohol sipping after 12 months). This design was chosen to identify a neurocognitive risk factor that is mediated by caffeinated soda intake in predicting alcohol sipping. See **Supplementary Materials** for more details on the mediation analysis.

RESULTS

Caffeinated soda intake and risk factors for SUDs

Our first question was whether caffeinated soda intake is associated with well-known neurocognitive risk factors for SUDs (**Figure 1A**). **Figure 2A** shows the multivariate profiles from the LASSO regression distinguishing the daily-drinking group from the non-drinking group. Sex (being male) and low parental education were the two strongest predictors of daily consumption,

along with a family history of drug use, high Behavioral Activation System (BAS) scores [38], lack of sleep, and low family income. **Figure 2B** shows a receiver-operation characteristic (ROC) curve and its mean area under the curve (AUC) for classification of the daily drinking and non-drinking groups. The mean AUC values were 0.82 and 0.73 for the training and test sets, respectively.

Among the risk factors for SUDs, high impulsivity measured using the BAS was the most predictive of daily caffeinated soda intake (**Figure 2C**). A higher Urgency–Premeditation–Perseverance–Sensation Seeking–Positive Urgency (UPPS-P) impulsive behavior score [39] and a lower Behavioral Inhibition System (BIS) score [38] were related to daily intake. Additionally, hyperactivation in the nucleus accumbens (NAc) and pars triangularis in the inferior frontal gyrus (IFG) and hypoactivation in the caudal anterior cingulate cortex (ACC) and caudate nucleus during the stop signal task (SST) predicted the classification of the daily drinking group. Among the WM measures, poor performance on the list sorting test, card sort test, and 0-back performance in the emotional N-Back (EN-back) task predicted daily intake of caffeinated soda. In addition, hypoactivation of the pars orbitalis of the IFG and greater activation of the NAc, caudate nucleus, inferior parietal lobule (IPL), and thalamus proper during the EN-back task (2-back vs. 0-back) also predicted daily caffeinated soda intake (**Figure 2C)**. The daily drinking group showed a smaller difference in accuracy between the reward and neutral trials on the monetary incentive delay (MID) task compared to the non-drinking group, suggesting reduced motivation to achieve the monetary reward. Additionally, hyperactivity in the medial orbitofrontal cortex (OFC) and hypoactivity in the rostral ACC during the MID task (reward vs. neutral anticipation) predicted the classification into the daily drinking group.

These results support that low WM, high impulsivity, and blunted reward anticipation are significantly associated with daily caffeinated soda consumption. Along with some other demographic factors (male sex, family history of drug use, low socioeconomic status (SES), low parental monitoring, high externalizing behaviors, less sleep, high body mass index (BMI), older age, and low physical activity), the three neurocognitive risk factors for SUDs distinguished the daily drinking group from the non-drinking group.

Caffeinated soda intake and future alcohol sipping

We first conducted a three-level hierarchical logistic regression analysis to address our second main question of whether caffeinated soda intake predicts future alcohol sipping, (**Table 1**). Specifically, we examined whether caffeinated soda intake accounted for additional variance than did other confounding variables. The adjusted R-square value of Model 3 revealed a significant difference compared with Model 1 ($F(4, 8{,}854)=177.58$, $p<2.20e-16$) and Model 2 ($F(3,8{,}854)=6.61$, $p<0.001$), supporting the hypothesis that caffeinated soda drinking behavior in childhood can predict future alcohol drinking (**Figure 3A**). Higher caffeinated soda consumption significantly predicted alcohol sipping after 12 months even after controlling for confounding variables and baseline alcohol sipping (**Table 1**).

Next, we performed LASSO regression predicting alcohol sipping after 12 months, using all of the neurocognitive risk factors and confounding variables collected at baseline. As shown in **Figure 3B**, caffeinated soda intake (mean estimate of coefficients=0.138, 95% confidence interval (CI)=[0.123, 0.155]) was identified as a predictor that distinguished alcohol sipping after 12 months, even after including alcohol sipping at baseline as predictors. The mean AUC values of the predictive model were 0.81 and 0.76 for the training and test sets, respectively (**Figure 3C**).

Caffeinated soda intake, risk factors for SUDs, and future alcohol sipping

We examined the integrated relationships among the risk factors for SUDs, caffeinated soda intake, and alcohol sipping after 12 months. We tested three mediation models using each neurocognitive risk factor (WM, impulsivity, and reward processing) as the independent variable. The models that used WM or reward processing as an independent variable showed inconclusive total effects (WM model: B=−0.007, 95% CI=[−0.013. −0.001], p=0.232; reward processing model: B=0.004, 95% CI=[−0.002. 0.010], p=0.457). However, as shown in **Figure 4**, the model using impulsivity as an independent variable revealed significant total effects (B=0.023, 95% CI=[0.018, 0.028], p<0.001). The model detected significant indirect effects of impulsivity on alcohol sipping after 12 months, with caffeinated soda intake and family risk factors mediating the relationships (caffeinated soda intake: B=0.002, 95% CI=[0.001, 0.003], p=0.013; family risk

factor: B=−0.002, 95% CI=[−0.003, −0.001], p=0.006). These results suggest caffeinated soda intake mediates impulsivity as the SUD risk factors toward future alcohol sipping.

DISCUSSION

In this study, we investigated whether caffeinated soda intake in childhood is associated with a higher risk of alcohol use in the future. Using the large dataset from the ABCD study (N=4,529), we identified the relationships between caffeinated soda intake and the neurocognitive risk factors for SUDs, evaluated the predictive ability of caffeinated soda on alcohol sipping after 12 months, and tested the hypothesis that caffeinated soda intake mediates neurocognitive risk factors and alcohol sipping after 12 months. Our findings suggest that frequent consumption of caffeinated soda in children is closely related to the neurocognitive risk factors for SUDs and can predict future alcohol sipping, particularly by mediating impulsivity.

The machine learning approach revealed a strong association between caffeinated soda intake and the neurocognitive risk factors for SUDs. High impulsivity scores, low WM performance, and blunted responses to monetary reward distinguished daily caffeinated soda drinkers from non-drinkers (**Figure 2**). In particular, we showed higher self-reported impulsivity in the daily drinking group based on the UPPS-P and BIS/BAS scores along with altered activation in regions implicated in impulsivity, i.e., hypoactivity in the ACC and caudate nucleus and hyperactivity in the IFG and NAc during the SST. Consistent with our findings, reduced activities in the ACC and caudate nucleus are commonly reported in children with attention deficit hyperactivity disorder (ADHD) during response inhibition tasks [40–44], and activation of the ventral striatum is greater in individuals with SUDs, implying dysregulation of impulsivity [45–47]. We detected hyperactivity in the IFG among daily soda drinkers compared with non-drinkers. Previous studies have reported reduced activity in the IFG as neural markers of substance abuse and ADHD [48–50]. However, increased activity in the IFG has also been reported in individuals with tobacco use disorder [51], and increased IFG activity suggests that more preparatory effort is required for successful inhibition [52].

We also showed behavioral WM impairments in the daily drinking group on the list sorting test, card sort test, and the 0-back accuracy in the EN-back task, accompanied by hypoactivation in the IFG and hyperactivation in the NAc, caudate nucleus, IPL, and thalamus during the EN-back task. These results are consistent with the developmental mismatch hypothesis, which states that subcortical structures of affect and reward processing develop earlier than prefrontal structures involved in the top-down regulation of behavior in children and adolescents [53,54]. Based on the previous studies that cognitive control during the EN-back task is related to WM capacity in the prefrontal cortex and simultaneous emotional regulation in the limbic system [30,55], the low WM performance in the daily drinking group may be related to increased activation in the limbic system and decreased activation in the IFG activation during the WM task.

Blunted reward anticipation was associated with caffeinated soda intake. Along with a smaller motivation to achieve the reward, activation in the ACC was lower and activation in the medial OFC was higher during the MID task in the daily drinking group than in the non-drinking group. Hyperactivation in the medial prefrontal cortex (mPFC) regions during reward anticipation is supported by previous literature suggesting increased prefrontal region activity, although these findings do not always replicate [56–60].

We showed that frequent consumption of caffeinated soda predicted alcohol sipping after 12 months using hierarchical regression (**Table 1**) and LASSO regression (**Figure 3**). Among the significant predictors in the LASSO regression, caffeinated soda intake was the second strongest predictor of future alcohol sipping, following the baseline alcohol sipping (**Figure 3B**). Other survived predictors include predictors for daily caffeinated soda intake (**Figure 2A**) while others showed the opposite direction in predicting daily caffeinated soda intake and alcohol sipping after 12 months. For example, higher SES, greater physical activity, no family history of drug use, younger age, and reduced activity in the ACC during the EN-back task and in the medial OFC during the MID task were associated with the participants who experienced alcohol sipping. Interestingly, predictors of caffeinated soda intake were similar to the risk factors for SUDs [18,61], suggesting that caffeinated soda intake during childhood and SUDs share similar neurocognitive vulnerabilities. Note that the majority of the cohort was substance-naïve [62], and

we evaluated alcohol sipping measures instead of actual administration of the substance. Thus, it would be informative to track the predictive ability of caffeinated soda and alcohol use and investigate changes in the direction of the predictors as the children get older.

The mediation analysis revealed that caffeinated soda consumption is a mediator between impulsivity and future alcohol sipping (**Figure 4**). This finding suggests that caffeinated soda itself may not directly cause children to initiate substance use, but the drinking behavior of the beverages could indicate high impulsivity, which may be linked to a high risk of initiating substance use in the near future. Because caffeinated soda contains two addictive substances, sugar and caffeine, it is somewhat natural for children to prefer and seek the beverages. While this taste preference could lead to a seeking behavior and habitual consumption, previous studies have shown impulsivity as one of the most common traits of SUDs [63–65]. Therefore, the behavior of frequently consuming caffeinated soda could indicate a high risk of initiating substance use in the future, although further research is needed to disentangle this complex relationship. Along with caffeinated soda intake, family risk factors also mediated the relationship between impulsivity and future alcohol sipping; higher impulsivity was associated with having more family risk factors, which led to less alcohol sipping after 12 months. Notably, some previous studies suggested that family risk factors, such as low SES, increase the risk of future alcohol use [66–69], while others suggested the opposite [70,71].

To our knowledge, this is the first study to investigate the direct link between caffeinated soda intake in childhood and the risk of substance use. The results are consistent with studies on caffeine consumption during adolescence and its association with future substance misuse [10,13], supporting a higher risk of caffeinated soda consumption in childhood, particularly regarding vulnerability to future substance misuse. Such information is invaluable, as caffeinated soda is incomparably the most common medium for caffeine consumption in childhood, and the risk of substance misuse should be detected before adolescence, the most common period of substance use onset.

Our results have important implications for public health recommendations, as our study provides novel insight into the neurocognitive correlates of caffeinated soda consumption in

children, which has rarely been evaluated. At the same time, a few limitations of our research and future directions for further investigations should be discussed. First, we did not perform functional connectivity analyses or multivoxel pattern analyses, which may have provided additional insight into the effects of caffeinated soda intake. Second, as the 9–10-year-old children in this study had not yet started other substances except for alcohol, such as tobacco or marijuana, future work using the longitudinal 10-year follow-up data of the ABCD study should examine whether frequent consumption of caffeinated soda is associated with alcohol or other substance misuse. Third, we acknowledge that multiple variables other than caffeinated soda intake and family risk factors may mediate the relationship between neurocognitive risk factors and future alcohol use; thus, extensive investigation of how caffeinated soda intake interacts with other SUD risk/protective factors is needed in the future. Lastly, the ABCD dataset included only a small set of measures of food/drink consumption. Future studies would benefit by including more diverse measures of foods or drinks containing caffeine or sugar; for example, by determining if similar results are found with non-caffeinated soda or other sugary beverages.

In conclusion, our results revealed the potential risks of caffeinated soda consumption in children by investigating the associations between caffeinated soda consumption and risk factors for SUDs, examining the ability of caffeinated soda consumption to predict future alcohol sipping, and revealing that caffeinated soda consumption mediates impulsivity and future alcohol sipping, using the large ABCD dataset. While previous research on the side effects of caffeinated soda consumption has been limited to negative physical consequences, the present results strongly suggest that caffeinated soda drinking in children is also associated with changes in neurocognitive function and can predict alcohol sipping after 12 months. Our study further suggests a strong need to develop evidence-based recommendations for caffeinated soda [2], as there is no consensus on a safe dose of caffeinated soda in children, and some children are at higher risk of adverse events from frequent caffeinated soda intake. Further clarification on the causal relationships and neuro-developmental evidence are needed to determine whether caffeinated soda is a warning sign for future substance misuse and whether it induces neurocognitive impairments in children.

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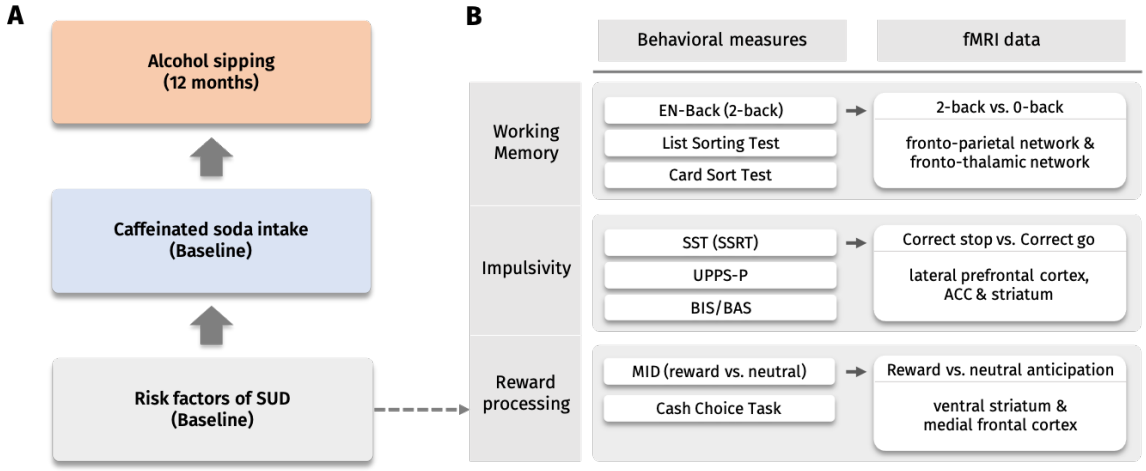
Figure 1. An overview of the study design

A. Diagram of the research aims. First, the association between the risk factors for substance use disorders (SUDs) and caffeinated soda intake was examined. Then, we assessed whether caffeinated soda intake predicts alcohol sipping after 12 months, and whether caffeinated soda intake works as a mediator between the risk factors and future alcohol sipping. **B.** The variables used to measure the three main neurocognitive risk factors: working memory, impulsivity, and reward processing. Working memory was measured from the performance of list sorting test, card sort test, and 2-back in the emotional N-Back Task (EN-back) performed inside a functional magnetic resonance imaging (fMRI) scanner. The fMRI data from the EN-back task were analyzed based on the contrast of 2-back versus 0-back, using regions in the frontoparietal and fronto-thalamic network as the regions of interest (ROIs). Impulsivity was measured by Urgency-Premeditation-Perseverance-Sensation Seeking-Positive Urgency (UPPS-P), and Behavioral Inhibition System/ Behavioral Activation System (BIS/BAS), and the stop signal reaction time (SSRT) during the stop signal task (SST) performed inside the fMRI scanner. The fMRI data from the SST were analyzed based on the contrast of correct stop versus correct go, using regions in the lateral prefrontal cortex, anterior cingulate cortex (ACC), and striatum as the ROIs. Reward processing was measured by cash choice task, and also by comparing the success rate of reward versus neutral conditions during the monetary incentive delay (MID) task performed inside the fMRI scanner. The fMRI data from the MID task were analyzed based on the contrast of reward anticipation versus neutral anticipation, using regions in the ventral striatum and medial frontal cortex as the ROIs. The ROIs were selected based on the Destrieux atlas [72].


A
Alcohol sipping
(12 months)
Caffeinated soda intake
(Baseline)
Risk factors of SUD
(Baseline)
B
Behavioral measures
fMRI data
Working Memory
EN-Back (2-back)
List Sorting Test
Card Sort Test
2-back vs. 0-back
fronto-parietal network &
fronto-thalamic network
Impulsivity
SST (SSRT)
UPPS-P
BIS/BAS
Correct stop vs. Correct go
lateral prefrontal cortex,
ACC & striatum
Reward processing
MID (reward vs. neutral)
Cash Choice Task
Reward vs. neutral anticipation
ventral striatum &
medial frontal cortex

1

Figure 2. Results of LASSO regression predicting daily caffeinated soda intake (daily drinking group vs. non-drinking group)

A. Estimates of coefficients of the survived variables (x axis: coefficient estimates; y axis: predictor). The site variables were excluded for clarify (see **Figure S1** for the site variables). **B.** Distribution of the area under the curve (AUC) values (left) and a representative receiver-operation characteristic (ROC) curve (right) for the training and test datasets. **C.** Regions of interest (ROIs) identified as having significant estimates of coefficients during the emotional N-Back Task (EN-back), stop signal task (SST), and monetary incentive delay (MID) task.

Abbreviations. LASSO, least absolute shrinkage and selection operator; BMI, body mass index; BIS, Behavioral Inhibition System; BAS, Behavioral Activation System; UPPS-P, Urgency-Premeditation-Perseverance-Sensation Seeking-Positive Urgency; SST, Stop Signal Task; SSRT, Stop Signal Reaction Time; MID, Monetary Incentive Delay Task; NAc, Nucleus Accumbens; IPL, Inferior Parietal Lobule; IFG, Inferior Frontal Gyrus; ACC, Anterior Cingulate Cortex; OFC, Orbitofrontal Cortex.

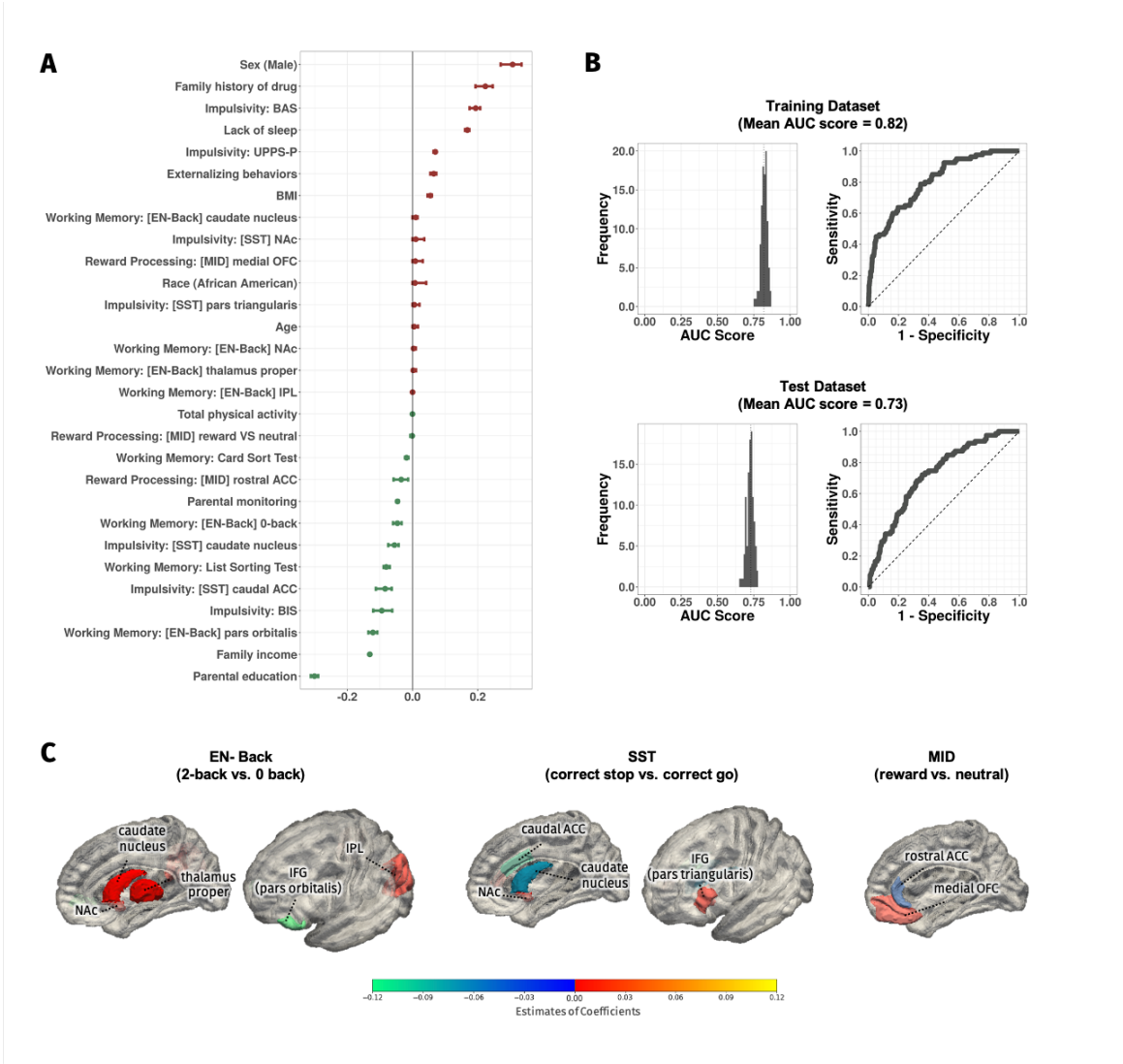

A
Sex (Male)
Family history of drug
Impulsivity: BAS
Lack of sleep
Impulsivity: UPPS-P
Externalizing behaviors
BMI
Working Memory: [EN-Back] caudate nucleus
Impulsivity: [SST] NAc
Reward Processing: [MID] medial OFC
Race (African American)
Impulsivity: [SST] pars triangularis
Age
Working Memory: [EN-Back] NAc
Working Memory: [EN-Back] thalamus proper
Working Memory: [EN-Back] IPL
Total physical activity
Reward Processing: [MID] reward VS neutral
Working Memory: Card Sort Test
Reward Processing: [MID] rostral ACC
Parental monitoring
Working Memory: [EN-Back] 0-back
Impulsivity: [SST] caudate nucleus
Working Memory: List Sorting Test
Impulsivity: [SST] caudal ACC
Impulsivity: BIS
Working Memory: [EN-Back] pars orbitalis
Family income
Parental education
-0.2
0.0
0.2
B
Training Dataset
(Mean AUC score = 0.82)
Frequency
AUC Score
Sensitivity
1 - Specificity
Test Dataset
(Mean AUC score = 0.73)
Frequency
AUC Score
Sensitivity
1 - Specificity
C
EN- Back
(2-back vs. 0 back)
caudate nucleus
thalamus proper
NAc
IPL
IFG (pars orbitalis)
SST
(correct stop vs. correct go)
caudal ACC
caudate nucleus
NAc
IFG (pars triangularis)
MID
(reward vs. neutral)
rostral ACC
medial OFC
Estimates of Coefficients

Figure 3. Results of LASSO regression predicting alcohol sipping after 12 months

A. Rate of alcohol sipping after 12 months in each group. **B.** Estimates of coefficients of the survived variables (x axis: coefficient estimates; y axis: predictor). Site variables were excluded for a clarity (see **Figure S2** for the site variables). **C.** Distribution of the area under the curve (AUC) values (left) and a representative receiver-operation characteristic (ROC) curve (right) for the training and test datasets.

*: $p<0.05$, **: $p<0.01$; ***: $p<0.001$

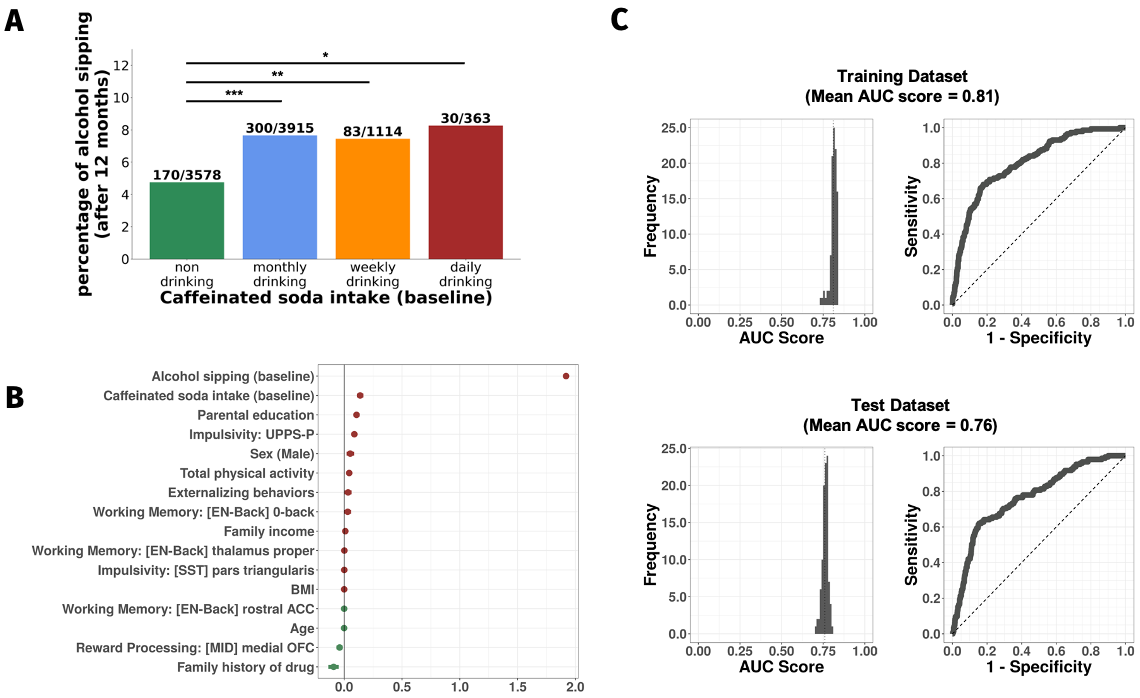
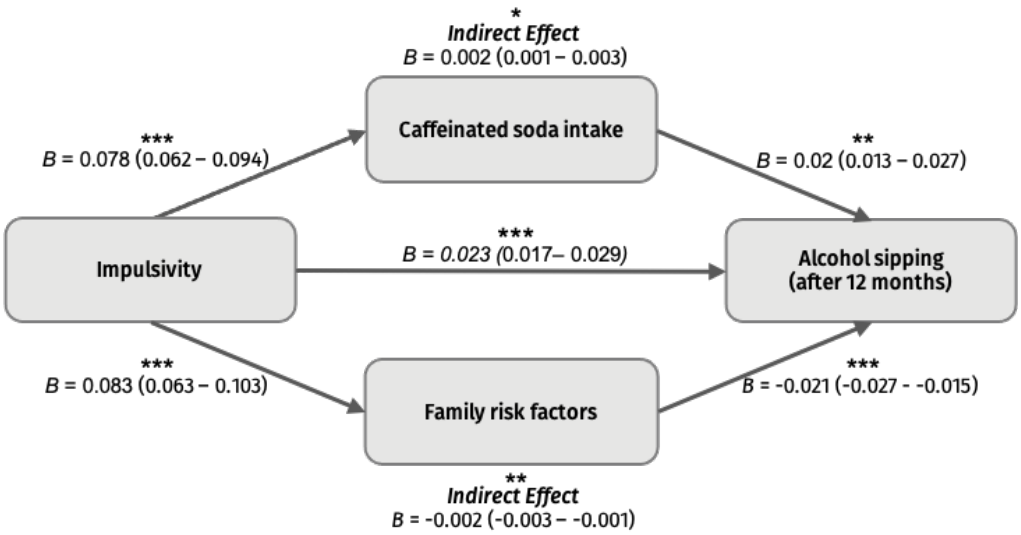


Figure 4. Caffeinated soda consumption at baseline as a mediator of the relationship between impulsivity and alcohol sipping after 12 months

Along with family risk factors, caffeinated soda intake was a significant mediator between impulsivity and future alcohol sipping. Significant paths are flagged with asterisks (*: $p<0.05$, **: $p<0.01$; ***: $p<0.001$). Indirect effects of caffeinated soda intake and family risk factors on the relationship between impulsivity and alcohol sipping after 12 months were significant (caffeinated soda intake: B=0.002, 95% CI=[0.001, 0.003], p=0.013; family risk factors: B=−0.002, 95% CI=[−0.003, −0.001], p=0.006).



1 **Table 1.** Results of hierarchical regression analysis predicting alcohol sipping after 12 months

Variables	Model 1	Model 2	Model 3
Sex (Male)	-0.020 (-0.031 - -0.010)***	-0.015 (-0.025 - -0.005)**	-0.013 (-0.023 - -0.003)**
Race (Caucasian)	0.032 (0.011 - 0.053)**	0.022 (0.002 - 0.042)*	0.022 (0.002 - 0.042)*
Race (African American)	0.001 (-0.024 - 0.026)	0.003 (-0.021 - 0.027)	0.003 (-0.021 - 0.027)
Family income	0.007 (0.000 - 0.015)*	0.005 (-0.002 - 0.012)	0.005 (-0.002 - 0.012)
Parental education	0.009 (0.002 - 0.015)*	0.007 (0.001 - 0.014)*	0.009 (0.002 - 0.015)*
Parental monitoring	-0.003 (-0.009 - 0.002)	-0.002 (-0.007 - 0.003)	-0.001 (-0.006 - 0.004)
Family history of drug	-0.003 (-0.015 - 0.009)	-0.005 (-0.017 - 0.007)	-0.005 (-0.017 - 0.006)
Family history of alcohol	-0.008 (-0.019 - 0.003)	-0.010 (-0.020 - 0.001)	-0.010 (-0.021 - 0.001)
BMI	0.007 (0.002 - 0.012)**	0.006 (0.001 - 0.011)*	0.006 (0.001 - 0.011)*
Physical activity	0.007 (0.001 - 0.012)*	0.005 (0.000 - 0.010)	0.005 (0.000 - 0.011)
Lack of sleep	0.000 (-0.005 - 0.006)	0.002 (-0.004 - 0.007)	0.001 (-0.004 - 0.007)
Externalizing behaviors	0.009 (0.003 - 0.015)**	0.007 (0.001 - 0.013)*	0.006 (0.000 - 0.013)*
Internalizing behaviors	-0.003 (-0.009 - 0.004)	-0.003 (-0.009 - 0.003)	-0.003 (-0.009 - 0.003)
Alcohol sipping (Baseline)		0.174 (0.161 - 0.187)***	0.172 (0.159 - 0.185)***
Monthly caffeinated soda intake			0.021 (0.010 - 0.032)***
Weekly caffeinated soda intake			0.024 (0.008 - 0.041)**
Daily caffeinated soda intake			0.036 (0.010 - 0.062)**

2 *Note.* The values are standardized regression coefficients (95% confidence intervals) from each
3 step in the hierarchical analyses predicting alcohol sipping after 12 months. Significant variables
4 predicting alcohol sipping are flagged with asterisks (*: $p<0.05$, **: $p<0.01$; ***: $p<0.001$). Higher
5 consumption of caffeinated soda intake (Model 3) predicted a higher tendency for alcohol sipping
6 after 12 months even after controlling for the confounding variables (13 variables from the top and
7 21 data collection sites in Model 1) and alcohol sipping collected at baseline (Model 2).
8 *Abbreviations.* BMI, Body Mass Index.
9