Title: Daily caffeinated soda intake in children is associated with neurocognitive vulnerabilities of substance misuse and predicts higher risk of alcohol sipping in 12 months

Abbreviated title: Daily soda intake in children and alcohol sipping

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Abstract

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 daily consumption of caffeinated soda and examined whether daily caffeinated soda intake is associated with a higher risk of alcohol initiation in children. By applying machine learning and hierarchical regression to a large dataset from the Adolescent Brain Cognitive Development (ABCD) Study, we investigated the relationship between daily caffeinated soda intake and the well-known risk factors of substance misuse, including impaired working memory, high impulsivity, and altered reward processing. We next examined whether daily caffeinated soda intake could predict greater alcohol sipping in 12 months. The results showed that daily consumption of caffeinated soda was associated with impaired working memory, higher impulsivity, and altered reward processing, with increased amygdala activation during the emotional working memory task and hypoactivity in the nucleus accumbens and posterior cingulate cortex during reward processing tasks. Daily drinkers reported higher rates of alcohol sipping compared to non-drinkers after 12 months, and daily intake of caffeinated soda mediated the relationship between the neurocognitive risk factors and future alcohol sipping. These results suggest that daily caffeinated soda intake in childhood (1) is associated with impaired neurocognitive functioning, and (2) may work as a predictor for alcohol initiation, which has significant implications for public health recommendations.

Significance Statement

Is daily caffeinated soda intake associated with higher risks of substance misuse? If so, which specific risk factors of substance misuse are involved? Moreover, can daily caffeinated soda intake predict future alcohol initiation? These are the questions that many parents are asking but surprisingly there is no clear guideline, and its potential vulnerabilities of substance misuse remain largely unknown. Here, by applying machine learning and hierarchical regression

approaches, we demonstrate that daily caffeinated soda intake is associated with neurocognitive risk factors of substance misuse including impaired working memory, higher impulsivity, and altered reward processing. We also present that daily caffeinated soda consumption could predict higher alcohol sipping rates in 12 months. These results have significant implications for public health recommendations.

Introduction

Caffeinated soda combines two addictive substances, sugar and caffeine, both of which affect neurocognitive functions and cause physical side effects (Nehlig, 1999; Avena et al., 2008; Sylvetsky et al., 2020). Not surprisingly, the consequences of excessive consumption of both sugar and caffeine have been well documented (Porciúncula et al., 2013), including a strong association between caffeinated beverages consumption in adolescents and future substance use (Arria *et al.*, 2011; Miyake and Marmorstein, 2015; Barrense-Dias *et al.*, 2016; Kristjansson *et al.*, 2018; Marmorstein, 2018; Leal and Jackson, 2019). 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-users (Miyake and Marmorstein, 2015; Marmorstein, 2018; Leal and Jackson, 2019). Others have also shown that coffee or energy drink consumption in developing children could significantly predict future substance use such as tobacco and alcohol (Arria et al., 2011; Barrense-Dias et al., 2016; Marmorstein, 2018).

Existing literature examining the associations between caffeine consumption and later substance use focused more on adolescents who drink multiple caffeinated beverages on a daily basis, partially due to the fact that consumption level of coffee and energy drink is extremely low in children, 0.4% for coffee and less than 0.1% for energy drinks in 9-10 years old (Lisdahl et al., 2021). However, caffeinated soda is the most preferred and accessible mode of caffeine intake in children (Temple, 2009; Vercammen et al., 2019; Sylvetsky et al., 2020). Moreover, it is well known that adolescence is the most common period of substance use initiation, and an earlier onset of substance use predicts greater addiction severity (Wagner and Anthony, 2002; Chambers et al., 2003; Barry et al., 2016; Jordan and Andersen, 2017). Therefore, there is a critical need to investigate the link between caffeinated soda intake during preadolescence 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. Even though few studies have directly examined the effects of frequent caffeinated soda intake in adolescents and children, they either targeted only behavioral aspects using surveys or self-

reports without obtaining neural data, or did not target children but only adolescents (James et al., 2011; Solnick and Hemenway, 2013; Suglia et al., 2013; Miyake and Marmorstein, 2015).

Here, we addressed the unanswered question of whether daily intake of caffeinated soda in children could indicate a higher risk of later substance misuse, using the Adolescent Brain Cognitive Development (ABCD) Study. First, we examined the relationship between daily caffeinated soda intake and three well-known neurocognitive risk factors of SUDs in children: impaired working memory (WM), high impulsivity, and altered reward processing (Casey et al., 2018). From the baseline data of the ABCD study, we used psychological, behavioral, and neurological indices related to each risk factor (**Figure 1A**), and employed both univariate (hierarchical regression) and multivariate (machine learning) approaches to rigorously investigate the associations between daily caffeinated soda intake and the risk factors of SUDs. **Figure 1B** shows the two different analytical methods that have different predictive directionalities. We next examined whether daily caffeinated soda intake could predict future alcohol sipping, in that (1) alcohol sipping has been reported to predict future alcohol abuse (Donovan and Molina, 2011; Jackson et al., 2015; Watts et al., 2021), and (2) alcohol sipping is the most common gateway behavior toward other substances of abuse (Kirby and Barry, 2012; Barry et al., 2016). Lastly, we identified the best model explaining how the interaction of daily caffeinated soda intake and the risk factors of SUDs leads to later alcohol sipping behavior. Together, we tried to provide insight into possible underlying risks of daily caffeinated soda intake in childhood.

Method

Participants

The ABCD study has collected data from 11,875 children aged 9- and 10-years-old. The participants were recruited through school systems from 21 different sites in the US. More information about the recruitment and study design is available in Garavan et al. (2018). Further details of the demographic, physical, and mental health assessments are described in Barch et al. (2018).

To include as many samples as possible, we used different sample sizes for each analysis. For the first analysis examining the relationship between caffeinated soda intake and the risk factors of SUDs, 3,966 participants at the baseline data collection (Data Release 2.0) without any missing data in the following curated datasets were included: task-based functional magnetic resonance imaging (fMRI) data for three tasks (Emotional N-Back (EN-Back) Task (Cohen et al., 2015), Stop Signal Task (SST) (Logan et al., 1984), and Monetary Incentive Delay (MID) Task (Knutson et al., 2000)), behavioral data obtained from cognitive tasks (the List Sorting Test, Card Sort Test, and Cash Choice Task) and from psychological surveys, and demographic data. The task-based fMRI data were collected from three different MRI scanners (Siemens, General Electric, and Philips); data from the Philips scanner were incorrectly processed in the curated dataset and were therefore excluded from the analysis (*N*=527). For the second analysis testing the link between caffeinated soda intake and future alcohol sipping, we included 8,953 participants without any missing data in soda intake measure and control variables (i.e., psychological surveys and demographic information) in the baseline data and in alcohol sipping measure in the year 1 data (Data Release 3.0). For the third analysis testing the link between daily caffeinated soda intake, alcohol sipping, and the risk factors of SUDs, 3,827 participants were analyzed based on the same criteria as the first analysis, in addition to having a complete set of data in the year 1 data.

Measures

Caffeinated soda intake

In every analysis sample, the participants were divided into four groups based on their caffeinated soda consumption over the last 6 months, which was assessed using the participants' self-report in response to the question, "Typically, how many drinks of the following beverages have you had per week in the past 6 months? – soda with caffeine (Mountain Dew, Jolt, Coke, Pepsi, Dr. Pepper, Barq's root beer)". The non-drinking group reported 0 cans per week, the monthly-drinking group reported <1 can per week, the weekly-drinking group reported 1–7 cans per week, and the daily-drinking group reported ≥7 cans per week. These criteria for group

allocation were defined by referring to the population-based cohort study of Mullee et al. (2019). For the main analyses, we focused on the daily-drinking group and non-drinking group to ensure adequate separation between habitual drinkers (daily-drinking group) and non-drinkers (non-drinking group).

Risk factors of SUDs

As shown in **Figure 1**, we focused on the three well-known psychological risk factors for SUDs (WM, impulsivity, and reward processing), measured by self-report surveys, behavioral tasks, and fMRI, as described below.

To obtain behavioral measures of WM, we used the List Sorting Working Memory Test (List Sorting Test) and Dimensional Change Card Sort Test (Card Sort Test) from the NIH Toolbox (Tulsky et al., 2013), and the EN-Back task. The List Sorting Test requires participants to sort and sequence visual and auditory stimuli. For the Card Sort Test, participants are asked to sort cards according to either color (when the target card has a contour) or shape (when the card without a contour is shown). The EN-Back task (Cohen et al., 2015), which measures WM and emotion regulation, was conducted inside the MRI scanner. The task consists of two different blocks: the 0-back block requires participants to respond when the current stimulus is the same as a target, and the 2-back block requires participants to respond when the current stimulus is the same as the one shown in two trials before. Due to the difference in WM load between the two blocks, accuracy during the 2-back block is commonly used as a behavioral measure of WM, and the 2-back block vs. 0-back block contrast is commonly used to examine the neural correlates of WM (Casey et al., 2018). Unlike the traditional N-Back task, in which the stimuli are numbers, the EN-Back task displays emotional (happy, fearful, and neutral) face stimuli and place (non-emotional) stimuli. Therefore, the task also allows us to test the effect of emotional processing in WM. The regions of interest (ROIs) of the EN-Back task include the amygdala, a region that is well-known for emotional processing and has also been linked with working memory function (Banks et al., 2007), as well as the hippocampus and dorsolateral prefrontal cortex (DLPFC),

which are critical for WM (Barbey et al., 2013). See Casey et al. (2018) for more details about the task.

Impulsivity, particularly trait impulsivity, was measured using the short form Urgency-Premeditation-Perseverance-Sensation Seeking-Positive Urgency (UPPS-P) impulsive behavior scale for children (the 20-item short version for youths, Barch et al., 2018) and parental report of ABCD Youth Behavioral Inhibition System/ Behavioral Activation System (BIS/BAS). The BAS is related to goal-directed efforts, such as motor activation in response to impending rewards, while the BIS is engaged when inhibition toward a goal occurs, such as the avoidance of punishment (Carver and White, 1994). The existing literature suggests that Behavioral Inhibition is associated with depression and anxiety, while Behavioral Activation is associated with impulsive behaviors, compulsive behaviors, substance misuse, and aggression (Newman et al., 2005).

To identify the neural correlates of impulsivity, participants completed the SST (Logan et al., 1984) inside the scanner. The SST measures impulsivity related to impulse control or response inhibition when performing an action. The SST requires participants to withhold motor responses to a “Go” stimulus when a “Stop” signal is unpredictably presented after a short delay. The delay between the “Go” stimulus presentation and the “Stop” signal presentation is termed the stop signal delay (SSD). The SSD was initially set to 50ms. Following a successful inhibition or an unsuccessful inhibition, the SSD was increased or decreased by 50ms to make the task more difficult or easier, respectively. Each run contained 180 trials, and each trial began with the presentation of the “Go” cue. Participants were instructed to respond to the cue as quickly and accurately as possible. Thirty trials from a single run (16.67%) presented a "Stop" signal, which was an upward arrow displayed for 300 ms. Stop signal reaction time (SSRT) was used as a behavioral measure of impulsivity, calculated by subtracting the mean SSD from the mean “Go” response time (Logan et al., 1984; Schachar and Logan, 1990); a shorter SSRT means better response inhibition. For the fMRI analysis, a “correct stop vs. correct go” contrast was used, and the caudal anterior cingulate cortex (ACC) and the inferior frontal gyrus (IFG) were selected as ROIs; both areas have been associated with impulsivity and impulse control (Stadler et al., 2007; Jacobson et al., 2011). More information about the SST is available in Casey et al. (2018).

Reward processing is closely linked to impulsivity, in that impulsive people often show reward-seeking behavior (Zuckerman, 2001). Previous literature suggests that people with SUDs show hyperresponsiveness toward drug-related cues (Robinson and Berridge, 2008; Bechara et al., 2019) while showing blunted responsiveness toward generalized reward (e.g. monetary reward) (Balodis and Potenza, 2015; Luijten et al., 2017). We used the Cash Choice Task (Luciana et al., 2018), which measures delayed gratification by assessing impulsivity in receiving a monetary reward when asked the following single-item question: “Let’s pretend a kind person wanted to give you some money. Would you rather have $75 in three days or $115 in 3 months?” The former choice reflects poor delayed gratification, with a higher delay discounting rate, while the latter choice implies a smaller delay discounting rate. Responses were scored as 1 ($75 in three days) or 2 ($115 in 3 months).

The MID task (Knutson et al., 2000) is widely used to measure the neural correlates of reward processing, such as the anticipation of monetary rewards and losses. Each trial of the MID task begins with an incentive cue of five possible trial types (Win $20, Win $5, Lose $0.2, Lose $5, and $0 – no money at stake), followed by a delay (1500 ms~4000 ms) and a presentation of a target during which the participant chooses to either win money or avoid losing money, and ends with feedback on whether the participant won or lost money. Each participant performed 40 reward anticipation, 40 loss anticipation, and 20 no money anticipation trials, resulting in a total of 100 trials. The differences in accuracy between reward and neutral trials, and loss and neutral trials indicate motivation to win reward or avoid loss. The contrast of “Reward vs. Neutral” at the cue onset, which reflects reward anticipation, was used for fMRI analysis, with the ROIs as the nucleus accumbens (NAc) and the posterior cingulate cortex (PCC), which are known to play a key role in reward processing, particularly in reward anticipation (Day and Carelli, 2007). See Casey et al. (2018) for more details about the MID task.

Alcohol sipping

Alcohol sipping was measured with a self-report from youth using iSay Sip Inventory, which is being collected once a year and asked only to children who had heard of alcohol (see

Lisdahl *et al.* (2021) for more details). From the year 1 data (Data Release 3.0), we used a binary response to a single question asking if they have sipped alcohol outside of a religious ceremony. We considered those who have not heard of it as having yet to sip alcohol (i.e., no alcohol sipping).

Confounding variables

We included the following variables as control variables in data analysis: Family history of substance use, parental monitoring, sleep deprivation, and externalizing/internalizing behaviors. Family history of substance use was measured using a parental yes/no response to the following question: “Has any blood relative of your child ever had any problems due to drugs, such as: Marital separation or divorce; Fired from work; Arrests or DUI (Driving Under Influence); Adverse health effects; In a drug treatment program; Suspended or expelled from school two or more times; Isolated oneself from the family, caused arguments, or often intoxicated.” To measure the family history of alcohol use, the same question was asked, except that “drug” was replaced with “alcohol”.

Parental monitoring was measured using the ABCD Parental Monitoring Survey, in which children answered five questions (“How often do your parents/guardians know where you are?”, “How often do your parents know who you are with, or when you are not at school and away from home?”, “If you are at home when your parents or guardians are not, how often do you know how to get in touch with them?”, “How often do you talk to your parent or guardian about your plans for the coming day, such as your plans about what will happen at school or what you are going to do with friends?”, “In an average week, how many times do you eat dinner with your parents/guardians?”). Responses ranged from 1 (Never) to 5 (Always or Almost Always), and the mean of all five responses was used for the analysis. The SES measures the total combined family income and parents’ highest education level. Parents’ education was calculated as the mean of both parents, or of the responding parent only in the case of single parents.

The sleep deprivation was measured using the ABCD Parent Sleep Disturbance Scale for Children, for which parents responded to the question, “How many hours of sleep does your child

get on most nights?" (1=9–11 hours, 2=8–9 hours, 3=7–8 hours, 4=5–7 hours, 5=less than 5 hours). Physical activity was measured using the ABCD Parent Sports and Activities Involvement Questionnaire, which asks whether the child has ever continuously participated in specific sports and activities, such as football, field hockey, climbing, or basketball, for four months or more. The number of "yes" responses to 29 questions was summed for the analysis. BMI was calculated according to the children's body weight and height.

Externalizing and internalizing behaviors were measured using the parental report of the Child Behavior Checklist (Achenbach, 2009), which comprises 113 items about child behavior over the past six months. Internalizing and externalizing scores were measured based on the following syndrome scores: anxious/depressed, withdrawn/depressed, somatic complains, social problems, though problems, rule-breaking behavior, and aggressive behavior (Thompson et al., 2018).

MRI Protocol

Imaging-derived phenotype scores provided by the ABCD study were used. Data acquisition protocol was matched for the three 3T scanners used (Siemens Prisma, General Electric 750, and Philips). We analyzed beta weights within each ROI for the 2-back vs. 0-back contrast in the EN-Back task, the correct stop vs. correct go contrast in the SST, and the reward vs. neutral anticipation contrast in the MID task. More details about fMRI imaging protocols such as scanning parameters in the ABCD study are reported by Casey et al. (2018).

Analysis

Daily caffeinated soda intake and risk factors of SUDs

To identify a multivariate profile of risk factors that can differentiate the daily-drinking group (*N*=1,640) from the non-drinking group (*N*=141), we performed the least absolute shrinkage and selection operator (LASSO) regression analysis (Tibshirani, 1996), a machine learning algorithm, with all possible variables from the baseline data. LASSO regression offers automatic variable selection through a penalized least squares method, which increases the interpretability

of the findings especially when the multiple variables share a common characteristic to some extent. For example, each task measure (e.g., the EN-Back task, List Sorting Test, and Card Sort Test) within cognitive risk factors are often moderately correlated with one another because they share common cognitive processing (e.g., WM). In this case, LASSO regression shrinks coefficients of variables with less explanatory power to zero and selects only variables with the highest power for further analyses (Tibshirani, 1996, 2011).

In the main LASSO-based prediction model, we used all the risk factors and the confounding variables as an input (i.e., predictor) to classify each individual into either daily drinking group (codes as "1") or non-drinking group (coded as "0) (**Figure 1B**), given that the primary interest was to identify the potential risk of daily soda-drinking behavior. More specifically, forty candidate predictors included every measure for the three cognitive factors as well as other control variables (y-axis of **Figure 2A**). We used an R package called “easyml” (v0.1.1), a toolkit to easily build and evaluate machine learning models using the glmnet package (Friedman et al., 2010) for LASSO regression and several other machine learning algorithms (https://github.com/CCS-Lab/easyml; Ahn et al., 2017). The mixing parameter alpha was set to 1 to conduct the LASSO (1 for LASSO, 0 for ridge, and a value between 0 and 1 for elastic net). We trained the model using k-fold cross-validation (k=10) within the training set, and this generated an estimated coefficient 100 times for a particular train-test split, whereby we calculated the mean and standard deviation of the estimated coefficients. By replicating predictions many times for a particular train-test split, averaging the predictions across 10 iterations and using 1000 divisions of train-test splits, we could avoid intrinsic random errors (see Ahn et al., 2014, 2017 & Ahn and Vassileva, 2016 for more details). Given that previous results have revealed that the elastic net often performs better for highly correlated predictors than for LASSO regression (Zou and Hastie, 2005), we tested the elastic net by setting alpha to a value between 0 and 1. However, there were no significant differences between the LASSO and elastic net results, so we only report the LASSO results.

In addition to the multivariate approach, we also performed the univariate level of regression analysis to confirm the link between each risk factor and daily caffeinated soda intake.

To this end, we conducted a hierarchical regression analysis using the "lm" function in R and tested whether daily caffeinated soda intake was a significant predictor of each of the three cognitive factors (**Figure 1B**). Each measure was set as the dependent variable, including the brain activation of each ROI (**Figure 3**). The main predictor of interest was the caffeinated soda intake group, whether the individual belongs to the daily-drinking or non-drinking groups. To ensure that the caffeinated soda intake accounted for more variance than did the confounding variables, we set a three-level hierarchical model. At the first level, predictors only included the confounding variables, including sex, age, race, family income, parental education, physical activity, parental monitoring, family history of drug and alcohol abuse, and externalizing and internalizing behaviors. At the second level, we included sleep deprivation as an additional predictor, which is strongly linked to caffeine intake (Roehrs and Roth, 2008). Finally, at the third level, the caffeinated soda intake group (daily-drinking vs non-drinking group) was added as a predictor to examine the effect of daily consumption of caffeinated soda. To conclude that caffeinated soda intake is responsible for group differences in each cognitive factor, two conditions should be satisfied. First, we conducted an analysis of variance (ANOVA) between the third-level analysis and the other two lower-level analyses; the third level should show a higher significance than the previous levels. Also, the categorical caffeinated soda intake regressor should be statistically significant ($p<0.05$) in the third-level analysis. We tested for these conditions to determine whether caffeinated soda intake was a significant predictor of the dependent variable in question.

Daily caffeinated soda intake and future alcohol sipping

Hierarchical logistic regression analysis was used to test whether caffeinated soda intake at baseline could predict alcohol sipping after 12 months. All the procedures, including the first, second, and third models, and the criteria of significance are identical to the first analysis (see Method – Daily caffeinated soda intake and risk factors of SUDs). The only difference was that the dependent variable was alcohol sipping after 12 months. Among 8,952 participants, 356 were

daily-drinking group, and 3,574 were the non-drinking group. Therefore, 3,930 samples were used in hierarchical regression analysis.

Daily caffeinated soda intake, alcohol sipping, and risk factors of SUDs

To provide a more integrated insight into how the interactions between daily caffeinated soda intake and the risk factors of SUDs lead children to later alcohol sipping, we performed the mediation analysis. Among the risk factors, we selected significant predictors of daily caffeinated soda intake from the LASSO regression (**Figure 2A**), which results in eighteen variables including four WM measures (e.g. List Sorting Test, [EN-back] 0-back, [EN-back] L amygdala, [EN-back] R amygdala), three impulsivity measures (e.g. BAS, UPPS-P, [SST] SSRT), four reward processing measures (e.g. [MID] earned money, [MID] L NAc, [MID] reward vs. neutral, [MID] L PCC), three family characteristics (e.g. parental monitoring, family income, parental education), three demographic measures (e.g. BMI, sex, race), and sleep deprivation. We then performed a principal component analysis (PCA) and extracted the first principal component (PC1) for the risk factors that could be grouped as the following six clusters: (1) neurocognitive risk factors consisting of eleven measures related to WM, impulsivity, and reward processing; (2) environmental/demographic risk factors with seven measures other than the neurocognitive risk factors; (3) WM-related risk factors; (4) impulsivity-related risk factors; (5) reward-processing-related risk factors; (6) family-related risk factors. This leads to twenty-four indices of risk factors (eighteen variables survived from LASSO regression and six PC1 scores), which could be included in the models, along with a categorical index of caffeinated soda intake and the single measure of alcohol sipping collected after 12 months.

With selected variables, we tried to find the best fitting model using the "lavaan" package (v0.6-8) in R with four elements mediation design: independent variable (X), two mediators (M1, M2), and dependent variable (Y) (**Figure 4B**). This design was chosen to examine how the interactions between the three types of risk factors (e.g., caffeinated soda intake, neurocognitive risk factors, and environmental/demographic risk factors) lead to future alcohol sipping. The dependent variable was fixed to alcohol sipping, while all possible combinations of the other three

elements were tested (e.g. daily caffeinated soda intake as X and the other two as mediators). Unlike daily caffeinated soda intake which consists of a single measure, neurocognitive risk factors and environmental/demographic risk factors consist of multiple indices; therefore, one index was selected for one model. This results in a total of 405 models for 3 combinations: ${}_{15}C_1$ (neurocognitive risk factors) * ${}_{9}C_1$ (environmental/demographic risk factors) = 135 models for one combination. See **Table 4-1** in the Supplemental Material to check the models.

For all possible models, we computed the Akaike Information Criterion (AIC) and the Bayesian Information Criterion (BIC) values, common measures of model comparison; lower AIC/BIC values suggest a model having a better fit to the data than other models with higher values (Gana and Broc, 2018). We then determined the one best fitting model with the lowest AIC/BIC values that best explains the relationship between caffeinated soda intake, alcohol sipping in 12 months, and neurocognitive and environmental/demographic risk factors. See the Supplemental Material for examples of the tested models; among 405 models, we selected (1) models with significant total effect (123 out of 405 models), and (2) models with at least one significant indirect effect (63 out of 123 models; see **Figure 4-1** and **Table 4-1**).

Results

Sample Characteristics

To characterize group differences as a function of caffeinated soda intake level, we performed a one-way ANOVA with group factor (four levels of soda intake: non-drinking, monthly-drinking, weekly-drinking, daily-drinking groups) on all the risk factors and confounding variables.

As a result, ANOVA revealed a significant main effect of group on soda intake per week ($F(3, 3962)=1161$, $p<0.001$) and on all demographic factors, including family income ($F(3, 3962)=46.06$, $p<0.001$), parental education ($F(3, 3962)=51.50$, $p<0.001$), parental monitoring ($F(3, 3962)=7.88$, $p<0.001$), BMI ($F(3, 3962)=19.37$, $p<0.001$), physical activity ($F(3, 3962)=11.47$, $p<0.001$), sleep deprivation ($F(3, 3962)=33.19$, $p<0.001$), externalizing behaviors ($F(3, 3962)=7.74$, $p<0.001$), and internalizing behaviors ($F(3, 3962)=3.31$, $p=0.019$).

For the neurocognitive risk factors, all the behavioral measures of WM showed a main effect of group (List Sorting Test: $F(3, 3962)=14.16$, $p<0.001$; Card Sort Test: $F(3, 3962)=5.68$, $p<0.001$; [EN-Back] 2-back: $F(3, 3962)=3.74$, $p=0.011$; [EN-Back] 0-back: $F(3, 3962)=5.60$, $p<0.001$). Except for the left amygdala activation ($F(3, 3962)=4.69$, $p<0.001$), there was no main group effect on fMRI activation during the EN-Back task (R hippocampus: $F(3, 3962)=1.46$, $p=0.224$; L hippocampus: $F(3, 3962)=1.08$, $p=0.356$; R amygdala: $F(3, 3962)=2.56$, $p=0.054$; R DLPFC: $F(3, 3962)=0.16$, $p=0.923$; L DLPFC: $F(3, 3962)=0.14$, $p=0.936$). For impulsivity, there was a significant main effect on all behavioral measures except for the SSRT and BAS (SSRT: $F(3, 3962)=1.70$, $p=0.165$; BIS: $F(3, 3962)=0.29$, $p=0.836$; UPPS-P: $F(3, 3962)=12.62$, $p<0.001$; BAS: $F(3, 3962)=16.67$, $p<0.001$), but not on any neural data during the SST (R caudal ACC: $F(3, 3962)=0.58$, $p=0.631$; L caudal ACC: $F(3, 3962)=0.81$, $p=0.489$; R IFG: $F(3, 3962)=0.53$, $p=0.661$; L IFG: $F(3, 3962)=2.12$, $p=0.095$). Lastly, for the reward processing measures, there was no group difference in behavioral data ([MID] difference in hit rates between reward and neutral trials: $F(3, 3962)=2.34$, $p=0.072$; [MID] difference in hit rates between loss and neutral trials: $F(3, 3962)=1.99$, $p=0.113$), but main effect of group was found for all neural data except for the activity in the right NAc (L PCC: $F(3, 3962)=6.77$, $p<0.001$; R PCC: $F(3, 3962)=5.79$, $p<0.001$; L NAc: $F(3, 3962)=3.21$, $p=0.022$; R NAc: $F(3, 3962)=0.72$, $p=0.539$).

Table 1 shows Tukey's posthoc comparison results of demographic factors among the four groups (non-drinking, monthly-drinking, weekly-drinking, daily-drinking). Several demographic factors were significantly different among the four groups. Higher caffeinated soda intake was associated with a lower SES (parental income & parental education), lower parental monitoring, higher BMI, lower amount of physical activity, and less sleep. Low WM (lower performance in the List Sorting Test, Card Sort Test, and EN-Back task), high impulsivity (higher score on the UPPS-P and BAS), and indifference toward monetary rewards (smaller difference in performance between the reward vs. neutral trials and loss vs. neutral trials) were found in the daily-drinking group compared to the non-drinking group. Among the ROIs, the amygdala showed hyperactivation in the daily-drinking group (compared to the non-drinking group) during the EN-Back task.

Daily caffeinated soda intake and risk factors of SUDs

ANOVA results suggest that daily consumption of caffeinated soda might be a risk factor and a predictor of future substance misuse. However, such group differences could be driven by confounding variables, not by daily consumption of caffeinated soda. Thus, we performed LASSO regression to identify significant predictors of daily caffeinated soda intake. LASSO offers automatic variable selection, which increases the interpretability of the findings especially when some of the variables are significantly correlated with each other. **Figure 2A** shows the multivariate profiles from LASSO regression classifying the daily-drinking group from the non-drinking group. Low parental education was the strongest predictor of daily consumption, along with greater sleep deprivation and low family income. Being male, African American, and/or with a high BMI also strongly predicted allocation to the daily-drinking group.

Among the risk factors of SUDs, high impulsivity measured with the BAS was most predictive of daily caffeinated soda intake. A higher SSRT, indicative of delayed response inhibition, and a higher UPPS-P score were related to the daily intake. Among the WM measures, poor performance in the List Sorting Test and 0-back performance during the EN-Back task predicted daily intake of caffeinated soda. In addition, bilateral amygdala activation during the EN-Back task (2-back vs. 0-back) also predicted daily caffeinated soda intake (**Figure 2C)**. For reward processing, the daily-drinking group showed a smaller accuracy difference between reward trials and neutral trials in the MID task, implying a reduced motivation to achieve the monetary reward. Also, hypoactivity in the left PCC and left NAc during the MID task (reward vs. neutral anticipation) predicted the membership of the daily-drinking group (**Figure 2D**). Only the left PCC was negatively correlated with the accuracy difference between reward and neutral trials (left PCC: $r(3964)=-0.03$, $p<0.05$, 95% CI=[-0.06, 0]; left Nac: $r(3964)=0.008$, $p=0.6$, 95% CI=[-0.02, 0.039]), but the correlation was not significant when analyzed separately by group (daily-drinking group: $r(139)=-0.19$, $p=0.1$, 95% CI=[-0.3, 0.03]; non-drinking group: $r(1638)=-0.02$, $p=0.52$, 95% CI=[-0.06, 0.03]). The left Nac was negatively correlated with the UPPS-P score only in the daily-drinking group ($r(139)=-0.2$, $p<0.05$, 95% CI=[-0.357, -0.04]), but not in the non-drinking group ($r(1638)=0.04$, $p=0.07$, 95% CI=[-0.004, 0.093]. **Figure 2B** shows the receiver-

operation characteristic (ROC) curve and its mean area under the curve (AUC) for the classification of daily-drinking and non-drinking groups. The mean AUC was 0.77 and 0.71 for the training and test sets.

Next, we performed hierarchical regression analysis to test whether daily caffeinated soda intake was a significant predictor of each measure of WM, impulsivity, and reward processing, including the brain activation of each ROI (**Figure 3)** while controlling for confounding variables (see **Methods**). Specifically, we examined whether caffeinated soda intake accounted for additional variance than did the other confounding variables. **Table 2** shows the results of the hierarchical regression analysis using the binary caffeinated soda intake (whether the subjects are daily drinkers or non-drinkers). Daily consumption of caffeinated soda was negatively associated with the List Sorting Test score and positively associated with the trait impulsivity scores of the UPPS-P, the BAS score, and SSRT. The left amygdala showed hyperactivation during the EN-Back task (2-back vs. 0-back) in the daily-drinking group; although the effect size is small due to the heterogeneous nature of the ABCD dataset (Karcher et al., 2019; Paulus et al., 2019; Rosenberg et al., 2020; Cheng et al., 2021), activation of the left amygdala was negatively correlated with WM capacity, measured by 2-back performance ($r(3964)=-0.03$, $p=0.027$, 95% confidence interval (CI)=[-0.06, -0.0004]) and by the List Sorting Test score ($r(3964)=-0.04$, $p=0.003$, 95% CI=[-0.07, -0.016]).

These results suggest that low WM and high impulsivity are significantly associated with daily caffeinated soda consumption in both analytic approaches (**Figure 1B**). Furthermore, we found from the LASSO regression that the indifference toward reward during the MID task, and some other demographic factors (low SES, less sleep, being male, being African American, and high BMI) could also distinguish the daily-drinking group from the non-drinking group.

Daily caffeinated soda intake and future alcohol sipping

We tested whether daily caffeinated soda intake could predict alcohol sipping after 12 months by conducting hierarchical logistic regression analysis. Even after controlling the confounding variables (see **Methods**), daily caffeinated soda consumption could significantly

predict alcohol sipping after 12 months (**Table 3**). Along with lower parental education *(B*=- *i.*041, *p*<0.05), lower family income (*B*=0.011, *p*<0.01), and higher BMI (*B*=0.04, *p*<0.05), daily consumption of caffeinated soda at baseline (*B*=0.06, *p*<0.001) could predict alcohol sipping after 12 months. Also, the adjusted R-squared of the Model 2 and Model 3 showed a significant difference (model 2 vs. model 3: *F*(1, 3916)=12.04, *p*<0.001), supporting the hypothesis that future alcohol initiation could be predicted by caffeinated soda drinking behavior in childhood (**Figure 4A**). These results remained significant even after controlling the alcohol sipping at baseline (daily caffeinated soda intake: *B*=0.043, *p*<0.01; model 2 vs. model 3: *F*(1, 3915)=7.14, *p*<0.01).

Daily caffeinated soda intake, alcohol sipping, and risk factors of SUDs

Lastly, we examined all possible mediation models explaining the relationships between caffeinated soda intake, alcohol sipping in 12 months, and the risk factors of SUDs. The finally selected best model based on the AIC and BIC values among 405 possible models (see **Methods** and **Figure 4-1** and **Table 4-2** in the Supplemental Material) showed significant indirect effects of neurocognitive risk factors on alcohol sipping after 12 months through family risk factors and daily caffeinated soda intake mediating the relationships (indirect effect of family risk factor: *B*=0.019, SE=0.002, *p*<0.05; indirect effect of caffeinated soda intake: *B*=-0.008, SE=0.036, *p*<0.05; direct effect: *B*=-0.059, SE=0.025, *p*<0.01). These results also support our hypothesis that daily caffeinated soda intake could predict future alcohol sipping, and suggest possible mechanisms of alcohol use initiation and the risk factors from SUDs.

Discussion

The present results demonstrated that daily caffeinated soda consumption in childhood is associated with well-known neurocognitive risk factors of SUDs, and could predict future alcohol sipping. The results of this study are consistent with previous studies of caffeine consumption during adolescence and its association with future substance misuse (Barrense-Dias et al., 2016; Leal and Jackson, 2019), supporting a higher risk of daily caffeinated soda consumption in

childhood, particularly regarding vulnerabilities to future substance misuse. However, this is the first study investigating the direct link between caffeinated soda intake in childhood and the risks of substance use. Such information is invaluable since caffeinated soda is incomparably the most common medium of caffeine consumption in childhood and the risk of substance misuse should be detected before adolescence, the most common period of the onset of substance use.

The first evidence suggesting the risks of daily consumption of caffeinated soda was its strong association with the neurocognitive risk factors of SUDs. For the robustness of the results, we utilized multiple analytic approaches with two analytical methods (LASSO regression and hierarchical regression; **Figure 1B**). Low WM performance (List Sorting Test score) and high impulsivity scores (high UPPS-P and BAS) were consistently associated with greater caffeinated soda consumption across all different approaches. In particular, we showed hyperactivity of the amygdala during the EN-Back task in children with daily caffeinated soda consumption, and found greater behavioral WM impairments during the task in the daily-drinking group than in the non-drinking group. These results are consistent with the developmental mismatch hypothesis, which denote 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 (Somerville et al., 2010; Mills et al., 2014). Based on the previous literature 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 (Gee et al., 2013; Casey et al., 2018), it is possible that the hyperactivation of the amygdala and the negative association between the left amygdala and WM capacity observed in daily caffeinated soda drinkers was due to the unsuccessful suppression of emotional processes during WM processing. We also found altered reward processing in the daily-drinking group; that is, lower activation in the left NAc was associated with higher trait impulsivity in the daily-drinking group. This finding supports previous literature suggesting that blunted reward sensitivity in the ventral striatum might motivate impulsive or risky behaviors, such as the use of substances or pathological gambling, to receive sufficient satisfaction (Beck et al., 2009; Balodis et al., 2012).

The second evidence was acquired from examining whether daily intake of caffeinated soda could predict alcohol sipping in 12 months. In the hierarchical regression controlling other confounding variables, daily consumption of caffeinated soda could significantly predict future alcohol sipping. This relationship could be explained by our third analysis, where we explored all possible mediation models with daily caffeinated soda consumption, future alcohol sipping, and the risk factors of SUDs that came out to be significant predictors of caffeinated soda intake in LASSO regression. The best model (**Figure 4B**) suggests that daily intake of caffeinated soda could work as a mediator between the neurocognitive risk factors of SUDs and future alcohol sipping. These findings suggest that caffeinated soda itself would not directly cause children to initiate substance use, but the daily drinking behavior of the beverages could indicate a high risk of substance initiation in the near future. Because caffeinated soda combines two addictive substances, sugar and caffeine, it is somewhat natural for children to prefer and seek the beverages. While the preference of the taste could lead to a seeking behavior and habitual consumption, previous literature has shown impulsivity as one of the most common traits of SUDs (Whiteside and Lynam, 2003; Magid and Colder, 2007; Cyders et al., 2009). Therefore, the behavior of daily consuming caffeinated soda daily could indicate a high risk of substance initiation in the future, though further research should clearly disentangle the complex relationships.

Along with daily caffeinated soda intake, family risk factors (PC1 of parental monitoring, family income, and parental education) also mediated the relationship between neurocognitive risk factors and future alcohol sipping (**Figure 4B**). This finding is in line with previous literature, suggesting that parental monitoring and high socioeconomic status could have protective effects on future alcohol use or alcohol-related problems (Kendler et al., 2014; Carroll et al., 2016; Collins, 2016; Calling et al., 2019). We acknowledge that multiple mediators could exist between neurocognitive risk factors and future alcohol use other than caffeinated soda intake, so future research should extensively investigate how caffeinated soda intake interacts with other risk/protective factors of SUDs.

Our results have important implications for public health recommendations since our study provides novel insights into the neurocognitive correlates of daily caffeinated soda consumption in children, which has been rarely tested yet. At the same time, we should mention a few limitations in our research and future directions for further investigations. First, because we used an ROI-based approach to analyze the neuroimaging data, we could not perform functional connectivity analyses or multivoxel pattern analysis, which might provide additional valuable insights into the effects of daily caffeinated soda intake. Second, since the samples of 9-10-year-old children have 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 daily caffeinated soda consumption is associated with alcohol or other substance misuses as well.

In conclusion, our results revealed the potential risks of caffeinated soda consumption in children by (1) investigating the associations between daily caffeinated soda consumption and SUD risk factors, and (2) examining the predictive abilities of daily caffeinated soda consumption for future alcohol sipping, in a large dataset of the ABCD study. While previous research regarding the side effects of caffeinated soda has been mostly limited to negative physical consequences, the present results strongly suggest that daily caffeinated soda drinking in children is also associated with alterations in neurocognitive functions, and can predict alcohol sipping in 12 months. Our study further suggests that there is a strong need to develop evidence-based recommendations on caffeinated soda (Temple, 2018), as there is no consensus on a safe dose of caffeinated soda for children and a possibility that certain children are at higher risk for adverse events from habitual caffeinated soda intake. Further clarification on causal relationships and neuro-developmental evidence is needed to determine whether caffeinated soda is indeed 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. Variables used to measure three main cognitive functions: working memory, impulsivity, and reward processing. Working Memory was measured from the performance of 2-back in the Emotional N-Back Task (EN-Back) performed inside the functional magnetic resonance imaging (fMRI) scanner, List Sorting Test, and Card Sort Test. The EN-Back task's fMRI data was analyzed based on the contrast of 2-back vs. 0-back, with hippocampus, amygdala, and dorsolateral prefrontal cortex as the regions of interest (ROIs). Impulsivity was measured by stop signal reaction time (SSRT) during the Stop Signal Task (SST) performed inside the fMRI scanner, Urgency-Premeditation-Perseverance-Sensation Seeking-Positive Urgency (UPPS-P), and Behavioral Inhibition System/ Behavioral Activation System (BIS/BAS). The SST's fMRI data was analyzed based on the contrast of correct stop vs. correct go, with posterior cingulate cortex and inferior frontal gyrus as the ROIs. Reward processing was measured by comparing the success rate of reward vs. neutral and loss vs. neutral during the Monetary Incentive Delay (MID) Task performed inside the fMRI scanner and cash choice task. The MID task's fMRI data was analyzed based on the contrast of reward anticipation vs. neutral anticipation, anterior cingulate cortex and nucleus accumbens as the ROIs. **B.** Two different analytic methods were performed. Hierarchical regression examines whether caffeinated soda intake is a significant predictor of each neurocognitive variables, while a machine learning approach examines which variables are significant predictors of caffeinated soda intake.

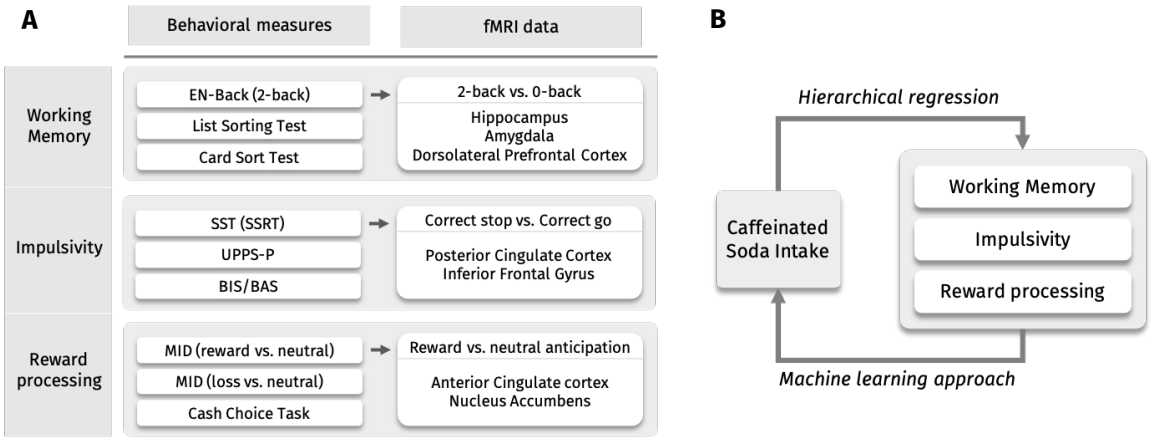

A
Behavioral measures
fMRI data
Working Memory
EN-Back (2-back)
List Sorting Test
Card Sort Test
2-back vs. 0-back
Hippocampus
Amygdala
Dorsolateral Prefrontal Cortex
Impulsivity
SST (SSRT)
UPPS-P
BIS/BAS
Correct stop vs. Correct go
Posterior Cingulate Cortex
Inferior Frontal Gyrus
Reward processing
MID (reward vs. neutral)
MID (loss vs. neutral)
Cash Choice Task
Reward vs. neutral anticipation
Anterior Cingulate cortex
Nucleus Accumbens
B
Hierarchical regression
Caffeinated Soda Intake
Working Memory
Impulsivity
Reward processing
Machine learning approach

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

A. The estimates of coefficients (x axis: coefficient estimates; y axis: predictor). **B.** Representative receiver-operation characteristic (ROC) curve (left) and a distribution of area under the curve (AUC) scores (right) in training and test datasets. **C.** Regions of interest (ROIs) identified as having significant estimates of coefficients during the Emotional N-Back Task (EN-Back). **D.** ROIs identified as having significant estimates of coefficients during the Monetary Incentive Delay (MID) Task. The bar graph at the top of **C** and **D** displays activation pattern of entire four groups (error bars represent ±1 standard error of the mean). The color bar indicates the estimates of coefficients of LASSO regression.

Abbreviations. LASSO, least absolute shrinkage and selection operator; AA, African American; 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; DLPFC, Dorsolateral Prefrontal Cortex; NAc, Nucleus Accumbens; PCC, Posterior Cingulate Cortex; IFG, Inferior Frontal Gyrus; ACC, Anterior Cingulate Cortex.

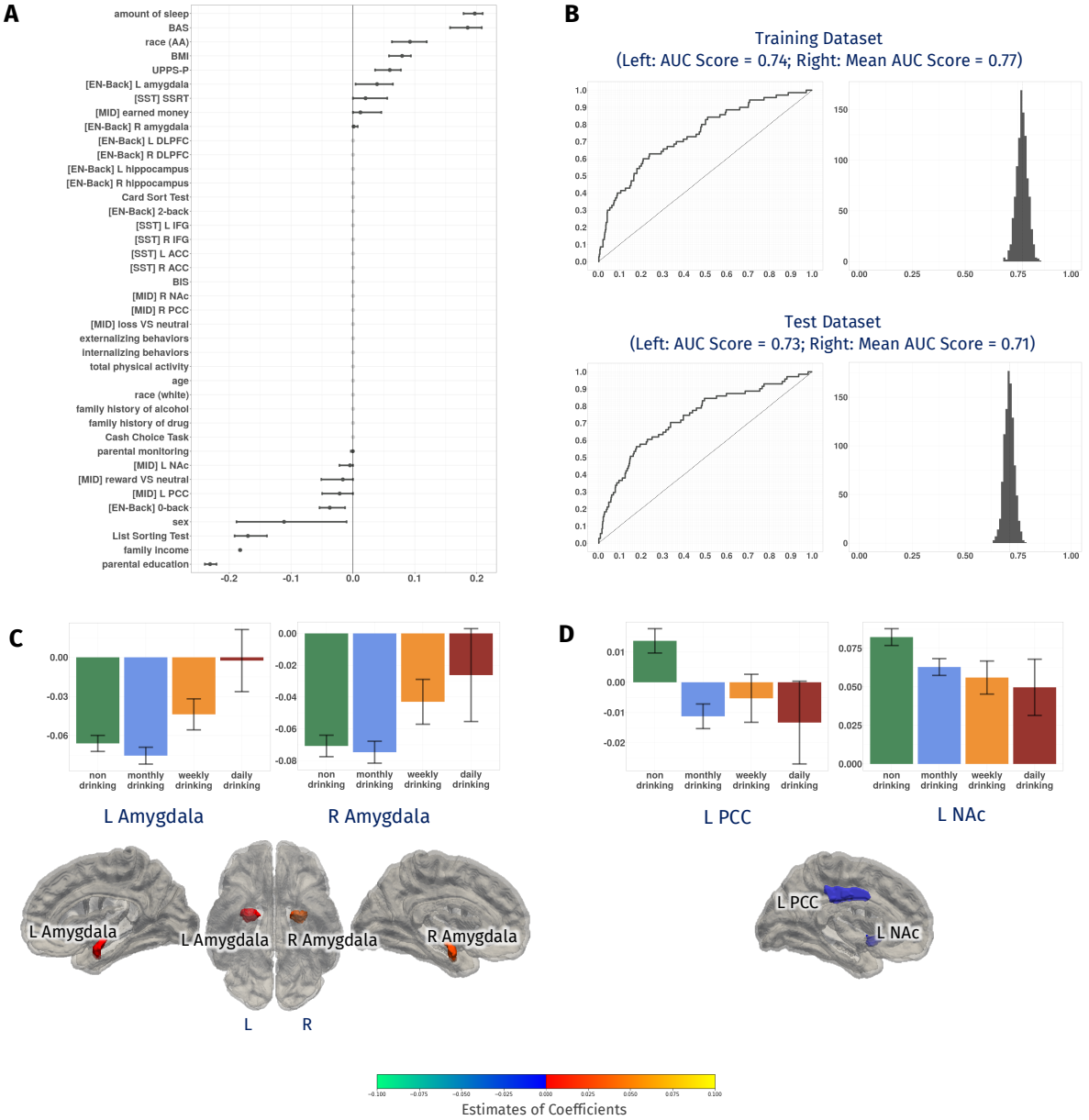

A
amount of sleep
BAS
race (AA)
BMI
UPPS-P
[EN-Back] L amygdala
[SST] SSRT
[MID] earned money
[EN-Back] R amygdala
[EN-Back] L DLPFC
[EN-Back] R DLPFC
[EN-Back] L hippocampus
[EN-Back] R hippocampus
Card Sort Test
[EN-Back] 2-back
[SST] L IFG
[SST] R IFG
[SST] L ACC
[SST] R ACC
BIS
[MID] R NAc
[MID] R PCC
[MID] loss VS neutral
externalizing behaviors
internalizing behaviors
total physical activity
age
race (white)
family history of alcohol
family history of drug
Cash Choice Task
parental monitoring
[MID] L NAc
[MID] reward VS neutral
[MID] L PCC
[EN-Back] 0-back
sex
List Sorting Test
family income
parental education
-0.2
-0.1
0.0
0.1
0.2
B
Training Dataset
(Left: AUC Score = 0.74; Right: Mean AUC Score = 0.77)
Test Dataset
(Left: AUC Score = 0.73; Right: Mean AUC Score = 0.71)
C
non drinking
monthly drinking
weekly drinking
daily drinking
L Amygdala
R Amygdala
D
L PCC
L NAc
L
R
Estimates of Coefficients

Figure 3. Outline of hierarchical regression analysis

Independent variables were added hierarchically: control variables in the first level, sleep deprivation added in the second level, and caffeinated soda intake in the third level. Dependent variables were put into hierarchical model one by one. Therefore, a total of 24 models were tested, including each behavior measure (BIS and BAS each), and left and right regions of interest of fMRI data.

Abbreviations. SES, Socioeconomic status; BMI, body mass index; EN-Back, Emotional N-Back task; SST, Stop Signal Task; SSRT, Stop Signal Reaction Time; UPPS-P, Urgency-Premeditation-Perseverance-Sensation Seeking-Positive Urgency; BIS/BAS, Behavioral Inhibition System/ Behavioral Activation System; MID, Monetary Incentive Delay Task; DLPFC, Dorsolateral Prefrontal Cortex; ACC, Anterior Cingulate Cortex; IFG, Inferior Frontal Gyrus; PCC, Posterior Cingulate Cortex; NAc, Nucleus Accumbens.

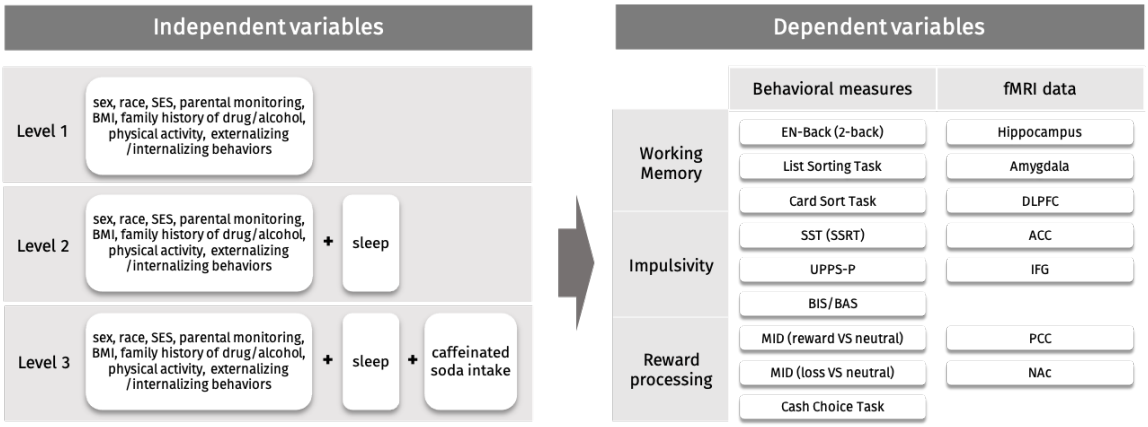
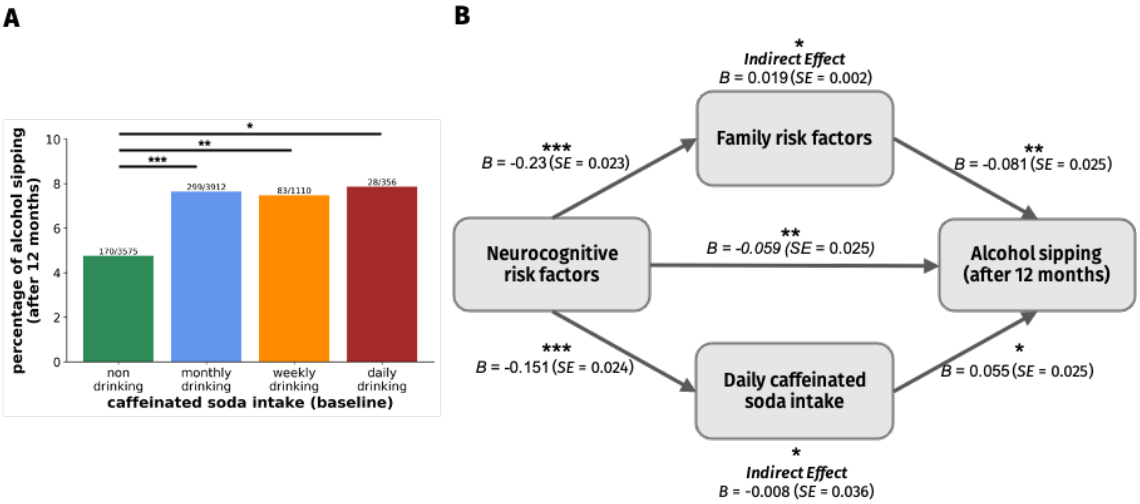


Figure 4. Association between caffeinated soda consumption at baseline and alcohol sipping after 12 months

A. Caffeinated soda intake at baseline predicting alcohol sipping after 12 months. **B.** The best model explaining the relationships between daily caffeinated soda intake and alcohol sipping after 12 months. See **Figure 4-1** and **Table 4-1** in the Supplemental Material for more examples of the tested models.

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



1 **Table 1.** Baseline characteristics of participants

variable	Non-drinking (0 can)	Monthly-drinking (< 1 can /week)	Weekly-drinking (< 7 can / week)	Daily-drinking (≥ 7 can / week)
Sample size	1640	1721	464	141
Soda intake / week	0	0.46 (0.01)***	2.86 (0.06)***	14.92 (1.32)***
demographic variables				
Women, No. (%)	917 (0.56)	820 (0.48)	173 (0.37)	66 (0.47)
Age	9.5 (0.01)	9.55 (0.01)**	9.64 (0.02)***	9.49 (0.04)
Family income	8.06 (0.04)	7.8 (0.05)***	7.07 (0.11)***	6.65 (0.21)***
Parental education	17.4 (0.05)	16.9 (0.06)***	16.19 (0.11)***	15.83 (0.22)***
Parental monitoring	4.47 (0.01)	4.44 (0.01)	4.37 (0.02)***	4.35 (0.05)*
Family history (drug)	0.29 (0.01)	0.3 (0.01)	0.36 (0.02)*	0.34 (0.04)
Family history (alcohol)	0.43 (0.01)	0.48 (0.01)**	0.46 (0.02)	0.42 (0.04)
BMI	17.9 (0.09)	18.5 (0.09)***	19.11 (0.2)***	19.6 (0.45)***
Physical activity	4.20 (0.06)	3.94 (0.06)*	3.52 (0.11)***	3.44 (0.20)**
Sleep deprivation	1.50 (0.02)	1.61 (0.02)***	1.81 (0.04)***	1.93 (0.08)***
Externalizing behaviors	44.01 (0.23)	44.12 (0.23)	46.14 (0.48)***	45.93 (0.91)
Internalizing behaviors	44.61 (0.26)	44.10 (0.25)*	45.84 (0.51)	46.62 (0.93)
Working memory				
Behavioral measures				
List Sorting Test	104.61 (0.34)	103.54 (0.33)	101.59 (0.63)***	97.91 (1.34)***
Card Sort Test	99.88 (0.38)	99.39 (0.37)	95.64 (1.23)*	95.57 (1.15)**
[EN-Back] (2-back)	0.81 (0.002)	0.80 (0.002)	0.80 (0.004)	0.79 (0.007)*
[EN-Back] (0-back)	0.88 (0.002)	0.88 (0.002)	0.87 (0.004)	0.85 (0.008)***
fMRI data				
[EN-Back] Right hippocampus	-0.07 (0.005)	-0.07 (0.005)	-0.06 (0.01)	-0.047 (0.02)
[EN-Back] Left hippocampus	-0.079 (0.005)	-0.082 (0.005)	-0.07 (0.01)	-0.057 (0.018)
[EN-Back] Right DLPFC	0.062 (0.006)	0.059 (0.006)	0.064 (0.012)	0.051 (0.021)
[EN-Back] Left DLPFC	0.042 (0.005)	0.04 (0.006)	0.044 (0.012)	0.031 (0.02)
[EN-Back] Right amygdala	-0.071 (0.007)	-0.075 (0.007)	0.043 (0.014)	-0.026 (0.029)
[EN-Back] Left amygdala	-0.066 (0.006)	-0.075 (0.006)	-0.044 (0.012)	-0.003 (0.024)*

Impulsivity				
Behavioral measures				
UPPS-P	39.70 (0.18)	40.82 (0.18)***	41.56 (0.37)***	41.94 (0.63)**
BIS	9.43 (0.09)	9.53 (0.09)	9.52 (0.17)	9.57 (0.32)
BAS	19.58 (0.16)	20.54 (0.16)***	21.35 (0.31)***	22.53 (0.58)***
[SST] SSRT	299.51 (1.62)	302.29 (1.55)	297.27 (2.87)	308.76 (5.59)
fMRI data				
[SST] Right caudal ACC	0.068 (0.003)	0.073 (0.003)	0.072 (0.007)	0.062 (0.012)
[SST] Left caudal ACC	0.062 (0.003)	0.068 (0.003)	0.07 (0.007)	0.061(0.01)
[SST] Right IFG	0.103 (0.004)	0.109 (0.004)	0.101 (0.007)	0.104 (0.014)
[SST] Left IFG	0.057 (0.003)	0.069 (0.003)*	0.058 (0.006)	0.059 (0.013)
Reward processing				
Behavioral measures				
Cash Choice Task	1.61 (0.01)	1.59 (0.01)	1.61 (0.02)	1.60 (0.04)
[MID] earned money	21.23 (0.30)	22.14 (0.29)*	21.983(0.58)	22.34 (1.11)
[MID] reward vs. neutral	0.12 (0.003)	0.11 (0.003)	0.106 (0.006)	0.09 (0.01)*
[MID] loss vs. neutral	0.095 (0.003)	0.093 (0.003)	0.083 (0.006)	0.071(0.012)*
fMRI data				
[MID] Right PCC	0.024 (0.004)	-8.7e-05 (0.004)***	0.006 (0.008)*	0.004 (0.015)
[MID] Left PCC	0.014 (0.004)	-0.011 (0.004)***	-0.005 (0.008)*	-0.013 (0.014)
[MID] Right nucleus accumbens	0.060 (0.005)	0.05 (0.005)	0.057 (0.01)	0.063 (0.02)
[MID] Left nucleus accumbens	0.082 (0.005)	0.063 (0.005)	0.050 (0.02)	0.044 (0.017)

Note. Data are Mean (Standard Error); *: p<0.05, **: p<0.01; ***: p<0.001 (each soda drinking groups (monthly-drinking, weekly-drinking, daily-drinking) compared with the non-drinking group) *Abbreviations.* BMI, Body Mass Index; EN-Back, Emotional N-Back Task; DLPFC, Dorsal Lateral Prefrontal Cortex; SST, Stop Signal Task; ACC, Anterior Cingulate Cortex; IFG, Inferior Frontal Gyrus; MID, Monetary Incentive Delay Task; [MID] reward vs. neutral, difference in percentage of

correct trials between reward trial and neutral trial; [MID] loss vs. neutral, difference in percentage of correct trials between loss trial and neutral trial; PCC, Posterior Cingulate Cortex.

Table 2. Results of hierarchical regression analysis predicting each neurocognitive risk factor of SUDs

variable	Working Memory		Impulsivity		
	List sorting Test	[EN-Back] L amygdala	SSRT	UPPS-P	BAS
sex	-.051*	-.008	.021	-.125***	-.112***
race (African American)	-.133*	-.018	-.112	-.023	.052
race (others)	.042	-.023	.03	.031	-.038
parental education	.161***	-.081**	-.014	.015	-.028
family income	.024	-.021	.03	-.013	-.055
parental monitoring	.057*	-.042	-.022	-.185***	.055
body mass index (BMI)	-.012	.007	.009	-.029	.01
family history (drug)	.001	-.019	-.046	.022	.04
family history (alcohol)	.009	-.01	.05	-.013	-.04
externalizing behaviors	-.032	.012	.025	.212***	.118***
internalizing behaviors	-.028	-.024	-.077**	-.112***	-.084**
sleep deprivation	-.042	-.023	-.009	.033	.086***
daily caffeinated soda intake	-.221**	.146*	.146*	.160*	.232**

Note. The values are standardized regression coefficients from the third step in the hierarchical analyses among the 24 dependent variables, the five variables were significantly associated with daily consumption of caffeinated soda, even after controlling the controlled variables (eleven variables from the top) and the sleep deprivation. Higher score in the List sorting Test score was associated with lower intake of caffeinated soda, while other four variables (left amygdala activation during the Emotional N-Back Task (EN-Back), stop signal reaction time (SSRT), Urgency-Premeditation-Perseverance-Sensation Seeking-Positive Urgency (UPPS-P), and Behavioral Activation System (BAS) were associated with higher intake of caffeinated soda.

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

Table 3. Results of hierarchical regression analysis predicting alcohol sipping after 12 months

Variables	Model 1	Model 2	Model 3
sex	-.03*	.032*	-.029
race (African American)	-.036	-.038	-.045
race (others)	-.147	-.149	-.137
parental education	.034	.035	-.041*
family income	.079*	.08*	.011*
parental monitoring	.002*	.002	.028
BMI	.005	.005*	.004*
family history (drug)	-.03	-.029	-.03
family history (alcohol)	.341	.34	.346
externalizing behaviors	.025	.024	.02
internalizing behaviors	-.001	-.001	-.001
amount of sleep		.004	.003
daily caffeinated soda intake			.1***

Note. The values are standardized regression coefficients from each step in the hierarchical analyses predicting alcohol sipping after 12 months. Daily consumption of caffeinated soda intake could predict higher alcohol sipping tendency after 12 months even after controlling the controlled variables (eleven variables in Model 1) and the sleep deprivation.

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