

1 **Title:** Daily caffeinated soda intake is associated with impaired working memory and higher
2 impulsivity in children

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1 **Abstract**

2 While the negative impacts of caffeinated soda on children's physical health have been well
3 documented, it remains unexplored if habitual caffeinated soda intake is associated with
4 intellectual capacities in children. Here, we investigated the behavioral and neural correlates of
5 daily consumption of caffeinated soda on neurocognitive functions including working memory,
6 impulsivity, and reward processing. We rigorously tested the link between caffeinated soda intake
7 and the neurocognitive functions by applying machine learning and hierarchical linear regression
8 to a large dataset from the Adolescent Brain Cognitive Development (ABCD) Study ($N=3,966$;
9 age=9-10 years). The results showed that daily consumption of caffeinated soda in children was
10 associated with impaired working memory and higher impulsivity, and increased amygdala
11 activation during the emotional working memory task. The machine learning results also showed
12 hypoactivity in the nucleus accumbens and the posterior cingulate cortex during reward
13 processing. These results findings have significant implications for public health
14 recommendations.

1 **Statement of Relevance**

2 Is caffeinated soda bad for children's brain development? If so, which specific intellectual capacity
3 is affected? It is a question that many parents and caregivers are asking but surprisingly there is
4 no clear guideline. Caffeinated soda is the most preferred route of caffeine intake in childhood
5 and known to have physical side effects on children, but the link between habitual drinking of
6 caffeinated soda in children and intellectual capacities remains largely unknown. Here, by
7 applying machine learning and hierarchical regression approaches to a large dataset, we
8 demonstrate that daily intake of caffeinated soda is associated with neurocognitive deficits
9 including impaired working memory and higher impulsivity. These results have significant
10 implications for public health recommendations.

1 **1. Introduction**

2 One of the impacts of COVID-19 has been a significant increase in the consumption of
3 sugary drinks and snacks (Pietrobelli et al., 2020). In Mexico, which has the world's fourth-highest
4 recorded COVID-19-related death toll (November, 2020), some states have banned selling high-
5 sugar foods and beverages to children and adolescents under 18 years, given that two-thirds of
6 those who died had an underlying medical condition related to obesity (Reiley, 2020). Sugar-
7 sweetened beverages have been referred to as a “bottled poison” by one health official in Mexico
8 (Reiley, 2020), and their excessive consumption is known to increase the risk of obesity (Ludwig,
9 Peterson, & Gortmaker, 2001).

10 The increasing concern about sugary beverages is particularly regarding caffeinated soda
11 that combines two addictive substances, sugar and caffeine, both of which have been found to
12 affect neurocognitive functions and cause physical side effects. Caffeine is known to be addictive
13 (Nehlig, 1999), and multiple diagnoses related to caffeine dependence are included in the
14 Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (APA, 2013), including
15 caffeine use disorder, caffeine intoxication, caffeine-induced anxiety, and caffeine-induced sleep
16 disorders. Some researchers also consider sugar, which activates reward pathways, as highly
17 addictive, much like other addictive substances (Avena, Rada, & Hoebel, 2008; Gearhardt,
18 Corbin, & Brownell, 2008). Indeed, foods with refined carbohydrates such as sugar can trigger
19 addiction-like behaviors, and this observation has fueled the ongoing discussion on “food
20 addiction” (Gearhardt et al., 2008; Gearhardt, Roberto, Seaman, Corbin, & Brownell, 2013). The
21 consequences of excessive consumption of both sugar and caffeine have been well documented
22 (Porciúncula, Sallaberry, Mioranza, Botton, & Rosemberg, 2013), and include negative health
23 outcomes such as obesity and dental caries (Bremer & Lustig, 2012; Ludwig et al., 2001). Animal
24 studies have also shown that excessive sugar intake (Colantuoni et al., 2001) and caffeine
25 consumption (Larson, O'Neill, Palumbo, & Bachtell, 2019; O'Neill et al., 2015) in childhood and
26 adolescence predicted higher future substance use.

27 These negative effects of sugar and caffeine are known to be more severe in children
28 than in adults (Bremer & Lustig, 2012; Temple, 2009), and habitual consumption of caffeinated

1 beverages among children and adolescents has been related to sleep deficits, fatigue,
2 impulsivity, poor concentration, and irritability (Temple, 2009, 2018). A strong association
3 between caffeinated beverages consumption and future substance use is also well documented
4 (Arria et al., 2011; Barrense-Dias, Berchtold, Akre, & Surís, 2016; Kristjansson et al., 2018; Leal
5 & Jackson, 2019; Marmorstein, 2018; Miyake & Marmorstein, 2015). In prospective studies
6 tracking the effects of substance use, the percentage of regular energy drink users who became
7 alcohol or marijuana users after 1-2 years was approximately five times higher than that of non-
8 users (Leal & Jackson, 2019; Marmorstein, 2018; Miyake & Marmorstein, 2015). Others have
9 also shown that coffee or energy drink consumption could significantly predict future substance
10 use, including tobacco and alcohol (Arria et al., 2011; Barrense-Dias et al., 2016; Marmorstein,
11 2018).

12 While the existing literature focused on adolescents who are known to drink even multiple
13 caffeinated beverages including coffee and energy drinks on a daily basis, it remains unknown if
14 caffeinated soda intake in childhood is associated with future substance misuse. However, note
15 that consumption level of coffee and energy drink is low in children, and caffeinated soda is the
16 most preferred and accessible mode of caffeine intake in children (Temple, 2009). Therefore,
17 there is a critical need to investigate the link between caffeinated soda intake during childhood
18 and substance misuse and its vulnerabilities such as associated neurocognitive deficits.

19 Multiple studies have warned that soda consumption in childhood is associated with
20 negative health outcomes and behavior problems (Suglia, Solnick, & Hemenway, 2013; Temple,
21 2009). However, despite the addictive nature of caffeinated soda and its possible negative
22 consequences, the effects of frequent consumption of caffeinated soda on neurocognitive
23 functions remain unexplored. While numerous studies on this topic exist, most have focused on
24 the immediate positive aspects of caffeine administration, mostly in adults (Brunyé, Mahoney,
25 Lieberman, & Taylor, 2010; Koppelstaetter et al., 2008), and few have studied adolescents or
26 children (Graczyk et al., 2018). Also, even though few studies have directly examined the effects
27 of frequent caffeinated soda intake in adolescents and children, these either used only surveys or

1 self-reports, and did not obtain neural data (James, Kristjánsson, & Sigfúsdóttir, 2011; Solnick &
2 Hemenway, 2013; Suglia et al., 2013).

3 In the current study, we examined the relationship between caffeinated soda intake and
4 neurocognitive factors in children. Among the neurocognitive factors related to SUDs, working
5 memory (WM), impulsivity, and reward processing have been the most studied; low WM, high
6 impulsivity, and blunted reward responsiveness processing have been reported as risk factors for
7 SUDs. Previous work has suggested that WM moderates sensation seeking and impulsivity,
8 whereby an impaired WM could lead to maladaptive decision making, such as substance misuse
9 (Bechara & Martin, 2004; Khurana et al., 2013). Low WM and high impulsivity have been strongly
10 associated with future substance misuse, including misuse of marijuana, alcohol, nicotine, and
11 methamphetamine (Ivanov, Schulz, London, & Newcorn, 2009; Khurana et al., 2013; López-
12 Caneda, Holguín, Cadaveira, Corral, & Doallo, 2014). In particular, high impulsivity has been
13 reported to be a causal factor, or even an endophenotype, for SUDs (Dawe & Loxton, 2004;
14 Ersche, Turton, Pradhan, Bullmore, & Robbins, 2010), and accumulating evidence suggests that
15 emotional dysregulation is a common feature of those with SUDs (Clark, Thatcher, & Tapert,
16 2008; Fox, Hong, & Sinha, 2008). The role of reward processing, however, remains unclear:
17 some studies have reported that individuals with SUDs display hyperresponsiveness toward
18 reward, while others have reported hypo-responsiveness (Balodis & Potenza, 2015; Madden,
19 Petry, Badger, & Bickel, 1997). Hypersensitivity toward reward induces sensation-seeking
20 behavior, which could lead to substance misuse (Ersche et al., 2010; Volkow et al., 2010), while
21 blunted reward sensitivity might motivate the use of substances to receive a satisfactory reward
22 (Blum et al., 2000; Goldstein & Volkow, 2002). Here, we investigated the relationship between
23 daily intake of caffeinated soda and three main cognitive functions related to SUDs: WM,
24 impulsivity, and reward processing. From the baseline data of the Adolescent Brain Cognitive
25 Development (ABCD) study, we used psychological, behavioral, and neurological factors related
26 to the three cognitive functions (**Fig. 1a**). We employed both univariate (hierarchical regression)
27 and multivariate (machine learning) approaches to rigorously investigate the associations

1 between daily caffeinated soda intake and neurocognitive measures. **Fig. 1b** shows the two
2 different analytical methods that have different predictive directionalities.

3

4 **2. Method**

5 **2.1. Participants**

6 The ABCD study has collected data from 11,875 children (data were downloaded in
7 2019). The participants were recruited through school systems from 21 different sites in the US.
8 During sampling and recruitment, age, sex, race, socioeconomic status (SES), and urbanicity
9 were considered to reflect the socio-demographics of the US. More information about the
10 recruitment and study design is available in Garavan et al. (2018). Further details of the
11 demographic, physical, and mental health assessments are described in Barch et al. (2018).

12 Among the 11,875 children enrolled in the study, we included data from 3,966 children
13 who were aged 9–10 years at the first-year data collection and who had no missing data in the
14 following curated datasets: task-based functional magnetic resonance imaging (fMRI) data for
15 three tasks (Emotional N-Back (EN-Back) Task (Cohen et al., 2015), Stop Signal Task (SST)
16 (Logan, Cowan, & Davis, 1984), and Monetary Incentive Delay (MID) Task (Knutson, Westdorp,
17 Kaiser, & Hommer, 2000)), behavioral data obtained from cognitive tasks (the List Sorting Test,
18 Card Sort Test, and Cash Choice Task) and from psychological surveys, and demographic data.
19 In addition, the task-based fMRI data were collected from three different MRI scanners (Siemens,
20 General Electric, and Philips); data from the Philips scanner were incorrectly processed in the
21 curated dataset (<https://github.com/ABCD-STUDY/fMRI-cleanup>), and were therefore excluded
22 from the analysis (n=527).

23 The participants were divided into four groups based on their caffeinated soda consumption over
24 the last 6 months, which was assessed using the participants' self-report in response to the
25 question, "Typically, how many drinks of the following beverages have you had per week in the
26 past 6 months? – soda with caffeine (Mountain Dew, Jolt, Coke, Pepsi, Dr. Pepper, Barq's root
27 beer)". The non-drinking group reported 0 cans per week (n=1640), the monthly-drinking group
28 reported <1 can per week (n=1721), the weekly-drinking group reported 1–7 cans per week

1 (n=464), and the daily-drinking group reported ≥ 7 cans per week (n=141). These criteria for group
2 allocation were defined by referring to the population-based cohort study of Mullee et al. (2019),
3 which examined the association between soft drink consumption and mortality in adults (<1 glass
4 per month (50.1%), 1–4 glasses per month (14.5%), 1–6 glasses per week (26.7%), 1–2 glasses
5 per day (0.05%), and 2 glasses per day (0.04%)). Given the difference of populations between
6 our study (children; mean age=9.5; SD=0.5 and Mullee et al. (adults; mean age=50.8, SD=9.8),
7 we adjusted the grouping criteria to approximately match the percentage of participants in the
8 least and most drinking groups of Mullee et al. (2019) Specifically, we modified the criteria of the
9 least drinking group from “<1 glass per month” to “no cans of soda” (non-drinking group), and set
10 the criterion of the most drinking group to “more than 1 can per day” (daily-drinking group).

11

12 **2.2 Measures**

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

16

17 *2.2.1. Working Memory*

18 To obtain behavioral measures of WM, we used the List Sorting Working Memory Test
19 (List Sorting Test) and Dimensional Change Card Sort Test (Card sort Test) from the NIH
20 Toolbox (Tulsky et al., 2013), and the EN-Back Task. The List Sorting Test requires participants
21 to sort and sequence visual and auditory stimuli. For the Card Sort Test, participants are asked to
22 sort cards according to either color (when the target card has a contour) or shape (when the card
23 without a contour is shown).

24 The EN-Back Task (Cohen et al., 2015), which measures WM and emotion regulation,
25 was conducted inside the MRI scanner. The task consists of two different blocks: the 0-back
26 block requires participants to respond when the current stimulus is the same as a target, and the
27 2-back block requires participants to respond when the current stimulus is the same as the one
28 shown two trials before. Due to the difference in WM load between the two blocks, accuracy

1 during the 2-back block is commonly used as a behavioral measure of WM, and the 2-back block
2 vs. 0-back block contrast is commonly used to examine the neural correlates of WM (Casey et al.,
3 2018). Unlike the traditional N-Back Task, in which the stimuli are numbers, the EN-Back Task
4 displays emotional (happy, fearful, and neutral) face stimuli and place (non-emotional) stimuli.
5 Therefore, the task also allows us to test the effect of emotional processing in WM. The ROIs of
6 the EN-Back Task include the amygdala, a region that is well-known for emotional processing
7 and has also been linked with working memory function (Banks, Eddy, Angstadt, Nathan, & Phan,
8 2007), as well as the hippocampus and dorsolateral prefrontal cortex (DLPFC), which are critical
9 for WM (Barbey, Koenigs, & Grafman, 2013). See Casey et al. (2018) for more details about the
10 task.

11

12 *2.2.2. Impulsivity*

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

23 To identify the neural correlates of impulsivity, participants completed the SST (Logan et
24 al., 1984) inside the scanner. The SST measures impulsivity related to impulse control or
25 response inhibition when performing an action. The SST requires participants to withhold motor
26 responses to a “Go” stimulus when a “Stop” signal is unpredictably presented after a short delay.
27 The delay between the “Go” stimulus presentation and the “Stop” signal presentation is termed
28 the stop signal delay (SSD). The SSD was initially set to 50ms. Following a successful inhibition

1 or an unsuccessful inhibition, the SSD was increased or decreased by 50ms to make the task
2 easier or more difficult, respectively. Each run contained 180 trials, and each trial began with the
3 presentation of the “Go” cue. Participants were instructed to respond to the cue as quickly and
4 accurately as possible. Thirty trials (16.67%) were “Stop” trials in which the “Stop” Signal was
5 presented, which was an upward arrow presented for 300 ms. Stop signal reaction time (SSRT)
6 was used as a behavioral measure of impulsivity, and was calculated by subtracting the mean
7 SSD from the mean “Go” response time (Logan et al., 1984; Schachar & Logan, 1990); a shorter
8 SSRT means better response inhibition. For the fMRI analysis, a “correct stop vs. correct go”
9 contrast was used, and the caudal anterior cingulate cortex (ACC) and the inferior frontal gyrus
10 (IFG) were selected as regions of interest (ROIs); both areas have been associated with
11 impulsivity and impulse control (Jacobson, Javitt, & Lavidor, 2011; Stadler et al., 2007). More
12 information about the SST is available in Casey et al. (2018).

13

14 *2.2.3. Reward Processing*

15 Reward processing is closely linked to impulsivity, in that impulsive people often show
16 reward-seeking behavior (Zuckerman, 2001). While the previous literature suggests that people
17 with SUDs have altered reward processing relative to the healthy population, previous findings
18 have not been consistent; some studies have reported a hypersensitivity and others a hypo-
19 responsiveness toward monetary rewards among people with SUDs (Balodis & Potenza, 2015).
20 Keeping this in mind, we tested the inconsistent findings with the ABCD data. We used the Cash
21 Choice Task (Luciana et al., 2018), which measures delayed gratification by assessing impulsivity
22 in receiving a monetary reward using the following single-item question: “Let’s pretend a kind
23 person wanted to give you some money. Would you rather have \$75 in three days or \$115 in 3
24 months?” The former choice reflects poor delayed gratification, with a higher delay discounting
25 rate, while the latter choice implies a smaller delay discounting rate. Responses were scored as 1
26 (\$75 in three days) or 2 (\$115 in 3 months).

27 The MID Task (Knutson et al., 2000) is widely used to measure the neural mechanisms of
28 reward processing, such as the anticipation of monetary rewards and losses. Each trial of the

1 MID Task begins with an incentive cue of five possible trial types (Win \$20, Win \$5, Lose \$0.2,
2 Lose \$5, and \$0 – no money at stake), a delay (1500 ms~4000 ms), a target during which the
3 participant chooses to either win money or avoid losing money, and feedback on whether the
4 participant won or lost money. Each participant performed 40 reward anticipation, 40 loss
5 anticipation, and 20 no money anticipation trials, resulting in a total of 100 trials. The differences
6 in accuracy between reward vs. neutral trials, and loss vs. neutral trials indicate motivation to win
7 reward or avoid loss. The contrast of “Reward vs. Neutral” at the cue onset, which reflects reward
8 anticipation, was used for fMRI analysis, and the ROIs were the nucleus accumbens (Nac) and
9 the posterior cingulate cortex (PCC), which are known to play a key role in reward processing,
10 particularly in reward anticipation (Day & Carelli, 2007). See Casey et al. (2018) for more details
11 about the MID Task.

12

13 *2.2.4. Control Variables*

14 We also collected data on demographic variables, family characteristics, physical health
15 related measures, and externalizing and internalizing behaviors. Demographic variables included
16 race, sex, and age of the participants. Family characteristics included any family history of
17 substance use, parental monitoring, and SES of the family. Family history of substance use was
18 measured using a parental yes/no response to the following question: “Has any blood relative of
19 your child ever had any problems due to drugs, such as: Marital separation or divorce; Fired from
20 work; Arrests or DUI (Driving Under Influence); Adverse health effects; In a drug treatment
21 program; Suspended or expelled from school two or more times; Isolated oneself from the family,
22 caused arguments, or often intoxicated.” To measure the family history of alcohol use, the same
23 question was asked, except that “drug” was replaced with “alcohol”.

24 Parental monitoring was measured using the ABCD Parental Monitoring Survey, in which
25 children were asked to respond to five questions (“How often do your parents/guardians know
26 where you are?”; “How often do your parents know who you are with, or when you are not at
27 school and away from home?”; “If you are at home when your parents or guardians are not, how
28 often do you know how to get in touch with them?”; “How often do you talk to your parent or

1 guardian about your plans for the coming day, such as your plans about what will happen at
2 school or what you are going to do with friends?"; "In an average week, how many times do you
3 eat dinner with your parents/guardians?"). Responses ranged from 1 (Never) to 5 (Always or
4 Almost Always), and the mean of all five responses was used for the analysis. The SES
5 measures the total combined family income and parents' highest education level. Parents'
6 education was calculated as the mean of both parents, or of the responding parent only in the
7 case of single parents.

8 Physical measures included sleep quality, physical activity, and body mass index (BMI).
9 The amount of sleep was measured using the ABCD Parent Sleep Disturbance Scale for
10 Children, for which parents are asked to respond to the question, "How many hours of sleep does
11 your child get on most nights?" (1=9–11 hours, 2=8–9 hours, 3=7–8 hours, 4=5–7 hours, 5=less
12 than 5 hours). Physical activity was measured using the ABCD Parent Sports and Activities
13 Involvement Questionnaire, which assesses whether the child has ever continuously participated
14 in specific sports and activities, such as football, field hockey, climbing, or basketball, for 4
15 months or more. The number of "yes" responses to 29 questions was summed for the analysis.
16 BMI was calculated according to the children's body weight and height.

17 Externalizing and internalizing behaviors were measured using the parental report of the
18 Child Behavior Checklist (Achenbach, 2009), which comprises 113 items about child behavior
19 over the past six months. Internalizing and externalizing scores are measured based on the
20 following syndrome scores: anxious/depressed, withdrawn/depressed, somatic complains, social
21 problems, though problems, rule-breaking behavior, and aggressive behavior (Thompson et al.,
22 2018).

23

24 **2.3. MRI Protocol**

25 Imaging-derived phenotype scores provided by the ABCD study were used. Data
26 acquisition protocol was matched for the three 3T scanners used (Siemens Prisma, General
27 Electric 750, and Philips). We analyzed beta weights within each ROI for the 2-back vs. 0-back
28 contrast in the EN-Back Task, the correct stop vs. correct go contrast in the SST, and the reward

1 vs. neutral anticipation contrast in the MID Task. More details about fMRI imaging protocols such
2 as scanning parameters in the ABCD study are reported by Casey et al. (2018).

3

4 **2.4. Analysis**

5 First, we conducted a hierarchical regression analysis to identify whether caffeinated soda
6 intake influenced WM, impulsivity, and reward processing while controlling for confounding
7 demographic variables. Next, we used a machine learning algorithm called the least absolute
8 shrinkage and selection operator (LASSO) regression (Tibshirani, 1996) to identify multivariate
9 predictors for caffeinated soda intake.

10

11 *2.4.1. Hierarchical Regression*

12 Hierarchical regression analysis was performed to test whether caffeinated soda intake
13 was a significant predictor of each of the three cognitive factors. Each measure was set as the
14 dependent variable respectively, including the brain activation of each ROI (**Fig. 2**). The main
15 predictor of interest was the caffeinated soda intake group; given that the primary interest was to
16 identify the potential risk of daily or heavy soda-drinking behavior, we focused on the comparison
17 between daily-drinking and non-drinking groups. To ensure that the caffeinated soda intake
18 accounted for more variance than did the demographic and confounding variables, we performed
19 a hierarchical linear regression analysis using the 'lm' function in R. At the first level, predictors
20 only included the control variables, including sex, age, race, family income, parental education,
21 physical activity, parental monitoring, family history of drug and alcohol abuse, and externalizing
22 and internalizing behaviors. At the second level, we included the amount of sleep as an additional
23 predictor, which is strongly linked to caffeine intake (Roehrs & Roth, 2008). Finally, at the third
24 level, caffeinated soda intake group (non-drinking vs daily-drinking group) was added as a
25 predictor to examine the effect of daily consumption of caffeinated soda. To conclude that
26 caffeinated soda intake is responsible for group differences in each cognitive factor, two
27 conditions should be satisfied. First, we conducted an ANOVA between the third-level analysis
28 and the other two lower-level analyses; the third level should show a higher significance than the

1 previous levels. Also, the categorical caffeinated soda intake regressor should be statistically
2 significant ($p < 0.05$) in the third-level analysis. We tested if these conditions were satisfied to
3 determine whether caffeinated soda intake was a significant predictor of the dependent variable
4 in question.

5

6 *2.4.2. Machine Learning (LASSO Regression)*

7 The goal of LASSO regression analysis was to identify significant predictors that can
8 classify the daily-drinking group from the non-drinking group. Caffeinated soda intake was a
9 dependent variable, and all the neurocognitive measures related to WM, impulsivity, and reward
10 processing and all the control variables were predictors, which is the opposite of the hierarchical
11 regression analysis. The results of the multiple metrics used to measure each cognitive factor
12 (e.g., the EN-Back Task, List Sorting Test, and Card Sort Test for WM) are often moderately
13 correlated with one another. Therefore, to capture the multivariate pattern of predictors and select
14 only important variables, we used a penalized regression algorithm called LASSO regression.

15 LASSO regression is a penalized least squares method and performs automatic variable
16 selection by shrinking coefficients of unimportant variables to zero (Tibshirani, 1996, 2011). The
17 dependent variable was categorical caffeinated soda intake, which was coded as “0” for the non-
18 drinking group and “1” for the daily-drinking group. Forty candidate predictors included every
19 measure for the three cognitive factors as well as other control variables (y axis of **Fig. 3a**). We
20 used an R package called “easym1”, a toolkit for easily building and evaluating machine learning
21 models using the glmnet package (Friedman, Hastie, & Tibshirani, 2010) for LASSO regression
22 and several other machine learning algorithms (<https://github.com/CCS-Lab/easym1>) (Ahn,
23 Hendricks, & Haines, 2017). The mixing parameter alpha was set to 0 to conduct the LASSO (0
24 for LASSO, 1 for ridge, and a value between 0 and 1 for elastic net). We trained the model using
25 k-fold cross validation ($k=10$) within the training set, and this generated estimated coefficient 100
26 times for a particular train-test split, whereby we calculated the mean and standard deviation of
27 the estimated coefficients. By replicating predictions many times for a particular train-test split,
28 averaging the predictions across 10 iterations and using 1000 divisions of train-test splits, we

1 were able to avoid intrinsic random errors (see Ahn et al. (2017) for more details). Furthermore,
2 we also tested the elastic net by setting alpha to a value between 0 and 1, given that previous
3 results have revealed that the elastic net often performs better for highly correlated predictors
4 than for LASSO regression (Zou & Hastie, 2005). There were no significant differences between
5 the LASSO and elastic net results, so we only report the LASSO results.

6

7 *2.4.3. Additional Analyses*

8 To ensure that our results would be robust across both continuous caffeinated soda
9 intake data and categorical caffeinated soda intake data, we also analyzed continuous data
10 additionally. With this approach, we were able to use data from all 3,996 participants instead of
11 the reduced dataset only (n=2071; the non-drinking and daily-drinking groups). For the
12 hierarchical (Bayesian) regression analysis with the continuous soda intake data, we used the R
13 package ‘brms’ (Bürkner, 2017). In this analysis, all variables were identical to those used in the
14 hierarchical regression analysis, except that the main predictor was the continuous soda intake
15 data, and the sample size was larger. To conclude that variables and/or caffeinated soda intake
16 were significantly associated with each dependent variable (each measure of WM, impulsivity,
17 and reward processing; **Fig. 2**), the 95% Bayesian credibility should not contain zero, and the
18 model with the third-level should have the lowest (i.e., the best) Leave One Out Cross-Validation
19 value. For the LASSO regression with the continuous caffeinated soda intake data, because the
20 distribution of the caffeinated soda intake data was highly skewed (mean=1.063, SD=4.091,
21 min=0, max=112), we used the ‘brms’ package in R and the zero-inflated negative binomial
22 distribution for the dependent variable. With family set to zero inflated negative binomial
23 distribution and LASSO regression for prior, we ran 4,000 iterations per chain using four chains.

24

25 **3. Results**

26 **3.1. Participant Characteristics**

27 We examined the pattern of differences in each measure among the four groups using
28 an analysis of variance (ANOVA) and post-hoc pairwise comparison (see the **Supplemental**

1 **Material** for additional information). ANOVA revealed a significant main effect of group on soda
2 intake per week ($F(3, 3962)=1161, p<0.001$), and all demographic factors. See **Table S1 in the**
3 **Supplemental Material** for more details.

4

5 **3.2. A hierarchical regression approach: Is daily caffeinated soda intake a predictor for** 6 **neurocognitive measures?**

7 We performed hierarchical regression analysis to test whether daily caffeinated soda
8 intake was a significant predictor of each measure of WM, impulsivity, and reward processing,
9 including the brain activation of each ROI (**Fig. 2**) while controlling for confounding demographic
10 variables (see **Methods**). Specifically, we examined whether caffeinated soda intake accounted
11 for additional variance than did the demographic and confounding variables. **Table 1** shows the
12 results of the hierarchical regression analysis using the binary caffeinated soda intake (whether
13 the subjects are daily-drinkers or non-drinkers). Daily consumption of caffeinated soda was
14 negatively associated with the List Sorting Test score, and it showed a positive association with
15 the trait impulsivity scores of the UPPS-P, the BIS/BAS score, and SSRT. Also, the left amygdala
16 showed hyperactivation during the EN-Back Task (2-back vs. 0-back) in the daily-drinking group;
17 although the effect size is small, activation of the left amygdala was negatively correlated with
18 WM capacity, measured by 2-back performance ($r(3964)=-0.03, p=0.027, 95\%$ confidence
19 interval (CI)=[-0.06, -0.0004]) and by the List Sorting Test score ($r(3964)=-0.04, p=0.003, 95\%$
20 CI=[-0.07, -0.016]).

21

22 **3.3. A machine learning approach: Which variables are predictors for daily caffeinated** 23 **soda intake?**

24 LASSO regression (Tibshirani, 1996, 2011) was performed to identify significant
25 predictors of daily caffeinated soda intake. LASSO offers automatic variable selection, which
26 increases the interpretability of the findings especially when some of the variables are
27 significantly correlated with each other. **Fig. 3a** shows the multivariate profiles classifying the
28 daily-drinking group compared with the non-drinking group identified using LASSO regression.

1 Low parental education was the strongest predictor of daily consumption, along with a small
2 amount of sleep and low family income. Being male, African American, and/or with a high BMI
3 also strongly predicted allocation to the daily-drinking group.

4 Among the risk factors of SUDs, high impulsivity as measured with the BAS was most
5 predictive of daily caffeinated soda intake. A higher SSRT, which indicates delayed response
6 inhibition, along with a higher UPPS-P score, was also related to the daily intake. Among the WM
7 measures, poor performance in the List Sorting Test and 0-back performance during the EN-Back
8 Task predicted daily intake of caffeinated soda. In addition, bilateral amygdala activation during
9 the EN-Back Task (2-back vs. 0-back) also predicted daily caffeinated soda intake (**Fig. 3c**). For
10 reward processing, the daily-drinking group earned more money in total and had smaller
11 accuracy difference between reward trials and neutral trials in the MID Task, implying reduced
12 motivation to achieve a reward. Also, hypoactivity in the left PCC and left NAc during the MID
13 Task (reward vs. neutral anticipation) predicted the membership of the daily-drinking group (**Fig.**
14 **3d**); only the left PCC was negatively correlated with the accuracy difference between reward vs.
15 neutral trials (left PCC: $r(3964)=-0.03$, $p<0.05$, 95% CI=[-0.06, 0]; left NAc: $r(3964)=0.008$, $p=0.6$,
16 95% CI=[-0.02, 0.039]). These results suggest that in line with the results of hierarchical linear
17 regression, low WM and high impulsivity are significantly associated with daily caffeinated soda
18 consumption. In addition, we found that the indifference toward reward during the MID Task, and
19 some other demographic factors (low SES, less sleep, being male, being African American, and
20 high BMI) could also classify the daily-drinking group from the non-drinking group. **Fig. 3b** shows
21 the receiver-operation characteristic (ROC) curve and its mean area under the curve (AUC) for
22 the classification of daily-drinking and no-drinking groups. The mean AUC was 0.77 and 0.71 for
23 the training and test sets.

24

25 **3.4. Additional Analyses: Using the continuous measure of caffeinated soda intake**

26 We have so far compared daily-drinking and non-drinking groups. In addition, we have
27 tested the robustness of the results by using the continuous measure of caffeinated soda intake
28 in all 3,996 participants (see **Methods**).

1 For the hierarchical regression, we found the consistent results when using categorical
2 and continuous measures; with the continuous measure of caffeinated soda intake, higher
3 caffeinated soda intake was again associated with lower WM and higher impulsivity. While
4 caffeinated soda consumption was consistently associated with the List Sorting Test score (beta
5 estimate=-.152, SE=.052, 95% confidence interval (CI)=[-.255, -.051]), the only impulsivity-related
6 measure that was well predicted by caffeinated soda intake was higher UPPS-P score (beta
7 estimate=.055, SE=.028, 95% CI=[.002, .109]). In addition, differences in performance between
8 loss and neutral conditions in the MID Task (beta estimate=-.001, SE=.001, 95% CI=[-.002, 0])
9 were associated with continuous caffeinated soda consumption. However, no fMRI results were
10 significantly associated with caffeinated soda intake when we used the continuous measure of
11 caffeinated soda intake.

12 For the LASSO regression, the List Sorting Test score in the WM measures and higher
13 UPPS-P score and BAS score in the impulsivity measures predicted larger amount of caffeinated
14 soda intake. Higher caffeinated soda consumption was well predicted by poor WM, especially low
15 List Sorting Test scores (beta estimate=-.007, SE=.003, 95% CI=[-.013, -.002]), and higher
16 impulsivity scores of the UPPS-P (beta estimate=.014, SE=.005, 95% CI=[.004, .024]) and BAS
17 (beta estimate=.032, SE=.012, 95% CI=[.009, .055]). Other demographic predictors were being
18 male (beta estimate=-.192, SE=.075, 95% CI=[-.337, -.041]), having a low SES (parental income:
19 beta estimate=-.059, SE=.023, 95% CI=[-.106, -.013]; parental education: beta estimate=-.086,
20 SE=.020, 95% CI=[-.124, -.047]), lower amount of sleep (beta estimate=.129, SE=.053, 95%
21 CI=[.028, .234]), less parental monitoring (beta estimate=-.156, SE=.080, 2.5% 95% CI=[-.315,
22 -.011]), and higher externalizing behaviors (beta estimate=.014, SE=.004, 95% CI=[.006, .023]).

23

24 **4. Discussion**

25 The present results demonstrated that daily caffeinated soda consumption in childhood is
26 associated with well-known neurocognitive risk factors of SUDs, including low WM and high
27 impulsivity. For robustness, we utilized multiple analytic approaches with two analytical methods
28 (hierarchical regression and LASSO regression; **Fig. 1b**), and two different types of independent

1 variables (categorical and continuous caffeinated soda consumption). Low WM performance (List
2 Sorting Test score) and high impulsivity scores (high UPPS-P and BAS) were consistently
3 associated with greater caffeinated soda consumption across all different approaches.

4 fMRI findings in our study are also consistent with existing literature. In the hierarchical
5 regression using categorical soda consumption, we showed hyperactivity of the amygdala during
6 the EN-Back Task in children with daily caffeinated soda consumption, and we found greater
7 behavioral WM impairments during the task in the daily-drinking group than in the non-drinking
8 group. These results are consistent with the developmental mismatch hypothesis, which refers to
9 that subcortical structures involved in affect and reward processing develop earlier than prefrontal
10 structures involved in the top-down regulation of behavior in children and adolescents (Mills,
11 Goddings, Clasen, Giedd, & Blakemore, 2014; Somerville, Hare, & Casey, 2010). Note the
12 negative correlation between the left amygdala activation and WM performance, and the previous
13 literature that cognitive control during the EN-Back Task is related to WM capacity in the
14 prefrontal cortex and simultaneous emotional regulation in the limbic system (Casey et al., 2018;
15 Gee et al., 2013), it is possible that the hyperactivation of the amygdala observed in daily
16 caffeinated soda drinkers was due to the unsuccessful suppression of emotional processes
17 during WM processing.

18 In this study, we revealed significant relationships between daily consumption of
19 caffeinated soda in childhood and well-known risk factors of SUDs, which may have important
20 implications. Previous studies investigating general caffeine consumption or the intake of typical
21 caffeinated beverages like energy drinks have suggested that frequent intake of caffeine in
22 adolescence is related to later substance use (Barrense-Dias et al., 2016; Leal & Jackson, 2019).
23 However, since adolescents are already at a high risk of initiating the use of addictive
24 substances, identifying risk factors during childhood (before adolescence) is critically for the early
25 intervention and prevention. Thus, our study demonstrated the link between daily exposure to
26 caffeinated soda during childhood and neurocognitive risk factors of SUDs.

27 Our study has several limitations. First, follow-up analyses are required before clarifying
28 the causal relationship between cognitive deficits and daily caffeinated soda intake, since our

1 results are correlational. Future work using the longitudinal 10-year follow-up data of the ABCD
2 study should examine whether caffeinated soda consumption affects the cognitive functioning
3 later or whether pre-existing traits lead to excessive caffeinated soda consumption. Second, due
4 to the processing issue regarding the Philips scanner, we could only analyze data from 3,996 out
5 of 4,493 participants (those who had no missing data). A future study including the excluded data
6 will allow us to validate our findings. Third, because we used an ROI-based approach to analyze
7 neuroimaging data, we could not perform functional connectivity analyses or multivoxel pattern
8 analysis, which might provide additional valuable insights regarding the effects of daily
9 caffeinated soda intake.

10 We also found some discrepancies in the results across data types. The number of
11 measures significantly associated with daily caffeinated soda intake and the statistical power of
12 the results were greater with categorical caffeinated soda intake data than with continuous
13 caffeinated soda intake; this could be because the categorical data consisted of two extreme
14 groups: the daily-drinking and non-drinking groups. While our primary interest was to test whether
15 the daily consumption of caffeinated soda is associated with neurocognitive factors, we also
16 investigated whether our findings could be extended to continuous caffeinated soda drinking data.
17 Supporting our main findings with categorical caffeinated soda intake data, continuous
18 caffeinated soda intake was also related to poor WM and high impulsivity, but there was a lack of
19 neuroimaging support for these findings. While further investigations are needed, a possible
20 explanation for the inconsistency of neural correlates is that even a small increase in the intake of
21 caffeinated soda might be associated with behavioral discrepancies relative to non-drinkers, while
22 it may not significantly affect children's brain function or we failed to detect neural correlates with
23 fMRI due to insufficient statistical power. This idea could be tested using the future ABCD dataset
24 since caffeinated soda drinking behavior is likely to increase as the children grow up and its
25 impacts are cumulative; furthermore, drinking behavior might either be affected by neurocognitive
26 differences or might magnify these differences.

27 In conclusion, our results revealed the potential risks of caffeinated soda consumption in
28 children by investigating the associations between daily caffeinated soda consumption and SUD

1 risk factors in a large dataset of the ABCD study. While previous research regarding the side
2 effects of caffeinated soda has been mostly limited to physical negative consequences, the
3 present results strongly suggest that daily caffeinated soda drinking in children is also associated
4 with alterations in neurocognitive functions. Note that there is no consensus on safe dose of
5 caffeinated soda for children and it is possible that certain children are at higher risk for adverse
6 events from habitual caffeinated soda intake. Our study further suggests that there is a strong
7 need to develop evidence-based recommendations on caffeinated soda (Temple, 2018). Further
8 investigation of causal relationships and neuro-developmental evidence are needed to determine
9 whether caffeinated soda is indeed a “bottled poison”, and whether it induces neurocognitive
10 impairments in children.

11

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4

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11

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Figures and Tables

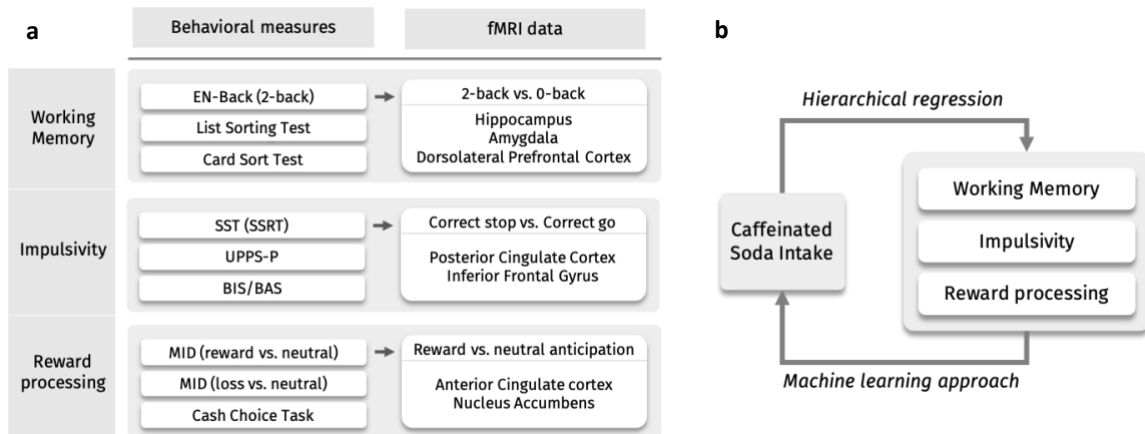


Fig. 1. An overview of the study design

The schematic (a) shows the variables used to measure three main cognitive functions: Working memory, impulsivity, and reward processing. Working Memory was measured using the performance of 2-back in the Emotional N-Back Task (EN-Back), List Sorting Test, and Card Sort Test, while EN-Back was performed during the functional magnetic resonance imaging (fMRI). The fMRI data was analyzed based on the contrast of 2-back vs. 0-back, and the regions of interest (ROIs) were hippocampus, amygdala, and dorsolateral prefrontal cortex. Impulsivity was measured by stop signal reaction time (SSRT) during the stop signal task (SST), Urgency-Premeditation-Perseverance-Sensation Seeking-Positive Urgency (UPPS-P), and Behavioral Inhibition System/ Behavioral Activation System (BIS/BAS), while SST was performed during the fMRI. The fMRI data was analyzed based on the contrast of correct stop vs. correct go, and the ROIs were posterior cingulate cortex and inferior frontal gyrus. Reward processing was measured by comparing the success rate of reward vs. neutral and loss vs. neutral during the Monetary Incentive Delay (MID) Task and cash choice task. The fMRI data was analyzed based on the contrast of reward anticipation vs. neutral anticipation, and the ROIs were anterior cingulate cortex and nucleus accumbens. The diagram (b) describes two different analytic methods. 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.

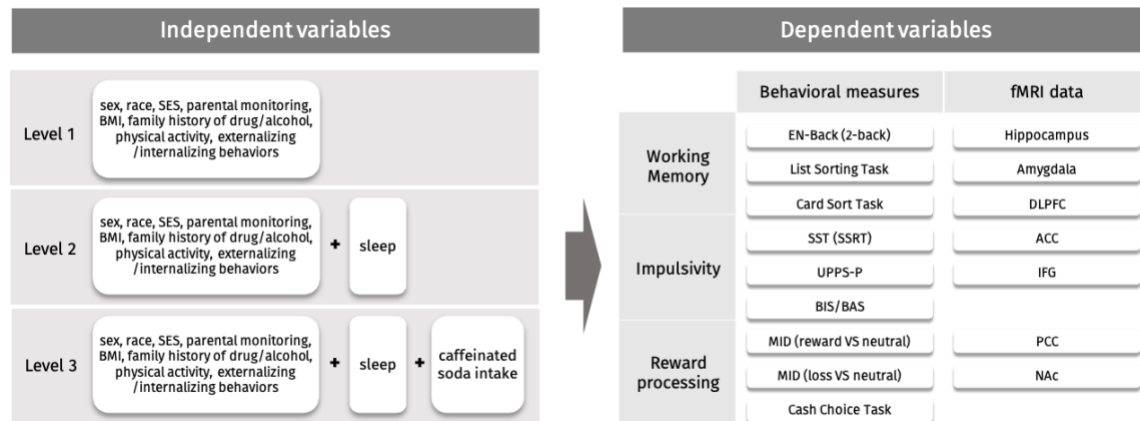


Fig. 2. Outline of hierarchical regression analysis

Independent variables were added hierarchically, control variables in the first level, sleep deficit 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.

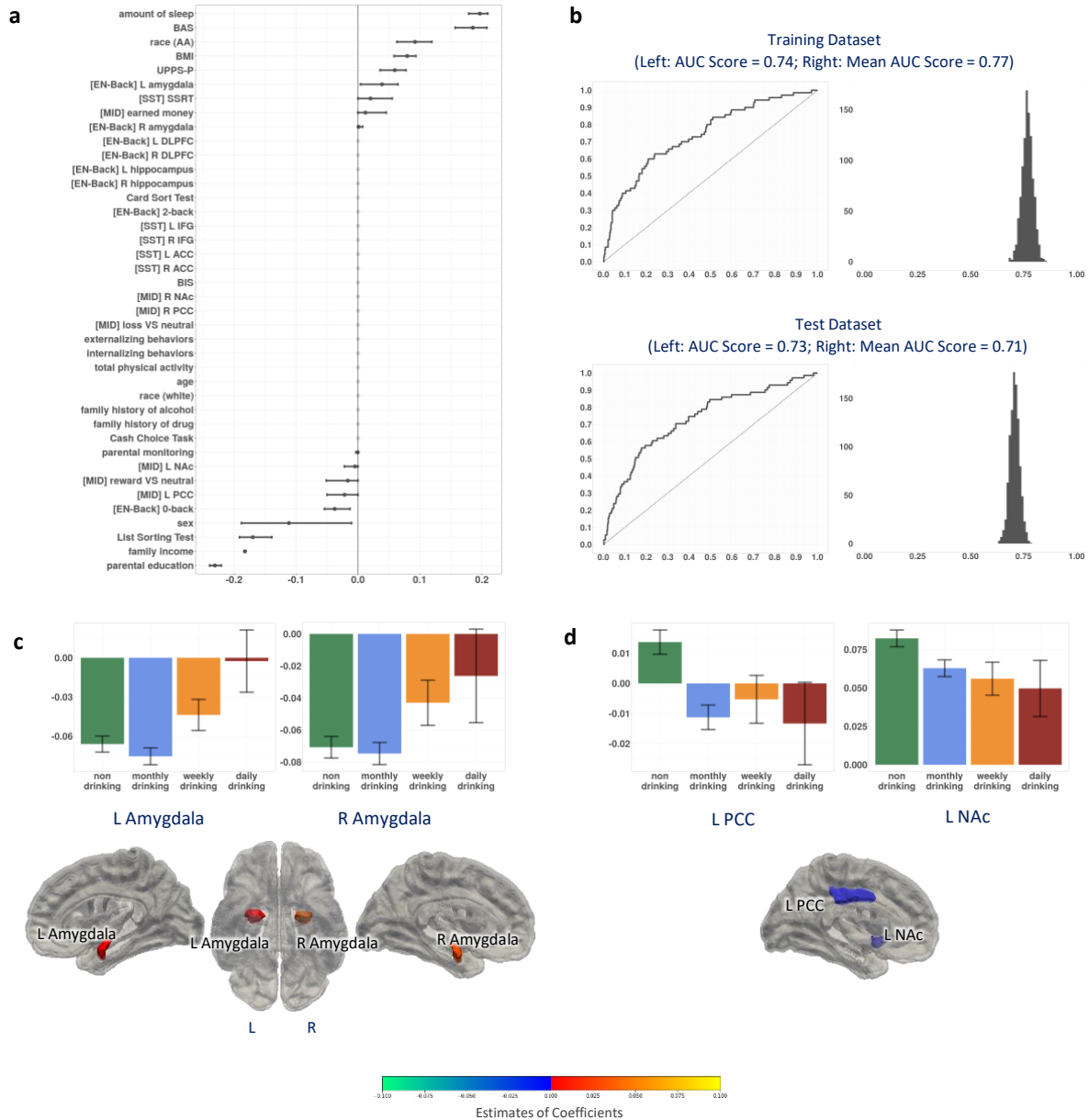


Fig. 3. Results of LASSO regression with categorical caffeinated soda intake (non-drinking group vs. daily-drinking group).

The bar graph (a) shows the estimates of coefficients (x axis: coefficient estimates; y axis: predictor). The plots (b) are a representative receiver-operation characteristic (ROC) curve (left) and a distribution of area under the curve (AUC) scores (right) in training and test datasets. The brain images (c) show regions of interest (ROIs) identified as having significant estimates of coefficients during the Emotional N-Back Task (EN-Back). The other brain image (d) shows 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.

Table 1. Results of hierarchical regression analysis

variable	Working Memory			Impulsivity		
	List sorting Test	[EN-Back] L amygdala	SSRT	UPPS-P	BIS	BAS
sex	-.051*	-.008	.021	-.125***	-.027	-.112***
race (African-American)	-.133*	-.018	-.112	-.023	.024	.052
race (others)	.042	-.023	.03	.031	-.03	-.038
parental education	.161***	-.081**	-.014	.015	-.016	-.028
family income	.024	-.021	.03	-.013	-.067*	-.055
parental monitoring	.057*	-.042	-.022	-.185***	.034	.055
body mass index (BMI)	-.012	.007	.009	-.029	.002	.01
family history (drug)	.001	-.019	-.046	.022	.039	.04
family history (alcohol)	.009	-.01	.05	-.013	-.043	-.04
externalizing behaviors	-.032	.012	.025	.212***	.087**	.118***
internalizing behaviors	-.028	-.024	-.077**	-.112***	-.021	-.084**
amount of sleep	-.042	-.023	-.009	.033	.097***	.086***
soda intake	-.221**	.146*	.146*	.160*	.170*	.232**

Note. Data are standardized regression coefficients from the third step in the hierarchical analyses. Among the 24 dependent variables, the six variables were significantly associated with categorical caffeinated soda intake (daily-drinking group versus non-drinking group), even after controlling the controlled variables and the amount of sleep. Higher score in the List sorting Test score was associated with lower intake of caffeinated soda, while other five 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), Behavioral Inhibition System (BIS), and Behavioral Activation System (BAS)) were associated with higher intake of caffeinated soda.

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