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Authors
Meruelo, Alejandro D
Castro, Norma
Nguyen-Louie, Tam
et al.

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Substance use initiation and the prediction of subsequent academic achievement

Alejandro D. Meruelo[1], **Norma Castro**[1], **Tam Nguyen-Louie**[2], **Susan F. Tapert**[1]

[1]Department of Psychiatry, University of California San Diego, 9500 Gilman Drive, La Jolla, CA 92093, USA

[2]San Diego State University/University of California San Diego Joint Doctoral Program in Clinical Psychology, San Diego, CA, USA

Abstract

Academic performance significantly influences educational advancement, career opportunities, and life outcomes. The extent to which adolescent substance use and brain morphology predict academic achievement has not been extensively explored. We examined grade point average (GPA) at the time alcohol and cannabis use often starts (7th – 9th grade) and subsequently during 11th and 12th grade in a 170 physically healthy adolescents in a longitudinal study. Covariance analysis examined predictive features from 36 metrics of middle school academic performance and initiation of alcohol and cannabis use. Using a machine learning approach, GPA from 7th, 8th, and 9th grade strongly predicted 11th and 12th grade GPA, followed in predictive power by alcohol use age of onset. A machine learning approach determined 16 (from 336) baseline neuroimaging features that reflected lower thickness, area, or volume in average high school GPA drinkers compared to nondrinkers. Features that distinguished average performing drinkers from nondrinkers suggested accelerated gray matter loss during adolescence for drinkers, while high performing drinkers compared to nondrinkers may have attenuated gray matter maturation. Additional possibilities are discussed.

Keywords

Academic performance; Adolescence; Magnetic resonance imaging; Alcohol use; Cannabis use; Machine learning

Introduction

Academic performance has important bearings on scholastic advancement, including the opportunity to attend college, graduate school, professional school, and other career-determining educational programs (Shaw 2007; Meda et al. 2017). Intelligence quotient (IQ) has historically been considered a strong predictor of academic performance (Zax and Rees 2002).

Cannabis use is prevalent among adolescents, with past month cannabis users varying from 7 to 8% (Azofeifa et al. 2016a, b). Cannabis use has been reported to be associated with higher rates of academic dropout in high school, poorer academic performance, and reduced socioeconomic status and employability over the long term (Henry et al. 2007; Schulenberg et al. 1994; Paulson et al. 1990; Mensch and Kandel 1988; Bryant et al. 2003; Hawkins et al. 1992; Jackson et al. 2016; Ellickson et al. 1998). Persistent cannabis use across high school in subjects from an upper middle class community has been associated with poorer quantitative academic performance (Meier et al. 2015). Early cannabis has also been found to be associated with a variety of adverse outcomes related to mental health and behavioral issues (Fergusson et al. 1996; Brook et al. 1999, 199). Amotivational syndrome as a result of heavy cannabis use has been observed in a number of populations (Lac and Luk 2018). Early substance use has been associated with adverse outcomes related to academic self-esteem and later achievement (Bergen et al. 2005; Jeynes 2002; Bryant et al. 2003; Judith S. Brook et al. 2008). This may suggest that there might be a feedback loop between academic performance and cannabis use that implies that both poor academic performance (as it relates to academic self-esteem) can lead to increased cannabis use and heavy cannabis use can lead to poor academic performance (Bergen et al. 2005; Jeynes 2002; Bryant et al. 2003; Brook et al. 1999). While some more specialized and smaller studies have been conducted (Henry et al. 2007), it is important to better understand how initiation of cannabis use relates to poor quantitative academic performance.

Similarly, alcohol use has been associated with a decrease in number of years of schooling and likelihood of completing school; conflicting studies suggest such effects are minimal or not significant (Chatterji 2006; Chatterji and DeSimone 2005; Cook and Moore 1993; Gil-Lacruz and Molina 2007). In addition to early substance initiation being associated with adverse outcomes related to academic self-esteem and later achievement (Bergen et al. 2005; Jeynes 2002; Bryant et al. 2003; Judith S. Brook et al. 2008), additional work has also been done investigating the effects of binge drinking on academic performance in college individuals (Pascarella et al. 2007). However, there remains a knowledge gap in understanding the effect on quantitative academic performance at the high school level.

Therefore, determining the relationship between alcohol and cannabis use, and academic performance is highly relevant to expanding educational interventions for those attending middle and high school. If initiation of substance use is found to predict poorer academic performance, additional resources and interventions can be targeted to reducing substance use among adolescents at an earlier stage.

We hypothesized that the initiation of alcohol use and cannabis use was associated with poorer academic performance. We also hypothesized that prior middle school performance would be a good predictor of future high school performance. We test the validity of these hypotheses here.

We also proposed neuroanatomical hypotheses that might explain the differences between drinkers and non-drinkers as high and average performers in high school. Substance use has been noted to impair orbitofrontal-dependent learning tasks (Schoenbaum and Shaham 2008). In addition, substance users have also been noted to have reduced grey matter volume of the insula cortex (Droutman et al. 2015) and atrophy of the medial frontal regions of the anterior cingulate (Sinha 2011). Finally, those with alcohol use disorder in the adolescent population have demonstrated reduced hippocampal volume in a number of studies (Nagel et al. 2005; De Bellis et al. 2000). We hypothesized that in drinkers compared to nondrinker average performers, regions involved in impulsivity such as the orbitofrontal cortex (Schoenbaum and Shaham 2008; Squeglia et al. 2017), insula (Droutman et al. 2015), and cingulate cortex (Sinha 2011) might be lower in thickness, surface area, or volume, and that regions involved in learning such as the temporal lobe (Squire et al. 2007) might be lower in thickness, surface area, or volume. In contrast, we hypothesized that in drinkers compared to nondrinker high performers, the opposite regional patterns would be expected or atypical regions (e.g., lingual regions) would have evolved to provide additional advantage for higher performance despite increased alcohol consumption.

We also proposed neuroanatomical hypotheses that might explain the differences between moderate-heavy cannabis users and low users as high and average performers in high school. A number of studies have observed differences in attention, memory, and executive functions that recover with abstinence (Pope et al. 2001; Solowij et al. 2002a, b). Attention, memory, visuospatial, and executive functions have been associated with the anterior cingulate (Sinha 2011), orbitofrontal cortex (Schoenbaum and Shaham 2008; Squeglia et al. 2017), parietal (Schweinsburg et al. 2008), temporal (Squire et al. 2007), and frontal regions (Cohen and Weinstein 2018). For average-performing moderate-heavy cannabis compared to low cannabis users in high school, we hypothesized that these regions would be lower in thickness, surface area, or volume. For high performing users, we hypothesized that in moderate-heavy cannabis users compared to low users, the opposite regional patterns would be expected in order to provide additional advantage for higher performance despite increased cannabis usage.

Our work, to our knowledge, is the only one of its kind to characterize the impact of substance use and prior academic performance in middle school age adolescents on predicting high school academic performance through a longitudinal study. This work is an important precursor to future longitudinal study work such as the National Consortium on Alcohol and Neurodevelopment in Adolescence (NCANDA) and Adolescent Brain Cognitive Development (ABCD).

Methods

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study was approved by the UCSD Human Research Protections Program (Project #090269).

Informed Consent

All participants underwent parental consent and youth assent when participation occurred prior to age 18, and informed consent after age 18.

Participants

Study participants ($N = 295$; R01 AA13419) were recruited from eight San Diego County public middle schools at age 12–14 years (average age 13.2 ± 0.8), defined as the baseline year. All were physically healthy adolescents (half female), and half were youth at risk for developing substance use disorders based on family history and/or externalizing behaviors. Middle schools were traditional format, and most students matriculated to high schools with advanced placement (AP) course offerings, providing grades up to 5.0. Recruitment of subjects did not include those from special education focused schools. The student body percentage sampled from each school was not tracked. Each student was assessed annually with neuropsychological testing and high resolution MRI, in addition to quarterly interviews on substance use and general functioning for 9 years. Grade point average (GPA) was collected in 11th and 12th grade of high school, in addition to at 6th/7th/8th (i.e., at baseline) grades of middle school for prior performance. Subjects with missing data (38) at any required grade level (6th, 7th, 8th, and 11th or 12th grade) were excluded from these analyses. Subjects lacking 3 Tesla imaging data (87) at baseline (see below) were also excluded from the study. Other exclusionary criteria included history of psychiatric, learning, or neurological disorder. These exclusionary criteria resulted in a reduced sample of $N = 170$ participants. 30% of the cohort started heavy drinking. These heavy drinking youth (1/3 female) typically started drinking heavily (as defined in Fig. 1) at age 17, and 1/3 meet criteria for AUD; and 2/3 report past-month use of marijuana, 1/3 for tobacco, and 16% for other drug use. Complete study procedures are described in further detail (Jacobus et al. 2012; Squeglia et al. 2015, 2017; Nguyen-Louie et al. 2016).

Measures

The Diagnostic Interview Schedule for Children Predictive Scales (Lucas et al. 2001; Shaffer et al. 1996) was obtained from child and parent to exclude those with Axis I disorders other than conduct disorder or oppositional defiant disorder at baseline, and measure subthreshold symptom endorsement. Examples of axis I disorders include bipolar disorder, major depression, or schizophrenia. These were excluded so that neuroimaging differences related to axis I disorder would not confound understanding neuroimaging differences related to typical adolescent brain development. Family history of substance use disorders in first and second degree relatives was obtained from parent interview using the

Family History Assessment Module (Rice et al. 1995). Grade point average and other demographic information including parental income were obtained during a private interview with parent and youth at baseline and annually thereafter. The Customary Drinking and Drug Use Record (Brown et al. 1998) assessed lifetime alcohol, cannabis, tobacco, and other drug use defined as the cumulative use (e.g., cannabis) episodes at baseline. The Beck Depression Inventory (Beck et al. 1988) and Spielberger State Trait Anxiety Inventory (Spielberger et al. 1983) were used to assess subject depression and state anxiety.

Image acquisition and processing

Magnetic resonance imaging (MRI) was obtained from all participants at the baseline year (age 12–14 years) and at follow-ups; the present analyses focus on imaging from the baseline time point only. All scans were acquired on a single 3.0 T CXK4 short bore Excite-2 magnetic resonance system (General Electric, Milwaukee, WI) with an eight-channel phase array head coil at the UCSD Center for Functional MRI. Subjects were instructed to remain motionless while a high-resolution T1-weight anatomical spoil gradient recall (SPGR) scan was obtained (TE/TR = min full, field of view = 24 cm, resolution = 1 mm^3, 170 continuous slices). For the present analyses, structural MRIs were acquired on a single occasion at baseline. Cortical thickness, area, and volume estimates were obtained in the same manner as previously published by our laboratory (Jacobus et al. 2014, 2015). FreeSurfer (version 5.1, surfer.nmr.mgh.harvard.edu) was used for cortical surface reconstruction and to obtain cortical thickness estimates (Fischl et al. 1999; Dale et al. 1999). The cross-sectioning process, cortical thickness calculation, and parcellation procedure have previously been described in detail (Jacobus et al. 2015). The Desikan-Killiany atlas was used for generating parcellation units.

Data analysis

For feature selection analysis, substance use variables were extracted as input training data to distinguish those with exemplary versus lesser academic performance in high school. Variables included age of onset of alcohol, cannabis, tobacco, and other drug use. In addition, the number of drug use days for grades 6th through 11th for alcohol, cannabis, tobacco, and other drugs were included. Quantity of cannabis use was not assessed. Additional variables included average drinks per month, peak drinks, tobacco use past month, and maternal education level. The mean GPA of subjects was determined to be 3.54 ± 0.60 (range: 1.35 to 5.00) and consequently subjects were divided into high (GPA ≥ 3.54; $n = 87$) and average (GPA < 3.54; $n = 83$) academic performers.

Predictors of high school GPA using machine learning

To identify predictive features of high school GPA using machine learning with a naïve Bayes classifier, we applied 4 algorithms for selection and reduction of attributes (CfsSubset with RankSearch for Attribute Selection, CfsSubset with LinearForwardSelection for Attribute Selection, Information Gain Analysis with Ranker for Attribute Selection, Chi-squared with Ranker for Attribute Selection) using Weka (Hall et al. 2009) to 53 metrics of middle school academic performance/initiation of substance use. Group differences between parameters of predictive regions for high versus average academic performers were

identified by performing independent *t-test* comparisons using IBM SPSS v22. Significance was determined at the $p < 0.05$ level. Demographic analysis was completed using independent *t-test* comparisons between high and average academic performers across age, annual household income, mood scores at baseline, familial alcohol density, gender, ethnicity, lifetime substance use, and presence of DSM-5 (American Psychiatric Association 2013) psychiatric conditions using the Diagnostic Interview Schedule for Children (DISC) Predictive Scales (Leung et al. 2005; Lucas et al. 2001). Significance was determined at the $p < 0.05$ level. Covariance analysis used StatPlus (http://www.analystsoft.com/en/products/statplus/) and Pearson correlation coefficients between longitudinal baseline age, socioeconomic status (SES), familial alcohol density, and pubertal developmental score, and predictive attributes (see Supplementary Table 1 for findings).

Neural predictors of future average (and high) GPA alcohol users from nonusers using machine learning

Next, we followed up on the ability of machine learning to predict average GPA moderate to heavy alcohol users from average GPA non-drinkers (see Fig. 1). Our hope was that by looking at the differences between drinkers and nondrinkers in the academically average-performing group, we might characterize the important differences in brain regions that distinguish academically struggling drinkers from nondrinkers in school.

Average-performing (GPA < 3.54) performers were divided into drinkers (moderate and heavy drinkers; see Fig. 1) and non-drinkers according to the Customary Drinking and Drug Use Record (Brown et al. 1998). Surface area, cortical thickness, and subcortical volume information was then used to classify drinkers versus non-drinkers using a naïve Bayesian classifier. A total of 336 brain regions were used as input to the naïve Bayesian classifier. We then applied the CfsSubset with BestFirst algorithm for selection and reduction of attributes using Weka (Hall et al. 2009). CfsSubset evaluates the worth of a subset of attributes by considering the individual predictive ability of each feature along with the degree of redundancy between them; subsets of features that are highly correlated with the binary class while having low intercorrelation are preferred (Hall et al. 2009). BestFirst searches the space of attribute subsets by greedy hillclimbing augmented with a backtracking facility (Hall et al. 2009). Beginning with the empty set of attributes, it searches forwards or backwards. It stops searching when the accuracy is higher than a given threshold or there is no more improvement (Hall et al. 2009). Subcortical and white matter volumes were normalized using regression-based intracranial volumes to account for intrasubject intracranial volume (ICV) differences. As ICV normalization methods vary in their ability to accurately capture morphometric measures, we also performed predictive analysis as described below without ICV correction.

For the average-performing drinkers and nondrinkers, sample size was sufficient to allow for dividing the sample in half with 50% used for training and 50% used for validation. However, for high-performing drinkers and nondrinkers, the sample size was insufficient for this type of validation so instead 10-fold cross validation was performing using training and testing sets. Group differences between parameters of predictive regions for drinking v. non-drinking average (or high) academic performers were identified by performing independent

t-test comparisons using IBM SPSS v22. Significance was determined at the $p < 0.05$ level. Bonferroni correction for multiple comparisons was then applied based on the number of t-tests performed under each hypothesis subgroup.

Neural predictors of future average (and high) GPA moderate-high cannabis users from low users using machine learning

We followed up on the ability of machine learning to predict average GPA moderate—high cannabis users from average GPA low cannabis users. Our expectation was that by looking at the differences between moderate-heavy cannabis users and low users in the academically average-performing group, we might be able to characterize the important differences in brain regions that distinguish academically struggling moderate-high cannabis users from low cannabis users in school.

Average-performing (GPA < 3.54) performers were divided into moderate-heavy cannabis users and low cannabis users according to the Customary Drinking and Drug Use Record (Brown et al. 1998). Lifetime cannabis uses at 11th grade was used to determine stratify users into moderate-heavy cannabis users with 50 or more lifetime episodes and low cannabis users as those with fewer than 50 uses. Surface area, cortical thickness, and subcortical volume information was then used to classify moderate-heavy cannabis users versus low users using a naïve Bayesian classifier. A total of 336 brain regions were used as input to the naïve Bayesian classifier. We then applied the CfsSubset with BestFirst algorithm for selection and reduction of attributes using Weka (Hall et al. 2009). CfsSubset evaluates the worth of a subset of attributes by considering the individual predictive ability of each feature along with the degree of redundancy between them; subsets of features that are highly correlated with the binary class while having low intercorrelation are preferred (Hall et al. 2009). BestFirst searches the space of attribute subsets by greedy hillclimbing augmented with a backtracking facility (Hall et al. 2009). Beginning with the empty set of attributes, it searches forwards or backwards. It stops searching when the accuracy is higher than a given threshold or there is no more improvement (Hall et al. 2009). Subcortical and white matter volumes were normalized using regression-based intracranial volumes to account for intrasubject intracranial volume (ICV) differences. As ICV normalization methods vary in their ability to accurately capture morphometric measures, we also performed predictive analysis as described below without ICV correction.

For both high and average-performing moderate-heavy cannabis users and low users, sample size was sufficient to allow for dividing the sample in half with 50% used for training and 50% used for validation. Group differences between parameters of predictive regions for drinking v. non-drinking average (or high) academic performers were identified by performing independent *t-test* comparisons using IBM SPSS v22. Significance was determined at the $p < 0.05$ level. Bonferroni correction for multiple comparisons was then applied based on the number of t-tests performed under each hypothesis subgroup.

Results

Demographic characteristics at baseline of subjects have been provided in Table 1; statistical comparison of demographic and diagnostic screening variables at baseline have been provided between high and average academic performers.

To address generalizability of our findings, we compared lifetime cannabis and alcohol use in 8th grade from our sample to that of the Monitoring Future Study (https://www.drugabuse.gov/trends-statistics/monitoring-future/monitoring-future-study-trends-in-prevalence-various-drugs). In our sample, 18% reported lifetime alcohol use (1 or more times) by 8th grade. This is slightly lower than 2017 national levels of 23% of 8th graders with lifetime alcohol use from Monitoring the Future. For cannabis, 10% of our sample versus 14% of the Monitoring the Future sample endorsed any cannabis use by 8th grade. Therefore, while use is somewhat lower in our sample, it is comparable to national data and suggests that these findings are fairly generalizable (Table 2).

Predictors of high school grade point average (GPA) using linear regression and machine learning: alcohol, cannabis, and middle school GPA

A total of 53 metrics of middle school academic performance/initiation of cannabis use were employed in the naïve Bayesian classifier. Middle school (6th/7th/8th) GPA predicted high school GPA better than substance use (frequency measures and initial age of use) with a sensitivity and specificity of 0.57 and 0.55, respectively. This was followed in predictive power by alcohol use age of onset for predicting high school GPA with a sensitivity and specificity of 0.54 and 0.52, respectively. Earlier age of onset for alcohol and cannabis had positive correlation coefficients indicating later age of use associations with higher academic performance. We also performed a linear regression analysis to see if middle school performance could predict alcohol and cannabis use age of onset. We found that middle school performance did not significantly predict alcohol use age of onset (R-squared = 0.11) nor did middle school performance predict cannabis use age of onset (R-squared = 0.05). We completed two machine learning analyses with similar results. We investigated whether binary classification into light versus moderate-heavy cannabis users could be predicted by middle school GPA. Sensitivity and specificity were 0.89 and 0.18, respectively with a 50/50% split for validation. We investigated whether binary classification into drinkers and nondrinkers could be predicted by middle school GPA. Sensitivity and specificity were 0.63 and 0.38, respectively with 10-fold cross validation.

Predictors of future average GPA alcohol users from nonusers using machine learning

A naïve Bayesian classifier approach differentiated average (<3.54) high school GPA alcohol users from nonusers (as defined under Methods) based on 336 neuroimaging features at baseline. This machine learning analysis revealed a number of predictive regions with a sensitivity/specificity of 0.75/0.75 with intracranial volume (ICV) correction (see Table 3 and Fig. 2). Predictive regions were found to be identical with and without ICV correction. Independent *t-test* analyses looking at the identified regions between average GPA alcohol users and nondrinkers found all regions to be decreased (e.g., decreased

thickness, decreased area, or decreased volume) in drinkers compared to nondrinkers, except in the left transverse temporal thickness, which was increased.

Problem behaviors commonly related to earlier drinking and cannabis use are a potential confound, and rule-violating types of behaviors may particularly impact those in the average GPA group. We examined baseline externalizing problem behavior T-score in relation to baseline GPA and found a non-significant correlation ($r = -0.07$, $p = .25$) in this sample (Table 4).

Predictors of future high GPA alcohol users from nonusers using machine learning

A naïve Bayesian classifier approach to differentiating high ($> = 3.54$) GPA alcohol users from nonusers based on 336 neuroimaging features revealed the two most predictive regions with a sensitivity/specificity of 0.63/0.54 with ICV correction (see Table 3). The 3rd ventricle was found to be greater in drinkers compared to nondrinkers, but not statistically significant.

Predictors of future average GPA cannabis moderate-heavy users from light users using machine learning

A naïve Bayesian classifier approach to differentiating average (< 3.54) GPA moderate-heavy cannabis users from low users based on 336 neuroimaging features revealed one most predictive region with a sensitivity/specificity of 0.66/0.39 with ICV correction (see Table 5). The right superior parietal thickness was found to be greater in moderate-heavy cannabis users compared to low users, but not statistically significant.

Predictors of future high GPA cannabis moderate-heavy users from light users using machine learning

A naïve Bayesian classifier approach to differentiating high ($> = 3.54$) GPA moderate-heavy cannabis users from low users based on 336 neuroimaging features revealed several predictive regions with a sensitivity/specificity of 0.71/0.57 with ICV correction (see Table 6). Most surface areas were found to be greater in moderate-heavy cannabis users compared to low users, except for the right transverse temporal surface area.

Discussion

We had originally hypothesized that alcohol and cannabis use would predict poorer high school performance. We also hypothesized that good middle school performance would predict good high school performance. The results were consistent with our initial hypothesis that alcohol and cannabis use predicted high school GPA. Specifically, we found that amongst all substance use variables, ages of onset of alcohol and cannabis use most strongly predicted high school GPA. As expected (Kobrin and Michel 2006), middle school GPA predicted high school GPA, despite increases in the sophistication of material presented at later grade levels compared to middle school. In contrast, attempts to use both linear regression and machine learning to investigate whether middle school performance predicted substance use (cannabis, alcohol) proved unfruitful. We found that middle school performance did not significantly predict alcohol use age of onset (R-squared = 0.11) nor did

middle school performance predict cannabis use age of onset (R-squared = 0.05). Middle school GPA only very weakly predicted classification of cannabis users into light and moderate-heavy users with a sensitivity and specificity of 0.89 and 0.18, respectively. Middle school GPA similarly weakly predicted classification of alcohol drinkers into drinkers and nondrinkers with a sensitivity and specificity of 0.63 and 0.38, respectively. The stronger predictive direction of poorer academic performance by metrics of initiation of alcohol use and cannabis use appeared most prevalent within our subjects.

The identified brain regions (i.e., orbitofrontal cortex, cingulate, temporal lobe, and insula) in adolescents ages 12–14 years old prior to the initiation of alcohol, cannabis, or drug use represent brain systems previously implicated in reward, addiction, memory, and learning processes (Droutman et al. 2015; Schoenbaum and Shaham 2008; Sinha 2011). The orbitofrontal cortex is thought to facilitate behavioral control according to consequences and is altered in alcohol misuse (Schoenbaum and Shaham 2008). Lower cortical thickness of the isthmus cingulate has been found to be predictive of future drinking in a similar age group (Squeglia et al. 2017) as was found in our work. Finally, reduced insula gray matter volume in addicts has been found in neuroimaging studies (Droutman et al. 2015).

Our findings were in agreement with some of the findings of Meda et al. 2017, though our samples differed significantly in age (Meda et al. 2017). Meda et al. 2017 looked at college students and their academic performance whereas we examined middle school imaging and high school academic performance with regard to substance use (Meda et al. 2017). In agreement, we both found that alcohol and cannabis use was associated with decreased academic performance (Meda et al. 2017). In addition, we also found in agreement with Meda et al. 2017 in a different paper that decreased volumes, cortical thicknesses, and surface areas were predictive of lower academic performance (Meda et al. 2017). It should be emphasized that these neuroimaging findings were in substance naïve subjects at age 12–14 years old (with a very small amount of cannabis use times used 0.1 ± 0.4 at baseline in average performers) whereas Meda et al. 2017 was looking at those who had heavily used alcohol in which they saw accelerated grey matter volume decline (Meda et al. 2017). This may suggest that some individuals may have increased vulnerability for increased drinking because of these brain imaging features, though this may change based on environmental exposures.

A natural question in understanding the impact of substance use and its relationship to high school academic performance is examining brain regions that can predict future drinking. Previous work by Squeglia et al. 2017 established a number of neural predictors for future drinking in this age group. We hoped to build on this work by focusing on neuroimaging predictors for future drinking while isolating for difficulties in school performance that might suggest early cognitive dysfunction. These differences in those who struggled in school were hypothesized in regions related to impulsivity such as the orbitofrontal cortex (Schoenbaum and Shaham 2008; Squeglia et al. 2017), insula (Droutman et al. 2015), cingulate cortex (Sinha 2011), in addition regions involved in learning such as the temporal lobe (Squire et al. 2007). Future neuroimaging predictors of drinking in those who over perform in high school was also sought. We hypothesized that regional differences would

reflect opposite patterns in expected or atypical regions (e.g., lingual regions) to provide additional advantage for higher performance despite increased alcohol consumption.

Among those with average GPAs (< 3.54), drinkers showed smaller surface area, thickness and volumes than non-drinkers (see Table 3). Smaller surface areas may represent environmental influences near the medial temporal lobe and genetic influences in the frontal and parietal cortices (Eyler et al. 2011, 20; Rimol et al. 2010). The frontal and temporal regions stood out as distinguishing features between drinkers and nondrinkers as highlighted in Table 3. These findings were consistent with the fact that frontal lobe maturation occurs to a greater degree than other regions of the adolescent brain. Smaller volumes and cortical thicknesses may suggest less brain maturation in early adolescence for future drinkers (Somerville 2016). However, smaller volumes and less cortical thicknesses may also suggest more brain maturation as the grey matter refines over the adolescent years after a period of growth in childhood (Giedd et al. 1999). The volume reduction and cortical thinning in adolescence may reflect synaptic pruning and refinement (Giedd et al. 1999). The reasons for these contradictory findings related to cortical thickness have been explored previously (Walhovd et al. 2016). Small volumes and cortical thicknesses may alternatively be a result of genetic differences or unmeasured confounds. Ample sample size for both average-performing drinkers ($n = 77$) and nondrinkers ($n = 29$) facilitated elucidating a distinction between these groups. The lesser specificity for distinguishing average-performing drinkers versus nondrinkers may be the result of a smaller sample size for nondrinking individuals who were average performing and/or complexity of variation between average performers.

Comparing those with higher GPAs (> = 3.54), we found that drinkers compared to non-drinkers demonstrated increased left middle temporal thickness and left lingual surface area. The increased thickness of the left middle temporal lobe has been seen in associations with increased intelligence quotient (Menary et al. 2013). The left lingual surface area may be under less genetic and more environmental control, and therefore more prone to modification by environmental insults, such as alcohol use (Eyler et al. 2011; Rimol et al. 2010). The lesser specificity and sensitivity for distinguishing high-performing drinkers versus nondrinkers may be the result of a smaller sample size for drinking individuals who were high performing and/or the complexity of variations between such high-performing individuals. The lower specificity and sensitivity for high-performing drinkers versus nondrinkers limits our interpretation of the differences between these groups, but we included the findings for completeness of our analyses.

For those with average GPAs (< 3.54), using cannabis moderately to heavily was linked to thicker right superior parietal lobe cortices than low/no users (see Table 5). This region is often implicated in visuospatial functioning and larger volumes or thicker cortices have been observed in chronic cannabis using youth (Jacobus et al. 2015; Lopez-Larson et al. 2011). While these findings were a trend, the differences were not statistically significant in this sample.

Lastly, for those with higher GPAs (> = 3.54), moderate-heavy cannabis use was linked to greater surface areas in most predictive regions compared to low users, except for temporal regions where surface was statistically similar. Surface areas may represent environmental

influences near the medial temporal lobe and genetic influences in the parietal cortices (Eyler et al. 2011; Rimol et al. 2010). The parietal and temporal regions stood out as distinguishing features between moderate-heavy cannabis users and low users, as highlighted in Table 6. The pericalcarine area is the location of the primary visual cortex (Bedny et al. 2012) and may be enhanced in a compensatory manner in high performing moderate-heavy cannabis users. Similarly, the supramarginal area is responsible for language perception and processing and may be also enhanced in high performing moderate-heavy cannabis users (Binder 2015). The temporal area has an important role in memory and learning, and may also be enhanced on moderate-heavy cannabis users (Nilakantan et al. 2017).

This study has several limitations. First, our study focused on GPA as a marker of academic performance. A natural question arises as to how GPA maps onto cognitive and life outcomes after high school graduation, and even to verbal IQ (full-scale IQ data was not available as part of our study). Baseline Wechsler Vocabulary scores, often used as a proxy for Verbal IQ (Sattler 2018), correlated moderately and positively with baseline GPA (Pearson r = 0.23, *p* < .0001). Similarly, other studies have found moderate correlations between Verbal IQ measured by Wechsler Adult Intelligence Scale-Revised (WAIS-R) and GPA (*Clinical Assessment of Child and Adolescent Personality and Behavior | Paul J. Frick | Springer* n.d.). Second, findings only generalize to the population studied, which tended to be higher performing youth from San Diego school compared to students nationally. Findings do not address those with significant learning disabilities or very poor academic performance. Third, GPA may not be as valid or complete a measure of academic performance as standardized academic achievement or aptitude tests (Coyle et al. 2011; Frey and Detterman 2004). High school GPAs reflects intelligence, but also following rules in the classroom, test-taking skills (Kuncel et al. 2005), difficulty of school curricula, and teacher bias, although with standardized AP course offerings this variability has been reduced (Kuncel et al. 2005).

Fourth, the comparable reliability and validity of cortical thickness, cortical surface area, and subcortical volumes must be considered given that these metrics were all used as input for the machine learning approach taken (B. Fischl and Dale 2000; Clarkson et al. 2011; Cardinale et al. 2014). Based on a review of the literature, test-retested correlations, intraclass correlation coefficients, and percent differences for cortical thickness, cortical surface area, and subcortical volume were 0.82/0.88/0.88, 0.81/0.87/0.88, and 0.86/1.19/1.39, respectively (Iscan et al. 2015), suggesting that subcortical volumes would be the most reliable and cortical thickness the least. However, our machine learning approach validated on an independent data set not previously trained on demonstrated that to the contrary, a combination of metrics across subcortical volumes, surface areas, and cortical thickness was more predictive than any particular subcortical volume parameter. This may be because, while generalizations can be made of the reliability of classes of metrics in general, some measures may simply be more predictive independent of the reliability of a particular class of metrics.

In summary, alcohol and cannabis use, prior academic performance, and high school academic performance show important relationships. Alcohol use age of onset and cannabis

use age of onset were highlighted as robust in predicting academic performance. Neural predictors of drinking in average-performers and high performers shed some light on differences in baseline brain maturation and development that help us better understand the challenges that those vulnerable to increased alcohol use face as they are growing up. Alcohol use and cannabis use ages of onset likely have a significant impact on the developing brain during this critical developmental window in adolescents, hence their increased predictive value. These findings apply to our sample, but might vary in a different sample.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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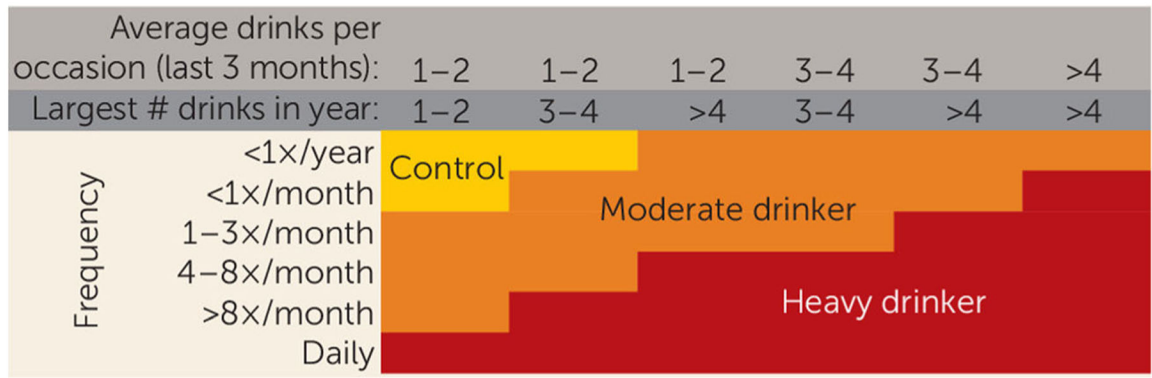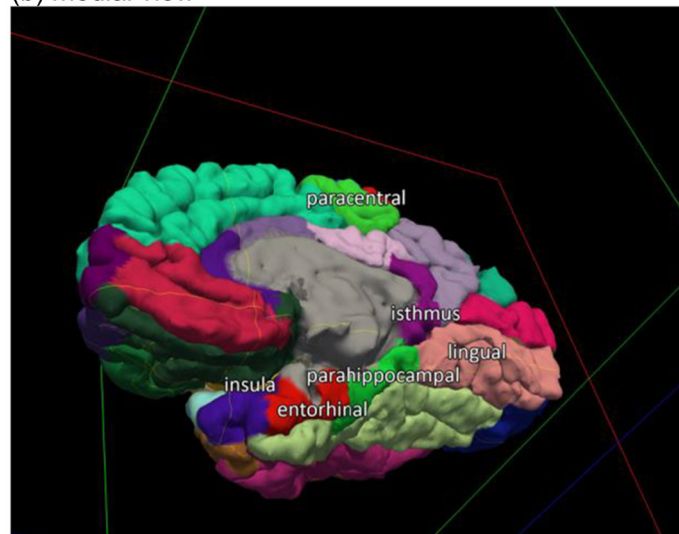
Fig. 1.
Definition of youth drinking categories, depicting how study participants were divided into nondrinker (control) and moderate to heavy drinkers (as one group) (Squeglia et al. 2017)
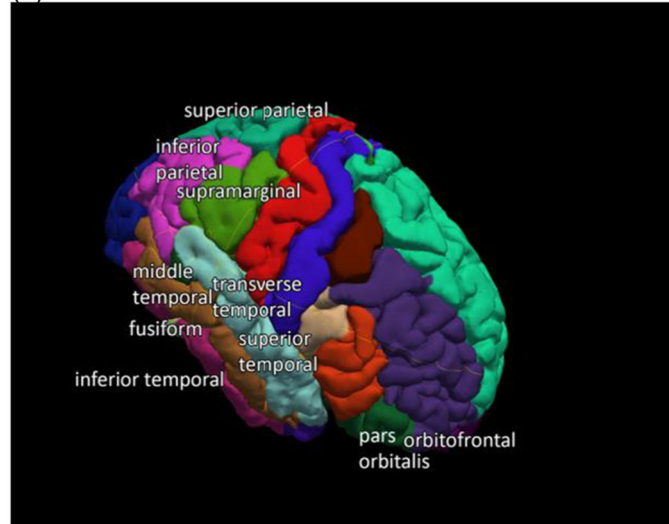
Fig. 2.
Machine-learning predictive regions for Average-Performing (GPA < 3.54) Drinkers v.
Nondrinkers. Mean GPA of 3.54 ± 0.60 (range:1.35 to 5.00) with subjects divided into high
(GPA   3.54; $n = 87$) and average (GPA < 3.54; $n = 83$)

Table 1

Demographic Characteristics at Baseline for high versus average academic performers [*]

	High academic performers (n = 87)	Average academic performers (n = 83)	All	Group comparison
	Mean ± SD or %	Mean ± SD or %	Mean ± SD or %	P value
Age	13.1 ± 0.7	13.2 ± 0.8	13.1 ± 0.7	0.44
Annual household income ($K)	93 ± 109	78 ± 85	91 ± 99	0.42
Familial alcohol use disorder density	0.00 ± 0.03	0.01 ± 0.06	0.01 ± 0.05	0.39
% Male	54	61	58	-
% Hispanic/Latino	13	39	25	-
% white	75	53	64	-
Times used tobacco, lifetime	0.1 ± 0.6	0 ± 1	0.1 ± 0.9	0.41
Days used alcohol per month in past 3 months	0.0 ± 0.2	0.0 ± 0.2	0.0 ± 0.2	0.97
Times used cannabis, lifetime	0 ± 0	0.1 ± 0.4	0.0 ± 0.3	0.1
Times used other drug, lifetime	0 ± 0	0.0 ± 0.1	0.0 ± 0.1	0.31
Beck Depression Inventory total	1 ± 2	2 ± 4	2 ± 3	0.01
Spielberger State Anxiety T-score	48 ± 4	47 ± 5	47 ± 5	0.38

[*] Mean GPA of 3.54 ± 0.60 (range: 1.35 to 5.00)

Table 2

Age of onset of substance use

	Average ± standard deviation	Minimum	Maximum	% who reported more than 1 use of this substance at baseline	Lifetime total use episodes prior to baseline
Age of onset alcohol use	16 ± 2	11	22	6	20
Age of onset cannabis use	16 ± 2	12	22	3	4
Age of onset drug use	16 ± 2	13	23	0	1
Age of onset tobacco use	16 ± 3	6	23	2	10

Table 3

Independent *t-tests* for Predictive Regions for Average-Performing (GPA < 3.54) Drinkers v. Nondrinkers

Independent *t-tests* for Predictive Regions	Mean for drinker category		P value
	Drinkers (n = 77)	Nondrinkers (n = 29)	(nonequal variances)
R Lateral Orbitofrontal surface area * (mm²)	2731	3103	0.000
R Medial Orbitofrontal surface area * (mm²)	1850	2067	0.000
R Pars orbitalis surface area * (mm²)	835	950	0.000
L Fusiform surface area * (mm²)	3354	3906	0.000
L Parahippocampal surface area * (mm²)	705	800	0.000
R Superior Parietal area surface area * (mm²)	5430	6179	0.000
R Fusiform surface area * (mm²)	3204	3820	0.000
R Inferior Temporal surface area * (mm²)	3209	3653	0.000
R Inferior Parietal surface area * (mm²)	5661	6451	0.000
L Inferior Parietal surface area * (mm²)	4741	5495	0.000
L Supramarginal surface area * (mm²)	3987	4519	0.000
R Lingual surface area * (mm²)	3137	3479	0.000
3rd Ventricle Volume * (mm³)	104	114	0.000
4th Ventricle Volume * (mm³)	1379	1480	0.000
L Paracentral Thickness * (mm)	2.64	2.734	0.001
L Banks Superior Temporal Sulcus surface area (mm²)	1069	1184	0.011

L Left, *R* Right

*
Bonferroni correction for multiple comparisons requires p < 0.05/16 = 0.003

Table 4

Independent *t-tests* for Predictive Regions for High-Performing (GPA > 3.54) Drinkers *v.* Nondrinkers

Independent *t-tests* for Predictive Regions	Mean for drinker category		*P* value (nonequal variances)
	Drinkers (*n* = 28)	Nondrinkers (*n* = 68)	
3rd Ventricle (mm³)	110	109	0.383

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Table 5

Independent *t-tests* for Predictive Regions for Average-Performing (GPA < 3.54) Cannabis Moderate-Heavy Users *v*. Low Users

Independent *t-tests* for Predictive Regions	Mean for cannabis category		*P value*
	Low Users (*n* = 143)	Moderate-Heavy Users (n = 29)	*(nonequal variances)*
R Superior Parietal Thickness (mm)	2.510	2.538	0.341

R Right

Table 6

Independent *t-tests* for Predictive Regions for High-Performing (GPA < 3.54) Cannabis Moderate-Heavy Users v. Low Users

Independent *t-tests* for Predictive Regions	Mean for cannabis category		P value
	Low Users (*n* = 101)	Moderate-Heavy Users (*n* = 15)	*(nonequal variances)*
R Pericalcarine Surface Area (mm^2)	1598	1756	0.019
R Temporal Pole Surface Area (mm^2)	421	477	0.011
R Transverse Temporal Surface Area (mm^2)	353	352	0.947
L Supramarginal Surface Area (mm^2)	4237	4666	0.039

L Left, *R* Right

Bonferroni correction for multiple comparisons requires p < 0.05/4 = 0.01