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Initiation of Moderately Frequent Cannabis use in Adolescence and Young Adulthood is Associated with Declines in Verbal Learning and Memory: A Longitudinal Comparison of Pre- versus Post-Initiation Cognitive Performance

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Abstract

Objective: Cannabis use is associated with relative cognitive weaknesses as observed by cross-sectional as well as longitudinal research. Longitudinal studies, controlling for relevant confounds, are necessary to differentiate premorbid from post-initiation contributions to these effects. **Methods:** We followed a sample of adolescents and young adults across ten years. Participants provided neurocognitive data and substance use information at two-year intervals. Participants who initiated cannabis and/or alcohol use were identified ($n = 86$) and split into alcohol-only initiators ($n = 39$) and infrequent ($n = 29$) and moderately frequent ($n = 18$) cannabis initiators. Participants completed the Rey Auditory Verbal Learning Task (RAVLT) and the Iowa Gambling Task (IGT). Group differences before and after substance use initiation and the extent to which alcohol, nicotine, and cannabis use frequencies contributed to cognitive functions over time were examined. **Results:** After controlling for parental education, RAVLT new learning was worse in moderately frequent cannabis users prior to use initiation. RAVLT total learning and delayed recall showed significant declines from pre- to post-initiation in moderately frequent cannabis users. Regression analyses confirmed that frequencies of cannabis, but not alcohol, use contributed to post-initiation variations. Nicotine use showed an independent negative association with delayed memory. Findings for the IGT were not significant. **Conclusions:** Verbal learning and memory may be disrupted following the initiation of moderately frequent cannabis use while decreased new learning may represent a premorbid liability. Our use of a control group of alcohol-only users adds interpretive clarity to the findings and suggests that future studies should carefully control for comorbid substance use.

Keywords: Verbal memory, Cannabis, Adolescence, Substance use, Decision-making, Working memory

INTRODUCTION

Cannabis use is prevalent in the United States (Johnston et al., 2020) and is associated with various cognitive decrements. Because most studies are cross-sectional, differences observed between users and non-users could be due to premorbid differences as opposed to neurotoxic effects. Longitudinal studies that follow substance naïve individuals into use initiation may help to address these interpretive complexities.

Case-control studies indicate relative performance decrements in cannabis users (CU) in attention (Dougherty et al., 2013; Fontes et al., 2011; Jacobus et al., 2015; Lisdahl & Price, 2012), processing speed (Jacobus et al., 2015; Petker et al., 2019), and psychomotor abilities (Bolla et al., 2002; Lisdahl & Price, 2012). Relative decrements have also been observed in executive functions such as inhibitory control (Battisti et al., 2010; Bolla et al., 2002; Fontes et al., 2011; Gruber, Sagar, Dahlgren, Racine, & Lukas, 2012) and set-shifting (Fontes et al., 2011; Gruber, Dahlgren, Sagar, Gönenç, & Killgore, 2012; Gruber, Sagar et al., 2012; Lane, Cherek, Tcheremissine, Steinberg, & Sharon, 2007). Findings are inconsistent for working memory and spatial processes (Becker, Collins, & Luciana, 2014; Harvey, Sellman, Porter, & Frampton, 2007).

A robust finding in the literature involves verbal learning and memory, typically measured by word list-learning tasks such as the Rey Auditory Verbal Learning Task (RAVLT) or the California Verbal Learning Task (Broyd, van Hell, Beale,

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Yucel, & Solowij, 2016; Grant, Gonzalez, Carey, Natarajan, & Wolfson, 2003). Numerous laboratories have demonstrated verbal learning and memory decrements in adolescent and adult CU (Becker et al., 2014; Gonzalez et al., 2012; Gruber et al., 2012; Harvey et al., 2007; Solowij et al., 2011; Tait, Mackinnon, & Christensen, 2011) which may persist over time with continued use (Becker et al., 2018; Jacobus et al., 2015), perhaps improving with abstinence (Bolla et al., 2002; Hanson et al., 2010; Scott et al., 2018).

Studies of decision-making that focus on CU and utilize measures such as the Iowa Gambling Task (IGT) are inconsistent, finding in many cases that frequent heavy users show relative weaknesses (Becker et al., 2014; Casey & Cservenka, 2020; Fridberg et al., 2010, Grant, Chamberlain, Schreiber, & Odlaug, 2012; Moreno et al., 2012; Solowij et al., 2012; Verdejo-Garcia et al., 2007; Whitlow et al., 2004) although others report no effects (Dougherty et al., 2013; Gilman et al., 2015; Gonzalez et al., 2012). Nearly all of these studies focus on young adults.

Several meta-analyses have attempted to resolve these discrepancies. In an analysis of 11 studies including 623 CU and 409 non- or minimal users, Grant et al. (2003) reported a small effect of long-term cannabis consumption on learning and memory but negligible effects for other cognitive domains. Scott and colleagues (2018) as well as Schreiner and Dunn (2012) concurred that the largest effects are observed for learning, memory, executive functioning, processing speed, and attention. A synthesis of meta-analyses published before 2019 (Duperrouzel, Granja, Pacheco-Colón, & Gonzalez, 2020) concluded that among non-clinical samples of CU, decrements in the learning of new information consistently showed the largest effect sizes. Figuerido et al. (2020) analyzed 13 studies, including 499 chronic cannabis users and 883 controls with minimal or no lifetime cannabis use. Chronic cannabis use was associated with relative decrements in cognitive impulsivity, flexibility, attention, short-term verbal memory, and long-term verbal memory. In another recent meta-analysis of 30 studies that included 849 adult long-term recreational CU and 764 controls (Lovell et al., 2020), cannabis use was associated with significant but small-magnitude decrements in executive function, learning, and memory. More moderate decrements were noted for decision making. Cannabis use duration and age of onset did not influence outcomes.

Thus, verbal learning and executive functions such as decision-making should be the focus of longitudinal studies, which are needed to assess whether cognitive differences between users and non-users predate cannabis use onset, whether age of use onset influences long-range cognitive performance, and whether use in higher amounts or frequencies over time is associated with greater performance decrements (Gonzalez, Pacheco-Colón, Duperrouzel, & Hawes, 2017). The ongoing Adolescent Brain Cognitive Development (ABCD) study will contribute to the goal of following participants from no cannabis use into cannabis use initiation (Luciana et al., 2018), but post-initiation data is not yet available. Fried, Watkinson, and Gray (2005) were perhaps the first to follow participants from infancy to ages 17–21, identifying 113 participants who could be classified over time as controls, light cannabis users, heavy users, or former users. They measured IQ, processing speed, memory, attention, and abstract reasoning at ages 9–12 and again at ages 17–21. After controlling for pre-cannabis-initiation test performance as well as confounds such as parental income and education, academic history, age, sex, maternal age, and prenatal substance exposure, current heavy users had significantly lower IQs, influenced by visual processing speed, relative to non-users. They also displayed relatively poor immediate and delayed memory.

Similar to Fried et al. (2005), Meier and colleagues (2012) followed a birth cohort of 1,037 individuals, identifying 874 participants who either remained abstinent or who reported using cannabis at least 4 times a week for 1, 2, or 3+ study waves. Participants with persistent cannabis dependence exhibited greater IQ declines from ages 7 to 13 to 38 relative to non-users, even when controlling for relevant covariates. Critics suggested that the findings were due to confounding SES and personality factors (Daly, 2013; Rogeberg, 2013) as well as sample size attenuation over time. A subsequent co-twin control study (Jackson et al., 2016) found that lower IQ scores in young adult CU were attributable to premorbid characteristics. Castellanos-Ryan, Pingault, Parent, Vitaro, Tremblay, and Séguin (2017) observed an association between cannabis use and decrements in verbal IQ in a community sample of boys that was accounted for by level of educational attainment. A prospective analysis of participants in the Avon Longitudinal Study of Parents and Children found that heavy cannabis use before age 15 was associated with lower IQ when controlling for childhood IQ (Mokrysz, Landy, Gage, Munafò, Rosier, & Curran, 2016). This relationship was attenuated when use of other substances was controlled, with cigarette use having the most marked influence. More recently, substance use patterns and performance on a neurocognitive battery were tracked annually in a community sample over 14 years, beginning when participants were ages 12–15 (Infante, Nguyen-Louie, Worley, Courtney, Coronado, & Jacobus, 2020). After accounting for age, a greater mean percent days of cannabis use was associated with worse performance on measures of inhibitory control and visuospatial functioning, but not verbal memory or processing speed. Increased alcohol use was associated with visuospatial decrements, further highlighting the importance of examining the influences of each substance.

Finally, Barthelemy et al. (2019) prospectively assessed an urban African-American sample with intrauterine substance exposure ($n = 119$), examining associations between various aspects of verbal learning/memory and cannabis use as it emerged over time. Individuals with cannabis use onset before age 16 showed a decline in structured verbal learning (story memory) performance between adolescence and young adulthood. Trajectories of learning ability were impacted by factors such as educational attainment, recent substance use, and presence of psychopathology.

Together, these studies affirm conclusions drawn by Gonzalez et al. (2017): even within longitudinal studies, the magnitude of observed effects of CU on cognition are modest in size (consistent with cross-sectional meta-analyses), performance decrements tend to be observed only among the heaviest or more frequent CU, and control over relevant confounds, such as sociodemographic factors and comorbid substance use, is needed. Many of the aforementioned studies had gaps of nearly 6–7 years or more between measurements of pre- and post-initiation cognition (Castellanos-Ryan et al., 2017; Meier et al., 2012; Mokrysz et al., 2016). Minimizing the amount of time between measurements permits a more fine-grained analysis of when cognitive decrements emerge relative to use onset.

To examine verbal learning, memory and decision-making before versus after substance use initiation, the current study utilized data from a prospective longitudinal study that followed adolescents and young adults over 10 years, with a comprehensive neurocognitive battery and substance-use information collected every two years. We identified participants who initiated cannabis as well as alcohol use ($n = 47$) as well as those who initiated alcohol but not cannabis use ($n = 39$). Motivation for the tasks included in this analysis derives from our prior findings (Becker et al., 2014, 2018), which focused on the longitudinal progression of cognitive performance in a college sample that had already initiated cannabis use at their baseline. These daily CUs showed significant performance decrements, as compared to non-using controls, in verbal memory (RAVLT) as well as IGT-based decision-making. The relative weaknesses in memory persisted over time with continued heavy use. That analysis could not address whether decrements were evident prior to cannabis use onset or the extent to which comparable performance decrements might have been observed in equivalently heavy users of alcohol but not cannabis. Thus, the current study followed individuals from before substance use initiation into cannabis and/or alcohol use, allowing post-initiation learning, memory, and decision-making performance to be evaluated relative to pre-initiation performance for users of each substance. Based on the literature suggesting maximal impairments post-initiation in heavier or more frequent cannabis users (Gonzalez et al., 2017), we hypothesized that more frequent cannabis users would produce significantly lower RAVLT and IGT scores relative to alcohol-only and infrequent cannabis users.

METHODS

The study was approved by the University of Minnesota's human subjects committee (protocol 0405M59982). Participants ranged in age from 9 to 23 years at baseline, and were invited to complete four subsequent assessments, spaced approximately two years apart. For minors, families were recruited through a community database maintained by the University of Minnesota Institute of Child Development. When their child was born, parents throughout the metro area indicated an interest in participating in University-sponsored research, allowing adolescents to be identified within the database. Additionally, invitation postcards were mailed to nonacademic University employees who might be parents. Young adults (aged 18+) were recruited through community postings.

At baseline, families completed a phone screening followed by an in-person clinical assessment (Kiddie-SADS-Present and Lifetime Version (KSADS-PL): Kaufman, Birmaher, Brent, Rao, & Ryan, 1996) that determined study eligibility. The KSADS-PL is a semi-structured interview with excellent psychometric properties, administered in this study to the youth and parent, that assesses developmental and social history as well as Axis-I childhood and adult disorders as defined by DSM-IV (American Psychiatric Association, 2000). Baseline exclusions included histories of neurological or psychiatric disorders, preterm birth, other birth complications, current or past substance abuse, prior head injury, learning disabilities, current psychoactive prescription use, non-native English speaking, and uncorrected vision/hearing. As this study also involved neuroimaging (not presented here), non-right-handers and those with imaging contraindications were excluded.

At baseline, 197 individuals were enrolled. Substance use was assessed using the Personal Experiences Inventory (PEI: Henley & Winters, 1989), the Achenbach Youth and Adult Self-Report scales (Achenbach & Rescorla, 2001, 2003), and the KSADS-PL. The KSADS-PL includes screening questions that query presence/absence of specific substances used as well as more comprehensive questions about problematic use if an individual reports regular ingestion of a given substance. The Achenbach scales include questions about amounts of nicotine used daily in the past six months. The PEI self-report questionnaire queries substance use frequencies, including alcohol and cannabis, for the prior 5 years (or lifetime for adolescents), prior 12 months, and prior 3 months. Participants indicated on a five-point scale the frequency of use within the designated time period. Responses to the adolescent and adult PEI versions were harmonized to eliminate minor differences in response formats. Values of 0 indicated no use of a particular substance; 1 = 1–5 uses; 2 = 6–20 uses; 3 = 21–49 uses; 4 = 50–99 uses; 5 = over 100 uses within the specified time period.

Verbal learning and memory were assessed at each study wave with the Rey Auditory Verbal Learning Test (RAVLT: Rey, 1993) under standardized conditions. Participants were read a 15-word list over 5 learning trials and were instructed to state as many words as they could remember following each trial. Following five learning trials, an interference trial of 15 different words (List B) was presented and recalled, followed by immediate recall of words from the first list. Thirty minutes later, participants recalled words from the first list (delayed recall). Alternate forms with different word lists were used across study waves.

Performance metrics reflected verbal learning (total correct recollections across the first five learning trials), new learning (performance on the first trial as well as the List B

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interference trial, averaged), immediate recall, and 30-minute delayed recall. Delayed recall divided by the total correct on the last learning trial (Trial 5) was calculated to quantify the proportion of information consolidated over time (Takagi et al., 2011).

Participants completed a computerized 100-trial variant of the Iowa Gambling Task (IGT: Almy, Kuskowski, Malone, Myers, & Luciana, 2018; Hooper, Luciana, Conklin, & Yarger, 2004), a measure of feedback-guided decision making. Participants began with a fixed amount of loaned money and then selected from four simulated card decks on each trial. Participants received feedback on monetary gains and losses from each choice. Choices were unlimited from each deck. Selections from two decks resulted in long-term monetary gains (advantageous decks). Selections from two decks resulted in long-term losses (disadvantageous decks). Deck contingencies are described in Almy et al. (2018). Participants kept earned winnings, which did not exceed $5.00. The layout of the four decks was shuffled across study waves.

Performance metrics included the difference between the participants' total number of advantageous and disadvantageous deck choices (a) across all 100 trials as well as (b) within the first 40 trials, summed, which reflect decision-making under ambiguity, and (c) the last 60 trials, summed, which reflect decision-making under risk (Almy et al., 2018). For the RAVLT and IGT, raw scores were used in the analyses.

IQ was estimated from performance on the full Wechsler Abbreviated Scale of Intelligence (WASI: Wechsler, 1999). Demographic data, including socioeconomic, health, and family information, were collected from parents (for minor participants) and from participants (if over age 18).

STATISTICAL APPROACH

Data were analyzed using SPSS version 26 for Windows. After examining participants' reported past five years' cannabis and alcohol usage levels across assessments using the PEI and KSADS, participants were identified who completed more than one assessment ($n = 168$ of 197). Of these, $n = 99$ were substance naïve at baseline, and either initiated substance use during the course of the study ($n = 86$) or remained substance naïve ($n = 13$). This analysis focuses on the 86 individuals who initiated substance use. Those classified as persistent non-users were not included, because the sample is small, they were younger at study intake than the substance use initiators, and they completed significantly fewer assessment waves. Of 86 substance use initiators, $n = 39$ initiated use of alcohol but not cannabis; $n = 47$ initiated cannabis use. The study wave at which use initiation was detected was recorded as the post-initiation time point. The study wave prior to that one was recorded as the pre-initiation time point. Of those who initiated cannabis use, all also initiated alcohol use. Those who initiated cannabis use comprised two groups (Fried, Watkinson, James, & Gray, 2002; Fried et al., 2005; Gonzalez et al., 2017) based on their frequencies of reported use: infrequent cannabis users ($n = 29$) and moderately frequent cannabis users ($n = 18$). Infrequent cannabis users transitioned from no reported use at one time point to 1–5 uses within the past year at the post-initiation time point. Moderately frequent cannabis users transitioned from no use at one time point to six or more uses within the past year post-initiation. Longitudinal retention was generally acceptable. Of the 86 substance use initiators, $n = 63$ were retained through the last assessment (wave 5) of the study, $n = 72$ were retained through wave 4, $n = 81$ were retained through wave 3, and $n = 86$ were retained through wave 2.

For alcohol initiators ($n = 39$), 25 were retained through wave 5; 32 were retained through wave 4, 35 were retained through wave 3, and 39 were retained through wave 2. For less frequent marijuana initiators ($n = 29$), 24 were retained through wave 5, 26 were retained through wave 4, and 28 were retained through wave 3, and 29 were retained through wave 2. For more frequent marijuana initiators ($n = 18$), 14 were retained through wave 5, 15 were retained through wave 4, 17 were retained through wave 3, and 18 were retained through wave 2.

Table 1 indicates when in the course of the study alcohol and cannabis use initiation were detected in each group.

The groups were compared using one-way analyses of variance on age, IQ, parental (average of mother and father) years of education, family income, number of study visits before substance use initiation was identified, and substance use frequencies after initiation. Gender and race/ethnicity distributions were compared between groups using chi-square tests.

RAVLT and IGT performance metrics were based on raw scores and were analyzed as follows. Pre-initiation performance was contrasted between groups using generalized linear models with cognitive performance as a univariate factor and group as a between-subjects factor. Parental education was covaried (rationale below). The difference between pre-initiation and post-initiation performance was calculated for each cognitive variable of interest and contrasted by group using ANCOVA; covariates included pre-initiation performance and parental education. As planned follow-up tests for each ANCOVA, *a priori* contrasts on the estimated marginal means were conducted pairwise between groups, with Bonferroni adjustment of the nominal $p < .05$ threshold for statistical significance.

In addition, hierarchical linear regressions were utilized for the full sample of substance use initiators, regardless of group status, to assess the extent to which quantitative frequencies of cannabis, alcohol, and nicotine use contributed to observed cognitive function post-initiation, controlling for pre-initiation performance levels as well as parental education.

RESULTS

Sample characteristics

As indicated in Table 2, the 86 substance use initiators were from middle to upper-middle class backgrounds and had

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Table 1. Substance use initiation patterns across time by group

	Total # Initiated	Alcohol-only Users	Infrequent Cannabis Users	Moderately frequent Cannabis Users
Wave 2:	26	15	8	3
Wave 3:	18	7	8	3
Wave 4:	25	12	7	6
Wave 5:	17	5	6	6
Total:	86	39	29	18

Values represent numbers of individuals who reported substance use initiation at each assessment wave post-baseline. All were substance naïve at the Wave 1 baseline assessment.

estimated IQs in the above average range. When subgrouped, those who were infrequent versus moderately frequent users of cannabis were comparable in gender distribution, pre-initiation age, post-initiation age, ethnic composition, estimated IQ scores, self-reported frequencies of alcohol use in the past year, and the number of study visits prior to the capture of substance use initiation. Parental education levels were significantly lower for moderately frequent cannabis users versus infrequent cannabis users. Nicotine use was higher in the moderately frequent cannabis users post-initiation as compared to the other groups but was infrequent overall: only 7 of 86 individuals reported any nicotine use. Cannabis use frequencies differed between groups. Alcohol-only users as compared to cannabis users had higher levels of parental education, higher family incomes, and lower frequencies of alcohol, nicotine, and cannabis use. Thus, the groups varied in frequencies of alcohol, nicotine, and cannabis use but also in parental education.

Bivariate correlations between demographic variables and task performance are shown for descriptive purposes in Table 3. Pre-initiation task performance was examined in relation to demographic variables. Parental education was marginally associated with the RAVLT total learning score (summed performance across trials 1–5: $r = .201$, $p = .067$) and significantly associated with the IGT total number of advantageous relative to disadvantageous choices ($r = .418$, $p = .000$). Age was also associated with this IGT total score ($r = .226$, $p = .040$) but not with RAVLT outcomes. IQ was significantly associated with IGT performance ($r = .295$, $p = .007$) but not with RAVLT outcomes.

Pre-initiation cognitive performance

Pre-initiation task performance was contrasted between groups using ANCOVAs, controlling for parental education (Table 4). RAVLT new learning (the average of Trial 1 and List B total correct raw scores) differed between groups: $F(2,80) = 3.79$, $p = .027$, $\eta_p^2 = .09$. Follow-up pairwise contrasts indicated that those who subsequently initiated moderately frequent cannabis use produced lower scores than those who initiated alcohol-only ($p = .039$) as well as infrequent cannabis ($p = .045$) use (see Figure 1).

Change in cognitive performance with substance use initiation

When change scores were similarly contrasted between the groups (Table 5), group differences were observed in total verbal learning (sum of raw scores across the five RAVLT learning trials), $F(2,78) = 3.70$, $p = .03$, $\eta_p 2 = .09$, with declines in performance over time in the moderately frequent cannabis users relative to infrequent cannabis users ($p = .04$).

The magnitude of change over time in 30-minute delayed recall also varied by group, $F(2,78) = 4.55$, $p = .014$, $\eta_p^2 = .10$. The moderately frequent cannabis users showed declines in delayed recall over time relative to infrequent cannabis users ($p = .011$). Neither group differed from alcohol-only users (Figure 2). Accordingly, we examined the post-initiation proportion of learned information consolidated over time (total raw score for delayed recall divided by total raw score for Trial 5). The proportion of consolidated information differed between groups, $F(2,79) = 3.45$, $p = .037$, $\eta_p^2 = .08$, with moderately frequent cannabis users performing marginally worse (retaining M = .74, SE = .05 of learned information) than each of the other two groups (alcohol-only users: M = .87, SE = .03, $p = .064$; infrequent cannabis users: M = .88, SE = .04, $p = .051$). As indicated in Table 5, this finding is reduced in significance ($p = .053$) when difference scores are analyzed.

IGT performance was evaluated by analyzing group differences in decision-making performance (total number of advantageous minus disadvantageous choices) over all 100 trials both before and after substance use initiation. Performance under conditions of initial ambiguity (first 40 trials) and under conditions of known risk (last 60 trials) was also evaluated (Almy et al., 2018). No significant group differences were detected (Tables 4 and 5).

Contributions of cannabis, alcohol, and nicotine use to post-initiation RAVLT performance

Hierarchical regressions using continuous substance-use variables, as compared to ANCOVA groupings, confirmed that the observed effects were due to levels of cannabis and not alcohol use. Nicotine use exerted an effect on some performance variables. Analyses focused on the RAVLT total

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Table 2. Demographics: alcohol and cannabis use initiators

		A	B	C	D			
	Total Sample	Alcohol-only Users	Cannabis Users (Total)	Infrequent Cannabis Users	Moderately frequent Cannabis Users	A vs. B	C vs. D	A vs. C vs. D
n =	86	39	47	29	18	–	–	–
Age (Pre-initiation)	16.38 (2.57)	16.36 (2.4)	16.40 (2.7)	16.8 (2.4)	15.8 (27)	$F = .007$; $p = .933$	$F = 1.40$, $p = .244$	$F = .764$, $p = .469$
Age Range (Pre-initiation)	10.72–24.05	11.74–20.96	10.72–24.05	11.88–24.05	10.72–20.51	–	–	–
Age (Post-Initiation)	19.23 (2.44)	19.03 (2.2)	19.40 (2.6)	19.4 (2.8)	19.4 (2.4)	$F = .492$; $p = .485$	$F = 0.006$, $p = .940$	$F = .246$, $p = .782$
Age Range (Post-Initiation)	14.01–26.09	14.01–22.59	14.17–26.09	14.24–26.09	14.17–23.42	–	–	–
Gender (#M; #F; #Other)	47:39:0	19:20:0	28:19:0	18:11:0	10:8:0	X^2=1.01, $p = .314$	$X^2 = .196$, $p = .763$	$X^2 = 1.20$, $p = .548$
WASI-estimated IQ[a] (Pre-initiation)	115.0 (11.5)	116.6 (9.8)	113.7 (12.5)	113.2 (12.8)	114.5 (12.3)	$F = 1.40$, $p = .240$	$F = .123$, $p = .727$	$F = .768$, $p = .467$
White:Non-White Ethnicity	78:8	38:1	40:7	24:5	16:2	X^2=4.35, $p = .227$	X^2=2.14, $p = .543$	X^2=7.37, $p = .288$
Parental Education (averaged; years)	15.96 (1.99)	16.4 (2.1)	15.6 (1.9)	16.1 (1.9)‘	14.8 (1.4)	$F = 3.21$, $p = .077$	$F =$ **5.64**, $p =$ **.022**	$F =$ **4.09**, $p =$ **.020**
Family Income US Dollars (study baseline)	95537.5 (66279.6)	111944.4 (89381.0)	82113.6 (34035.7)	79038.5 (30855.1)	86555.6 (38661.8)	$F =$ **4.17**, $p =$ **.044**	$F = .513$, $p = .478$	$F = 2.13$, $p = .125$
Past six months daily nicotine use frequency Pre-initiation[b]	0.00	0.00	0.00	0.00	0.00	**–**	–	–
Past six months daily nicotine use frequency Post-initiation[b]	0.28 (1.61)	0.03 (0.16)	0.57 (2.32)	0.00 (0.00)	1.50 (3.62)	$F = 2.17$, $p = .144$	$F =$ **5.05**, $p =$ **.030**	$F =$ **5.83**, $p =$ **.004**
Alcohol Use Frequency Past 12 months, Pre-initiation[c]	0.28 (0.66)	0.00 (0.00)	0.75 (0.92)	0.90 (0.97)	0.50 (0.80)	$F =$ **17.38**, $p =$ **.000**	$F = 1.45$, $p = .238$	$F =$ **10.28**, $p =$ **.000**
Alcohol Use Frequency Past 12 months Post-initiation[c]	1.94 (1.14)	1.41 (0.97)	2.38 (1.10)	2.34 (1.17)	2.44 (0.98)	$F =$ **18.71**, $p =$ **.000**	$F = .090$, $p = .765$	$F =$ **9.31**, $p =$ **.000**
Cannabis Use Frequency Past 12 months Post-initiation[c]	0.81 (1.82)	0.00 (0.00)	1.49 (0.95)	0.86 (0.35)	2.5 (0.71)	$F =$ **95.14**, $p =$ **.000**	$F =$ **112.2**, $p =$ **.000**	$F =$ **267.71**, $p =$ **.000**
Study visits before initiation	1.99 (0.91)	1.87 (0.83)	2.09 (0.97)	2.10 (0.94)	2.10 (1.06)	$F = 1.16$, $p = .284$	$F = .026$, $p = .872$	$F = .590$, $p = .567$

Unless otherwise indicated, values represent means and, in parentheses, one standard deviation.
[a]WASI-estimated IQs are based on four subtests: Vocabulary, Matrix Reasoning, Similarities, and Block Design.
[b]Nicotine use = the number of reported uses per day in the past six months assessed by the Achenbach self-report inventories.
[c]Alcohol and cannabis use frequencies for the twelve months prior to each assessment were assessed with the Personal Experiences Inventory (PEI): 0=0 use; 1=1–5 times; 2 = 6–20 times; 3 = 21–49 times; 4=50–99 times.

Table 3. Bivariate correlations between demographic variables and pre-initiation RAVLT and IGT performance metrics

Pre-initiation variable	RAVLT Total Learning (Trials 1–5)	RAVLT New Learning (Trial 1, List B)	RAVLT 30-minute delayed recall	RAVLT proportion of information consolidated	IGT Total Advantageous minus Disadvantageous Choices	IGT Total Advantageous minus Disadvantageous: Choices Made Under Ambiguity (Trials 1–40)	IGT Total Advantageous minus Disadvantageous: Choices Made Under Risk (Trials 41–100)
Age	.022	.036	.009	−.056	**.226***	.049	**.278***
Estimated Full-Scale IQ	.169	−.030	.078	−.077	**.295****	**.256***	**.261***
Number of study visits before detection of substance use	.041	.053	−.034	−.034	**.263***	**.279***	.208
Gender (1=male; 2=female)	.204	**.265***	−.014	−.195	−.001	.035	−.020
Average reported family income (US dollars)	.014	.071	.119	.039	.050	.040	.047
Average parental education	.201	.102	.014	−.109	**.418****	**.250***	**.429****

* two-tailed $p < .05$; ** two-tailed $p < .01$; Values represent Pearson r coefficients.

learning score across trials 1–5, RAVLT new learning, RAVLT 30-minute delayed recall total correct, and the RAVLT proportion of consolidated information. For each of these analyses, the dependent variable was post-initiation level of performance. Step 1 predictors included parental education and pre-initiation levels of performance. Step 2 predictors included post-initiation alcohol use and post-initiation nicotine use. Step 3 predictors included post-initiation cannabis use. See Table 6 for full statistics.

For the analysis of new learning, Step 1 model was significant, but Steps 2 and 3 were not incrementally predictive. Significant unique predictors of better post-initiation performance included higher parental education and higher pre-initiation performance levels. For the total words learned across trials 1–5, Step 3 model was incrementally significant. Significant unique predictors of better post-initiation performance included higher levels of pre-initiation performance as well as lower frequencies of cannabis use. For 30-minute delayed recall as well as proportion of information retained over time, again Step 3 model was incrementally significant. Significant unique predictors of better post-initiation performance for both delayed memory variables included better pre-initiation performance as well as lower frequencies of cannabis use. Additionally, a lower frequency of nicotine use was associated with a greater proportion of information consolidated over the RAVLT recall period ($p = .047$) and with the absolute level of delayed recall ($p = .037$). Alcohol use frequency was not a significant independent predictor of any performance variable.

DISCUSSION

Although many studies provide evidence of relative decrements in cognition in recreational cannabis users, few have followed adolescents from a substance naïve pre-initiation period into the initiation of use. Fewer still have distinguished the effects of cannabis, nicotine, and alcohol use on cognitive outcomes even though cannabis users frequently report use of other substances (Mejia, Wade, Baca, Diaz, & Jacobus, 2021; Patrick, Terry-McElrath, Lee, & Schulenberg, 2019). This study expanded upon our prior analyses of cognition in daily cannabis users (Becker et al., 2014, 2018) and focused on the Rey Auditory Verbal Learning Task, a commonly used measure of verbal learning and memory, as well as the Iowa Gambling Task, a measure of feedback-guided decision-making.

Concordant with recent reviews and meta-analyses (Broyd et al., 2016; Lovell et al., 2020; Schoeler, Kambeitz, Behlke, Murray, & Bhattacharyya, 2016) indicating that decrements in verbal learning and memory performance are among the most consistently observed cognitive effects in the context of cannabis use and that these functions may be longitudinally impacted by use (Gonzalez et al., 2017), we observed that overall verbal learning across the first five trials of the RAVLT was diminished after the onset of moderately frequent cannabis use, after controlling for parental education

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Table 4. Pre- and post-initiation neuropsychological test scores for participants who initiated infrequent use of cannabis, moderately frequent use of cannabis, and use of alcohol but not cannabis

	Pre-Initiation			Post-Initiation			Group Differences	
Cognitive Measure	Infrequent Cannabis Users (IF)	Moderately Frequent Cannabis users (MF)	Alcohol-Only Users (AO)	Infrequent Cannabis Users (IF)	Moderately Frequent Cannabis Users (MF)	Alcohol-only Users (AO)	Pre-Initiation Only	Nature of group differences
n =	29	18	39	29	18	39	–	–
RAVLT							*F (p)/* η_p^2	
Sum Total Correct: Trials 1–5	53.55 (1.49)	51.24 (1.93)	53.56 (1.29)	56.61 (1.63)	49.41 (2.10)	52.77 (1.44)	0.59/.574/.01	
Trial 1	7.21 (.34)	6.06 (.44)	7.32 (.29)	7.55 (.29)	6.28 (.38)	7.09 (.26)	N/A; values presented	
Trial 2	9.45 (.39)	9.05 (.51)	10.15 (.34)	10.56 (.41)	8.93 (.53)	9.77 (.36)	for descriptive pur-	
Trial 3	11.51 (.39)	11.13 (.51)	11.38 (.33)	12.13 (.39)	10.86 (.50)	11.65 (.34)	poses	
Trial 4	12.61 (.38)	12.18 (.49)	11.99 (.33)	13.03 (.40)	11.26 (.52)	11.82 (.36)		
Trial 5	12.77 (.32)	12.82 (.41)	12.73 (.27)	13.35 (.40)	12.13 (.52)	12.78 (.35)		
New Learning (Average: Trial 1, ListB)	6.84 (.27)	5.73 (.35)	6.83 (.24)	6.87 (.23)	5.95 (.30)	6.72 (.21)	**3.79/.027/.09**	MF < AO; MF < IF
List B interference trial	6.47 (.30)	5.41 (.39)	6.23 (.26)	6.18 (.27)	5.62 (.34)	6.35 (.23)	N/A; values presented for descriptive purposes	
Immediate recall	11.20 (.46)	11.11 (.59)	11.38 (.40)	12.07 (.47)	10.79 (.61)	11.54 (.42)	0.08/.922/.00	
30-minute delayed recall	10.93 (.51)	10.65 (.65)	11.19 (.44)	11.70 (.51)	9.54 (.66)	11.07 (.45)	0.24/.791/.01	
Proportion of consolidated information (Delayed recall/Total correct trial 5)	0.86 (.03)	0.83 (.04)	0.88 (.03)	.88 (.04)	.74 (.05)	.87 (.03)	0.52/.596/.01	
Iowa Gambling Task								
Total Adv-Disadv choices	13.1 (6.6)	8.1 (8.8)	19.5 (5.8)	28.42 (6.5)	20.81 (8.4)	24.10 (5.7)	0.62/.539/.02	
Total Adv-Disadv choices for Trials 1–40: Decisions under ambiguity	1.50 (14.23)	−1.29 (18.08)	2.00 (13.42)	2.79 (2.62)	0.74 (3.50)	0.26 (2.34)	0.00/.997/.00	
Total Adv-Disadv choices for Trials 41–100: Decisions under risk	12.64 (24.07)	0.59 (33.72)	20.70 (27.25)	26.64 (4.46)	20.38 (5.98)	22.71 (4.00)	1.10/.339/.03	

Notes. Estimated marginal means and standard errors are presented, controlling for parental education. Comparisons where *p*-values are statistically significant ($p<.05$) are bolded. Unless otherwise specified, values represent raw total correct scores for each trial of the RAVLT; raw scores were also used for IGT calculations.

Table 5. Pre- and post-initiation difference scores by group

Cognitive Measure	Post- minus Pre-Initiation: Infrequent Cannabis Users (IF)	Post- minus Pre-Initiation: Moderately Frequent Cannabis users (MF)	Post- minus Pre-Initiation: Alcohol-Only Users (AO)	Group Differences: Post-Initiation minus Pre-Initiation Controlling for Pre-Initiation Performance	Group Differences: Nature of Significant group differences
n =	29	18	39	–	–
RAVLT				F $(p)/\ \eta_p^2$	
Sum Total Correct: Trials 1–5	3.34 (1.5)	−2.81 (1.9)	−0.56 (1.3)	**3.70/.029/.09**	MF < IF
New Learning (Average: Trial 1, ListB)	0.38 (.45)	−0.84 (.60)	0.07 (.39)	1.29/.281/.03	–
Immediate recall	0.85 (.41)	−0.39 (.53)	0.23 (.36)	1.75 /.181/.04	–
30-minute delayed recall	0.74 (.40)	−1.25 (.52)	−0.06 (.35)	**4.55/.014/.10**	MF < IF
Proportion of consolidated information (Delayed recall/Total correct trial 5)	0.02 (.33)	−0.11 (.04)	−0.00 (.03)	3.05/.053/.07	–
Iowa Gambling Task					
Total Adv-Disadv choices	14.00 (5.8)	6.23 (7.80)	7.75 (5.2)	.50/.609/.013	–
Total Adv-Disadv choices for Trials 1–40: Decisions under ambiguity	1.71 (18.98)	−0.94 (16.55)	−0.89 (17.54)	0.28/.760/.01	–
Total Adv-Disadv choices for Trials 41–100: Decisions under risk	12.80 (4.46)	6.52 (5.98)	8.86 (4.00)	0.41/.668/.01	–

Estimated marginal means and standard errors are presented, controlling for parental education and pre-initiation performance.
Comparisons where p-values are statistically significant (p<.05) are bolded.

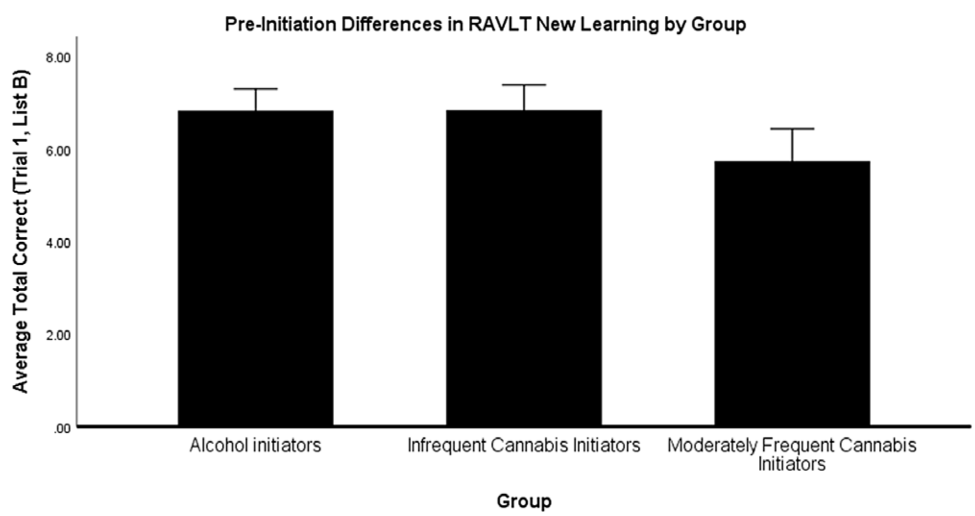

Fig. 1. Pre-initiation RAVLT new learning scores were calculated by averaging the total raw correct responses to trial 1 and List B. Values represent estimated marginal means ± the 95% confidence interval. As indicated, there was a main effect of group on performance with worse performance in the moderately frequent cannabis users relative to alcohol-only users (p = .039) and infrequent cannabis users (p = .045).

and premorbid variations. The observed performance decrements were not associated with post-initiation alcohol or nicotine use, as suggested by our regression analyses, which was important to demonstrate given that alcohol use was associated with deviations in RAVLT-based verbal learning in a recent co-twin control analysis of adolescent users (Malone, Wilson, Bair, McGue, & Iacono, 2020). Moderately frequent cannabis users also showed pre-initiation decrements in new learning performance, consistent with the idea that those with poor baseline executive function, such as working memory, are vulnerable to behavioral dysregulation including reduced control of substance use (Khurana, Romer, Betancourt, & Hurt, 2017; Kim-Spoon et al., 2017).

Learning ability, as well as working memory, can be impacted by general ability (Mohn, Sundet, & Rund, 2014) and by age, though it should be emphasized that participants had mean estimated IQs in the above-average range, and age did not vary between groups. Moreover, age and IQ were not

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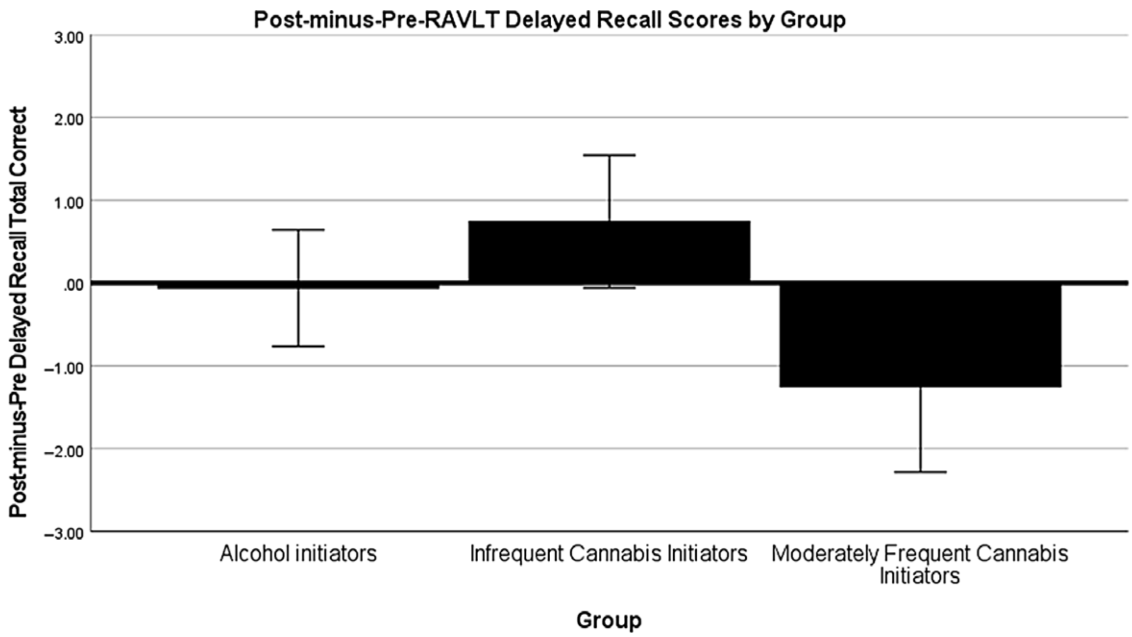

Fig. 2. Differences between pre- and post-initiation RAVLT 30-minute delayed recall scores are presented for each group, controlling for parental education and pre-initiation performance. Values are estimated marginal means ± the 95% confidence interval. Positive scores reflect increases over time; negative scores reflect decreases over time. Those who initiated moderately frequent use of cannabis showed declines in performance from pre-to-post-initiation relative to less frequent users of cannabis ($p = .011$).

associated with RAVLT performance. However, parental education significantly predicted RAVLT new learning and total learning performance, and parental education levels were lower particularly for those who reported moderately frequent cannabis use. To explain the pattern that we observed, one might speculate that additional pre-initiation factors may have impacted performance. For instance, higher levels of state anxiety that contribute to higher frequencies of cannabis use (e.g., as self-medication) could interfere with learning and memory performance on more challenging tasks. However, recent reviews and empirical assessments challenge this notion and suggest that, in fact, verbal memory tests are not markedly vulnerable to test anxiety in neuropsychological patients (Gass & Curiel, 2011; Dorenkamp & Vik, 2018) nor are they vulnerable to the impacts of acute stressors (Hoffman & al'Absi, 2004) in healthy volunteers. A critical difference between those studies and the present study is that they focused on adult samples. Accordingly, additional studies addressing whether test anxiety might impact verbal memory performance in adolescence and young adults are needed.

A major finding from this study is our observation of relatively greater post-initiation declines in delayed memory recall following list learning in moderately frequent cannabis users, a decline that was not observed in infrequent cannabis users and alcohol users. This finding is consistent with cross-sectional work (Jacobus et al., 2015; Solowij et al., 2011) as well as Barthelemy et al. (2019) who also observed verbal memory declines over time in adolescent users. The finding of a decrement in only the most frequent users of cannabis provides evidence in support of a dose–response association as suggested by others (Gonzalez et al., 2017). Moreover, the finding of worse verbal memory after but not before substance use initiation adds interpretive clarity to our prior observation of similar decrements in chronic users (Becker et al., 2018). Poor verbal memory in the context of daily life might contribute to the adverse educational and psychosocial outcomes frequently observed in adolescent CU (Silins et al., 2014). While Infante et al. (2020) did not observe decrements in verbal learning or memory as a function of alcohol or cannabis use in their 14-year follow-up of adolescent users, that finding was unexpected and the length of the follow-up period may have impacted their findings.

Leveraging continuous substance use-frequency variables, we supported the observed between-group differences with regression analyses indicating that, independent of group membership, post-initiation frequencies of cannabis use predicted worse verbal memory performance independently of both alcohol use frequencies and pre-initiation performance levels. Higher levels of nicotine use also conferred verbal memory disadvantages, but in the current study, nicotine use was rare and largely comorbid with cannabis use in smokers/vapers, thus the study was not optimized to fully dissociate effects of the two substances. Co-use of nicotine is common in cannabis-using adolescents, often at higher levels than we observed (Mejia et al., 2021; Kennedy, Caraballo, Rolle, & Rock, 2016; Schauer, Berg, Kegler, Donovan, & Windle, 2016). A recent review (Mejia et al., 2021) noted that although attempts have been made to isolate independent effects of each substance, focused studies of co-users are limited currently with only 9 human and three preclinical studies available for analysis.

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Table 6. Prediction of post-initiation learning and memory performance from substance use frequencies

(a) Post-Initiation Learning (Sum of RAVLT Total Correct Trials I–V)

Model	R^2	F	p	Signif R^2-change	b	SE(b)	t	p
Step 1	.26	14.59	.000	.000				
Parental education					.90	.44	2.03	.045
Pre-initiation RAVLT Learning					.49	.11	4.50	<.001
Step 2	.26	7.23	.000	.858				
Parental education					.89	.46	1.95	.055
Pre-initiation RAVLT Learning					.49	.11	4.37	<.001
Post-initiation alcohol use frequency					−.03	.77	−0.04	.968
Post-initiation nicotine use frequency					−.28	.50	−0.55	.582
Step 3	.31	7.10	.000	.026				
Parental education					.50	.48	1.06	.291
Pre-initiation RAVLT Learning					**.46**	**.11**	**4.23**	**<.001**
Post-initiation alcohol use frequency					.76	.83	0.92	.360
Post-initiation nicotine use frequency					.01	.51	0.01	.989
Post-initiation cannabis use frequency					**−2.22**	**−2.26**	**.026**	**.98**

(b) New Learning (Average of RAVLT Total Correct Trial 1, List B)

Model	R^2	F	p	Signif R^2-change	b	SE(b)	t	p
Step 1	.24	12.81	.000	.000				
Parental education					**.18**	**.07**	**2.68**	**.009**
Pre-initiation RAVLT Learning					**.35**	**.09**	**4.00**	**<.001**
Step 2	.24	6.39	.000	.876				
Parental education					.18	.07	2.65	.010
Pre-initiation RAVLT Learning					.34	.09	3.90	<.001
Post-initiation alcohol use frequency					−.05	.12	−0.39	.699
Post-initiation nicotine use frequency					−.03	.08	−0.33	.744
Step 3	.26	5.61	.000	.136				
Parental education					.14	.07	1.93	.057
Pre-initiation RAVLT Learning					.30	.09	3.30	<.001
Post-initiation alcohol use frequency					.04	.13	0.31	.761
Post-initiation nicotine use frequency					.00	.08	0.04	.969
Post-initiation cannabis use frequency					− .24	−1.51	.136	.16

(c) Post-Initiation RAVLT 30-minute Delayed Recall

Model	R^2	F	p	Signif R^2-change	b	SE(b)	t	p
Step 1	.41	29.90	.000	.009				
Parental education					.38	.12	3.15	.002
Pre-initiation RAVLT Learning					.62	.09	7.02	<.001
Step 2	.47	17.97	.006	.023				
Parental education					.36	.12	3.02	.003
Pre-initiation RAVLT Learning					.61	.09	6.97	<.001
Post-initiation alcohol use frequency					.20	−0.36	.718	−.07
Post-initiation nicotine use frequency					−.37	.13	−2.77	.007
Step 3	.51	16.65	.000	**.013**				
Parental education					.24	.12	1.94	.056
Pre-initiation RAVLT Learning					**.60**	**.09**	**7.03**	**<.001**
Post-initiation alcohol use frequency					.16	.22	0.74	.462
Post-initiation nicotine use frequency					**−.28**	**.13**	**−2.12**	**.037**
Post-initiation cannabis use frequency					**−.66**	**.013**	**.26**	**−2.55**

(d) Post-Initiation Proportion of Consolidated Information (RAVLT Delayed Recall/Trial 5)

Model	R^2	F	p	Signif R^2-change	b	SE(b)	t	p
Step 1	.18	9.16	.000	.000				

(*Continued*)

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Table 6. (*Continued*)

(d) Post-Initiation Proportion of Consolidated Information (RAVLT Delayed Recall/Trial 5)

Model	R^2	F	p	Signif R^2-change	b	SE(b)	t	p
Parental education					.02	.01	2.48	.015
Pre-initiation RAVLT Learning					.43	.12	3.74	<.001
Step 2	.25	6.73	.000	.029				
Parental education					.02	.01	2.28	.025
Pre-initiation RAVLT Learning					.41	.11	3.67	<.001
Post-initiation alcohol use frequency					.02	−0.20	.844	−.00
Post-initiation nicotine use frequency					−.03	.01	−2.71	.008
Step 3	.32	7.36	.000	**.007**				
Parental education					.01	.01	1.15	.254
Pre-initiation RAVLT Learning					**.40**	**.11**	**3.64**	**<.001**
Post-initiation alcohol use frequency					.02	.02	0.98	.328
Post-initiation nicotine use frequency					**.01**	**−2.02**	**.047**	**−.02**
Post-initiation cannabis use frequency					**−.06**	**.02**	**−2.78**	**.007**

Three human studies of adolescent or young adult users (Hindocha, Freeman, Xia, Shaban, & Curran, 2017; Jacobsen, Pugh, Constable, Westerveld, & Mencl, 2007; Schuster, Crane, Mermelstein, & Gonzalez, 2015) suggest that nicotine use may, under some conditions, exert a protective effect on episodic memory processes in CU, particularly when used proximal to the time of cognitive testing. This is not the pattern of results that we observed, and the nicotine-using participants in the current study were abstinent on the day of testing. Preclinical evidence is more mixed, suggesting that females may be more vulnerable to adverse effects of co-use on memory processes (Mateos et al., 2011). A more comprehensive effort to dissociate the impacts of nicotine and cannabis co-use is clearly needed, particularly given recent accelerations in vaping activity among adolescents. This activity has been associated with both e-cigarettes containing nicotine as well as the vaping of cannabis products, further supporting the notion that the effects of each substance as well as their interactions should be a focus of continued study (Chadi, Hadland, & Harris, 2019).

While we did not use functional magnetic resonance imaging to address directly the neural mechanisms that underpin the verbal learning and memory decrements in moderately frequent cannabis users, an abundance of evidence indicates that hippocampal functioning is disrupted by THC (Kruk-Slomka, Dzik, Budzynska, & Biala, 2017; Solowij & Battisti, 2008). The endogenous cannabinoid system includes two broad receptor types (CB1 and CB2). CB1 receptors are distributed throughout the cortex, amygdala, hippocampus, striatum, and cerebellum. Preclinical work in adult animals indicates that CB1 agonists, including THC, impair learning acquisition as demonstrated through several hippocampally sensitive paradigms (Kruk-Slomka et al., 2017; Lisman & Grace, 2005; Lupica, Hu, Devinsky, & Hoffman, 2017). Long-term potentiation and depression, core substrates of learning, are disrupted by THC (Kruk-Slomka et al., 2017). Moreover, hippocampal circuits interact with the prefrontal cortex, which facilitates strategic aspects of free recall (Long, Oztekin, & Badre, 2010) as required by the RAVLT. Via connections between the hippocampal CA3 subfield and midbrain dopamine neurons, THC disruption of hippocampal circuitry alters incentive motivation, impacting reward salience (Loureiro, Renard, Zunder, & Laviolette, 2015; Lupica, Riegel, & Hoffman, 2004).

Contrary to these predicted effects of cannabis use on motivational processes, cannabis use was not associated with IGT performance. This pattern was unexpected given that impulsive decision-making is increasingly recognized as a vulnerability factor for substance misuse (Lovell et al., 2020; Mallorquí-Bagué et al., 2016; Verdejo-Garcia et al., 2007), and several studies, including those from our own lab (Becker et al., 2014), suggest IGT-based decision-making impairments in young adults. IGT-based decision-making shows pronounced developmental change during adolescents (Almy et al., 2018), and individual variation in performance was pronounced for participants in the current analysis. Despite shuffling the spatial layout of IGT deck contingencies over assessment waves, it may have been difficult for us to demonstrate longitudinal declines in performance given that the novelty of the task is reduced after a participant detects the presence of a set of contingencies to guide deck choices. This knowledge might facilitate decision-making on subsequent re-testing (Almy et al., 2018). It may also be that motivated decision-making processes are affected primarily by clinical levels of substance abuse and dependence (Ernst et al., 2003), rather than light-to-moderate use levels as reported in this study.

Limitations

Our sample size, while similar to other longitudinal studies of substance use initiators (Barthelemy et al., 2019; Fried et al., 2005), is modest, particularly as compared to recently initiated epidemiologically informed samples such as ABCD. Although the sample matched local demographics at study onset, there is limited representation of non-white and

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Hispanic ethnic and racial groups as well as individuals in low socioeconomic strata. While the results may not generalize to disadvantaged groups who may experience cumulative adversities over time (Green, Doherty, & Ensminger, 2017), the observation of cognitive declines post-initiation in more advantaged individuals who are assumed to have greater levels of cognitive reserve (Cutuli, Ladrón de Guevara-Miranda, Castilla-Ortega, Santín, & Sampedro-Piquero, 2019) is significant. To mitigate the potential effects of sociodemographic factors that may impact substance misuse (Swendsen et al., 2009), all analyses controlled for parental education. Larger studies (e.g., ABCD) will be better powered to disentangle the effects of socioeconomic variables on performance trajectories and will likely be better powered to include a control group of persistent non-users. In addition, while we assessed at each assessment wave whether individuals were actively engaged in substance use and how frequently they used, we did not undertake a more fine-grained assessment of quantity of cannabis used per occasion of use. Going forward, a more detailed assessment of cannabis use with regard to actual grams used and the potency of cannabis products used, especially as concentrates grow in popularity, will be increasingly important for future studies that attempt to draw conclusions regarding dose–response associations (Hindocha, Nordberg, & Tomko, 2018). The same is true for nicotine.

Because this study was initially designed to address adolescent brain and behavioral development, we did not conduct formal drug screenings. We asked about the timing of recent substance use, and 24 hours of self-reported abstinence was required. Research assistants observed participants for signs of acute or residual intoxication. While we cannot exclude the possibility that participants engaged in substance use prior to arrival, cognitive testing was unlikely to have been impacted, since participants arrived for testing at 8 AM, typically with a parent, and cognitive testing began several hours after the start of each session. Nonetheless, external validation of recent abstinence remains a best practice (e.g., Infante et al., 2020).

The study is notable for several strengths, including a multi-wave longitudinal assessment and the incorporation of well-validated measures of learning, memory, and decision-making, enhancing the rigor of the work. This is one of the first studies to demonstrate significant declines in verbal learning and memory pre-to-post-substance use-initiation in a non-clinical sample. It may be the first to incorporate a group of alcohol-only users as a control group. Findings affirm that verbal learning and memory should be a continued focus as we investigate the longitudinal impacts of adolescent and young adult cannabis use on the brain, behavior, and long-range outcomes.

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CONFLICTS OF INTEREST

The authors have no conflicts to disclose.

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