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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(RECEIVED September 18, 2020; FINAL REVISION March 30, 2021; ACCEPTED April 21, 2021)

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, Göñenc, & 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,
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; Jacobs 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. Figueredo 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 (Mokrýsz, 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
Participants completed a computerized 100-trial variant of the Iowa Gambling Task (IGT: Almy, Kuskowski, Malone, Myers, & Luciana, 2018; Hooper, Luciana, Conklin, & Yager, 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 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.

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RESULTS

Sample characteristics

As indicated in Table 2, the 86 substance use initiators were from middle to upper-middle class backgrounds and had
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: $F(2,80) = 3.79, p = .027, \eta^2_p = .09$. 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), $F(2,78) = 3.70, p = .03, \eta^2_p = .09$, 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, $F(2,78) = 4.55, p = .014, \eta^2_p = .10$. 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, $F(2,79) = 3.45, p = .037, \eta^2_p = .08$, 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

| Wave 2: | Total # | Alcohol-only Users | Infrequent Cannabis Users | Moderately frequent Cannabis Users |
|--------|---------|--------------------|---------------------------|-----------------------------------|
|        | 26      | 15                 | 8                         | 3                                 |
|        | 18      | 7                  | 8                         | 3                                 |
|        | 25      | 12                 | 7                         | 6                                 |
|        | 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.

### Table 1. Substance use initiation patterns across time by group
|                        | A Total Sample | B Alcohol-only Users | C Cannabis Users (Total) | D Infrequent Cannabis Users | C vs. D Infrequent Cannabis Users | C vs. D Moderately frequent Cannabis Users | D A vs. B | D C vs. D | 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   | F = 1.40   | F = .764 |
| F = .933               | p = .344       |                      |                          |                             |                                  |                                              |            |           |                |
| Age Range (Pre-initiation) | 10.72–24.05   | 11.74–20.96          | 10.72–24.05              | 11.88–24.05                | 10.72–20.51                      |                                              | F = .492   | F = 0.006  | F = .246 |
| F = .855               | p = .940       |                      |                          |                             |                                  |                                              |            |           |                |
| Age (Post-Initiation)  | 19.23 (2.44)   | 19.03 (2.2)          | 19.40 (2.6)              | 19.4 (2.8)                  | 19.4 (2.4)                       |                                              | F = .485   | F = .944   | F = .782 |
| F = .196               | p = .548       |                      |                          |                             |                                  |                                              |            |           |                |
| Age Range (Post-Initiation) | 14.01–26.09   | 14.01–22.59          | 14.17–26.09              | 14.24–26.09                | 14.17–23.42                      |                                              | F = .614   | F = .196   | F = .120 |
| F = .764               | p = .467       |                      |                          |                             |                                  |                                              |            |           |                |
| Gender (#M; #F; #Other)| 47:39:0        | 19:20:0              | 28:19:0                  | 18:11:0                    | 10:8:0                           |                                              | X² = 1.01  | X² = 1.96  | X² = 1.20 |
| F = .341               | p = .548       |                      |                          |                             |                                  |                                              |            |           |                |
| WASI-estimated IQa (Pre-initiation) | 115.0 (11.5) | 116.6 (9.8) | 113.7 (12.5) | 113.2 (12.8) | 114.5 (12.3) | X² = 4.35 | X² = 2.14 | X² = 7.37 |
| White:Non-White Ethnicity | 78:8        | 38:1                 | 40:7                     | 24:5                       | 16:2                             |                                              | F = 3.21   | F = 5.64   | F = 4.09 |
| Parental Education (averaged; years) | 15.96 (1.99) | 16.4 (2.1) | 15.6 (1.9) | 16.1 (1.9) | 14.8 (1.4) | X² = 0.77 | X² = 0.022 | X² = 0.20 |
| 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) | X² = 0.44 | X² = 0.077 | X² = 0.125 |
| Past six months daily nicotine use frequency Pre-initiation | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | F = 2.17 | F = 5.05 | F = 5.83 |
| Past six months daily nicotine use frequency Post-initiation | 0.28 (1.61) | 0.03 (0.16) | 0.57 (2.32) | 0.00 (0.00) | 1.50 (3.62) | F = 0.144 | F = 0.030 | F = 0.004 |
| Alcohol Use Frequency Past 12 months, Pre-initiation | 0.28 (0.66) | 0.00 (0.00) | 0.75 (0.92) | 0.90 (0.97) | 0.50 (0.80) | F = 17.38 | F = 1.45 | F = 10.28 |
| Alcohol Use Frequency Past 12 months Post-initiation | 1.94 (1.14) | 1.41 (0.97) | 2.38 (1.10) | 2.34 (1.17) | 2.44 (0.98) | F = 0.000 | F = 0.238 | F = 0.000 |
| Cannabis Use Frequency Past 12 months Post-initiation | 0.81 (1.82) | 0.00 (0.00) | 1.49 (0.95) | 0.86 (0.35) | 2.5 (0.71) | F = 95.14 | F = 112.2 | F = 267.71 |
| 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 = 0.116 | F = 0.026 | F = 0.590 |

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.
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 measure of feedback-guided decision-making and 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.

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 |
|-----------------------------------------------|-----------------------------------|-------------------------------------|-------------------------------|------------------------------------------|------------------------------------------------|---------------------------------------------------|
| Age                                           | .022                              | .036                                | .009                          | −.056                                    | .226*                                            | .049                                              |
| Estimated Full-Scale IQ                       | .169                              | −.030                               | .078                          | −.077                                    | .295**                                           | .256*                                              |
| Number of study visits before detection of substance use | .041                              | .053                                | −.034                         | −.034                                    | .263*                                            | .279*                                              |
| Gender (1=male; 2=female)                     | .204                              | .265*                               | −.195                         | −.001                                    | .050                                            | .035                                              |
| Average reported family income (US dollars)   | .014                              | .071                                | .119                          | .039                                     | .208                                            | .040                                              |
| Average parental education                    | .201                              | .102                                | .014                          | −.109                                    | .418**                                           | .250*                                              |

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

| 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**                                |                                 |                                         |                         |                                 |                                         |                         |                      |                          |
| 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)            |                      |                          |
| Trial 1                                  | 7.21 (.34)                      | 6.06 (.44)                              | 7.32 (.29)              | 7.55 (.29)                      | 6.28 (.38)                              | 7.09 (.26)              |                      |                          |
| Trial 2                                  | 9.45 (.39)                      | 9.05 (.51)                              | 10.15 (.34)             | 10.56 (.41)                     | 8.93 (.53)                              | 9.77 (.36)              |                      |                          |
| Trial 3                                  | 11.51 (.39)                     | 11.13 (.51)                             | 11.38 (.33)             | 12.13 (.39)                     | 10.86 (.50)                             | 11.65 (.34)             |                      |                          |
| 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)              |                      |                          |
| Immediate recall                         |                                 |                                         |                         |                                 |                                         |                         |                      |                          |
| 30-minute delayed recall                 | 11.20 (.46)                     | 11.11 (.59)                             | 11.38 (.40)             | 12.07 (.47)                     | 10.79 (.61)                             | 11.54 (.42)             | 0.08/922/.00         |                          |
| Proportion of consolidated information   | 0.86 (.03)                      | 0.83 (.04)                              | 0.88 (.03)              | 0.88 (.04)                      | .74 (.05)                               | .87 (.03)               | 0.52/959/.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 | 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| 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.
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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### Table 5. Pre- and post-initiation difference scores by group

| Cognitive Measure | Infrequent Cannabis Users (IF) | Moderately Frequent Cannabis Users (MF) | Alcohol-Only Users (AO) | Post-Initiation minus Pre-Initiation Group Differences |
|-------------------|--------------------------------|----------------------------------------|------------------------|------------------------------------------------------|
|                   | Post- minus Pre-Initiation     |                                       |                        | Group Differences                                    |
| SUM TOTAL CORRECT: Trials 1–5 | 3.34 (1.5) | −2.81 (1.9) | −0.56 (1.3) | **3.70/0.029/0.09** MF < IF |
| NEW LEARNING (Average: Trial 1, List B) | 0.38 (0.45) | −0.84 (0.60) | 0.07 (0.39) | 1.29/0.281/0.03 – |
| IMMEDIATE RECALL | 0.85 (.41) | −0.39 (.53) | 0.23 (.36) | 1.75 /1.181/04 – |
| 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) | 3.05/0.053/0.07 – |

*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.*

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**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).
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.

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).
**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 R²-change | b      | SE(b) | t    | p    |
|-------|-------|-------|-----|------------------|--------|-------|------|------|
| Step 1 | .26   | 14.59 | .000 | .000             | .90    | .44   | 2.03 | .045 |
|        |       |       |     |                  | .49    | .11   | 4.50 | <.001|
| Parental education |       |       |     |                  |        |       |      |      |
| Pre-initiation RAVLT Learning |       |       |     |                  |        |       |      |      |
| Step 2 | .26   | 7.23  | .000 | .858             | .89    | .46   | 1.95 | .055 |
|        |       |       |     |                  | .49    | .11   | 4.37 | <.001|
| Parental education |       |       |     |                  |        |       |      |      |
| Pre-initiation RAVLT Learning |       |       |     |                  |        |       |      |      |
| 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             | .50    | .48   | 1.06 | .291 |
|        |       |       |     |                  |        |       |      |      |
| Parental education |       |       |     |                  |        |       |      |      |
| 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 |       |       |     |                  |        |       |      |      |

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

| Model | $R^2$ | F     | p   | Signif R²-change | b      | SE(b) | t    | p    |
|-------|-------|-------|-----|------------------|--------|-------|------|------|
| Step 1 | .24   | 12.81 | .000 | .000             | .18    | .07   | 2.68 | .009 |
|        |       |       |     |                  | .35    | .09   | 4.00 | <.001|
| Parental education |       |       |     |                  |        |       |      |      |
| Pre-initiation RAVLT Learning |       |       |     |                  |        |       |      |      |
| Step 2 | .24   | 6.39  | .000 | .876             | .18    | .07   | 2.65 | .010 |
|        |       |       |     |                  | .34    | .09   | 3.90 | <.001|
| Parental education |       |       |     |                  |        |       |      |      |
| Pre-initiation RAVLT Learning |       |       |     |                  |        |       |      |      |
| 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             | .14    | .07   | 1.93 | .057 |
|        |       |       |     |                  | .30    | .09   | 3.30 | <.001|
| Parental education |       |       |     |                  |        |       |      |      |
| Pre-initiation RAVLT Learning |       |       |     |                  |        |       |      |      |
| 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 |       |       |     |                  |        |       |      |      |

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

| Model | $R^2$ | F     | p   | Signif R²-change | b      | SE(b) | t    | p    |
|-------|-------|-------|-----|------------------|--------|-------|------|------|
| Step 1 | .41   | 29.90 | .000 | .009             | .38    | .12   | 3.15 | .002 |
|        |       |       |     |                  | .62    | .09   | 7.02 | <.001|
| Parental education |       |       |     |                  |        |       |      |      |
| Pre-initiation RAVLT Learning |       |       |     |                  |        |       |      |      |
| Step 2 | .47   | 17.97 | .006 | .023             | .36    | .12   | 3.02 | .003 |
|        |       |       |     |                  | .61    | .09   | 6.97 | <.001|
| Parental education |       |       |     |                  |        |       |      |      |
| Pre-initiation RAVLT Learning |       |       |     |                  |        |       |      |      |
| Post-initiation alcohol use frequency |       |       |     |                  | -.20   | -.36  | .718 | -.07 |
| Post-initiation nicotine use frequency |       |       |     |                  | -.37   | .13   | -2.77| .007 |
| Step 3 | .51   | 16.65 | .000 | .013             | .24    | .12   | 1.94 | .056 |
|        |       |       |     |                  | .60    | .09   | 7.03 | <.001|
| Parental education |       |       |     |                  |        |       |      |      |
| Pre-initiation RAVLT Learning |       |       |     |                  |        |       |      |      |
| 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 R²-change | b      | SE(b) | t    | p    |
|-------|-------|-------|-----|------------------|--------|-------|------|------|
| Step 1 | .18   | 9.16  | .000 | .000             |        |       |      |      |

(Continued)
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 & Battistì, 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
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.

FINANCIAL SUPPORT

The research presented in this report was supported by the National Institute on Drug Abuse and National Institute on Alcohol Abuse and Alcoholism of the National Institutes of Health under award numbers DA017943 and AA020033 awarded to M. Luciana. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. HW was supported by a National Science Foundation Predoctoral Fellowship. NA was supported by a Multicultural Research Opportunity Program grant awarded by the University of Minnesota.

CONFLICTS OF INTEREST

The authors have no conflicts to disclose.

References

Achenbach, T.M., & Rescorla, L.A. (2001). Manual for the ASEBA School-Age Forms & Profiles. Burlington, VT: University of Vermont, Research Center for Children, Youth, & Families.
Achenbach, T.M., & Rescorla, L.A. (2003). Manual for the ASEBA adult forms & profiles. Research Center for Children, Youth, & Families. Burlington, VT: University of Vermont.
Almy, B., Kuskowski, M., Malone, S., Myers, E., & Luciana, M. (2018). A longitudinal analysis of adolescent decision-making with the Iowa Gambling Task. Developmental Psychology, 54(4), 689–702.
American Psychiatric Association (2000). Diagnostic and statistical manual of mental disorders: DSM-IV-TR. Washington, DC: American Psychiatric Association.
Barthelemy, O.J., Richardson, M.A., Heeren, T.C., Chen, C.A., Liebschutz, J.M., Forman, L.S., & Rose-Jacsobs, R. (2019). Do differences in learning performance precede or follow initiation of marijuana use?. Journal of Studies on Alcohol and Drugs, 80(1), 5–14. doi: 10.15288/jsad.2019.80.5
Battisti, R.A., Roodenrys, S., Johnstone, S.J., Pesa, N., Hermens, D.F., & Solowij, N. (2010). Chronic cannabis users show altered neurophysiological functioning on Stroop task conflict resolution. Psychopharmacology, 212(4), 613–624.
Becker, M.P., Collins, P.F., & Luciana, M. (2014). Neurocognition in college-aged daily marijuana users. Journal of Clinical and Experimental Neuropsychology, 36(4), 379–398.
Becker, M.P., Collins, P.F., Schultz, A., Urošević, S., Schmaling, B., & Luciana, M. (2018). Longitudinal changes in cognition in young adult cannabis users. Journal of Clinical and Experimental Neuropsychology, 40(6), 529–543.
Bolla, K.I., Brown, K., Eldreth, D., Tate, K., & Cadet, J.L. (2002). Dose-related neurocognitive effects of marijuana use. Neurology, 59(9), 1337–1343.
Broyd, S.J., van Hell, H.H., Beale, C., Yucel, M., & Solowij, N. (2016). Acute and chronic effects of cannabinoids on human cognitive and neurocognitive functioning. International Journal of Neuropsychopharmacology, 19(5), 557–567.
Casey, J.L. & Cservenka, A. (2020). Effects of frequent marijuana use on risky decision-making in young adult college students. Addictive Behaviors Reports, 11, 100253.
Castellanos-Ryan, N., Pingault, J.B., Parent, S., Vitari, F., Tremblay, R.E., & Seguin, J.R. (2017). Adolescent cannabis use, change in neurocognitive function, and high-school graduation: A longitudinal study from early adolescence to...
alcohol use: A three-year longitudinal study. Neuropsychology, 29(6), 829–843.

Jackson, N.J., Ison, J.D., Khoddam, R., Irons, D., Tuvblad, C., Iacono, W.G., & Baker, L.A. (2016). Impact of adolescent marijuana use on intelligence: Results from two longitudinal twin studies. Proceedings of the National Academy of Sciences: PNAS, 113(5), E500–E508.

Johnston, L.D., Miech, R.A., O’Malley, P.M., Bachman, J.G., Schulenberg, J.E., & Patrick, M.E. (2020): Monitoring the Future National Survey Results on Drug Use 1975-2019: Overview, Key Findings on Adolescent Drug Use. Ann Arbor: Institute for Social Research, University of Michigan.

Kauffman, J., Birmaher, B., Brent, D., Rao, U., & Ryan, N. (1996). Kiddie-SADS-Present and Lifetime (K-SADS-PL). Version 1.0. Pittsburgh, PA: University of Pittsburgh School of Medicine, Western Psychiatric Institute and Clinics. Retrieved from http://www.wpic.pitt.edu/research/AssessemntTools/ChildAdolescent/kcsadsp1.pdf

Kennedy, S.M., Caraballo, R.S., Rolle, I.V., & Rock, V.J. (2016). Not just cigarettes: A more comprehensive look at marijuana and tobacco use among African American and white youth and young adults. Nicotine & Tobacco Research, 18(Suppl 1), S65–S72.

Khurana, A., Romer, D., Betancourt, L.M., & Hurt, H. (2017). Working memory ability and early drug use progression as predictors of adolescent substance use disorders. Addiction, 112(7), 1220–1228.

Kim-Spoon, J., Kahn, R.E., Lauharatanahirun, N., Deater-Deckard, K., Bickel, W.K., Chiu, P.H., & King-Casas, B. (2017). Executive functioning and substance use in adolescence: Neurobiological and behavioral perspectives. Neuropsychologia, 100, 79–92.

Krak-Słomka, M., Dzik, A., Badzynska, B., & Biala, G. (2017). Endocannabinoid system: The direct and indirect involvement in the memory and learning processes—a short review. Molecular Neurobiology, 54(10), 8332–8347.

Lane, S.D., Cherek, D.R., Tcheremissine, O.V., Steinberg, J.L., & Sharon, J.L. (2007). Response perseveration and adaptation in heavy marijuana-smoking adolescents. Addictive behaviors, 32(5), 977–990.

Lisdahl, K.M. & Price, J.S. (2012). Increased marijuana use and gender predict poorer cognitive functioning in adolescents and emerging adults. Journal of the International Neuropsychological Society, 18(4), 678–688.

Lisman, J.E. & Grace, A.A. (2005). The hippocampal-VTA loop: Controlling the entry of information into long-term memory. Neuron, 46, e703–e713.

Long, N.M., Oztetkin, I., & Badre, D. (2010). Separable prefrontal cortex contributions to free recall. The Journal of Neuroscience, 30(33), 10967–10976.

Lovell, M.E., Khallurj, J., Padgett, C., Garry, M.I., & Matthews, A. (2020). Cognitive outcomes associated with long-term, regular, recreational cannabis use in adults: A meta-analysis. Experimental and Clinical Psychopharmacology, 28(4), 471–494.

Luciana, M., Bjork, J.M., Nagel, B., Barch, D.M., Gonzalez, R., Nixon, S.J., & Banich, M.T. (2018). Adolescent neurocognitive development and impacts of substance use: Overview of the Adolescent Brain and Cognitive Development (ABCD) baseline neurocognition battery. Developmental Cognitive Neuroscience, 32, 67–79.

Lupica, C.R., Hu, Y., Devinsky, O., & Hoffman, A.F. (2017). Cannabinoids as hippocampal network administrators. Neuropsychopharmacology, 124, 25–37.

Lupica, C.R., Riegel, A.C., & Hoffman, A.F. (2004). Marijuana and cannabinoid regulation of brain reward circuits. British Journal of Pharmacology, 143, e227–e234.

Loureiro, M., Renard, J., Zander, J., & Laviolette, S.R. (2015). Hippocampal cannabinoid transmission modulates dopamine neuron activity: Impact on rewarding memory formation and social interaction. Neuropsychopharmacology, 40, e1436–e1447.

Mallorquí-Bagué, N., Fagundo, A.B., Jimenez-Murcia, S., de la Torre, R., Baños, R.M., Botella C.,... Fernández-Arandá F. (2016). Decision making impairment: A shared vulnerability in obesity, gambling disorder and substance use disorders? PLoS One 11(9): e0163901. https://doi.org/10.1371/journal.pone.0163901.

Malone, S., Wilson, S., Bair, J., McGue, M., & Iacono, W.G. (2020). Cotwin-control analysis of adolescent and young adult drinking effects on learning and memory. Addiction. https://doi.org/10.1111/add.15334.

Mateos, B., Borcel, E., Loriga, R., Luesu, W., Bini, V., Llorente, R., & Viveros, M.-P. (2011). Adolescent exposure to nicotine and/or the cannabinoid agonist CP 55,940 induces gender-dependent long-lasting memory impairments and changes in brain nicotinic and CB1(1) cannabinoid receptors. Journal of Psychopharmacology, 25, 1676–1690.

Meier, M., Caspi, A., Ambler, A., Harrington, H., Houts, R., Keefe, R., & Moffitt, T. (2012). Persistent cannabis users show neuro-psychological decline from childhood to midlife. Proceedings of the National Academy of Sciences of the United States of America, 109(4), E2657.

Mejia, M.H., Wade, N.E., Baca, R., Diaz, V.G., & Jacobus, J. (2021). The influence of cannabis and nicotine co-use on neuromaturation: A systematic review of adolescent and young adult studies. Biological Psychiatry. https://doi.org/10.1016/j.biopsych.2020.09.021.

Mohn, C., Sundet, K., & Rund, B.R. (2014). The relationship between IQ and performance on the MATRICS consensus cognitive battery. Schizophrenia Research: Cognition. doi: 10.1016/j. scog.2014.06.003.

Mokrysz, C., Landy, R., Gage, S.H., Munafó, M.R., Roiser, J.P., & Curran, H.V. (2016). Are IQ and educational outcomes in teenagers related to their cannabis use? A prospective cohort study. Journal of Psychopharmacology, 30(2), 159–168.

Moreno, M., Estevez, A.F., Zaldívar, F., Montes, J.M.G, Gutiérrez-Ferre, V.E, Esteban, L., & Flores, P. (2012). Impulsivity differences in recreational cannabis users and binge drinkers in a university population. Drug and Alcohol Dependence, 124(3), 355–362. doi: 10.1016/j.drugalcdep.2012.02.011.

Patrick, M.E., Terry-McElrath, Y.M., Lee, C.M., & Schulenberg, J.E. (2019). Simultaneous alcohol and marijuana use among underage young adults in the United States. Addictive Behaviors, 88, 77–81.

Petker, T., Owens, M.M., Amlung, M.T., Oshri, A., Sweet, L.H., & MacKillop, J. (2019). Cannabis involvement and neuro-psychological performance: Findings from the Human Connectome Project. Journal of Psychiatry & Neuroscience, 44(6), 414–422.

Rye, A. (1993). Psychological examination of traumatic encephalopathy [originally published in Archives de Psychologie 1941; 28: 286340; translated by Corwin J, Bylsma F.]. Clinical Neuropsychologist, 7(1), 3–21.

Rogeberg, O. (2013). Correlations between cannabis use and IQ change in the Dunedin cohort are consistent with confounding from socioeconomic status. Proceedings of the National Academy of Sciences, 110(11), 4251–4254.
Scott, J.C., Slomiak, S.T., Jones, J.D., Rosen, A.F.G, Moore, T.M., & Gur, R.C. (2018). Association of cannabis with cognitive functioning in adolescents and young adults: A systematic review and meta-analysis. *JAMA Psychiatry, 75*, 585–595.

Schauer, G.L., Berg, C.J., Kegler, M.C., Donovan, D.M., & Windle, M. (2016). Differences in tobacco product use among past month adult marijuana users and nonusers: Findings from the 2003-2012 National Survey on Drug Use and Health. *Nicotine & Tobacco Research, 18*, 281–288.

Schoeler, T., Kambeitz, J., Behlke, I., Murray, R., & Bhattacharyya, S. (2016). The effects of cannabis on memory function in users with and without a psychotic disorder: Findings from a combined meta-analysis. *Psychological Medicine, 46*, 177–188.

Schuster, R.M., Crane, N.A., Mermelstein, R., & Gonzalez, R. (2015). Tobacco may mask poorer episodic memory among young adult cannabis users. *Neuropsychology, 29*, 759–766.

Schreiner, A.M. & Dunn, M.E. (2012). Residual effects of cannabis use on neurocognitive performance after prolonged abstinence: A meta-analysis. *Experimental and clinical psychopharmacology, 20*(5), 420–429. doi:10.1037/a0029117

Silins, E., Horwood, L.J., Patton, G.C., Fergusson, D.M., Olsson, C.A., Hutchinson, D.M., & Mattick, R.P. (2014). Young adult sequelae of adolescent cannabis use: An integrative analysis. *Lancet Psychiatry, 1*, 286–293.

Solowij, N. & Battisti, R. (2008). The chronic effects of cannabis on memory in humans: A review. *Current Drug Abuse Reviews, 1*, 81–98.

Solowij, N., Jones, K., Rozman, A., Davis, M., Ciarrochi, E., Heaven, S., & Yücel, J. (2011). Verbal learning and memory in adolescent cannabis users, alcohol users and non-users. *Psychopharmacology, 216*(1), 131–144.

Solowij, N., Jones, K.A., Rozman, M.E., Davis, S.M., Ciarrochi, J., Heaven, P.C.L., . . . Yücel, M. (2012). Reflection impulsivity in adolescent cannabis users: A comparison with alcohol-using and non-substance-using adolescents. *Psychopharmacology, 219*(2), 575–586. doi: 10.1007/s00213-011-2486-y

Swendsen, J., Conway, K., Degenhardt, L., & Kessler, R.C. (2009). Socio-demographic risk factors for alcohol and drug dependence: The 10-year follow-up of the national comorbidity survey. *Addiction, 104*(8), 1346–1355.

Tait, R., Mackinnon, A., & Christensen, H. (2011). Cannabis use and cognitive function: 8-year trajectory in a young adult cohort. *Addiction, 106*(12), 2195–2203.

Takagi, M.J., Yücel, M., Cotton, S.M., Baliz, Y., Tucker, A., Elkins, K., & Lubman, D.I. (2011). Verbal memory, learning, and executive functioning among adolescent inhalant and cannabis users. *Journal of Studies on Alcohol and Drugs, 72*(1), 96–105.

Verdejo-Garcia, A., Benbrook, A., Funderburk, F., David, P., Cadet, J.L., & Bolla, K.I. (2007). The differential relationship between cocaine use and marijuana use on decision-making performance over repeat testing with the Iowa Gambling Task. *Drug and Alcohol Dependence, 90*(1), 2–11. doi: 10.1016/j.drugalcdep.2007.02.004

Wechsler, D. (1999). *Manual for the Weschler Abbreviated Scale of Intelligence*. San Antonio, TX: The Psychological Corporation.

Whitlow, C.T., Liguori, A., Livengood, L.B., Hart, S.L., Mussat-Whitlow, B.J., Lamborn, C.M., & Porrino, L.J. (2004). Long-term heavy marijuana users make costly decisions on a gambling task. *Drug & Alcohol Dependence, 76*(1), 107–111. doi: 10.1016/j.drugalcdep.2004.04.009