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Early Onset Marijuana Use Is Associated with Learning Inefficiencies

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Abstract

Objective—Verbal memory difficulties are the most widely reported and persistent cognitive deficit associated with early-onset marijuana use. Yet, it is not known what memory stages are most impaired in those with early marijuana use.

Method—Forty-eight young adults, aged 18–25, who used marijuana at least once per week and 48 matched non-using controls (CON) completed the California Verbal Learning Test, Second Edition (CVLT-II). Marijuana users were stratified by age of initial use: 'early onset' users (EMJ), who started using marijuana at or before age 16 (n = 27), and 'late onset' marijuana user group (LMJ), who started using marijuana after age 16 (n = 21). Outcome variables included trial immediate recall, total learning, clustering strategies (semantic clustering, serial clustering, ratio of semantic to serial clustering, and total number of strategies used), delayed recall, and percent retention.

Results—Learning improved with repetition, with no group effect on the learning slope. EMJ learned fewer words overall than LMJ or CON. There was no difference between LMJ and CON in total number of words learned. Reduced overall learning mediated the effect on reduced delayed recall among EMJ, but not CON or LMJ. Learning improved with greater use of semantic versus serial encoding, but this did not vary between groups. EMJ was not related to delayed recall after adjusting for encoding.

Conclusions—Young adults reporting early onset marijuana use had learning weaknesses, which accounted for the association between early onset marijuana use and delayed recall. No amnestic effect of marijuana use was observed.

Keywords

Marijuana; Cannabis; Memory; Learning; Neurocognition; Adolescence; Verbal Learning

Verbal memory difficulties are the most widely reported and persistent cognitive deficit associated with early marijuana use (for reviews, see Crane, Schuster, Fusar-Poli, & Gonzalez, 2013; I. Grant, Gonzalez, Carey, Natarajan, & Wolfson, 2003; Schweinsburg,

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Brown, & Tapert, 2008). These deficits persist up to six weeks following discontinuation of use (Schweinsburg et al., 2008). Marijuana is thought to affect verbal memory through a cannabinoid receptor (CB1) mechanism. CB1 receptors are the most abundant metabotropic receptors in the brain, and are densely localized in brain regions critically involved in learning and memory, including the hippocampus, prefrontal cortex, anterior cingulate, basal ganglia and cerebellum (Herkenham et al., 1990; Tsou, Brown, Sanudo-Pena, Mackie, & Walker, 1998). Cannabinoids, when present in these regions, disrupt physiological processes such as neuronal firing rhythms and long-term potentiation that are required for learning and memory (Hampson & Deadwyler, 2000). Early adolescent onset of marijuana use is associated with greater verbal memory deficits (Solowij & Battisti, 2008) and aberrant functional brain activation patterns such as increased fronto-parietal activation during verbal learning and spatial working memory tasks (Becker, Wagner, Gouzoulis-Mayfrank, Spuentrup, & Daumann, 2010; Gruber, Dahlgren, Sagar, Gonenc, & Lukas, 2014; Gruber, Sagar, Dahlgren, Racine, & Lukas, 2012; Schweinsburg et al., 2005; Schweinsburg, Schweinsburg, Nagel, Eyler, & Tapert, 2011; Tapert, Pulido, Paulus, Schuckit, & Burke, 2004; Wilson et al., 2000). This apparent period of increased vulnerability of verbal memory processes to marijuana exposure may be due to the normal ongoing process of rapid development of the endocannabinoid system that takes place during adolescence (Mechoulam & Parker, 2013; Viveros et al., 2012).

Verbal memory is a multi-stage process, comprised of learning (i.e., the immediate recall or acquisition of novel information over repeated trials), consolidation (i.e., the ability to transfer and maintain novel information into long-term store), and retrieval (i.e., the ability to access previously learned information from long-term store), each associated with unique underlying cellular processes in discrete brain regions (Dickerson & Eichenbaum, 2010; Jeong, Chung, & Kim, 2015; Rugg & Vilberg, 2013). Earlier studies suggest that marijuana use may compromise encoding (i.e., learning) but not consolidation or retrieval (Becker, Collins, & Luciana, 2014; Mahmood, Jacobus, Bava, Scarlett, & Tapert, 2010; Solowij et al., 2011; Takagi et al., 2011). However, the specificity of marijuana's effects on the stages of memory has not been directly tested.

The goal of this study was to build on early work demonstrating an effect of marijuana use on verbal memory by (1) evaluating performance on learning, consolidation, and retrieval separately in groups with differing age of onset of marijuana use and (2) developing an explanatory model of the relationship between age of onset of marijuana use with components of verbal memory performance that contribute to overall performance. This study was designed to allow us to distinguish between two plausible explanatory paths: 1) marijuana users, particularly early onset marijuana users, may have reduced learning, perhaps secondary to a diminished ability to semantically organize verbal stimuli, and poor delayed recall is reflective of low initial learning rather than a deficiency in consolidation or retrieval; or 2) poor initial learning and recall are independently impacted by marijuana use or age of onset of use. The latter is supported by reports that reduced depth of initial processing of items to be learned is associated with reduced durability of long-term storage for these items (Craik & Lockhart, 1972).

We hypothesized that reduced learning would be the principal memory deficit among marijuana users, particularly among those who began using marijuana early in adolescence. We also postulated a mechanism of greater reliance on serial organization strategies for learning and less reliance on more efficient semantic organization at the time of learning among marijuana users, particularly those who started using earlier in development. We suspected that less organized acquisition of verbal information (i.e., more serial clustering and less semantic clustering) would result in less structured memory representations, thereby reducing learning and subsequent delayed recall. An organizational deficit at the time of learning was hypothesized in light of mounting evidence for dysfunction in the prefrontal cortex with marijuana use (Medina et al., 2009; Price et al., 2015; Shollenbarger, Price, Wieser, & Lisdahl, 2015), a region that (among other functions) mediates strategic aspects of memory such as active strategies of learning information (Dahmani & Bohbot, 2015; Hawco, Berlim, & Lepage, 2013; Kirchhoff, Gordon, & Head, 2014; Miotto et al., 2014).

Methods

Participants

Study participants were 48 young adults, aged 18–25, who reported using marijuana at least once per week and 48 age and gender matched controls (CON) who reported using marijuana fewer than five times in their lives and no use in the prior 90 days. Participants were recruited through advertisements in the community by email, web and bulletin board announcements posted within the local site network community, and were part of a larger study (Gilman, Calderon, Curran, & Evins, 2015). Marijuana users were stratified by age of first marijuana use, as done in several prior reports (e.g., Battistella et al., 2014; Becker et al., 2014). Twenty-seven participants started using marijuana at or before age 16 and comprised the group of ‘early onset’ users (EMJ). Twenty-one participants started using marijuana after age 16 and comprised the ‘late onset’ marijuana user group (LMJ). In addition to the non-user and marijuana-specific eligibility criteria, all participants had to be competent and willing to provide written informed consent; able to communicate in English; medically healthy including no history of diabetes, cardiovascular disease, HIV, Hepatitis C, migraines, head injury or prolonged unconsciousness greater than 24 hours; and psychiatrically healthy with no current or lifetime psychiatric disorders in the CON group, and no current or lifetime psychiatric disorder other than marijuana for the marijuana using groups (verified by the Structured Clinical Interview for DSM-IV Non-Patient Version; SCID; First, 2002). Additionally, all participants had less than five lifetime occasions of any illicit drug use, except marijuana in the marijuana cohort. All participants gave written informed consent to a protocol approved by the Massachusetts General Hospital Institutional Review Board. Participants were asked to refrain from using any substances on the day of their study visit.

Measures

Study participants completed toxicology tests, self-report questionnaires, semi-structured interviews and neurocognitive testing. Marijuana and alcohol use were assessed with a Timeline Followback protocol, in which participants were asked to mark off the days on a 90-day calendar that they had used marijuana or alcohol. These calendars were used to

quantitatively assess for frequency, amount and recency of use in the past 90 days (reported in detail in Gilman et al., 2015; Gilman et al., 2014; Gilman, Treadway, Curran, Calderon, & Evins, 2015), Nicotine use was assessed by self-report only.

Participants completed the California Verbal Learning Test, Second Edition (CVLT-II; Delis, Kramer, & Kaplan, 2000), which involves verbal presentation of a 16-word list consisting of four non-adjacent words from four different semantic categories (i.e., vegetables, modes of travel, animals, furniture). The list is presented five consecutive times, and participants recalled the words after each learning trial. After a 20-minute delay, participants recalled as many words as they could remember. Primary outcome variables included: trial immediate recall (total words recalled for each of trials one through five; range: 0–16), total learning (sum of words recalled in each of five learning trials; range 0–80), delayed recall (total words recalled after a 20-minute delay; range: 0–16), and percent retention (delayed recall/words recalled in Trial five; range: 0–100%).

In addition, we evaluated the order in which words were recalled to infer strategies used to learn the word list. Semantic clustering was assumed when two adjacently recalled words were from the same semantic category whereas serial clustering was inferred when two adjacently recalled words were in the original presentation order. Each cluster-type score was adjusted by what would be expected by chance, with higher values indicating greater reliance on that respective strategy (Stricker, Brown, Wixted, Baldo, & Delis, 2002). Semantic and serial clustering scores were calculated for each recall trial and averaged across all five immediate recall trials based on the formula presented in the CVLT-II manual (Delis et al., 2000). Semantic chance-adjusted clustering scores range from −3 to 9 and serial chance-adjusted clustering scores range from −1.88 to +13.13. We also calculated a total strategy score, reflecting the sum of semantic and serial chance-adjusted clustering scores. Finally, we calculated a strategy ratio score by dividing semantic chance-adjusted clustering score by serial chance-adjusted clustering score, after adding 3.00 to the semantic score and 2.88 to the serial score to make them positive and larger than or equal to 0 and 1, respectively. This strategy use ratio variable was used in mediation analyses because 1) it reflects, in a single variable, the preferential use of semantic versus serial clustering strategies, 2) prior studies recommend modeling both semantic and serial clustering together simultaneously when predicting learning and recall (Sunderaraman, Blumen, DeMatteo, Apa, & Cosentino, 2013), and 3) it is less influenced by total number of words learned than individual semantic and serial clustering scores or the total number of strategies used.

Analytic Approach

We inspected data for non-normal distribution and outliers, and performed rank-based nonparametric procedures (Kruskall-Wallis and Mann-Whitney U tests) when assumptions of normality were violated. To examine patterns of learning on the CVLT-II, a multilevel mixed-effects ordered logistic regression with random intercepts and slopes was fit to the data to examine if learning across 5 learning trials varied by group. Kruskall-Wallis and Mann-Whitney U tests were used to examine group differences in delayed recall. One-way analysis of variance (ANOVA) tests were conducted to compare groups on total number of strategies used and use of semantic clustering, and independent sample t-tests were

conducted to evaluate significant and marginally significant (p<0.10) group effects. A Kruskall-Wallis test was conducted to examine group differences in serial clustering due to non-normality.

To investigate the causal pathway from marijuana use to delayed recall performance on the CVLT-II, we tested a serial mediation model using ordinary least squares path analysis. The multi-categorical independent variable, age of marijuana use onset, was coded into two indicator variables, D_1 and D_2, denoting late and early marijuana use onset, respectively, and leaving the CON group (no marijuana use) as the reference group. To highlight the relative importance of semantic versus serial clustering strategies employed, we calculated a strategy ratio variable that was used as the first mediator in the model. The second mediator was total learning, and the outcome was delayed recall (see Figure 3). The significance of indirect effects was evaluated through percentile confidence intervals based on 10,000 bootstrap samples. A separate, simplified moderated mediation model was conducted to determine if age of marijuana use onset moderated the relationships between strategy use ratios, total learning, and delayed recall (see supplementary materials). Age and gender were used as covariates in both the main mediation model and the simplified moderated mediation model for sensitivity analysis. The mediation analysis was performed using the PROCESS macro (Hayes, 2013) in SAS 9.4 with indicator coding for the multi-categorical independent variable (Hayes & Preacher, 2014). Results were statistically significant when p-values<0.05 or bootstrap confidence intervals of effect estimates excluded zero.

Results

Participant Characteristics

The groups were comparable across most assessed demographic and substance use indices. EMJ were younger than the other groups, and LMJ had more years of regular marijuana use than EMJ. Cumulative marijuana exposure (number of joints smoked per year multiplied by the number of years of regular marijuana use) was comparable between LMJ and EMJ, controlling for age. Baseline characteristics of the samples are presented in Table 1.

Group Effects in Learning and Delayed Recall

CON and LMJ generally performed in the normatively high average range and EMJ performed in the normatively average range (see Table 1). There was a group difference in overall learning such that EMJ encoded fewer words than LMJ or CON (OR=0.11, 95% CI=0.03 to 0.45, b=−2.20, p=0.002). There was no difference between LMJ and CON in total words encoded (OR=1.29, 95%CI=0.28 to 5.88, b=.26, p=0.74). All groups acquired more words with each successive learning trial (p's<0.0001), and this pattern of change did not vary by group (p's>0.44; Figure 1).

There was a group difference in delayed recall (X^2 (2) =10.98, p=0.004): EMJ recalled fewer words (Md =13) after a delay than LMJ (Md = 15; r= 0.39, p=0.007) and CON (Md = 15; r= 0.36, p=0.002). There was no difference between LMJ and CON in delayed recall (r= −0.03, p=0.78). When delayed recall was adjusted for recall during the learning phase of the

task, there was no group difference in delayed recall (percent retention: 95.2%, 97.8% and 98.4% for EMJ, LMJ and CON, respectively, *r's*=−0.01 to 0.11; X^2 (2)=0.88, p=0.63).

Group Effects in Use of Learning Strategies

There was an effect of group in total strategy use (semantic + serial) during learning (F(2, 93) =3.50, p=0.03). EMJ used fewer overall learning strategies (M=2.76, SD=1.84) than CON (M=4.03, SD=2.00, d=0.66; t(73)=2.73, p=0.008). All other pairwise comparisons for total strategy use were not significant (LMJ: M=3.70 SD=2.25; *d's*=0.12 to 0.46, p's>0.12). The group difference in semantic clustering was not significant (F(2, 93) =2.72, p=0.07); however, EMJ used less semantic clustering than CON (d=0.54, t(73) = 2.15, p=0.035), while other group comparisons were not significant (*d's*= 0.06 to 0.42, p's>0.12). There were no group differences on use of serial clustering (*r's*= −0.13 to 0.10; X^2 (2) =2.74, p=0.25; Figure 2).

Mediation Analyses

A mediation analysis was conducted to determine if observed differences in delayed recall were due to differences in the use of learning strategies and overall learning by EMJ or LMJ compared to CON. EMJ but not LMJ was associated with poorer total learning compared to CON (a_{22} = −4.556, p=0.021 vs. a_{12} = 2.661, p=0.174, respectively), but neither EMJ nor LMJ had an effect on learning strategy use (see Figure 3 and Tables 2 and 3). For all participants, higher semantic to serial clustering strategy use ratios increased total learning (d_{21} = 2.518; p<0.0001), and greater total learning resulted in greater delayed recall (b_2 = 0.160; p<0.0001), but the ratio of semantic to serial clustering strategy use did not impact delayed recall (b_1 = 0.045; p=0.69; see Figure 3 and Tables 2 and 3). Overall, EMJ but not LMJ was associated with poorer delayed recall compared to CON (total effects: c_2 = −1.368, p= 0.009 vs. c_1 = 0.156, p=0.76, respectively), and the negative effect of EMJ on delayed recall was fully mediated (direct effect: c'_2 = −0.368, p=0.34) by EMJ's effect on total learning ($a_{22}b_2$ = −0.730, 95%CI: −1.617 to −0.068; Table 3). The indirect effects of EMJ on delayed recall through strategy ratio ($a_{21}b_1$ = −0.027, 95%CI: −0.160 to 0.118) and through both strategy ratio and total learning ($a_{21}d_{21}b_2$ = −0.243, 95%CI: −0.623 to 0.045; Table 3) were not significant. LMJ did not have an effect on delayed recall (Table 3) and did not differ from CON in any mediation path coefficient (Table 2). The simplified moderated mediation model of the effect of clustering strategy ratio on delayed recall, mediated by learning, indicated that neither EMJ nor LMJ moderated any of these paths (see supplementary Figure 1).

Discussion

We examined the mechanisms through which marijuana use may impact verbal memory functioning. To do so, we developed a model of the unique influence of early versus late onset marijuana use on differences in learning strategies, total learning and delayed recall. Results support an overall learning deficit with early onset marijuana use that results in reduced delayed recall. Results, however, do not support a primary deficit in delayed recall *per se*. Consistent with hypotheses, reduced overall learning was responsible for the effect

on reduced delayed recall among early onset marijuana users, but not controls or late onset marijuana users.

Results replicate a long line of prior work demonstrating poor delayed recall with marijuana use (e.g., Becker et al., 2014; Crane, Schuster, Mermelstein, & Gonzalez, 2015; Dougherty et al., 2013; Gonzalez et al., 2012; Hanson et al., 2010; Harvey, Sellman, Porter, & Frampton, 2007; Schuster, Crane, Mermelstein, & Gonzalez, 2015; Solowij et al., 2011). However, findings from this study point to the likely mechanism through which this effect occurs: learning. The data from this study show that the weaknesses in learning fully explain the weakness in delayed recall, given 1) the high correlation between these two memory domains (r=.74), 2) the comparable variance estimates between the effects of marijuana use on learning (R^2 = 0.340) and marijuana use on delayed recall (R^2 = 0.375), 3) the absence of a group difference in percent retention, and 4) the lack of a direct effect of marijuana use on delayed recall after adjusting for total learning. Additionally, associations among learning clustering strategy, learning, and delayed recall, were independent of age of marijuana use onset. Thus, age of marijuana use onset was critical in understanding memory functioning insofar as it was associated with total learning, which subsequently influenced delayed recall. This suggests that learning weaknesses represent the defining characteristic of memory impairment with early onset adolescent marijuana use, and that consolidation into and retrieval from memory are likely unaffected.

Poor learning among early onset marijuana users may reflect a primary weakness in executive functioning. Executive functioning weaknesses have been documented among adolescent marijuana users (Clark, Roiser, Robbins, & Sahakian, 2009; Grant, Chamberlain, Schreiber, & Odlaug, 2012; Pope & Yurgelun-Todd, 1996; Solowij et al., 2012), particularly among those who initiate use early (Jacobus et al., 2015). Early marijuana use may impede learning via disruption in brain regions such as the prefrontal and parietal cortices that are implicated in the memory learning network (Dickerson & Eichenbaum, 2010; Uncapher & Wagner, 2009). This hypothesis is supported by dense localization of CB1 receptors and anandamide, the endogenous cannabinoid, in the prefrontal cortex, as well as frontal grey (Bhattacharyya et al., 2009; Bossong et al., 2012) and white matter disruptions in marijuana using adolescents (Ashtari et al., 2011; Churchwell, Lopez-Larson, & Yurgelun-Todd, 2010; Medina, Nagel, & Tapert, 2010; Yucel et al., 2010).

Differences in clustering strategy use in early onset marijuana users' did not explain weaknesses in learning in this study, despite prior findings of abnormalities in semantic processing and organization with marijuana use (Belmore & Miller, 1980; Kiang et al., 2013; Miller, McFarland, Cornett, Brightwell, & Wikler, 1977). However, greater use of semantic clustering improved learning in all groups, consistent with prior work (Delis et al., 2000; Donders, 2008; Sunderaraman et al., 2013). This may because all adolescents develop greater use of semantic organization with age (Kirchhoff et al., 2014) and maturation is associated with refined functional interactions between the mesial temporal lobe and prefrontal cortex (Menon, Boyett-Anderson, & Reiss, 2005), and age was controlled for in analyses.

Late onset marijuana users' total learning was comparable to non-users. However, there was a ceiling effect in CVLT-II performance, and deficits may have emerged with increased task difficulty. Late onset marijuana users appear to have used an intermediary amount of total clustering strategies during learning, somewhere between non-users and early onset users, but this difference was not significant. Learning weaknesses only in early onset marijuana users support early adolescence being a time of specific vulnerability to exogenous cannabinoids, likely because of continued development of brain networks that mediate higher-order cognitive capacities (Gogtay et al., 2004; Tamnes et al., 2010). Neuroimaging studies have found earlier age of marijuana use onset is associated with abnormalities in cerebral gray and white matter (Batalla et al., 2013; Lorenzetti, Solowij, Fornito, Lubman, & Yucel, 2014), such as atypical morphometry and neurocognitive correlates in the hippocampus (Medina, Schweinsburg, Cohen-Zion, Nagel, & Tapert, 2007), prefrontal cortex (Medina et al., 2009), and cerebellum (Medina et al., 2010) as well as disruptions in white matter integrity in fronto-temporal and fronto-parietal pathways (Bava et al., 2009; Bava & Tapert, 2010; Jacobus et al., 2009; Jacobus, Squeglia, Bava, & Tapert, 2013). This does not suggest that marijuana use later in adolescence is "safe," as its impact on other cognitive capacities, mental health and psychosocial functioning still need to be fully understood.

There are several clinical implications of these findings. Non-users and late onset marijuana users scored largely in the normatively average to high average range on the CVLT-II. Weaknesses across memory domains among early onset marijuana users were generally on the low end of the normatively average range and were approximately one standard deviation from controls and late onset marijuana users, and therefore do not constitute clinical impairment. However, although our early onset sample was comprised of high functioning individuals with normatively average intelligence (M IQ = 112) and the vast majority were enrolled in college or beyond, a pivotal question remains: given the relative weaknesses demonstrated in learning, is marijuana keeping these young adults from achieving at an even higher potential? These findings alongside others that show reductions in intelligence across time (Meier et al., 2012) raise concerns about the potential impact of marijuana use, albeit likely subtle, on adolescent academic functioning and potential for long-term achievement. Marijuana-using adolescents may have more difficulty learning new information, and as a consequence, may not perform optimally (Lynskey & Hall, 2000), have lower grades (Medina, Hanson, et al., 2007), and need to work harder to achieve at grade level (Tapert et al., 2007). We showed early onset marijuana use was associated with lower overall learning, but not with differences in slopes of learning, indicating a normal ability to obtain information with repetition, consistent with prior reports (e.g., Solowij et al., 2011). In school, marijuana users with early initiation may normally acquire (and retain) new information with successive exposures to class material, but may do so at an overall lower level. Future studies are needed that determine the impact of this effect on achievement, as well as the reversibility of this effect with interventions to enhance learning (e.g., use of acronyms and/or mnemonics to help students memorize information) and with sustained marijuana abstinence.

Results of this study should be considered in the context of the following limitations. First, the cutoff of 16 years at first marijuana initiation for early onset use was used in part due to

conventions in the literature as well as to achieve groups of generally equal sample sizes. However, it is likely that risk for poor learning exists along an age onset continuum. Future studies with larger sample sizes should examine the various factors that dictate when peak neurocognitive vulnerability from initial marijuana exposure occurs. Along these lines, future studies should examine whether similar effects replicate when considering age of regular use onset or whether these findings are specific to the age of initial marijuana exposure, as studies have found age of regular use to also predict learning or memory-related outcomes (for a review, see Lisdahl, Gilbard, Wright & Shollenbarger, 2013). Second, our study's sample size was modest, and non-significant effects due insufficient power should be ruled out in future studies. Third, this study assumed comparable levels of cumulative marijuana exposure in LMJ and EMJ groups. Cumulative marijuana exposure was calculated by multiplying the number of joints smoked per year by the numbers of years used MJ, which may only yield a rough approximation of lifetime exposure particularly among young adults who may not have a consistent yearly pattern of use. Future prospective studies with detailed accounting of lifetime use of marijuana (as well as other substances such as alcohol and tobacco) are needed to increase confidence that learning differences are driven by age of onset rather than cumulative marijuana exposure and/or co-morbid substance use. Fourth, it possible that withdrawal may have influenced findings, although this is unlikely as those in the MJ group were only asked to abstain from use on the day of the study visit, most participants used proximal to the time when their memory was assessed (i.e., within 1 to 4 days of the study visit), and time since last use was the same in both EMJ and LMJ minimizing the possibility that withdrawal may be systematically influencing results. Finally, we were not able to rule out the influence of pre-existing differences on observed effects. That is, we were not able to say that early onset marijuana use *caused* poor learning, but instead that poor learning accounted for poor delayed recall only among those who initiated marijuana use before the age of 16. However, groups were comparable of several factors including intelligence and education that are known to influence memory, and this study used stringent inclusion criteria to maximize sample homogeneity and minimize confounding. The primary distinguishing factor between early and late onset marijuana users is the age at which marijuana use was first initiated. Regardless, future studies that assess youth prior to first use and longitudinally follow cognitive development will help tease apart whether learning weaknesses predate or are a consequence of early drug use.

This study demonstrated that early onset marijuana use is associated with acquisition of information into memory directly. No amnestic effect of marijuana use was observed. Although this sample of early onset marijuana users is high functioning among the general population, this does not rule out the possibility that they are achieving below their own potential. It also remains unknown whether adolescents with more risk factors (e.g., lower estimated intelligence or baseline cognitive reserve, lower socioeconomic status, presence of comorbid psychiatric or medical disorders, co-use of other substances, genetic risk) are vulnerable to more exaggerated cognitive weaknesses and perhaps subsequent academic and occupational consequences.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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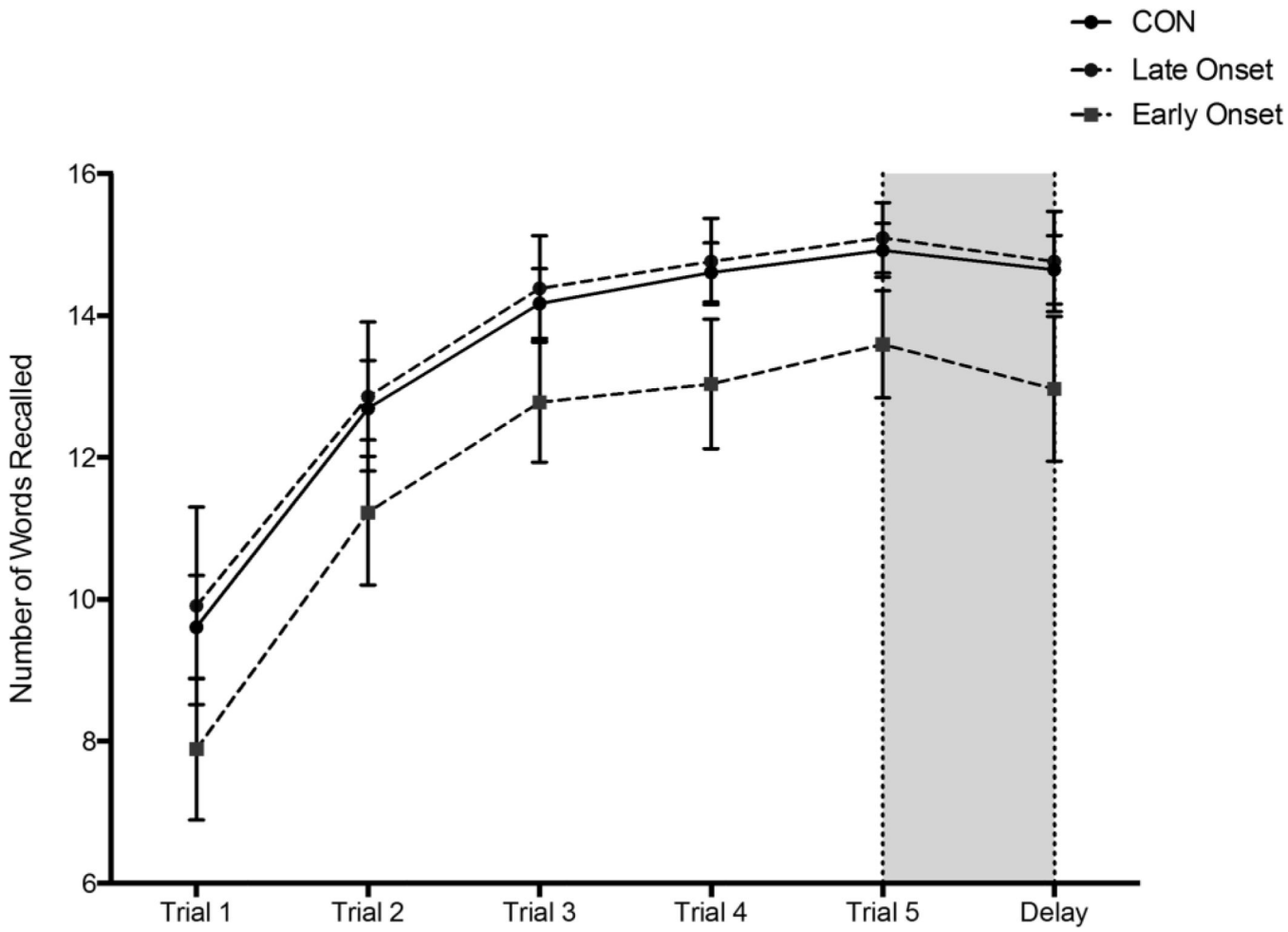

Figure 1.

Differences in Learning Across Five Learning Trials among Controls, Late Onset Marijuana Users and Early Onset Marijuana Users

Note. Groups were significantly different in overall learning (EMJ < LMJ, CON; LMJ = CON). Recall improved significantly and similarly over time across all groups. Groups were significantly different in delayed recall (EMJ < LMJ, CON; LMJ = CON), but similar in percent retention.

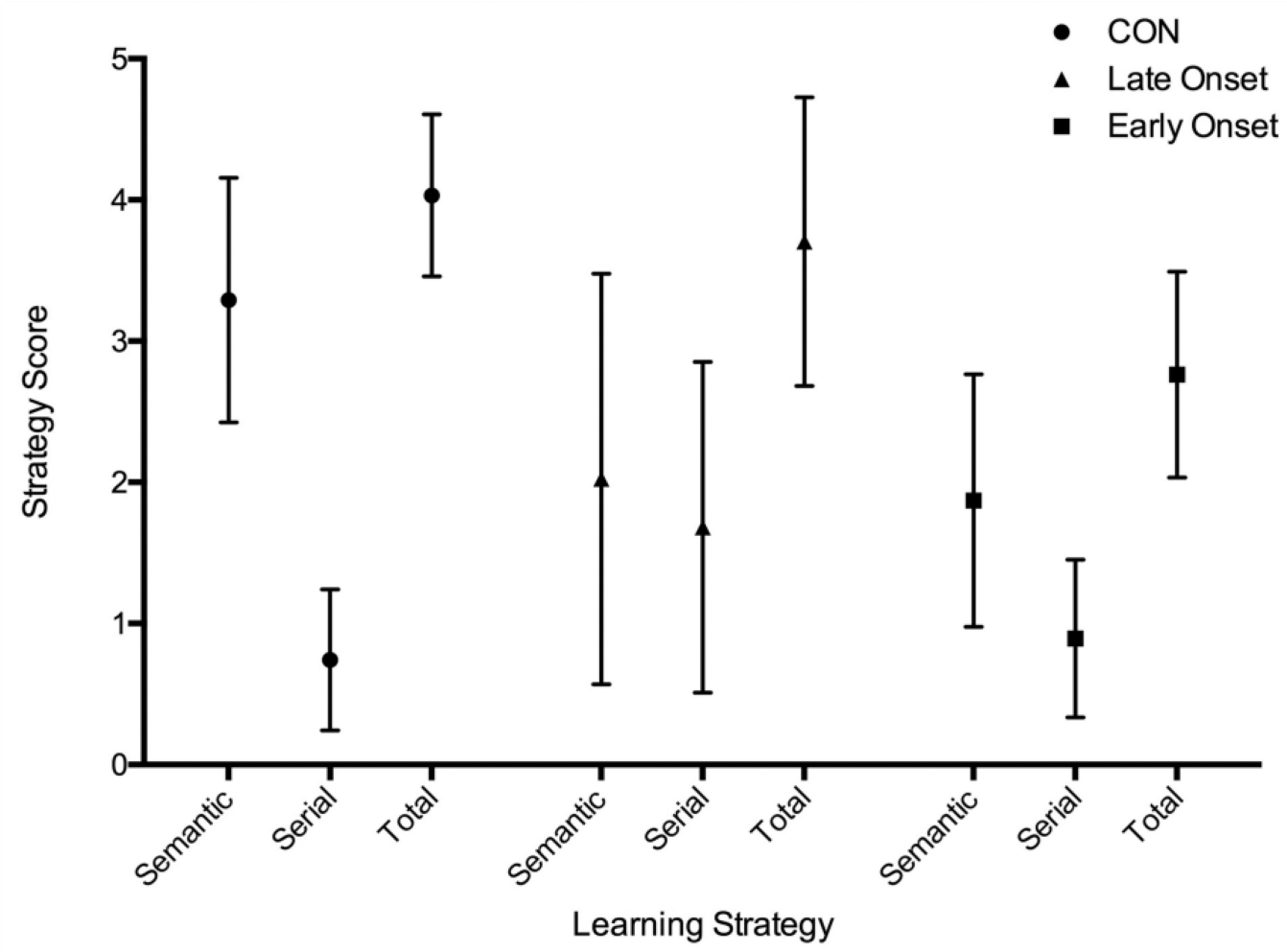

Figure 2.

Differences in Use of Learning Strategies among Controls, Late Onset Marijuana Users and Early Onset Marijuana Users

Note. There was a significant difference in total strategy use (EMJ < CON; EMJ = LMJ; LMJ = CON). There was not an overall group difference in use of semantic strategies, but the pairwise comparison between EMJ and CON was significant (EMJ < CON; EMJ = LMJ; LMJ = CON). There were no group differences in use of serial strategies.

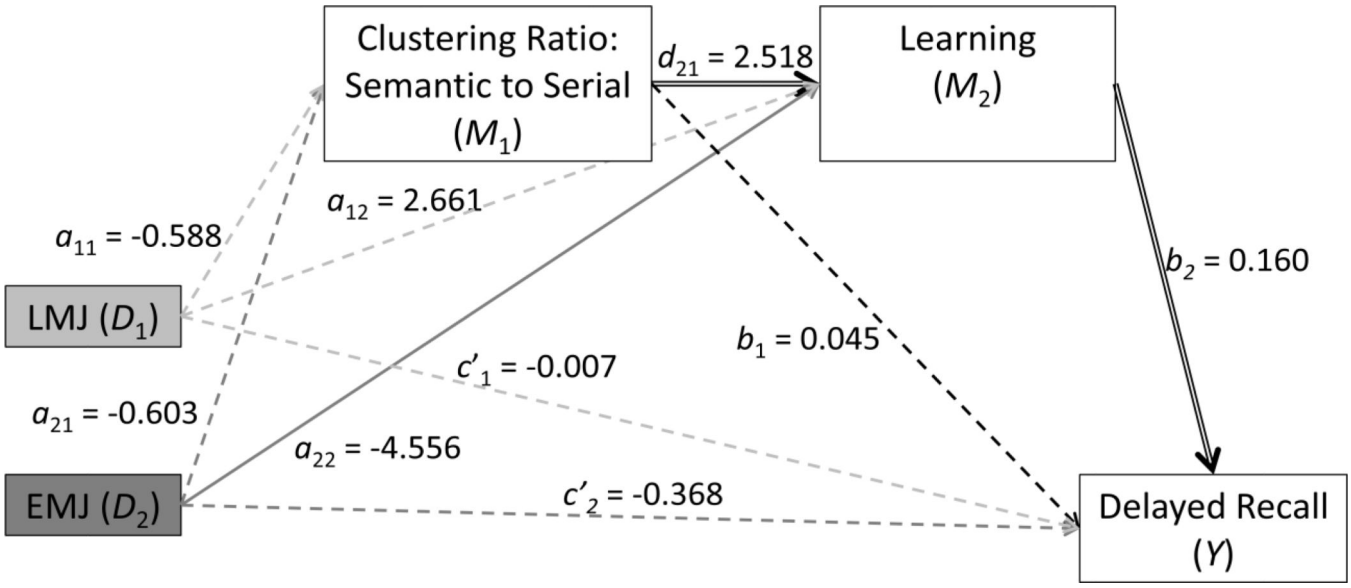

Figure 3.

Total Learning Mediates the Relationship between Early Onset Marijuana Use, but not Late Onset Marijuana Use, and Delayed Recall (Controlling for Age and Gender)

Table 1

Participant Descriptives

	CON(Group 1; n=48)	LMJ (Group 2; n=21)	EMJ (Group 3; n=27)	Omnibus Tests	Post-Hoc Tests
Demographics					
% Male	47.9%	47.6%	55.6%	X^2 (2) =.46, p=.79	1 = 2 = 3
Age	21.5 (2.0)	21.2 (1.8)	19.6 (2.1)	F(2, 93) = 8.3, p=.0005	1 = 2 1, 2 > 3
%Enrolled in College or Beyond	100%	100%	92.6%	X^2 (2) =5.2, p=.07	1 = 2 = 3
% Right-Handed	90%	86%	85%	p=.78 (Fisher's exact)	1 = 2 = 3
% English First Language	92%	90%	92%	p=1.00(Fisher's exact)	1 = 2 = 3
Ethnicity (%Hispanic)	10%	29%	11%	p=.16(Fisher's exact)	1 = 2 = 3
Race				p=.29(Fisher's exact)	1 = 2 = 3
White	65%	76%	48%		
Black	10%	5%	22%		
Other	25%	19%	30%		
Premorbid Functioning					
Predicted FSIQ (WTAR)	113.9 (4.7)	115.7 (4.9)	112.2 (7.0)	F(2, 86) = 2.3, p=.11	1 = 2 = 3
Personality (TIPI)					
Extraversion	8.1 (2.9)	9.5 (3.5)	9.1 (2.7)	F(2, 93) = 2.2, p=.12	1 = 2 = 3
Agreeableness	10.1 (2.1)	9.7 (2.4)	9.7 (2.2)	F(2, 93) = .31, p=.73	1 = 2 = 3
Conscientiousness	11.4 (2.2)	10.5 (2.2)	10.7 (2.7)	F(2, 93) = 1.5, p=.23	1 = 2 = 3
Openness	8.1 (2.9)	9.5 (3.5)	9.1 (2.7)	F(2, 93) = 19.1, p=.12	1 = 2 = 3
Substance Use					
Alcohol					
Drinks/Week (TLFB)	2.5 (2.2)	2.8 (2.3)	2.6 (2.0)	F(2, 89) = .10, p=.91	1 = 2 = 3
AUDIT	3.6 (1.8)	4.5 (1.7)	4.0 (2.0)	F(2, 85) = 1.6, p=.20	1 = 2 = 3
Binge Frequency (≥6 drinks)				p=.52 (Fisher's exact)	1 = 2 = 3
Never	41.5%	30%	37%		
Less than monthly	48.8%	50%	40.8%		
Monthly	7.3%	20%	22.2%		
Weekly	2.4%	0%	0%		

	CON(Group 1; n=48)	LMJ (Group 2; n=21)	EMJ (Group 3; n=27)	Omnibus Tests	Post-Hoc Tests
Daily or almost daily	0%	0%	0%		
Nicotine					
# Current Daily Smokers	0	0	1	p=1.00 (Fisher's exact)	1 = 2= 3
Marijuana					
THC, % Positive	N/A	7	5	p=.33	2 = 3
# MJ Use Days/week (TLFB)	N/A	2.9 (1.6)	2.9 (1.7)	F(1, 46) = .01, p=.92	2 = 3
# MJ Joints per week (TLFB)	N/A	1.5 (1.0)	1.4 (.59)	F(1, 46) = .39, p=.54	2 = 3
Age of Onset (years; TLFB)	N/A	17.8 (.83)	15.1(.96)	t(46)=10.2, p<.0001	2 > 3
Years of Regular Use (TLFB)	N/A	5.5 (1.7)	3.8 (2.1)	t(46)= 3.0, p=.004	2 > 3
Number of Joints during Years of Regular Use (Cumulative Exposure; TLFB)	N/A	15,377.81 (16,082.05)	13,483.03 (9,478.33)	t(45) = −.29, p=.77	2 = 3
Days from Memory Assessment of Last Use (TLFB)	N/A	Md = 2 [IQR 1, 4]	Md = 2 [IQR 1, 4]	z =.7, p =.50	2 = 3
Neurocognition					
CVLT-II					
Trial 1					1 = 2
• Raw	9.6 (2.5)	9.9 (3.1)	7.9 (2.5)	F(2, 93) = 4.6, p=.01	1, 2 > 3
• Z Score	1.3 (1.4)	1.3 (1.7)	.31 (1.4)		
Total Learning					1 = 2
• Raw	66.0 (7.6)	67.0 (7.8)	58.5 (9.7)	F(2, 93) = 8.7, p=.0003	1, 2 > 3
• T Score	65.3 (10.7)	67.6 (9.6)	57.1 (11.5)		
Learning Slope					1 = 2 = 3
• Raw	1.3 (.59)	1.2 (.64)	1.3 (.63)	F(2, 93) = .21, p=.81	
• Z Score	−.32 (1.1)	−.45 (1.1)	−.35 (1.2)		
Semantic Clustering					1 = 2
• Raw	3.3 (3.0)	2.0 (3.2)	1.9 (2.3)	F(2, 93) = 2.7, p=.07	2 = 3
• Z Score	1.5 (1.9)	.69 (2.0)	.70 (1.4)		1 > 3
Serial Clustering					1 = 2 = 3
• Raw	.74 (1.7)	1.7 (2.6)	.89 (1.4)	X^2 (2) =2.7, p=.25	
• Z Score	.02 (1.6)	.81 (2.0)	.24 (1.7)		
Delayed Recall [Md, IQR]					

	CON(Group 1; n=48)	LMJ (Group 2; n=21)	EMJ (Group 3; n=27)	Omnibus Tests	Post-Hoc Tests
• Raw	15 (14, 16)	15 (14, 16)	13 (11, 15)	X^2 (2) =9.7, p=.008	1 = 2
• Z Score	1 (1, 1.5)	1 (1, 1.5)	.5 (0, 1)		1, 2 > 3
% Retention	98.4 (10.6)	97.8 (8.3)	95.2 (12.6)	F(2, 93) = .83, p=.44	1 = 2 = 3

Note: all values are means, standard deviations, unless otherwise noted; CON, controls; LMJ, late onset marijuana users; EMJ, early onset marijuana users; MJ, marijuana; FSIQ, Wechsler Test of Adult Reading Full Scale IQ; TIPI, Ten Item Personality Inventory; TLFB, Timeline Followback (past 90 days); AUDIT, Alcohol Use Disorders Identification Test; CVLT-II, California Verbal Learning Test, Second Edition.

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Table 2

Estimated unstandardized coefficients for the effect of late (D_1) and early (D_2) onset of marijuana use compared to no use on CVLT-II delayed recall (Y), mediated by clustering strategy use (M_1) and total learning (M_2).

	Outcomes							
	Strategy ratio (M_1)		Total learning M_2)		Delayed recall (Y)			
					mediated		unmediated	
Predictors:		**Coefficient (SE)**		**Coefficient (SE)**		**Coefficient (SE)**		**Coefficient (SE)**
Constant	i_1	0.751 (1.828)	i_2	46.930* (9.034)	i_3	3.070 (1.991)	i_4	10.921* (2.390)
Late onset MJ use (D_1)	a_{11}	−0.588 (0.389)	a_{12}	2.661 (1.944)	c'_1	−0.007 (0.380)	c_1	0.156 (0.508)
Early onset MJ use (D_2)	a_{21}	−0.603 (0.389)	a_{22}	−4.556* (1.946)	c'_2	−0.368 (0.387)	c_2	−1.368* (0.509)
Strategy ratio (M_1)		---	d_{21}	2.518* (0.518)	b_1	0.045 (0.112)		---
Total learning (M_2)		---		---	b_2	0.160* (0.020)		---
Gender	a_{31}	0.256 (0.308)	a_{32}	1.656 (1.525)	c'_3	−0.117 (0.297)	c_3	0.263 (0.402)
Age	a_{41}	0.053 (0.078)	a_{42}	0.501 (0.387)	c'_4	0.051 (0.076)	c_4	0.155 (0.102)
	R^2 = 0.062		R^2 = 0.358		R^2 = 0.564		R^2 = 0.163	
	$F(4,91) = 1.496$ $p = 0.21$		$F(5,90) = 10.016$ $p < 0.0001$		$F(6,89) = 19.181$ $p < 0.0001$		$F(4,91) = 4.435$ $p = 0.0025$	

*Significant at α=0.05.

Table 3

Estimated total, direct, and indirect effects of late (D_1) and early (D_2) onset of marijuana use compared to no use on CVLT-II delayed recall (Y).

	Unstandardized effects				Partially standardized indirect effects			
	Effect	**SE**	**95% LCI**	**95% UCI**	**Effect**	**SE**	**95% LCI**	**95% UC**
Late onset of MJ use (*D*1)								
Total effect	0.156	0.508	−0.854	1.165	---	---	---	---
Direct effect	−0.007	0.380	−0.761	0.747	---	---	---	---
Indirect effects, total:	0.163	0.344	−0.489	0.890	0.084	0.180	−0.259	0.443
*D*1 -> *M*1 -> *Y*	−0.026	0.072	−0.199	0.104	−0.014	0.039	−0.108	0.055
*D*1 -> *M*1 -> *M*2 -> *Y*	−0.237	0.193	−0.672	0.100	−0.123	0.099	−0.339	0.053
*D*1 -> *M*2 -> *Y*	0.426	0.333	−0.165	1.158	0.221	0.170	−0.090	0.585
Early onset of MJ use (*D*2)								
Total effect	−1.368	0.509	−2.378	−0.358	---	---	---	---
Direct effect	−0.368	0.387	−1.138	0.401	---	---	---	---
Indirect effects:	−0.999	0.447	−1.959	−0.210	−0.499	0.196	−0.896	−0.120
*D*1 -> *M*1 -> *Y*	−0.027	0.066	−0.160	0.118	−0.013	0.034	−0.084	0.058
*D*1 -> *M*1 -> *M*2 -> *Y*	−0.243	0.169	−0.623	0.045	−0.121	0.081	−0.297	0.024
*D*1 -> *M*2 -> *Y*	−0.730	0.395	−1.617	−0.068	−0.364	0.179	−0.734	−0.038

Note: The partially standardized effect rescales the direct and indirect effects in the mediation model to the standard deviation of Y but keeps X in its original metric (Hayes, 2013). Standard errors (SE) and 95% confidence intervals (95% LCI and 95% UCI) are based on ordinary least squares regression for model coefficients, total effects, and direct effects, and are based on percentile-based bootstrap methods for indirect effect SEs and confidence intervals.