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Research Article

Cannabis use and episodic memory performance among adolescents: Moderating effects of depression symptoms and sex

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Abstract

Objective: Cannabis use has been linked to poorer episodic memory. However, little is known about whether depression and sex may interact as potential moderators of this association, particularly among adolescents. The current study addresses this by examining interactions between depression symptoms and sex on the association between cannabis use and episodic memory in a large sample of adolescents. **Method:** Cross-sectional data from 360 adolescents ($M_{age} = 17.38$, $SD = .75$) were analyzed at the final assessment wave of a two-year longitudinal study. We used the Drug Use History Questionnaire to assess for lifetime cannabis use, and the Computerized Diagnostic Interview Schedule for Children, Fourth edition to assess the number of depression symptoms in the past year. Subtests from the Wechsler Memory Scale, Fourth Edition and the California Verbal Learning Test, Second Edition were used to assess episodic memory performance. **Results:** The effect of the three-way interaction among cannabis use, depression symptoms, and sex did not have a significant impact on episodic memory performance. However, follow-up analyses revealed a significant effect of the two-way interaction of cannabis use and depression symptoms on episodic memory, such that associations between cannabis use and episodic memory were only significant at lower and average levels of depression symptoms. **Conclusions:** Contrary to our hypotheses, we found that as depression symptoms increased, the negative association between cannabis use and episodic memory diminished. Given the use of a predominantly subsyndromic sample, future studies should attempt to replicate findings among individuals with more severe depression.

Keywords: cannabis; episodic memory; depression; sex differences; adolescence; moderation

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Introduction

Cannabis remains one of the most widely used substances among adolescents in the United States (Johnston et al., 2021). Notably, episodic memory deficits are one of the most frequently reported consequences of cannabis use (Blest-Hopley et al., 2020; Broyd et al., 2016; Figueiredo et al., 2020; Scott et al., 2018). Given the vulnerability toward substance use in adolescence (Arain et al., 2013; Blakemore & Choudhury, 2006; Ghetti & Bunge, 2012) and the central role of episodic memory in the daily functioning of human life (Ghetti & Bunge, 2012), it is important to evaluate factors that may serve to exacerbate episodic memory problems from cannabis use among adolescents.

Multiple systematic reviews and meta-analyses have synthesized the vast literature on the effects of cannabis use on neurocognition with results continuing to suggest adverse effects in the domain of episodic memory. For instance, a recent meta-analysis was performed on 13 adult population studies and found an association between chronic cannabis use and memory impairments (Figueiredo et al., 2020). Additionally, a meta-analysis by Scott et al. (2018) examined 69 studies on adolescents and adults and found effect sizes (ranging from mean *d*, −0.33 to −0.21) across cognitive domains with one of the largest effect sizes in delayed memory ($d = -0.26$). Furthermore, a recent review focusing exclusively on the effects of cannabis use and the adolescent brain noted impaired cognitive functioning across several domains including episodic memory (Blest-Hopley et al., 2020). The aforementioned meta-analyses and reviews demonstrate adverse effects of cannabis use on episodic memory. However, inconsistencies were noted across these studies, emphasizing the need for future research to examine the impact of other potentially confounding variables such as mental health and sex (Figueiredo et al., 2020; Scott et al., 2018). Examination of potential moderating effects has important implications for further understanding the associations between cannabis use and neurocognitive deficits and could serve to inform future prevention and intervention efforts.

Mental health problems often emerge during adolescence, with depression among the most common (Avenevoli et al., 2015; Mojtabai et al., 2016). Much of the literature on depression and episodic memory performance has focused on adult populations and has found higher levels of depressive symptoms to be associated with poorer episodic memory performance (Ahern & Semkovska, 2017; Goodall et al., 2018; McDermott & Ebmeier, 2009). A meta-analysis from Ahern & Semkovska (2017) focusing

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on the first episode of major depression in adults found a broad range of impairments across cognitive domains compared to healthy controls, including small to moderate effects across a variety of episodic memory tasks. These results appear to extend to adolescent samples. Indeed, a meta-analysis focusing on adolescents and young adults (ages 12 to 25) with a diagnosis of depressive disorder found small effects of depression diagnosis on performance on episodic memory tasks (Goodall et al., 2018). Additionally, a study conducted by Barch et al., (2019) examined the effects of depression on cognitive functioning among a sample of adolescents and found a negative association between depression severity and episodic memory performance. Overall, this expanding literature continues to find significant effects, indicating the need for further exploration of the role of depression as a risk factor for decreased episodic memory function in adolescents.

Few studies have examined the combined effects of cannabis use and depression on memory performance. A study by Roebke et al., (2014) found main effects of both major depressive disorder (MDD) and cannabis use on episodic memory performance among adults but did not find significant differences in learning and episodic memory performance between adult cannabis dependent participants with and without a comorbid depressive disorder (diagnosed with either [MDD] or dysthymic disorder). In contrast, a similar study among young adults found the same main effects, with both depressed individuals and cannabis users recalling fewer words in short and long-delay recall trials than controls (Radoman et al., 2019); however, they also found an additive effect of MDD and cannabis use on verbal learning and memory recall, such that cannabis users who had a diagnosis of MDD showed the worst performance (Radoman et al., 2019). The conflicting results found from the aforementioned studies highlight the need for further exploration and consideration for adolescent samples.

Finally, it is important to consider that there may be sex differences in the interactive effect of cannabis use and depression on episodic memory. The literature reports differences among male and female depression rates, with females almost twice as likely to experience symptoms of depression starting in adolescence (Ferrari et al., 2013; Salk et al., 2017). Additionally, the association between frequency of cannabis use and poorer episodic memory performance has been documented more often among females than males (Crane et al., 2013). To our knowledge, the current study will be the first to examine interactive effects of cannabis use, MDD symptoms, and sex on episodic memory among adolescents.

The current study aimed to replicate existing literature on cannabis and episodic memory in an adolescent sample ($N = 360$), and extend results by examining the moderating roles of both past year MDD symptoms and sex on this association. The examination of these interactions among adolescents is needed to advance the understanding of risk factors that might negatively impact episodic memory, and to better understand individual differences that may place teens at risk for adverse outcomes from cannabis use. We hypothesized that (a) greater lifetime frequency of cannabis use would be associated with worse episodic memory performance, and that (b) this association would be stronger among individuals with more past year MDD symptoms. Furthermore, we hypothesized that (c) the impact of past year MDD symptoms on the association between lifetime frequency of cannabis use and episodic memory would be stronger among females than males.

Method

Participants and procedures

Participants were 360 adolescents ($M_{age} = 17.38$, $SD = .75$) whose data were collected as part of a larger longitudinal study examining the associations between decision-making, episodic memory performance, and cannabis use trajectories (R01 DA031176; PI: RG). Participants were recruited throughout the greater Miami area at middle and high schools, parks, movie theaters, and word-of-mouth. Participants were 14–17 years old at baseline and ranged from 15–19 years old at the final assessment wave [time point five (T5)], approximately 2 years after the initial baseline visit. Phone screens were used to assess study eligibility with inclusion criteria consisting of the ability to read and write in English. Additionally, the goal of the sample was to recruit adolescents who were at risk for cannabis use escalation; therefore, participants needed to self-report any lifetime use of alcohol, cigarettes, or cannabis – even if minimal (i.e., only a sip or a puff). However, we recruited about 10% of the sample with no substance use history to eliminate the risk of participants being identified as substance users through study participation. Briefly, exclusion criteria consisted of any history of psychiatric or mood disorders (i.e., received a diagnosis *and* were either prescribed psychotropic medication for *or* underwent therapy in relation to specific diagnosis), self-reported neurological condition, history of cannabis or alcohol use disorder, birth complications, or traumatic brain injury or loss of consciousness > 10 min. However, participants diagnosed with a psychiatric or mood disorder, or cannabis or alcohol use disorder, after completing the baseline assessment were maintained in the study. Participant inclusion and exclusion criteria at baseline have been described previously in further detail (Pacheco-Colón et al., 2021). Data were collected over a two-year period consisting of five different visits scheduled approximately six months apart. Participants completed semi-structured interviews and self-report measures assessing mental health and substance use. Neuropsychological testing was administered at three separate time points each one year apart. The sample population was majority Hispanic/Latino (89.2%), consistent with the demographics of Miami-Dade County. All participant characteristics are reported in Table 1. Due to the greatest amount of cumulative cannabis use reported at the final time point of the larger longitudinal study, data for the current study was analyzed at T5. At T5, 4.4% of the sample reported experiencing a major depressive episode (MDE) in the past year and 23.1% met criteria for current cannabis use disorder. Written adolescent assent and parental/guardian consent were obtained prior to each assessment, and the Institutional Review Board at Florida International University provided approval for the study. Additionally, this study was completed in compliance with institutional research standards for human research and in accordance with the Declaration of Helsinki.

Measures

Participant History Questionnaire (PHQ)

This semi-structured interview was administered at baseline to assess participant and parental demographic information such as age, sex, ethnicity, race, and history of psychological disorders. Age at T5 was calculated and used as a covariate in all analyses.

Wide Range Achievement Test 4 – Word Reading Subtest (WRAT-4)

The Word Reading subtest of the WRAT-4 (Wilkinson & Robertson, 2006) was administered at baseline and used to calculate participants' estimated intelligence.

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Table 1. Participant demographics and characteristics at time point 5 (T5)

Participant characteristics ($N = 360$)	% or Mean (SD)	Range
Demographics (at baseline)		
WRAT-4 reading standard score	108.1 (14.7)	73, 145
Sex		
Male	53.1%	
Female	46.9%	
Ethnicity		
Hispanic	89.2%	
Race		
White	76.1%	
Black	7.8%	
More than one race	12.5%	
Not Listed	3.6%	
Age (at T5)	17.38 (.75)	15, 19
Years of education	11.1 (.83)	9, 14
Substance Use		
Lifetime frequency (# of days used in lifetime)		
Alcohol Use (Md, [IQR])	23.5 [7, 73]	0, 1002
Nicotine Use (Md, [IQR])	2.0 [0, 19.75]	0, 1288
Cannabis Use (Md, [IQR])	108.0 [8.25, 485.50]	0, 1708
Current cannabis use disorder (%)	23.1%	
Current alcohol use disorder (%)	3.1%	
Mental health		
CDISC-IV MDD (# of symptoms in past year)	4.4 (4.2)	0, 20
CDISC-IV GAD (# of symptoms in past year)	2.1 (2.1)	0, 11
CDISC-IV MDE (% of participants with episode in past year)	4.4%	
CDISC-IV GAD (% of participants with episode in past year)	1.1%	
Episodic memory performance		
CVLT-II short-delay free recall (Trials 1-5 total T-score)	51.0 (11.2)	16, 79
CVLT-II long-delay free recall (T-score)	50.2 (10.2)	20, 65
WMS-IV - logical memory I (scaled score)	9.0 (2.9)	1, 15
WMS-IV - logical memory II (scaled score)	9.5 (2.6)	1, 16
WMS-IV - designs memory I (scaled score)	9.8 (2.8)	4, 17
WMS-IV - designs memory II (scaled score)	10.8 (2.8)	4, 18

Note. All numbers are reported from time point 5, unless otherwise specified. SD = Standard Deviation; Md = Median; IQR = Interquartile Range; WRAT-4 = Wide Range Achievement Test; CDISC-IV = Computerized Diagnostic Interview Schedule for Children, Fourth Edition; CVLT-2 = California Verbal Learning Test, Second Edition; WMS = Wechsler Memory Scale; MDD; Major Depressive Disorder; MDE = Major Depressive Episode; GAD = Generalized Anxiety Disorder; Other Race = American Indian/Alaska Islander, Asian, Native Hawaiian or Other Pacific Islander, or Unknown.

Computerized Diagnostic Interview Schedule for Children-IV (CDISC-IV)

The CDISC-IV (Shaffer et al., 2000) is a structured interview designed to assess symptoms and diagnoses of mental health disorders among youth within the last year, including generalized anxiety disorder (GAD) and MDD. The CDISC-IV has previously demonstrated strong reliability and construct validity (Malgady et al., 1992). The current study used the total number of past year MDD symptoms at T5 as a main variable of interest.

Drug Use History Questionnaire (DUHQ)

The DUHQ (Gonzalez et al., 2012; Rippeth et al., 2004) is a semi-structured interview used to obtain a detailed self-report history of substance use during a participant's lifetime, the past six months, and past 30 days. Lifetime frequency of cannabis use (i.e., number of days used), and lifetime amount of cannabis use (i.e., number of grams) were calculated at baseline, with past 6-month use further assessed at subsequent measurement waves. These were summed to obtain lifetime frequency of cannabis use and lifetime amount of cannabis use variables at the last assessment; we used the former as our main measure of cannabis use, while the latter was used for post hoc analyses.

Wechsler Memory Scale – Fourth Edition (WMS-IV): Logical Memory and Designs Subtests

Two subtests were used from the WMS-IV (Logical Memory and Design Memory) to assess episodic memory performance (Wechsler, 2009a). The Logical Memory subtest consists of two brief stories that are read aloud to the participant, who is then asked to recall the story immediately after each is presented (Logical Memory-I). After a 20- to 30-min delay the participants are again asked to recall the stories (Logical Memory-II).

The Designs subtest consists of four trials of abstract designs presented on a grid to the participants for 10 s. Participants are then asked to immediately select the designs from a set of cards and place the cards on the grid in the same place as previously shown (Designs-I). After a 20-min delay, participants are again asked to reproduce the designs on the grid (Designs-II). The age-corrected scaled scores from the immediate and delayed free recall trials of the Logical Memory and Designs subtests at T5 were first transformed to Z-scores, and then transformed into T-scores to be used as part of the outcome measures for the current study (Wechsler, 2009b). This was done so that all episodic memory measures were on the same scale to facilitate interpretation of findings.

California Verbal Learning Test, Second Edition (CVLT-II)

The CVLT-II (Delis et al., 2000) was used to assess episodic verbal learning and memory performance at T5. Each participant was presented with a list of 16 words over five trials (List A) and asked to recall as many words as possible after each list was read aloud (Immediate Free Recall). An interference list of 16 words was then read aloud for one trial (List B) and participants were asked to recall as many words from the interference list as possible. Participants were then asked to recall freely as many words from List A as possible. After a 20-min delay, participants were asked again to freely recall the words from List A (long-delay free recall). Normative data for the CVLT-II includes participants as young as 16 years old (Woods et al., 2006). Two participants from the current study were 15 years old, to which we applied the 16-year-old norms and controlled for age in analyses. CVLT-II forced choice recognition was examined using cutoff scores from Delis et al., (2000). We found that only one participant had ≤ 14 correct responses on the forced choice recognition trial. Given that this participant scored correctly on 13 out of 16 responses on the forced choice recognition trial and did not appear to show signs of low effort throughout the protocol, their data were retained in the current study.

Episodic Memory Composites

For data reduction and to minimize Type I error, two composite variables were generated: Immediate Free Recall and Delayed Free Recall. Similar composites have been employed in previously published meta-analyses on cannabis use and neurocognition (Grant et al., 2003; Schreiner & Dunn, 2012). Specifically, a composite variable was created for immediate free recall by taking the average short-delay free recall T-scores from the WMS-IV Logical Memory and Designs Memory subtests and the average short-delay free recall scores from the CVLT-II to generate an average immediate free recall outcome variable. Similarly, a composite variable was created for delayed free recall by taking the average long-delay free recall T-scores from the WMS-IV Logical Memory and Designs Memory subtests and the average long-delay free recall scores from the CVLT-II to generate an average delayed free recall outcome variable.

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Data analytic plan

All analyses were run in version 3.5 of PROCESS (Hayes, 2018). Age of the participants at T5 was added as a covariate in all primary analyses to control for effects of age on the outcome variables of interest. Additionally, a correlation matrix was run to examine potential variables associated with the immediate or delayed free recall outcome variables. Based on the results from the correlation matrix presented in Table 2, lifetime frequency of nicotine (number of days used) was also included as a covariate in all primary analyses. Assumptions for linear regression were evaluated and found that the linearity, normality of residuals, and independence of residuals' assumptions were met (Cohen et al., 2002). However, evidence of heteroscedasticity was found after examination of scatter plots of residuals for both outcome variables. Therefore, bootstrapping was performed with robust estimators using 5,000 samples for all primary analyses.

Two separate multiple linear regression models were run to examine the impact of lifetime frequency of cannabis use, past year MDD symptoms, and sex to predict immediate and delayed free recall. The first model included the variables of interest as well as all two-way interactions and the three-way interaction. The second model subsequently removed the three-way interaction and examined all two-way interactions with the variables of interest. Lifetime frequency of cannabis use and past year MDD symptoms were continuous variables that were mean centered prior to conducting analyses. All significant interactions were followed up with simple slopes difference tests (Aiken et al., 1991), with past year MDD symptoms set at one standard deviation above the mean (higher MDD symptoms $\geq$ 8.58 symptoms), at the mean (average MDD symptoms = 4.36 symptoms), and one standard deviation below the mean (lower MDD symptoms $\leq$ .13 symptoms). Subsequent multiple linear regression analyses were run in PROCESS to examine two-way interactions and main effects only after the three-way interaction was found to be non-significant.

Missing data procedures

A missing value analysis was conducted on the full sample (N = 401) and found that nine percent of the data were missing for the current study. Fourteen participants did not complete the final measurement wave which accounted for 3.5% of the missing data. The lifetime frequency of substance use variables including cannabis, alcohol, and nicotine accounted for the additional 5.5% of missingness. Mechanisms for missing data were analyzed using logistic regression. Both outcome variables (immediate free recall, delayed free recall) were coded into binary variables for missing and non-missing data (0 = not missing, 1 = missing). The binary outcome variables were then placed in a series of logistic regression analyses examining potential demographic, mental health, and substance use variables for predictors of missingness in the data. None of the variables placed in the logistic regression analyses were significant predictors of missingness and the missing data for the current study were presumed missing at random.

We then applied multiple imputation (MI) for dealing with missing data (Rubin, 1987) using 20 imputed datasets, and the analyses for each dataset were pooled. The results from the linear regression analyses were similar using MI and listwise deletion, so listwise deletion was used for all further analyses for easier interpretation. The final sample used for all analyses after exclusion of participants with missing data was 360 participants.

Results

We first analyzed results from the multiple linear regression for both outcome variables, with all variables of interest included in the model (see Table 3). The three-way interaction between lifetime frequency of cannabis use, past year MDD symptoms, and sex was not significant for either immediate (p = .260) or delayed (p = .203) free recall. However, a significant main effect of lifetime frequency of cannabis use was found on both immediate (p = .015) and delayed (p = .023) free recall, such that an increase in lifetime frequency of cannabis use (more days used) was associated with a decrease in both immediate and delayed free recall. Additionally, there was a main effect of sex on immediate (p = .042) free recall such that males performed better on immediate free recall compared to females. Additional information describing participant demographics and characteristics by sex can be found in Table S1 of the Supplemental Materials.

Subsequent multiple linear regression analyses revealed no significant two-way interactions between lifetime frequency of cannabis use and sex, or past year MDD symptoms and sex on episodic memory. Nonetheless, there were significant effects of the two-way interaction between lifetime frequency of cannabis use and past year MDD symptoms on both immediate (p = .010) and delayed (p = .003) free recall (see Table 4). As shown in Figure 1, simple slopes difference tests revealed that lifetime frequency of cannabis use was significantly associated with poorer performance on immediate free recall at lower (p < .001), and average (p = .001) levels of MDD symptoms, but not at higher (p = .323) levels. Similarly, lifetime frequency of cannabis

Table 2. Correlations for possible covariates

Variable (N = 360)	1	2	3	4	5	6	7	8	9
1. Age	–								
2. MDD Symptoms	.040	–							
3. GAD Symptoms	.019	.590***	–						
4. Sex	.088	−.140**	−.170**	–					
5. Lifetime Frequency Alc[a]	.194***	.120*	.013	−.026	–				
6. Lifetime Frequency Ni[a]	.122*	.131*	−.014	.119*	.549***	–			
7. Lifetime Frequency CU[a]	.200***	.135*	−.042	.193***	.445***	.479***	–		
8. Immediate Free Recall	−.005	−.012	.043	.046	−.051	−.154**	−.200***	–	
9. Delayed Free Recall	.013	−.052	.032	.022	−.060	−.154**	−.189***	.889***	–

Note. All correlations use Pearson's r unless otherwise noted. For sex, 0 = female, 1 = male. Variables were not mean centered. MDD = major depressive disorder; GAD = generalized anxiety disorder; Alc = alcohol; Ni = nicotine; CU = cannabis use.
[a]Rows use Spearman's rho correlation coefficients. *p < .05. **p < .01. ***p < .001. Two-tailed.

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Table 3. Regression analyses with three-way interaction in model

	Immediate Free Recall					Delayed Free Recall				
Predictor	*b*	*SE*	*t*	95% CI	*p*	*b*	*SE*	*t*	95% CI	*p*
Lifetime frequency CU	−0.006	0.003	−2.444	[−0.011, −0.001]	.015*	−0.005	0.002	−2.290	[−0.010, −0.001]	.023*
MDD symptoms	0.018	0.132	0.139	[−0.241, 0.277]	.890	−0.058	0.125	−0.462	[−0.305, 0.189]	.644
Sex	1.819	0.889	2.047	[0.071, 3.568]	.042*	1.194	0.846	1.410	[−0.471, 2.858]	.159
CU × MDD symptoms	0.001	0.001	1.485	[−0.000, 0.001]	.139	0.001	0.001	1.665	[−0.000, 0.001]	.097
CU × sex	0.003	0.003	0.920	[−0.003, 0.008]	.358	0.003	0.003	0.969	[−0.003, 0.008]	.334
MDD symptoms × sex	0.009	0.206	0.044	[−0.396, 0.414]	.965	−0.028	0.196	−0.144	[−0.414, 0.357]	.885
CU − MDD symptoms − Sex	0.001	0.001	1.128	[−0.001, 0.002]	.260	0.001	0.001	1.276	[−0.000, 0.002]	.203
Model R^2	.085					.085				
Model *F*	3.626					3.631				

Note. For sex, 0 = female, 1 = male. Confidence Intervals show lower and upper limits of the unstandardized beta coefficients. *b* = unstandardized beta coefficient; *SE* = Standard Error; CU = cannabis use; MDD = major depressive disorder; CI = confidence interval. *$p < .05$.

Table 4. Interaction between lifetime frequency of cannabis use and past year MDD symptoms

	Immediate Free Recall					Delayed Free Recall				
Predictor	*b*	*SE*	*t*	95% CI	*p*	*b*	*SE*	*t*	95% CI	*p*
Lifetime frequency CU	−0.004	0.001	−3.323	[−0.007, −0.002]	.001**	−0.004	0.001	−3.114	[−0.006, −0.001]	.002**
MDD symptoms	−0.009	0.098	−0.094	[−0.202, 0.183]	.925	−0.088	0.093	−0.945	[−0.271, 0.095]	.346
CU × MDD symptoms	0.001	0.001	2.575	[0.000, 0.001]	.010*	0.001	0.000	2.990	[0.000, 0.001]	.003**
Model R^2	.066					.071				
Model *F*	4.993					5.411				

Note. Confidence Intervals show lower and upper limits of the unstandardized beta coefficients. *b* = unstandardized beta coefficient; *SE* = Standard Error; CU = cannabis use; MDD = major depressive disorder; CI = confidence interval. *$p < .05$. **$p < .01$.

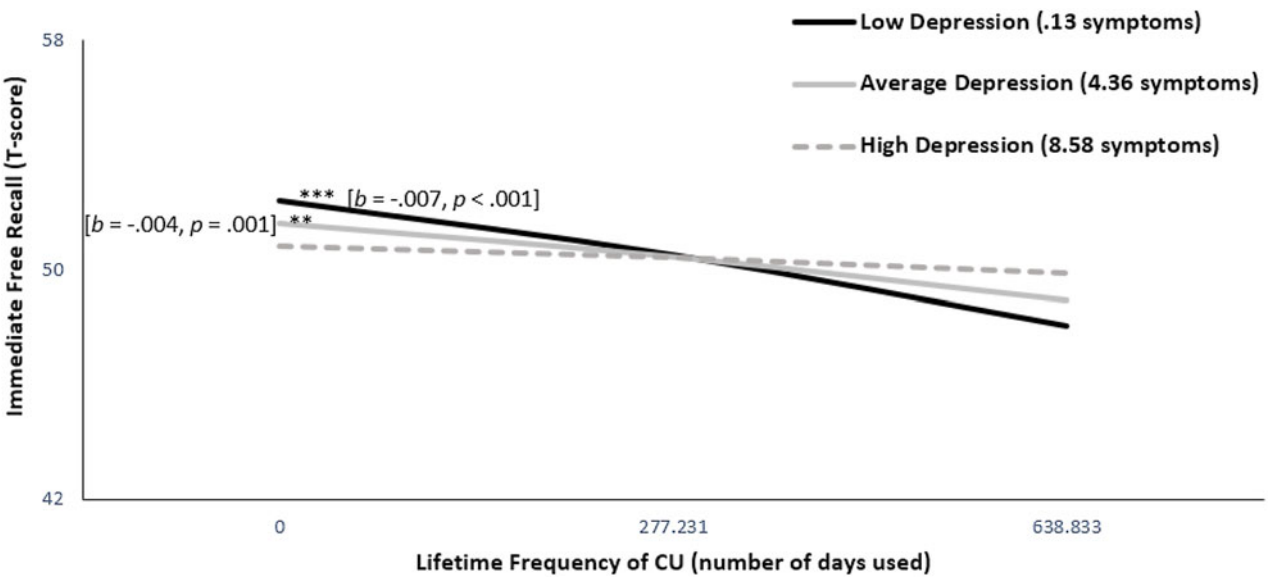

Figure 1. Lifetime frequency of cannabis use and past year MDD symptoms on immediate free recall.
Note. Lifetime frequency of cannabis use and depression variables were not mean centered for easier interpretation. *b* = unstandardized beta coefficient; CU = cannabis use; MDD = major depressive disorder. *$p < .05$. **$p < .01$. ***$p < .001$.

use was significantly associated with poorer performance on delayed free recall at lower ($p < .001$), and average ($p = .002$) levels of MDD symptoms, but not at higher ($p = .592$) levels (see Figure 2).

Post hoc analyses

Post hoc exploratory analyses using ANOVA tests were performed by splitting the continuous lifetime frequency of cannabis use and continuous MDD variables into separate tertile groups to further examine results from the simple slopes difference tests. In contrast to the original analyses, the past year symptoms of MDD and lifetime frequency of cannabis use variables were converted from continuous to categorical variables for all post hoc exploratory analyses. Specifically, the past year MDD variable was split into tertiles to create low (≤ 2 symptoms), average (3–5 symptoms), and high (≥ 6 symptoms) groups. Additionally, the lifetime frequency of cannabis use variable was also split into tertiles to create low (≤ 21 days used), average (22 – 285 days used), and high

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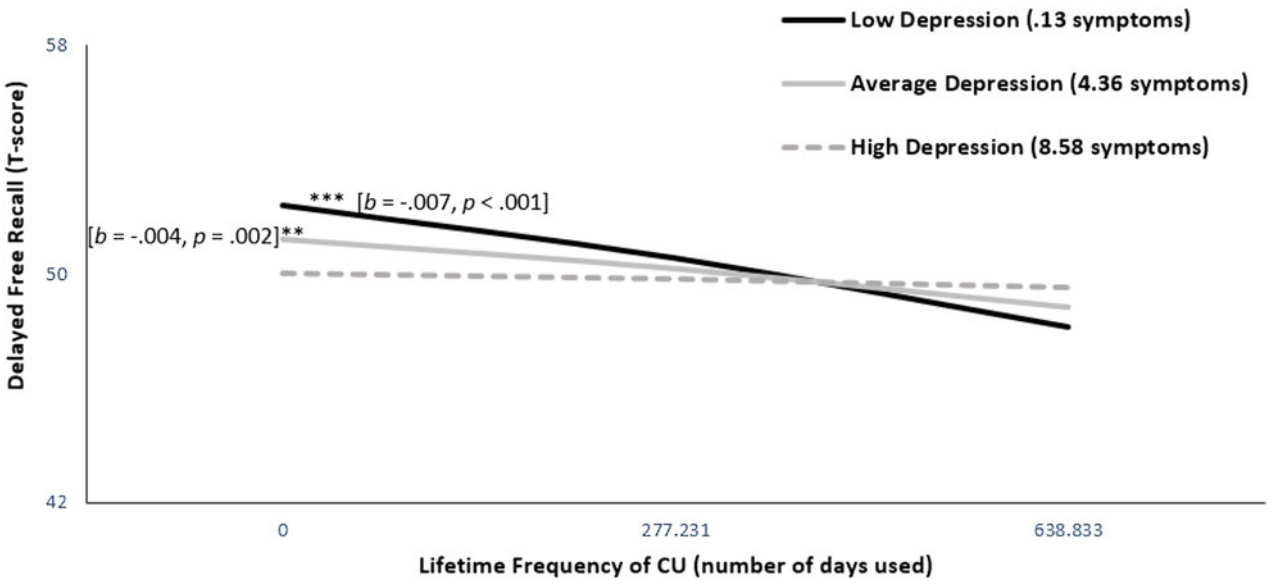

Figure 2. Lifetime frequency of cannabis use and MDD symptoms on delayed free recall.
Note. Lifetime frequency of cannabis use and depression variables were not mean centered for easier interpretation. *b* = unstandardized beta coefficient; CU = cannabis use; MDD = major depressive disorder. **p* < .05. ***p* < .01. ****p* < .001.

(≥ 286 days used) groups. The MDD groups consisted of 150 participants in the low depression group ($M = .75$ symptoms), 91 participants in the average group ($M = 3.76$ symptoms), and 119 participants in the high group ($M = 9.36$ symptoms) based on the number of MDD symptoms endorsed in the past year. The lifetime frequency of cannabis use groups were created based on the number of cannabis use days endorsed in a participant's lifetime. There were 120 participants in the low cannabis group ($M = 4.39$ days used), 118 participants in the average cannabis group ($M = 120.81$ days used), and 122 participants in the high cannabis group ($M = 696.89$ days used). We explored whether there were differences among the MDD groups in lifetime frequency of cannabis use (number of days used), or amount of cannabis used (number of grams) (i.e., whether the group with the highest number of MDD symptoms reported lower frequency of cannabis use or smaller amounts of cannabis used). We found no significant differences in lifetime frequency or amount of cannabis used among the MDD groups. Additionally, we explored whether the cannabis use groups differed significantly on the number of MDD symptoms (i.e., whether the group with the lowest frequency of cannabis use reported more MDD symptoms); however, no significant results were found.

Discussion

The current study examined the interactive effects of lifetime frequency of cannabis use, past year MDD symptoms, and sex on episodic memory in order to understand how MDD symptoms may influence the association between cannabis use and episodic memory among adolescents, and whether this association differs for males and females. Contrary to our hypotheses, we did not find a significant three-way interaction, indicating that the impact of MDD symptoms on the magnitude of the association between lifetime frequency of cannabis use and episodic memory did not differ for males or females.

However, we did find a significant association between lifetime frequency of cannabis use and episodic memory, such that as lifetime frequency of cannabis use increased (more days used), episodic memory performance decreased. This finding is in concordance with prior literature and further highlights the negative relationship between cannabis use and episodic memory (Figueiredo et al., 2020; Scott et al., 2018). Previous literature has attempted to elucidate this finding by examining alterations in brain structure and function among adolescent cannabis users compared to controls. A previous study found that adolescent cannabis users had significantly smaller bilateral hippocampal volumes compared to non-using controls (Ashtari et al., 2011). However, despite the smaller hippocampal volumes, both the non-using controls and cannabis users performed similarly on a verbal memory task, suggesting an alteration in the functional mechanisms used among the cannabis users. It is important to note that all participants in the aforementioned study met diagnostic criteria for cannabis dependence (Ashtari et al., 2011). Further research is needed to examine possible neurobiological mechanisms underlying the association between subclinical adolescent cannabis use and episodic memory performance.

Furthermore, our results revealed a significant two-way interaction between lifetime frequency of cannabis use and past year MDD symptoms on episodic memory. However, inconsistent with our hypotheses, this significant association was found only at lower (≤ .13 symptoms) and average (4.36 symptoms) levels of past year MDD symptoms, but not at higher (≥ 8.58 symptoms) levels. This finding indicates that at higher levels of MDD symptoms, the negative association between lifetime frequency of cannabis use and episodic memory diminished. To better understand these results, post hoc exploratory analyses using ANOVA tests were performed to examine results from the simple slopes difference tests. We wanted to explore whether the high lifetime cannabis use group (≥ 286 days used) or high MDD symptoms group (≥ 6 symptoms) revealed any significant differences relative to the average and low groups to account for the lack of significant association found between lifetime frequency of cannabis use and episodic memory performance at high levels of MDD symptoms. However, none of the exploratory analyses revealed significant differences between these tertile groups.

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Nonetheless, examination of prior literature may provide insight into these results. Two prior studies have examined the interaction between cannabis use and depression on episodic memory (Radoman et al., 2019, Roebke et al., 2014). Both studies found main effects of MDD and cannabis use on episodic memory among adult and young adult samples; however, they did not find significant interactions between these variables. Radoman et al., (2019) only included participants in the depression group who either met lifetime criteria for MDD or had a current diagnosis of MDD (~34% of participants met criteria for current MDD). Similarly, all participants in the depression group of the Roebke et al., (2014) study had a current diagnosis of either MDD or dysthymic disorder, demonstrating high rates of depression among these participant samples. Therefore, results from the current study are somewhat consistent with these prior study findings, illustrating that at higher levels of depression (i.e., ≥ 8.58 symptoms for current study; current or lifetime MDD diagnosis for prior studies), there is no significant interaction between cannabis use and episodic memory.

Nonetheless, the current study did find significant interactive effects at lower and average levels of depression. To our knowledge, these are novel findings within the literature, prompting future studies to replicate these results with additional adolescent samples. Furthermore, given the stringent exclusion criteria at baseline, only 4.4% of participants in the current study met diagnostic criteria for an MDE in the past year. In comparison, at the time of data collection for the current study in 2015, 12.5% of adolescents in the United States experienced an MDE in the past year according to the Center for Behavioral Health Statistics and Quality (2016). The considerably lower rates of MDE from the current sample suggests future studies should examine how both clinical and subclinical levels of depression influence cannabis use and its effects on episodic memory among adolescents.

The current study also examined the influence of sex differences on the interaction between lifetime frequency of cannabis use and past year MDD symptoms on episodic memory among adolescents. Given that prior literature has found greater depression rates among female compared to male adolescents (Ferrari et al., 2013; Salk et al., 2017), as well as greater adverse impacts on episodic memory among female cannabis users compared to male cannabis users (Crane et al., 2013), we hypothesized that the impact of MDD symptoms on the association between lifetime frequency of cannabis use and episodic memory would be stronger among female than male adolescents. Contrary to our hypotheses, the three-way interactive effect was not significant. This again might be explained by the low rates of depression in our sample and that these associations may vary as a function of sex only among samples with clinical levels of depression. However, a significant main effect of sex was found for immediate free recall, such that males showed a slight advantage over females. This finding is inconsistent with prior literature that has demonstrated a female advantage among tasks of episodic memory in both adolescents and adults (Asperholm et al., 2019; Boman, 2004; Herlitz & Rehnman, 2008; Kramer et al., 1997). Sex differences in age of cannabis use onset may partially explain our finding. A previous study by Crane et al., (2015) found that earlier age of first use of cannabis was associated with poorer immediate free recall for female compared to male young adults. Given that the participants in the current sample were between 15–19 years of age and had been participating in the larger parent study for two years prior to T5, it is plausible that the mean age of first use for our sample is similar or possibly younger than the mean age of first use ($M = 15.80$) reported in the Crane et al. (2015) study. Though age of first use of cannabis may be a confounding variable influencing our findings with sex, particularly given the higher rates of lifetime cannabis use among males than females (see Table S1), age of first use was not controlled for in the current study and should be examined in future research to determine whether it is driving these associations.

Results from the current study should be interpreted considering the following limitations. First, the cross-sectional design of the study prevents the ability to determine timing and causality. Additionally, exclusion of participants at baseline with a history of significant psychological disorders may limit generalizability of the results to adolescents with subclinical or clinical MDD symptoms. As previously noted, only 4.4% of participants in the current sample met criteria for a past year MDE, compared to 12.5% of adolescents in the United States who met criteria for a past year MDE (Center for Behavioral Health Statistics and Quality, 2016). Similarly, due to the limited number of participants reporting symptoms of MDD in the sample, the current study focused on symptoms of MDD in the past year instead of current symptoms of MDD. Future studies may attempt to replicate findings from the current study among adolescent samples with higher rates of reported MDD. Additionally, we note that episodic memory was examined as a composite variable in the current study, future studies may reveal different results when examining distinct sub-components of episodic memory such as visual and auditory memory, or the various indices from the CVLT. It is also worth noting that post hoc exploratory analyses did not correct for Type I error; however, none of the post hoc analyses revealed significant results. Furthermore, there are many potential confounding variables that we were not able to examine in the current study, including cannabis potency, method of use, cannabis use age of onset, and ratio of cannabidiol (CBD) to delta-9-tetrahydrocannabinol (THC), all of which could conceivably influence results. Finally, practice effects may have impacted results given that participants had completed tests of episodic memory on two prior occasions, each one year apart; it is therefore possible that memory tests were less sensitive over time. However, we did find a significant main effect for cannabis use on memory performance.

In summary, findings from the current study extend prior literature on adolescent cannabis use and episodic memory by showcasing the moderating role of MDD symptoms. Although further work is needed to better understand the influence of subclinical and clinical levels of depression symptoms, our findings inform treatment efforts focused on improving episodic memory function by tailoring approaches based on an individual's history of cannabis use and depression symptoms.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S135561772300005X.

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