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# The role of sleep in the link between cannabis use and memory function: evidence from a cross-sectional study

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## ABSTRACT

**Background:** It is known that cannabis use affects memory and sleep problems independently. However, to date, how memory and sleep problems may interact as a result of cannabis use remains unknown.

**Objectives:** We performed a secondary analysis of existing data to determine whether sleep quality mediates the association between cannabis use and memory and whether sex moderated these effects.

**Methods:** A total of 141 adults with cannabis use disorder (CUD) (83 men) and 87 without CUD (39 men) participated in this study. Outcome measures included self-reported sleep problems from the past 7 days (Marijuana Withdrawal Checklist), learning and memory performance via the short visual object learning task (sVOLT), short visual object learning task delayed (sVOLTd), and verbal memory via the N-back. Bootstrapped mediation and moderated mediation analyses were run to test if sleep quality mediated the association between cannabis use and memory outcomes and whether sex moderated these effects, respectively.

**Results:** Sleep quality mediated the effect of group (i.e. adults with and without CUD) on sVOLT efficiency scores (indirect effect  $\beta = -.08$ , 95% CI [-0.14, -0.04]) and sVOLTd efficiency scores (indirect effect  $\beta = -.09$ , 95% CI [-0.14, -0.04]), where greater sleep difficulties was associated with poorer memory performance (decreased efficiency scores). Sex did not moderate these relationships.

**Conclusion:** These initial findings of a mediating role of sleep in the association between CUD and visual learning memory highlight potential critical downstream effects of disrupted sleep in those with CUD and suggest the importance of investigating sleep in CUD.

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Sleep; memory; cannabis; visual learning


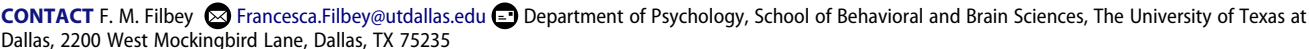
## Introduction

The most consistently reported cognitive impairment related to cannabis use is in episodic memory (1–12). This association is suggested to be dose-dependent with greater memory deficits associated with higher levels of  $\Delta$ -9-tetrahydrocannabinol ( $\Delta$ -9-THC), the primary psychoactive ingredient in cannabis (4).  $\Delta$ -9-THC disrupts memory processes through its impact on the brain's endocannabinoid system (ECS) which includes areas that underlie learning and memory functions such as the hippocampus, amygdala, and prefrontal cortex (13).

Because the ECS is also involved in circadian rhythm modulation and sleep (14), impaired memory due to long-term cannabis use may also in part be a downstream effect of  $\Delta$ -9-THC's impact on sleep, similar to what has previously been described in terms of depression (15,16). Indeed, sleep disturbances such as shorter sleep duration, reduced rapid eye movement (REM) sleep, and slow wave sleep (SWS) (17–20) are often reported in individuals

who use cannabis at a higher rate compared to those who do not use cannabis (21–24). Reductions in REM and SWS are known to impair hippocampal-dependent learning (25), and inhibit memory consolidation (26), respectively. Reduction of glutamatergic activity in the hippocampus by  $\Delta$ -9-THC (27) may also lead to decreased fast sleep spindle activity (13–15 Hz) efficiency associated with memory recall performance (28).

To date, however, findings on the effects of cannabis use on sleep have been mixed, suggesting a nuanced relationship that remains unresolved. Inconsistency in findings may be related to moderators related to cannabis use (e.g., age of onset, timing effects – acute vs. persistent effects) (29), or demographic characteristics such as sex. For instance, studies suggest that sleep is impacted in women at a higher rate than men from long-term cannabis use (30,31), especially in those with early onset of use (30), and particularly during abstinence (32). The moderating role of sex on these

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effects is not surprising given known differences in sleep-wake cycles in men and women (33).

Hence, the effects of cannabis use on circadian rhythm via the ECS could further potentiate underlying sex-specific effects on sleep (34). In sum, the moderating effect of sex is important to consider when determining the effects of cannabis on sleep and memory.

Despite the understanding that cannabis impacts both sleep and memory independently, and the crucial role of sleep on learning and memory processes, there is a need to examine how sleep may mediate these outcomes from cannabis use. In this explorative study, we tested if poorer learning and memory performance ( $y$ ) in individuals with a cannabis use disorder (CUD) relative to controls ( $x$ ) are mediated by sleep problems ( $m$ ). Furthermore, we predicted that this relationship would be moderated by biological sex ( $z$ ) where greater effect of sleep on learning and memory will be found in females compared to males.

## Methods

This study was approved by the Institutional Review Board of the University of Texas at Dallas and the Department of Psychology at the University of Amsterdam, and all participants completed a consent form before participating. Methods were standardized across the two sites to ensure consistency. Specifically, research assistants from each site received side-by-side training including regular reliability and matching checks.

## Participants

Participants were recruited from two sites using similar protocols in Dallas, TX, United States (US) and Amsterdam, the Netherlands (NL) for a larger study investigating the neurocognitive effects of cannabis use [e.g. (35)]. The participants consisted of 141 adults with CUD (18–31 years of age,  $M_{age} = 22.78$ ,  $SD = 3.36$ , NL: 79; US: 62) and 87 non-CUD controls (18–30 years of age,  $M_{age} = 23.04$ ,  $SD = 3.35$ , NL: 48; US: 39). Adults with CUD were defined as using cannabis >5 days per week during the previous year and with mild to severe CUD as determined by the Mini International Neuropsychiatric Interview 7.0.2 (MINI (36)). The non-CUD control group consisted of adults without cannabis use in the past 3 months as well as  $\leq 25$  lifetime separate occasions of cannabis use with  $\leq 5$  times in the past year. Participants were excluded if they had ever been diagnosed with a severe physical condition, a psychological condition other than anxiety, depression, or ADHD, had lifetime monthly uses of drugs other than alcohol, nicotine,

excessively used alcohol (Alcohol Use Disorder Identification Task; AUDIT score >12 (37)), used psychotropic medications or had a positive urine drug screen for other illicit substances. To minimize the effect of acute cannabis intoxication during the time of testing, participants with CUD were asked to refrain from cannabis use 24 hours prior to their appointment, which was verified through self-report (see Table 1 for participant characteristics).

## Outcome measures

Standardized assessments were translated from English to Dutch. CUD severity was assessed using the Cannabis Use Disorder Identification Task-Revised (CUDIT-R). Substance Use History (SUH) questionnaire was used to assess other drug use as well as frequency and quantity of cannabis use (i.e. weekly cannabis use, grams used per day). A single item from the Marijuana Withdrawal Checklist (MWC (38)) was used to assess sleep. Of note, the MWC instructions and questions were generalized to experiences within the past week and not constrained to those related to cannabis withdrawal. Additionally, the survey was not labeled as MWC and instructions for both CUD and non-CUD participants were as follows: “Below is a list of physical and psychological symptoms. Please indicate to what extent you experienced these symptoms during the past week.” Thus, ratings of sleep were not explicitly within the context of cannabis withdrawal. Self-reported sleep problems were rated as past week level of “sleep difficulty” on a Likert-type scale of 0 (none) – 3 (severe) (see Supplemental Table 1).

## Memory assessments

Cognitive assessments were conducted using the Penn Computerized Neurocognitive Battery’s CNB (39). Given high English proficiency in the NL, instructions were not translated in English. Visuospatial learning and memory outcomes from the Short Visual Object Learning Task (sVOLT) and the Short Visual Object Learning Task delayed (sVOLTd) from the Penn CNB were used as variables of interests in the analyses. Participants completed the sVOLT to assess their immediate recall of 20 shapes, then completed other Penn CNB tasks for ~19 minutes before assessing their delayed recall with the sVOLTd that consisted of correctly identifying 10 previously presented shapes after a 1 minute time delay.

Outcome variables from both sVOLT and sVOLTd included total correct and mean reaction time (RT) for the correct trials. Additional memory efficiency scores

**Table 1.** Characteristics of the participants across demographic variables (1a), memory variables (1b) and cannabis use variables (1c).

Variables	(a) Demographic variables						
	Individuals with CUD (N = 141)			Individuals without CUD (N = 87)			CUD vs. non-CUD p-value & Cohen's d
	Males Mean (SD)	Females Mean (SD)	All Mean (SD)	Males Mean (SD)	Females Mean (SD)	All Mean (SD)	
Group by Sex							
<b>Sex (N)</b>	83	58	–	39	48	–	<b>p = .02, 0.28</b>
<b>Age mean</b>	22.29 (3.25)	23.53 (3.39)	22.78 (3.36)	22.46 (3.14)	23.39 (3.41)	23.04 (3.35)	p = .28
<i>Within group t-test between males and females</i>	<b>p = .02</b>			<b>p = .09</b>			
<b>Years of formal education</b>	15.56 (2.66)	15.24 (2.61)	15.38 (2.65)	16.54 (2.33)	16.65 (2.96)	16.63 (2.68)	<b>p &lt; .001, 0.46</b>
<i>Within group t-test between males and females</i>	<b>p = .24</b>			<b>p = .43</b>			
<b>Drinking days per month</b>	4.78 (5.39)	3.48 (5.39)	4.21 (4.94)	4.92 (5.89)	5.44 (5.03)	5.15 (5.41)	p = .09
<i>Within group t-test between males and females</i>	<b>p = .07</b>			<b>p = .33</b>			
<b>Sleep difficulty rating</b>	.89 (.92)	.9 (.89)	.89 (.9)	.33 (.66)	.29 (.71)	.31 (.68)	<b>p &lt; .001, 0.71</b>
<i>Within group t-test between males and females</i>	<b>p = .97</b>			<b>p = .78</b>			
Variables	(b) Memory Variables						
	With CUD			Without CUD			CUD vs. non-CUD p-value & Cohen's d
	Males Mean (SD)	Females Mean (SD)	All Mean (SD)	Males Mean (SD)	Females Mean (SD)	All Mean (SD)	
Group by Sex							
<b>sVOLT total correct</b>	16.34 (2.49)	15.49 (2.3)	15.94 (2.43)	17.2 (1.95)	16.1 (1.99)	16.61 (2.04)	<b>p = .04, 0.29</b>
<i>Within group t-test between males and females</i>	<b>p = .11</b>			<b>p = .04</b>			
<b>sVOLTd total correct</b>	15.93 (2.07)	15.08 (2.76)	15.53 (2.44)	16.6 (2.39)	15.83 (2.4)	16.19 (2.41)	p = .11
<i>Within group t-test between males and females</i>	<b>p = .15</b>			<b>p = .19</b>			
<b>Ln sVOLT RT</b>	3.25 (0.1)	3.25 (0.08)	3.25 (0.09)	3.25 (0.09)	3.27 (0.11)	3.26 (0.1)	p = .26
<i>Within group t-test between males and females</i>	<b>p = .89</b>			<b>p = .34</b>			
<b>Ln sVOLTd RT</b>	3.19 (0.08)	3.16 (0.37)	3.18 (0.26)	3.17 (0.06)	3.19 (0.10)	3.18 (0.08)	p = .78
<i>Within group t-test between males and females</i>	<b>p = .35</b>			<b>p = .77</b>			
<b>sVOLT efficiency score</b>	1.96 (0.49)	1.72 (0.47)	1.85 (0.49)	1.94 (0.55)	1.89 (0.43)	1.91 (0.49)	p = .99
<i>Within group t-test between males and females</i>	<b>p = .16</b>			<b>p = .87</b>			
<b>sVOLTd efficiency score</b>	1.95 (0.45)	1.7 (0.47)	1.84 (0.48)	1.97 (0.55)	1.93 (0.47)	1.95 (0.51)	p = .58
<i>Within group t-test between males and females</i>	<b>p = .12</b>			<b>p = .97</b>			
<b>N-back 1 total correct</b>	56.38 (2.67)	54.43 (4.69)	55.56 (3.76)	57.29 (2.35)	56.5 (2.47)	56.5 (2.47)	<b>p = .04, .38</b>
<i>Within group t-test between males and females</i>	<b>p = .02</b>			<b>p = .5</b>			
<b>N-back 2 total correct</b>	52.29 (6.83)	49.53 (8.07)	51.13 (7.46)	54.33 (4.43)	51.92 (6.23)	52.88 (5.67)	p = .11
<i>Within group t-test between males and females</i>	<b>p = .1</b>			<b>p = .21</b>			
<b>N-back total correct</b>	166.55 (11.33)	161.74 (12.67)	164.54 (12.09)	168.5 (8.67)	167 (8.78)	167.6 (8.69)	p = .16
<i>Within group t-test between males and females</i>	<b>p = .1</b>			<b>p = .7</b>			
<b>Ln N-back 1 RT</b>	6.3 (0.12)	6.34 (0.13)	6.32 (0.13)	6.28 (0.16)	6.32 (0.09)	6.3 (0.13)	p = .52
<i>Within group t-test between males and females</i>	<b>p = .24</b>			<b>p = .31</b>			
<b>Ln N-back 2 RT</b>	6.33 (0.12)	6.36 (0.13)	6.34 (0.12)	6.31 (0.16)	6.34 (0.1)	6.33 (0.12)	p = .67
<i>Within group t-test between males and females</i>	<b>p = .44</b>			<b>p = .4</b>			
<b>Ln N-back total RT</b>	6.31 (0.12)	6.34 (0.13)	6.32 (0.12)	6.23 (0.15)	6.32 (0.1)	6.31 (0.12)	p = .63
<i>Within group t-test between males and females</i>	<b>p = .31</b>			<b>p = .33</b>			
<b>N-Back 1 efficiency score</b>	8.95 (0.47)	8.59 (0.8)	8.8 (0.65)	9.13 (0.46)	8.94 (0.4)	9.02 (0.43)	p = .052
<i>Within group t-test between males and females</i>	<b>p = .01</b>			<b>p = .32</b>			
<b>N-Back 2 efficiency score</b>	8.26 (1.1)	7.79 (1.28)	8.06 (1.2)	8.6 (0.77)	8.19 (0.98)	8.36 (0.92)	p = .09
<i>Within group t-test between males and females</i>	<b>p = .08</b>			<b>p = .16</b>			
<b>N-Back total efficiency score</b>	26.4 (1.9)	25.53 (2.14)	26.03 (2.04)	26.51 (1.83)	25.91 (1.89)	26.22 (1.88)	p = .14
<i>Within group t-test between males and females</i>	<b>p = .07</b>			<b>p = .49</b>			

(Continued)

**Table 1.** (Continued).

Variables	(c) Cannabis Use Variables		
	With CUD		Without CUD
Group by Sex	Males (SD)	Females (SD)	All Mean (SD)
<b>Grams used per day</b>	2.52 (4.15)	1.58 (2.06)	2.31 (3.48)
<i>Within group t-test between males and females</i>	$p = .12$		n/a
<b>Years of weekly use</b>	4.65 (3.33)	6.39 (6.91)	5.38 (5.19)
<i>Within group t-test between males and females</i>	$p = .06$		n/a
<b>CUD severity</b>	16.42 (5.74)	15.67 (5.11)	16.11 (5.49)
<i>Within group t-test between males and females</i>	$p = .43$		n/a

CUD = Cannabis Use Disorder, sVOLT = Short Visual Object Learning Task, sVOLTd = Short Visual Object Learning Task Delayed, Ln = Natural log, RT = Reaction Time, MWC = Marijuana Withdrawal Checklist.

were computed to detect group differences in accuracy and speed together rather than separately (40). The efficiency scores were computed by dividing the number of total correct responses by the natural log of the mean RT of correct trials. Higher efficiency scores indicated better performance.

Verbal memory was assessed using the N-back task with letter stimuli collected during a functional MRI scan (41–43). The task consisted of 12 blocks with 3 memory loads that were presented 4 times in a fixed order beginning with high memory load (2-back), followed by recognition (0-back), and low memory load (1-back). The participants were instructed to indicate if the letter presented on the screen matched a previous letter displayed by pressing a target or non-target for 1-back and 2-back trials. For the 0-back trials, participants were asked to indicate only when the letter “X” was presented. Participants were not provided with feedback during or after the task. Outcome measures from the task included RT’s for correct trials and accuracy for overall (i.e., all trials combined), 0 back, 1 back, and 2 back. Efficiency scores for overall performance and each condition was computed by dividing the number of total correct responses to the task by the natural log of the mean RT of correct trials. Only the behavioral data were analyzed in this report. The fMRI data are reported in Kroon et al. (35).

### Mediation model specification

The mediation analyses were computed using Hayes Macro Process v4.2 (model 4) in SPSS v27 specified covaried mediation models using path analysis. The moderated mediation models were computed with Macro Process 4.2 v (model 59).

We computed mediation analyses that specified sleep disruptions as a mediator of the effect of group (i.e., participants with or without CUD) on memory

accuracy, RTs, and efficiency scores on the sVOLT task, sVOLTd task, and N-back loads (i.e. overall, 1 back, and 2 back). Mediation analyses were replicated with the same specifications as the models testing effects of CUD (i.e. covariates, mediation of sleep, and memory outcomes) but only included participants with CUD to test cannabis use metrics’ (i.e. CUD severity, years of weekly use, and grams used per day) effects on sleep and memory outcomes. Considering the number of models tested, we applied a conservative threshold of  $p < .01$ , and confidence intervals for indirect effects and model paths were bootstrapped with 5000 samples.

### Results

ANOVAs with Bonferroni-corrected comparisons revealed differences in participants recruited across the two sites. The US sample was significantly older and had less years of formal education than the NL sample. Individuals with CUD in the US had significantly more females and reported more years of weekly cannabis use compared to the NL. Individuals without CUD in the NL reported more monthly days of drinking alcohol and had faster RT’s during the N-back tasks (see Supplemental Table 2).

Pearson’s correlation analyses were computed to determine whether demographic variables (i.e. alcohol use, sex, education, and age) may be correlated with memory and sleep outcomes and revealed significant correlations between these variables (Table 2). Thus, alcohol use, education, sex, and age were used as covariates for the mediation models, while sex was changed to the moderator in the moderated-mediation models.

### Mediation analyses in adults with and without CUD

The 15 mediation models testing the mediating role of sleep on CUD and memory indicated an indirect effect

**Table 2.** Pearson's correlations between demographic variables and memory outcomes.

Outcome Measures	Age <i>r</i>	Sex <i>r</i>	Educa- tion <i>r</i>	Alcohol Use <i>r</i>	Sleep <i>r</i>
sVOLT	-.122*	.177**	-0.009	.153*	-0.01
Total Correct					
sVOLTd	-0.072	.148*	0.106	0.106	-0.11
Total Correct					
sVOLT	0.041	-0.043	-0.082	-0.060	0.11
RT					
sVOLTd	.129*	0.016	-0.014	0.016	.129*
RT					
sVOLT	-.301**	.146*	.193**	.277**	-.277**
Efficiency					
sVOLTd	-.283**	.149*	.251**	.225**	-.325**
Efficiency					
N-Back 1 Correct	-.152*	.206**	.174*	0.092	-0.07
N-Back 2	-0.084	.165*	.128*	0.108	-0.11
Correct					
N-Back	-0.081	.138*	.204**	0.122	-0.1
Total Correct					
N-Back 1	0.013	-0.097	-.168*	-0.083	0.06
RT					
N-Back 2	-0.004	-0.063	-.167*	-0.086	0.06
RT					
N-Back	0.030	-0.117	-.131*	-0.052	0.03
Total RT					
N-Back 1	0.022	0.028	0.064	-0.100	-0.004
Efficiency					
N-Back 2	-0.046	0.086	0.021	-0.023	-0.04
Efficiency					
N-Back	-0.086	.164*	.221**	.128*	-0.1
Total Efficiency					

Education = number of years of formal education; Alcohol Use = total score on the Alcohol Use Disorder Identification Task (AUDIT); sVOLT = short visual object learning task, sVOLTd = short visual object learning task delayed, RT = reaction time, \* $p < .05$ , \*\* $p < .01$ .

of sleep problems on CUD and sVOLT efficiency (indirect effect  $\beta = -.08$ , 95% CI [-0.14, -0.04]) and sVOLTd efficiency ( $\beta = -.09$ , 95% CI [-0.14, -0.04]). The

efficiency scores for the sVOLT and sVOLTd were highly correlated ( $r = .88$ ) (see Figures 1 and 2). CUD group reported more sleep problems than non-CUD group (*a* path). The effect of sleep problems on sVOLT efficiency scores and sVOLTd efficiency scores (*b* path) indicated that sleep problems negatively affected memory efficiency (*ab* path). CUD and non-CUD groups were not significantly different in their memory performance (*c'* path).

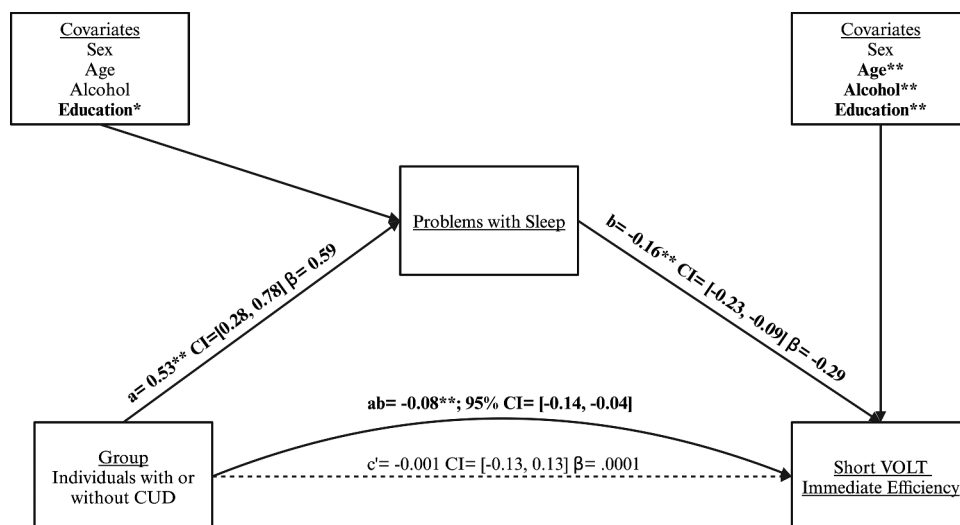
There was no mediation effect of sleep on N-back performance measures or sVOLT and sVOLTd RTs or the total correct trials (see Supplemental Figure 1). The sex moderated-mediation models did not indicate a moderating role of sex on the mediation of sleep on CUD and sVOLT efficiency or sVOLTd efficiency (see Supplemental Figure 2).

### Mediation analyses in those with CUD

Sleep did not mediate the relationships between cannabis use measures (i.e. CUD severity, years of weekly use, and grams used per day) and memory variables (see Supplemental Figure 1), and the sex moderated-mediation models did not indicate sex moderated any of the relationships (see Supplemental Figure 2).

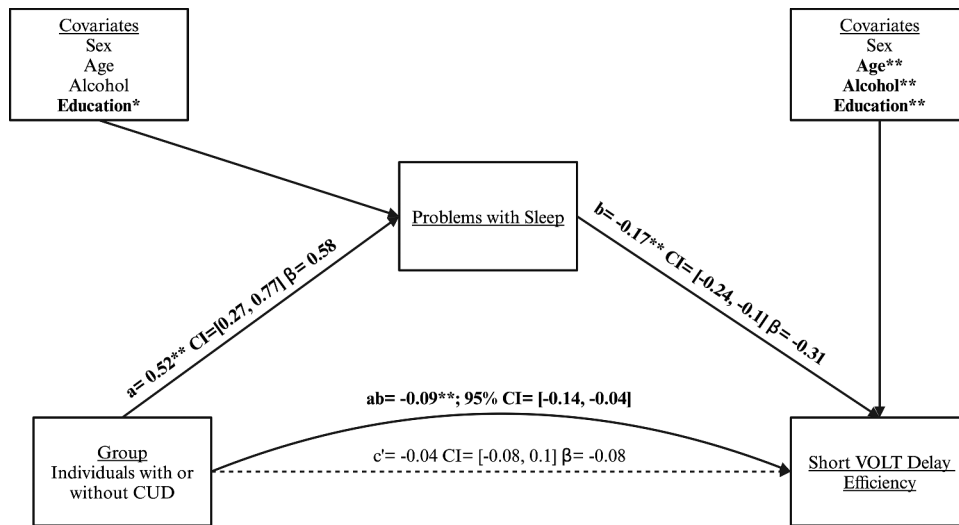
### Test of temporal precedence

Because of the cross-sectional nature of the data, we performed a test of temporal precedence by interchanging the predictor and mediator variables. Given that group is a categorical variable, we used Mplus v.8.4 (44)



**Figure 1.** Sleep problems mediate the relationship between cannabis use disorder (CUD) and Short Visual Object Learning Task (sVOLT) efficiency scores. Dotted lines indicate no significant effect while solid lines indicate significant effects. The unstandardized effects are noted with (a) and (b) while the standardized effects are noted with ( $\beta$ ). \* $p < .05$ ; \*\* $p < .01$ . Figure created with Biorender.com.





**Figure 2.** Sleep problems mediate the relationship between cannabis use disorder (CUD) and Short Visual Object Learning Task Delay (sVOLTd) efficiency scores. Dotted lines indicate no significant effect while solid lines indicate significant effects. The unstandardized effects are noted with (a) and (b) while the standardized effects are noted with ( $\beta$ ). \* $p < .05$ ; \*\* $p < .01$ . Figure created with Biorender.com.

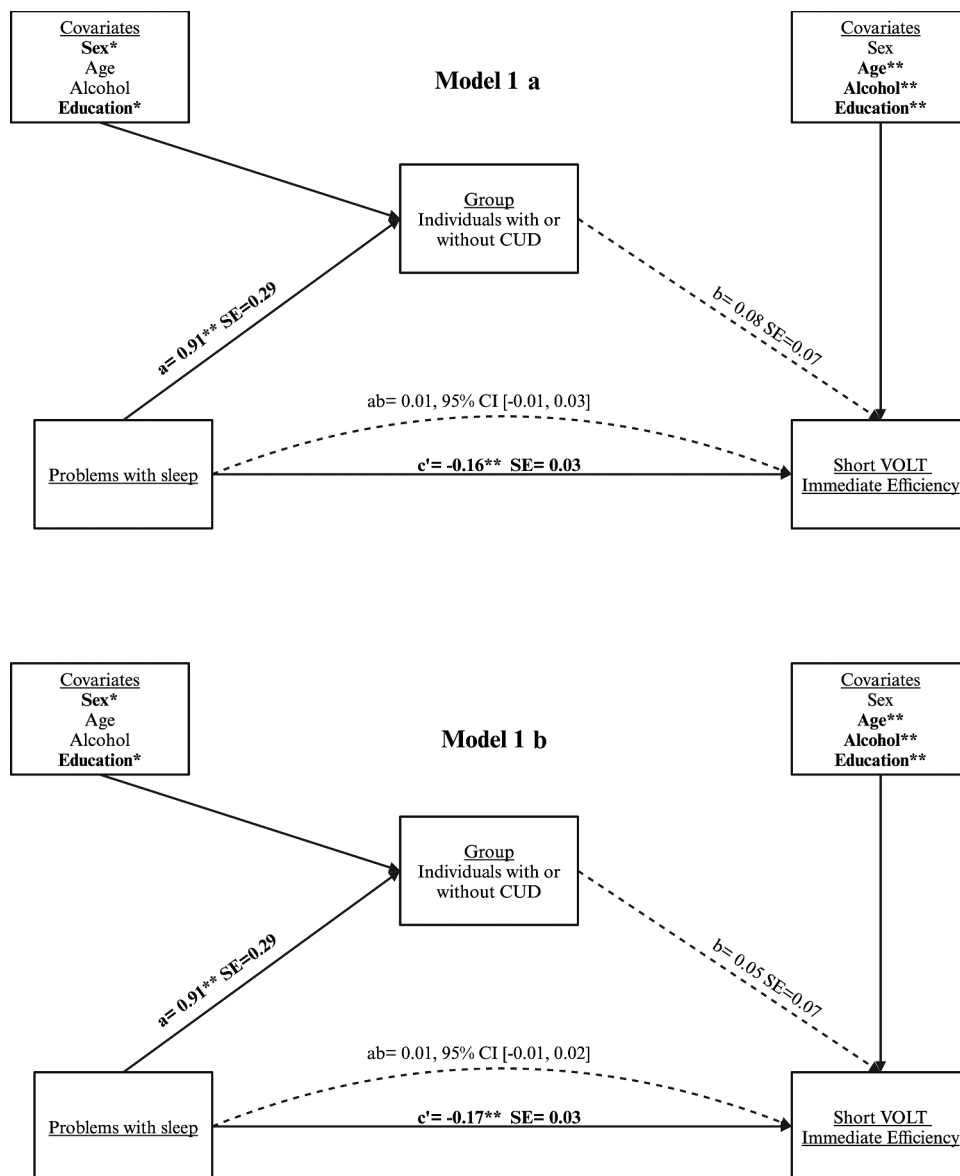
(vs. SPSS). Covariates were controlled for by regressing them on the mediator ( $a$  path) and outcome variable ( $b$  path) while confidence intervals for indirect effects were obtained by bootstrapping with 5000 samples. The results did not indicate a mediating relationship of group (i.e. individuals with and without CUD) on the relationship between sleep and sVOLT or sVOLTD efficiency scores (see Figure 3).

## Discussion

To date, how cannabis affects sleep and memory is widely studied but evaluated independently of each other (3,20,45–50). This study is the first, to our knowledge, to examine how sleep mediates the relationship between cannabis use and memory performance. Using existing cross-sectional data, these initial findings indicate (1) a mediating relationship of self-reported sleep quality on group (i.e. those with or without CUD) and immediate and delayed visual learning and memory; where CUD increased reported sleep difficulties and sleep difficulties related to poorer learning and memory performance (i.e. decreased efficiency scores), and (2) sex did not moderate these relationships. Given THC's influence on CB1 receptors that leads to reductions in REM and SWS (34), it is not surprising to find a mediating relationship on learning and memory outcomes. Against expectations, we did not find that sex moderated these outcomes. It is possible that our ability to detect sex effects was limited by the relatively small number of males compared to females in our study sample.

The relationship of sleep and CUD on memory performance was found primarily on spatial memory outcomes, and not verbal memory outcomes. Although this finding is unexpected, previous studies of sleep impacts on spatial memory, but not verbal memory suggested a potential lateralization effect of persistent (vs. acute) sleep deficiencies (e.g. reduced amounts of sleep for consecutive days) (43). Specifically, persistent sleep problems may have a greater impact on right hemispheric functions such as spatial memory due to lower amounts of SWS that affect right hippocampal function related to spatial memory formation (41,51,52). This is in contrast to sleep deprivation (e.g.  $\geq 24$  hours with no sleep) (41,53), which affects left-hemispheric functions such as verbal memory. The notion of right-lateralized effects of persistent sleep problems is further supported by reports that improvements in general sleep quality resolve spatial memory deficits (54–60). These right-lateralized effects may explain our findings of sleep-mediated impairment in visuospatial memory but not verbal memory given that our sleep outcome variable assessed *general* (i.e., persistent) sleep problems rather than sleep deprivation per se.

Interestingly, we did not find significant associations between sleep problems and memory performance when testing differences in cannabis use behaviors among individuals with CUD. This is surprising given previous studies suggesting the effects of cannabis use on sleep are dose-dependent (2,3). This lack of association with cannabis use measures may be due to the limited variability in our sample of



**Figure 3.** Test of temporal precedence. These models tested group (m) as a mediator of the association between problems with sleep (x) and memory performance (y): Short Visual Object Learning Task (sVOLT) efficiency (1a) and sVOLT delay efficiency (1b). No significant mediating effect emerged. Dotted lines indicate no significant effect while solid lines indicate significant effects. \* $p < .05$ ; \*\* $p < .01$ . Figure created with Biorender.com.

individuals with CUD given the study's inclusion requirement of near daily use in addition to meeting the requirement of CUD. Alternatively, the literature suggests that cannabis has differential effects over time related to tolerance. Specifically, sleep-promoting effects are more observable among cannabis-naïve individuals during initial use (20) whereas chronic cannabis use is thought to disrupt sleep due to dysregulation in ECS from prolonged exposure to THC (61). Regardless, future studies of dose-dependent effects of cannabis should consider including a wider range of CUD severity and other cannabis use measures such as frequency and duration of use.

### Limitations and conclusions

While these initial findings of the mediating effect of sleep on the relationship between CUD and memory indicate the importance of taking sleep into consideration in future CUD research, some limitations are worth bearing in mind. First, the cross-sectional nature of this study limits inferences on causation. Despite our test of temporal precedence, longitudinal designs are needed to better understand the temporal relationship between CUD, sleep, and memory impairment. Second, given our parameter demanding models, a larger sample size may be needed to better account for covariates (i.e.



gender, age, alcohol use, and education) related to memory and sleep outcomes. Lastly, although sleep problems were evaluated in a generalized context despite being derived from a single item from the MWC, it is possible that participants still viewed this question as it pertains to cannabis withdrawal. Furthermore, the narrow rating scale (i.e. 0–3) for the sleep item may have likely reduced our ability to detect effects. Future studies should consider using comprehensive sleep measures (e.g., Pittsburgh Sleep Quality Index (4)).

The use of cannabis for sleep is one of the most prevalent reasons for using cannabis in both clinical and non-clinical populations (62). Thus, these initial findings suggesting a role of sleep between CUD and memory function are important to consider for the optimization of cannabis' potential therapeutic effects on sleep, while mitigating potential harm. These initial findings also indicate that sleep may be an important entry point to improve cognitive function in those with CUD. Determining these risks and benefits of cannabis use is important for informed decision making for clinical guidance and risk management. These initial findings can also inform regulations around cannabis use, particularly concerning its availability as a sleep aid.

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