Taylor & Francis
Taylor & Francis Group

The American Journal of Drug and Alcohol Abuse
Encompassing All Addictive Disorders

ISSN: (Print) (Online) Journal homepage: www.tandfonline.com/journals/iada20

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

T. Brown, R. A. Ackerman, E. Kroon, L. Kuhns, J. Cousijn & F. M. Filbey

To cite this article: T. Brown, R. A. Ackerman, E. Kroon, L. Kuhns, J. Cousijn & F. M. Filbey (25 Jun 2024): The role of sleep in the link between cannabis use and memory function: evidence from a cross-sectional study, The American Journal of Drug and Alcohol Abuse, DOI: 10.1080/00952990.2024.2362832

To link to this article: https://doi.org/10.1080/00952990.2024.2362832

Published online: 25 Jun 2024.

THE AMERICAN JOURNAL OF DRUG AND ALCOHOL ABUSE
https://doi.org/10.1080/00952990.2024.2362832

Taylor & Francis
Taylor & Francis Group

ORIGINAL ARTICLE

OPEN ACCESS Check for updates

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

T. Brown[a], R. A. Ackerman[a], E. Kroon[b,c], L. Kuhns[b,c], J. Cousijn[b,c], and F. M. Filbey[a]

[a]Department of Psychology, School of Behavioral and Brain Sciences, University of Texas at Dallas, Dallas, Texas, USA; [b]Neuroscience of Addiction (NofA) Lab, Department of Psychology, Education & Child Studies, Erasmus University Rotterdam, Rotterdam, The Netherlands; [c]Department of Psychology, University of Amsterdam, Amsterdam, The Netherlands

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 ß = –.08, 95% CI [–0.14, –0.04]) and sVOLTd efficiency scores (indirect effect ß = –.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.

ARTICLE HISTORY
Received 10 November 2023
Revised 29 April 2024
Accepted 29 May 2024

KEYWORDS
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 Δ-9-tetrahydrocannabinol (Δ-9-THC), the primary psychoactive ingredient in cannabis (4). Δ-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 Δ-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 Δ-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

CONTACT F. M. Filbey Francesca.Filbey@utdallas.edu Department of Psychology, School of Behavioral and Brain Sciences, The University of Texas at Dallas, 2200 West Mockingbird Lane, Dallas, TX 75235

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 ≤25 lifetime separate occasions of cannabis use with ≤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 extend 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).

(a) Demographic variables

Variables	Individuals with CUD ($N = 141$)			Individuals without CUD ($N = 87$)			
Group by Sex	Males Mean (SD)	Females Mean (SD)	All Mean (SD)	Males Mean (SD)	Females Mean (SD)	All Mean (SD)	CUD vs. non-CUD *p*-value & Cohen's *d*
Sex (N)	83	58	–	39	48	–	***p* = .02, 0.28**
Age mean	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
Within group t-test between males and females	***p* = .02**			*p* = .09			
Years of formal education	15.56 (2.66)	15.24 (2.61)	15.38 (2.65)	16.54 (2.33)	16.65 (2.96)	16.63 (2.68)	***p* < .001, 0.46**
Within group t-test between males and females	*p* = .24			*p* = .43			
Drinking days per month	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
Within group t-test between males and females	*p* = .07			*p* = .33			
Sleep difficulty rating	.89 (.92)	.9 (.89)	.89 (.9)	.33 (.66)	.29 (.71)	.31 (.68)	***p* < .001, 0.71**
Within group t-test between males and females	*p* = .97			*p* = .78			

(b) Memory Variables

Variables	With CUD			Without CUD			
Group by Sex	Males Mean (SD)	Females Mean (SD)	All Mean (SD)	Males Mean (SD)	Females Mean (SD)	All Mean (SD)	CUD vs. non-CUD *p*-value & Cohen's *d*
sVOLT total correct	16.34 (2.49)	15.49 (2.3)	15.94 (2.43)	17.2 (1.95)	16.1 (1.99)	16.61 (2.04)	***p* = .04, 0.29**
Within group t-test between males and females	*p* = .11			***p* = .04**			
sVOLTd total correct	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
Within group t-test between males and females	*p* = .15			*p* = .19			
Ln sVOLT RT	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
Within group t-test between males and females	*p* = .89			*p* = .34			
Ln sVOLTd RT	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
Within group t-test between males and females	*p* = .35			*p* = .77			
sVOLT efficiency score	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
Within group t-test between males and females	*p* = .16			*p* = .87			
sVOLTd efficiency score	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
Within group t-test between males and females	*p* = .12			*p* = .97			
N-back 1 total correct	56.38 (2.67)	54.43 (4.69)	55.56 (3.76)	57.29 (2.35)	56.5 (2.47)	56.5 (2.47)	***p* = .04, .38**
Within group t-test between males and females	***p* = .02**			*p* = .5			
N-back 2 total correct	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
Within group t-test between males and females	*p* = .1			*p* = .21			
N-back total correct	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
Within group t-test between males and females	*p* = .1			*p* = .7			
Ln N-back 1 RT	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
Within group t-test between males and females	*p* = .24			*p* = .31			
Ln N-back 2 RT	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
Within group t-test between males and females	*p* = .44			*p* = .4			
Ln N-back total RT	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
Within group t-test between males and females	*p* = .31			*p* = .33			
N-Back 1 efficiency score	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
Within group t-test between males and females	***p* = .01**			*p* = .32			
N-Back 2 efficiency score	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
Within group t-test between males and females	*p* = .08			*p* = .16			
N-Back total efficiency score	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
Within group t-test between males and females	*p* = .07			*p* = .49			

(*Continued*)

Table 1. (Continued).

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

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

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 ß= −.08, 95% CI [−0.14, −0.04]) and sVOLTd efficiency (ß = −.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)

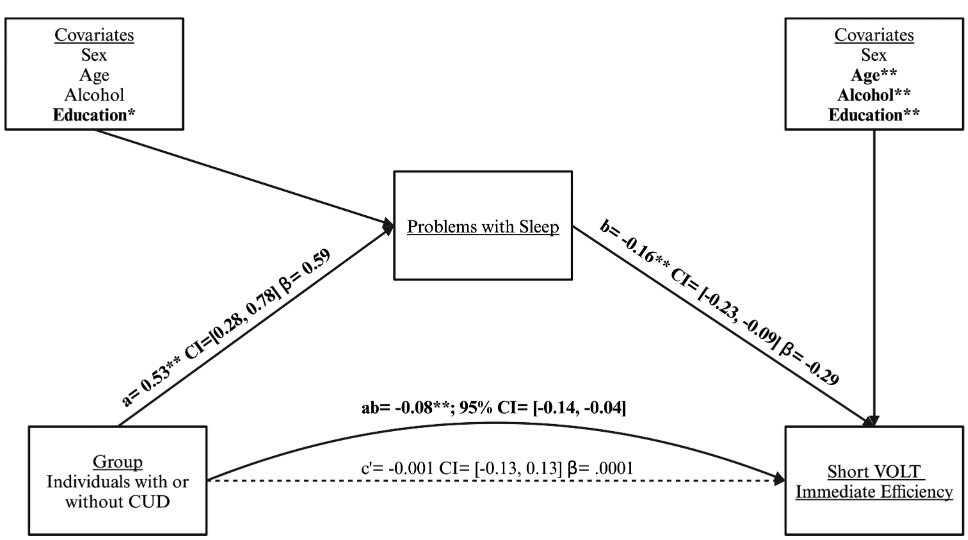

Figure 1. Sleep problems mediate the relationship between cannabis use disorder (CUD) and Short Visual Object Learning Task (sVOLT) efficiency scores. Dotted lines indicate no significant effect while solid lines indicate significant effects. The unstandardized effects are noted with (a) and (b) while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

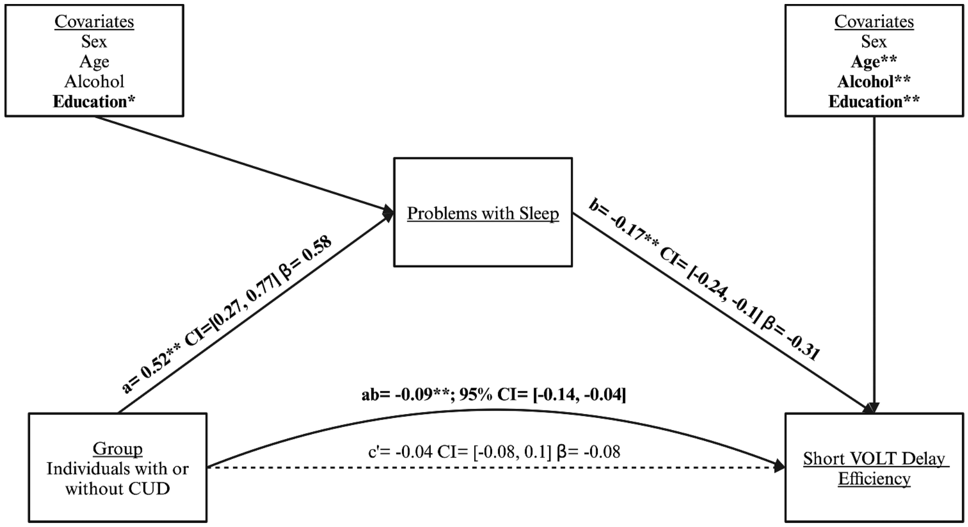

Figure 2. Sleep problems mediate the relationship between cannabis use disorder (CUD) and Short Visual Object Learning Task Delay (sVOLTd) efficiency scores. Dotted lines indicate no significant effect while solid lines indicate significant effects. The unstandardized effects are noted with (a) and (b) while the standardized effects are noted with (β). **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. ≥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

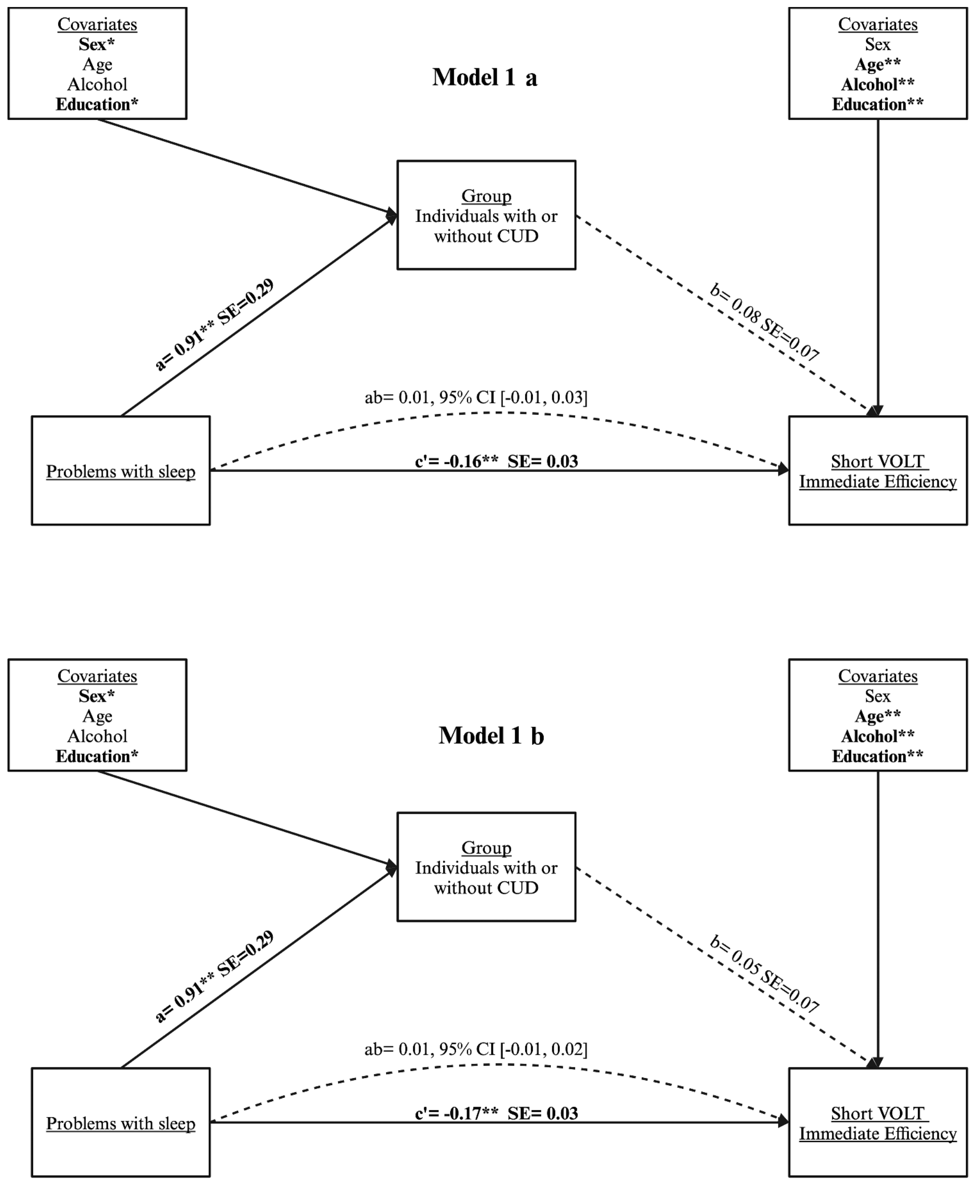

Figure 3. Test of temporal precedence. These models tested group (m) as a mediator of the association between problems with sleep (x) and memory performance (y): Short Visual Object Learning Task (sVOLT) efficiency (1a) and sVOLT delay efficiency (1b). No significant mediating effect emerged. Dotted 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.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

This research was supported by grant 1R01 DA042490 awarded to Francesca Filbey and Janna Cousijn from the National Institute on Drug Abuse/National Institute of Health.

References

1. Blest-Hopley G, Giampietro V, Bhattacharyya S. A systematic review of human neuroimaging evidence of memory-related functional alterations associated with cannabis use complemented with preclinical and human evidence of memory performance alterations. Brain Sci. 2020;10:102. doi:10.3390/brainsci10020102.
2. Prini P, Zamberletti E, Manenti C, Gabaglio M, Parolaro D, Rubino T. Neurobiological mechanisms underlying cannabis-induced memory impairment. Eur Neuropsychopharmacol. 2020;36:181–90. doi:10.1016/j.euroneuro.2020.02.002.
3. Bhattacharyya S, Schoeler T. The effect of cannabis use on memory function: an update. Subst Abuse Rehabil. 2013:11. doi:10.2147/SAR.S25869.
4. Solowij N. Cognitive functioning of long-term heavy cannabis users seeking treatment. JAMA. 2002;287:1123. doi:10.1001/jama.287.9.1123.
5. Lovell ME, Akhurst J, Padgett C, Garry MI, Matthews A. Cognitive outcomes associated with long-term, regular, recreational cannabis use in adults: A meta-analysis. Exp Clin Psychopharmacol. 2020;28:471–94. doi:10.1037/pha0000326.
6. Scott JC, Slomiak ST, Jones JD, Rosen AFG, Moore TM, Gur RC. Association of cannabis with cognitive functioning in adolescents and young adults. JAMA Psychiarty. 2018;75:585. doi:10.1001/jamapsychiatry.2018.0335.
7. McKetin R, Parasu P, Cherbuin N, Eramudugolla R, Anstey KJ. A longitudinal examination of the relationship between cannabis use and cognitive function in mid-life adults. Drug Alcohol Depend. 2016;169:134–40. doi:10.1016/j.drugalcdep.2016.10.022.
8. Battisti RA, Roodenrys S, Johnstone SJ, Respondek C, Hermens DF, Solowij N. Chronic use of cannabis and poor neural efficiency in verbal memory ability. Psychopharmacol (Berl). 2010;209:319–30. doi:10.1007/s00213-010-1800-4.
9. Cengel HY, Bozkurt M, Evren C, Umut G, Keskinkilic C, Agachanli R. Evaluation of cognitive functions in individuals with synthetic cannabinoid use disorder and comparison to individuals with cannabis use disorder. Psychiatry Res. 2018;262:46–54. doi:10.1016/j.psychres.2018.01.046.
10. Levar N, Francis AN, Smith MJ, Ho WC, Gilman JM. Verbal memory performance and reduced cortical thickness of brain regions along the uncinate fasciculus in young adult cannabis users. Cannabis Cannabinoid Res. 2018;3:56–65. doi:10.1089/can.2017.0030.
11. Schuster RM, Hoeppner SS, Evins AE, Gilman JM. Early onset marijuana use is associated with learning inefficiencies. Neuropsychology. 2016;30:405–15. doi:10.1037/neu0000281.
12. Solowij N, Battisti R. The chronic effects of cannabis on memory in humans: a review. Curr Drug Abuse Rev. 2008;1:81–98. doi:10.2174/1874473710801010081.
13. Lorenzetti V, Lubman DI, Whittle S, Solowij N, Yücel M. Structural MRI findings in long-term cannabis users: what do we know? Subst Use Misuse. 2010;45:1787–808. doi:10.3109/10826084.2010.482443.
14. Iversen L. Cannabis and the brain. Brain. 2003;126:1252–70. doi:10.1093/brain/awg143.
15. Babson KA, Boden MT, Bonn-Miller MO. Sleep quality moderates the relation between depression symptoms and problematic cannabis use among medical cannabis users. Am J Drug Alcohol Abuse. 2013;39:211–16. doi:10.3109/00952990.2013.788183.
16. Maple KE, McDaniel KA, Shollenbarger SG, Lisdahl KM. Dose-dependent cannabis use, depressive symptoms, and FAAH genotype predict sleep quality in emerging adults: a pilot study. Am J Drug Alcohol Abuse. 2016;42:431–40. doi:10.3109/00952990.2016.1141913.
17. Feinberg I, Jones R, Walker JM, Cavness C, March J. Effects of high dosage delta-9-tetrahydrocannabinol on sleep patterns in man. Clin Pharmacol Ther. 1975;17:458–66. doi:10.1002/cpt1975174458.
18. Garcia AN, Salloum IM. Polysomnographic sleep disturbances in nicotine, caffeine, alcohol, cocaine, opioid,

and cannabis use: a focused review. Am J Addict. 2015;24:590–98. doi:10.1111/ajad.12291.
19. Bolla KI, Lesage SR, Gamaldo CE, Neubauer DN, Funderburk FR, Cadet JL, David PM, Verdejo-Garcia A, Benbrook AR. Sleep disturbance in heavy marijuana users. Sleep. 2008;31:901–8. doi:10.1093/sleep/31.6.901.
20. Nicholson AN, Turner C, Stone BM, Robson PJ. Effect of Δ-9-tetrahydrocannabinol and cannabidiol on nocturnal sleep and early-morning behavior in young adults. J Clin Psychopharmacol. 2004;24:305–13. doi:10.1097/01.jcp.0000125688.05091.8f.
21. Cohen-Zion M, Drummond SPA, Padula CB, Winward J, Kanady J, Medina KL, Tapert SF. Sleep architecture in adolescent marijuana and alcohol users during acute and extended abstinence. Addict Behav. 2009;34:976–79. doi:10.1016/j.addbeh.2009.05.011.
22. Troxel WM, Ewing B, D'Amico EJ. Examining racial/ethnic disparities in the association between adolescent sleep and alcohol or marijuana use. Sleep Health. 2015;1:104–08. doi:10.1016/j.sleh.2015.03.005.
23. Vorspan F, Guillem E, Bloch V, Bellais L, Sicot R, Noble F, Lepine J-P, Gorelick DA. Self-reported sleep disturbances during cannabis withdrawal in cannabis-dependent outpatients with and without opioid dependence. Sleep Med. 2010;11:499–500. doi:10.1016/j.sleep.2009.12.001.
24. Winiger EA, Hitchcock LN, Bryan AD, Cinnamon Bidwell L. Cannabis use and sleep: expectations, outcomes, and the role of age. Addict Behav. 2021;112:106642. doi:10.1016/j.addbeh.2020.106642.
25. Watts A, Gritton HJ, Sweigart J, Poe GR. Antidepressant suppression of non-REM sleep spindles and REM sleep impairs hippocampus-dependent learning while augmenting striatum-dependent learning. J Neurosci. 2012;32:13411–20. doi:10.1523/JNEUROSCI.0170-12.2012.
26. Diekelmann S, Born J. The memory function of sleep. Nat Rev Neurosci. 2010;11:114–26. doi:10.1038/nrn2762.
27. Zou S, Kumar U. Cannabinoid receptors and the endocannabinoid system: signaling and function in the central nervous system. Int J Mol Sci. 2018;19:833. doi:10.3390/ijms19030833.
28. Schabus M, Gruber G, Parapatics S, Sauter C, Klösch G, Anderer P, Klimesch W, Saletu B, Zeitlhofer J. Sleep spindles and their significance for declarative memory consolidation. Sleep. 2004;27:1479–85. doi:10.1093/sleep/27.7.1479.
29. Choi S, Huang BC, Gamaldo CE. Therapeutic uses of cannabis on sleep disorders and related conditions. J Clin Neurophysiol. 2020;37:39–49. doi:10.1097/WNP.0000000000000617.
30. McPherson KL, Tomasi DG, Wang G-J, Manza P, Volkow ND. Cannabis affects cerebellar volume and sleep differently in men and women. Front Psychiatry. 2021;12:12. doi:10.3389/fpsyt.2021.643193.
31. Gorelick DA, Goodwin RS, Schwilke E, Schroeder JR, Schwope DM, Kelly DL, Ortemann□Renon C, Bonnet D, Huestis MA. Around-the-clock oral THC effects on sleep in male chronic daily cannabis smokers. Am J Addict. 2013;22:510–14. doi:10.1111/j.1521-0391.2013.12003.x.
32. Herrmann ES, Weerts EM, Vandrey R. Sex differences in cannabis withdrawal symptoms among treatment-seeking cannabis users. Exp Clin Psychopharmacol. 2015;23:415–21. doi:10.1037/pha0000053.
33. Spitschan M, Santhi N, Ahluwalia A, Fischer D, Hunt L, Karp NA, Lévi F, Pineda-Torra I, Vidafar P, White R, et al. Sex differences and sex bias in human circadian and sleep physiology research. eLife. 2022;11:11.
34. Kesner AJ, Lovinger DM. Cannabinoids, endocannabinoids and sleep. Front Mol Neurosci. 2020;13:13. doi:10.3389/fnmol.2020.00125.
35. Kroon E, Kuhns L, Colyer□Patel K, Filbey F, Cousijn J. Working memory□related brain activity in cannabis use disorder: the role of cross□cultural differences in cannabis attitudes. Addict Biol. 2023;28:28. doi:10.1111/adb.13283.
36. Tiet QQ, Leyva YE, Browne K, Moos RH. Screen of drug use: diagnostic accuracy for cannabis use disorder. Addict Behav. 2019;95:184–88. doi:10.1016/j.addbeh.2019.02.010.
37. Sunders JB, Aasland OG, Babor TF, DE La Fuente JR, Grant M. Development of the alcohol use disorders identification test (AUDIT): WHO collaborative project on early detection of persons with harmful alcohol consumption-II. Addiction. 1993;88:791–804. doi:10.1111/j.1360-0443.1993.tb02093.x.
38. Budney AJ, Novy PL, Hughes JR. Marijuana withdrawal among adults seeking treatment for marijuana dependence. Addiction. 1999;94:1311–22. doi:10.1046/j.1360-0443.1999.94913114.x.
39. Swagerman SC, de Geus EJC, Kan K-J, van Bergen E, Nieuwboer HA, Koenis MMG, Hulshoff Pol HE, Gur RE, Gur RC, Boomsma DI, et al. The computerized neurocognitive battery: Validation, aging effects, and heritability across cognitive domains. Neuropsychology. 2016;30:53–64. doi:10.1037/neu0000248.
40. Heitz RP. The speed-accuracy tradeoff: history, physiology, methodology, and behavior. Front Neurosci. 2014;8:150. doi:10.3389/fnins.2014.00150.
41. Lo JC, Groeger JA, Santhi N, Arbon EL, Lazar AS, Hasan S, von Schantz M, Archer SN, Dijk D-J Effects of partial and acute total sleep deprivation on performance across cognitive domains, individuals and circadian phase. PLOS ONE. 2012;7:e45987. doi:10.1371/journal.pone.0045987.
42. Hautzel H, Mottaghy FM, Schmidt D, Zemb M, Shah NJ, Müller-Gärtner H-W, Krause BJ. Topographic segregation and convergence of verbal, object, shape and spatial working memory in humans. Neurosci Lett. 2002;323:156–60. doi:10.1016/S0304-3940(02)00125-8.
43. Hennecke E, Lange D, Steenbergen F, Fronczek□Poncelet J, Elmenhorst D, Bauer A, Aeschbach D, Elmenhorst E-M. Adverse interaction effects of chronic and acute sleep deficits on spatial working memory but not on verbal working memory or declarative memory. J Sleep Res. 2021;30:30. doi:10.1111/jsr.13225.
44. Muthén LK, Muthén BO. Mplus user's guide. 8th ed. Los Angeles (CA): Muthén & Muthén; 2017.

45. Becker MP, Collins PF, Luciana M. Neurocognition in college-aged daily marijuana users. J Clin Exp Neuropsychol. 2014;36:379–98. doi:10.1080/13803395.2014.893996.
46. Solowij N, Pesa N. Cognitive abnormalities and cannabis use. Rev Bras Psiquiatr. 2010;32:531–40. doi:10.1590/S1516-44462010000500006.
47. Binkowska AA, Jakubowska N, Gaca M, Galant N, Piotrowska-Cyplik A, Brzezicka A. Not just a pot: visual episodic memory in cannabis users and polydrug cannabis users: ROC and ERP preliminary investigation. Front Hum Neurosci. 2021;15:677793. doi:10.3389/fnhum.2021.677793.
48. Feinberg I, Jones R, Walker J, Cavness C, Floyd T. Effeets of marijuana extract and tetrahydrocannabinol on electroencephalographic sleep patterns. Clin Pharmacol Ther. 1976;19:782–94. doi:10.1002/cpt1976196782.
49. della Monica C, Johnsen S, Atzori G, Groeger JA, Dijk D-J. Rapid eye movement sleep, sleep continuity and slow wave sleep as predictors of cognition, mood, and subjective sleep quality in healthy men and women, aged 20–84 years. Front Psychiatry. 2018;9. doi:10.3389/fpsyt.2018.00255.
50. Kolla BP, Hayes L, Cox C, Eatwell L, Deyo-Svendsen M, Mansukhani MP. The effects of cannabinoids on sleep. J Prim Care Community Health. 2022;13:215013192210812. doi:10.1177/21501319221081277.
51. Whitehurst LN, Fogler K, Hall K, Hartmann M, Dyche J. The effects of chronic marijuana use on circadian entrainment. Chronobiol Int. 2015;32:561–67. doi:10.3109/07420528.2015.1004078.
52. Thomason ME, Race E, Burrows B, Whitfield-Gabrieli S, Glover GH, Gabrieli JDE. Development of spatial and verbal working memory capacity in the human brain. J Cogn Neurosci. 2009;21:316–32. doi:10.1162/jocn.2008.21028.
53. Piber D. The role of sleep disturbance and inflammation for spatial memory. Brain Behav Immun Health. 2021;17:100333. doi:10.1016/j.bbih.2021.100333.
54. Mu Q, Mishory A, Johnson KA, Nahas Z, Kozel FA, Yamanaka K, Bohning DE, George MS. Decreased brain activation during a working memory task at rested baseline is associated with vulnerability to sleep deprivation. Sleep. 2005;28:433–48. doi:10.1093/sleep/28.4.433.
55. Konakanchi S, Raavi V, Ml HK, Shankar Ms V. Impact of chronic sleep deprivation and sleep recovery on hippocampal oligodendrocytes, anxiety-like behavior, spatial learning and memory of rats. Brain Res Bull. 2023;193:59–71. doi:10.1016/j.brainresbull.2022.12.002.
56. Brodt S, Inostroza M, Niethard N, Born J. Sleep—A brain-state serving systems memory consolidation. Neuron. 2023;111:1050–75. doi:10.1016/j.neuron.2023.03.005.
57. Simon KC, Clemenson GD, Zhang J, Sattari N, Shuster AE, Clayton B, Alzueta E, Dulai T, de Zambotti M, Stark C, et al. Sleep facilitates spatial memory but not navigation using the minecraft memory and navigation task. Proc Natl Acad Sci. 2022;119:e2202394119. doi:10.1073/pnas.2202394119.
58. Noack H, Doeller CF, Born J. Sleep strengthens integration of spatial memory systems. Learn Mem. 2021;28:162–70. doi:10.1101/lm.053249.120.
59. Guan Z, Peng X, Fang J. Sleep deprivation impairs spatial memory and decreases extracellular signal-regulated kinase phosphorylation in the hippocampus. Brain Res. 2004;1018:38–47. doi:10.1016/j.brainres.2004.05.032.
60. Stiver J, Fusco-Gessick B, Moran E, Crook C, Zimmerman ME. Variable objective sleep quality is related to worse spatial learning and memory in young adults. Sleep Med. 2021;84:114–20. doi:10.1016/j.sleep.2021.05.034.
61. Valentino RJ, Volkow ND. Drugs, sleep, and the addicted brain. Neuropsychopharmacology. 2020;45:3–5. doi:10.1038/s41386-019-0465-x.
62. Altman BR, Mian MN, Slavin M, Earleywine M. Cannabis expectancies for sleep. J Psychoactive Drugs. 2019;51:405–12. doi:10.1080/02791072.2019.1643053.