Journal of the International Neuropsychological Society (2021), **27**, 581–591

doi:10.1017/S1355617721000217

Female Sex as a Protective Factor in the Effects of Chronic Cannabis Use on Verbal Learning and Memory

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(Received July 31, 2020; Final revision December 22, 2020; Accepted January 26, 2021)

Abstract

Objective: The variability of findings in studies examining the effects of chronic cannabis use on neuropsychological functioning highlights the importance of examining contributing factors. Few studies examine the role of sex in the relationship between cannabis and neuropsychological functioning, despite known neurobiological structural differences between males and females. This study examined whether males and females experience differential cognitive effects of chronic cannabis use. **Method:** Chronic cannabis users (3+ days per week for >12 months, $n = 110$, 72% male) and non-users ($n = 71$, 39% male) completed a neuropsychological test battery. Two multivariate analyses of covariance (MANCOVAs) examined for sex differences in performance within users and non-users on neuropsychological tests, controlling for potential confounding variables. Bonferroni corrections were applied to adjust for multiple comparisons. **Results:** Male and female cannabis users did not differ in cannabis use variables. Female cannabis users performed better than males on multiple subtests of the California Verbal Learning Test-II (CVLT-II), a verbal learning and memory test. Male cannabis users performed better than female users on Trial 1 of the CVLT-II ($p = .002$), and Trail Making Test B ($p = .001$), which measure attention and cognitive flexibility, respectively. Non-user males and females performed comparably, with the exception of Trail Making Test B ($p = .001$). **Conclusions:** Results suggest that chronic cannabis use differentially impacts males and females, with females exhibiting better verbal learning and memory despite males demonstrating better attention and cognitive flexibility. Further research is needed to understand the potential protective mechanism of female sex on learning and memory effects of cannabis use.

Keywords: Marijuana, Gender, Cannabis, Memory, Recall, Attention

INTRODUCTION

The decriminalization and legalization of cannabis for both medicinal and recreational purposes have been growing rapidly over the past several decades. Cannabis is the most widely grown, distributed, and abused substance, with 2.5% of the global population reporting previous year use and much higher prevalence in countries and states that have legalized it for medicinal and/or recreational purposes [World Health Organization (WHO), 2020]. For instance, in 2018, 15.9% of individuals aged 12 and older sampled across the United States of America reported using cannabis in the past year [Substance Abuse and Mental Health Services Administration (SAMHSA), 2019]. Prevalence rates significantly rose in young adults (aged 18–25) and adults (aged 26+) over the previous 4 years, with more males than females reporting cannabis use (2019). Medicinal cannabis use is now legal in 20 countries and 34 United States of America states, and recreational use is legal in 4 countries and 11 United States of America states (Brady, 2020). More individuals may be considering cannabis for medicinal treatment, given the increasing legalization for this purpose. This increased prevalence in use for both recreational and medicinal purposes emphasizes the importance of understanding the potential negative health consequences of cannabis use, including its impact on neuropsychological functioning.

Research findings consistently show the negative effects of acute cannabis intoxication on cognition, primarily in the domains of learning and memory, but also in attention, psychomotor abilities, and inhibition (for review, see Broyd, van Hell, Beale, Yücel, & Solowij, 2016). However, findings on the long-term cognitive effects of chronic cannabis use are less consistent. Several studies report that chronic cannabis users exhibit worse performances on measures of attention (Jacobus et al., 2015), verbal learning and memory

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(Auer et al., 2016; Hanson et al., 2010), processing speed (Meier et al., 2012), psychomotor functioning (Bosker et al., 2013), and intelligence (IQ) with more persistent use (e.g., Meier et al., 2012). Yet, some studies show intact performances by chronic cannabis users on tests of attention (Lyons et al., 2004) and particular memory subdomains, such as delayed recall, episodic memory, and short-term memory (Tait et al., 2011). Furthermore, some researchers suggest lower performance on particular subdomains of executive functioning, such as decision-making (Bolla et al., 2005; Verdejo-Garcia et al., 2007), while other studies fail to demonstrate differences in executive functions between chronic cannabis users and non-users (e.g., Hooper et al., 2014; Medina et al., 2010). Neuroimaging studies evidence neuroanatomical differences in chronic cannabis users compared to non-users, especially in brain regions with high concentrations of endogenous cannabinoid receptors (e.g., anterior cingulate cortex, dorsolateral prefrontal cortex, striatum, hippocampus), which attract the primary psychoactive constituent in cannabis, delta-9-tetrahydrocannabinol (THC; Lorenzetti et al., 2019; Yanes et al., 2018). These findings indicate functional and structural alterations in regions associated with motivation, memory, inhibition, attention, vision, and reward processes (Lorenzetti et al., 2019; Yanes et al., 2018). However, other neuroimaging studies report contradictory findings (e.g., DeLisi et al., 2006) in that no structural differences were identified. The mixed findings in both neuroimaging and neuropsychological performance preclude researchers' understanding of the long-term effects of chronic cannabis use and underscore the need to investigate confounding factors that contribute to the variability in research findings.

Several factors may contribute to the inconsistencies in the neuropsychological effects of cannabis use, including sample demographics, method of administration (e.g., inhaled, edibles, etc.), strain, potency, amount, and duration of cannabis use, age of cannabis use onset, motivation to perform well on testing, and examiner expectancy effects (e.g., Batalla et al., 2013; Gruber et al., 2012; Hirst et al., 2017; Pope et al., 1997; Sodos et al., 2018). These factors are frequently either variable across studies or even unaccounted for in cannabis use research (Schreiner & Dunn, 2012). In particular, differences in the distribution of participants' sex across cannabis and control groups are common in studies examining the effects of cannabis on cognition. Because male cannabis users outnumber females in the general population (SAMHSA, 2019), cannabis-using groups in research studies are often disproportionately male. In contrast, healthy volunteer participants in psychological studies tend to be mostly female (Oswald et al., 2013). While some studies match by sex (e.g., Lisdahl & Price, 2012), many rely upon statistically controlling for the effect of sex, which precludes the ability to examine for differential effects of cannabis on males and females. Therefore, sex is a potential contributor to the inconsistencies in neuropsychological findings for the long-term cognitive effects of cannabis.

There are known differences in the neurological and cognitive characteristics between males and females that might account for variations in the effects of cannabinoid exposure. In healthy individuals, females generally have larger hippocampi than males, which may contribute to better learning and memory performances (particularly on verbal tasks) in females (Cosgrove et al., 2007), while males often perform better on visuospatial tasks (Hirnstein et al., 2019). Research has also shown that age moderates these sex differences in episodic memory performances, particularly in verbal-related memory tasks. Sex differences in verbal episodic memory performances are least prominent early and late in life, with increasing differences from childhood to adulthood and most prominent differences at the age of 50 (for review, see Asperholm et al., 2019). That review article suggests that this may be due to environmental influences (e.g., gender expectations, interests), sex differences in the development of brain structures related to memory (e.g., the hippocampi), and endogenous sex hormone levels, which relate to memory performance. Further, Laurikainen et al. (2019) found that females had 41% greater CB1 receptor availability than males, and therefore may be more sensitive to exogenous cannabinoid exposure in regions with the highest concentration of CB1 receptors. Regions with prominent CB1 receptor availability include the hippocampus, cerebral cortex (particularly frontal regions), cerebellum, and basal ganglia (Wilson & Nicoll, 2002), which are involved in cognitive functions such as attention, learning and memory, emotional processing, and motor control and coordination (Madras, 2015). Further, given the lipophilic properties of cannabis and the larger body fat percentage in females compared to males, more THC may be preserved by fat cells in females (Fattore & Fratta, 2010). Thus, THC may affect females at weaker levels than males because most of the THC is retained rather than metabolized (Fattore & Fratta, 2010). Female users also demonstrate a differential neural response associated with greater subjective craving for cannabis, relative to males (Prashad et al., 2020). Given the differences in neuroanatomical structures related to learning and memory and cannabinoid receptor availability between males and females described above, there also may be differing cognitive effects of exogenous cannabinoid exposure by sex. Yet, these biological differences have not been adequately explored in human participants, and the contribution to differential neuropsychological performance in males and females remains unknown.

There are only a few studies examining differences in the cognitive effects of cannabis use between males and females. Pope et al. (1997) showed worse visuospatial task performance in female heavy cannabis users (i.e., using 29 out of the past 30 days) compared to female light users (i.e., using 1 out of the past 30 days), but no within-group differences for their male counterparts. This finding could reflect that males' generally stronger visuospatial skills may have been more resistant to the effects of heavy cannabis use than females. Lisdahl and Price (2012) showed a greater psychomotor slowing in male cannabis users relative to females. Anderson et al. (2010) investigated sex differences in the acute effects of cannabis use on attention, cognitive

https://doi.org/10.1017/S1355617721000217 Published online by Cambridge University Press

flexibility, time estimation, and visuospatial processing tasks. While the authors did not observe sex differences in performances on those cognitive tasks, their findings did suggest that females may have a lower tolerance to cannabinoid exposure because female participants discontinued dosage earlier than males when self-administering cannabis prior to testing. This could indicate greater sensitivity to cannabis exposure in females, and also supports the greater prevalence of cannabis use in males. Another study found that female chronic cannabis users (i.e., those who used cannabis greater than 200 times in lifetimes, greater than 4 times per week at peak usage, and at least once in the last 45 days) with an earlier onset of cannabis use showed poorer performances on a verbal learning task than later onset female users, while males did not show this difference (Crane et al., 2015). Taken together, these findings raise evidence for sex differences in the cognitive effects of cannabis use, particularly in the domains of learning and memory, which are further supported by biological and hormonal differences in neurophysiology amongst males and females.

More empirical support is needed to draw firm conclusions about differential sex effects of cannabis on cognitive functioning; therefore, the current study examined the role of sex on the cognitive effects of chronic cannabis use in male and female adult cannabis users. Given that cannabis affects verbal learning and memory in cannabis users and there are sex differences in verbal learning and memory, we expected to see memory differences in this domain in particular. Thus, the authors hypothesized that female cannabis users would outperform their male counterparts on measures of verbal learning and memory, while male cannabis users would outperform female users on measures of visual learning and memory tests.

METHOD

Participants

This quasi-experimental research design included a participant sample ($n = 181$, 59.12% male, mean age = 20.27 years, $SD = 2.74$) collected from a two-wave recruitment process. The overall sample consisted of 110 chronic cannabis users (72% male) and 71 non-users (39% male). The first wave of recruitment included participants from a public northeastern university who received class credit for study compensation (see Macher & Earleywine, 2012). The second wave included participants from Northern California communities who were recruited via local advertisements, online postings, and local universities. These second-wave participants received a $50 gift card for study compensation. Data collection from the first and second waves of recruitment spanned a 10-year period (2009–2019). The two waves of participants did not differ in sex or premorbid functioning; however, the second wave was slightly older (21.55 years *vs.* 19.23 years), more educated (14.22 years *vs.* 12.67 years), and more diverse (69% non-White *vs.* 30% non-White) than the first wave, as expected given the different methods of recruitment. Therefore, age- and education-adjusted normed scores were utilized where applicable, and ethnicity was included as a covariate in analyses. All data were collected in compliance with the regulations of the university's Institutional Review Board and in compliance with the Helsinki Declaration.

Inclusion criteria consisted of age between 18 and 40 years (to reduce the likelihood of any age-related impact on cognitive performance). In order to meet the criteria as a chronic cannabis user, the individual must have used cannabis at least three times per week for a period of at least 1 year. Non-users, on the other hand, must have used cannabis at least once but no more than five times in their lifetime and not within the past 30 days. This inclusion criterion was selected as previous research has indicated potential personality and cognitive differences (e.g., risk-taking) between individuals who have never tried cannabis and those who have experimented with cannabis a limited number of times (Pope et al., 2001). Lastly, participants must have been fluent in English and educated in English since age six, to reduce language effects on cognitive performance.

Exclusion criteria consisted of illicit substance use (e.g., stimulants, hallucinogens, etc.) more than five times (per drug class) in their lifetime. Excessive alcohol use, as determined by two or more drinks in a sitting occurring four or more times per week for a period of 1 month or longer, also barred individuals from participation. Additional exclusion criteria included the presence of psychiatric diagnoses (other than specific phobia), history of head injury with associated loss of consciousness or hospitalization, current use of psychotropic/psychoactive medications, or current medical or neurological diagnoses that are known to interfere with cognitive performance (e.g., multiple sclerosis, epilepsy, etc.). These exclusion criteria meet suggested expectations of cannabis research experts in the field (e.g., Gonzales et al., 2002).

Procedure and Measures

Prospective participants completed a brief phone or online screening survey that collected information regarding demographics, history of cannabis use, and other inclusion/exclusion criteria to determine eligibility for the study. Researchers asked eligible participants to abstain from any substance use, including alcohol, for at least 24 h prior to their testing appointment, and they completed a brief field sobriety test (balancing on one foot for 30 s) on the day of testing in order to ensure that they were not acutely intoxicated. Trained doctoral-level graduate students administered the neuropsychological battery, which evaluated all cognitive domains (attention/working memory, visuospatial processing, language, learning/memory, and executive functioning). Examiners were at least in their second year of their graduate school and were trained in neuropsychological assessment both formally in coursework and personally by the principal investigator; further, all assessments were double scored by these graduate students as well as the principal investigator to enhance inter-rater reliability. Study

https://doi.org/10.1017/S1355617721000217 Published online by Cambridge University Press

examiners were kept blind to the participants' cannabis user status throughout the evaluation. On the day of testing, additional demographic information was collected, including age, sex/gender, race/ethnicity, years of education, and handedness, and presence of hearing and/or visual impairments that could influence cognitive performance (none were reported). As part of a larger study, participants from both recruitment waves were then randomly assigned to either a motivational statement condition or a neutral statement condition prior to testing (further details in Macher & Earleywine, 2012). The motivational statement was part of a prior study examining whether enhancing effort improved cognitive performance in adult cannabis users. Additionally, examiners privately noted whether they believed the participant was a cannabis user or not. Both effects of the motivational statement and examiner expectancies were statistically controlled for in the current study, given that this was not the focus of the present study.

Examiners then administered a battery of well-established, reliable, and valid neuropsychological tests selected based upon the frequency of administration by clinical neuropsychologists (Rabin et al., 2016). These tests included the California Verbal Learning Test – Second edition (CVLT-II; Delis et al., 2000; for verbal learning and memory); the Digit Span (DS) subtest of the Wechsler Adult Intelligence Scale – Third edition (WAIS-III; Wechsler, 1997; including DS Forward for simple attention and DS Backward for working memory); the Rey–Osterrieth Complex Figure Test (RCFT; Rey, 1941; for visuospatial functioning and visual learning and memory); the Trail Making Test of the Halstead-Reitan Neuropsychological Battery (TMT; Reitan & Wolfson, 1992; for visual attention/processing speed and cognitive flexibility/set-shifting); the National Adult Reading Test – Revised (NART-R; Blair & Spreen, 1989; for estimating premorbid verbal IQ in the absence of a current measure of full-scale IQ); the Word Memory Test (WMT; Green, 2003; as a stand-alone performance validity test); as well as three embedded performance validity measures, including the Forced Choice (FC) subtest of the CVLT-II (Root et al., 2006), Reliable Digit Span of the WAIS-III (RDS; Etherton et al., 2005), and the Trail Making Test B/A Ratio (TMT Ratio; Ruffolo et al., 2000).

RESULTS

Demographic Features and Validity Testing Performance

Participant demographic information for cannabis users, non-users, and the entire sample are presented in Table 1. All reported interpretations of effect sizes are based on interpretation suggestions by Ferguson (2016). A 2 × 2 multivariate analysis of variance (MANOVA) analysis revealed no significant differences among female and male cannabis users and non-users in age and estimated premorbid IQ (based upon NART-R performance). However, there was a significant difference in years of education among female and male users and non-users ($F = 2.67$, $p = .049$, $\eta_p^2 = .04$) with a small-to-medium effect size. Within the user group, female users reported more years of education ($M = 13.87$, $SD = 1.31$) than male users ($M = 13.01$, $SD = 1.19$; $F = 11.05$, $p = .001$, $\eta_p^2 = .09$), though this difference was less than 1 year of education even though the effect size was within the medium to large range. Despite observed educational sex differences, there were no significant differences between female and male users in performance on the NART-R, indicating comparable estimated premorbid verbal IQ. There were no significant differences between female and male users in age, age at first cannabis use, frequency of current cannabis use (days per week), total days of lifetime cannabis use, or length of cannabis use (in total months). A series of chi-square tests of association demonstrated that race/ethnicity was equally distributed between female and male users and non-users for the overall, combined sample. However, race/ethnicity was unevenly distributed, with a greater proportion of White participants in one of the two sampling pools ($\chi^2 = 42.60$, $p < .0001$; $\phi = .49$ indicating a large effect size). Therefore, ethnicity was included as a covariate in the remaining analyses. Sex was unevenly distributed, with more male users but more female non-users ($\chi^2 = 18.72$, $p < .001$; $\phi = .32$ indicating a medium effect size; see Table 2). This is consistent with the general population of cannabis users, in that males are more likely to use cannabis than females (SAMHSA, 2019). Therefore, the remaining analyses were conducted within each user group. All participants passed a stand-alone performance validity test (WMT) and multiple embedded measures of performance validity (CVLT-II FC, RDS, and TMT Ratio), suggesting that individuals put forth adequate effort throughout the evaluation and performance on neuropsychological measures are valid representations of their current cognitive functioning.

Statistical Analyses and Included Covariates

As part of a larger study, several additional variables were examined using a 2 × 2 MANOVA to determine whether group differences existed among female and male users and non-users. Similar to previous findings using a subset of these data (Macher & Earleywine, 2012; Sodos et al., 2018), there were group differences in performance on several neuropsychological measures by motivational condition and examiner's belief of the participants' user status within the user and non-user groups. Therefore, the motivational condition and examiner expectancy variables were included as covariates within the primary analyses, as they were not the focus of the present study. Additionally, years of education were also included as a covariate even for measures that account for education within the norms, given the group differences between female and male users in years of education described above. Race/ethnicity was also included as a covariate in both analyses, as described above. Finally, normed scores were used for several of the CVLT-II variables (e.g., Free Recall Trials of Trial 1, Trial 5, Sum of Trials 1–5,

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Table 1. Demographic information: total sample, cannabis users, and non-users

	Total sample ($n = 181$)	Users ($n = 110$)	Non-users ($n = 71$)	F or χ^2	p-value	η_p^2 or ϕ
Age (years)	20.27 (2.74)	20.30 (2.49)	20.21 (3.10)	.05	.831	.000
Years of education	13.28 (1.52)	13.25 (1.28)	13.32 (1.83)	.10	.752	.001
Estimated premorbid verbal intelligence	102.49 (10.33)	101.77 (11.29)	103 .61 (8.59)	1.37	.244	.008
Percent males (n)	59.12 ($n = 107$)	71.82 ($n = 79$)	39.44 ($n = 28$)	18.72	.001***	.322
Percent White (n)	54.69 ($n = 99$)	56.36 ($n = 62$)	52.11 ($n = 37$)	13.23	.01**	.270

Means (standard deviations in parentheses).
**$p < .01$.
***$p < .001$.

Table 2. 2 × 2 MANOVA results comparing demographic variables by sex and user status

	Users		Non-users				
	Female	Male	Female	Male	F	p-value	η_p^2
Sample size (n)	31	79	43	28	–	–	–
Years of education	13.87 (1.31)	13.01 (1.19)	13.42 (1.74)	13.18 (1.98)	2.67	.049*	.04
Age (years)	20.42 (2.22)	20.25 (2.60)	20.26 (3.06)	20.14 (3.23)	.32	.808	.001
Estimated premorbid verbal intelligence	101.91 (10.75)	101.71 (11.56)	105.54 (8.59)	100.64 (7.84)	.57	.642	.03
Days per week cannabis used[a]	5.39 (1.45)	5.46 (1.36)	–	–	.04	.835	.00
Total days cannabis used[a]	290.58 (392.30)	368.43 (442.23)	–	–	.81	.371	.01
Total months cannabis used[a]	29.97 (21.60)	34.39 (27.17)	–	–	.69	.416	.01
Age cannabis first used[a]	17.00 (1.81)	16.35 (1.74)	–	–	3.08	.082	.03

[a]Represents a separate MANOVA examining cannabis use specific variables. Means (standard deviations in parentheses).
*$p < .05$.

Short Delay, and Long Delay) when examining group differences, given known sex differences in performance on this measure in healthy individuals. Raw scores for the CVLT-II were used for Short-Delay Cued Recall, Long-Delay Cued Recall, and Recognition Hits variables for the overall sample, as normative data was not available. The commonly used Bonferroni correction (Blakesley et al., 2009; Huizenga et al., 2007) was applied for each within-group analysis to decrease the likelihood of Type I family-wise error due to multiple comparisons. The critical p-value was adjusted to $p \leq .004$ for the primary statistical tests ($p \leq .05/14$ outcomes variables = .004) comparing neuropsychological performance between female and male participants within the user and non-user groups separately.

Sex Effects on Neuropsychological Performance Within Non-Users

Within the non-user group, the estimated premorbid verbal IQ, based upon NART-R score, for females ($M = 105.54$, $SD = 8.59$) was significantly higher than males ($M = 100.64$, $SD = 7.84$; $F = 3.23$, $p = .026$, $\eta_p^2 = .13$, indicating a medium to large effect size). Given these observed differences, the NART-R was also included as a covariate for the non-user analysis. The MANCOVA included five covariates (examiner expectancy effects, motivational condition, race/ethnicity, years of education, and NART-R score). Although the results revealed that female non-users outperformed males in delayed memory for verbal information (CVLT-II LD-FR) and in cognitive flexibility under timed conditions (TMT B), and male non-users outperformed females in attention and working memory (WAIS-III DS Total), adjusting for multiple comparisons with the Bonferroni correction showed that CVLT-II LD-FR and DS were no longer significant (see Table 3). After adjusting for multiple comparisons, there were no sex differences in neuropsychological performance within the non-user group among any of the other neuropsychological measures within the battery, after controlling for potential confounding variables.

Sex Effects on Neuropsychological Performance Within Cannabis Users

Within the user group, a MANCOVA examined the effect of sex on the neuropsychological outcome variables. The MANCOVA included four covariates (examiner expectancy effects, motivational condition, race/ethnicity, and years of education). The findings indicated significant differences between female and male users on most subtests of the CVLT-II, showing better verbal learning and memory performance in female cannabis users (see Table 4). After using the Bonferroni correction to adjust for multiple comparisons, the significant findings remaining showed that females performed better than males on the CVLT-II Sum of Trials 1–5 Free Recall ($F = 4.82$, $p = .001$, $\eta_p^2 = .188$ indicating a large

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Table 3. Neuropsychological performance by sex within non-users

	Female	Male	*F*	*p*-value	η_p^2
Neuropsychological measure					
CVLT-II Trial 1 Free Recall[a]	−0.59 (0.70)	0.55 (0.64)	.48	.820	.04
CVLT-II Trial 5 Free Recall[a]	−0.12 (1.03)	−0.39 (1.01)	.77	.597	.07
CVLT-II Sum Trials 1–5 Free Recall[b]	51.91 (8.44)	48.54 (11.27)	.65	.694	.06
CVLT-II Short-Delay Free Recall[a]	0.16 (1.06)	−0.36 (1.05)	1.86	.102	.15
CVLT-II Short-Delay Cued Recall	12.86 (2.71)	11.54 (2.67)	1.52	.185	.13
CVLT-II Long-Delay Free Recall[a]	0.01 (1.06)	−0.61 (1.17)	2.32	.043^	.18
CVLT-II Long-Delay Cued Recall	13.26 (2.47)	11.36 (2.83)	2.10	.065	.17
CVLT-II Recognition Hits	15.16 (1.05)	14.43 (1.73)	1.57	.171	.13
WAIS-III Digit Span Total Score[c]	10.23 (2.49)	10.89 (3.16)	2.41	.037^	.18
RCFT Copy	34.14 (1.61)	33.89 (1.47)	.80	.572	.07
RCFT Immediate Recall	21.65 (6.00)	22.55 (5.57)	.78	.590	.07
RCFT Delayed Recall	22.24 (5.20)	22.80 (4.80)	.70	.652	.06
TMT A[b]	48.70 (11.74)	44.89 (8.13)	2.14	.071	.14
TMT B[b]	52.09 (13.50)	52.07 (14.90)	4.79	<.001**	.31

Means (standard deviations in parentheses). Raw scores are unless otherwise noted.
[a]Indicates *Z* score.
[b]Indicates *T* score.
[c]Indicates scaled score.
^$p < .05$ (not significantly different after Bonferroni correction).
*$p < .01$.
**$p < .001$.

Table 4. Neuropsychological test performance by sex within users

	Female	Male	*F*	*p*-value	η_p^2
Neuropsychological Measure					
CVLT-II Trial 1 Free Recall[a]	−0.74 (0.82)	−0.42 (0.83)	4.05	.002*	.16
CVLT-II Trial 5 Free Recall[a]	−0.35 (0.88)	−0.25 (0.99)	1.09	.373	.05
CVLT-II Sum Trials 1–5 Free Recall[b]	49.84 (8.72)	48.94 (10.67)	4.82	.001**	.19
CVLT-II Short-Delay Free Recall[a]	0.13 (0.72)	−0.24 (1.09)	3.58	.005^	.15
CVLT-II Short-Delay Cued Recall	12.68 (2.01)	11.22 (2.77)	4.79	.001**	.19
CVLT-II Long-Delay Free Recall[a]	−0.18 (0.80)	−0.46 (1.16)	2.75	.022^	.12
CVLT-II Long-Delay Cued Recall	13.13 (1.71)	11.62 (2.95)	5.04	<.001**	.20
CVLT-II Recognition Hits	15.32 (1.17)	14.89 (1.19)	.94	.459	.04
WAIS-III Digit Span Total Score[c]	10.19 (2.30)	11.19 (2.60)	2.67	.026^	.11
RCFT Copy	33.55 (2.37)	33.36 (2.51)	.64	.672	.03
RCFT Immediate Recall	20.29 (7.38)	21.06 (6.41)	1.60	.166	.07
RCFT Delayed Recall	20.35 (7.34)	21.04 (6.45)	1.69	.142	.08
TMT A[b]	45.52 (10.22)	48.62 (10.42)	1.70	.140	.08
TMT B[b]	48.81 (11.35)	52.56 (12.03)	6.71	<.001**	.24

Means (standard deviations in parentheses). Raw scores are unless otherwise noted.
[a]Indicates *Z* score.
[b]Indicates *T* score.
[c]Indicates scaled score.
^$p < .05$ (not significant after Bonferroni correction).
*$p < .01$.
**$p < .001$.

effect size), CVLT-II SD-CR ($F = 4.79$, $p = .001$, $\eta_p^2 = .187$ indicating a large effect size), and LD-CR ($F = 5.04$, $p = .0004$, $\eta_p^2 = .195$ indicating a large effect size) subtests. Although no longer significant after correcting for multiple comparisons, female users also outperformed males on several other verbal learning and memory subtests, including the SD-FR and LD-FR subtests of the CVLT-II. Interestingly, males performed better than females on the CVLT-II Trial 1 ($F = 4.05$, $p = .002$, $\eta_p^2 = .163$ indicating a large effect size), which is the first list learning trial in which the list of words is presented to the participant, and therefore measures short-term attention rather than recall and retrieval.

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Taken together, it appears that male cannabis users' initial attentional abilities for learning verbal information are better than females, while female cannabis users demonstrated a better ability to encode and later recall verbal information after several learning trials. When presented with semantic cues, female cannabis users' retrieval memory is better than males. Recognition memory between female and male users was comparable. There were no sex differences within the user group for performance on TMT A, which measures processing and psychomotor speed. However, males performed better than females on the TMT B ($F = 6.71$, $p < .0012$, $\eta_p^2 = .24$ indicating a large effect size), which measures cognitive flexibility under timed conditions. Although male cannabis users performed slightly better than females on WAIS-III DS Total, a test measuring simple attention and working memory, the significance of this finding did not survive multiple comparison adjustments. Female and male users' performance was comparable on all subtests of the RCFT, which measures visuoconstruction and visual memory.

DISCUSSION

As recreational and medicinal marijuana use rises in the United States of America, the need to clarify factors that could contribute to secondary cognitive deficits also rises. Prior research on the neuropsychological effects of chronic cannabis use has yielded somewhat inconsistent results, which may be attributable to unaccounted for variables such as participants' sex. Therefore, the current study sought to clarify the presence and scope of differential sex effects of cannabis use on cognitive functioning.

As hypothesized, female users outperformed male users in verbal learning and memory, as measured by multiple subtests of the CVLT-II, including the sum of the learning trials, and the short- and long-delay cued and free recall trials, even when test scores were normed for gender. Given that male and female users did not differ in age of onset of cannabis use, frequency of use, or duration of total use, this finding suggests that comparable chronic cannabis use impacted the verbal learning and memory of males to a greater degree than females. There are several possible reasons for the present results. As described above, structural differences (i.e., hippocampal size) and hormonal differences between males and females may contribute to stronger verbal learning and memory in healthy females (Asperholm et al., 2019), and our findings suggest that female cannabis users may be more resilient to the effects of prolonged cannabis use over time. It is possible that, because females, in general, have a stronger baseline verbal memory than males, they may exhibit a greater "cognitive reserve" upon which to rely as protection against the effects of cannabis on memory. If that hypothesis is true, then the present results would be consistent with the findings of a previous study showing that male heavy cannabis users did not exhibit worse visual memory performance compared to light users, while females did exhibit that pattern (Pope et al., 1997). It is possible that, in that study, males' stronger baseline visuospatial skills acted as a buffer against the negative effects of heavy cannabis use on visuospatial memory. Further, one previous study showed that male cannabis users exhibited worse cognitive slowing relative to females (Lisdahl & Price, 2012). Slowed cognitive processing could lead to greater difficulty with encoding and then retrieving new information (Lezak et al., 2012), which would be consistent with the findings of the present study. As cannabis use increases in the general population, evidence of sex differences in verbal memory deficits may critically influence the interpretation of neuropsychological evaluation results for females in a variety of medical and forensic contexts. For instance, Sundermann et al. (2017) have suggested that diagnoses relying on verbal memory assessments (e.g., Alzheimer's disease) may be susceptible to a type of ceiling effect for females. While previous studies investigating the effects of chronic cannabis use often control for gender in the analyses, these results provide evidence for the importance of examining within-group differences to determine how males and females may be differentially impacted. Further, individual differences in learning and memory performance prior to the initiation of cannabis use would be interesting to explore further, to determine what role premorbid memory abilities may play on the effects of chronic cannabis use on learning and memory performance. Individuals with higher verbal learning and memory performance at baseline (such as females) may experience less vulnerability to the effects of cannabis on learning and memory functioning. Future research may wish to consider a study of individual differences in learning and memory performance pre- and post-cannabis use with a within-subjects design to explore the implications of this finding further.

Contrary to the authors' second hypothesis, male users did not demonstrate stronger visual learning and memory relative to female users, suggesting that the typically stronger baseline visuospatial skills expected in most males did not have a greater protective effect against chronic cannabis use in male users than in female users. Notably, the RCF is a measure of incidental visual learning and recall (i.e., examinees are not warned that they will have to recall the visual information later). It is possible that purposeful visual learning and recall tests could show the anticipated protective effect of male sex on the effect of chronic cannabis use on visual memory, and future studies may wish to investigate these other types of visual memory measures to see if this finding is consistent across multiple types of visual memory assessments. Interestingly, however, male users outperformed female users on the first learning trial of the CVLT-II, which reflects short-term attention. This finding offers evidence for sex discrepancies in cannabis users in the domain of simple attention. Similarly, males performed slightly better than females on the DS subtest, which also measures attention, though the significance of that result did not survive adjusting for multiple comparisons. Generally speaking, research has not shown males to have stronger attention than females in the healthy population (Grissom & Reyes, 2019), although it is worth noting that

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male non-users also outperformed female non-users on DS (though again, the significance did not survive adjustment for multiple comparisons). Therefore, it is possible that males' short-term attention may be more resistant to the effects of chronic cannabis use than females, though the etiology of these findings is unclear at this time. The better attention in male users make the enhanced verbal learning and memory results in females even more surprising, as typically, enhanced attention would lead to better encoding and later retrieval (Lezak et al., 2012). However, verbal learning and memory require more than just attention and short-term memory – individuals must encode and then later be able to successfully retrieve the information that they learned (Lezak et al., 2012). Thus, the present findings are even more compelling in that despite male cannabis users' better attention, they were still unable to successfully encode and later retrieve learned verbal information to the same degree that female cannabis users did.

An unexpected finding was that male cannabis users performed better on TMT B, a measure of cognitive flexibility under timed conditions, a finding that was significant even after adjusting for multiple comparisons and that had a large effect size. Yet within the non-user group, females performed slightly better than males. Further research is needed to better understand the potential differential effects of cannabis on males and females within the domain of executive functioning. Future studies should investigate these results further, as confirmation of male-specific resilience in these domains may elucidate the mixed findings on executive function deficits described in the Introduction above (e.g., Bolla et al., 2005; Verdejo-Garcia et al., 2007; Hooper et al., 2014; Medina et al., 2010). There were no significant differences found between male and female users on the remaining neuropsychological assessments.

The present results have important implications for the neuropsychological evaluation of chronic cannabis users, as critical differences in cognitive performance by sex in response to regular cannabis use can influence the interpretation of patients' assessment results. Most broadly, the identification of sex differences in the effects of cannabis on memory supports the recommendation that future research should incorporate within-group analyses to better examine the potential cognitive differences that exist amongst cannabis users, rather than solely comparing them to non-using controls. The present findings also amplify the nuanced interpretation necessary for clinicians to accurately account for cannabis's effects when interpreting neuropsychological assessment results, which are not identical for all demographic groups. Especially in measures that do not provide sex-based norms, evidence that female cannabis users may be more resilient to the effects of prolonged cannabis use on memory over time may, for example, enable clinicians to identify neurodegenerative disorders in chronic cannabis users earlier and more accurately. This is especially pertinent given the increasing prevalence of dementia in the aging population, as well as the rising recreational and medicinal use amongst older adults due to progressively permissive cannabis use laws (Han & Palamar, 2020). Finally, as our understanding of the benefits of medicinal cannabis use rises, patients considering cannabis treatment would benefit from the enhanced knowledge regarding possible consequences to their cognitive functioning. Should the present results be upheld with further research, they may reassure female patients who are concerned about potential memory deficits resulting from cannabis treatment, whereas males considering initiating cannabis may choose to exercise greater caution. The same is also true for individuals considering recreational cannabis use.

Limitations and Advantages of the Present Study

The present study is not without limitations, which may be addressed in future studies. First, Rosen et al. (2018) have demonstrated that pure cannabis users such as those used in the present study (i.e., individuals without co-occurring substance use or psychiatric diagnoses, with no medical conditions or head injuries that could impact neuropsychological performance) are not necessarily representative of the general population of cannabis users. When using the stringent inclusion/exclusion criteria in the present study, approximately 95% of potential participants may be screened out due to polysubstance use, the presence of a psychiatric diagnosis, or another medical condition that could influence cognitive functioning (Rosen et al., 2018). However, using a sample of "pure" chronic cannabis users circumvents the need to control for the presence of other confounding explanations to the observed sex differences. As such, the results of the current study should be applied cautiously until future studies can replicate these findings with more representative samples to increase generalizability.

The present study was also limited by the lack of more stringent measures of cannabis sobriety, such as urinalysis or a lengthier abstinence period. Funding and recruitment difficulty due to strict inclusion/exclusion criteria made those options impractical. Therefore, we chose to use field sobriety tests and a 24-hour abstinence period to safeguard against the effects of acute cannabis intoxication, as used in other research studies (e.g., see Papafotiou et al., 2005; Declues et al., 2016). Future studies may choose to add the collection of biomarkers or lengthier abstinence periods to reduce the residual effects of cannabis intoxication on neuropsychological functioning.

Another consideration when interpreting the present results is the potential for inaccurate self-report of cannabis use by participants. While the possibility of misreporting is inherent to research involving self-report, it is possible that the chronic cannabis users may incorrectly estimate or report their frequency or duration of cannabis use. The authors sought to include a large sample in the present study to offset any potential self-report errors. Similarly, the present study did not account for possible variability resulting from the use of different strains of cannabis, different methods of ingestion, or quantity of use on each day. Though differences

https://doi.org/10.1017/S1355617721000217 Published online by Cambridge University Press

in pharmacokinetic properties of ingestion and strain-specific cannabinoid availability were beyond the scope of the present study, future research may wish to include these variables in their methodology. Further, future studies should assess the amount of cannabis used in a typical day to ensure that sex differences in the amount used did not contribute to the findings. Measuring hormonal levels or menstrual cycle characteristics may also be useful, given that research in rats suggests that hormonal bioavailability can interact with cannabinoid exposure (Cooper & Craft, 2018), though this finding has not yet been demonstrated in humans. In addition, although the two sexes in this sample did not differ in age of onset of cannabis use, frequency of use, or total days of use, it is possible that males used more cannabis per day than females. Future studies should assess the amount of cannabis used in a typical day to ensure that sex differences in amount used did not contribute to the findings. Also, the relatively low proportion of female cannabis users in the general cannabis-using population made it difficult for the authors to recruit a large number of female users for this study, and the tendency for psychological study control volunteers to be mostly female made it difficult to match the groups based upon sex. Future studies may wish to more actively recruit additional male non-users to match the two user groups so that separate within-user group analyses are not necessary.

Another area of limitation which future studies might expound on is the operationalization of verbal memory with a list-learning test. Future studies may wish to administer alternative verbal memory measures, such as story memory tests, to see if the findings are upheld across multiple types of verbal recall. Finally, the total sample included participants from two waves of recruitment, from different demographic areas. Demographic differences were controlled for through the use of norms (e.g., age, level of education) or controlled for as covariates, and the two samples did not differ in the proportion of users *versus* non-users, or males *versus* females. The second sample did have fewer total days of use relative to the first; however, both samples were recruited for and met the same stringent inclusion/exclusion criteria. Therefore, the authors provide evidence that this is a representative and reasonably consistent sample of chronic cannabis users.

Despite these limitations, the current study design offers several meaningful advantages. As noted above, the inclusion of a "pure" sample of chronic cannabis users increases confidence that the observed discrepancies are in fact due to sex characteristics and not other confounding factors. Importantly, sex differences were found on only one neuropsychological measure of the battery within the non-user group (and not on any of the verbal learning and memory subtests), supporting the conclusion that the observed differences in verbal learning and memory within the user group are due to cannabis' differential effects on each sex rather than sex effects alone. Further, these sex differences within cannabis users were found even when sex-normed scores were used to account for females' better verbal learning and memory. Finally, the fairly large sample size for a study including a neuropsychological battery gives greater confidence that the significant results are not spurious and instead represent meaningful group differences in performance.

In sum, the results of the present study demonstrate that female chronic cannabis users may not demonstrate the same cognitive deficits in verbal learning and memory as male cannabis users do, perhaps due to enhanced premorbid verbal learning and memory skills found in the general population. These findings were observed despite the fact that male cannabis users exhibited better initial simple attention on the same list learning task. This study illustrates a direction for future research to more closely examine the differential effects of chronic cannabis use within males and females separately, particularly within the domains of attention and verbal learning and memory.

ACKNOWLEDGEMENTS

All research was conducted in compliance with institutional research standards for human research, under approval of the institutional review board, and in accordance with the Helsinki Declaration.

FUNDING STATEMENT

There were no sources of financial support for this study.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to disclose.

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