Psychiatry Research: Neuroimaging 285 (2019) 58–63

Contents lists available at ScienceDirect

Psychiatry Research: Neuroimaging

journal homepage: www.elsevier.com/locate/psychresns

Preliminary results from a pilot study examining brain structure in older adult cannabis users and nonusers

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ARTICLE INFO

Keywords:
Aging
Older adults
Cannabis
Neuroimaging
Volume
Cortical thickness

ABSTRACT

Exploring associations among cannabis use, brain structure, and cognitive function in older adults offers an opportunity to observe potential harm or benefit of cannabis. This pilot study assessed structural magnetic resonance imaging in older adults who were either current cannabis users (n = 28; mean age 69.8 years, 36% female) or nonusers (n = 28; mean age 66.8 years, 61% female). Recruitment targeted users who reported at least weekly use for at least the last year, although users had 23.55 years of regular cannabis use on average (SD = 19.89, range 1.5–50 years). Groups were not significantly different in terms of sex, years of education, alcohol use, or anxiety symptoms, but were significantly different in age and depression symptoms. Users and nonusers did not differ in terms of total gray or white matter volumes controlling for age and depression symptoms, but users showed greater regional volume of left putamen, lingual cortex, and rostral middle frontal cortex. No significant differences between groups were observed in performance on a brief computerized cognitive battery. These results suggest that cannabis use likely does not have a widespread impact on overall cortical volume while controlling for age.

1. Introduction

Older adult cannabis users are a growing population (Han et al., 2017), and factors related to aging may help clarify harm or benefit of cannabis use to brain structure and cognition. Older adults are at risk for neurocognitive disorders, and some cognitive decline is expected with normal aging, but it is unclear how these processes may be impacted by cannabis use. Cannabis use into late adulthood may put users at greater risk of cognitive decline and brain atrophy (Lorenzetti et al., 2016a), or the neuroprotective effects of certain cannabinoids may have beneficial anti-inflammatory effects (Campos et al., 2017; Chiarlone et al., 2014). Evidence from structural neuroimaging and cognitive studies suggests that long-term cannabis use is most often associated with reduced hippocampal volume (Nader and Sanchez, 2018) and poorer memory (Sagar and Gruber, 2018), but other studies have found no effect of cannabis use when accounting for confounding factors such as alcohol use (Thayer et al., 2017; Weiland et al., 2015). In the general older adult population, global cortical thinning and gray matter volume loss are associated with poorer neuropsychological test scores and cognitive decline (Draganski et al., 2013). Exploring associations among cannabis use, brain structure, and cognitive function in this understudied age group offers an opportunity to observe potential harm or benefit of cannabis.

This pilot study assessed structural magnetic resonance imaging (MRI) in adults 60 years and older who were either current cannabis users or nonusers. No previous studies of brain structure and cannabis use among older adults have been previously published. Gray and white matter volume and cortical thickness were examined to provide preliminary information about associations between cannabis use and brain structure among older adults. A brief cognitive battery was also administered to measure attention, episodic memory, working memory, vocabulary knowledge, oral reading skill, executive function, and processing speed. Previous studies have found no significant effects of cannabis use on brain structure when also accounting for alcohol use (Thayer et al., 2017; Weiland et al., 2015), while alcohol use has a widespread association with lower cortical volumes (Thayer et al., 2016). In this context, it was hypothesized that cannabis users would show no differences in total volumes of cerebrospinal fluid (CSF), gray, or white matter compared to nonusers (i.e., no widespread effect of cannabis use, when controlling for alcohol, that would be expected to indicate cognitive decline (Draganski et al., 2013), but may show a difference in hippocampal volume. It was also hypothesized that users would demonstrate poorer memory than nonusers but no other differences in cognitive performance.

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https://doi.org/10.1016/j.pscychresns.2019.02.001
Received 20 September 2018; Received in revised form 8 February 2019; Accepted 9 February 2019
Available online 10 February 2019

2. Methods

2.1. Participants

Adults aged 60 years and older who reported consuming cannabis at least once per week for at least the last year (n = 28) or who reported never using cannabis (n = 28) were recruited from the Boulder-Denver metro through online advertisements and direct mail flyers. Exclusion criteria were >20 pack years of tobacco use; uncontrolled diabetes, or insulin use; uncontrolled hypertension; history of antipsychotic medications or serious mental illness; or MRI contraindications. Participants with any history of alcohol or other substance use disorder [other than Cannabis Use Disorder (CUD)] were also excluded. The Institutional Review Board of the University of Colorado Boulder approved all study procedures (Protocol 15-0457).

2.2. Measures

All participants completed a demographics questionnaire, basic questions about cannabis use (age of first use, duration of regular use), the Alcohol Use Disorder Identification Test (AUDIT; Babor et al., 2001), the Beck Depression Inventory-II (BDI-II; Beck et al., 1996), and the Beck Anxiety Inventory (BAI; Beck, 1990).

All users (n = 28) and a subset of nonusers (n = 10) also completed additional measures. The NIH Toolbox Cognition Battery (Gershon et al., 2013) is a computerized battery that requires 30 min to complete and includes 7 tests assessing attention, episodic memory, working memory, vocabulary knowledge, oral reading skill, executive function, and processing speed. Primary measures were age-normed scores for each test, and the age-normed Total Composite score for general cognition.

This same subset of participants also completed the Timeline Follow-Back (TLFB; Sobell and Sobell, 1992) for the 90 days prior to the scanning session to measure days of alcohol and cannabis use and amount used per day. Preferred marijuana potency and method of administration (e.g., smoked, vaporized, consumed in edible form) were also collected.

Finally, cannabis users completed the Marijuana Dependence Scale based on DSM-V symptoms of CUD (e.g., "When I smoked marijuana, I often smoked more or for longer periods of time than I intended"; Lozano et al., 2006).

2.3. Imaging acquisition and processing

Neuroimaging was acquired on a 3T Siemens MAGNETOM Prisma system with a 32-channel head coil. For optimal contrast, a multi-echo MPRAGE (MEMPR) sequence was collected with the following parameters: TR/TE/TI = 2400/2.07/1000 ms, flip angle = 8°, FoV = 256 × 256 mm, Slice thickness = 0.8 mm, Slices per slab = 224, 3D voxel resolution = 0.8 × 0.8 × 0.8 mm, Pixel bandwidth = 240 Hz. A fieldmap for distortion correction was also acquired: TR/TE = 7220 ms/73 ms, FoV = 248 × 248 mm, in-plane voxel resolution = 3.0 × 3.0 × 3.0 mm, 56 slices.

For Voxel-Based Morphometry (VBM), tools from FMRIB Software Library (FSL v5.0.1) were used for automated segmentations of subcortical regions and whole-brain probability maps. Automated segmentations were obtained through the FIRST model-based segmentation and registration tool (Patenaude et al., 2011). Whole-brain maps were prepared through the FSL-VBM analysis pipeline (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FSLVBM) following standard automated processing (Ashburner and Friston, 2000; Good et al., 2001). Images were brain-extracted and segmented before non-linear registration to Montreal Neurological Institute (MNI) standard space (Andersson et al., 2007). Resulting images were averaged to create a study-specific template, to which native images were non-linearly registered and modulated. The modulated segmented images were smoothed with an isotropic Gaussian kernel with a sigma of 3, yielding full-width half-maximum (FWHM) of 6.9 mm. Resulting subject-specific probability maps were input into general linear models (GLMs) via FSL's Randomise program. Models were corrected for multiple comparisons through Monte Carlo simulations with 5000 permutations and threshold free cluster enhancement for whole-brain corrected $p < 0.05$.

For Surface-Based Morphometry (SBM), FreeSurfer v5.3 (https://surfer.nmr.mgh.harvard.edu/) standard processing was used to perform cortical reconstruction and volumetric segmentation. These methods included skull stripping, Talairach transformation, and segmentation and parcellation of cortical and subcortical regions (Dale et al., 1999; Fischl et al., 2004). Resulting subject-specific volume maps were input into GLMs in FreeSurfer's Qdec with multiple comparison correction through Monte Carlo simulations for $p < 0.05$.

2.4. Statistical analyses

Power analysis (conducted in G*Power 3.1; Faul et al., 2009) suggested ability to detect a moderate effect size (f^2 = 0.15) at two-tailed alpha of 0.05 and power level of at least 0.80 for a single regression coefficient in linear multiple regression in the full sample (N = 56) for neuroimaging data, although power dropped to 0.64 for the sample with cognitive data (N = 38). Continuously scaled variables were examined for normality of distributions according to the Shapiro–Wilk test. Age (μ = 68.29, SD = 5.66, median = 67.50, range = 60–83) and depression symptoms (μ = 4.38, SD = 4.10, median = 4.00, range = 0–18) were positively skewed and were log transformed prior to further analysis.

Independent samples t-tests were conducted for automated segmentation values for global volumes (CSF, total gray matter, and total white matter in VBM; SBM additionally included bilateral cerebellum gray and white matter) and subcortical volumes (brainstem, accumbens, amygdala, caudate, hippocampus, pallidum, putamen, and thalamus bilaterally for a total of 15 segmentations). Additional independent samples t-tests were conducted for each of the 7 cognitive test age-normed scores and the total composite score. All tests were subjected to false discovery rate (FDR) correction (Radua and Albajes-Eizagirre, 2019, https://www.sdmproject.com/utilities/?show=FDR). Whole-brain GLMs that included terms for group, age, and BDI-II score were then run in VBM (volume) and SBM (volume and cortical thickness). Effect sizes are reported as η_p^2 values (0.01: small; 0.09: medium; 0.25: large; Cohen et al., 2003). Bivariate Pearson's r correlations examined associations between extracted volumes showing significant group differences and the 8 cognitive performance scores. Correlations were also corrected according to FDR. Finally, post hoc analyses investigated whether adding AUDIT score or total intracranial volume as a covariate in GLMs changed group results; and whether region volumes showing group difference were correlated with age.

3. Results

3.1. Sample characteristics

Sample characteristics are presented in Table 1. None of the participants were current tobacco users. Nonusers endorsed slightly greater symptoms of depression [$t(54)$ = 1.99, p = 0.05]. Users were significantly younger than nonusers [$t(54)$ = 2.06, p = 0.04]. Depression symptoms and age were therefore included as covariates in neuroimaging analyses. Groups did not otherwise significantly differ in demographics, alcohol use, or anxiety symptoms.

Overall, the user group (n = 28) was heterogeneous in terms of cannabis use metrics. On average, users reported average age of first use of 20.04 years (SD = 8.11, range 14–58 years) and 23.55 years of regular cannabis use (SD = 19.89, range 1.5–50 years, median 19.5 years). Users reported an average of less than 1 dependence symptom (M = 0.79, SD = 1.17), although 25% of the user group could possibly

Table 1
Sample characteristics and cognition age standard scores.

	Nonusers Mean (SD; range)	Cannabis users Mean (SD; range)	$t^{\dagger}$	p
Demographics	$N = 28$	$N = 28$		
Race/Ethnicity			4.32‡	0.12
White	23	27		
Hispanic/Latino	1	1		
Asian	4	0		
Females:Males	17:11	10:18	3.50‡	0.06
Age	69.79 (5.71; 61–83)	66.79 (5.28; 60–80)	2.06	0.04
Years education	16.29 (2.59; 12–22)	16.46 (2.33; 13–22)	−0.27	0.79
AUDIT total score	3.39 (2.22; 0–9)	4.14 (3.66; 0–18)	−0.93	0.36
BDI-II total score	5.00 (3.36; 0–11)	3.75 (4.71; 0–18)	1.99	0.05
BAI total score	3.68 (4.35; 0–21)	2.39 (2.83; 0–12)	1.31	0.20
90-day Timeline Follow-Back	$N = 10$	$N = 28$		
Alcohol use days	27.30 (34.724; 0–88)	33.89 (29.59; 0–88)	−0.58	0.57
Drinks per drinking day	1.18 (0.88; 0–3)	1.50 (1.02; 0–4)	−0.86	0.40
Cannabis use days	0.00 (0.00; 0–0)	63.46 (24.87; 12–90)	−8.00	<0.001
NIH Toolbox Cognition Battery	$N = 10$	$N = 28$		
Picture vocabulary	113.60 (9.71; 93–124)	118.39 (8.54; 102–135)	−1.47	0.15
Flanker inhibitory control	97.90 (8.41; 89–117)	93.25 (11.85; 71–123)	1.14	0.26
List sorting working memory	112.00 (10.65; 100–132)	103.21(11.81; 84–127)	2.07	0.05
Dimensional change card sort	119.30 (12.97; 99–147)	112.46 (17.34; 87–151)	1.14	0.26
Pattern comparison processing speed	94.40 (22.54; 57–140)	94.75 (20.69; 49–128)	−0.05	0.96
Picture sequence memory	94.10 (19.40; 76–136)	94.86 (12.77; 73–123)	−0.14	0.89
Oral reading	107.80 (12.97; 77–125)	111.04 (8.16; 95–123)	−0.92	0.37
Total composite	109.50 (13.67; 91–138)	108.87 (10.96; 86–129)	0.15	0.88

SD: standard deviation; AUDIT: Alcohol Use Disorders Identification Test; BDI-II: Beck Depression Inventory-second edition; BAI: Beck Anxiety Inventory; NIH: National Institutes of Health.
† $df = 54$ for demographics and $df = 36$ for Timeline Follow-Back and NIH toolbox; ‡Pearson Chi-Square.

meet criteria for mild to moderate CUD [$n = 6$ endorsed 2–3 symptoms (mild), and $n = 1$ endorsed 4 symptoms (moderate)]. On the TLFB, $n = 16$ users reported smoking, $n = 9$ reported consuming edibles, and $n = 3$ reported both smoking and consuming edibles in the past 90 days. A total of $n = 7$ participants were able to report a preference for strength of cannabis strain in terms of THC content ($n = 3$ preferred THC of 20% and $n = 4$ preferred THC of 25% or greater), and $n = 1$ participant reported having grown the same strain on her property for the last 40–50 years (assumed 4% THC content; ElSohly et al., 2016). The majority of participants ($n = 20$) were unsure of strain characteristics and may be assumed to consume cannabis with average THC content (15% in Colorado; Vergara et al., 2017). Depression and anxiety symptoms were not significantly correlated with estimated years of regular cannabis use or TLFB cannabis use days (all $p > 0.22$).

3.2. Automated segmentations

Users and nonusers were not different in total intracranial volume, and it was therefore not included as a covariate in initial analyses. See Table 2 for VBM results and Table 3 for SBM results. No group differences were observed in total volume of CSF, gray matter, or white matter in VBM or SBM (including cerebellum measures). In subcortical regions and accounting for age and depression symptoms, users showed greater VBM volume than nonusers in left putamen [$F(1,53) = 11.49$, FDR corrected $p = 0.02$, $\eta_p^2 = 0.18$], and in right putamen and left pallidum, though those latter effects did not survive FDR correction. Bilateral putamen volume was also greater in users than nonusers in SBM, but this effect also did not survive FDR correction.

Age showed expected negative associations with gray matter and positive associations with CSF. Among subcortical regions, age was most negatively associated with hippocampal volume, followed by thalamus, accumbens, and amygdala. BDI-II score was not significantly associated with any volumetric measure.

3.3. Whole-brain GLMs

No group differences survived multiple comparison correction in VBM. In SBM, users showed greater cortical volume than nonusers in left lingual cortex (cluster size = 1618 mm^2, peak $t = 3.62$, $\eta_p^2 = 0.21$) and rostral middle frontal cortex (cluster size = 1433 mm^2, peak $t = 3.89$, $\eta_p^2 = 0.21$). No group differences in cortical thickness survived multiple comparison correction.

3.4. Cognitive performance

Users and nonusers were not different in cognitive performance (see Table 1), and no scores fell below the average range. Cognitive scores were not significantly correlated with extracted volumes for left putamen (all $p > 0.25$), lingual cortex (all $p > 0.08$), or rostral middle frontal cortex (all $p > 0.17$).

3.5. Post hoc analyses

Group difference results did not change with AUDIT score or total intracranial volume added as a covariate. Of the three regions of group difference, only left putamen volume was correlated with age [$r(54) = -0.42$, FDR corrected $p < 0.05$]. When tested within groups, this association was stronger in users [$r(26) = -0.45$, FDR corrected $p < 0.05$] than nonusers [$r(26) = -0.26$, $p = 0.19$], although the test of the group by age interaction was not significant.

Table 2
Automated segmentation volumes across groups in Voxel-Based Morphometry (VBM).

	Group Mean (SD)		Group			Age			Depression		
	Nonusers	Cannabis Users	*F*	*p*	η_p^2	*F*	*p*	η_p^2	*F*	*p*	η_p^2
Total CSF	347,167.35 (46,431.81)	344,613.77 (49,450.72)	0.70	0.41	0.01	10.49	0.002	0.17	0.57	0.46	0.01
Total GM	544,940.84 (56,434.98)	571,053.79 (50,728.65)	1.65	0.20	0.03	10.01	0.003	0.16	1.21	0.28	0.02
Total WM	499,086.66 (63,912.68)	525,944.87 (54,508.67)	2.44	0.12	0.05	2.08	0.16	0.04	1.09	0.30	0.02
Brainstem	22,231.39 (2959.62)	22,288.51 (2423.18)	0.05	0.83	0.00	0.03	0.87	0.00	0.53	0.47	0.01
Accumbens L	397.59 (118.93)	466.60 (119.80)	2.24	0.14	0.04	8.52	0.005	0.14	0.24	0.63	0.00
Accumbens R	317.90 (117.51)	376.87 (104.74)	1.68	0.20	0.03	11.43	0.001	0.18	0.47	0.50	0.01
Amygdala L	1230.78 (390.56)	1256.96 (235.70)	0.21	0.65	0.00	0.21	0.65	0.00	0.13	0.72	0.00
Amygdala R	1295.56 (334.37)	1367.20 (254.06)	0.07	0.79	0.00	6.62	0.01	0.11	0.06	0.80	0.00
Caudate L	3259.86 (409.06)	3415.17 (436.25)	1.38	0.25	0.03	2.87	0.10	0.05	1.51	0.22	0.03
Caudate R	3452.09 (440.96)	3529.40 (468.47)	0.41	0.52	0.01	1.20	0.28	0.02	1.71	0.20	0.03
Hippocampus L	3580.54 (484.90)	3577.36 (553.71)	1.06	0.31	0.02	5.29	0.03	0.09	2.61	0.11	0.05
Hippocampus R	3584.26 (454.17)	3579.02 (513.68)	2.34	0.13	0.04	17.32	<0.001	0.25	2.52	0.12	0.05
Pallidum L*	1578.93 (291.00)	1838.94 (437.883)	4.38	0.04	0.08	1.50	0.23	0.03	0.49	0.49	0.01
Pallidum R	1653.28 (198.65)	1778.14 (357.88)	1.27	0.27	0.02	0.88	0.35	0.02	0.22	0.65	0.00
Putamen L**	4005.98 (639.95)	4645.50 (539.89)	11.49	0.001	0.18	6.74	0.01	0.12	0.29	0.60	0.01
Putamen R*	4298.97 (535.40)	4746.22 (574.18)	6.80	0.01	0.12	5.59	0.02	0.10	1.35	0.25	0.03
Thalamus L	7013.23 (807.39)	7239.75 (670.24)	0.43	0.52	0.01	9.07	0.004	0.15	1.39	0.24	0.03
Thalamus R	6839.06 (785.00)	7071.99 (611.90)	0.62	0.43	0.01	7.83	0.007	0.13	1.34	0.25	0.03

SD: standard deviation; CSF: cerebrospinal fluid; GM: gray matter; WM: white matter; L: left; R: right.
* $p \leq 0.05$ uncorrected group difference.
** $p < 0.05$ FDR corrected.

4. Discussion

This study compared overall brain structure and cortical and subcortical gray matter between adults 60 years and older who were current cannabis users or nonusers. Users and nonusers did not differ in terms of total CSF, gray, or white matter volume, but users showed greater regional volume of left putamen, lingual cortex, and rostral middle frontal cortex, and these were medium to large in effect size. These results suggest that cannabis use does not have a widespread impact on overall cortical volumes while controlling for age, despite over two decades of regular cannabis use on average. This is in contrast to the large, widespread effects of alcohol on cortical volumes (e.g., Thayer et al., 2016) that might be expected to negatively impact cognitive performance (Draganski et al., 2013). However, other studies have also documented regional differences; specifically, larger volume of putamen in cannabis users compared to controls (Moreno-Alcázar et al., 2018). Regional differences in putamen, lingual gyrus, and middle frontal cortex, which are implicated in default mode and salience networks (Shirer et al., 2012), may reflect alteration in functional connectivity and reward processing as reported in recent meta-analyses (Blest-Hopley et al., 2018; Yanes et al., 2018).

To our knowledge there have been no other neuroimaging investigations of cannabis use among older adults. The existing structural neuroimaging literature on younger adult users presents mixed results including cannabis use-related differences in volume (Gruber and Sagar, 2017), as well as evidence that most brain regions are not structurally impacted by cannabis use in any systematic way (Gillespie et al., 2018; Thayer et al., 2017). Additionally, a recent meta-analysis on the impact of cannabis use on cognitive function among young adults found an overall small effect size and further diminished effects

Table 3
Automated segmentation volumes across groups in Surface-Based Morphometry (SBM).

	Group Mean (SD)		Group			Age			Depression		
	Nonusers	Cannabis Users	*F*	*p*	η_p^2	*F*	*p*	η_p^2	*F*	*p*	η_p^2
Total CSF	37,842.20 (18,202.86)	34,362.57 (17,178.59)	0.01	0.91	0.00	5.13	0.03	0.09	0.82	0.34	0.02
Total GM	590,305.18 (59,386.63)	619,591.68 (57,294.15)	2.21	0.14	0.04	4.62	0.04	0.08	0.63	0.43	0.01
Total WM	426,519.82 (63,090.83)	453,441.07 (49,634.46)	2.42	0.13	0.04	4.80	0.03	0.09	1.31	0.26	0.03
Cerebellum GM L	51,004.42 (6594.29)	51,404.09 (5748.23)	0.05	0.82	0.00	0.38	0.54	0.01	0.43	0.52	0.01
Cerebellum GM R	52,475.52 (7023.73)	51,736.27 (5798.43)	0.09	0.77	0.00	0.24	0.63	0.01	0.84	0.36	0.02
Cerebellum WM L	14,281.41 (2190.61)	14,475.29 (1588.37)	0.22	0.64	0.00	0.47	0.50	0.01	1.35	0.25	0.03
Cerebellum WM R	13,982.95 (1990.89)	14,131.41 (1515.82)	0.01	0.94	0.00	2.28	0.14	0.04	0.47	0.50	0.01
Brainstem	22,305.59 (3152.59)	22,210.70 (2246.69)	0.00	0.96	0.00	0.03	0.86	0.00	0.70	0.41	0.01
Accumbens L	376.76 (71.68)	400.78 (66.13)	1.18	0.28	0.02	4.49	0.04	0.08	2.21	0.14	0.04
Accumbens R	430.40 (115.56)	484.00 (87.33)	1.06	0.31	0.02	12.69	0.001	0.20	0.02	0.89	0.00
Amygdala L	1346.26 (233.17)	1446.04 (218.19)	1.33	0.25	0.03	2.43	0.13	0.05	0.00	0.95	0.00
Amygdala R	1380.87 (217.46)	1489.25 (186.06)	0.94	0.34	0.02	8.85	0.004	0.15	0.96	0.33	0.02
Caudate L	3533.27 (546.16)	3601.89 (523.33)	0.12	0.73	0.00	1.75	0.19	0.03	0.75	0.39	0.01
Caudate R	3612.26 (609.64)	3686.73 (519.61)	0.32	0.57	0.01	0.70	0.41	0.01	0.92	0.34	0.02
Hippocampus L	3779.68 (554.35)	3920.44 (389.08)	0.13	0.72	0.00	22.16	<0.001	0.30	1.78	0.19	0.03
Hippocampus R	3915.53 (557.22)	4115.04 (451.93)	0.00	0.95	0.00	41.94	<0.001	0.45	0.52	0.48	0.01
Pallidum L	1258.75 (264.53)	1325.29 (198.96)	0.93	0.34	0.02	0.28	0.60	0.01	0.35	0.56	0.01
Pallidum R	1360.40 (198.87)	1414.18 (219.13)	0.15	0.70	0.00	4.60	0.04	0.08	0.02	0.89	0.00
Putamen L*	4383.21 (631.82)	4799.24 (589.61)	3.96	0.05	0.07	4.38	0.04	0.08	0.19	0.66	0.00
Putamen R*	4172.16 (626.54)	4616.03 (535.70)	4.37	0.04	0.08	6.30	0.02	0.11	0.00	0.98	0.00
Thalamus L	7439.15 (937.66)	7806.45 (1122.40)	0.95	0.34	0.02	8.10	0.006	0.14	2.33	0.13	0.04
Thalamus R	6613.48 (892.27)	6980.99 (784.23)	1.95	0.17	0.04	6.79	0.01	0.12	2.11	0.15	0.04

SD: standard deviation; CSF: cerebrospinal fluid; GM: gray matter; WM: white matter; L: left; R: right.
* $p \leq 0.05$ uncorrected group difference.

with abstinence longer than 72 h (Scott et al., 2018). While the volumetric decreases reported in previous studies in regular cannabis users (e.g., reduced hippocampus; e.g., Lorenzetti et al., 2016a) were absent in the current study, emerging research suggests that some structural changes may be related to CUD rather than regular use (e.g., Chye et al., 2017; Lorenzetti et al., 2016b). Thus, the low symptom endorsement in the current sample may reflect an accurate representation of older adult users who do not have CUD. The strongest correlate of hippocampal volume in this sample was age rather than cannabis use, consistent with other studies (Bettio et al., 2017). Interestingly, of the three regions that were different between users and nonusers, only left putamen volume was negatively correlated with age, with a larger correlation in users than nonusers. This preliminary finding may suggest an interaction effect of age and cannabis use similar to other substances (Sullivan et al., 2018; Thayer et al., 2016), and this trend should be tested in future studies with larger sample sizes.

The current study was tightly focused on older adults, but also attempted to address several pitfalls that have limited prior research examining associations between cannabis use and brain structure (e.g., other drugs like alcohol, mental health symptoms; Curran et al., 2016). Groups were carefully examined for differences in reported recent alcohol use and contributions of depression and anxiety, as well as the major contributing factor of age to brain structure (e.g., Thayer et al., 2016). However, this study was exploratory and impacted by important limitations, most importantly in that it was cross-sectional. While several longitudinal studies exist among young adults (e.g., Koenders et al., 2017), such studies have not yet been done in older adults and would be challenging given very long periods of use. The sample size for neuroimaging was powered to detect moderate effect size, and cognitive performance analyses were underpowered. The NIH Toolbox Cognition Battery (Gershon et al., 2013) has well-validated age norms but is best conceptualized as a cognitive screen, given that it includes a single estimate of performance for each of the tested cognitive domains. While exclusion criteria addressed many health problems in attempting to isolate the association of cannabis use with brain structure and cognitive performance, it is possible that as a result these participants may be in better health than the general older adult population. These participants were also highly educated, which may impact both brain regional volumes and cognitive performance from the perspective of cognitive reserve (e.g., O'Shea et al., 2018).

Finally, the most significant limitations of the current study relate to challenges in measuring cannabis use, which is a well-known limitation across the literature (Volkow et al., 2016). The current study recruited broadly for current users, and the resulting sample was heterogeneous in duration of use, frequency of use, and method of consumption, all of which may impact study results. While the average THC concentration in legally available cannabis in Colorado is 15% (Vergara et al., 2017), the majority of participants could not report a preference for strain or THC concentration. Future studies should consider conducting thorough interviews to capture any information available about strain preference, particularly over time. Further, although formulas exist for equating exposure considering factors such as how much THC is lost burning cannabis flower product (e.g., suggested by the State of Colorado; Orens et al., 2015), consuming THC via edibles versus smoking results in different rates of metabolism (e.g., Newmeyer et al., 2017) and therefore likely impacts the concentration of THC available to reach the brain. Given the popularity of edible consumption in the current study (i.e., 43% of users reported primarily consuming edibles or using both edibles and smoking), further study of this issue is warranted.

The current study was able to explore cannabis use in a novel older adult population that has seen recent dramatic increases in cannabis use (Han and Palamar, 2018), while controlling for likely confounding variables (e.g., alcohol use). The participants in this study were generally healthy and highly educated, and it is in this context that cannabis use showed limited effects on brain structural measures or cognitive performance. Future work should examine a broader range of older adult cannabis users to explore whether there are subgroups for whom cannabis may represent a health risk, with the goal of better informing public health recommendations.

Conflicts of interest

None.

Acknowledgment

This work was supported by the National Institutes of Health [grant numbers R36DA040020, R01AG043452].

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