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Sex differences in normative modeling of cortical thickness in cannabis use disorder

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HIGHLIGHTS

- Sex differences in brain normative modeling of cannabis use disorder are unknown.
- Average z-scores across all regions were within the normal range for both sexes.
- Females had greater cortical thickness z-scores than males around the central and lateral sulci.
- 3 sexually dimorphic regions were associated with cannabis-related problems.
- Investigations into the biological mechanisms implicated in these sex differences are warranted.

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ABSTRACT

Cannabis use disorder (CUD) is associated with sexually dimorphic behavioral and neurobiological effects, but sex differences in a broader sampling of brain structures in CUD assessed relative to normative reference values have not been examined. Here, we assessed sex differences in brain regions measured via 3 T MRI in 72 adults (50 males, 22 females) with CUD. T1-weighted images, segmented via FreeSurfer, were used to derive Normative Morphometry Imaging Statistics z-scores (accounting for age, sex, intracranial volume, and image quality). Z-scores were then compared between sexes and associated with behavioral data. We found that average z-scores were within normative ranges for both sexes. There were no sex differences in total brain, cerebral white matter, and subcortical gray matter z-scores, but total cortical thickness z-scores were greater in females. Fourteen cortical regions surrounding the central and lateral sulci had greater z-scores in females than in males, but the medial orbitofrontal cortex z-score was greater in males. Of these regions, 3 were positively correlated with cannabis-related problems. Findings suggest sexual dimorphism in brain structure in CUD primarily in the frontal, medial parietal, and superior temporal lobes, with some association with cannabis-related problems even in the context of normative brain structure. Future research is needed to clarify causal mechanisms of morphometric differences in CUD.

1. Introduction

In 2020, estimated global prevalence of cannabis use disorder (CUD) was 23.8 million people (Shah et al., 2024). Cannabis use is most prevalent in North America (United Nations Office on Drugs and Crime, 2024), and in the United States nearly 7 % of individuals aged 12 or

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older meet past-year DSM-5 criteria for cannabis use disorder (CUD) (SAMHSA, 2024). While more men use cannabis and meet criteria for CUD than women (Hasin et al., 2015; Kerridge et al., 2018), the gender gap in cannabis use is narrowing (Chapman et al., 2017). As cannabis use continues to increase among women (SAMHSA, 2020), so too does the need to study sex differences in CUD in order to best inform treatment development. Behaviorally, women progress more quickly from first use to CUD (Kerridge et al., 2018; Khan et al., 2013)—a phenomenon referred to as "telescoping"—and report more severe cannabis withdrawal (Herrmann et al., 2015) relative to men. Contrasting these well-characterized behavioral trends, investigations of sex differences in in vivo brain morphometry of heavy cannabis use in humans have remained limited thus far, and those conducted have shown disparate results.

Small studies comparing adults that use cannabis and healthy controls using structural brain MRI have found no evidence of sex differences in gray matter volumes (Chye et al., 2019, 2017b; Cousijn et al., 2012; Garimella et al., 2020; Price et al., 2015), although notably three of these studies were focused only on the hippocampus and its subregions (Chye et al., 2019, 2017b; Garimella et al., 2020). In contrast, larger studies have found significant group-by-sex interactions whereby individuals that use cannabis heavily, particularly females, had lower cerebellar and lateral orbitofrontal cortical volume than controls (Chye et al., 2017a; McPherson et al., 2021; Rossetti et al., 2021). Of note, all these studies limited their analyses to the hippocampus, insula, cingulate, orbitofrontal cortex, and/or the cerebellum. While the a priori selection of regions was well-motivated (these regions being known for high cannabinoid receptor expression), these are unlikely to be the only regions upon which cannabis may impart effects. In addition, these studies used study-specific controls. Particularly in studies with small sample sizes, this design may introduce bias if controls are not representative of the broader population.

Thus, the aim of the present study was to examine sex differences in brain regions using measures derived from normative modeling, which is a nascent but growing approach in neuropsychiatric disorders (e.g. ENIGMA Clinical High Risk for Psychosis Working Group, 2024). With normative modeling, one can evaluate the extent to which individual-level measures of a comprehensive set of brain regions deviate from the same measures obtained from a large, normative reference population. The use of a normative reference population improves generalizability over reliance on smaller, locally-recruited control samples, which may be subject to selection bias and therefore compromise internal validity (Savitz and Wellenius, 2016). When normative modeling-derived z-scores are compared by sex, the results indicate differences in each group's deviation from their age- and sex-matched peers; such scores provide insights into the potential clinical significance of observed deviations from healthy brain trajectories. We therefore tested for differences in normed z-scores between males and females with CUD using baseline data from two clinical trials. Of regions that demonstrated a sex difference, we examined whether these z-scores correlated with relevant behavioral variables to substantiate their potential clinical relevance. Given the existing literature on behavioral and morphometric sex differences in CUD, we hypothesized that females with CUD would demonstrate normatively lower z-scores than males, and that z-scores would be associated with adverse self-reported consequences of cannabis use.

2. Material and methods

2.1. Participants

The present study used pre-treatment baseline data from two clinical trials for CUD at the Medical University of South Carolina. Trials examined the use of a pharmacological intervention (varenicline, $n = 37$;NCT02892110) (McRae-Clark et al., 2021) or repetitive transcranial magnetic stimulation (TMS, n = 36; NCT03144232) (Sahlem et al., 2024) on symptoms of CUD. Trial enrollment was based on participant interest, availability, and minor differences in inclusion/exclusion criteria (e.g. varenicline sensitivity). Both trials were approved by the Medical University of South Carolina Institutional Review Board (IRB) and the TMS trial was additionally approved by the Stanford University IRB. Both trials were conducted in accordance with the Declaration of Helsinki.

Overall inclusion criteria for these trials were similar: individuals had to be seeking treatment for cannabis use, meet criteria for DSM-5 CUD, be at least 18 years old, and report cannabis use at least 3 days per week in the past month. Individuals were excluded from study participation if they met criteria for a moderate or severe substance use disorder other than cannabis or tobacco use disorder; were pregnant or breastfeeding; had lifetime incidence of a bipolar or psychotic disorder, or had an untreated depressive or anxiety disorder; experienced recent suicidality; were prescribed psychiatric medications other than non-MAOI antidepressants, non-benzodiazepine anxiolytics, or medications for attention deficit/hyperactivity disorder; or had any other unstable general medical conditions. Individuals were excluded from imaging procedures for ferromagnetic metal implant(s), use of a pacemaker or cardiac defibrillator, or severe claustrophobia. One participant enrolled in the varenicline trial was excluded from the present analysis for excessive head motion in the scanner. The final sample included 72 participants (50 males, 22 females).

2.2. Procedures

Participants were primarily recruited through media and online advertisements. Interested individuals completed a brief phone screening followed by an extended screening visit to assess the above eligibility criteria. Informed consent was provided prior to the in-person extended screening visit. If eligible, participants completed the behavioral and imaging procedures included in this study prior to receipt of experimental treatment.

Participant sex was determined by self-report during a physical exam conducted as part of screening procedures. Participants completed self-report measures of cannabis craving (Marijuana Craving Questionnaire; MCQ) (Heishman et al., 2001), cannabis-associated problems (Marijuana Problems Scale; MJPS) (Stephens et al., 2000), and impulsivity (Barratt Impulsiveness Scale; BIS) (Patton et al., 1995). Subscale scores for the MCQ (compulsivity, emotionality, expectancy, purposefulness) and BIS (non-planning, cognitive/attentional, motor) were computed in addition to total scores. Age of first cannabis use and age of lifetime heaviest cannabis use onset were also obtained via self-report. Cannabis use disorder severity and other psychiatric conditions were assessed using the Mini-International Neuropsychiatric Interview (MINI) (Sheehan, 2015) for the varenicline study; for the TMS study, CUD severity was determined using the Structured Clinical Interview for DSM-5 (SCID) (First, 2015).

Cannabis, tobacco, and alcohol use in the 28 days prior to imaging were estimated using the Time-Line Follow-Back method (TLFB) (Sobell and Sobell, 1992). Cannabis use was quantified as both days when any cannabis was used and as the number of individual "sessions" per day, defined as distinct cannabis use periods separated by at least one hour of non-use. Urine cannabinoid levels were assessed using semi-quantitative enzyme immunoassay (Abbott MULTIGENT®) and normalized using simultaneous urine creatinine to control for dilution (Cone et al., 2009).

2.3. MRI acquisition and normative modeling

Participants were instructed to abstain from cannabis and alcohol use for 24 hours prior to scanning and abstinence was confirmed via saliva sample (SalivaConfirm®; Confirm Biosciences, Inc.). A six-panel saliva drug test (HE-SWI-264) was used to confirm abstinence from amphetamine, cocaine, methamphetamine, opioids, and benzodiazepines, as well as THC. T1-weighted MRI was obtained from a single site

using a Siemens 3 T Prisma (Siemens Healthineers). The parameters of the magnetization-prepared rapid gradient-echo sequence were: TR/TE= 1900/2.26 ms; FA= 9°; FOV= 256 mm^2; voxel size= 1 mm^2; slice thickness= 1 mm; number of slices= 192. All data passed visual quality control examination using standardized operating procedures (Backhausen et al., 2016).

Individual participant T1-weighted images were segmented using FreeSurfer v6.0 recon-all (Fischl et al., 2002). This command produces an aseg.stats file for each participant containing volumetric and cortical thickness measurements. Thus, there is no co-registration or normalization across subjects; all image segmentation occurs in subject space. The aseg.stats file for each participant was then input into the NOrmative Morphometry Image Statistics (NOMIS) software which computes normative z-scores of participant-level measurements relative to a large sample of healthy adults ages 18–100 (n = 6909), accounting for age, sex, intracranial volume, and image quality (Potvin et al., 2022, 2017, 2016). The normative values for 1344 FreeSurfer-segmented brain regions were derived from k-fold cross-validated regression models, using which participant-level normative z-scores can be generated via a freely available Python-based script (https://github.com/medicslab/NOMIS).

2.4. Statistical analyses

Sex differences in demographic and behavioral characteristics were assessed using Welch's t-test, Wilcoxon rank sum test, or Fisher's exact test as appropriate. Relative sex representation from each study included in the combined analysis was assessed via Chi-square test. A top-down approach to morphometric analysis was used to minimize type I error; the exception to this approach was focused analyses of hippocampal and cerebellar z-scores, with the intention of replicating sex analyses previously reported in the literature (Chye et al., 2019, 2017b; Garimella et al., 2020; McPherson et al., 2021). That is, sex differences in z-scores of gross segmentations (i.e. whole brain [brainsegvol], total cerebral white matter [cerebralwhitemattervol], total subcortical gray matter [subcortgrayvol], and total cortical thickness [cortexvol]) were first assessed using Welch's t-tests. If significant differences were found in these larger segmentations, individual regions within that domain were compared using Welch's t-tests to identify the specific regions driving these gross sex differences. Effect sizes for sex differences were calculated using Cohen's d. To address potential for confounding, additional analysis of covariance (ANCOVA) testing using Type-III Sum of Squares was conducted including significant demographic or behavioral differences as covariates in addition to a main effect of sex; effect sizes for ANCOVA were calculated using partial eta-squared (η^2). Any reported past-month cigarette smoking was included as a covariate in all ANCOVA tests due to known impacts of smoking on cortical thickness (Karama et al., 2015) though no sex differences in smoking behavior were observed in our sample. Regions with statistically significant sex differences in z-scores were correlated with behavioral outcomes using general linear models (GLMs) with sex included as an interaction term; results are presented as betas (β) and associated standard errors (SE). Follow-up sensitivity analyses including relevant demographic or behavioral variables and past-month cigarette smoking were conducted for GLMs demonstrating a significant association between morphometric outcomes and self-reported behavioral measures. Significance for all statistical testing was indicated at $p < 0.05$. Given the large number of regions assessed for sex differences in thickness, the Benjamini-Hochberg procedure was used to control false discovery rate (Benjamini and Hochberg, 1995). Adjusted p-values (p_{adj}) were generated for all cortical thickness comparisons and are presented alongside p-values generated from t-tests. Analyses were conducted in R (Version 4.2.2).

3. Results

3.1. Demographics and cannabis use characteristics

Participants were 31 years old on average (*SD*=9.8; range=18–64), were predominantly non-Hispanic white (61 %), unmarried (71 %), and about half had at least some post-secondary education (53 %). There were no sex differences in demographic characteristics (Table 1). There also were no sex differences in CUD severity, impulsivity, or recent cannabis, alcohol, or tobacco use. While no sex difference was observed in age of first cannabis use (*W*=401, $p = 0.084$), males reported an earlier onset of lifetime heaviest cannabis use relative to females (*W*=334, $p = 0.011$). Sex differences were also observed in cannabis craving as assessed by the MCQ (*W*=387, $p = 0.046$), particularly in the compulsivity (*W*=388, $p = 0.047$) and expectancy subscales (*W*=385, $p = 0.044$), for which scores were higher in females. To account for a sex difference in heaviest use onset that may affect brain structure, sensitivity analyses were conducted that included age of heaviest use onset as a covariate.

3.2. Sex differences in normative morphometric imaging statistics

Average z-scores across all regions were well within ± 1.0 standard deviations of the normative z = 0 mean for both males and females. No sex differences were observed in whole brain (Males: M=-0.36, SD=1.84; Females: M=0.29, SD=1.22), total cerebral white matter (Males: M=-0.08, SD=1.45; Females: M=0.24, SD=1.18), or total subcortical gray matter (Males: M=0.27, SD=1.51; Females: M=0.26, SD=1.01) volume z-scores (all p's > 0.05). However, a significant sex difference was observed in total cortical thickness ($t(59) = 3.01$, $p = 0.004$, Cohen's d= 0.71), wherein males had lower z-scores (M=-0.62, SD=1.47) than females (M=0.26, SD=0.97). (Because z-scores for all cortical regions were significantly correlated across hemispheres [Supplementary Table 1], bilateral averages were used in subsequent analyses.) This effect appeared to be driven by sex differences in 15 cortical regions predominantly in the frontal and parietal lobes (Fig. 1; Table 2). All regions showing significant sex differences had greater cortical thickness z-scores in females relative to males except the medial orbitofrontal cortex, which was greater in males (Fig. 2). Thickness z-scores in these regions were, on average, positive in females and negative in males, except the medial orbitofrontal cortical thickness z-scores which were on average negative for both sexes.

Of the 15 cortical regions showing sex differences via *t*-test, sensitivity analyses that included age of heaviest use onset and any past-month cigarette smoking in the model confirmed statistical significance in 9 regions: the superior frontal gyrus ($F(1,68)= 4.56$, $p = 0.037$, partial $\eta^2= 0.09$), caudal middle frontal gyrus ($F(1,68)= 4.18$, $p = 0.030$, partial $\eta^2= 0.10$), pars opercularis ($F(1,68)= 7.34$, $p = 0.009$, partial $\eta^2= 0.14$), precentral gyrus ($F(1,68)= 8.50$, $p = 0.005$, partial $\eta^2= 0.11$), paracentral gyrus ($F(1,68)= 5.15$, $p = 0.027$, partial $\eta^2= 0.10$), medial orbitofrontal cortex ($F(1,68)= 8.84$, $p = 0.004$, partial $\eta^2= 0.09$), postcentral gyrus ($F(1,68)= 6.26$, $p = 0.015$, partial $\eta^2= 0.10$), supramarginal gyrus ($F(1,68)= 8.99$, $p = 0.004$, partial $\eta^2= 0.14$), and cuneus ($F(1,68)= 4.77$, $p = 0.033$, partial $\eta^2= 0.08$). Each of these regions maintained significant sex differences when controlling for false discovery rate, except for the medial orbitofrontal cortex.

Hippocampal and cerebellar gray matter z-scores were additionally compared across sexes to replicate previous work (averaged bilaterally, given the significant correlations across hemispheres; see Supplementary Table 2). A significant sex difference was observed in cerebellar ($p = 0.030$), but not hippocampal ($p = 0.613$) z-scores; cerebellar z-scores were greater in males relative to females. This sex difference did not maintain statistical significance after covarying for age of heavy cannabis use onset and past-month cigarette smoking.

Table 1
Demographic, behavioral, and substance use variables by sex.

	Males	*n*	Females	*n*	*p*-value
Demographics					
Age (years)	29.7 ± 7.9	50	33.5 ± 12.8	22	0.200[a]
Race, n (%)		50		22	0.272[b]
African-American	14 (28.0 %)		8 (36.4 %)		
Non-Hispanic White	30 (60 %)		14 (63.6 %)		
Other	6 (12.0 %)		0 (0.0 %)		
Married, n (%)	11 (22.0 %)	50	9 (40.9 %)	21	0.089[b]
Education, n (%)		50		22	0.147[b]
Less than high school	3 (6.0 %)		1 (4.6 %)		
High school	22 (44.0 %)		8 (36.4 %)		
2-year degree	10 (20.0 %)		3 (13.6 %)		
4-year degree	15 (30.0 %)		7 (31.8 %)		
Graduate degree	0 (0.0 %)		3 (13.6 %)		
Study, n (%)		50		22	1.000[c]
TMS	25 (50.0 %)		11 (50.0 %)		
Varenicline	25 (50.0 %)		11 (50.0 %)		
Behavioral Measures					
DSM−5 CUD Severity, n (%)		50		22	1.000[c]
Moderate	6 (12.0 %)		3 (13.6 %)		
Severe	44 (88.0 %)		19 (86.4 %)		
MCQ Total*	44.0 [30.0 – 51.5]	50	53.0 [38.0 – 64.5]	22	0.046[d]
MCQ Compulsivity*	8.2 [5.0 – 10.0]	50	10.0 [8.3 – 12.8]	22	0.047[d]
MCQ Emotionality	9.0 [6.0 – 14.0]	50	11.5 [8.0 – 16.8]	22	0.168[d]
MCQ Expectancy*	11.5 [9.0 – 15.0]	50	13.0 [11.3 – 18.0]	22	0.044[d]
MCQ Purposefulness	13.0 [9.0 – 16.0]	50	15.5 [10.3 – 18.0]	22	0.193[d]
MJPS Total	6.0 [3.0 – 12.8]	50	11.5 [7.3 – 14.0]	22	0.053[d]
BIS Total	60.0 [52.0 – 69.0]	47	62.0 [57.5 – 71.3]	19	0.260[d]
BIS Non-Planning	21.5 [17.5 – 26.1]	48	24.2 [22.0 – 26.4]	21	0.061[d]
BIS Cognitive/Attentional	17.6 [13.0 – 21.0]	49	19.0 [16.0 – 22.0]	21	0.445[d]
BIS Motor	23.0 [20.0 – 25.9]	47	20.8 [19.6 – 26.9]	21	0.750[d]
Substance Use					
Age of Cannabis Use Onset	15.0 [14.0 – 17.0]	49	16 [15.0 – 17.0]	22	0.084[d]
Age of Heaviest Use Onset*	18.0 [16.0 – 21.0]	49	22.5 [18.3 – 26.0]	22	0.011[d]
Urine Creatinine: Cannabinoid Ratio	1.5 [1.1 – 4.6]	45	2.3 [1.0 – 4.5]	22	0.500[d]
Cannabis Using Days (Past 28 Days)	28.0 [22.5 – 28.0]	47	27.0 [24.0 – 28.0]	21	0.989[d]
Total Cannabis Use Sessions (Past 28 Days)	76.0 [47.5 – 115.0]	47	64.0 [49.0 – 84.0]	21	0.377[d]
Any Cigarette Smoking Days (Past 28 Days)	23 (48 %)	48	7 (33 %)	21	0.390[c]
Cigarette Smoking Days (Among Individuals with Smoking Days; Past 28 Days)	28.0 [28.0 – 28.0]	23	28.0 [13.5 – 28.0]	7	0.378[d]
Total Cigarettes Smoked (Among Individuals with Smoking Days; Past 28 Days)	112.0 [56.0 – 437.5]	22	140.0 [70.0 – 140.0]	7	0.682[d]
Total Drinking Days (Past 28 Days)	3.0 [1.0 – 7.0]	47	6.0 [1.0 – 9.0]	21	0.487[d]
Total Drinks (Past 28 Days)	8.0 [1.5 – 26.0]	47	17.0 [2.0 – 29.0]	21	0.650[d]

Note: *p*-values derived from [a]*t*-tests, [b]Fisher's exact tests, [c]χ-square tests, and [d]Wilcoxon rank-sum tests. Values are reported as Counts (Percentages), Means ± Standard Deviations, or Medians [Q1 – Q3].
*$p < 0.05$

3.3. Associations with behavioral outcomes

Regions showing significant sex differences in cortical thickness z-scores were associated with behavioral variables including craving (MCQ), cannabis-associated problems (MJPS), and impulsivity (BIS), with sex included as an interaction term. Cortical thickness z-scores in 3 regions were significantly associated with MJPS total score (pars orbitalis: β=0.23, SE=0.11, p = 0.043; superior parietal cortex: β=0.21, SE=0.08, p = 0.014; precuneus: β=0.28, SE=0.10, p = 0.004); associations were retained in sensitivity analyses including age of heaviest cannabis use onset and past-month cigarette smoking, and no significant sex interactions were observed. Postcentral gyral thickness z-scores were negatively associated with MCQ total scores without a sex interaction (β=-0.11, SE=0.05, p = 0.017), and this association retained significance in sensitivity analyses (p = 0.004). All other associations were non-significant (p's > 0.05).

4. Discussion

This study found sexually dimorphic cortical thickness in adults with CUD, though on average cortical thickness measurements were within the normative range for both sexes. This contrasts with the lack of sex differences seen in the broader population, outside of well-established sex differences in total brain size (Eliot et al., 2021). Lower cortical thickness z-scores in males relative to females was observed in several regions around the central and lateral sulci, with the exception of higher medial orbitofrontal cortex z-scores in males. No sex difference was observed in hippocampal gray matter z-scores, but significantly lower cerebellar gray matter z-scores were observed in females relative to males, mirroring previous work (Chye et al., 2019, 2017b; Garimella et al., 2020; McPherson et al., 2021), though this finding was no longer significant after inclusion of covariates. Similarly, controlling for age of lifetime heaviest cannabis use onset and past-month cigarette smoking restricted findings to large effect size sex differences in cortical regions predominantly in the frontal and parietal lobes. Across both sexes, z-scores of 3 of these sexually dimorphic regions (pars orbitalis, superior parietal cortex, precuneus) were associated with cannabis-related problems, and postcentral gyrus z-scores were negatively associated with cannabis craving. Taken together, our study shows cortical thickness may on average be "normal" in adults with CUD relative to their peers, supporting some (Koenis et al., 2021), but contrasting other (Harper et al., 2021; Manza et al., 2020), previous work. However, among individuals with CUD, large sex differences emerge wherein thicker cortices in a subset of regions may relate to more cannabis-associated problems.

Findings of normative morphometric cortical thickness values in CUD argue against cannabis-induced neurotoxicity insofar as it could result in clinically significant cortical atrophy (Filbey et al., 2014; Rocchetti et al., 2013). This is consistent with a mega-analysis of FreeSurfer-generated segmentations, where pooled data found no differences in gray matter or cortical thickness between cannabis-dependent adults and controls (Mackey et al., 2019). Our finding of a sexually dimorphic effect in CUD, though, is unique and may potentially stem from sex-specific disruption of neurodevelopmental trajectories of cortical development. Participants in this study initiated cannabis use during mid-adolescence on average and used most heavily during late adolescence or early adulthood on average. A recent review of cannabis use in adolescents and emerging adults reported that, in studies that found sex effects, females that used cannabis had thicker frontal and parietal cortices relative to female controls, whereas males had thinner frontal and parietal cortices relative to male controls (Francis et al., 2022). Thus, within the context of neurodevelopmental trajectories of adolescent cortical thinning (Shaw et al., 2008), it is possible that relative to non-using peers, normative thinning may be attenuated in females with CUD compared to males, and that this effect can persist into adulthood. Our findings that relate greater cortical thickness to more cannabis-related problems suggest that CUD-associated neurodevelopmental aberration may be especially detrimental to females, but these associations were limited in number and effect size, and necessitate replication, especially in light of no

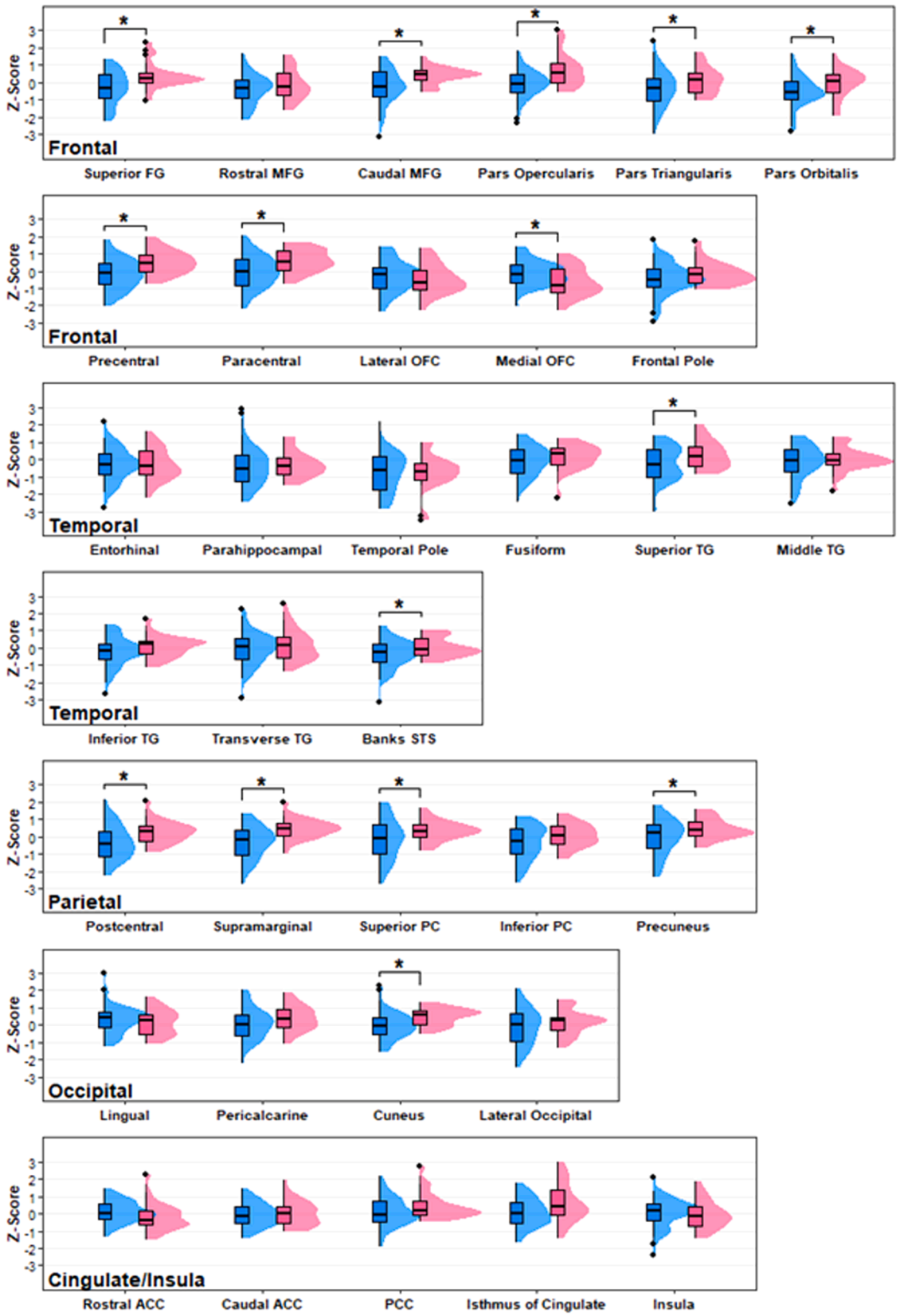

Fig. 1. Sex differences in cortical thickness by region. Mean thickness for each cortical region assessed is presented with males in blue and females in pink; * indicates a sex difference at $p < 0.05$ assessed via *t*-test, outliers are presented as single points. FG/TG=Frontal/Temporal Gyrus, FC/PC=Frontal/Parietal Cortex, CC=Cingulate Cortex, STS=Superior Temporal Sulcus.

Table 2
Sex differences in cortical thickness normed z-scores by region.

	Males	Females	*t*	*p*	p_{adj}	Cohen's d
Frontal						
Superior Frontal Gyrus*	**−0.31 ± 0.97**	**0.37 ± 0.77**	**3.16**	**0.003**	**0.015**	**0.77**
Rostral Middle Frontal Gyrus	−0.40 ± 0.88	−0.13 ± 0.92	1.16	0.254	0.345	0.30
Caudal Middle Frontal Gyrus*	**−0.26 ± 1.03**	**0.39 ± 0.50**	**3.58**	**0.001**	**0.011**	**0.80**
Pars Opercularis*	**−0.09 ± 0.86**	**0.71 ± 1.00**	**3.26**	**0.003**	**0.015**	**0.86**
Pars Triangularis*	−0.37 ± 1.10	0.12 ± 0.82	2.09	0.041	0.100	0.50
Pars Orbitalis*	−0.55 ± 0.94	0.08 ± 0.89	2.03	0.048	0.109	0.51
Precentral Gyrus*	**−0.19 ± 0.90**	**0.49 ± 0.70**	**3.49**	**0.001**	**0.011**	**0.85**
Paracentral Gyrus*	**−0.05 ± 0.95**	**0.57 ± 0.67**	**3.14**	**0.003**	**0.015**	**0.75**
Lateral Orbitofrontal Cortex	−0.32 ± 0.91	−0.45 ± 0.90	−0.56	0.582	0.682	−0.14
Medial Orbitofrontal Cortex*	**−0.14 ± 0.72**	**−0.63 ± 0.87**	**−2.31**	**0.027**	**0.081**	**−0.61**
Frontal Pole	−0.47 ± 0.94	−0.17 ± 0.70	1.47	0.143	0.232	0.36
Temporal						
Entorhinal Cortex	−0.31 ± 0.97	−0.31 ± 0.94	−0.01	0.992	0.992	0.00
Parahippocampal Gyrus	−0.42 ± 1.15	−0.32 ± 0.80	0.45	0.658	0.717	0.11
Temporal Pole	−0.78 ± 1.16	−0.71 ± 1.14	0.22	0.829	0.854	0.06
Fusiform Gyrus	−0.11 ± 0.89	0.13 ± 0.78	1.16	0.251	0.345	0.29
Superior Temporal Gyrus*	−0.24 ± 1.02	0.27 ± 0.84	2.22	0.031	0.081	0.55
Middle Temporal Gyrus	−0.16 ± 1.00	−0.03 ± 0.73	0.61	0.548	0.665	0.15
Inferior Temporal Gyrus	−0.24 ± 0.87	0.05 ± 0.64	1.53	0.132	0.224	0.37
Transverse Temporal Gyrus	−0.04 ± 0.97	0.19 ± 0.95	0.93	0.357	0.467	0.24
Banks of Superior Temporal Sulcus*	−0.38 ± 0.85	0.04 ± 0.58	2.24	0.029	0.081	0.53
Parietal						
Postcentral Gyrus*	**−0.36 ± 1.01**	**0.25 ± 0.67**	**3.03**	**0.004**	**0.017**	**0.71**
Supramarginal Gyrus*	**−0.34 ± 0.97**	**0.43 ± 0.62**	**4.07**	**< 0.001**	**0.003**	**0.95**
Superior Parietal Cortex*	−0.16 ± 1.23	0.32 ± 0.58	2.25	0.028	0.081	0.50
Inferior Parietal Cortex	−0.35 ± 1.01	0.03 ± 0.70	1.83	0.073	0.146	0.43
Precuneus*	−0.03 ± 1.07	0.41 ± 0.60	2.24	0.028	0.081	0.51
Occipital						
Lingual Gyrus	0.31 ± 0.82	0.16 ± 0.76	−0.74	0.461	0.581	−0.19
Pericalcarine Gyrus	0.07 ± 0.92	0.39 ± 0.76	1.54	0.131	0.224	0.38
Cuneus*	**−0.03 ± 0.82**	**0.48 ± 0.50**	**3.26**	**0.002**	**0.015**	**0.76**
Lateral Occipital Cortex	−0.13 ± 1.09	0.14 ± 0.75	1.22	0.227	0.336	0.29
Cingulate/Insula						
Rostral Anterior Cingulate Cortex	0.09 ± 0.62	−0.19 ± 0.85	−1.39	0.176	0.272	−0.38
Caudal Anterior Cingulate Cortex	−0.09 ± 0.69	0.00 ± 0.76	0.48	0.638	0.717	0.12
Posterior Cingulate Cortex	0.06 ± 0.86	0.41 ± 0.78	1.70	0.097	0.183	0.43
Isthmus of Cingulate	0.06 ± 0.83	0.60 ± 1.16	1.99	0.056	0.119	0.54
Insula	0.03 ± 0.85	−0.07 ± 0.87	−0.42	0.675	0.717	−0.11

Note: Values are reported as Means ± Standard Deviations.
*$p < 0.05$ assessed via *t*-test; bolded items maintained statistical significance after covarying for age of lifetime heaviest cannabis use onset and any past-month cigarette smoking.

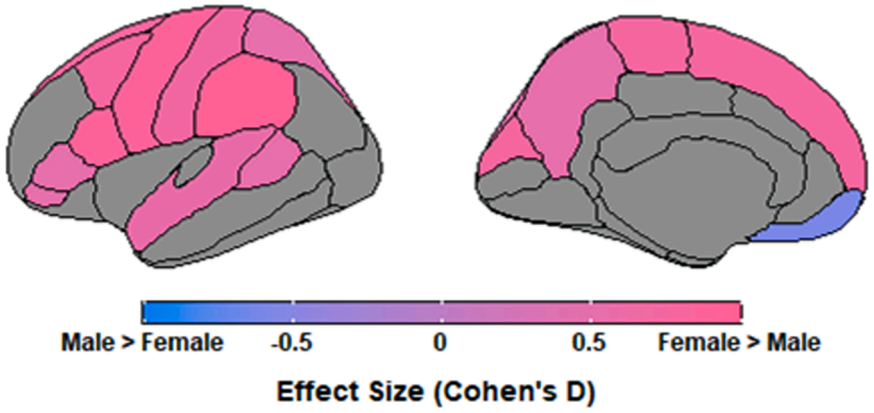

Fig. 2. Mapped effect sizes in cortical regions indicating sexual dimorphism. Effect sizes are presented for all regions with significant sex differences in thickness (assessed via *t*-test); pink regions are thicker in females relative to males and blue regions are thicker in males relative to females.

interaction effect of sex in our statistical models. Nonetheless, it is important to further test these speculations in future or ongoing studies of neurodevelopment and emergent cannabis use (Lisdahl et al., 2018).

Although our study does not explicitly examine this, results invoke the broader literature on hormonal influences on brain structure and the endocannabinoid system. Many of the sexually dimorphic regions identified in this study show sensitivity to hormonal variation (Pletzer et al., 2010). In addition, gonadal hormones show a bidirectional modulatory relationship with endocannabinoids which may be disrupted by chronic THC exposure (Gorzalka and Dang, 2012), altering hormone-associated cortical thinning which typically takes place during adolescence (Wong et al., 2018). Sex-divergent effects of adolescent

cannabinoid exposure on prefrontal cortical synaptic development have also been observed preclinically (Renard et al., 2016; Rubino et al., 2015). It is possible that differences in brain structure may be a result of sexually divergent effects of THC on Hebbian plasticity, a process modulated by endocannabinoids in the prefrontal cortex under non-use conditions (McLaughlin et al., 2014). Taken together, these findings support a possible interaction between sex and cannabis use in neurodevelopment.

This study has unique strengths, such as: inclusion of a well-characterized sample of adults with CUD with demographically and clinically comparable samples of males and females; application of a widely-used, validated, and easily replicable segmentation algorithm (FreeSurfer); use of normative morphometric values rather than study-specific controls, which can introduce sampling bias; and replication of results obtained by other research groups. Nonetheless, limitations of this work include: modest sample sizes, although our sample is still nearly double most of those used in previous studies of individuals that use cannabis heavily (Chye et al., 2017b; Cousijn et al., 2012; Garimella et al., 2020; Price et al., 2015); reliance on retrospective reporting of cannabis use; and restrictive inclusion/exclusion criteria that may impact the generalizability of these results to the broader population of individuals that use cannabis. As this work was a secondary analysis of baseline data from two randomized controlled trials, factors that may influence cortical thickness such as hormonal contraceptive use (Petersen et al., 2015; Pletzer et al., 2010), menstrual cycle phase (De Bondt et al., 2013; Pletzer et al., 2010), time of day when scans were conducted (Dieleman et al., 2017), tobacco use (Karama et al., 2015), or specific physiological states and medical comorbidities (Dieleman et al., 2017) were not systematically controlled. With respect to tobacco use, previous work indicates differential effects of tobacco and cannabis use on brain structure (Wetherill et al., 2015) as well as sex differences in the effects of tobacco use on brain structure (Franklin et al., 2014). Our observed sex differences might therefore be affected by tobacco use, particularly long-term use prior to the past month, despite comparable recent use across sexes. Future, more adequately powered studies should assess sex differences in normative brain structure in individuals that use both cannabis and tobacco given the high prevalence of co-use of these substances (Gravely et al., 2022). Moreover, a modest sample of females enrolled in this study means there is a possibility that our females are not as representative of the greater population of females with CUD; we also did not control for hormonal contraceptive use or menstrual cycle phase, which may have some influence on our results that we could not account for. Most importantly, this work is a cross-sectional observational study; as such, our hypothesis that sex differences in cortical thickness are due to disruption of neurodevelopmental processes by cannabis use remains speculative. This study also only assessed sex via self-report, rather than by karyotype or hormone concentration. The influence of these factors, beyond what can be inferred from typical male or female presentation, cannot be determined from this work. Finally, while cortical thickness measurements analyzed in our study were within the "normal" range on average, several individuals fell outside this range across most regions. Future work involving a larger sample of participants may examine how these z-scores relate to adverse outcomes in CUD.

5. Conclusion

We found sexual dimorphism in cortical thickness in adults with CUD, with both males and females demonstrating cortical thickness measurements that were, on average, within the normative range. Greater cortical thickness z-scores were modestly correlated with cannabis-associated problems, but behavioral measurements were limited. The relationship between sex differences in cortical thickness and other known behavioral sex differences in CUD is therefore unknown. Future research should assess longitudinal sex differences in normative modelling of brain structure in individuals with CUD to determine the clinical relevance of our findings.

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CRediT authorship contribution statement

Andreana Benitez: Writing – review & editing, Writing – original draft, Data curation, Conceptualization. **Aimee McRae-Clark:** Writing – review & editing, Investigation, Funding acquisition. **Gregory Sahlem:** Writing – review & editing, Investigation, Funding acquisition. **Kathryn Thorn:** Writing – review & editing, Data curation. **Laura Campbell:** Writing – review & editing, Writing – original draft. **Erin Martin:** Writing – review & editing, Writing – original draft, Visualization, Formal analysis.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Erin Martin reports financial support was provided by National Institute on Drug Abuse. Aimee McRae-Clark reports financial support was provided by National Institute on Drug Abuse. Gregory Sahlem reports financial support was provided by National Institute on Drug Abuse. Laura Campbell reports financial support was provided by National Institute on Aging. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.dadr.2025.100318.

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