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REGULAR RESEARCH ARTICLE

Neurostructural Correlates of Cannabis Use in Adolescent Bipolar Disorder

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Abstract

Background: Little is known regarding the association of cannabis use with brain structure in adolescents with bipolar disorder (BD). This subject is timely, given expanded availability of cannabis contemporaneously with increased social acceptance and diminished societal constraints to access. Therefore, we set out to examine this topic in a sample of adolescents with BD and healthy control (HC) adolescents.

Methods: Participants included 144 adolescents (47 BD with cannabis use [BD_{CB+}; including 13 with cannabis use disorder], 34 BD without cannabis use [BD_{CB-}], 63 HC without cannabis use) ages 13–20 years. FreeSurfer-processed 3T MRI with T1-weighted contrast yielded measures of cortical thickness, surface area (SA), and volume. Region of interest (amygdala, hippocampus, ventrolateral prefrontal cortex, ventromedial prefrontal cortex, and anterior cingulate cortex) analyses and exploratory vertex-wise analysis were undertaken. A general linear model tested for between-group differences, accounting for age, sex, and intracranial volume.

Results: Vertex-wise analysis revealed significant group effects in frontal and parietal regions. In post-hoc analyses, BD_{CB+} exhibited larger volume and SA in parietal regions, and smaller thickness in frontal regions, relative to HC and BD_{CB-}. BD_{CB-} had smaller volume, SA, and thickness in parietal and frontal regions relative to HC. There were no significant region of interest findings after correcting for multiple comparisons.

Conclusion: This study found that cannabis use is associated with differences in regional brain structure among adolescents with BD. Future prospective studies are necessary to determine the direction of the observed association and to assess for dose effects.

Key Words: cannabis, bipolar disorder, adolescent, neuroimaging

Bipolar disorder (BD) is a highly complex and impairing condition characterized by recurrent mood episodes (Birmaher et al., 2006). BD affects 2%–5% of adolescents and is the fourth leading cause of adolescent disability worldwide (Kozloff et al., 2010). In addition to mood symptoms, approximately 1 in 3 adolescents with BD have comorbid substance use disorders (Wilens

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Significance Statement

Approximately 1 in 3 adolescents with bipolar disorder (BD) have comorbid substance use disorder, with cannabis being the most commonly used drug. In adults with BD, cannabis use and cannabis use disorders are associated with decreased treatment adherence and more severe illness course, including increased symptom severity and delayed recovery. However, adolescence is a critical period of dynamic neurobiological and behavioral changes. Due to this critical developmental epoch, adolescents are more susceptible to developmental disturbances induced by exogenous substances. However, there is a lack of research regarding the brain-based implications of cannabis use in adolescents with BD. Therefore, this study examined the neuro-structural associations of cannabis use in adolescents with BD. This study will inform future studies regarding the mechanism and directionality of cannabis use in adolescents with BD, leading to further understanding of the causes and effects of cannabis use.

et al., 2004; Goldstein et al., 2008). Similar to adults, cannabis is the most commonly used drug among adolescents with BD (Goldstein et al., 2008). Furthermore, adolescents with BD have higher rates of cannabis use and greater likelihood of progression to cannabis use disorders (CUD) relative to the general population (Wittchen et al., 2007; Tyler et al., 2015). Cannabis use has been associated with increased symptom severity and decreased treatment response in individuals with BD (Van Rossum et al., 2009; Agrawal et al., 2011). In addition to the association of cannabis use with concurrent and future psychiatric symptoms and disorders, cannabis use has been associated with brain structure alterations in individuals with and without mood disorders (Lim et al., 2013; Jacobus and Tapert, 2014).

Compared with adulthood, adolescence is a critical period of neurodevelopment and maturation. During this period, the brain is particularly sensitive to the deleterious effects of environmental factors; substance use, including cannabis, is thought to interfere with the natural process of brain maturation and potentially lead to psychosocial and/or biological consequences (Squeglia et al., 2009). While a number of studies have reported cannabis-related differences in grey matter structure in adolescents, the directionality of these results vary (Squeglia et al., 2009; Ashtari et al., 2011; Lopez-Larson et al., 2011; Jacobus and Tapert, 2014). For example, some studies have shown that heavy cannabis users display smaller hippocampal volumes and smaller thickness in prefrontal cortical regions compared with controls (Ashtari et al., 2011; Lopez-Larson et al., 2011), whereas other studies have found no differences in hippocampal volume as well as larger parietal thickness (Medina et al., 2009; Lopez-Larson et al., 2011).

The inconsistency regarding neuroanatomical correlates of cannabis use may be due to a number of factors such as duration, frequency, and potency of cannabis use as well as age of cannabis use onset (Nader and Sanchez, 2018). Although there are numerous studies regarding the association of brain structure and cannabis use and regarding the association of brain structure and BD, only 1 prior study, to our knowledge, has examined neuro-structural correlates of cannabis use in adolescents with BD). The study included 14 adolescents with BD (n = 7 with CUD) and found increased frontal grey matter regional volumes and decreased temporal grey matter regional volumes in those with CUD in areas also implicated in BD (Jarvis et al., 2008). Thus far, there are no studies to our knowledge focused on cannabis use among adolescents with BD that have included a control group or that have evaluated structural neuroimaging phenotypes other than volume.

Given the high prevalence of cannabis use and CUD in adolescents with BD, together with the paucity of literature on this topic, it is important to further examine the neuro-structural correlates of cannabis use within this population. With an increase in global legalization, including Canada, and the related increase in access to cannabis and decrease in perceptions of cannabis risks, understanding the neuro-structural correlates of cannabis use among adolescents with BD is especially timely (Fischer and Rehm, 2017; Picard, 2017; Rotermann, 2020). We therefore set out to investigate this topic in a sample of adolescents with BD and healthy control (HC) adolescents. Based on prior neuroimaging studies regarding BD and cannabis use independently, we evaluated cortical volume, surface area (SA), and thickness in the following regions of interest (ROI): amygdala, hippocampus, prefrontal cortex (PFC), and anterior cingulate cortex, as well as in an exploratory vertex-wise analysis. Although volume is a product of thickness and SA, we examined each of these 3 MRI phenotypes as they are driven by different environmental, genetic, and developmental processes (Lochhead et al., 2004; Frazier et al., 2005; Wierenga et al., 2014). While cognizant that the cross-sectional design of this study precludes causal inferences, hypotheses were based on the premise of enhanced susceptibility to putative neurotoxic effects of cannabis. We hypothesized that brain structure measures would decline linearly across groups: BD cannabis users (BD_{CB+}) < BD non-users (BD_{CB-}) < HC.

MATERIALS AND METHODS

This study was approved by the Research Ethics Board at Sunnybrook Health Sciences Centre. Written informed consent was obtained from all participants and their parent/guardian(s).

Participants

A total of 144 adolescent participants, ages 13 to 20, were recruited for this study, including 81 with BD (type I, type II, or not otherwise specified) and 63 HC. There were 47 adolescents in the BD_{CB+} group and 34 adolescents in the BD_{CB-} group. BD participants were primarily recruited from the Centre for Youth Bipolar Disorder, a subspecialty clinical research program located at Sunnybrook Health Sciences Centre in Toronto, Canada. HC participants were recruited primarily from the community via advertisements. HC participants had no lifetime history of major psychiatric disorders, including mood and psychotic disorders, no anxiety disorders or alcohol/drug dependence in the past 3 months, and no first- or second-degree family history of BD or psychosis.

For all participants, current and lifetime psychiatric diagnoses were assessed using the Kiddie Schedule for Affective

Disorders and Schizophrenia for School-Age Children Present and Lifetime Version (KSADS-PL) (Kaufman et al., 1997), a semi-structured diagnostic interview incorporating information from the adolescent and their parent/guardian. To assess mood symptoms, we used the expanded KSADS Mania Rating Scale (Axelson et al., 2003) and KSADS Depression Rating Scale (Chambers et al., 1985). Cannabis use was evaluated during the KSADS-PL interview. Participants were asked whether they have ever used cannabis before, even if they have only tried it once. If participants answered yes, a substance use supplement was administered to determine whether they met diagnostic criteria for a CUD. Lifetime history of physical and/or sexual abuse was obtained from the KSADS-PL post-traumatic stress disorder screening questions. The Hollingshead Four-Factor Index was used to assess the socioeconomic status of parents and the Children's Global Assessment Scale was used as a measure of current and lifetime functioning (Hollingshead, 1975; Shaffer et al., 1983). Participants were enrolled from 2012 to 2019. DSM-V was published in 2013, and the DSM-V version of K-SADS-PL was only available in 2016. Diagnoses in the current study are therefore based on DSM-IV. All interviewers had bachelors and/or masters degrees and completed rigorous training under the supervision of the principal investigator. Diagnoses and symptom ratings were reviewed and confirmed by a licensed child-adolescent psychiatrist.

The current study was a secondary analysis based on 2 other studies that employed the following exclusion criteria: (1) unable to give informed consent; and/or (2) had any infectious illness within the past 14 days; and/or (3) had an existing cardiac condition, auto-immune illness, or inflammatory illness; and/or (4) were currently taking any anti-inflammatory, anti-platelet, anti-lipidemic, anti-hypertensive, or hypoglycemic agents; and/or (5) had any MRI contraindications (i.e., cardiac pacemaker, or any metal in the body); and/or (6) had a history of severe neurological or cognitive impairments; and/or (7) substance dependence in the last 3 months. Lifetime cannabis use was not an exclusion criteria for those studies, and there were 7 HC participants with lifetime cannabis use. Due to the small cell size and lack of HC participants with CUD, these 7 HC were excluded from the present analyses.

MRI Methods

MRI data was collected on a 3 Tesla Philips Achieva medical scanner using an 8-channel head receiver coil and body coil transmission. Structural images were collected using T1 weighted high-resolution fast-field echo images, which were used to achieve grey matter and white matter image contrast. The following parameters were used for the T1 weighted image: repetition time = 9.5 milliseconds, echo time = 2.3 milliseconds, inversion time = 1400 milliseconds, spatial resolution = 0.94 × 1.17 × 1.2 mm, 256 × 164 × 140 matrix, flip angle = 8°, field of view = 240 × 191 mm^2, scan duration = 8 minutes 56 seconds, 140 slices.

Prior to pre-processing, T1-weighted images were visually inspected by 2 independent raters to assess for motion or other image artifacts. For each image, a score between 0 and 3 was given based on overall image quality (i.e., number of artifacts due to excessive movement while in the scanner, contrast between white matter and grey matter, or otherwise poor image quality). If the scores between raters were incongruent, images were inspected a second time to ensure that a consensus was achieved following discussion. T1-weighted images found to be of poor quality (those images with a score of 3) were excluded from the data set before processing. Quality control and parcellation accuracy were also completed after pre-processing. T1 quality and parcellation accuracy were assessed using a scoring system by raters to exclude poor-quality images from the data set. If possible, parcellations with poor accuracy were edited.

Estimates of cortical volume, SA, and thickness were performed using FreeSurfer v6.0 (Fischl, 2012). Pre-processing included resampling the original 3D coronal images to 1-mm isotropic voxel resolution, intensity normalization (Sled et al., 1998), registration to Montreal Neurological Institute space, and automated skull stripping (Ségonne et al., 2004). Automated parcellation (Fischl et al., 2002, 2004) then proceeded with cortical surface reconstruction. This included generation of binary white matter masks in 2 hemispheres, which were used to produce a mesh of white matter surface smoothed to remove voxel-based effects and also corrected for topological defects (Fischl et al., 2001). White matter and pial surfaces were then extracted and spherically inflated to be registered to a canonical template (Fischl et al., 1999). Lastly, a parcellation algorithm was used to map the individual brains to the Destrieux cortical atlas (Destrieux et al., 2010) and based on spatial landmarks, curvatures, and sulcal depth to assign gyral labels of interest (Fischl et al., 2004). For subcortical volumes, automated segmentation occurred independently and involved nonlinear registration to the MNI305 probabilistic atlas to label various subcortical structures (Fischl et al., 2002).

To create cortical and subcortical ROI measurements, multiple individual regions were summed using the Desikan-Killiany atlas (Desikan et al., 2006). The anterior cingulate cortex included the caudal anterior cingulate, and rostral anterior cingulate, the ventromedial prefrontal cortex included the lateral and medial orbitofrontal cortex, and the ventrolateral PFC included the pars orbitalis and pars triangularis. Bilateral amygdala was considered as a single estimate and similarly for the hippocampus. Cortical measures of volume and SA were calculated by summing the values of each region. Thickness was calculated proportional to the SA of each component region.

Statistical Analysis

BD and HC participants were age and sex matched. For demographic and clinical characteristics, normality was evaluated using the Shapiro-Wilks test for all continuous variables. ANOVA or Kruskal-Wallis was used to assess between-group differences for all continuous variables, while independent samples *t* tests or Mann-Whitney U tests were used to assess within-BD differences for continuous variables. Categorical variables were examined using chi-squared tests. Two-tailed statistical significance was set as $P < .05$.

For ROI analysis, all assumptions were tested prior to analysis, which was conducted in MATLAB R2018b using a GLM. ROI measures were the outcome variables, group membership was the fixed factor (i.e., BD_{CB+}, BD_{CB-}, HC), and age and sex were covariates. For volume and SA analyses only, intracranial volume was added as an additional covariate. Statistical significance was defined as $P < .05$; the family-wise error approach was used to correct for multiple comparisons (i.e., correcting for the number of ROIs examined, $P < .01$).

For whole-brain vertex-wise analysis, a GLM FreeSurfer-based shell script was used (Fischl, 2012). Sex, age, and intracranial volume were used as covariates for volume and SA, whereas only sex and age were used as covariates for thickness. In this analysis, we corrected for multiple comparisons using Monte Carlo simulations thresholded at 1.3 ($P < .05$). Surface-based smoothing

with a full width at half-maximum of 10 mm was selected based on previous literature (Fischl, 2012). Post-hoc analyses were completed similarly to ROI analysis in MATLAB using a GLM.

RESULTS

Demographic characteristics are summarized in Table 1. There were significant between-group differences in age, which was therefore included as a covariate in subsequent analyses. Clinical characteristics of the BD group are summarized in Table 2. In addition, within the HC group, 1 had smoked, 8 had ADHD, 2 had physical abuse, 1 had police contact, 3 had suicidal ideation, 5 had any anxiety, 1 had SSRI use, and 4 had stimulant use at some point in their lifetime.

ROI Analysis

ROI analysis revealed a group effect in left ventromedial PFC ($P = .04$), which did not survive correction for multiple comparisons ($P = .01$). There were no other significant ROI findings.

Vertex-Wise Analysis

Vertex-wise analysis revealed significant group differences in 8 clusters: left and right precuneus volume ($P < .001$; $P < .001$), left inferior parietal lobe volume ($P < .001$), left superior parietal lobe SA ($P < .001$), left and right superior frontal gyri thickness ($P < .001$; $P < .001$), left precentral gyrus thickness ($P = .001$), and left medial orbitofrontal cortical thickness ($P < .001$). Post-hoc analysis revealed that, relative to HC, BD_{CB+} had larger left inferior parietal lobe volume ($P = .003$), left and right precuneus volume ($P < .001$; $P < .001$), and left superior parietal lobe SA ($P = .009$) as well as smaller precentral gyrus thickness ($P = .001$), medial orbitofrontal cortical thickness ($P < .001$), and left and right superior frontal gyri thickness ($P < .001$; $P < .001$). Relative to BD_{CB-}, BD_{CB+} had larger left precuneus volume ($P < .001$), left inferior parietal lobe volume ($P < .001$), and left superior parietal lobe SA ($P < .001$) as well as smaller left medial orbitofrontal cortical thickness ($P = .003$). Finally, relative to HC adolescents, BD_{CB-} had smaller left inferior parietal lobe volume ($P = .01$), left superior parietal lobe SA ($P = .002$), left precentral gyrus thickness ($P = .003$), and left and right superior frontal gyri thickness ($P = .001$; $P = .002$). All post-hoc results remained significant after correcting for multiple comparisons ($P < .017$). Tables 3 and 4 display the vertex-wise results for group analyses as well as post-hoc analyses. Figures 1 and 2 depict the findings in the left precuneus and left superior frontal gyrus. All findings remained unchanged in sensitivity analysis further controlling for nicotine use.

Discussion

This study examined brain volume, SA, and thickness among adolescents in 3 groups: BD_{CB+}, BD_{CB-}, and HC. Between-group differences were observed in 8 frontal and parietal regions. Overall, there was a pattern of findings whereby BD_{CB+} had larger volume and/or SA in parietal regions and smaller thickness in frontal regions compared with both HC and BD_{CB-}. Furthermore, BD_{CB-} displayed smaller volume, SA, and thickness in these regions compared with HC. This study advances prior research on this subject by virtue of a larger sample size, integrating a control group, and evaluating multiple structural neuroimaging phenotypes.

The direction of the between-group differences in this study differs according to brain region and imaging phenotype. Regional differences in genetic vs environmental effects may be contributory. A study examining regional differences in genetic and environmental influences on brain structure in a healthy adolescent population found that regions with primarily environmental influences (>80%) were predominantly in the parietal lobe and regions with primarily genetic contributions (>80%) were predominantly in the frontal lobe (Yang et al., 2012). Different neurostructural phenotypes (i.e., volume, SA, thickness) are also differentially affected by environmental and genetic factors (Lenroot et al., 2009; Winkler et al., 2010). Moreover, SA shows much more variation both within and between subjects compared with thickness, and genetic factors that control SA appear to differ from those that influence thickness (Lenroot et al., 2009; Winkler et al., 2010). Furthermore, while volume measures are based on the product of SA and thickness, volume appears to be driven by SA more so than by thickness (Winkler et al., 2010). Taken together, these studies suggest that current findings regarding SA in the parietal lobe are more susceptible to environmental influences, whereas thickness in the frontal lobe is more related to genetic influences.

Cannabis is known to have pleiotropic neurodevelopmental effects, with both increases and decreases in regional brain

Table 1. Demographic Characteristics

	BD_{CB+}	BD_{CB-}	HC			
	(n = 47)	(n = 34)	(n = 63)	Test statistic	*P* value	Effect size
Age	17.45 ± 1.18	17.07 ± 1.70	16.99 ± 1.68	F = 1.30	.27	$\eta^2 = 0.02$
Sex (% female)	31 (66.0)	20 (58.82)	34 (53.97)	$\chi^2 = 1.60$	.45	V = 0.11
SES	4.15 ± 0.98	4.38 ± 0.78	4.27 ± 0.95	H = 1.10	.58	$\eta^2 = 0.01$
Race (% Caucasian)	35 (74.47)	26 (76.47)	32 (50.79)	$\chi^2 = 9.35$	.009[a,b]	V = 0.26
Intact family	26 (55.32)	23 (67.65)	43 (68.25)	$\chi^2 = 2.23$	.33	V = 0.12
Tanner Stage (1–5)	4.49 ± 0.62	4.32 ± 0.68	4.25 ± 0.65	H = 3.82	.15	$\eta^2 = 0.01$
BMI (adjusted)	24.40 ± 4.30	23.19 ± 4.57	21.94 ± 3.60	H = 11.38	.003[a]	$\eta^2 = 0.07$
CGAS: most severe past episode	43.66 ± 8.96	43.73 ± 8.60	—	U = 770.0	.96	d = 0.008
CGAS: highest past year	68.04±11.69	68.67 ± 10.38	88.56 ± 13.69	F = 83.36	<.00[a,b]	$\eta^2 = 0.54$
CGAS: current episode (past month)	64.23 ± 12.56	64.58 ± 11.98	88.29 ± 6.68	F = 96.53	<.001[a,b]	$\eta^2 = 0.58$

Abbreviations: BD_{CB-}, BD non-users; BD_{CB+}, BD cannabis users; BMI = body mass index; CGAS, Children's Global Assessment Scale; HC, healthy controls; SES, socio-economic status.

Values are reported in mean ± SD unless otherwise indicated.

[a]Significant (BD_{CB+} vs HC).

[b]Significant (BD_{CB-} vs HC).

Table 2. Clinical Characteristics of BD_{CB+} and BD_{CB-}

	BD_{CB+} (n = 47)	BD_{CB-} (n = 34)	Test statistic	*P* value	Effect size
BD-I	20 (42.6)	10 (29.4)	$\chi^2 = 1.68$		
BD-II	13 (27.7)	10 (29.4)		.43	V = 0.14
BD-NOS	14 (29.8)	14 (41.2)			
Age of onset	15.25 ± 2.5	14.30 ± 2.9	U = 583.0	.06*	d = 0.36
Clinical characteristics					
Lifetime psychosis	7 (14.9)	3 (8.8)	$\chi^2 = 0.67$	.41	V = 0.09
Lifetime suicide attempts	12 (25.5)	1 (2.9)	$\chi^2 = 7.47$	.006*	V = 0.30
Lifetime self-injurious behavior	23 (48.9)	17 (50.0)	$\chi^2 = 0.01$	.93	V = 0.01
Lifetime suicidal ideation	29 (61.7)	22 (64.7)	$\chi^2 = 0.08$	.78	V = 0.03
Police contact/arrest	12 (25.6)	7 (20.6)	$\chi^2 = 0.27$	.60	V = 0.06
Lifetime physical and/or sexual abuse	3 (6.4)	2 (5.9)	$\chi^2 = 0.009$	.93	V = 0.01
Lifetime psychiatric hospitalization	24 (51.1)	14 (41.2)	$\chi^2 = 0.77$	.38	V = 0.10
Current depression score	16.28 ± 12.85	14.14 ± 9.40	U = 722.0	.46	d = 0.19
Lifetime depression score	30.60 ± 11.98	28.68 ± 12.67	t = 0.70	.49	d = 0.16
Current mania score	9.83 ± 11.10	8.94 ± 9.28	U = 783.0	.88	d = 0.09
Lifetime mania score	30.98 ± 11.31	31.03 ± 10.34	t = −0.21	.98	d = 0.005
Lifetime comorbid diagnoses					
ADHD	21 (44.7)	16 (47.1)	$\chi^2 = 0.05$	.83	V = 0.02
Any anxiety	37 (78.7)	26 (76.5)	$\chi^2 = 0.06$	.81	V = 0.03
SUD	16 (34.0)	2 (5.9)	$\chi^2 = 9.05$	.003*	V = 0.33
ODD	13 (27.7)	7 (20.6)	$\chi^2 = 0.53$	.47	V = 0.08
CD	2 (4.3)	1 (2.9)	$\chi^2 = 0.10$	.76	V = 0.03
Nicotine use (yes/no)	10 (21.3)	2 (5.9)	$\chi^2 = 3.71$	.05	V = 0.21
Alcohol dependence (yes/no)	7 (14.89)	0	$\chi^2 = 5.54$	.02*	V = 0.26
Alcohol abuse (yes/no)	6 (12.77)	1 (2.94)	$\chi^2 = 2.41$	.12	V = 0.17
Family psychiatric history					
Mania/hypomania	8 (17.0)	9 (26.5)	$\chi^2 = 1.22$	.27	V = 0.12
Depression	25 (53.2)	19 (55.9)	$\chi^2 = 0.15$	.70	V = 0.04
Anxiety	26 (55.3)	14 (41.2)	$\chi^2 = 1.29$	.26	V = 0.13
ADHD	12 (25.5)	8 (23.6)	$\chi^2 = 0.02$	.90	V = 0.02
Lifetime medications					
SGA	34 (72.3)	26 (76.5)	$\chi^2 = 0.18$	.68	V = 0.05
Lithium	11 (23.4)	9 (26.5)	$\chi^2 = 0.10$	.75	V = 0.04
SSRI antidepressants	16 (34.0)	9 (26.5)	$\chi^2 = 0.53$	.47	V = 0.08
Non-SSRI antidepressants	11(23.4)	5 (14.7)	$\chi^2 = 0.94$	.33	V = 0.11
Stimulants	7 (14.9)	9 (26.5)	$\chi^2 = 1.67$	.20	V = 0.14
Current medications					
SGA	29 (61.7)	20 (58.8)	$\chi^2 = 0.07$	0.80	V = 0.03
Lithium	8 (17.0)	7 (20.6)	$\chi^2 = 0.17$	0.68	V = 0.05
SSRI antidepressants	4 (8.5)	3 (8.8)	$\chi^2 = 0.002$	0.96	V = 0.005
Non-SSRI antidepressants	2 (4.3)	2 (5.9)	$\chi^2 = 0.11$	0.74	V = 0.04
Stimulants	1 (2.1)	4 (11.8)	$\chi^2 = 3.16$	0.08	V = 0.20

Abbreviations: ADHD, attention deficit-hyperactivity disorder; BD_{CB-}, BD non-users; BD_{CB+}, BD cannabis users; CD, conduct disorder; HC, healthy controls; NOS, not otherwise specified; ODD, oppositional defiant disorder; SGA, second-generation antipsychotic; SSRI, selective serotonin reuptake inhibitor; SUD, substance use disorder.

Values are reported in mean ± SD unless otherwise indicated. Depression score based on depression rating scale; mania score based on mania rating scale.

*Significant.

structures (Lopez-Larson et al., 2011; Jacobus and Tapert, 2014). In studies of adolescents and adults with BD who have identified differences in parietal lobe structure, these have primarily been in the direction of smaller structure (Frazier et al., 2005; Li et al., 2011; Altamura et al., 2018; Hibar et al., 2018). In contrast, studies of adolescents and adults using cannabis have found both larger and smaller parietal regions relative to controls (Mata et al., 2010; Lopez-Larson et al., 2011; Jacobus and Tapert, 2014; Price et al., 2015). Prior studies in adolescents have found that cannabis use and BD are each associated with differences in PFC structure, primarily reduction (Dickstein et al., 2005; Price et al., 2015; Nader and Sanchez, 2018). While most research on this topic has been cross-sectional, there is prior evidence that smaller volumes in frontal regions predate initiation of

cannabis and other substance use in adolescents (Cheetham et al., 2012; Lippard et al., 2017).

In this cross-sectional study, it cannot be determined whether observed differences comprise causes or effects of cannabis use. We speculate that our findings regarding larger parietal lobe volume and SA may reflect effects of cannabis on the brain, whereas our findings regarding reduced frontal cortical thickness may reflect genetic predisposition to cannabis use. Previous literature has shown us that smaller PFC structure and reduced activity have been linked to impaired impulse and decision-making in adults and adolescents with BD (Dickstein et al., 2005; Ha et al., 2009; Mazzola-Pomietto et al., 2009; Chen et al., 2011). Studies have also shown poorer white matter integrity in fronto-parietal circuitry among adolescent cannabis users (Bava et al., 2019; Jacobus and Tapert, 2014). White matter integrity in these regions has been linked to neurocognitive performance on measures of attention, processing speed, and working memory as well as to emotional functioning and prospective risk taking in substance users (Medina et al., 2007; Jacobus et al., 2013). Finally, the findings of smaller volume, SA, and thickness in frontal and parietal regions of the in BD_{CB-} relative to HC converge with prior studies (Frazier et al., 2005; Li et al., 2011; Lim et al., 2013).

Several limitations of this study warrant consideration. First, the cross-sectional methodology precludes causal or directional inferences. As previously mentioned, the current study cannot directly examine whether present findings reflect predisposition to and/or consequences of cannabis use. Second, the sample size was not powered to detect small effect sizes such that there may be additional regions also associated with cannabis use that were not detected in this study. This study was also not powered for the complicated multivariable models that would be needed to parse the independent association of cannabis use with brain structure after controlling for various clinical characteristics such as comorbidity, treatment, and family psychiatric history. Such studies are needed and will require substantially larger sample sizes. Third, this study did not have an HC cannabis use group, hindering our ability to examine whether neuro-structural correlates of cannabis use differ between BD and HC groups. Fourth, urine toxicology was not used in this study; this could have led to underreporting of cannabis use and biased the results towards negative findings. Finally, this study did not collect information regarding cannabis potency, quantity or duration of use, and could not evaluate for related associations with brain structure.

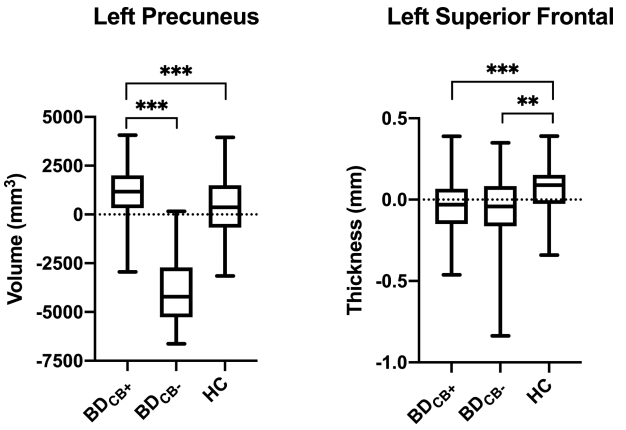

Figure 1. Graphs for vertex-wise analyses. There was a significant group effect in the left precuneus ($P < .001$) and left superior frontal gryus ($P < .001$). Post-hoc analyses revealed volume in the left precuneus was larger in BD_{CB+} relative to BD_{CB-} and HC, whereas thickness in the left superior frontal gyrus was smaller in BD_{CB+} and BD_{CB-} relative to HC.

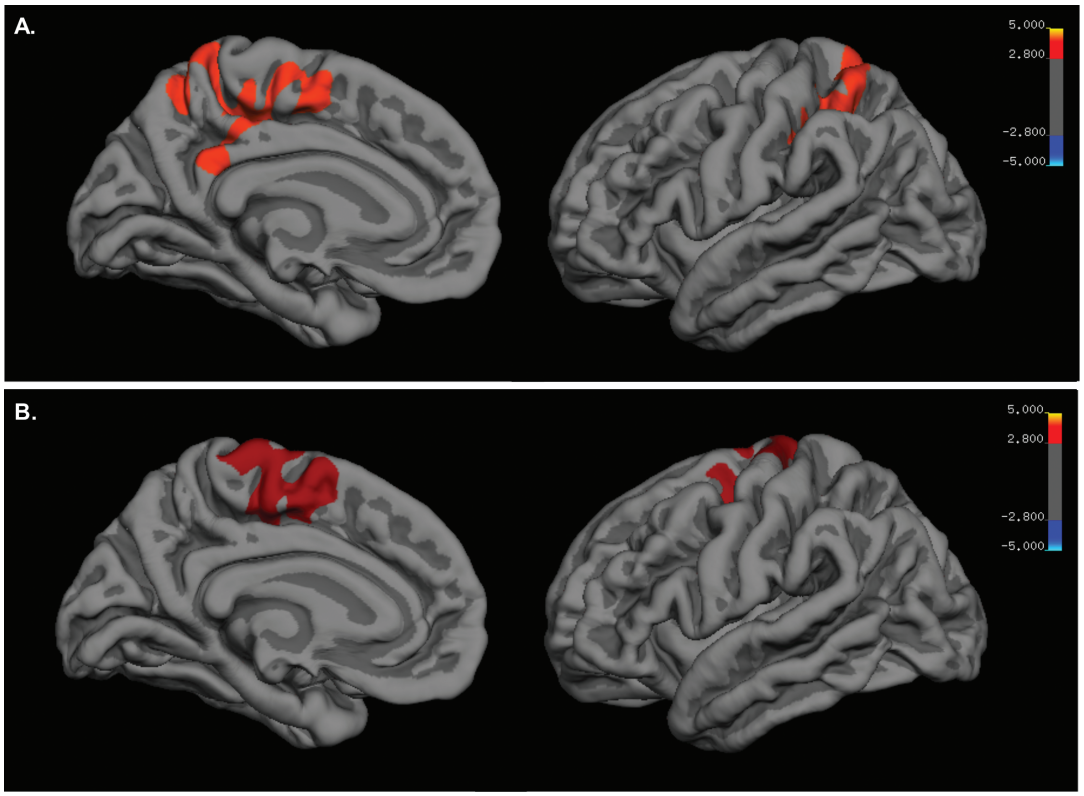

Figure 2. Brain maps for vertex-wise analyses. (A) Brain map of the left hemisphere of a cluster with the peak vertex located in the left precuneus ($P < .001$). (B) Brain map of the left hemisphere of a cluster with the peak vertex located in the left superior frontal gyrus ($P = .001$).

Table 3. Vertex-Wise Analyses

			MNI coordinates				
Peak cluster region	Cortical measure	Cluster Size (mm^2)	cwp	x	y	z	Additional region/s
Left superior parietal	Surface Area	2528.33	0.0105	−29.7	−47.5	37.6	Inferior parietal
Left precuneus	Volume	3514.5	0.0001	−11.4	−57.8	54.1	Supramarginal, superior parietal, inferior parietal, postcentral, paracentral, isthmus cingulate, posterior cingulate, superior frontal
Left inferior parietal	Volume	1948.11	0.0009	−29.1	−67	36.8	Superior parietal
Right precuneus	Volume	1854.35	0.0009	9.7	−70	38.9	Superior parietal, inferior parietal
Left superior frontal	Thickness	1912.88	0.0012	−6.3	−2.2	57.9	Precentral gyrus, paracentral
Left precentral gyrus	Thickness	1638.33	0.0045	−47.2	1.1	46.6	Caudle middle frontal
Left medial orbitofrontal	Thickness	1218.21	0.0302	−6.9	24.6	−12.2	Rostral middle frontal, frontal pole, lateral orbitofrontal, rostral middle frontal
Right superior frontal	Thickness	1030.91	0.0444	8.1	22.9	41.1	No other regions present

Abbreviations: cwp, cluster wide *P* value; MNI, Montreal Neurological Institute and Hospital.
Monte Carlo Z simulation threshold was set at 1.3 for all analyses.

Table 4. Vertex-Wise Post-Hoc Analyses

Post-hoc groups	Cortical measure	Peak cluster region	Test statistic (F)	*P* value	Effect size (η^2)
$BD_{CB+} > BD_{CB-}$	Left superior parietal	Surface Area	23.346	<.001*	0.303
	Left precuneus	Volume	25.913	<.001*	0.330
	Left inferior parietal	Volume	22.986	<.001*	0.299
	Right precuneus	Volume	12.541	<.001*	0.175
$BD_{CB+} < BD_{CB-}$	Left superior frontal	Thickness	0.260	.611	0.004
	Left precentral gyrus	Thickness	0.152	.698	0.002
	Left medial orbitofrontal	Thickness	8.750	.004*	0.119
	Right superior frontal	Thickness	0.573	.450	0.008
$BD_{CB+} > HC$	Left superior parietal	Surface Area	6.935	.009*	0.101
	Left precuneus	Volume	14.508	<.001*	0.199
	Left inferior parietal	Volume	9.172	.003*	0.131
	Right precuneus	Volume	19.477	<.001*	0.259
$BD_{CB+} < HC$	Left superior frontal	Thickness	12.642	<.001*	0.168
	Left precentral gyrus	Thickness	10.497	.001*	0.141
	Left medial orbitofrontal	Thickness	19.415	<.001*	0.247
	Right superior frontal	Thickness	13.606	<.001*	0.180
$BD_{CB-} < HC$	Left superior parietal	Surface Area	10.042	.002*	0.142
	Left precuneus	Volume	3.989	.048*	0.059
	Left inferior parietal	Volume	6.790	.010*	0.099
	Left superior frontal	Thickness	10.758	.001*	0.145
	Left precentral gyrus	Thickness	9.460	.003*	0.128
	Left medial orbitofrontal	Thickness	1.895	.171	0.027
	Right superior frontal	Thickness	9.853	.002*	0.133
$BD_{CB-} > HC$	Right precuneus	Volume	0.806	.371	0.012

Abbreviations: BD, bipolar disorder; BD_{CB+}, BD cannabis users; BD_{CB-}, BD non-users.
*Significant.

Despite these limitations, the current study advances knowledge regarding the association between cannabis use and brain structure in relation to adolescent BD. Future studies based on larger samples, using prospective methodology, and examining dose effects (e.g., potency, frequency, duration) are warranted. Future research should also include neurocognitive measures and other measures that would signal whether observed neuro-structural differences are beneficial or detrimental. In Canada, cannabis has been legalized for adults at least 19 years of age, and increased availability and acceptance of cannabis use is anticipated (Fischer and Rehm, 2017; Picard, 2017). While preliminary and cross-sectional, our findings suggest that adolescents with BD may comprise a group in whom cannabis-related neuro-structural effects are pronounced. In conclusion, in this case control study regarding the association of cannabis use with brain structure in adolescent BD, we found significant findings driven by larger volume and/or SA, and smaller cortical thickness among BD_{CB+} vs HC. Given the context of increasing global legalization, increased

potency, and increased belief regarding salutary health effects of cannabis, addition research on this topic is greatly needed.

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