Research Paper

Cannabis use and resting state functional connectivity in adolescent bipolar disorder

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Background: Adolescents with bipolar disorder have high rates of cannabis use, and cannabis use is associated with increased symptom severity and treatment resistance in bipolar disorder. Studies have identified anomalous resting-state functional connectivity among reward networks in bipolar disorder and cannabis use independently, but have yet to examine their convergence. **Methods:** Participants included 134 adolescents, aged 13 to 20 years: 40 with bipolar disorder and lifetime cannabis use, 31 with bipolar disorder and no history of cannabis use, and 63 healthy controls without lifetime cannabis use. We used a seed-to-voxel analysis to assess the resting-state functional connectivity of the amygdala, the nucleus accumbens and the orbitofrontal cortex, regions implicated in bipolar disorder and cannabis use. We used a generalized linear model to explore bivariate correlations for each seed, controlling for age and sex. **Results:** We found 3 significant clusters. Resting-state functional connectivity between the left nucleus accumbens seed and the left superior parietal lobe was negative in adolescents with bipolar disorder and no history of cannabis use, and positive in healthy controls. Resting-state functional connectivity between the right orbitofrontal cortex seed and the right lateral occipital cortex was positive in adolescents with bipolar disorder and lifetime cannabis use, and negative in healthy controls and adolescents with bipolar disorder and no history of cannabis use. Resting-state functional connectivity between the right orbitofrontal cortex seed and right occipital pole was positive in adolescents with bipolar disorder and lifetime cannabis use, and negative in adolescents with bipolar disorder and no history of cannabis use. **Limitations:** The study did not include a cannabis-using control group. **Conclusion:** This study provides preliminary evidence of cannabis-related differences in functional reward circuits in adolescents with bipolar disorder. Further studies are necessary to evaluate whether the present findings reflect consequences of or predisposition to cannabis use.

Introduction

Bipolar disorder affects approximately 2% to 5% of adolescents worldwide, and is characterized by recurrent mood episodes, including depression and mania or hypomania.[1,2] Bipolar disorder is associated with increased rates of substance use and substance use disorders.[3,4] Approximately 1 in 3 adolescents with bipolar disorder have comorbid substance use disorders, and cannabis is the most commonly used drug.[5,6] Cannabis use and cannabis use disorder have been associated with a more severe course of bipolar disorder, including delayed recovery, increased number of symptoms and episodes, increased functional disability and decreased treatment adherence and response.[5,7–9]

Previous structural and functional imaging studies have implicated reward-related brain circuits in cannabis use and bipolar disorder independently. Regions identified in these studies are relevant to reward-related decisions and behaviours such as impulse control, decision-making and emotional regulation.[10–13] Key hubs in reward circuits include the prefrontal cortex, the amygdala, the nucleus accumbens and the striatum.[14] However, despite the relevance of reward circuits to both cannabis use and bipolar disorder, few studies have examined these topics together,[15–17] and none have examined the resting-state functional connectivity correlates of cannabis use in bipolar disorder.

Adolescence is a period of dynamic neurobiological and behavioural change.[18] This critical developmental epoch is also a period of heightened vulnerability to the use and deleterious effects of exogenous substances on the brain.[19,20] Cannabis comprises more than 100 components known as cannabinoids, of which tetrahydrocannabinol (the main psychoactive component of cannabis) and cannabidiol are among the most studied.[21] Both compounds interact with the endocannabinoid system, an intracellular signalling system found in the brain and throughout the body.[22] There are 2 primary cannabinoid receptors: type 1 is most concentrated in the brain, and type 2 is most concentrated in the periphery.[21] The endocannabinoid

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system is one of the most important physiologic systems involved in establishing and maintaining human health, with complex actions in the nervous system, the immune system and multiple organ systems.[23,24]

Resting-state functional connectivity represents a specific functional MRI technique that measures the temporal synchronization of functional MRI signals between spatially distinct brain areas.[25–28] To our knowledge, 1 task-based functional MRI study in adolescent bipolar disorder has used a cannabis-cue paradigm to elicit brain activation patterns during visual stimuli (i.e., neutral v. cannabis-related images).[17] Adolescents with bipolar disorder but no cannabis use disorder (n = 14) exhibited greater activation than adolescents with bipolar disorder and comorbid cannabis use disorder (n = 25) or controls (n = 15) in the amygdala, the nucleus accumbens, the thalamus and the striatum — regions involved in emotional processing and reward. There were no significant differences for adolescents with bipolar disorder and cannabis use disorder compared to controls.[17]

The purpose of the present study was to investigate differences in resting-state functional connectivity in the reward network among the following groups: adolescents with bipolar disorder and lifetime cannabis use (from infrequent cannabis use to cannabis use disorder); adolescents with bipolar disorder and no history of cannabis use; and healthy controls. Using a seed-to-voxel analysis, we examined resting-state functional connectivity in 3 different regions of interest (ROIs): the amygdala, the nucleus accumbens and the orbitofrontal cortex. We hypothesized that adolescents with bipolar disorder and lifetime cannabis use would have different resting-state functional connectivity patterns in the chosen ROIs compared to adolescents with bipolar disorder and no history of cannabis use, and to healthy controls. Because of a paucity of previous related research, these hypotheses did not specify directionality (i.e., increased v. decreased). Identifying the neural signatures of cannabis use in adolescents with bipolar disorder can offer important insights into the functional disruptions that may underlie the predisposition to and consequences of cannabis use in this population, in whom the clinical correlates of such use is particularly pernicious.

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 parents or guardians.

Participants

The analyzed sample included 134 English-speaking adolescents aged 13 to 20 years: adolescents with bipolar disorder and lifetime cannabis use (n = 40); adolescents with bipolar disorder and no history of cannabis use (n = 31); and healthy controls (n = 63). Participants with bipolar disorder were recruited from the Centre for Youth Bipolar Disorder, a subspecialty clinical research program at Sunnybrook Health Sciences Centre in Toronto, Ontario, Canada. Healthy controls were recruited primarily via community advertisements.

We assessed current and lifetime psychiatric diagnoses for all participants using the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children, Present and Lifetime Version (KSADS-PL),[29] a semistructured interview completed with both the adolescents and their parent(s) or guardian(s). We used the expanded KSADS Mania Rating Scale[30] and the KSADS Depression Rating Scale[31] to assess mood symptoms. We also used the KSADS-PL interview to assess cannabis use. Participants were asked whether they had ever used cannabis before, and for those who answered yes, we administered the KSADS substance use supplement to determine if the participant met the diagnostic criteria for cannabis use disorder. Participants were classified as adolescents with bipolar disorder and lifetime cannabis use if they reported any lifetime cannabis use. We obtained participants' lifetime history of sexual and physical abuse using the KSADS-PL posttraumatic stress disorder screening questions. We measured current and lifetime functioning of each adolescent using the Children's Global Assessment Scale,[32] and we assessed the socioeconomic status of the parents or guardians using the Hollingshead Four-Factor Index.[33] All interviewers had bachelor's or master's degrees and had completed rigorous training under the supervision of the principal investigator (B.G.). Diagnoses and symptom ratings were reviewed and confirmed by a licensed child–adolescent psychiatrist. Diagnoses of bipolar disorder I and bipolar disorder II were based on DSM-IV criteria, because our sample was recruited from 2012 to 2019, and the DSM-5 version of the KSADS-PL was not available until December 2016. For bipolar disorder not otherwise specified, we adopted the operationalized criteria specified in the Course and Outcome of Bipolar Illness study: elated mood plus 2 associated mania symptoms (3 if irritable mood only); change of functioning; minimum 4 hours' duration in 24 hours; and 4 or more cumulative lifetime days meeting the criteria.[34]

Exclusion criteria were as follows: unable to provide informed consent; a pre-existing cardiac, autoimmune or inflammatory illness; currently taking any anti-inflammatory, antiplatelet, antilipidemic, antihypertensive or antihyperglycemic agent(s); any infectious illness within the previous 14 days; any MRI contraindications (e.g., any metal in the body, claustrophobia); any severe neurologic or cognitive impairments; and substance dependence in the previous 3 months. Current cannabis abuse, current recreational use and previous cannabis dependence were not relevant exclusion criteria for this study. In addition to the criteria above, healthy controls were also excluded if they had a major psychiatric disorder (i.e., no lifetime mood or psychotic disorder and no anxiety disorder in the previous 3 months), or any first- or second-degree relative with bipolar disorder or a psychotic disorder. The present study was a secondary analysis based on participants from 2 other studies (see funding sources); although cannabis use was not an exclusion criterion for those studies, 9 healthy controls were excluded from the present analyses because of small cell size and the absence of cannabis use disorder in the healthy controls group.

MRI acquisition

We collected neuroimaging data using a 3 T Philips Achieva scanner with an 8-channel head receiver coil and body coil transmission. We acquired structural images using T_1-weighted high-resolution fast-field echo images with the following parameters: repetition time 9.5 ms, echo time 2.3 ms, inversion time 1400 ms, spatial resolution 0.94 × 1.17 × 1.2 mm, matrix 256 × 164 × 140, flip angle 8°, field of view 240 × 191 mm^2, scan duration 8 m 56 s, 140 slices. We collected resting-state functional MRIs in the axial plane using T_2*-weighted echo planar imaging with the following parameters: repetition time 1500 ms, echo time 30 ms, spatial resolution 3 × 3 × 4 mm, matrix 76 × 60 × 28, flip angle 70°, field of view 230 × 181 mm, scan duration 5 m 50 s, 230 volumes.

During the resting-state scan, participants were instructed to keep their eyes open, focus on a blank screen and think about nothing in particular.

Functional MRI analysis

We completed preprocessing steps and the following analyses using the CONN toolbox (version 17) in Matlab.[35] We removed the first 3 volumes of functional data to account for signal equilibration. We completed preprocessing of functional volumes using the default pipeline for volume-based analysis in the CONN toolbox, including functional realignment and unwarping (participant motion estimation and correction), structural and functional translation, slice-timing correction, functional outlier detection (Artifact Detection Tools based identification of outlier scans for scrubbing), structural and functional segmentation, and normalization to Montreal Neurological Institute space (simultaneously grey/white/cerebrospinal fluid segmentation), as well as functional smoothing (8 mm full width at half maximum Gaussian filter). Head motion was accounted for in the CONN toolbox by identifying problematic time points using Artifact Detection Tools. Images were considered outliers if the global mean image intensity was more than 3 standard deviations from the mean image intensity for the entire resting scan, or if there was a displacement of more than 1.0 mm from the previous frame in an *x*, *y*, or *z* direction. We also examined all volumes manually for motion outliers (> 2 mm or 2° rotation in any direction: *x*, *y*, *z*), and excluded participants if they had any volumes with motion outliers (35 participants excluded: 9 adolescents with bipolar disorder and lifetime cannabis use, 7 adolescents with bipolar disorder and no history of cannabis use, and 19 healthy controls). We used CONN's default pipeline for denoising, which combines 2 steps: a linear regression of potential confounds in the blood-oxygen-level-dependent signal (including white matter, cerebrospinal fluid, realignment, scrubbing and the effect of rest), and band-pass filtering (temporal frequencies below 0.008 Hz or above 0.09 Hz were removed). After denoising, 2 independent raters examined the histograms from the functional connectivity values, which revealed normally distributed data for all participants who were not excluded for head motion.

We determined seed selection a priori and included the amygdala, nucleus accumbens and orbitofrontal cortex, defined using the FMRIB Software Library Harvard–Oxford structural atlas generated by the CONN toolbox and parcellated into left and right hemispheres.

Statistical analysis

We analyzed categorical variables using χ^2 tests and continuous variables using independent-samples *t* tests or analysis of variance (for 3-way analyses). We used nonparametric tests (Mann–Whitney *U* tests, Kruskal–Wallis tests) for variables that were not normally distributed. Two-tailed statistical significance was set at $p < 0.05$.

For the functional connectivity analyses, we used a seed-to-voxel approach. We computed bivariate correlation coefficients between the time series for each bilateral seed region and all other voxel blood-oxygen-level-dependent time series to produce seed-to-voxel functional connectivity maps. Connectivity maps were normalized using Fisher *z* transformation, and β values represent Fisher-transformed correlation coefficient values. We used a generalized linear model to investigate 3-way between-group differences, including demeaned age and sex as covariates.[35] Using *p* values corrected for false discovery rate, we set the voxel-wise height threshold at $p < 0.001$ and cluster thresholding at $p < 0.05$. We applied Bonferroni correction for multiple comparisons for the number of between-group contrasts (i.e., $p < 0.017$). Significant clusters from the generalized linear model analyses were exported as masks to conduct post hoc pair-wise comparisons in an ROI-to-ROI analysis, applying Bonferroni correction for the number of post hoc pair-wise tests (i.e., $p < 0.017$).

Results

Demographic and clinical characteristics

Demographic characteristics for all participants are presented in Table 1. The groups did not differ significantly in terms of age or sex. No healthy controls had a history of cannabis use. Clinical characteristics for adolescents with bipolar disorder are presented in Table 2. Adolescents with bipolar disorder and lifetime cannabis use had more suicide attempts, police contact or arrest, substance use disorders and alcohol dependence than adolescents with bipolar disorder and no history of cannabis use. Among the adolescents with bipolar disorder and lifetime cannabis use, 13 met the criteria for lifetime cannabis use disorder (cannabis abuse $n = 13$; cannabis dependence $n = 10$).

Seed-to-voxel analyses

Our analysis of adolescents with bipolar disorder and lifetime cannabis use compared to healthy controls and adolescents with bipolar disorder and no history of cannabis use revealed altered between-group resting-state functional connectivity in the left nucleus accumbens and the right orbitofrontal cortex seeds (Table 3).

Table 1: Demographic characteristics

Characteristic	Bipolar disorder and lifetime cannabis use $n = 40$	Bipolar disorder and no history of cannabis use $n = 31$	Healthy controls $n = 63$	Test statistic	p value	Effect size
Age, yr	17.49 ± 1.25	17.39 ± 1.91	16.90 ± 1.63	$F = 2.03$	0.14	$\eta^2 = 0.03$
Female	25 (62.5)	19 (61.3)	34 (54.0)	$\chi^2 = 0.89$	0.64	$V = 0.08$
Socioeconomic status*	4.20 ± 0.97	4.35 ± 0.80	4.37 ± 0.87	$H = 0.76$	0.68	$\eta^2 = 0.01$
Race or ethnicity, White	31 (77.5)	23 (74.2)	32 (50.8)	$\chi^2 = 9.35$	0.009§¶	$V = 0.26$
Intact family	22 (55.0)	21 (67.7)	42 (66.7)	$\chi^2 = 1.76$	0.42	$V = 0.12$
Tanner stage†	4.48 ± 0.64	4.39 ± 0.67	4.29 ± 0.61	$H = 2.77$	0.25	$\eta^2 = 0.02$
Body mass index (adjusted), kg/m^2	24.46 ± 4.41	23.57 ± 4.77	21.91 ± 3.69	$H = 11.11$	0.004§	$\eta^2 = 0.08$
Children's Global Assessment Scale score						
Most severe previous episode	43.30 ± 8.95	44.73 ± 8.91	—	$U = 643.50$	0.60	$d = 0.16$
Highest score in past year‡	67.33 ± 12.34	69.90 ± 10.68	89.48 ± 5.07	$F = 93.47$	< 0.001§¶	$\eta^2 = 0.58$
Score in past month‡	64.18 ± 11.81	65.90 ± 11.28	89.49 ± 4.53	$F = 132.93$	< 0.001§¶	$\eta^2 = 0.66$

Values are reported as mean ± standard error or n (%).
*Based on the Hollingshead Four Factor Index.[33]
†Measured on a scale of 1 to 5.
‡Homogeneity of variance violated; Welsh test reported.
§Significant at $p < 0.05$ (adolescents with bipolar disorder and lifetime cannabis use v. healthy controls).
¶Significant at $p < 0.05$ (adolescents with bipolar disorder and no history of cannabis use v. healthy controls).

The left nucleus accumbens seed yielded a significant difference in resting-state functional connectivity in the left superior parietal lobe (β = 0.25, $F_{2,129} = 18.31$, $p < 0.001$), and this finding remained significant after correction for multiple comparisons (Figure 1). Analyses of the left nucleus accumbens to the left superior parietal lobe showed a significant anticorrelation: adolescents with bipolar disorder and no history of cannabis use had negative connectivity, and healthy controls had positive connectivity (β = 0.31, $F_{1,90} = 39.34$, $p < 0.001$). We found no significant differences for adolescents with bipolar disorder and lifetime cannabis use in this analysis.

The right orbitofrontal cortex seed revealed altered resting-state functional connectivity in 3 significant clusters. First, we found a significant difference in resting-state functional connectivity between the right orbitofrontal cortex and the right lateral occipital cortex (β = 0.18, $F_{2,129} = 10.93$, $p < 0.001$). Pair-wise post hoc analysis of the right orbitofrontal cortex to the right lateral occipital cortex showed a significant anticorrelation: adolescents with bipolar disorder and lifetime cannabis use had positive connectivity, and adolescents with bipolar disorder and no history of cannabis use had negative connectivity (β = 0.26, $F_{1,67} = 14.80$, $p = 0.003$). We also found a significant anticorrelation for adolescents with bipolar disorder and lifetime cannabis use and healthy controls: adolescents with bipolar disorder and lifetime cannabis use had positive connectivity, and healthy controls had negative connectivity (β = 0.25, $F_{1,99} = 17.25$, $p = 0.002$). For the right orbitofrontal cortex to the right lateral occipital cortex, we found no significant differences in resting-state functional connectivity between adolescents with bipolar disorder and no history of cannabis use and healthy controls. Second, we found a significant difference in resting-state functional connectivity between the right orbitofrontal cortex and the right occipital pole (β = 0.17, $F_{2,129} = 9.19$, $p = 0.007$). Pair-wise post hoc analysis showed a significant anticorrelation: adolescents with bipolar disorder and lifetime cannabis use had positive connectivity, and adolescents with bipolar disorder and no history of cannabis use had negative connectivity (β = 0.23, $F_{1,67} = 15.79$, $p = 0.003$). We found no significant differences between healthy controls and either group of adolescents with bipolar disorder for the right orbitofrontal cortex to the right occipital pole. The clusters in the right lateral occipital cortex and right occipital pole survived correction for multiple comparisons (Figure 2). Third, we found a significant difference in resting-state functional connectivity between the right orbitofrontal cortex and the left occipital pole (β = 0.12, $F_{2,129} = 7.23$, $p = 0.045$), but this cluster did not survive correction for multiple comparisons.

We found no significant differences in resting-state functional connectivity originating from the right nucleus accumbens seed, the left orbitofrontal cortex seed or the bilateral amygdala seeds.

We conducted sensitivity analyses using the same model as the original analyses, controlling for alcohol dependence, police contact or arrest and suicide attempts independently. In each case, the findings for the left nucleus accumbens remained significant, but findings for the right orbitofrontal cortex were no longer significant.

Discussion

The present study used a seed-to-voxel analysis to identify patterns of differential resting-state functional connectivity across adolescents with bipolar disorder and lifetime cannabis use, adolescents with bipolar disorder and no history of cannabis use, and healthy controls. We observed between-group differences in 3 significant clusters across 2 seeds in the reward network: the nucleus accumbens and the orbitofrontal cortex. For the left nucleus accumbens seed, we found

Table 2: Clinical characteristics of bipolar disorder groups

Characteristic	Bipolar disorder and lifetime cannabis use *n* = 40	Bipolar disorder and no history of cannabis use *n* = 31	Test statistic	*p* value	Effect size
Bipolar disorder characteristics					
Bipolar disorder I	16 (40.0)	8 (25.8)	$\chi^2 = 2.12$	0.35	$V = 0.17$
Bipolar disorder II	13 (32.5)	10 (32.3)			
Bipolar disorder NOS	11 (27.5)	13 (41.9)			
Age at onset	15.22 ± 2.53	14.32 ± 2.91	$U = 468.0$	0.12	$d = 0.33$
Clinical characteristics					
Lifetime psychosis	3 (7.5)	6 (19.4)	$\chi^2 = 2.22$	0.14	$V = 0.18$
Lifetime suicide attempt(s)	10 (25.0)	1 (3.2)	$\chi^2 = 6.32$	0.01†	$V = 0.30$
Lifetime self-injurious behaviour	19 (47.5)	16 (51.6)	$\chi^2 = 0.19$	0.73	$V = 0.04$
Lifetime suicidal ideation	23 (57.5)	19 (61.3)	$\chi^2 = 0.10$	0.75	$V = 0.04$
Police contact or arrest	12 (30.0)	3 (9.7)	$\chi^2 = 4.33$	0.04†	$V = 0.25$
Lifetime physical or sexual abuse	2 (5.0)	2 (6.5)	$\chi^2 = 0.07$	0.79	$V = 0.03$
Lifetime psychiatric hospitalization	21 (52.5)	11 (35.5)	$\chi^2 = 2.04$	0.15	$V = 0.17$
Current depression score*	15.83 ± 11.91	15.42 ± 9.58	$U = 597.0$	0.79	$d = 0.04$
Lifetime depression score*	30.40 ± 12.27	28.42 ± 11.39	$U = 569.0$	0.55	$d = 0.17$
Current mania score*	9.45 ± 10.73	8.65 ± 8.25	$U = 629.0$	0.92	$d = 0.08$
Lifetime mania score*	30.25 ± 10.91	30.32 ± 9.48	$t = –0.03$	0.98	$d = 0.01$
Lifetime comorbid diagnoses					
Attention-deficit/hyperactivity disorder	20 (50.0)	15 (48.4)	$\chi^2 = 0.02$	0.89	$V = 0.02$
Any anxiety	30 (75.0)	24 (77.4)	$\chi^2 = 0.06$	0.81	$V = 0.03$
Substance use disorder	14 (35.0)	2 (6.5)	$\chi^2 = 8.15$	0.004†	$V = 0.34$
Oppositional defiant disorder	13 (32.5)	7 (22.6)	$\chi^2 = 0.85$	0.36	$V = 0.11$
Conduct disorder	3 (7.5)	0	$\chi^2 = 2.43$	0.12	$V = 0.19$
Nicotine use	9 (22.5)	2 (6.5)	$\chi^2 = 3.44$	0.06	$V = 0.22$
Alcohol abuse	4 (10.0)	1 (3.2)	$\chi^2 = 1.22$	0.27	$V = 0.13$
Alcohol dependence	5 (12.5)	0	$\chi^2 = 4.17$	0.04†	$V = 0.24$
Family psychiatric history					
Mania/hypomania	6 (15)	8 (25.8)	$\chi^2 = 1.46$	0.23	$V = 0.14$
Depression	23 (57.5)	17 (54.8)	$\chi^2 = 0.01$	0.94	$V = 0.01$
Anxiety	22 (55.0)	14 (45.2)	$\chi^2 = 0.48$	0.49	$V = 0.08$
Attention-deficit/hyperactivity disorder	11 (27.5)	7 (22.6)	$\chi^2 = 0.16$	0.69	$V = 0.05$
Lifetime medications					
Second-generation antipsychotic	29 (72.5)	24 (77.4)	$\chi^2 = 0.22$	0.64	$V = 0.06$
Lithium	9 (22.5)	7 (22.6)	$\chi^2 = 0.00$	0.99	$V = 0.001$
SSRI antidepressant	14 (35.0)	9 (29.0)	$\chi^2 = 0.28$	0.59	$V = 0.06$
Non-SSRI antidepressant	8 (20.0)	5 (16.1)	$\chi^2 = 0.18$	0.68	$V = 0.05$
Stimulant	7 (17.5)	9 (29.0)	$\chi^2 = 1.33$	0.25	$V = 0.14$
Current medications					
Second-generation antipsychotic	25 (62.5)	17 (54.8)	$\chi^2 = 0.42$	0.51	$V = 0.08$
Lithium	6 (15.0)	6 (19.4)	$\chi^2 = 0.24$	0.63	$V = 0.06$
SSRI antidepressant	3 (7.5)	2 (6.5)	$\chi^2 = 0.03$	0.86	$V = 0.02$
Non-SSRI antidepressant	1 (2.5)	2 (6.5)	$\chi^2 = 0.67$	0.41	$V = 0.10$
Stimulant	2 (5.0)	3 (9.7)	$\chi^2 = 0.58$	0.45	$V = 0.09$

NOS = not otherwise specified; SSRI = selective serotonin reuptake inhibitor.
Values are reported as mean ± standard error or *n* (%).
*Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children, depression or mania rating scale.
†Significant at $p < 0.05$.

a significant cluster in the left superior parietal lobe; between-group differences were explained by findings of negative connectivity in adolescents with bipolar disorder and no history of cannabis use, and findings of positive connectivity in healthy controls. For the right orbitofrontal cortex seed, we found 2 significant clusters. In the right lateral occipital cortex cluster, adolescents with bipolar disorder and lifetime cannabis use displayed positive connectivity; adolescents with bipolar disorder and no history of cannabis use and healthy controls displayed negative connectivity. In the right

Table 3: Resting-state functional connectivity, ANCOVA

Seed	MNI coordinates, *x, y, z*	Cluster size, voxels	p_{FDR}	Main region	Additional region(s)
Left amygdala	No significant clusters				
Right amygdala	No significant clusters				
Left nucleus accumbens	–52, –50, 36	326	< 0.001	Left superior parietal lobe	Left supramarginal gyrus, left angular gyrus
Right nucleus accumbens	No significant clusters				
Left orbitofrontal cortex	No significant clusters				
Right orbitofrontal cortex	36, –88, –16	226	< 0.001	Right lateral occipital cortex	Right occipital pole, right fusiform gyrus
	26, –98, 0	133	0.007	Right occipital pole	NA
	–10, –104, –6	77	0.045*	Left occipital pole	NA

ANCOVA = analysis of covariance; FDR = false discovery rate; MNI = Montreal Neurological Institute; NA = not applicable.
*Did not survive Bonferroni multiple comparisons ($p < 0.017$).

occipital pole cluster, adolescents with bipolar disorder and lifetime cannabis use displayed positive connectivity, and adolescents with bipolar disorder and no history of cannabis use displayed negative connectivity. This study advances the literature by examining resting-state functional connectivity correlates of cannabis use in adolescents with bipolar disorder together in a comparatively large sample, and integrating a control group.

We found that adolescents with bipolar disorder and no history of cannabis use demonstrated negative connectivity relative to healthy controls, who exhibited positive connectivity between the left nucleus accumbens seed and left superior parietal lobe. The nucleus accumbens is part of the brain reward system, and it plays an important role in the processing and analysis of rewarding and reinforcing stimuli and contingencies.[14,36,37] The superior parietal lobe integrates multiple sources of sensory information to form a single perception and is implicated in introspective attentional bias.[38] Reward dysfunction is well established in bipolar disorder, but previous findings for resting-state functional connectivity have not robustly linked the nucleus accumbens with the parietal regions.[39,40] Our finding suggests that among adolescents with bipolar disorder and no history of cannabis use, introspection may have been less rewarding than for healthy controls. Such a perspective aligns with findings of high rates of anhedonia in bipolar disorder.[40–42] Negative connectivity between the nucleus accumbens and the parietal lobe, evident only in adolescents with bipolar disorder and no history of cannabis use, may explain in part why these participants have not sought out the potential rewarding effects of cannabis. However, the exact brain mechanism underlying emotion dysregulation in bipolar disorder is still not fully understood; further research is warranted to elucidate this topic. Nonetheless, with previous findings of alterations in reward network connectivity in the amygdala and frontal regions, the present findings add to the evidence of aberrant reward-related circuits in adolescent bipolar disorder.[43–47]

This study also found that adolescents with bipolar disorder and lifetime cannabis use exhibited positive connectivity between the right orbitofrontal cortex seed and the right lateral occipital cortex, relative to healthy controls and adolescents with bipolar disorder and no history of cannabis use, who exhibited negative connectivity. As well, adolescents with bipolar disorder and lifetime cannabis use exhibited positive connectivity relative to adolescents with bipolar disorder and no history of cannabis use, who exhibited negative connectivity between the right orbitofrontal cortex seed and the right occipital pole. The orbitofrontal cortex, part of the limbic system, is involved in executive function, particularly reward-related decision-making.[48–51] The occipital lobe is primarily responsible for visual processing.[52] The results from the present study could represent a stronger association between visual information and reward in adolescents with bipolar disorder and lifetime cannabis use compared to healthy controls and adolescents with bipolar disorder and no history of cannabis use. For example, adolescents with bipolar disorder and lifetime cannabis use may find visual cues of cannabis more rewarding and want to indulge in use or continue use. A previous study found elevated occipital activation during a visual attention task among young adults with chronic cannabis use relative to controls; given similar performance on visual tasks, these findings were inferred to reflect increased cognitive effort.[53] The fact that this anomalous activation was normalized after prolonged abstinence from cannabis suggests that this particular finding may reflect adaptation or compensation or both, rather than predisposition to cannabis use.[53] However, prospective studies and behavioural paradigms are needed to gain insight into the direction of these reward-related findings, as well as their association with other risk factors (e.g., abuse).[54]

Limitations

This study had several limitations that warrant consideration. Our cross-sectional, observational approach precluded us from making inferences of causation of direction. Longitudinal studies are needed to elucidate whether these connectivity patterns were a result of cannabis use or whether they precipitated cannabis use. This study did not include a control group with a history of cannabis use, limiting our ability to examine whether resting-state functional connectivity correlates of cannabis use differed between adolescents with bipolar disorder and healthy controls. We did not use urine toxicology in this study, and this could have led to underreporting of cannabis use and bias toward negative results. We

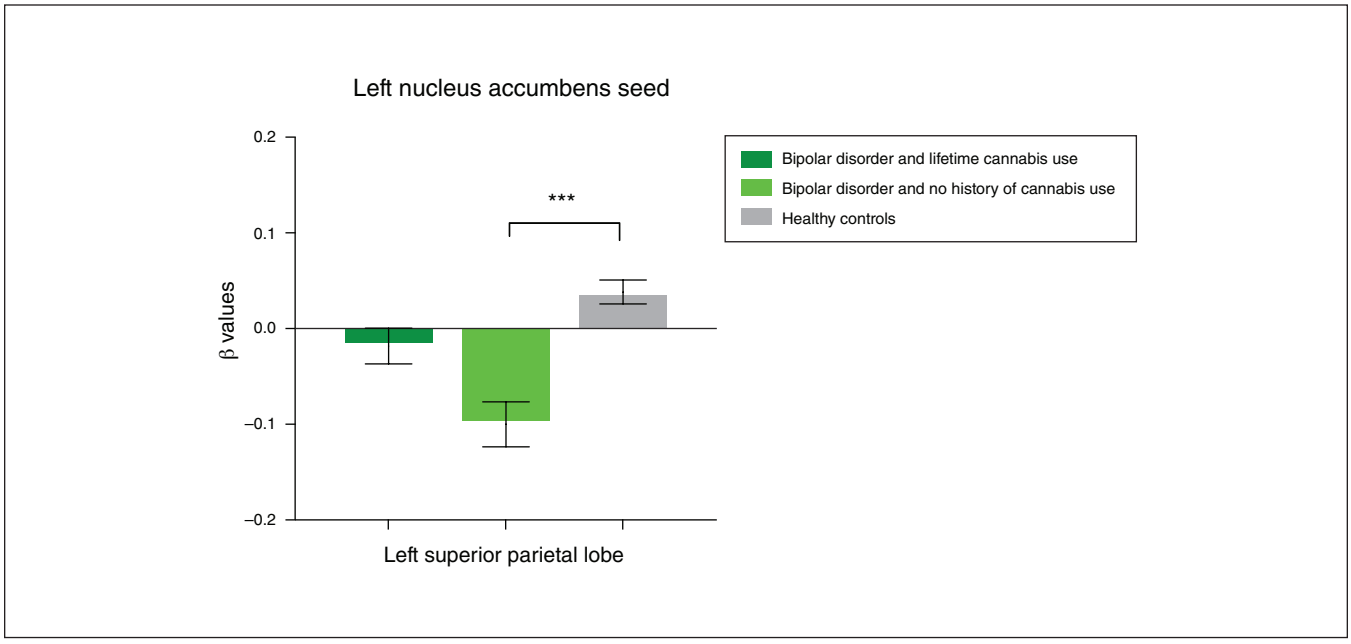

Figure 1: Significant cluster from the left nucleus accumbens seed. β values correspond to Fisher-transformed correlation coefficient values. Error bars denote standard error of the mean. ***$p < 0.001$.

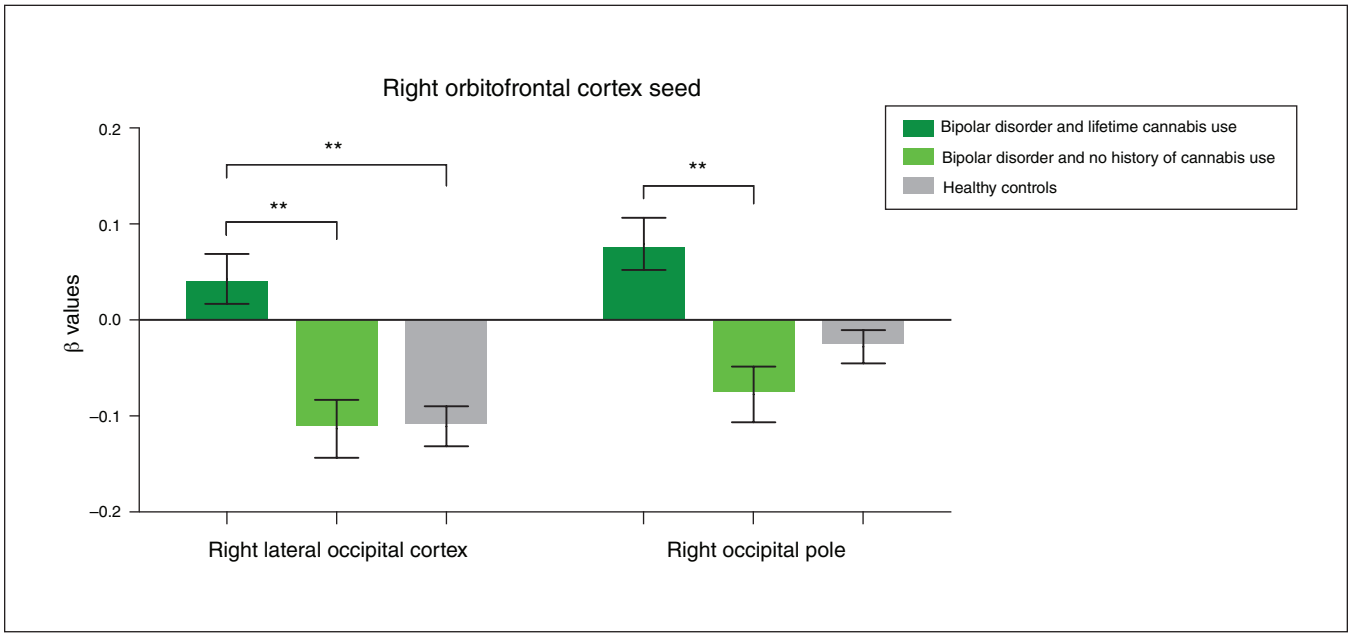

Figure 2: Significant clusters from the right orbital frontal cortex seed. β values correspond to Fisher-transformed correlation coefficient values. Error bars denote standard error of the mean. **$p < 0.01$.

did not collect data about the duration, frequency or potency of cannabis use and thus could not evaluate for related associations with brain structure. The sample size of this study was not powered to conduct complicated multivariable models, which are needed to parse the independent association of cannabis use with brain structure after controlling for various clinical characteristics such as treatment, comorbidity and family psychiatry history. Relatedly, the findings for the right orbitofrontal cortex were not robust to sensitivity analyses — evidence that larger, adequately powered studies are needed. Finally, other imaging modalities and approaches, such as independent component analysis or diffusion tensor imaging, are needed to provide further insight into regional connectivity and the tracts involved in cannabis use.

Conclusion

Despite the above limitations, the present study addresses a gap in the literature by identifying resting-state functional connectivity correlates of cannabis use in adolescents with bipolar disorder. Although we were unable to make causal inferences from these results, they do provide insight into the brain basis of the clinical symptoms associated with cannabis use. Furthermore, this study provides preliminary insight into resting-state network patterns that may underlie a predisposition to or a consequence of cannabis use. Future research using prospective methodology, examining dose effects and including a group of healthy controls with a history of cannabis use, are warranted. Future research should also include a cannabis-cue task-based analysis, as well as an independent component analysis to better understand the brain connectivity related to cannabis use.

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