Intrinsic Frontolimbic Connectivity and Mood Symptoms in Young Adult Cannabis Users

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Objective: The endocannbinoid system and cannabis exposure has been implicated in emotional processing. The current study examined whether regular cannabis users demonstrated abnormal intrinsic (a.k.a. resting state) frontolimbic connectivity compared to non-users. A secondary aim examined the relationship between cannabis group connectivity differences and self-reported mood and affect symptoms.

Method: Participants included 79 cannabis-using and 80 non-using control emerging adults (ages of 18–30), balanced for gender, reading ability, and age. Standard multiple regressions were used to predict if cannabis group status was associated with frontolimbic connectivity after controlling for site, past month alcohol and nicotine use, and days of abstinence from cannabis.

Results: After controlling for research site, past month alcohol and nicotine use, and days of abstinence from cannabis, cannabis users demonstrated significantly greater connectivity between left rACC and the following: right rACC ($p = 0.001$; corrected $p = 0.05$; $f^2 = 0.55$), left amygdala ($p = 0.03$; corrected $p = 0.47$; $f^2 = 0.17$), and left insula ($p = 0.03$; corrected $p = 0.47$; $f^2 = 0.16$). Among cannabis users, greater bilateral rACC connectivity was significantly associated with greater subthreshold depressive symptoms ($p = 0.02$).

Conclusions: Cannabis using young adults demonstrated greater connectivity within frontolimbic regions compared to controls. In cannabis users, greater bilateral rACC intrinsic connectivity was associated with greater levels of subthreshold depression symptoms. Current findings suggest that regular cannabis use during adolescence is associated with abnormal frontolimbic connectivity, especially in cognitive control and emotion regulation regions.

Keywords: cannabis, resting state fMRI, young adults, adolescents, affective symptoms, depressive symptoms, connectivity analysis

INTRODUCTION

Cannabis remains one of the most popular used substances worldwide (1). Approximately, 35% of high school seniors and young adults ages 19–28 reported using cannabis in the past year (2). Cannabis use during youth has been a recent focus in public health research, as it may influence one's risk for reporting symptoms of anxiety and depression (3–14). A potential mechanism underlying cannabis' influence on mood and affective symptoms may involve frontolimbic functioning [see (15, 16)]. Understanding differences in frontolimbic connectivity among young adults with frequent cannabis use may provide insight into the etiology of associated mood or affective risk.

Cannabinoids in cannabis, such as Δ9-tetrahydrocanabidiol (or THC) and cannabidiol (CBD), are chemicals that mimic endogenous neurotransmitters anandamide and 2AG by binding to endocannabinoid (eCB) receptors CB_1 and CB_2 (17–20). THC is the main psychoactive component of cannabis and is responsible for the subjective "high" individuals experience [see (20–22)]. CB_1 activity modulates the release of the neurotransmitters GABA and glutatmate (GLUT) [see (23)]. The eCB system modulates several functions related to physical (e.g., sleep, pain, and inflammation) and mental health, including regulation of emotional and stress responses [see (24–29)].

More specifically, the eCB system plays a role in mood and affect (28, 30–35), integrating reward feedback (36), and threat related signals (37–39). Brain regions primarily involved in the affective processing system include several interacting cortical and subcortical regions (e.g., amygdala, anterior cingulate gyrus or ACC, medial and inferior orbito-frontal, ventromedial or vmPFC, dorsomedial prefrontal cortex, ventral striatum, and insula) (40–44). This system is highly innervated with CB_1 receptors (45–49) and animal models demonstrate developmental changes in CB_1 expression within the mPFC, ACC and insula (50), suggesting the system demonstrates plasticity during adolescence. Therefore, repeated THC exposure during development may impact naturally occurring changes in eCB functioning within mesocorticolimbic regions (16). Indeed, daily cannabis users have shown decreased CB_1 receptor density within frontolimbic regions (prefrontal cortex (PFC), ACC, and insula) compared to non-users which recovered after a month of abstinence (51). Further, acute THC administration has resulted in abnormal performance on behavioral measures of emotional processing (52–54), amygdala reactivity (38), and altered functional connectivity and signaling in PFC regions (15, 16, 53, 55–58). However, additional research is needed to confirm the influence of repeated THC exposure on affective outcomes in adolescents and young adults.

Due to the neuromodulatory role of the eCB system, examining brain functional connectivity is an important outcome to study in regular cannabis users. These relationships can be examined during tasks and also at rest, when individuals are not actively engaging in any specific cognitive tasks, called resting state, or intrinsic functional connectivity (ifcMRI) (59). Connectivity patterns in frontolimbic regions continue to develop into late adolescence and emerging adulthood; prefrontal maturation purports enhanced emotion regulation

and behavior inhibition capabilities [see (60–68)], giving rise to a functional coupling between frontal and limbic regions (i.e., the frontolimbic network) (69). Collectively, the developmental changes in frontolimbic connectivity are thought to enhance socioemotional regulation [see (70–72)], specifically via functioning within the amygdala, medial PFC, vmPFC, ACC, insula, and inferior frontal gyrus (43, 73). A particular region within the PFC, the ACC, also undergoes significant age-related changes in intrinsic functional connectivity, particularly in rostral ACC (rACC) subregions involved in social cognition and emotion regulation (74). Therefore, this system may be particularly vulnerable to repeated THC exposure during development.

Thus far, studies have found slower response times in users when identifying emotional faces and more liberal criterion for selecting sadness (75), poorer facial recognition and emotion matching (76), and emotion identification and discrimination impairments (77) compared to non-users; though accuracy in emotion identification may not display a dose-dependent relationship (78). fMRI studies have found aberrant amygdala and ACC activity in young cannabis users during affective processing tasks, including blunted ACC and amygdala activation during sub-conscious facial viewing (79), blunted amygdala response among youth with comorbid cannabis dependence and depression (80), and greater amygdala reactivity to angry faces in young adolescents (81).

However, to date very few studies have examined intrinsic functional connectivity (ifcMRI) in adolescents and emerging adults (82–86). Studies to date in adolescent and young adult cannabis users (primarily male) have demonstrated increased intrinsic connectivity in frontal (superior, inferior frontal gyrus)-temporal gyrus-cerebellar regions (83), frontal-parietal-cerebellar network (84), increased middle-frontal and cingulate gyrus connectivity (85), and increased frontal gyrus activity along with reduced middle temporal activity (82). Increased connectivity patterns were linked with increased symptoms of cannabis dependence (83) and recent cannabis use frequency (84). In young adult males, cannabis use was linked with increased connectivity in insula and decreased connectivity in the anterior cingulate and midbrain, even after a month of abstinence (86). Thus, overall, young cannabis users appear to demonstrate increased intrinsic connectivity patterns, especially in frontal-limbic regions. Still, these studies were primarily in men (83, 84, 86), thus findings may not generalize to female users (87–90). Further, two studies did not control for comorbid alcohol use (83, 86) and despite the aforementioned link between cannabis use and affective processing, no studies to date have specifically examined affective processing networks in cannabis users. Therefore, additional research is needed to examine intrinsic connectivity in affective processing networks in larger samples that include both males and females, controlling for comorbid alcohol use.

The purpose of the current study was to explore whether regular cannabis use in adolescents and young adults was associated with aberrant ifcMRI frontolimbic connectivity at rest. We employed a priori region of interest analysis focusing on regions with reported cortical differences between young

cannabis users and controls, including: vmPFC (91, 92), ACC (81, 93, 94), insula (95), and amygdala (88, 96, 97). This project utilized ifcMRI data from three collection sites from the Imaging Data in Emerging Adults with Addiction (IDEAA) Consortium (University of Wisconsin-Milwaukee or UWM; McLean Hospital/Harvard University or McLean; University of Texas—Dallas or UTD). The strength of utilizing multi-site data sets include excellent reliability and validity when combining multi-site ifcMRI data (98–107), increased generalizability of more heterogenous groups (i.e., improving sex, ethnicity, and geographic diversity), and larger sample sizes. It was hypothesized that cannabis users would demonstrate increased intrinsic connectivity patterns in regions subserving emotional expression [amygdala, insula, and caudal (cACC) and rostral ACC (rACC)]. Lastly, in order to interpret the findings, a secondary aim examined if group differences in connectivity were associated with cannabis users' self-reported anxiety and depressive symptoms.

MATERIALS AND METHODS

Participants

Participants included 79 cannabis users (42 men and 37 women) and 80 (45 men and 35 women) controls aged 18–30 year old young adults devoid of major medical, psychiatric or neurologic comorbidities. This age restriction is to reduce potential differences in developmental stage since adolescents and emerging adults may have greater PFC and limbic development compared to adult participants (60–64, 68, 108). Study participants were selected from the IDEAA consortium subject pool (PIs: Krista Lisdahl, Ph. D., UWM; Staci Gruber, Ph. D., McLean Hospital/Havard, Susan Tapert, Ph.D., University of California-San Diego, and Francesca Filbey Ph.D., UTD; data from Dr. Tapert's lab did not include resting-state fMRI collection and therefore was not used in the current study).

Inclusion criteria included: right-handedness; had usable intrinsic ifcMRI data; fluency in English; and fit one of two groups: cannabis users (at least weekly cannabis use within the past 3 months, duration of use >1 year) and controls (never had a history of regular (>monthly) use; no recent past month use; no history of cannabis use disorder). *Exclusion criteria* included history of neurological illness or loss of consciousness >2 min; MRI contraindications (pregnancy, claustrophobia, weight over 250 lbs., ferromagnetic implants of any kind, pacemakers, or other devices in body); current use of psychoactive medication; current DSM-IV-TR (109) independent Axis I disorders (aside from substance use disorders); regular other illicit drug use (>20 times); and inability to remain abstinent from all drugs and alcohol for at least 12 h (ranged from 12 h to 21 days monitored abstinence across sites).

Procedures

The Institutional Review Board for each site approved all aspects of data collection. Participants underwent site-specific IRB-approved consenting procedures, and completed screening sessions to ensure inclusion/exclusion criteria. Following study inclusion, the participants completed psychological

questionnaires, underwent substance toxicology screening, and received an MRI at the individual collection sites. The ifcMRI data was collected before any fMRI task for each site.

Inventories and Questionnaires
Substance Use

Drug use prior to study participation was recorded by interview using temporal memory cues from a modified version of the Time-Line Follow-Back at each study site (110). Drug categories included quantity-standardized collection of: nicotine cigarettes (total number), alcohol (total standardized drinks), cannabis (total number of grams of dried flower[1]), and other illicit drugs (days used). Time-period covered for substance use assessment was 1 month [original data collected from each site ranged from 2 weeks (McLean), past 30 days (UTD), to past year (UWM); thus, total *past month* substance use was averaged for each participant collected from McLean, though all McLean users reported consistent daily patterns of use during this time].

Depressive Symptoms

The Beck Depression Inventory—second edition (BDI-II) (collected from all sites) measured self-reported symptoms of past 2-week depressive symptoms with a possible range of 0–63 total scores (111, 112). Low scores on the BDI-II are interpreted as ≤16 and elevated ≥17.

Estimated Verbal IQ

The Wechsler Abbreviated Scale of Intelligence (WASI)—Vocabulary subtest (113) (collected from McLean and UTD) and the Wide Range Achievement Test−4th edition (WRAT-IV). Reading subtest (114) (collected from UWM) measured verbal intelligence (115) and quality of education [see (116)]. Standardized (age-corrected) T-scores for each participant were used in the analyses.

MRI Acquisition and Preprocessing
MRI Acquisition Parameters

Image processing followed standardized recommendations for fMRI processing (117, 118). ifcMRI scans were combined from three research sites; de-identified raw DICOM files were uploaded to the McLean Hospital server. *UWM*: Structural MRI (sMRI) scans were collected using a 3T GE MR750 scanner and SPGR sequence with the following parameters: TR/TE/TI = 8.2/3.4/450 ms, flip angle = 12°, FOV = 240, matrix size: 256 × 256 mm, slice thickness = 1 mm (along left-right direction), voxel size = 1 × 1 × 1 mm, 150 slices, total scan time = 8 min. ifcMRI scans were collected using a gradient echo, echoplanar sequence with ramp sampling correction using the intercomissural line (AC-PC) as a reference (TR: 2,000 ms, TE: 25 ms, FOV: 240, flip angle = 77°, matrix size: 64 × 64, 40 slices, reps: 240, thickness 3.7 mm). *McLean*: sMRI scans were collected using a 3T Siemens Magnetom TrioTim sngo MR B17 and MPRAGE sequence with the following parameters: TR/TE/TI = 2,000/2.15/1,100 ms, flip angle = 12°, FOV = 256 × 256 mm, slice thickness = 1.33 mm (along left-right direction), voxel size =1.5 × 1.0 × 1.3 mm, total

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[1]Cannabis concentrate usage was very low in the sample (n = 3); cannabis concentrates were converted into estimated equivalent grams of flower.

scan time = 9 min. ifcMRI scans were collected using a gradient echo, echo-planar sequence (TR: 2,500 ms, TE: 30 ms, flip angle: 82° degrees, matrix size: mm, 41 slices, voxel size: 3.5 × 3.5 × 2.5 mm³). *UT Dallas*: sMRI images were collected using a 3T Philips whole body scanner equipped with Quasar gradient subsystem (40 mT/m amplitude, a slew rate of 220 mT/m/ms). A 32-channel receive head phased array coil combined with body coil transmission to achieve greater sensitivity in cortical areas. sMRI scans utylized an MPRAGE sequence with the following parameters: TR/TE/TI = 2,100/3.70/1,100 ms, flip angle = 12°, FOV = 256 × 256 mm, slab thickness = 160 mm (along left-right direction), voxel size = 1 × 1 × 1 mm, total scan time = 3 min 57 s. fMRI scans were collected using a gradient echo, echo-planar sequence with the intercomissural line (AC-PC) as a reference (TR: 2.0 s, TE: 29 ms, flip angle: 75 degrees, matrix size: 64 × 64, 39 slices, voxel size: 3.44 × 3.44 × 3.5 mm³).

Preprocessing Details
All images were preprocessed utilizing an identical pipeline, computing system, and software versions (no updates were conducted during data analysis) at UWM. *Anatomical preprocessing* utilized the CPAC analysis software for large multisite datasets (see: https://fcp-indi.github.io/), which utilized pre-existing imaging software, including AFNI (119), FSL (120), and ANTS (http://stnava.github.io/ANTs/). Data were deobliqued to align with X, Y, and Z coordinates; resampled to FSL friendly RPI anatomical convention; skull stripped; anatomical segmentation; and binarized threshold masks were created utilizing FSL's FAST; functional images were linearly registered to anatomical native space using FSL's FLIRT; anatomical images underwent non-linear transformation to MNI152 (voxel size = 2 mm³) standard brain template using ANTS. *fMRI* was also preprocessed using the CPAC software using the following steps: removal of the initial 5 time points to allow T1 stabilization; deoblique; resampling to RPI space; skull stripping; data was "scrubbed" using Framewise Displacement (121) with a maximum TR displacement set to 4 mm; image intensity normalization; linear and quadratic detrending to remove residual drift due to scanner heating and/or slower head movement; nuisance regression (white matter and cerebrospinal fluid) using 6 displacement and motion correction parameters using CompCor (applied prior to smoothing); spatial smoothing (Gaussian Kernal = 4 mm FWHM; Sigma = 2.54); and temporal filtering (Band Pass filter = 0.1–0.01 Hz). *Frontolimbic ROI's.* Cortical and subcortical ROI's were created using FreeSurfer's (122) cortical parcellation atlas [DKT40 atlas; (123)] and subcortical segmentation (124). ROI's included the bilateral rostral anterior cingulate (rACC), caudal anterior cingulate (cACC), ventral medial PFC (vmPFC), insula, and amygdala.

Data Analysis
fMRI Data Analysis; Primary Aim 1
For each subject, the average time series was extracted for all aforementioned ROI's using the CPAC software. Next, the correlation coefficients for the time series were created using MATLAB (Version 8.0.0.783 64-bit maci64, 2012). Lastly, a series of standard multiple regressions were run to predict

correlation coefficients between each set of ROIs; the primary predictor variable (cannabis group status), and covariates (past month nicotine use, past month alcohol use, MRI collection site, and duration of abstinence from cannabis prior to scan) were entered utilizing standard least squares multiple regression in SPSS (version 24). Specifically, the first block included all covariates (past month nicotine use, past month alcohol use, behavioral/MRI collection site, and duration of abstinence) and the second block included cannabis group status. False Discovery Rate correction [FDR; (125)] was implemented to correct for multiple comparisons. All correlation coefficients between ROIs were visually inspected for normality in distribution. Skewed distributions were transformed using a log_{10} transformation and used in the regression in place of the skewed correlation coefficients. There was no evidence of multicollinearity or homoscedasticity following inspection of the standardized residual for the variables of interest. Interpretations of statistical significance were made if $p < 0.05$. For ease of interpretation, regions with connectivity differences after correction for multiple comparisons were also displayed on an average template brain provided by BrainNet Viewer software [(126); see **Figure 2** below].

Brain-Behavior Relationships: Secondary Aim
Pearson r correlations were run between connectivity coefficients and total depressive symptoms among cannabis users (in regions predicted by cannabis use).

RESULTS
Demographic Variables
ANOVAs and χ^2's tests examined whether cannabis users and controls differed in demographic variables (see **Table 1**). Cannabis users and controls did not differ in age [F(1, 157) = 1.1, $p = 0.3$], ethnicity group [64.6% Caucasian for cannabis users and 52.5% for controls, χ^2 (1)2.4, $p = 0.12$], gender [46.8% female for cannabis users and 43.8% for controls, χ^2 (1)0.15, $p = 0.7$], and premorbid intelligence [F(1, 156) = 0.46, $p = 0.5$].

Substance Use
As expected, cannabis users differed from controls in past month total grams [F(1, 157) = 91.1, $p < 0.01$], past month total days of cannabis use [F(1,85) = 9,208.4, $p < 0.01$], past month total standard alcohol drinks [F(1,157) = 20, $p < 0.01$], and past month total cigarettes [F(1,157) = 7.3, $p = 0.01$]. The cannabis users were abstinent from cannabis for 12–24 h (27.8%); 2–3 days (39.2%); 4–7 days (5.1%); or 8 days or greater (27.8%).

Depressive Symptoms
Cannabis users reported significantly greater total BDI-II [F(1, 124) = 5.7, $p = 0.02$] scores compared to controls, although both groups' total BDI-II scores remained in the subclinical range.

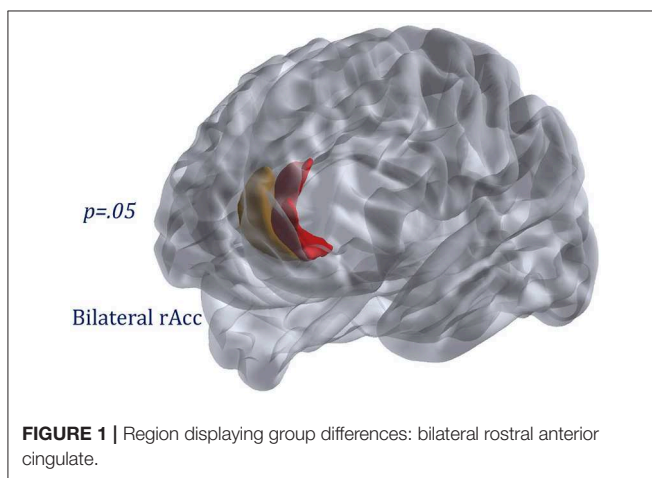### Primary Aim: ROI Intrinsic Connectivity
After controlling for MRI collection site, past month alcohol and cigarette use (in standard units), and days abstinent from

TABLE 1 | Demographics by group status.

	Cannabis users (n = 79)	Controls (n = 80)
Age	23.4 (3.4) [18–30]	22.9 (2.6) [18–29]
Premorbid intelligence Reading standardized score	53.1 (9.7) [31–74]	54.1 (8.9) [30–72]
Gender (% female)	46.8%	43.8%
% Caucasian	64.6%	52.5%
Beck depression inventory (BDI-II) total-2	7.1 (9.3)* [0–53]	3.9 (4.4)* [0–19]
Past month cannabis use Total grams	57.9 (54.3)** [0–217.5]	0 (0)** [0]
Past month total cigarettes Total number	6.9 (22.1)** [0–121]	0.24 (1.4)** [0–12]
Past month alcohol use Total standard drinks	22.3 (28.4)** [0–137]	7.1 (10.9)** [0–62.5]

*$p < 0.05$ and **$p < 0.01$.

FIGURE 1 | Region displaying group differences: bilateral rostral anterior cingulate.

FIGURE 2 | Scatterplot between total depression symptoms and bilateral rAcc connectivity (log transformed) in cannabis users.
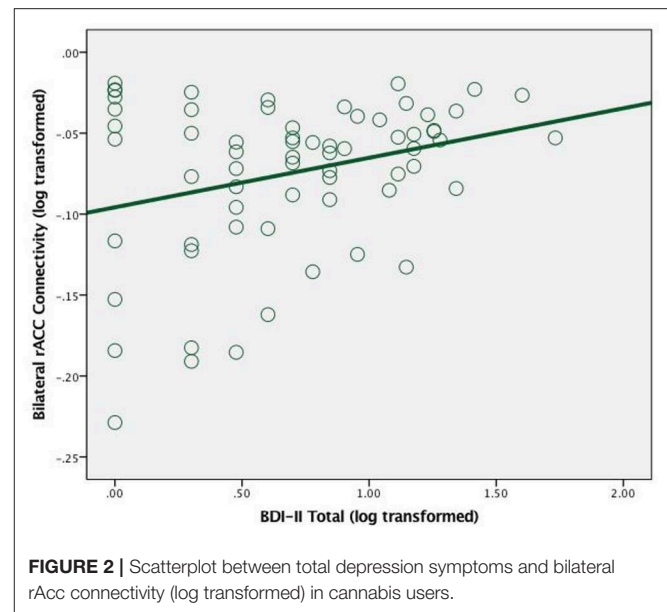
cannabis, cannabis users demonstrated significantly increased connectivity between left rACC and the following: right rACC [$t(80) = 3.3$, $beta = 0.59$, $p = 0.001$; FDR corrected $p = 0.05$; Cohen's $f^2 = 0.55$], left amygdala [$t(80) = 2.2$, $beta = 0.45$, $p = 0.03$; FDR corrected $p = 0.47$; Cohen's $f^2 = 0.17$], left insula [$t(80) = 2.2$, $beta = 0.45$, $p = 0.03$; FDR corrected $p = 0.47$; Cohen's $f^2 = 0.16$]. There were no group differences where cannabis users demonstrated significant decreases in connectivity compared to controls (see **Figure 1** for an image of the bilateral rACC).

Brain-Behavior Relationships
Among cannabis users, greater bilateral rACC connectivity was significantly associated with greater total depressive symptoms [$r = 0.29$, $n = 66$, $p = 0.02$] (see **Figure 2**).

DISCUSSION

The current study examined whether cannabis use was associated with frontolimbic intrinsic connectivity using a cross-sectional design in a sample devoid of independent Axis I anxiety

or mood disorders. After controlling for MRI collection site, recent alcohol, and nicotine use, and abstinence from cannabis use, cannabis users demonstrated increased intrinsic connectivity between the left rACC and the following: left insula, left amygdala, and right rACC in comparison to controls, though only group differences between bilateral rACC survived after correcting for multiple comparisons. Further, we found that increased bilateral rACC connectivity was associated with greater subclinical depressive symptoms in cannabis users.

Current findings parallel previous intrinsic functional studies indicating frequent cannabis use among youth is associated with greater connectivity between frontal and temporal regions (83), and increased ACC connectivity in males (85). Resting state connectivity increases in comparison to controls was also reported within the medial frontal gyrus among a high-risk mostly male adolescent group (82). The present study adds to existing literature by including more females, controlling for other substance use and cannabis abstinence period, and relating the observed connectivity differences to mood-related symptoms. Task-based studies also report altered medial PFC activity associated with cannabis use among emerging adults (79, 127–134), suggesting chronic cannabis use is associated with region-specific changes in brain activity and connectivity among regions implicated in emotion regulation, identification, and modulation.

The current findings of abnormal functional connectivity in the rACC and limbic regions, which is consistent with our previous structural findings. Our team recently reported that greater cannabis use was related to reduced left rACC volume among young cannabis users, and smaller rACC volumes were also significantly associated with lower performance in an emotional discrimination task (94). Further, we also found reduced right ACC cortical thickness in a sample of young cannabis users, including a subset of cannabis users with a

history of childhood attention deficit hyperactivity disorder, compared to non-using controls (93). The ACC undergoes significant developmental shifts in functional connectivity during young adulthood (74), has been implicated in ones' ability to detect and monitor self-produced errors (135, 136) whether one is conscious/aware of the error or not (137, 138). The ACC may be less engaged in cannabis users compared to controls during tasks requiring inhibitory control and error monitoring (131). The rostral subdivision of the ACC is functionally connected with the amygdala (139), forming a network for processing affective facets of behavior (140, 141). In concert with the insula, the ACC also serves to incorporate perceptual information with autonomic and emotional information (142). More specifically, the rACC has been posited to have top-down control influence, serving as a gatekeeper, between regions processing negative affective information and those integrating environmental stimuli [see (143, 144)], and demonstrates protracted development during young adulthood (74). The rACC is involved in implicit or automatic emotion regulation that occurs at a subconscious level (42). Indeed, lesions in the rACC are posited to impair ones' sensitivity to adjustments in personal performance during a cognitive control task (145). For example, cannabis users have demonstrated reduced P300 (attention to emotion) during implicit and empathic emotional processing paradigms, particularly for the highest using cannabis users that also demonstrated deficits in explicit processing of negative emotions (146). Thus, abnormalities in rACC structure and function may impact various behavioral aspects, including cognitive control and emotional regulation.

The current study suggests that chronic cannabis use may increase intrinsic connectivity between emotion regulation regions, which was opposite of our original hypothesis. A potential interpretation may include the inefficiency of prefrontal top-down regulation, as hypothesized by Behan et al. (84), suggesting reduced intrinsic amygdala responsiveness. Further, Pujol et al. (86) found reduced ACC and insula connectivity; however, the study did not examine subcomponents of the ACC and used seed-based rather than region of interest approaches. Thus, disruptions in rACC function may lead to challenges in modulating ones' mood, consistent with the current study findings, or adjusting to emotionally salient internal and external information. Indeed, we also found that increased depressive symptoms among cannabis users were associated with greater connectivity between the bilateral rACC. Alterations in rACC structure (147–150) and function [see (151–153)] have been previously linked with depressive and affective symptoms and antidepressant response (154). Though the current sample did not meet criteria for an Axis I mood or anxiety disorder, cannabis use may impact regions implicated in symptom manifestation. Although cannabis users reported significantly greater subclinical levels of depression, we are unable to determine whether the endorsed symptoms predated the initiation of cannabis use or whether the endorsed symptoms occurred during the course of regular cannabis use among users. Indeed, cross-sectional (8, 11–13) and longitudinal (5, 6, 13, 99, 155) studies among cannabis-using youth have found increased risk of mood and affective

symptoms. Even casual cannabis using young adults report greater depressive symptomatology (156). Thus, structural and functional abnormalities within the rACC observed in cannabis users may result in mood dysregulation. Alternatively, subtle mood dysregulation may be a risk-factor for riskier cannabis use consumption.

Proposed theories accounting for these functional and behavioral differences in cannabis users may have multiple underlying etiologies. Chronic young adult cannabis users demonstrate abnormal CB_1 receptor density in the ACC (51); thus, frequent cannabis use may influence continued white matter myelination and gray matter pruning within this region, impacting structural integrity (81, 91, 93, 157). Further, altering CB_1 availability and eCB signaling may impact GABA and GLUT signaling, which is observed in the ACC of adolescents with chronic cannabis use (158, 159), suggesting continued cannabis use may impact healthy ACC functioning. Indeed, rACC glutamate levels have been associated with interactions between task-positive (supragenual ACC) and task-negative (perigenual ACC) subregions (160), suggesting excitatory activity at rest may alter one's ability to engage networks involved in environmental interaction. Thus, altered inhibitory eCB activity may account for changes in intrinsic ACC connectivity among users. It is also possible that abnormalities in rACC and increased symptoms of depression place adolescents and young adults at increased risk for regular cannabis use. Prospective longitudinal studies are needed to address causality.

In terms of youth treatment, there are potential interventions that may target ACC functioning to improve emotional regulation and mood in cannabis users. For example, activation within the ACC was associated with positive treatment outcomes following change talk among a diverse group of cannabis-using youth (161). Mindfulness-based mediation and a combination of mindfulness with aerobic exercise have also been associated with ACC specific changes [see (162)].

Findings from the current study should be considered in light of potential limitations. Although comorbid use of nicotine products was measured, some participants may have smoked cannabis with nicotine mixed in (e.g., blunts); this was not measured in the current study. Given the cross-sectional nature of the current study, potential differences in frontolimbic connectivity and subclinical mood symptoms may exist *prior to* the onset of frequent cannabis use and serve as a risk factor for regular cannabis use during adolescence (163, 164). The relationships between such factors and substance use patterns among youth have previously been investigated [see (165–175)]. Therefore, prospective, longitudinal studies are necessary to determine timing and causality.

In conclusion, the present multisite imaging study found that among otherwise healthy young adults devoid of independent mood or affective disorders, regular cannabis users had greater intrinsic connectivity between left and right rACC. The current study also found that greater intrinsic bilateral rACC connectivity was associated with greater subthreshold depressive symptoms among cannabis users. Results coincide and expand upon

prior intrinsic and task-based imaging projects among young adults with chronic cannabis use, suggesting altered connectivity between regions with high cannabinoid receptor density that are imperative for emotional inhibition, recognition, and regulation. As THC content continues to rise (176–178), today's users may be at increased risk for elevated mood or anxiety symptoms (179–181). Considering these findings, it is recommended that youth delay regular use of cannabis until after peak brain maturation is achieved [see (182)]. In light of the current paper, cannabis interventions for youth may target improving anterior cingulate functioning, including aerobic exercise and mindfulness-based approaches [see (162, 183, 184)].

ETHICS STATEMENT

This study was carried out in accordance with the recommendations by the Institutional Review Board at each institution (UWM, McLean, and UTD). All subjects gave written informed consent in accordance with the Declaration of Helsinki.

AUTHOR CONTRIBUTIONS

FUNDING

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