

Association between cannabis use and brain imaging phenotypes in UK Biobank: an observational and Mendelian randomization study

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Abstract

Cannabis use during adolescence and young adulthood has been associated with brain structure and functional connectivity. However, despite a rapid increase in cannabis use among older adults in the past decade, the impact on brain structure and function in this population remains understudied. We examined 3,641 self-reported lifetime cannabis users (mean age = 61.00 years, standard deviation (SD) = 7.16) and 12,255 controls (mean age = 64.49 years, SD = 7.58) from the UK Biobank. Brain imaging-derived phenotypes (IDPs) were used as measures of structural and functional connectivity. Associations with cannabis use were assessed using multiple linear regression while controlling for potential confounders. After correcting for false discovery rate (FDR) for multiple testing, in exploratory analyses significant associations were observed with diffusion metrics in the genu of the corpus callosum and with resting-state functional connectivity (rsFC) between the default mode, central executive, and salience networks. Hypothesis-driven analyses did not show any significant association between cannabis use and hippocampal or amygdala volumes. Furthermore, mendelian randomization (MR) analyses did not support a causal relationship between cannabis use and brain structure or function. Our findings indicate that associations between lifetime cannabis use and later life brain structure and function are not likely causal in nature.

Introduction

In the past decade cannabis use has increased worldwide with its legalization for medical and recreational purposes, with more than 4% of the global population aged between 15 and 64 having used cannabis in 2020, which is a 23% increase since 2010.¹ While cannabis use has also increased in older adults,² studies on health-related outcomes in this group are still limited.³ There are reports of adverse cannabis effects on neuro-cognitive performance, brain structure and function,^{4, 5} but it is not known if there are safe upper levels of cannabis use for any of these harms.

Endocannabinoid secretion is essential for a variety of brain functions such as higher-order cognition, memory, reward, mood, and stress sensitivity.⁶ A possible mechanism by which Tetrahydrocannabinol (THC), the psychoactive component in cannabis, affects resting state functional connectivity (rsFC) in the brain is by activating cannabinoid receptor type 1 (CB1), thus disrupting the signalling of endogenous endocannabinoids.^{7, 8} These acute effects of THC on the brain may be associated with chronic changes that can be detected in past cannabis users. Such effects are likely to be greater with the increased concentrations of THC found in cannabis sold after the legalization of cannabis in different parts of the world.⁹

Past use of cannabis has been associated with changes in the structural and functional connectivity in the brain.¹⁰ Most studies have reported associations between cannabis use and grey matter volume, where a smaller hippocampal and amygdala grey matter volumes have been observed.^{8, 9} There are also diffusion tensor imaging (DTI) studies have reported an association with white matter microstructure in the corpus callosum and forceps minor, inferred by a lower fractional anisotropy (FA) and a higher mean diffusivity (MD).^{10, 11, 12} FMRI studies have observed differences in connectivity in regions underlying default mode network (DMN) and central executive network (CEN).^{11, 12, 13, 14, 15} While most studies have looked at the relationship between cannabis use and brain IDPs in adolescence and young adults, only a few studies have included mid-age to older age adults.^{16, 17} Amongst these studies, the focus has been on heavy or dependent users who appear to show abnormalities in structural and functional connectivity in different brain regions.^{11, 13, 18} Further, most studies have limited their analysis to certain brain regions and brain networks.

Here, we investigate associations between cannabis use and a rich set of measures of structure and function across the brain in a large cohort of older adults. We employ both hypothesis-driven and agnostic approaches, and triangulate our observational findings with Mendelian randomization, a method to investigate causal relationships.¹⁹ We hypothesized that cannabis use would be associated with structural and functional connectivity in brain regions and networks rich in CB1 receptors.

Methods

Study sample

The study comprised participants from the UK Biobank listed in Supplementary material (Figure S1). For the total sample of approximately 500,000 participants, the phenotypic data used in this study were from the first repeat assessment visit (2012-2013), and the first imaging visit (2014-2019). Self-reported cannabis use data from the assessment visit were available for 157,316 participants, and MRI data from the imaging visit for 47,920 participants. Data on sociodemographic measures used in the study were collected during the imaging visit. Participants provided informed consent via electronic signature at the time of recruitment. The ethical approval for UK Biobank has been granted by the National Information Governance Board for Health and Social Care and the NHS North-West Multi-centre Research Ethics Committee.²⁰

MRI acquisition and data processing

The imaging data were obtained on Siemens Skyra 3T MRI scanners equipped with 32-channel head coils. The UK Biobank team performed image processing, quality control checks, and automated brain tissue volume computations and their IDPs were made available to the researchers. The brain imaging protocol utilized in the UK includes structural, diffusion, and functional imaging from six distinct modalities: T1-weighted, T2-weighted flair, diffusion MRI (dMRI), susceptibility-weighted imaging (SWI), task functional MRI timeseries data (tfMRI), and resting-state functional MRI timeseries data (rsfMRI).²¹

T1-weighted MPRAGE and T2-weighted FLAIR volumes were obtained at 1×1×1mm (208×256×256 field of view [FOV] matrix) and 1.05×1×1mm (192×256×256 FOV matrix) respectively. Estimation of the grey matter was performed for a total of 139 regions of interest (ROIs) defined by the HarvardOxford cortical and subcortical atlases and the Diedrichsen cerebellar atlas. Subcortical volumes estimation was done using the population priors on shape and intensity variation across subjects. Image segmentation was performed to identify white matter hyperintensities (WMH). Additionally, periventricular WMH (pWMH) and deep WMH (dWMH), were defined based on subsets of total WM hyperintensities.

DMRI were obtained at 2×2×2mm (104×104×72 FOV matrix) using a multishell approach with two b-values ($b = 1000$ and 2000 s/mm²). 50 diffusion encoding directions were acquired for each diffusion-weighted shell and the tensor fitting was performed using the $b = 1000$ s/mm². This generated maps of fractional anisotropy (FA), axial diffusivity (AD), radial diffusivity (RD), and mean diffusivity (MD). Tract-Based Spatial Statistics (TBSS) processing was performed using these DTI maps and TBSS-derived measures were computed by averaging the skeletonized

images of each DTI map within a predefined set of 48 standard-space tract masks defined by the JHU White Matter Atlas (ICBM-DTI-81) (Mori et al 2005).²²

SWI was obtained at 0.8×0.8×3mm (256×288×48 FOV matrix). T2* and Quantitative susceptibility mapping (QSM) were used to generate the IDPs. First T1-weighted structural brain scan was used to derive subject-specific masks for 14 subcortical regions that correspond to the left and right of the 7 subcortical structure ROIs. Subsequently, image-derived phenotypes (IDPs) were calculated based on the median T2* and χ values for each of these regions.

tfMRI were obtained at 2.4×2.4×2.4mm (88×88×64 FOV matrix) involving Hariri faces/shapes “emotion” task with either angry or fearful faces. Participants were presented with blocks of trials where they were required to determine which of the two faces displayed at the bottom of the screen correspond to the face shown at the top, or which of the two shapes presented at the bottom match the shape displayed at the top.

RsfMRI were also obtained as per tfMRI at 2.4×2.4×2.4mm (88×88×64 FOV matrix). On a preprocessed sample of 4162 participants, grouped average independent component analysis (ICA) was carried out using MELODIC.^{22, 23} ICA was performed with dimensionality set to 25 and 100, which resulted in 21 and 55 components, respectively, after discarding the noise components. These 21×21 and 55×55 partial correlation matrices were used as measurements of functional connections. The ICA maps were mapped on each participant’s rsfMRI timeseries data in order to acquire one representative node timeseries per ICA component for each subject. These network ‘nodes’ are a measure of within-network functional connectivity. Subject-specific network-matrices (‘edges’) were also extracted from the node timeseries that provide a measure of functional connectivity between the nodes.²⁴

Genetic variants

We examined two cannabis phenotypes. Detailed information on the SNPs used to instrument these phenotypes is provided in Supplementary Table 1.

For the first exposure variable, we used the genome-wide association study (GWAS) summary statistics for *lifetime cannabis use* from the International Cannabis Consortium (ICC), 23andMe and UK Biobank (N = 184,765) from individuals of European ancestry. Participants reported if they had ever used cannabis during their lifetime and the response was recorded as yes or no. This GWAS identified 8 genome-wide significant independent single nucleotide polymorphisms (SNPs). The estimated SNP-heritability (h^2_{SNP}) for *lifetime cannabis use* was 11%²⁵ (STable 1).

The second exposure variable we used was the GWAS summary statistics for *cannabis use disorder* from the Psychiatric Genomics Consortium (PGC), iPSYCH,

and deCODE (N = 363,884), which consisted of individuals from European and African ancestry. Cases in the PGC met criteria for lifetime DSM-III-R or DSM-IV cannabis abuse or dependence, iPSYCH had ICD-10 codes of F12.1 (cannabis abuse) or F12.2 (cannabis dependence), or both in the Danish Psychiatric Central Research Register and deCODE cases met criteria for lifetime DSM-III-R or DSM-IV cannabis abuse or dependence or DSM-5 cannabis use disorder according to diagnoses made at the National Center of Addiction Medicine in Iceland. This GWAS identified two genome-wide significant independent SNPs: rs7783012 and rs4732724. The estimated h^2_{SNP} for *cannabis use disorder* ranged from 7 to 12%²⁶ (**STable 1**)

For the outcome variable, the summary statistics for each of the brain imaging-derived phenotypes (IDPs) were obtained from the GWAS conducted by the UK Biobank, involving approximately 33,000 participants.²⁷

Cannabis use data

Cannabis use was self-reported at the online follow-up during the first repeat assessment visit. Participants reported if they had “Ever taken Cannabis”. Possible answers were: ‘no’, ‘prefer not to say’, ‘yes, 1–2 times’, ‘yes, 3–10 times’, ‘yes, 11–100 times’, and ‘yes, more than 100 times’. All participants who responded ‘yes’ were categorized as lifetime cannabis users, and ‘no’ responders were categorized as controls. Cannabis users were further divided into two subgroups: (a) low-frequency cannabis use (lifetime cannabis use of 1-10 times), (b) high-frequency cannabis use (lifetime cannabis use of 11-100+ times). This subgroup categorization for cannabis users was introduced in a previous study.²⁸ Participants also reported their “Age when last taken cannabis” and we computed years since the participants last had cannabis by the difference between the age when last cannabis was used and the age when subjects were scanned.

Confounds

We adjusted for potential confounds, which were self-reported *at the time of the MRI scan*. Age at first scan (in years), sex (male and female), and also age², age³, and age-by-sex interaction were controlled for. Townsend deprivation is a measure of material deprivation based on census information. Current employment status was recorded as: in paid employment/self-employed, retired, looking after home and/or family, unable to work because of sickness or disability, unemployed, doing unpaid or voluntary work, full or part-time student or none of the above. Educational qualifications were recorded as: college or university degree, A level/AS levels or equivalent, O levels/GCSEs or equivalent, CSEs or equivalent, NVQ or HND or HNC or equivalent, other professional qualifications or none of the above. Smoking and alcohol drinking status was reported as: current, previous or never. Systolic and diastolic blood pressure were measured in mmHg and body mass index (BMI) in kg/m². For a measurement of mental health status, participants were asked if they had

‘seen a psychiatrist for nerves, anxiety, tension or depression’ and the response was noted as ‘yes’, or ‘no’.

We also accounted for a set of 613 brain imaging-related confounds in this sample as described in Alfaro-Almagro et al (2020).²⁹ These included: assessment centre, intracranial volume, head motion, table position, and scanner acquisition parameters (site, scanner software, protocol, scan ramp, head coil).

Statistical analyses

All statistical analysis was performed in R (version 4.0.0) and visualizations were performed in MATLAB (version R2018_a). Independent samples *t*-tests and chi-squared analyses were performed to assess potential univariate differences in the sociodemographic characteristics between the cannabis users and controls. Multiple linear regression was performed to determine the relationship between cannabis use and brain measures, accounting for confounds.

To begin with, in hypothesis-driven approach we examined the association between cannabis use and grey matter volume of the hippocampus and amygdala to test the hypotheses from previous studies that were conducted on samples consisting of adolescents and young adults. Subsequently, we employed an exploratory approach to examine the association between cannabis use and brain structure and function by utilizing all brain IDPs. A total of 3,921 brain IDPs were tested with an adjusted cut-off p-value of 0.05 using Bonferroni correction. For comparison, p-values in the analyses were also corrected for multiple testing using false discovery rate (FDR, 5%).

We then performed a couple of sensitivity analyses controlling for the covariates. These were performed for the cannabis-IDPs associations that remained statistically significant after adjusting for multiple comparisons using the FDR test. We performed two sensitivity analyses amongst cannabis users to assess whether: 1) years of cannabis abstinence, and 2) cannabis dose (low vs. high frequency), modified cannabis-brain associations.

Finally, we performed two-sample MR analyses by using the *TwoSampleMR* R package to investigate whether significant observed associations between cannabis use and brain IDPs were causal. P-values in the analyses were additionally adjusted for multiple testing FDR. We used 8 SNPs significantly associated with *lifetime cannabis use* and 2 SNPs significantly associated with *cannabis use disorders*. For the 8 SNPs significantly associated with *lifetime cannabis use*, five different MR methods were applied: inverse-variance weighted (IVW), MR Egger, weighted median, weighted mode, and simple mode. For the 2 SNPs significantly associated with *cannabis use disorder*, IVW was applied. The various MR methods make distinct assumptions regarding the nature of pleiotropy. The IVW method was utilized

because the instruments used in the study consisted of multiple SNPs. To ensure valid results, the IVW method requires that all instruments are associated with the exposure variable, but not directly associated with the outcome variable or any confounding factors affecting the relationship between the exposure and outcome. MR Egger tests for horizontal pleiotropy, which assumes that the pleiotropy effects are independent of the strength of the instrument used. The estimate obtained from the weighted median gives an estimate of the causal effect when at least half of the genetic variants used are valid instrumental variables. Weighted mode assumes that the validity of the instruments is based on the largest number of instruments with consistent MR estimates. Last, the simple mode approach uses the mode of the instrumental variable estimate to estimate the causal effect.

Results

Demographics

There were 3,641 cannabis users and 12,255 controls with complete data (**SFigure 1**). Cannabis users were significantly younger than non-users (**Table 1**). While the subjects were well matched for BMI and diastolic BP, the user group had significantly lower systolic BP, and were less socially deprived than the control group. There was a slightly higher proportion of males in the user group, a higher proportion of the user group were in employment and had college degrees. Concerning additional substance use, a higher proportion of users than controls drank alcohol and smoked. A higher proportion of the user group complained of nerves/anxiety/tension/depression (**Table 1**).

Table 1: Demographic characteristics

Variables	Cannabis users (n = 3,641)	Controls (n = 12,255)	Statistics	
	<i>Mean (SD) or % (n)</i>		<i>t or χ^2*</i>	<i>p-value</i>
Age at 1 st scan (years)	61.00 (7.07)	64.49 (7.51)	24.94	2.2e-16
Sex (male n(%))	52.40% (1,908)	43.96% (5,387)	80.29*	2.2e-16
Townsend deprivation index	-1.23 (2.99)	-2.24 (2.50)	-20.31	2.2e-16
Employment status (current; %)	52.89% (1,962)	34.30% (4,204)	519.4*	2.2e-16
College degree (%)	65.42% (2,382)	46.37% (5,683)	477.89*	2.2e-16
BMI (kg/m ²)	26.21 (4.23)	26.37 (4.36)	1.97	0.049
Diastolic BP (mmHg)	78.54 (10.46)	78.69 (10.70)	0.761	0.447
Systolic BP (mmHg)	137.36 (19.18)	141.19 (19.88)	10.30	2.2e-16
Alcohol use (current; n(%))	96.26% (3,505)	93.43% (11,450)	93.47*	2.2e-16
Smoking (current; n(%))	7.39% (269)	1.93% (337)	1320.1*	2.2e-16
Nerves, anxiety, tension or depression status n(%)	11.40% (415)	7.90% (968)	42.83*	5.975e-11

Abbreviations: SD, standard deviation; BMI, body mass index; BP, blood pressure

Legend Table 1: * χ^2 statistic

Observational Analysis

In view of previously observed associations with hippocampal and amygdala volume, we examined these as regions of interest in a hypothesis-driven approach. There were no significant associations observed with cannabis use (**STable 2**).

Out of 3,921 brain IDPs, cannabis use was significantly associated with 40 brain IDPs *after FDR* correction (0.05%, $p = 0.009$) (**Figure 1, Table 2, STable 3**). The strongest associations were with measures of white matter microstructure. Most significant associations identified in the DTI metrics were primarily found in the genu and body of the corpus callosum, demonstrating lower fractional anisotropy (FA) and intracellular volume fraction (ICVF), as well as higher mean diffusivity (MD), second eigenvalue (L2), and third eigenvalue (L3). Furthermore, a higher MD was observed in the left cingulum cingulate gyrus, while increased L2 was detected in the cingulum bundle, and higher L2 and L3 were observed in the anterior corona radiata (**Figure 2**).

A wide range of associations was observed across various rsFC analyses, particularly indicating either weaker or stronger connectivity between multiple networks. These networks predominantly included brain regions associated with the Default mode, Central executive, and Salience network. A visual representation of the resting-state networks as nodes and their connections that are significantly associated with cannabis use for both 21 and 55 resting-state networks obtained, respectively, from 25-component and 100-component group-ICA, is presented in **Figure 3**.

Cannabis use also associations with specific brain IDPs including a larger volume of the right inferior lateral ventricles, a larger surface area of the frontal pole, a greater thickness in the posterior ventral cingulum gyrus, a higher intensity in the right pallidum, and enhanced group-average BOLD activation to emotional faces/shapes during tfMRI.

Associations with six brain IDPs additionally survived the more stringent *Bonferroni-corrected* threshold ($p = 1.275 \times 10^{-5}$). Five of these associations showed lower FA and ICVF and higher MD, L2 and L3 in the genu of corpus callosum and one association in rsfMRI showed a lower FC between brain regions in the inferior frontal, middle frontal and precuneus regions, which are associated with the default mode and central executive network (**Table 3**).

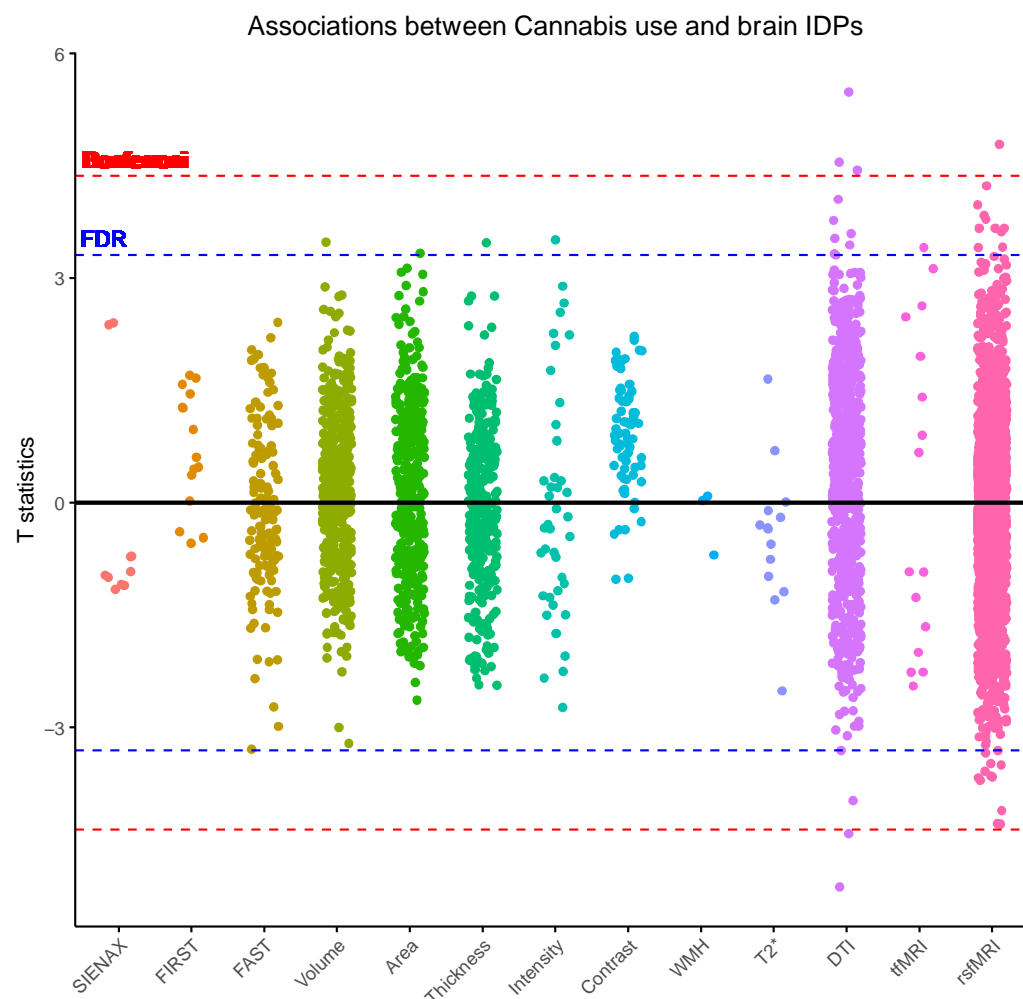


Figure 1: Associations between cannabis use and brain image-derived phenotypes (IDPs). Estimates were generated using multiple linear regression models adjusted for: age, sex, Townsend deprivation index, employment status, educational qualifications, alcohol drinking status, smoking status, body mass index, systolic and diastolic blood pressure, assessment center, nerves/anxiety/tension/depression status and brain imaging confounds. Red line indicates the Bonferroni threshold (3,921 tests, $p = 1.28 \times 10^{-5}$, T statistics = 4.36) and blue line indicated the False Discovery rate threshold (3,921 tests, $p = 9.38 \times 10^{-4}$, T statistics = 3.31). Abbreviations: DTI, diffusion tensor imaging; tfMRI, task functional magnetic resonance imaging; rsfMRI, resting-state functional magnetic resonance imaging

Table 2: Summary of the association between cannabis use and brain IDPs after False Discovery Rate correction (5%).

IDP type	Regions/Tasks/Networks		Association with Cannabis use
Volume	Right inferior lateral ventricles		Positive
Area	Left frontal pole		Positive
Thickness	Left posterior ventral cingulum gyrus		Positive
Regional and tissue Intensity	Right pallidum		Positive
Diffusion tensor imaging	FA	Genu and body of corpus callosum	Negative
	ICVF	Genu of corpus callosum	
	MD	Genu of corpus callosum, cingulum cingulate gyrus	Positive
	L2	Genu and body of corpus callosum, and left cingulum cingulate gyrus	
	L3	Genu and body of corpus callosum, genu, and right and left anterior corona radiata	
Task-based functional MRI	BOLD faces-shapes		Positive
Resting state functional MRI	Default mode network, central executive network, salience network, motor network, visual network, subcortical-cerebellum network, attention network and limbic network		Negative/Positive

Abbreviations: MRI – magnetic resonance imaging; FA, fractional anisotropy; MD, mean diffusivity; ICVF intracellular volume fraction; BOLD, blood oxygenation level dependent

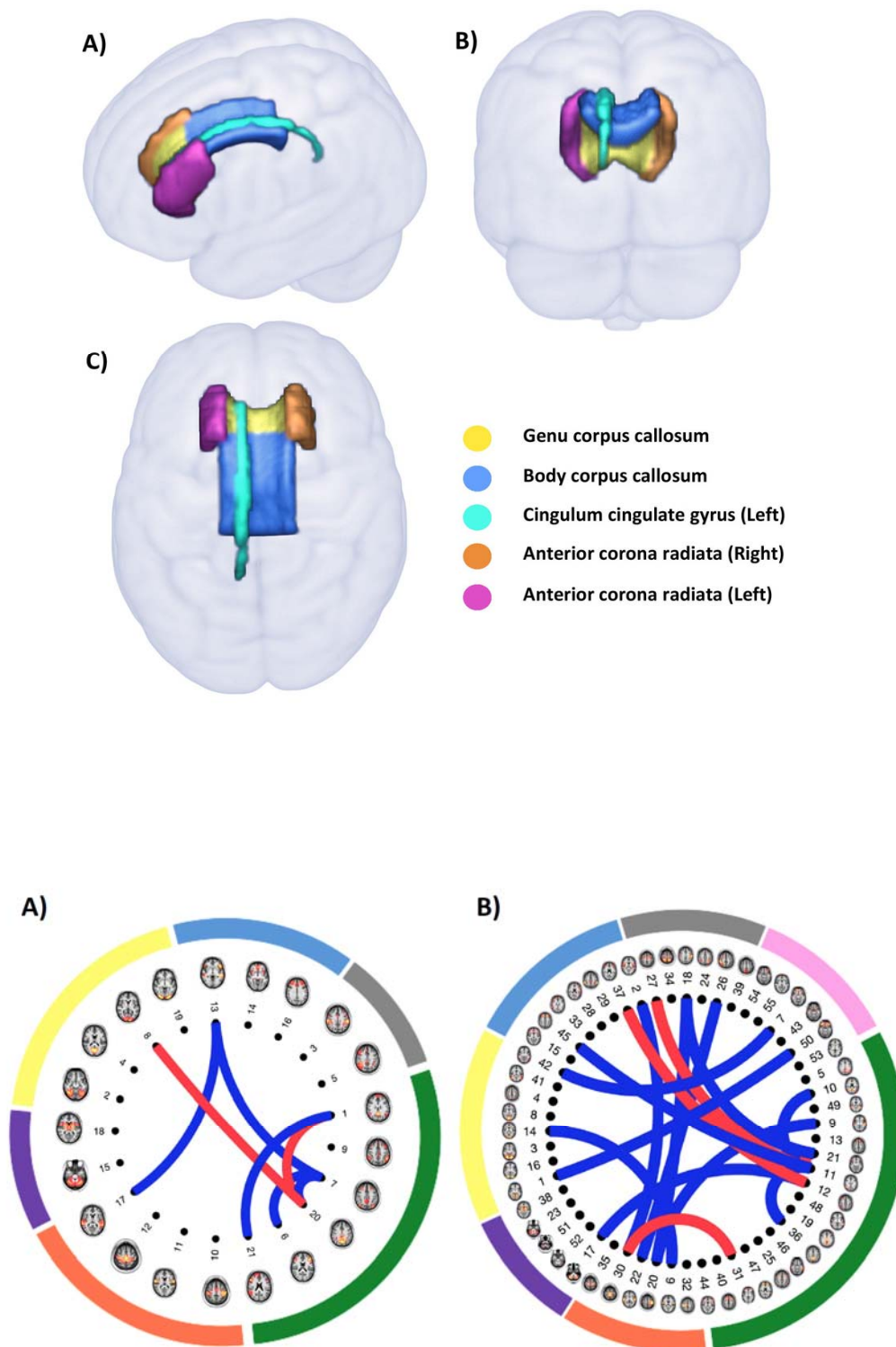


Figure 3: Functional connections significantly associated with cannabis use. Spatial maps of resting state networks nodes (n=21 and n=55) are illustrated in brain images. These were identified as non-noise components from: A) 25-component group-ICA proposed by Miller et al 2016. Nodes are grouped by networks as follows: DMN/CEN (green), motor network (orange)

subcortical-cerebellum network (purple), visual network (yellow), salience/DMN/CES (blue) and attention/DMN/CES (grey). B) 100-component group-ICA. Nodes are grouped by networks as follows: DMN/CEN (green), motor/attention network (orange) subcortical-cerebellum network (purple), visual/attention network (yellow), salience/DMN/CEN (blue), attention/salience/CEN (grey) and limbic/DMN (pink). Connecting lines indicate partial correlations between network nodes significant associated with cannabis (red lines indicate stronger connectivity and blue lines indicate weaker connectivity).

Table 3: Significant associations between cannabis use and brain image-derived phenotypes (IDPs) after correcting for Bonferroni. Estimates represent beta coefficients from multiple linear regression models adjusted for: age, sex, Townsend deprivation index, employment status, educational qualifications, alcohol drinking status, smoking status, body mass index, systolic and diastolic blood pressure, assessment centre, nerves/anxiety/tension/depression status and brain imaging confounds.

IDPs	Beta	LCI	UCI	p-value
FA Genu of corpus callosum	-0.098	-0.134	-0.06	2.95E-07
MD Genu of corpus callosum	0.080	0.044	0.114	8.99E-06
L2 Genu of corpus callosum	0.086	0.048	0.121	5.43E-06
L3 Genu of corpus callosum	0.102	0.064	0.135	4.23E-08
ICVF Genu of corpus callosum	-0.089	-0.127	-0.049	1.00E-05
rfMRI connectivity (ICA25 edge 21)	0.100	0.059	0.142	1.71E-06

LCI, lower confidence interval; UCI, upper confidence interval

Sensitivity Analyses

We assessed whether the duration of abstinence or dose impacted the relationships between cannabis use and brain IDPs that survived the FDR correction in the main analysis. Neither years of cannabis abstinence, nor cannabis dose (low vs. high-frequency use) modified associations between cannabis and brain IDPs.

Two-sample MR Analysis

There was no significant association between either genetically-predicted lifetime cannabis use (IVW beta= -0.048 [95% CI -0.145 to 0.049], $p=0.329$) or cannabis use disorder (IVW beta= -0.005 [95% CI -0.18 to 0.17], $p=0.956$) with FA genu of corpus callosum. No significant association was observed with other brain IDPs as well. There were no indications of horizontal pleiotropy as determined by the MR-Egger intercept test for any of the outcomes (**STable 4**).

Discussion

To the best of our knowledge, this is the largest-ever observational study of relationships between cannabis use and brain structure and function, and the first study to perform MR. Cannabis users had significant differences in brain structure and function, most markedly in white matter microstructure. MR analyses suggested a non-causal relationship underlies this association.

Cannabis users showed a decreased FA and an increased MD in the genu of the corpus callosum compared to non-users. Previous studies on the frequent use of high-potency cannabis by adolescents and young adults have reported disruption in the corpus callosum integrity indicating that the corpus callosum microstructural integrity might be sensitive to high THC concentration in both subjects with and without psychosis.^{30, 31} Cannabis users had lower white matter integrity, as proxied by higher L2 and L3 of the anterior corona radiata and increased MD in the left cingulum. Although no associations in these DTI metrics were reported or observed in past studies, disrupted microstructural integrity in these tracts was reported with other DTI measures showing decreased FA in anterior corona radiata and increased FA of the cingulum.^{32, 33}

Cannabis use significantly associated with rsFC mainly in the brain regions underlying DMN, central executive and salience networks. The brain regions underlying these networks were primarily located in the frontal lobe, temporal lobe, occipital cortex, supplementary motor area, precuneus, and cerebellum. In younger populations, these regions, which are characterized by a high density of CB1 receptors, have shown abnormal FC with cannabis use.^{11, 18, 34} A higher FC between the prefrontal cortex and occipital cortex was reported in young adult chronic cannabis users compared to controls¹². Altered patterns of FC, mostly a hypoconnectivity has been reported from the cerebellum to specific cortical regions including the prefrontal gyrus, disrupting the information flow that is essential for cognitive control and emotional regulation.³⁴ Additionally, an increased FC was reported in regions underlying OFC with precuneus and cerebellar regions, which is an indication of impairment in decision-making capacity and an increase in impulsive behaviour.¹⁸ Our findings however show a complex pattern of higher or lower FC between these regions with cannabis use.

There were also a few other brain structures that showed associations with cannabis use. Cannabis users showed a higher area of the left frontal pole and higher intensity in the right pallidum. While the literature has not previously reported any similar associations with these measures, others have reported a higher volume and a morphological deformation of the pallidum,^{35, 36} and a decreased gyrification of the frontal pole.³⁷ We also observed novel associations with left inferior lateral ventricle volume and left posterior ventral cingulum gyrus thickness.

In contrast, we did not replicate previously observed associations between cannabis use and grey matter volume in the hippocampus and amygdala. One possible explanation is the differing age ranges of subjects, as previous studies examined adolescents and young adults. White matter microstructural changes may also be more sensitive to cannabis effects than the grey matter measures used in this study. Longitudinal studies on the effect of cannabis on grey and white matter are needed to further investigate the changes that might occur over time.

We found no influence of the number of years an individual refrained from using cannabis before the brain scan and brain-cannabis relationships. Additionally, we did not find any significant differences in rsFC between low and high-frequency cannabis users, thus indicating the absence of a dose-response relationship. This may be a result of our sample, consisting of healthy volunteers and a few high cannabis users.

Using an MR approach we found no supporting evidence for a causal effect of cannabis use on brain structure or function. The disparity between observational and MR findings could result from a number of phenomena. First, the observational associations may be confounded by an unmeasured variable. Second, our MR analyses had less statistical power than observational analyses to detect small effects. Future larger-scale GWAS will be helpful in distinguishing these two hypotheses.

Limitations

Our study has several limitations. First, although our sample size was bigger than that of previous studies, UK Biobank is healthier than the general population. It suffers from selection bias with respect to sociodemographics such as the physical, lifestyle and health-related characteristics³⁸ and likely less heavy cannabis users. Second, as the age of cannabis initiation was not assessed, we were unable to examine the impact of the duration of cannabis use on the brain. Third, participants are susceptible to recall bias concerning the amount or frequency of cannabis intake in their lifetime, and their response might be affected by external biases arising from social desirability. Participants might also underreport cannabis use. Fourth, the self-report did not include the potency of cannabis consumed, which might differ across the participants and over time. Fifth, despite our effort to account for the potential confounds in our study, the presence of unmeasured confounding variables (residual confounding) that may have been overlooked cannot be ruled out. Sixth, since this is a cross-sectional study, our findings only suggest an association between cannabis use and brain measures and do not imply causality. Finally, MR relies on a number of assumptions, some of which are untestable.

Conclusion

Lifetime cannabis use is associated with several aspects of brain structure and function in later life, particularly in the corpus callosum. Genetic analysis did not provide support for these associations resulting from causal relationships, suggesting residual confounding may be responsible.

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