Standardization of Structural and Functional Brain Integration in Cannabis Users

Shetiz Dahal*

General Physician Lugansk State Medical University, Luhansk Oblast, 93000 Luhansk, Ukraine

Corresponding Author*

Shetiz Dahal

General Physician Lugansk State Medical University, Luhansk Oblast, 93000 Luhansk, Ukraine

E-mail : dahaltshetiz21@gmail.com

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Abstract

Cannabis is one of the most widely used and commercialized illegal drugs worldwide, notably amid young adults. The neuro-biological mechanisms of cannabis, particularly in adolescents, have yet to be identified. The purpose of this study was to evaluate a cohort of 73 cannabis users (ages 22-36, 19 females) and his 73 healthy controls (ages 22-36, females). We observed some momentous differences in local structural/functional network measures (such as grade along with clustering coefficient), extended in the insular and anterior cranial cortices, and in the lateral/medial temporal cortex .An abundant structural network of clubs showed a normal tendency to distribute in the bilateral frontal, temporal, and occipital regions. The superior and inferior temporal gyri of the two groups did, however, show a few minor variations. Functionally rich clavate nodes were located primarily in the parietal and posterior regions,with minor differences between the groups that were found primarily in the centrotemporal and parietal regions. In multiple regions, regional network metrics of structural/functional networks have been linked to Time of Cannabis Use (TUC). However, no differences between cannabis users and healthy control of global network measures were discovered, and there was no association with cannabis use in structural/functional networks, which demonstrated small-world ownership in both groups. With the exception of the link between termination within the subicule area and TUC, all significant associations between network measures and TUC were determined to be non-significant after FDR adjustment. In conclusion, our findings showed that local topological characteristics of structural and functional networks were altered in cannabis users, but overall brain network structure was unaltered.

Keywords: • Cannabis • Hippocampus • Frontal lobe • Occipital lobe • Parietal lobe • Temporal lobe

Introduction

Objectives

Cannabis is one of the foremost commonly utilized illegal drugs around the world, and its utilization has been on the rise in later a long time, coinciding with its legalization in numerous countries [1]. Investigate has appeared that reliance on cannabis is related with a extend of neurocognitive shortages, counting disabled long winded memory [2], engagement in unsafe behaviors, and destitute execution on cognitive errands that require executive function [3]. Within the past decades, morphometry and arrange examinations have been commonly utilized in most thinks about to explore the affiliation between cannabis utilize and brain structure and work. To consider changes in the local concentration (volume/thickness) of brain tissues, the morphometry-based technique is used [4]. Early considers found no critical morphological changes within the brain related with incessant cannabis use [5]. In any case, later ponders have appeared that the utilize of cannabis may lead to hippocampal, parahippocampal and horizontal atrophy [6-9]. Changes in brain morphology between different regions of the brain may also be responsible for changes in how the brain functions and is organized. By modeling the brain as a network, several studies have used resting-state functional and diffusion-weighted imaging data to examine changes in functional and structural brain connectivity resulting from chronic cannabis use. Here I am. Previous research on large-scale brain networks has shown mixed findings about the relationship between cannabis usage and patterns of structural and functional brain connectivity in cannabis users [10]. Preliminary results, using graph-theoretical means, show that structural brain network efficiency is low, in addition to changes in regional structural connectivity in zonal regions in a group of cannabis users [11, 12].The spleen of the corpus callosum, fornix, and commissural fibres were shown to have reduced structural connectivity in one of the first studies to look at the effects of long-term cannabis use on axonal connectivity [13]. Regular cannabis users had higher structural fractional anisotropy, which decreased with increased use [14]. Other research reported no statistically significant changes between cannabis users and controls in the general properties of brain anatomical networks [15-18]. Long-term cannabis use has been demonstrated to be related with a variety of changes in functional connectivity, despite the fact that most research concentrate on certain brain regions that are used for cognitive activities [19]. Large brain networks' resting-state functional connectivity has been investigated in a number of studies [20]. Increased regional functional connectivity was discovered by Manza et al in the ventral striatum, midbrain, brainstem, and lateral thalamus [21]. They found no appreciable alterations in functional connectivity between the aforementioned regions in cannabis users' and healthy controls' brains utilising seed-based connectivity analyses. In contrast to acute cannabis users, Ramaekers et al. [22], discovered that chronic cannabis users had extensive hyper-connectivity among important brain networks like the dorsal attention, limbic, subcortical, and cerebellar networks. Using graph theory analysis, no differences were found in the global and regional characteristics of resting-state functional networks between cannabis users and non-users [23]. There is growing interest in finding the brain networks' densely connected nodes, or "rich clubs," which have recently been demonstrated to be essential for information integration across anatomical and functional brain networks. Few studies have evaluated the relative abundance of related tissues in cannabis users' and non-users' structural brain networks [16, 17]. Despite a substantial amount of research, the effects of cannabis usage on functional and anatomical connectivity of brain networks have not been extensively explored. In the current study, we employed graph-theoretical indices to determine alterations in brain functional and structural connectivity as well as rich organisation of structural and functional brain networks in cannabis users as compared to healthy controls intended to investigate. We also assessed the association between cannabis use time and network actions. To establish how variation in letterscore, number of anti-VEGF injections received and compliance with guideline recommendations of the number of injections (3 months and 12 months) can be explained by social deprivation.

Materials and Methods

Subjects

This study included 146 subjects. All candidates contingent written informed consent. 109 individuals from this cohort (n=1206, ages 22–36, 54 men) had rs-fMRI and DWI imaging data and met the DSM–IV criteria for cannabis dependency. This subset did not include patients with concomitant drinking, DSM-level anxiety and depression outliers (3 SD from the mean for all 1206 HCP subjects), or subjects with subpar outlier image quality. 19.73 cannabis users were included in the final sample [23]. It is crucial to reduce

the potential confounding effects of these characteristics because it is advised to match groups based on demographic and lifestyle factors. Cannabis groups were matched by age, sex, education, BMI, alcohol and tobacco use using her MatchIt function in R(p>0.1). Subject sociodemographic information is shown in Table 1

Table 1. Summary of Socio-demographic and substance use characteristics of the subjects included in the study.

		Cannabis users	Healthy controls	p-value	t-statistic	df
N of total		73	73			
Mean Agea (SD)		28.58 (3.69)	27.72 (3.56)	0.1352	1.51	72
Gender (N of Male (%))		54 (73.97%)	59 (80.82%)			
Mean BMI (SD)		26.99 (4.91)	27.06 (4.54)	0.9309	− 0.087	72
Education (Years of education completed)	< 11	6 (8.21%)	3 (4.10%)	0.8163	− 0.233	72
	12	9 (12.32%)	15 (20.54%)			
	13	11 (15.06%)	4 (5.47%)			
	14	10 (13.69%)	13 (17.8%)			
	15	6 (8.21%)	5 (6.84%)			
	16	22 (30.13%)	25 (34.24%)			
	17 +	9 (12.32%)	8 (10.95%)			
Times used Cannabis (lifetime)	0 (never used)	–	41 (56.16%)	2.2014e−43	31	72
	1 (1–5 times)	–	23 (31.5%)			
	2 (6–10 times)	–	9 (12.32%)			
	3 (11–100 times)	13 (17.8%)	–			
	4(101–999 times)	20 (27.39%)	–			
	5 (> 1000 times)	40 (54.79%)	–			
Age at first use of cannabis	1 (< = 14)	23 (31.5%)	–			
	2 (15–17)	32 (43.83%)	–			
	3 (18–20)	15 (20.54%)	–			
	4 (> = 21)	3 (4.10%)	–			
Mean Alcohol use (SD)		0.31 (0.51)	0.32 (0.55)	0.9489	− 0.064	72
Mean Tobacco use (SD)		0.24 (0.78)	0.15 (0.59)	0.4566	0.748	72

Neurological imaging data

At the University of Washington, image data from each patient were collected using a Siemens 3T scanner equipped with a 32-channel coil, as seen in Figure 1 [24]. At an isotropic resolution of 0.7 mm, 3D T1- and T2-weighted MR images were obtained (FOV=224 mm, matrix=320, 256 slices). Using the High Angular Resolution Diffusion Imaging (HARDI) method [25], Diffusion-Weighted Images (DWI) were acquired isotropically at a high spatial resolution of 1.25 mm (TR/TE=5520 ms/89.5 ms), with 6 Shells having b=1000 s/mm^2, 2000 s/mm^2, and 3000 s/mm^2 and 270 q points dispersed over three runs and three different shells. The rs-fMRI data were collected in two sessions, with EPI sequences (multiband coefficient= 8, TR/TE=720 ms/33.1 ms, flip angle=52°, FOV=208 mm, spatial resolution =2 in each session) 2 mm × 2 mm). Participants were told not to fall asleep while lying down with their eyes open, relaxing and gazing at a white cross against a black background [26].

The preliminary processing of data

T1w pictures underwent minimum pre-processing for motion correction, normalization in MNI space, and correction of spatial distortion [27]. Intensity normalization to b0, EPI distortion correction, eddy current and motion correction, and gradient non-linearity correction were additional pre-processing steps applied to diffusion-weighted images. All rs-fMRI data were used in 'CIFTI' format. H. Combination of cortical gray matter data modeled on the surface and subcortical gray matter data modeled on volumetric packets included in the image. All functional images were subjected to gradient equalization, EPI distortion correction, motion correction, registration of T1w scans, high-pass filtering with a cutoff of 2000 s for linear de-trending, ICA-based de-noising for automatic artifact removal, Minimal preprocessing was done for bad images. Normalization of very low frequency and nonlinear components to MNI space. Details are described elsewhere [28]. The 15 minutes of high-pass filtered rs-fMRI data are processed using Independent Component Analysis (MELODIC, FSL-FIX) to remove artefact, "bad" components, and non-neuronal spatiotemporal components. To avoid removing interesting discrepancies from the data, a conservative, non-aggressive approach was still used in which a cutoff value of 2000 seconds was found to be better than 200 seconds in ICA-FIX [29]. The 'MSMall' algorithm was used to cross-register the rs-fMRI images between patients. Using characteristics from myelin, resting-state networks, and rs-fMRI visual field maps, this approach matches functional networks to cortical functional maps [30].

Network construction

Glasser Atlas containing 360 regions (180 regions per hemisphere) was used to create functional and structural views of the brain [30]. Since subcortical regions are often included in addiction studies, we used a modified version of this atlas containing 379 plots containing 19 subcortical regions. The subdivision scheme was based on modifications to 210 young, healthy adults with HCP30's brain cortical architecture, function, connection, and topography. For each individual, a structural connection matrix with N N elements representing normalized QA across areas was

created. The ideal threshold (the default threshold in DSI Studio) was set at 0.1% of each person's maximum structural connectivity. We then averaged the connectivity matrix elements for connections that were present in at least 75% of subjects to produce a weighted group structure matrix for each group [31]. In addition, a functional connectivity matrix for each individual was constructed by calculating the average time-course pairwise Pearson correlation coefficients of the 379 regions. The functional connectivity matrix was then thresholded using an ideal threshold of 0.2, 27 keeping 20% of the strongest connections. Based on a trade-off between density and overall efficiency, the ideal threshold was established. By averaging the individual matrices and keeping 20% of the strongest links, the binary group function matrix for both groups was also produced. In Figure 1, the overall process is displayed.

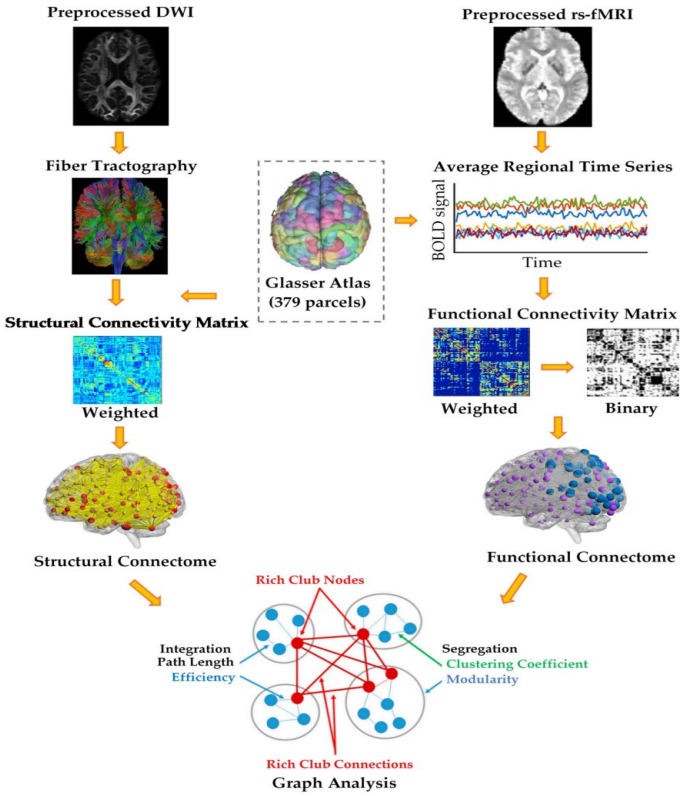

Figure 1. A processing channel for brain structural and functional network analysis.

In Figure 1, we used fiber tractography and a subdivision scheme to construct the structural connectome for each individual. A functional connectome for each individual was also constructed by calculating the average time-course pairwise Pearson correlation coefficients of the 379 regions. The topological characteristics and abundant club organization of anatomical and functional brain networks in both healthy controls and cannabis addicts were then investigated using graph theory analyses [32].

Rich-club organization

In addition, we examined the effects of cannabis on abundant club tissue in the brain using methods described in [33]. For this purpose, unweighted Rich-Club coefficients were calculated for each group mean functional network. The Rich-Crab coefficient $\Phi(k)$ was defined as the ratio of the number of connections in the sub-graph defined by nodes of less than degree k for each k in the range, the maximum degree in the network computes the total number of possible connections in the sub-graph.

$$\Phi(k) = \frac{2E_k}{N_k(N_k - 1)}$$

Where $N_k(N_k - 1)$ is the total number of connections that are feasible and E_k is the number of connections that have a degree lower than k

A weighted rich-club coefficient $\Phi^{\omega}(k)$ was calculated for each group structure network using a similar technique.

After ranking all weights of the structural network ω^{ranked} and $\Phi^{\omega}(k)$ was computed as follows:

$$\Phi^{\omega}(k) = \frac{\omega_k}{\sum_{l}^{E_k} \omega_l^{ranked}}$$

Where $\Phi^{\omega}(k)$ is the sum of the weights of links in the sub-graph of nodes with rank greater than k, and ω^{ranked} is the vector of weights of all links in the structural network, ordered from highest to lowest weight increased.

Then, we estimated the normalized Rich-Club coefficients norm k with respect to random $\Phi(k)$ for the structural and functional networks in each group. It was calculated using the average of 1000 randomly generated networks with the same size and connection dispersion. We evaluate whether the rich clubs of the real network considerably out number those of the null model using a 23-µm sample size ($p<0.05$). norm $\Phi(k)$ is greater than 1 and within k with $p<0.05$ suggested the presence of many club nodes for structural and functional networks of cannabis users and healthy controls. For the reason of this study, we selected k levels so that 30% of the network nodes might be classified as rich club nodes.

Statistical evaluation

Using t-tests, we looked at how cannabis users compared to healthy controls when it came to global plot metrics and local plot metrics. In addition, we used node-level linear regression analysis to examine the relationship between cannabis users' structural/functional network measures (grade and clustering coefficients) and Time of Cannabis Use (TUC). Statistical significance thresholds were used ($p < 0.05$), uncorrected $p<0.02$ $p<0.01$ $p<0.05$) and corrected $p < 0.005$. The majority of the correction errors were due to the use of False Discovery Rates (FDRs) for multiple comparisons, which can be over-conservative when dealing with a large number of nodes.

Informed consent

Informed consent was obtained from all subjects involved in the study.

Results

Graph measures

Table 2 displays the global network measures for both structural and functional networks (Global Efficiency, Typical Path Length, Modularity, and Small Size) for cannabis users versus healthy controls. No statistically significant difference was observed ($p>0.05$).

Table 2. The average values of the network's structural and functional characteristics for each group are shown in the table below.

Topological characteristic	Structural network			Functional network				
	Cannabis users	Healthy controls	p-value	Cannabis users	Healthy controls	p-value	t-statistic	df
Global efficiency	0.3185 ± 0.0215	0.3184 ± 0.0223	0.99	0.4864 ± 0.0292	0.4938 ± 0.0265	0.11	1.6	144
Characteristic path length	0.8234 ± 0.0652	0.8176 ± 0.0650	0.58	1.9604 ± 0.055	1.9538 ± 0.047	0.43	- 0.77	144
Modularity	0.3308 ± 0.0227	0.3222 ± 0.0280	0.05	0.2616 ± 0.0530	0.2697 ± 0.0459	0.33	0.97	144
Small-worldness	1.5792 ± 0.0928	1.5563 ± 0.1092	0.17	1.3042 ± 0.1939	1.3483 ± 0.1916	0.16	1.4	144
Degree	77.76 ± 5.21	78.53 ± 5.54	0.38	75.59 ± 1.43	75.59 ± 1.43	1	0	144
Clustering coefficient	0.2862 ± 0.02	0.2855 ± 0.0207	0.83	0.6257 ± 0.0183	0.6265 ± 0.0188	0.79	0.25	144

The results shown in Figure 2 and Tables 3-6 are statistically significant (p< 0.05), p<0.02, p<0.01, and p<0.005, uncorrected) in node degrees and clustering coefficients of structural and functional networks between groups. increase. As shown, the structural networks of cannabis users were less central (p<0.01, unmodified). Several nodes in the left parieto-occipital region, including V3CD, showed increased structural grade in cannabis users compared with controls. In functional networks, the left anterior cranial cranium showed a significant reduction in grade (p>0.005, uncorrected) in cannabis users. Cannabis users also showed higher regional segregation (clustering coefficient, p<0.01 uncorrected) within fronto-parietal regions, including the premotor cortex, the anterior cranial cortex, and the inferior frontal cortex of the structural network. The posterior Visual Cortex (VFC) and the V3CD (V3C) were among the areas with lower cluster density in cannabis users. Cannabis users also had higher cluster density ratios in the LIFC, VFC, FST, and TG dorsal regions. Compared with the control group, the cannabis group showed less regional functional segregation within the right hemisphere in the dorsolateral prefrontal cortex, para-hippocampal cortex 2, and the ventral region of the diencephalon. In summary, none of the statistically significant differences between the cannabis users and the healthy controls persisted after FDR correction.

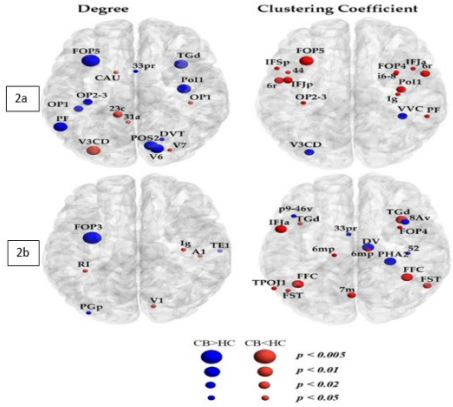

Figure 2. Regions showing (2a) degree and degree-to-cluster ratio for cannabis users vs. healthy controls (2b) in structural networks and functional networks. The color of the nodes indicates the significant increase (in red) or decrease (in blue) in degree (in red) and cluster (in blue) for CB vs. HC. The size of the nodes represents the difference in p values between the groups (p<0.05; p<0.02; p>0.01; and p<0.005; with larger nodes having smaller p values).

Rich-Club organization of structural and functional networks

Figure 3 and Tables 7-10 show the spatial distribution of structurally and functionally abundant club nodes in both groups. As shown, the structure-rich clavate in both groups was mainly Cannabis users had significantly higher and lower number of feature-rich club nodes in the superior temporal gyri compared to controls. Cannabis users had slightly higher and lower feature-rich node numbers in the parietal or posterior gyri, with slight differences between the two groups. Cannabis users had significantly higher feature-rich club node numbers in the centrotemporal or parietal gyri distributed in left bilateral frontal, temporal and occipital lobe regions and deep brain structures.

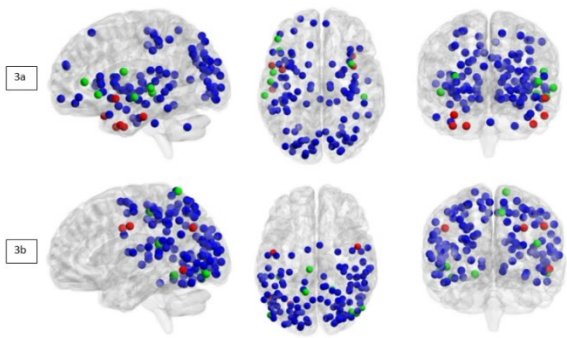

Figure 3. The rich club networks are divided into two groups: (3a) structural and (3b) functional for the cannabis user and healthy control. The typical rich club nodes are in blue, and only a few were found for healthy control (red) or cannabis user (green).

Post hoc analysis

Regression results are shown in Figure 4 and Tables 11 and 12, where plotted measures were statistically significant (p<0.05 uncorrected) in relation to TUC for Structural (SN) and Functional (FN) networks. In this figure, the nodes exhibit a rate of change in node degree (β coefficient) and a clustering coefficient higher than mean+2SD with increasing TUC. In several regions of the posterior region, structural networks (within the bilateral frontal cortex, left parieto-parieto-occipital junction, right V3CD) and functional networks (within the left parahippocampal region, left ventral-medial). The visual field, left PFC, left IPC, right hippocampus, and right medial temporal cortex grades correlated well with TUC in the SN (left DLPFC) and FN (right IFC, right PMFC). Clustering coefficients of frontal and occipital multiple nodes were also positively correlated with TUC in functional and structural networks, respectively (p<0.01, uncorrected). The left interparietal sulcus region in the SN and the left anterior abutment, anterior cingulate gyrus and medial temporal cortex in the FN were found to be negatively associated with TUC (p<0.01, uncorrected). The left inferior frontal cortex and right intra-parietal area in the SN and the right orbital and pole-frontal cortex, right anterior cranial cortex and left tail in the FN showed opposite trends (Table 7). The above important associations between network measurements and TUC did not survive the FDR amendment. After FDR correction, there was only a strong correlation between the grade and TUC in the presubiculum area.

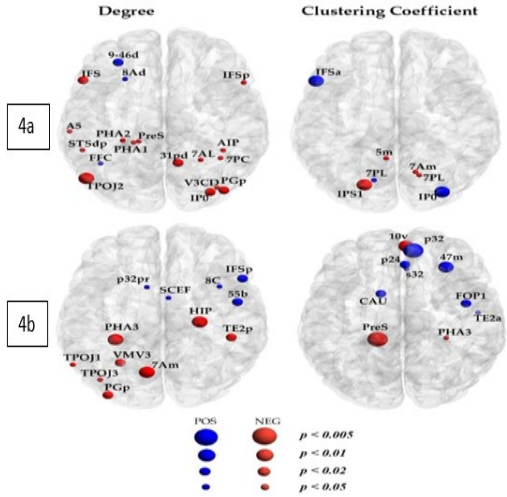

Figure 4. Regions that showed (4a) a strong relationship between times of cannabis use and (4b) Functional Networks. The red and blue nodes showed a negative NEG and positive POS association with times of cannabis use, respectively. The size of the node represented the significant level (P<0.05, P>0.02, P<0.01 and P<0.005 uncorrected), with bigger nodes having smaller p values. Only the PreS region showed a statistically significant relationship after FDR correction.

Discussion

Considering the fact that cannabis usage is very common in the world, little is known about how marijuana could affect the brain. This study compared the effects of cannabis use on the brain's structural and functional network with a large sample of healthy controls and cannabis users. The results showed that Cannabis users' brain structure and functional networks have a smaller world topology with rich-club organization. There was no significant difference between the groups when it came to global network measures. Regional integration and segregation were significantly lower or higher in cannabis users compared to healthy controls [34]. There was a significant correlation between local measures of sativa use and global measures of

sativa use. Collectively, the results demonstrated that cannabis users have altered regional characteristics of their brain's structural and functional networks. In line with previous studies, our results showed no significant alterations in structural and functional brain network network features in cannabis users compared to healthy controls ($p>0.05$ uncorrected). In keeping with earlier research on healthy persons [35], the small-world features of both structural and functional networks were also discovered to be comparable across the two groups.The findings indicated alterations in structural networks related to cannabis use, primarily in the cingulate cortex, dorsolateral, fronto/posterior tectum, fronto-medial cortex, insula, and temporal regions. These alterations in structural connectivity may be associated with regional alterations in gray matter thickness related to substance use disorders and the distribution of cannabinoid receptors within the brain. There are more isolated networks tend to have higher clustering coefficients, so increased clustering coefficients in some regions may indicate differences in the local processing power of these networks. These different patterns of global and local indicators may reflect different sample characteristics in the study. Based on the current data, we can see that club nodes are abundant in both the cortex and the subcortical region, in line with previous studies. Structurally abundant club nodules were found predominantly in bilateral frontal, temporal, mid-occipital and deep brain structures in both groups, whereas functional networks were predominantly located in the parietal and posterior regions. Our results suggest that the structural networks of cannabis users differ from those of healthy controls in rich clubs [35]. This is in contrast to other studies [16], which have not found any differences in the composition [36]. The majority of the functional Rich Club nodes in both groups were located in the posterior and parietal gyri, with slight variations in number of rich Club nodes. Cannabis users had slightly lower and slightly higher number of Centrotempora [37], or Parietal horn knots than controls, with only a few nodes at the back showing high levels of Rich Clubbing in the functional network of the user [38]. This domain is known to play a significant role in the formation of habit in addictive behaviors. These findings suggest the potential for an abnormal connectome related to cannabis use [39].This research findings also revealed a strong correlation between the number of lifetime cannabis users and the node degree/cluster coefficient of structural/functional networks [40]. According to prior research [41], the clustering coefficient of structural connectivity, a segregation measure, revealed a positive correlation between lifetime cannabis usage and the medial temporal cortex, as well as the dorsolateral prefrontal cortex in some cases shown a bad correlation. In the medial temporal cortex (pre-hippocampal), we also found a negative relationship between local metrics (structural network degree, functional network cluster coefficient, and TUC)[42]. The medial temporal cortex, temporoparieto-occipital junction, and hippocampus were the areas with the greatest negative correlation between degree of functional network and length of cannabis usage[43,44]. The hippocampus is a region of the brain that is characterized by the highest levels of CB1 receptor expression [45]. CB1-associated structural and functional alterations have been found to be common to this region in both humans and animal models. However, positive correlations between FNCs and TUCs were mainly seen in the AFC and MFCs. While some studies have reported no significant associations between duration of cannabis use, frequency of cannabis use, age of onset and adverse effects on brain networks, others have reported early onset of cannabis use or It has been suggested that prolonged prolongation can impair brain networks [46]. These differences may be attributed to variability in self-reported data, variability in cannabis user populations across studies, and variability in methodology. Numerous restrictions apply to current research. The HCP database, which is a cross-cutting database, first, offers scant details on cannabis usage and addiction. Age of onset and other existing metrics are level-based and imprecise. Cannabis usage habits, whether daily or chronic, may cause changes in connection patterns. Second, limited the cross-section to young adults aged 22 to 36. To more accurately describe how connectivity patterns within the sample vary over time, longitudinal data are required. Last but not least, given that functional connectivity and rs-fMRI are now generally believed to be temporally dynamic, dynamic connectivity analysis may help better uncover time-varying connectivity patterns linked to cannabis usage.

Table 3. Regions showing significant ($p<0.05$) differences between cannabis users and normal controls in the degree centrality of structural networks.

Region	Area Name	t-statistic
OP1	Area OP1/SII	2.22
$OP2{\sim}3_L$	Area OP2~3/VS	-2.45
$POI1_R$	Area Posterior Insular 1	-2.72
$FOP5_L$	Area Frontal Opercular 5	-3.45
$33pr_R$	Area 33 Prime	-2.34
$23c_L$	Area 23c	2.49
$POS2_R$	Parieto-Occipital Sulcus Area 2	-2.77
DVT_R	Dorsal Transitional Visual Area	-2.04
$31a_L$	Area 31a	2.14
PF_L	Area PF Complex	-2.84
$V7_R$	Seventh Visual Area	2.35
$V6_R$	Sixth Visual Area	-3.26
TGd_R	Area TG dorsal	-2.61
$V3CD_L$	Area V3CD	3.04
CAU_L	Caudate	2.16

Table 4. Regions showing significant ($p<0.05$) differences between cannabis users and normal controls in the clustering coefficient of structural networks.

Region	Area Name	Section	p-value
6r	Rostral Area 6	Premotor cortex	0.01
$i6{\sim}8_R$	Inferior 6-8 Transitional Area	Dorsolateral prefrontal cortex	0.042
$FOP4_R$	Frontal Opercular Area 4	Insular and frontal opercular cortex	0.027
$POI1_R$	Area Posterior Insular 1		0.017
Ig_R	Insular Granular Complex		0.027
$FOP5_L$	Area Frontal Opercular 5		0.009
44_L	Area 44	Inferior frontal cortex	0.04
$IFJp_L$	Area IFJp		0.015
$IFSp_L$	Area IFSp		0.04
$IFJa_R$	Area IFJa		0.036
$OP2{\sim}3_L$	Area OP2~3/VS	Posterior opercular cortex	0.04
PF_R	Area PF Complex	Inferior parietal cortex	0.034
VVC_R	Ventral Visual Complex	Ventral stream visual cortex	0.019
$V3CD_L$	Area V3CD	MT+ complex and neighboring areas	0.016

Table 5. Regions showing significant ($p<0.05$) differences between cannabis users and normal controls in the degree centrality of functional networks.

Region	Area Name	Section	p-value	t-statistic
Ig_R	Insular Granular Complex	Insular and frontal opercular cortex	0.03	2.2
$FOP3_L$	Frontal Opercular Area 3		0.003	-2.82
$A1_R$	Primary auditory cortex	Early auditory cortex	0.043	1.98
RI_L	Retro Insular Cortex		0.04	1.99
$TE1m_R$	Area TE I Middle	Lateral temporal cortex	0.041	-1.92

PGp_L	Area PGp	Inferior parietal cortex	0.03	-2.08
$V1_R$	Primary visual cortex	Primary visual cortex	0.04	1.88

Table 6. Regions showing significant (p<0.05) differences between cannabis users and normal controls in the clustering coefficient of functional networks.

Region	Area Name	Section	p-value	t-statistic
FFC	Fusiform Face Complex	Ventral stream visual cortex	0.008	2.67
FST	Area FST	MT+ complex and neighboring areas	0.04	2.03
$8Av_R$	Area 8Av	Dorsolateral prefrontal cortex	0.015	-2.44
$p9\text{-}46v_L$	Area posterior 9-46v		0.03	-2.27
$IFJa_L$	Area IFja	Inferior frontal cortex	0.007	2.69
$6mp_L$	Area 6mp	Paracentral lobular and mid-cingulate cortex	0.03	2.18
$33pr_L$	Area 33 prime	Anterior cingulate and medial prefrontal cortex	0.04	-1.98
$FOP4_R$	Frontal Opercular Area 4	Insular and frontal opercular cortex	0.03	2.15
52_R	Area 52	Early auditory cortex	0.03	-2.14
TGd	Area TG dorsal	Lateral/Medial temporal cortex	0.002	2.24
$PHA2_R$	Para Hippocampal Area 2		0.006	-2.77
$TPOJ1_L$	Area Temporo-Parieto-Occipital Junction 1	Temporo-Parieto-Occipital junction	0.04	2.05
$7m_L$	Area 7m	Posterior cingulate cortex	0.02	2.14
DV_R	Diencephalon Ventral	SUBCORTICAL	0.009	-2.62

Table 7. Regions whose degrees were significantly associated with times used cannabis (structural networks).

Region	Area Name	Section	p-value	t-statistic
$8Ad_L$	Area 8Ad	Dorsolateral prefrontal cortex	0.02	2.31
$9\text{~}46d_L$	Area 9~46d		0.01	2.45
$IFSp_R$	Area IFSp		0.04	-2.01
PGp_R	Area PGp		0.01	-2.51
$IP0_R$	Area Intraparietal 0		0.01	-2.44
$IFSa_L$	Area IFSa		0.01	-2.62
$A5_L$	Auditory 5 Complex	Auditory association cortex	0.02	-2.26
$STSdp_L$	Area STSd posterior		0.03	-2.14
$PHA1_L$	Para Hippocampel Area 1	Medial temporal cortex	0.02	-2.27
$PreS_L$	PreSubiculum		0.04	-2.01
$PHA2_L$	Para Hippocampal Area 2		0.03	-2.17
$TPOJ2_L$	Area Temporo-Parieto-Occipital junction 2	Temporo-Parieto-Occipital junction	0.006	-2.79
$7AL_R$	Lateral Area 7A	Superior Partial cortex	0.04	-2.01
$7PC_R$	Area 7PC		0.03	-2.19
AIP_R	Anterior Intraparietal Area		0.03	-2.15
$31pd_R$	Area 3 l pd	Posterior cingulate cortex	0.01	-2.39
FFC_L	Fusiform Face Complex	Ventral stream visual cortex	0.02	2.32
$V3CD_R$	Area V3CD	MT+ complex and neighboring areas	0.03	-2.14

Table 8. Regions whose clustering coefficients were significantly associated with times used cannabis (structural networks).

Region	Area Name	Section	p-value
$IFSa_L$	Area IFSa	Inferior frontal cortex	0.01
$5m_L$	Area 5m	Paracentral lobular and mid-cingulate cortex	0.03
7PL	Lateral Area 7P	Superior/ Inferior parietal cortex	0.03
$7Am_R$	Medial Area 7A		0.02
$IP0_R$	Area Intra Parietal 0		0.01
$IPS1_R$	Intra Parietal Sulcus Area 1	Dorsal stream visual cortex	0.01
$V3B_L$	Area V3B		0.04

Table 9. Regions whose degrees were significantly (p<0.05) associated with times used cannabis (functional networks).

Region	Area Name	Section
PHA3	Para Hippocampal Area 3	Medial temporal cortex
$TE2p_R$	Area TE2 posterior	
$TPOJ1_L$	Area Temporo-Parieto-Occipital Junction 1	Temporo-Parieto-Occipital junction
$TPOJ3_L$	Area Temporo-Parieto-Occipital Junction 3	
$55b_R$	Area 55b	Premotor cortex
$SCEF_R$	Supplementary and Cingulate Eye Field	Paracentral lobular and mid-cingulate cortex
$8C_R$	Area 8C	Dorsolateral prefrontal cortex
$IFSp_R$	Area IFSP	Inferior frontal cortex
PGp_R	Area PGp	Inferior parietal cortex
$7Am_L$	Medial Area 7A	Superior Parietal cortex
$p32pr_L$	Area p32 prime	Anterior cingulate and medial prefrontal cortex
$VMV3_L$	Ventro Medial Visual Area 3	Ventral stream visual cortex
HIP_R	Hippocampus	Subcortical

Table 10. Regions whose clustering coefficients were significantly ($p<0.05$) associated with times used cannabis (functional networks).

Region	Area Name	Section	p-value
$47m_R$	Area 47m	Orbital and polar frontal cortex	0.006
$10v_R$	Area 10v	Anterior cingulate and medial prefrontal cortex	0.009
$FOP1_R$	Frontal Opercular Area 1	Posterior opercular cortex	0.02
$PHA3_R$	Para Hippocampal Area 3	Medial temporal cortex	0.04
$TE2a_R$	Area TE2 anterior	Lateral temporal cortex	0.03
$s32_R$	Area s32	Anterior cingulate and medial prefrontal cortex	0.024
$P24_R$	Area posterior 24		0.01
$P32_R$	Area p32		0.003
$PreS_L$	PreSubiculum	Medial temporal cortex	0.003
CAU_L	Caudate	Subcortical	0.01

Table 11. Significant differences between two groups regarding the rich club organization of structural network.

	Region	Area Name	Section
RC nodes in cannabis users	FOP4	Frontal Opercular Area 4	Insular and frontal opercular cortex
	6r	Rostral Area 6	Premotor cortex
	STSdp	Area STSd posterior	Auditory association cortex
	A5	Auditory 5 Complex	
	STSda	Area STSd anterior	
	47l	Area 47l (47 lateral)	Inferior frontal cortex
	P47r	Area posterior 47r	
RC nodes in HC	PeEc	Perirhinal Ectorhinal Cortex	Medial temporal cortex
	TGd	Area TG dorsal	Lateral temporal cortex
	TGv	Area TG Ventral	
	TE2a	Area TE2 anterior	
	STGa	Area STGa	Auditory association cortex

Table 12. Significant differences between two groups regarding the rich club organization of functional network.

	Region	Area Name	Section
RC nodes	LO1	Area Lateral Occipital 1	MT+ complex and neighboring areas
(Cannabis users)	PIT	Posterior Infero-Temporal Complex	Ventral stream visual cortex
	VMV1	Ventro-Medial Visual Area 1	
	V4t	Area V4t	MT+ complex and neighboring areas
	24d	Dorsal Area 24d	Paracentral lobular and mid-cingulate cortex
	5L	Area 5L	
	OP1	Area OP1/SII	Posterior opercular cortex
RC nodes	PEF	Premotor Eye Field	Premotor cortex
(Healthy controls)	LIPd	Area Lateral Intra-Parietal dorsal	Superior Parietal cortex
	PHT	Area PHT	Lateral temporal cortex

Conclusion

This study examined the association between cannabis use and brain structural and functional connectivity. Graph-theoretical analysis was conducted to identify changes in brain connectivity associated with cannabis use. Whole brain functional and structural network measurements were conducted on cannabis users and non-users in both groups. Small-world characteristics were observed in both groups. Regional impacts on network segmentation and integration metrics were also identified, with greater significance for the insular and frontal opercar cortices, as well as the lateral and medial temporal cortices. However, the general characteristics of brain networks were still present. A typical structure was observed in the rich-objective analysis of functional networks, although there were some slight differences between the groups. A negative relationship between cannabis use frequency and regional Structural and Functional Network measurements was identified in some areas, including the hippocampus (HG1)-presubiculum (presubiculum). Future research will explore how functional connection patterns of cannabis users evolve over time.

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