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Chronic cannabis use associated with subcortical topological reorganization of structural connectivity in adults

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ABSTRACT

Background: Cannabis is commonly used in the United States. However, chronic cannabis use has been linked to alterations in white matter (WM) integrity. Studies investigating WM in people who use cannabis (PWC) have produced varying results, which may be due to a variety of factors, including a focus on individual WM tracts. Here, we examined WM connectivity using a module-based approach to help clarify whether cannabis use is associated with differences in WM organization.

Methods: Connectomics is used to map complex networks of inter and intra-connected cortical and subcortical regions. A key concept of brain organization is the presence of groups of densely interconnected regions, referred to as modules. Here, we used WM structural connectivity estimates to compare connectome organization between adults who used cannabis regularly (n=53), and adults who did not use cannabis (n=60). We quantified aspects of network organization both across the whole brain and within specific modules.

Results: There were no significant results between groups after correcting for multiple comparisons for whole-brain metrics. When considering group differences in network organization metrics for 10 identified modules, we observed that adult PWC showed higher within-module degree, local efficiency, and network strength in a right subcortical module relative to adults that did not use cannabis.

Conclusions: These results suggest that cannabis use in adults is associated with alterations of subcortical WM network organization. The observed differences in WM organization may be due to the involvement of the endocannabinoid system in the alteration of WM growth processes.

1. Introduction

Cannabis is one of the most commonly used illicit drugs in the United States and is currently legal for recreational use in 22 U.S. States (National Conference of State Legislatures 2023). The United States National Survey on Drug Use and Health reported that in 2019 48.2 million people, or 18 % of the population, used cannabis (Substance Abuse and Mental Health Services Administration, 2020). Chronic and frequent cannabis use, particularly daily, has been shown to be correlated with cognitive impairments, potentially due to decreased efficiency in learning and memory processes (Prini et al., 2020). Research has linked long-term cannabis use with deficits in global and prospective memory, immediate and delayed recall, and visual recognition (Schoeler et al., 2016).

These cognitive deficits may be related to the effect of cannabis use on brain structure. White matter (WM) structural integrity has been shown to be altered in people who use cannabis (PWC). Diffusion tensor imaging (DTI) has identified reduced WM integrity in the uncinate fasciculus, forceps minor, fornix, splenium of the corpus callosum, and commissural fibers in PWC relative to people who do not use cannabis (Zalesky et al., 2012; Shollenbarger et al., 2015). However, some studies have not observed differences in WM integrity related to cannabis use (Cousijn et al., 2022), and others have even shown increases in WM integrity (Filbey et al., 2014; Jakabek et al., 2016). The inconsistencies

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in reported results may be related to population differences, image acquisition, and processing techniques. For instance, most of the above listed investigations focused on individual WM tracts in their analyses.

The brain is organized into a complex network (Rubinov and Sporns, 2010). Therefore, the focus on WM integrity of individual tracts may mask larger-scale differences in structural connectivity distributed across multiple regions that better capture neural profiles associated with neuropsychiatric disease (Fornito and Bullmore, 2015). Connectomics is an innovative methodology to examine these large-scale differences in neural connectivity and organization. Aspects of connectomes that are thought to be particularly relevant to neuropsychiatric disease include the concepts of integration and segregation (van den Heuvel and Sporns, 2019). Specific gray matter regions of the brain are densely interconnected through WM and these interconnected regions are typically referred to as modules (Sporns and Betzel, 2016). Modules are defined as a sub-network of nodes that are densely connected to other nodes within the same sub-network, but have fewer connections to nodes located outside of the sub-network (Sporns and Betzel, 2016). Structural segregation is reflective of strong within-module connectivity, while structural integration refers to strong between-module connectivity (Rubinov and Sporns, 2010).

Few studies have examined WM connectivity using connectomics in PWC, and those that have reported no group differences between young adult PWC and healthy controls on global graph metrics (Kim et al., 2019; Soleimani et al., 2023). This includes both metrics probing network segregation (clustering coefficient and modularity), and metrics probing network integration (characteristic path length, global efficiency). For our investigation, we expanded upon the previous studies by quantifying network characteristics of individual modules in addition to whole-brain summary metrics. The presence of modules in the human brain network is thought to improve network efficiency by reducing the number of structural connections, and allows for concurrent specialized information processing (Sporns and Betzel, 2016). It is possible that there are module-specific differences of graph metrics that cancel each other out if summarizing across the whole-brain. Therefore, examining graph metrics within individual modules allows us to identify differences in subnetworks that may be masked by global metric analyses.

Here, we examined WM structural network connectivity between individuals who did and did not use cannabis. Based on the previous literature reporting differences in WM tracts in PWC, we hypothesized that cannabis use would be associated with greater network segregation due to decreased WM integrity in long-distance connective fibers in PWC relative to those that do not use cannabis. By examining modules, we can assess specific regions of the brain to examine more localized segregation of the human connectome relative to averaging segregation metrics across the whole brain.

2. Materials and methods

2.1. Participants

The sample included 113 adults aged 25–58 years and included PWC (n=53) and people without a history of cannabis use (CB-, n=60). The PWC group met the following criteria: $\geq$4 days of cannabis use in the past 30 days; $\geq$ 1 year of regular lifetime cannabis use; and smoking as the primary route of cannabis administration. CB- was defined as 0 days of cannabis use in the past 30 days, a THC-negative urine drug screen, and no history of regular cannabis use. In both groups, alcohol and nicotine use were permitted. For other illicit drugs, participants were excluded for a positive urine drug screen, $\geq$2 days of use in the past 30 days, any regular use in the past 5 years, or $>$2 years of regular lifetime use.

Additional exclusion criteria were: non-fluency in English, illiteracy, severe head trauma with loss of consciousness $>$30 min and persistent functional decline, neurological disorders or serious neurological events without return to normal cognition, severe mental illness, and MRI contraindications, including pregnancy.

2.2. Procedures

The sample was recruited in Durham, North Carolina, USA, and the surrounding area using advertisements and flyers in local community-based organizations, websites, and medical clinics. Following a brief telephone interview to assess preliminary eligibility, participants completed an in-person eligibility screening that included questionnaires and clinical interviews on substance use as well as medical and psychiatric history, urine drug testing, urine pregnancy testing (for participants of child-bearing potential), and HIV testing (all participants in this analysis had a non-reactive result). Participants also completed a mock MRI simulation to acclimate them to the scanning procedures and assess for contraindications. Eligible participants then completed an MRI scan, neuropsychological testing, another urine drug test, and another pregnancy test (if applicable). We had a larger amount of PWC who identified as male that responded to and met enrollment criteria during our enrollment period. Participants were compensated for their participation. Procedures were approved by the institutional review board at Duke University Health System.

2.3. Assessment measures

The Addiction Severity Index-Lite (ASI-Lite) assessed substance use and related behaviors (McLellan et al., 1992). Duration, frequency, and quantity of lifetime marijuana use were assessed using the Lifetime Drug Use Questionnaire (Czermak et al., 2005). Module E of the Structured Clinical Interview for DSM-5 (SCID-5) assessed substance use disorders (First et al., 2015). Modules A and B of SCID-5 assessed lifetime psychiatric disorders (First et al., 2015). Literacy was assessed using the word reading test of the Wide Range Achievement Test 4 (Wilkinson and Robertson, 2006). The urine drug toxicology test assessed the presence of 11 substances (marijuana, cocaine, opiates, methamphetamine, amphetamine, benzodiazepines, barbiturates, methadone, buprenorphine, ecstasy, oxycodone). Questionnaires assessed demographics and nicotine use. Medical records were reviewed to ensure no exclusionary medical conditions. Years of regular cannabis use was calculated as the sum of the length of all periods during which the participant was using at least 3 times per week. Age of first regular cannabis use was calculated as the age when use of 3 times a week or higher was first reported.

2.4. MRI data acquisition and processing

The data were acquired on a 3.0 T GE Discovery MR750 whole-body scanner with a 48-channel head coil. High-resolution T1-weighted (T1w) images were obtained using a BRAVO sequence with a SENSE factor of 2 (repetition time [TR] = 2234.94 ms, echo time [TE] = 3.076 ms, inversion time [TI] = 900 ms, voxel size = 0.9375 mm$\times$0.9375 mm x 1 mm, field of view [FOV] = 240 mm^2, 8° flip angle, 154 interleaved slice data acquisition). Two diffusion-sensitized parallel echo-planar imaging (EPI) sequences were collected in opposite polarities (TE=64.7, 144$\times$144 matrix, 2 shells, 45 diffusion directions, b-factor=1500 and 3000 s/mm^2 plus 5 b=0 acquisitions, multiband factor=2, 90° flip, 1.5 mm^3 voxel size).

Processing of the DWI data was primarily carried out using multi-shell multi-tissue constrained spherical deconvolution in MRtrix3 (Tournier et al., 2019). The two alternate phase-encoded images were both separately denoised using dwidenoise (Cordero-Grande et al., 2019) and then concatenated into a single time-series. Eddy and B0-correction was applied using FSL eddy (Andersson and Sotiropoulos, 2016). A mask was created from the B0 images and response function estimation was conducted using dwi2response (Dhollander et al., 2016). The estimation of fiber orientation distributions was done using dwi2fod and the data was then normalized using mtnormalise. T1-weighted anatomical images were skull-stripped using Freesurfer v6.0.0 (http:

//surfer.nmr.mgh.harvard.edu/). A five-tissue type (5TT) segmentation was performed using 5ttgen for anatomically constrained tractography (Smith et al., 2012). FSL's FLIRT was used to register the 5tt segmentation output to the B0 images (Jenkinson and Smith, 2001) and a mask was generated for seeding streamlines on the gray matter-white matter interface using 5ttgmwmi. Probabilistic tractography was conducted with an initial 10 million streamlines using tckgen and were then filtered to reduce streamline bias using spherical-deconvolution informed filtering of tracts resulting in one million streamlines (Tournier et al., 2010). We used the Brainnetome atlas (Fan et al., 2016) consisting of 246 nodes to define regions/nodes and constructed 246×246 connectivity matrices using tck2connectome with each entry representing a connection/edge between two nodes. Each edge was a quantification of the streamline count between a given pair of nodes. Edges were not retained if there were fewer than three streamlines connecting the regions. Edge weights were scaled by the inverse of the mean of the two node volumes.

2.5. Network measures

We obtained both whole-brain and module-specific metrics segregated into 10 distinct modules. Graph metrics were obtained using the Brain Connectivity Toolbox (BCT) MATLAB v.2019–03–03 (Rubinov et al., 2009). We examined network measures of integration (global efficiency), segregation (clustering coefficient, local efficiency, within-module degree), network strength, and degree. First, graph metrics were calculated for each individual across the entire brain. We then calculated 10 distinct modules using the entire sample. Finally, we calculated the average of the graph metrics specific to regions within each of the 10 modules.

Basic concepts and notation: N is the set of all nodes in the network, and n is the number of nodes. i,j is a link between nodes i and $j (i,j \in N)$. Links (i,j) are associated with connection weights w_{ij} , l^w is the sum of all weights in the network. Each of the metrics were calculated at the individual level, and except for modularity, were examined across the whole-brain and within each of the 10 created modules.

Modularity is a statistic that quantifies the degree to which the network is subdivided into clearly delineated subnetworks, or modules. The Louvain method was utilized with tau=0.75 (proportion of times a node must be in the same partition to be counted), number of times optimal partitions are generated=150, and number of times consensus cluster is partitioned=500.

$$Q = \frac{1}{2m}\sum_{ij}\left[A_{ij} \quad - \frac{k_i k_j}{2m}\right]\delta(c_i c_j)$$

where A_{ij} represents the edge weight between nodes i and j. $k^i k^j$ are the sum of the weights of the edges attached to nodes i and j. m is the sum of all edge weights in the graph. c_i and c_j are the communities of nodes.

Node degree is the number of weighted edges connected to the node averaged across the whole-brain.

$$k_i^w = \quad \sum\nolimits_{j \in N} W_{ij}$$

Global efficiency is the average inverse characteristic path length, which is the shortest path between two nodes, averaged across every pair of nodes.

$$E^w = \frac{1}{n}\sum_{i\in}\frac{\sum_{j \in N, \quad j \quad \neq i}\left(d_{ij}^w\right)^{-1}}{n-1}$$

where N_i is the number of nodes that are direct neighbors of node i and d_{ij}^w is the shortest path between nodes i and j.

Local efficiency is global efficiency calculated on a node's subnetwork averaged across the whole-brain.

$$E_{loc}^w = \quad \frac{1}{2}\sum_{i \in N}\frac{\sum_{j,h \in N, j \neq i}\left(w_{ij}w_{ih}\left[d_{jh}^w(N_i)\right]^{-1}\right)^{1/3}}{k_i(k_i-1)}$$

where d_{jh}^w is the shortest path length between nodes j and h.

Within-module degree is the degree of a node calculated for nodes within its module, or subnetwork.

$$D_i^w \quad = \quad k_i^w(m_i) - \overline{k^w(m_i)}$$

where m_i is the module containing node i, k_i^w is the within-module degree of i, meaning the sum of all links between i and other nodes within its module. We used weighted within-module degree that was not z-scored.

Network strength is the average of the strength across all nodes in the whole-brain network.

$$S_p(G) = \frac{1}{N}\sum_{i \in G} S(i)$$

For a network G where $S(i)$ is the sum of the edge weights w_{ij} for a weighted network linking to node i.

Clustering coefficient is the fraction of triangles of nodes around a node and is equivalent to the fraction of node's neighbors that are neighbors of each other, averaged across the whole-brain.

$$C^w = \quad \frac{1}{n}\sum\nolimits_{i \in N}\frac{2t_i^w}{k_i(k_i-1)}$$

where C^w is the weighted clustering coefficient of node i.

We also examined these network metrics within 10 modules constructed from all participants. For this, a group network was created consisting of the mean weights for edges present in at least 50 % of the participants. Following a method similar to that in Lancichinetti and Fortunato (2012), the group network was then converted into a "consensus" partition as follows. The group network was partitioned using the community_louvain() function in BCT using the 'modularity' objective function with gamma=1.0. As this partitioning can vary widely, it was repeated 150 times, and an agreement matrix was created using BCT's agreement() function to identify the number of times each pair of nodes was assigned to the same module over the 150 partitions. This agreement matrix was divided by the number of partitions to convert the agreement count to a value between 0 and 1, and then sent to BCT's consensus_und() with tau=0.75 and 500 iterations to create a consensus partition. We used multiple tau values and found that tau=0.75 produced the most stable modules across participants. We also examined modules specific to each group and did not find that the modular structure was different between groups. To further refine this partition, this full algorithm was repeated 10 times, to create a total of 10 consensus partitions, and the consensus partition with the highest similarity in a pairwise comparison to all the others (as defined as lowest median number of nodes that did not get assigned to the same network) was chosen. Each node was exclusive to a single module.

2.6. Analysis

Unthresholded graph metrics, meaning all connections were preserved after preprocessing, were analyzed using a general linear model in SPSS v28.0.0.0. We conducted between-subjects ANCOVAs and examined the effect of cannabis use on each graph metric, with age and years of education as covariates of no interest. Nicotine use was not included as a covariate in subsequent models due to its high collinearity with MJ use. After assessing the data for normality, it was found that local efficiency, degree, and global efficiency violated the assumptions of normality. For these graph metrics, we implemented a generalized linear model using a gamma log link function and examining Wald Chi-square statistics for significance. Results were corrected for multiple comparisons using FDR-correction within each of the 10 modules (5 metrics each) and whole-brain analysis for all included graph metrics (6 metrics).

3. Results

3.1. Participant characteristics

Participant characteristics by group are described in Table 1. The sample included 86 men and 27 women, primarily African-American (58.4 %), with a mean age of 37.7 years. Years of education ranged from 8 to 20 (M=15.3; SD=2.4). Groups did not differ by age, gender, or race, but PWC had significantly fewer years of education than CB-. For PWC, most individuals frequently used cannabis with 49 % of individuals using cannabis daily. Lifetime years of regular cannabis use ranged from 0.92 to 27 years (median = 10.58, IQR = 8.92) with a mean of 24.6 days (SD = 7.58) of use in the past 30 days. The mean age of initiation for regular use was 20.75 years (SD = 4.88). In the past 30 days, participants reported feeling the effects of cannabis for 4.75 hours per day (SD = 2.99). The majority of participants (89 %) met diagnostic criteria for a cannabis use disorder in the past 12 months.

3.2. Whole-brain structural network connectivity

Structural density, which is the percentage of structural white matter connections present out of the total possible structural white matter connections, did not differ across groups. Across whole-brain metrics, there was a significant effect of cannabis for local efficiency (p=.018), and global efficiency (p=.010), such that cannabis use was associated with higher graph metrics. These results were not significant after controlling for multiple comparisons.

3.3. Modules

Ten modules were constructed from group consensus connectomes that consisted of left and right frontal, fronto-parietal, subcortical, temporal-parietal, and occipital modules (see Supplementary Table 1 and Fig. 1.). The identified modules exhibited stable nodal assignments (i.e. nodes were consistently assigned to the same modules), even distribution of nodes to modules (i.e. approximately same number of nodes in each module), and bilateral groupings of neuroanatomically related regions. Of note, there was no difference in the network metric of modularity between PWC and CB-, suggesting that groups were comparable in degree of network segregation. We only report results that were significant after correcting for multiple comparisons within each module. For a full list of results see Supplementary Table 2. There was an effect of cannabis use in the right subcortical module for within-module degree (p=.018; η^2=.050), local efficiency (p=.028; Cohen's d=.21), and network strength (p=.014; η^2=.054) (see Table 2). For each metric, PWC had higher values, suggestive of more connections within the right subcortical module. Within-module degree, local efficiency, and network strength in the right subcortical module were significant after controlling for multiple comparisons (see Fig. 2.).

Table 1
Participant demographics.

	CB- (N = 60)	PWC (N = 53)	Statistic	*p*-value
Demographic Characteristics				
Male, %, N	75.0 %, 45	77.3 %, 41	$\chi^2(1) = 0.09$	0.77
Age in years, M (SD)	38.88 (9.11)	36.43 (7.84)	t(111) = 1.52	0.13
Race			$\chi^2(2) = 0.86$	0.65
African American, %, N	58.3 %, 35	58.5 %, 31		
Caucasian, %, N	33.3 %, 20	28.3 %, 15		
Other/Mixed, %	8.33 %, 5	13.2 %, 7		
Education in years, M (SD)	16.12 (2.17)	14.34 (2.38)	t(111) = 4.14	<0.01
Other Substance Use Characteristics				
Days of alcohol use in past 30 days, M (SD)	4.30 (6.66)	6.81 (8.40)	t(111) = −1.77	0.08
Current daily cigarette use, %	1.66 %, 1	30.2 %, 16	$\chi^2(1) = 17.9$	<0.01
Density, M (SD)	0.26 (0.22)	0.25 (0.29)	t(111) = 1.39	0.167

Abbreviations: M, mean; SD, standard deviation; IQR, interquartile range. Density is percentage of white matter connections present out of total possible connections.

4. Discussion

The primary finding of this research is that adult PWC showed higher network metrics of within-module degree and local efficiency, measures of segregation, and network strength relative to adults that did not use cannabis. These higher values were observed only within a right subcortical module after correcting for multiple comparisons. The right subcortical module consisted of parahippocampal, amygdala, hippocampus, basal ganglia, and thalamic regions. These results suggest that frequent cannabis use in adults has an impact on subcortical brain topography.

PWC showed higher within-module degree and local efficiency in the right subcortical module. Within-module degree is a metric of the number of connections of a node with all other nodes within a module. Higher metrics of intra-modular connectivity support higher segregation within PWC. This is because within-module degree is reflective of the edges within, and not between, modules (Guimera, 2005). Specifically, higher within-module degree in the right subcortical module reflects an increased number of WM connections in PWC. This result had a η^2=.05 reflecting a modest effect size for higher within-module degree. Local efficiency is reflective of the degree of inter-connectedness among the neighborhood of a node (Latora and Marchiori, 2001). In the context of our results, higher local efficiency within the right subcortical module also suggests higher levels of structural connectivity within this specific module for PWC relative to individuals that did not use cannabis. While there is no universally accepted single method for calculating the effect size for a Wald chi-square statistic, it is possible to calculate an analogous Cohen's d value by taking the square root of the Wald chi-square statistic divided by the sample size. This calculation resulted in an effect size of .21, which would be considered a small effect size.

PWC also showed higher network strength within the right subcortical module. Network strength is the sum of all neighboring edge weights for any node. The network strength would be representative of total connectedness within right subcortical regions. Therefore, higher network strength could reflect the increased intra-modular connections that was observed in PWC. This result had a η^2=.054 reflecting a modest effect size for higher network strength in PWC. Therefore, we hypothesize that higher network strength and within-module degree show the strongest differences in PWC relative to individuals that do not use cannabis as they had the largest effect sizes relative to local efficiency.

Subcortical regions are known to be heavily influenced by cannabis use (Orr et al., 2016; Manza et al., 2018; Cong et al., 2022). As there were no significant differences in global metrics, our results suggest that instead of global differences, cannabis use is associated with differences in structural connectivity within subcortical modules. Cannabis use results in the release of glutamate and dopamine in several subcortical regions corresponding with cannabis-related alterations including the nucleus accumbens, hippocampus, and amygdala (Colizzi et al., 2016; Mason et al., 2019). Animal models have shown that long-term cannabis exposure results in a shift of glutamatergic activation of the nucleus

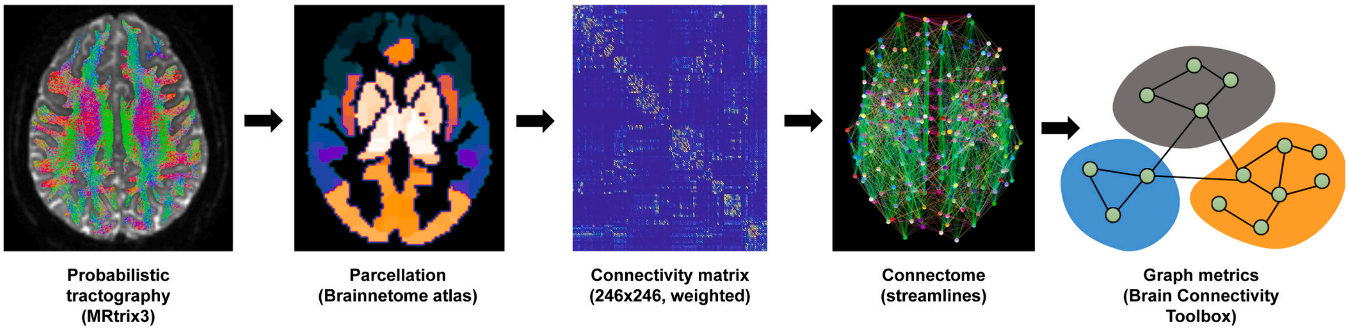

Fig. 1. Diffusion weighted imaging processing pipeline. Diffusion weighted images were processed using the MRtrix3 software and probabilistic tractography was performed resulting in 1 million filtered streamlines. Images were then parcellated using the Brainnetome atlas resulting in a weighted 246 ×246 connectivity matrix. Graph metrics were calculated using the Brain Connectivity toolbox.

Table 2
Right subcortical module.

Module	CB - (N = 60)	PWC (N = 53)	F	p-value
R. subcortical				
Local efficiency, M (SD)	.094 (.011)	.099 (.019)	4.83	**.028**
Clustering coefficient, M (SD)	.016 (.003)	.015 (.003)	.561	.456
Within-module degree, M (SD)	4.50 (.649)	4.80 (.598)	5.78	**.018**
Degree, M (SD)	67.3 (6.19)	66.3 (7.61)	1.23	.266
Network strength, M (SD)	7.00 (.714)	7.33 (.690)	6.18	**.014**

accumbens from cortical to limbic regions (Hwang and Lupica, 2020). The authors postulate that this shift results in deleterious changes to cognition due to altered nucleus accumbens function. Our results expand upon the current literature by showing that subcortical regions are not affected in isolation, but rather, their within-modular connectivity is altered. As stated in the introduction, we are only aware of two investigations of WM connectivity using network metrics in PWC. Consistent with our results, these studies found no differences in whole-brain network organization. That we did not observe significant differences in global metrics, lends further support to the notion that structural connectivity differences in PWC are distinct to modules.

Of interest is that PWC showed higher within-module degree, local efficiency and network strength relative to individuals that did not use cannabis. Basic science studies have suggested that the endocannabinoid system is involved in WM development, specifically, glial cell proliferation, axonal elongation, and formation of myelin (Galve-Roperh et al., 2009; Garcia-Arencibia et al., 2019). Animal studies on adolescent cannabis use have suggested that exposure to THC causes changes to the endocannabinoid system that result in altered neural pruning (Rubino and Parolaro, 2016). WM development is hypothesized to peak in the 30 through 40-year age range (Sowell et al., 2003; Westlye et al., 2010). Many studies on cannabis use only include adolescents or young adults. Here, our sample consisted primarily of adults with a mean age of 36. Our sample also had a relatively late onset of cannabis use with mean

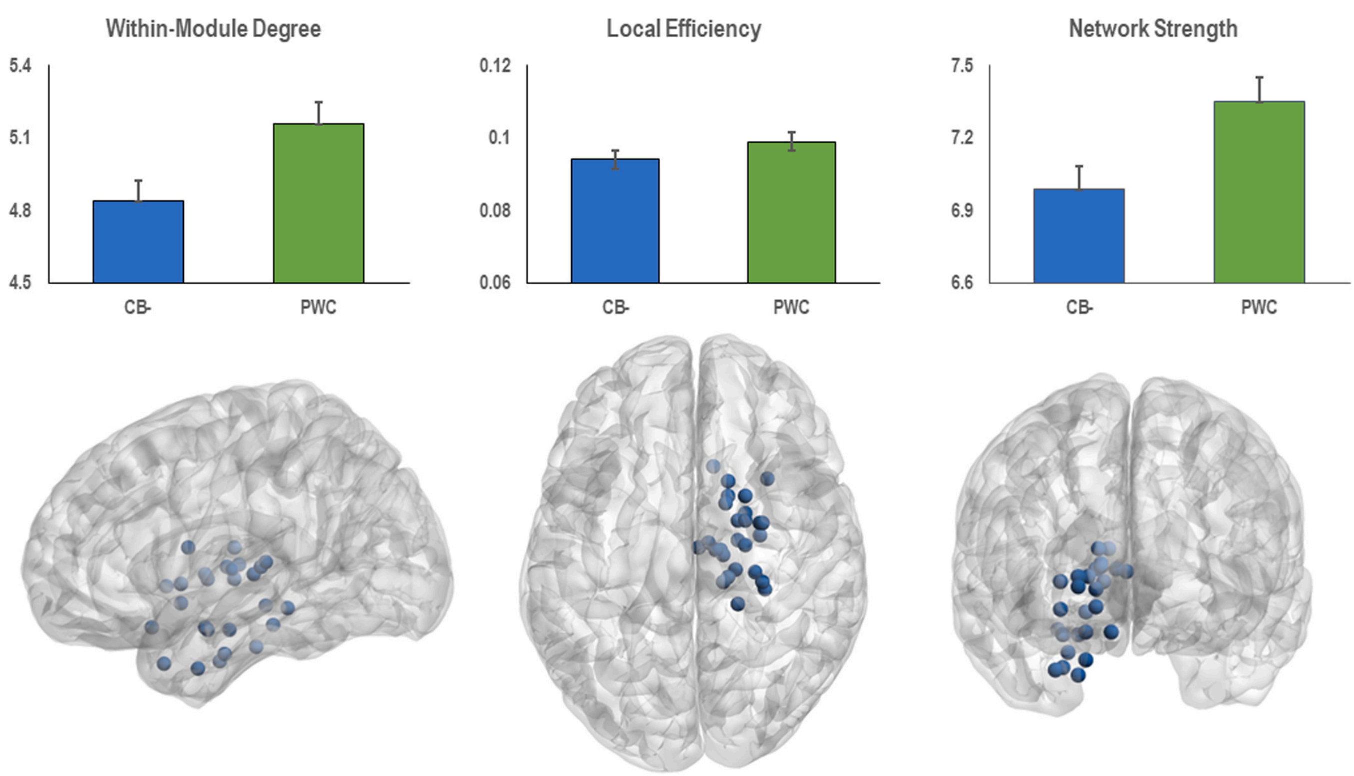

Fig. 2. Right subcortical module. The bar graphs represent the graph metric means of within-module degree, local efficiency, and network strength for CB- and PWC. Error bars are standard error of the mean. Brain images display the nodes that compose the right subcortical module.

age of onset of regular use being 21. Though our sample's age of regular use was not during adolescence, it would still fall in a period of significant WM development. There is supporting evidence that cannabis use results in WM changes in adulthood. It has been reported that adults with no history of cannabis use showed higher WM integrity six months after initiation of cannabis use for medical treatment of non-degenerative diseases (Dahlgren et al., 2022). The late onset of cannabis use could explain the relatively subtle differences in network organization that were seen, whereas more substantial differences might be observed in individuals who began using cannabis in early adolescence.

Cognitive impairments in PWC are hypothesized to be a result of decreased efficiency in learning and memory processes (Prini et al., 2020). The right subcortical module included regions of the hippocampus, which is strongly associated with memory processing (Sheldon and Levine, 2016). While outside of the scope of this analysis, increased deficits in memory processing over time could be related to concurrent alterations in right subcortical topology.

A strength of this analysis was that our participants who used cannabis reported almost daily use in the last month. Therefore, our results are generalizable to individuals with frequent cannabis use patterns. There are some limitations to our investigation. As this is a cross-sectional design, we are unable to determine causality. Future work will examine longitudinal changes in functional connectivity. There are alternative ways of calculating modularity including multislice modularity and block models. It is not known how the utilization of these models would change our identified modular structures. A higher percentage of men report using cannabis relative to women (Cuttler et al., 2016). However, our sample had a larger gender disparity due to the gender of participants willing to participate in the study. This is a limitation as it did not allow for the examination of effects of gender on WM organization and cannabis use.

4.1. Conclusion

Here, we found that adults who used cannabis displayed higher within-module degree, local efficiency, and network strength within a module consisting of subcortical regions relative to adults who did not use cannabis. We did not identify differences in brain topology when examining across the whole-brain. Our findings suggest that topological differences in PWC are distinct to regional modules, and that these differences are masked when assessing across the whole-brain. We postulate that these findings reflect the involvement of the endocannabinoid system in the alteration of WM growth processes. With the continued legalization of cannabis use, it is important to understand if there are deleterious effects on brain structure and organization at different life stages. Future studies can examine whether these differences in brain organization are related to impairments in cognitive function.

CRediT authorship contribution statement

Sheri L. Towe: Writing – review & editing. **Jessica R. Cohen**: Writing – review & editing. **Ryan P. Bell**: Writing – original draft, Formal analysis. **Christina S. Meade**: Writing – review & editing, Supervision, Conceptualization. **Allen W. Song**: Writing – review & editing. **Amelia Costello**: Data curation. **Kareem Al-Khalil**: Writing – review & editing. Syam Gadde: Software.

Role of funding source

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Declaration of Competing Interest

None

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.drugalcdep.2024.111405.

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