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Abnormal structural covariance networks in young adults with recent cannabis use

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ABSTRACT

Background: Recent cannabis use (RCU) exerts adverse effects on the brain. However, the effect of RCU on structural covariance networks (SCNs) is still unclear. This retrospective cross-sectional study aimed to explore the effects of RCU on SCNs in young adults in terms of whole cerebral cortical thickness (CT) and cortical surface area (CSA).

Methods: A total of 117 participants taking tetrahydrocannabinol (RCU group) and 896 participants not using cannabis (control group) were included in this study. All participants underwent MRI scanning following urinalysis screening, after which FreeSurfer 5.3 was used to calculate the CT and CSA, and SCNs matrices were constructed by Brain Connectivity Toolbox. Subsequently, the global and nodal network measures of the SCNs were computed based on these matrices. A nonparametric permutation test was used to investigate the group differences by Matlab.

Results: Regarding global network measures of CT, young adults with RCU exhibited altered small-worldness ($P = 0.020$) and clustering coefficient ($P = 0.031$) compared to controls, whereas there were no significant group differences in terms of SCNs constructed with CSA. Additionally, SCNs based on CT and CSA displayed abnormal nodal degree, nodal efficiency, and nodal betweenness centrality in vital brain regions of the triple network, including the dorsolateral and ventrolateral prefrontal cortex, and anterior cingulate cortex.

Conclusion: The effects of RCU on brain structure in young adults can be detected by SCNs, in which structural abnormalities in the triple network are dominant, indicating that RCU can be detrimental to brain function.

1. Introduction

The use of cannabis is rising globally; currently, 209 million cannabis users are reported worldwide, which is approximately twice the number reported at the beginning of the 2000s (Davis et al., 2018). Young adults (18–25 years old) exhibit the highest prevalence of cannabis use, which can be attributed to the legalization of the drug in certain regions and clinical research encouraging cannabis consumption (Mullins, 2013). While short-term cannabis use can provide euphoria or pain relief (Bonn-Miller et al., 2014), it can also increase the risk of psychosis significantly in adolescents (Tao et al., 2020). Previous research has found that the effects of cannabis on brain development in adolescents cause these neurological side effects (Zehra et al., 2018), which may be related to the main component of cannabis, tetrahydrocannabinol (THC), interacting with receptors of the endogenous cannabinoid signaling system, in turn leading to structural impairment of the brain (Zehra et al., 2018).

Prior research has indicated that widespread brain regions containing a dense density of cannabinoid receptor 1 (CB1), including the hippocampus, amygdala, cerebellum, cingulate cortex, and prefrontal cortex, are predominantly affected when adolescents are exposed to THC (Scott et al., 2019), and these regions are key components of the reward or emotional networks (Lorenzetti et al., 2019). Our previous longitudinal study revealed that the right hippocampus in young adults with cannabis use developed slowly related to that in controls (Xu et al., 2022). Additionally, gray matter volume of the orbitofrontal cortex was smaller in young cannabis users (Battistella et al., 2014; Price et al., 2015). However, a *meta*-analysis suggests that the structural brain abnormalities in cannabis users are currently not consistent (Lorenzetti et al., 2019), with the possible causes of focusing only on isolated brain

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regions, lacking of structural networks analysis, and single brain structure calculation method, all of which may lead to a narrower range of results without overall alteration of brain networks (Lorenzetti et al., 2019).

Further, the effect of recent cannabis use (RCU) on the human brain has been the subject of few studies. Individuals with RCU are defined as those with a positive cannabinoid urine screening test (THC +), specifically, one and three days after a single use or three to four weeks on average for heavy users (Musshoff & Madea, 2006). Thus, the selection of young adult RCUs contributes to the estimation of the impact of early cannabis use on brain structure. Further, to explore the structural alterations in the brains of young adult cannabis users, the structural covariance networks (SCNs) is an effective approach that focuses on covariate coordinated structures of the whole brain in gray matter morphology rather than one specific structure (Gong et al., 2012). SCNs can usually be constructed from cortical surface area (CSA) and cortical thickness (CT), CSA reflects the unfolding of cerebral cortex, and CT reflects the density and distribution of neuron cells(Winkler et al., 2018), which jointly comprise gray matter volume, with the advantage that CSA or CT may appear abnormal when no abnormality is detected in gray matter volume (Ducharme et al., 2016; Winkler et al., 2018). Moreover, because of distinct cellular regulatory mechanisms in CSA or CT, their responses to particular factors affecting the brain may differ (Evans, 2013). In addition, brain networks can provide information about interregional connectivity and can be used to distinguish whether functional networks are receiving effects based on changes of graph theory metrics, this can balance the network in whole and its nodes (Nestor et al., 2020), which can help to complement the gray matter changes which have been reported. However, no research has been reported in this direction.

Hence, this study constructed SCNs using CT and CSA from the Human Connectome Project (HCP) imaging data to calculate separation and integration network graph theory metrics in young adults with RCU. This study aimed to (i) detect regions of whole-brain SCNs abnormality in young adults with RCU compared to non-cannabis users and (ii) identify abnormal network architectures of whole-brain SCNs in young adults with RCU.

2. Methods

2.1. Participants

This study used the HCP Release S1200 dataset. Participants were recruited at Washington University in St. Louis over two days between August 2012 and October 2015 (Van Essen et al., 2013, Van Essen et al., 2012). The research ethics board of each institution approved the study protocols. This study was conducted in accordance with the Declaration of Helsinki, and all participants provided written informed consent. All the participants were young adults aged 22–35 years. The exclusion criteria were as follows: history of psychiatric disorder, substance abuse, neurodevelopmental disorder or damage, cardiovascular disease, severe health conditions (diabetes, multiple sclerosis, cerebral palsy, and premature birth), or magnetic resonance imaging (MRI) contraindications (large tattoos, non-removable piercings, metal devices in the body, and claustrophobia). The complete details of the inclusion and exclusion criteria and informed consent for participants can be found in references (Van Essen et al., 2013; Van Essen et al., 2012). There were totally 1206 participants from HCP, but 193 participants were omitted from subsequent analyses because of missing structural MRI (sMRI) scans (93), insufficient data on cannabis use (15), or for any covariates (85). Finally, 1013 participants were included in the final analysis (Table 1).

On the day of testing, participants underwent a urine drug screen to determine whether they had been recently exposed to THC, a psychoactive constituent of cannabis. The THC + status was adopted to indicate whether or not participants tested positive for the presence of THC in their urine.For heavy users, detection occurs 1–3 days after a single use and 3–4 weeks on average, whereas certain individuals may exhibit detectability even three months later (Musshoff & Madea, 2006). A total of 117 participants in this study exhibited THC + status, indicating that they were young adults with RCU; the remaining 896 participants with THC- status were regarded as controls.

Table 1
Demographic characteristics of young adults with RCU and controls from HCP dataset in this study.

Characteristic	Groups		Statistics	
	Young adults with RCU (N = 117)	*Controls* (N = 896)	t/χ^2	*P-value*
Age	28.06(3.83)	28.92 (3.63)	t_{145} = -2.31	0.27
Gender (F/M)	38/79	508/388	χ^2_1 = 23.46	0.00
BMI	26.59(5.52)	26.48 (5.07)	t_{145} = 0.19	0.84
Education	13.51(1.86)	15.13 (1.71)	t_{145} = -8.89	0.00
Total cognitive compositive	101.12(21.40)	115.22 (19.67)	t_{145} = -6.77	0.00
Total household income	3.61(2.13)	5.24(2.08)	t_{145} = -7.82	0.00
Total_Drinks_7days	8.06(10.08)	4.72(6.67)	t_{145} = 3.48	0.00
Frq_Alc_12months	3.82(1.69)	4.36(1.52)	t_{145} = -3.37	0.00
Total_Any_Tobacco_7days	24.49(37.08)	5.80 (21.56)	t_{145} = 5.33	0.00

Note. Demographics presented as mean (standard deviation) unless otherwise stated.
HCP: Human Connectome Project; RCU: recent cannabis use (positive test for THC); Total cognition composite is derived by combining scores on the individual tests in the NIH Toolbox, the age-adjusted version of the Total Cognition Composite was adopted here as participants' cognitive ability; F: Female; M: Male; BMI: Body mass index; Total_Drinks_7days: Total drinks in past 7 days; Frq_Alc_12months: Frequency of any alcohol use in past 12 months; Total_Any_Tobacco_7days: Total times used/smoked any tobacco in past 7 days.

2.2. Retrospective report of tobacco and alcohol use

A retrospective report on tobacco and alcohol use was obtained. From this, the total drinks consumed in the past seven days, frequency of alcohol use in the past 12 months, and total times used/smoked tobacco in the past seven days were derived to use as covariates.

2.3. MRI data acquisition and preprocessing

In the HCP dataset, T1-weighted structural images were collected using a 32-channel head coin on a 3 T Siemens Skyra scanner (Siemens AG, Erlanger, Germany) with the following scanning parameters: isotropic resolution = 0.7 mm^3, field of view = 224 mm × 240 mm, matrix size = 320 × 320, repetition time = 2400 ms, echo time = 2.14 ms, inversion time = 1000 ms, flip angle = 8°, and 256 sagittal slices. Data were reconstructed and preprocessed using a modified version of the FreeSurfer pipeline in FreeSurfer Image Analysis Suite version 5.3 (https://surfer.nmr.mgh.harvard.edu) (Fischl; Fischl, 2012).

For details of the acquisition parameters, reconstruction, and preprocessing of the HCP sMRI data, see references (Glasser et al., 2013; Van Essen et al., 2013, Van Essen et al. (2012)). Briefly, the FreeSurfer pipeline processing involved several steps, including motion correction, removal of non-brain tissue, Talairach transformation, intensity normalization, gray/white matter boundary tessellation, topology correction, surface deformation, registration to a common spherical atlas, and cortical surface reconstruction. All structural images were reviewed by a technician immediately after acquisition to ensure that the scans had no significant problems (artifacts and substantial

movement). For a detailed explanation of HCP quality control, check reference (Marcus et al., 2013). The quantitative measures of CT and CSA for cortical regions were defined using the Desikan atlas (Desikan et al., 2006).

2.4. Construction of SCNs

The statistical similarity between each two regions defined by the Desikan atlas was measured by computing Pearson's correlation coefficient across subjects, and an interregional correlation matrix (68 × 68) was constructed from each group. Therefore, group-level SCNs of the CT and CSA were constructed separately for the two groups. To improve the normality of the correlation, correlation coefficients r were then converted to *z-values* using the Fisher transformation. By binarizing the correlation matrix using a series of sparsity thresholds, which resulted in certain percentages of connections, a series of unweighted and undirected graphs were obtained for subsequent network analysis. Given that the selection of different threshold values could cause changes in small-world network parameters, we thresholded the correlation matrices over a wide range of sparsity (6 %–40 %) to avoid the uncertainty resulting from the threshold choice (He et al., 2007). The chosen range of sparsity allows the small-world network architectures to be properly estimated, and the number of spurious edges in each network is minimized, as indicated in previous studies (Achard & Bullmore, 2007; He et al., 2007). All networks in this paper demonstrated small-world architectures, as they had an almost identical path length (normalized path length ≈ 1) but were more locally clustered (normalized clustering coefficient > 1), consistent with previous studies. The lowest threshold was identified as the minimum network sparsity, in which the resultant networks were fully connected and estimable for small-worldness (Hui Xu et al., 2024).

2.5. Graph-based network analysis

Global and nodal network measures of SCNs were calculated using the Brain Connectivity Toolbox (Rubinov & Sporns, 2010). We computed the normalized characteristic path length (which is defined as the shortest path length between all pairs of nodes) and global efficiency (which measures how efficiently information is communicated between nodes) as measures of network integration and the normalized clustering coefficient (which evaluates the influence of different paths based on the connection weights of the node's neighbors) and local efficiency (which is defined as the number of connections in the neighborhood of a certain node divided by the maximum number of possible connections between the neighbors of this node) as measures of network segregation. Small-worldness, which reflects the optimal balance of network integration and segregation, was also computed. The nodal degree, nodal efficiency, and nodal betweenness centrality were examined to identify group differences in nodal network measures.

2.6. Statistical analysis

In the following analyses, the potential confounding factors which showed significant group differences (including gender, total cognitive compositive, total household income, alcohol and tobacco use) were included as covariates. A nonparametric permutation test was employed to investigate statistical differences in network metrics between the groups. First, a network measure (clustering, path length, efficiency, nodal efficiency, betweenness, and degree) was computed separately for young adults with RCU and controls. Following that, the CT or CSA values of each subject were allocated into two groups, yielding an identical sample size as the original groups. New values were obtained for network metrics after recalculating the SCNs for both groups. Each permutation test was repeated 1000 times, and P-value < 0.05 was statistically significant with false discovery rate (FDR) corrections after multiple comparisons. Considering various densities, we compared their area under the curve (AUC) (density range of 0.06:0.01:0.4) between the two groups. For demographic variables, the chi-square test was used to assess difference in gender between groups, whereas group differences in other demographic variables were evaluated using two independent samples t-tests.

3. Results

3.1. Participants and characteristics

There were no significant differences in age ($t_{145} = -2.31$, $P = 0.27$) and body mass index ($t_{145} = 0.19$, $P = 0.84$) between young adults with RCU and controls. There were significant differences in gender ($\chi^2_{(1)} = 23.46$, $P < 0.01$) between the groups. Compared with controls, young adults with RCU had significantly lower education level ($t_{145} = -8.89$, $P < 0.01$), total cognitive compositive ($t_{145} = -6.77$, $P < 0.01$), and total household income ($t_{145} = -7.82$, $P < 0.01$). Regarding alcohol use, young adults with RCU consumed a significantly higher number of total drinks in the past seven days ($t_{145} = 3.48$, $P < 0.01$); however, they exhibited lower frequency of alcohol use in the past 12 months ($t_{145} = -3.37$, $P < 0.01$), compared to controls. Moreover, young adults with RCU showed significantly higher total times used/smoked tobacco in the past seven days than controls ($t_{145} = 5.33$, $P < 0.01$). The demographic information of the participants is presented in Table 1.

3.2. Group differences in global network integration measures

In terms of CT, while no significant group differences existed in global network integration measures including normalized path length (Fig. 1A) and global efficiency (Fig. 1B), young adults with RCU displayed significantly altered small-worldness measures compared to the controls (Fig. 1C), which indicated altered balance of network integration and segregation in young adults with RCU. In terms of CSA, there were no significant group differences in normalized path length (Fig. 1D), global efficiency (Fig. 1E) and small-worldness measures (Fig. 1F). The P-values for these metrics are listed in Table 2.

3.3. Group differences in global network segregation measures

In terms of CT, young adults with RCU exhibited abnormal normalized clustering coefficients compared to controls (Fig. 2A). There was no significant group difference in local efficiency (Fig. 2B). In terms of CSA, there were no significant group differences in global network segregation measures including normalized clustering coefficients (Fig. 2C) and local efficiency (Fig. 2D). The P-values for these metrics are listed in Table 2.

3.4. Group differences in nodal network measures

According to permutation tests, nodal network measures, including nodal degree, nodal efficiency, and nodal betweenness centrality, showed significant group differences, as displayed in Fig. 3.

Regarding the CT, compared to controls, young adults with RCU exhibited an altered nodal degree of the left inferior parietal lobule, left rostral middle frontal gyrus, left superior frontal gyrus, right cuneus, right paracentral gyrus, and right insula; abnormal nodal efficiency of the left superior frontal gyrus, right paracentral gyrus, right superior parietal lobule, and right insula; and altered nodal betweenness centrality of the left lingual gyrus, left superior frontal gyrus, right paracentral gyrus, right pars triangularis, and right superior parietal lobule (Fig. 3A).

Concerning the CSA, compared with controls, young adults with RCU showed altered nodal degree of the left lateral occipital gyrus, left posterior cingulate cortex, left precentral gyrus, right banks of the superior temporal sulcus, right pars opercularis, and right precentral gyrus; abnormal nodal efficiency of the left lateral occipital gyrus and right

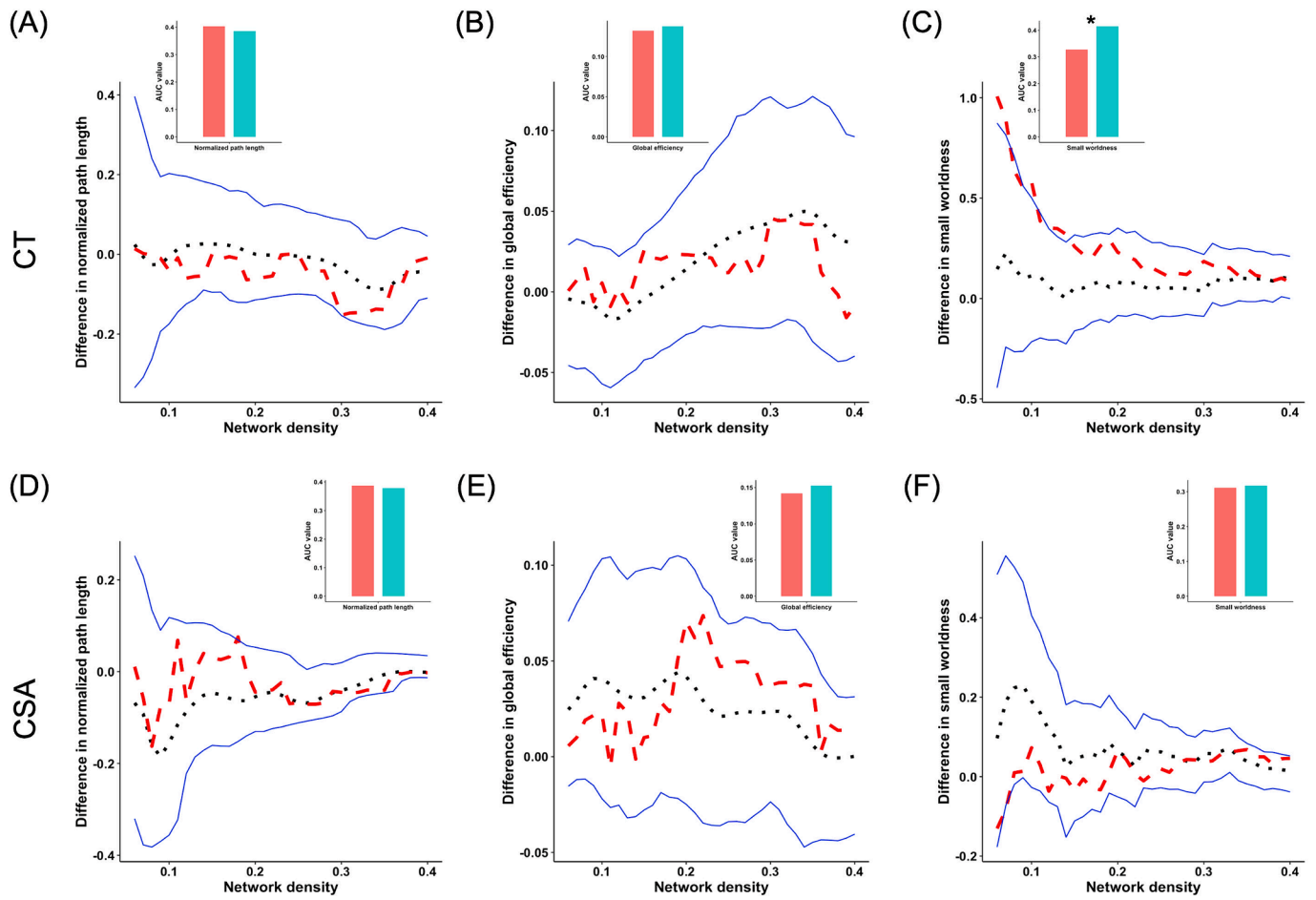

Fig. 1. Group differences in "integration" and "small-worldness" metrics of structural covariance networks based on cortical thickness (CT) and cortical surface area (CSA) at the range of 6 %-40 % network sparsity, including (A) (D) normalized path length, (B) (E) global efficiency, and (C) (F) "small-worldness". The upper and lower blue lines represented 95 % confidence interval, whereas the black dot line in the middle denoted the mean difference after 1000 permutations. The red line represented the true group differences, which fall outside the confidence interval indicated significant group differences ($P < 0.05$) under the current threshold. The positive values indicate young adults with recent cannabis use (RCU) > controls and negative values indicate young adults with RCU < controls. The subpanels showed group differences of the area under the curve (AUC) value in each metric of SCNs. Compared with controls, young adults with RCU showed significant altered AUC value of small-worldness in terms of CT. *, $P < 0.05$.

Table 2
Results of permutation tests for changes in the integration and segregation network measures of SCNs between groups.

P-values	Integration measures		Small-worldness	Segregation measures	
	Normalized path length	Global efficiency		Normalized clustering coefficient	Local efficiency
CT	0.347	0.585	0.020	0.031	0.287
CSA	0.822	0.374	0.895	0.900	0.639

SCNs: structural covariance networks; CSA: cortical surface area; CT: cortical thickness.

pars opercularis; and changed nodal betweenness centrality of the left caudal middle frontal, left postcentral gyrus, left posterior cingulate, right pars opercularis, and right rostral anterior cingulate cortex (Fig. 3B).

4. Discussion

This study is the first to investigate abnormal construction of the SCNs in young adults with RCU, considering both CT and CSA. The findings revealed that young adults with RCU exhibited significant alterations in small-worldness and clustering coefficients in CT compared with controls. However, no significant differences in the CSA were observed between the groups. Additionally, nodal network measurements displayed abnormalities in widespread brain regions, including the dorsolateral prefrontal cortex (DLPFC): caudal middle frontal gyrus, rostral middle frontal gyrus, and superior frontal gyrus), ventrolateral prefrontal cortex (VLPFC): pars opercularis and pars triangularis, and anterior cingulate cortex (ACC). These results highlight the implications of RCU on the structural organization of the brain in young adults.

4.1. Altered small-worldness and clustering coefficient based on CT

Defined as the ratio of the number of edges that are actually connected to a node to the number of possible edges, the clustering coefficient is a crucial metric for network organization, reflecting the information continuity around the node and is considered an indicator of local efficiency (Rubinov & Sporns, 2010). Small-world networks combine network integration and separation with a high coefficient of clustering, thereby minimizing the cost of connectivity and increasing information flow (Rubinov & Sporns, 2010). In this study, young adults with RCU exhibited abnormal clustering coefficients in terms of CT compared to controls, suggesting that RCU may affect the information processing of the structural network and induce a tendency for the network to segregate (Gentili et al., 2015). Moreover, according to a functional connectivity-based graph theory study, this separation occurs

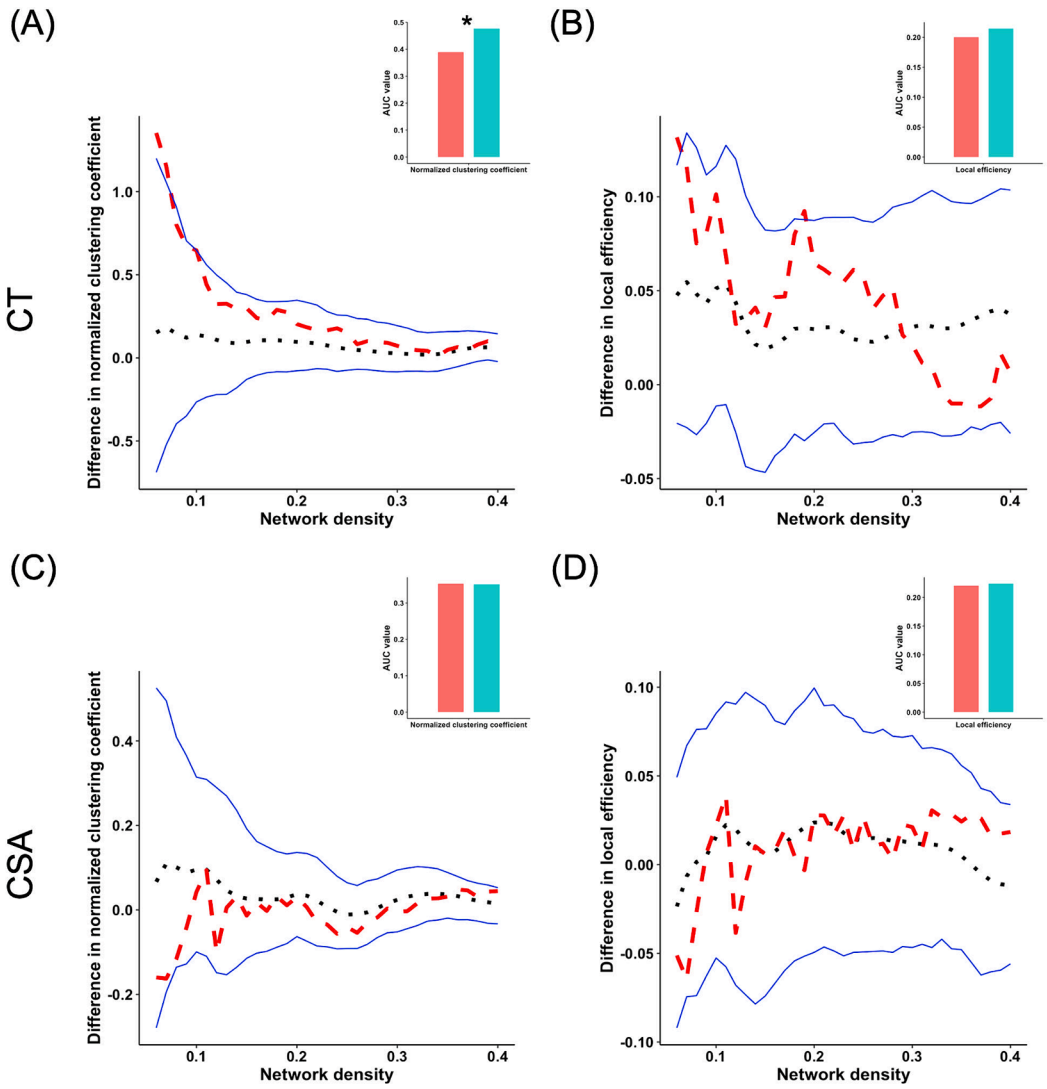

Fig. 2. Group differences in "segregation" metrics of structural covariance networks based on cortical thickness (CT) and cortical surface area (CSA) at the range of 6 %-40 % network sparsity, including (A) (C) normalized clustering coefficient, and (B) (D) local efficiency. The upper and lower blue lines represented 95 % confidence interval, whereas the black dot line in the middle denoted the mean difference after 1000 permutations. The red line represented the true group differences, which fall outside the confidence interval indicated significant group differences ($P < 0.05$) under the current threshold. The positive values indicate young adults with recent cannabis use (RCU) > controls and negative values indicate young adults with RCU < controls. The subpanels showed group differences of the area under the curve (AUC) value in each metric of SCNs. Compared with controls, young adults with RCU showed significant altered AUC value of normalized clustering coefficient in terms of CT. *, $P < 0.05$.

predominantly during reward-information processing (Nestor et al., 2020). Small-world alterations may also be associated with developmental abnormalities of the brain caused by cannabis usage, which may be related to cannabis-induced synaptic connectivity deficits, subsequently leading to abnormal interregional connectivity (Orr et al., 2019). The clustering coefficients and small-world network anomalies in the present study were consistent with the findings of a previous diffusion tensor imaging-based graph theory analysis, indicating that RCU affected the white matter and gray matter structures of the brain, which may be primarily represented by alterations in global network metrics. However, no significant anomalies were observed in the network separation and integration metrics based on CSA. This could perhaps be attributed to the differences in the spatial scale and biological significance of CSA and CT, which have different effects on the topology of the network. CSA may be associated with the strength of connections between regions, whereas CT may be more reflective of the density of neurons within a region (Sanabria-Diaz et al., 2010).

4.2. Altered nodal network measures of CSA and CT

Regarding the node network metrics, young adults with RCU exhibited anomalies in widespread brain regions (the DLPFC, posterior cingulate cortex (PCC), VLPFC, and insula), which belong to the ECN, DMN, and salience network (SN). The DLPFC is one of the core regions in the ECN and participates in several cognitive control processes, such as working memory, attention, planning, and decision-making (Panikratova et al., 2020; Xu et al., 2018). Aberrant performance on a working memory task from cannabis users was associated with altered DLPFC activation and positively correlated with cannabis usage frequency (Taurisano et al., 2016). Further, intervention by transcranial magnetic stimulation in the DLPFC can significantly reduce its abnormal activity, and this consequence decreases the frequency of cannabis use (Tang et al., 2021).

The PCC and VLPFC are key regions of the DMN that play a vital role in thought processes and emotion regulation functions (Buckner, 2013). The PCC constitutes a large CB1 receptor density that progressively

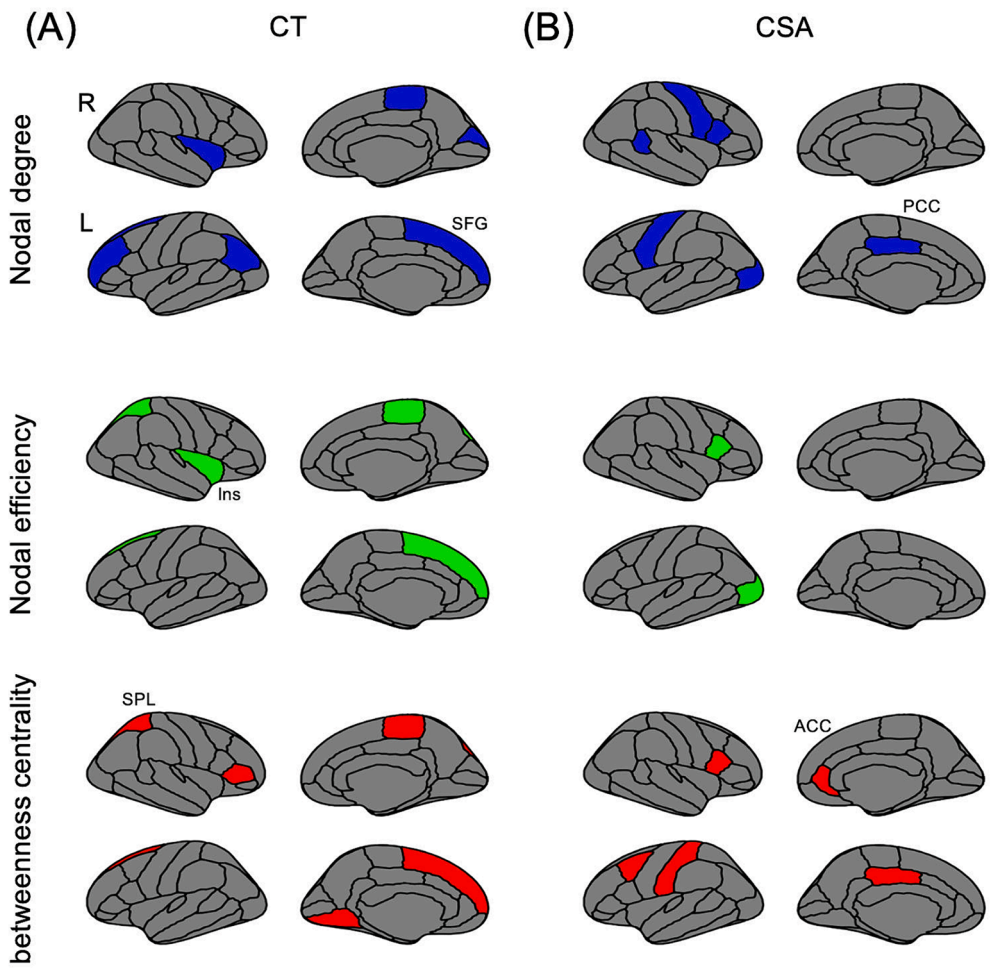

Fig. 3. Group differences in nodal network metrics (nodal degree, nodal efficiency, and nodal betweenness centrality) of structural covariance networks based on cortical thickness (CT) and cortical surface area (CSA). Regions that showed significant differences of AUC at the range from 6 % to 40 % network sparsity in nodal degree, nodal efficiency, and nodal betweenness centrality between groups were colored ($P < 0.05$, false discovery rate corrected). The blue colour represented regions that have altered nodal degree in young adults with recent cannabis use (RCU); The green colour denoted regions that have altered nodal efficiency in young adults with RCU; The red colour represented regions that have altered nodal betweenness centrality in young adults with RCU. SFG, superior frontal gyrus; PCC, posterior cingulate cortex; Ins, insula; SPL, superior parietal lobule; ACC, anterior cingulate cortex.

downregulates with cannabis use, affecting the structure of the PCC and potentially altering connectivity within the DMN, which may be a mechanism for cannabis-related changes in cognitive functioning (Wall et al., 2019). Our study found that PCC connectivity may change dynamically as a result of abstaining from cannabis for a period of time, which is consistent with previous studies (Hirvonen et al., 2012). This study found abnormal connectivity of the VLPFC; a previous study also demonstrated that the right VLPFC abnormality was particularly pronounced in the RCU when performing a working memory task (Ma et al., 2018). This anomaly could perhaps be related to the VLPFC compensating for the abnormal connectivity of the DLPFC (Ma et al., 2018). In addition, the DLPFC and VLPFC belong to two different but mutually reinforcing loops in memory-related tasks (Leh et al., 2010). This study illustrated that connectivity abnormalities in the VLPFC may originate from DLPFC abnormalities, and this alteration is reversible.

As a hub of the SN, the insula is responsible for information interactions and emotional processing (Menon & Uddin, 2010). Altered insula connectivity is a marker of inflammation, and the gray matter volume of the insula shrinks when immune function is impaired, affecting cognitive, motor, and pain pathways linked with the insula (Cottam et al., 2018; Zhou et al., 2017). Moreover, cannabis primarily affects the dorsal and ventral anterior insula, which shows reversible abnormal connectivities (Flannery et al., 2022). This study indicated that cannabis usage may induce an inflammatory response that causes insula-related network alterations. Additionally, we found that ACC showed abnormalities in betweenness centrality. The ACC is a key region in the SN that plays a role in decision-making and attentional control (Menon & Uddin, 2010). ACC has a high density of CB1 receptors, and its abnormal connections to sensorimotor regions may be a mechanism for THC-associated reduction of pain sensation (Weizman et al., 2018). Further, abnormal activity of the dorsal ACC is connected with abnormalities in the cannabis-related reward system (Weizman et al., 2018). In conjunction with our findings, these results suggested that early-period ACC abnormalities in RCU may be associated with addictive behaviors, with regional variation as cannabis use frequency changes. ECN and SN activity are correlated but inversely related to the DMN, where the SN functions as a switch between the DMN and the ECN (Goulden et al., 2014).

From the perspective of the entire network, abnormal interactions of key nodes in the DMN, ECN, and SN affect the structure and function of the triple networks, resulting in neuropsychiatric disease-related symptoms (De Ridder et al., 2022). A previous study found that THC and cannabidiol in cannabis affect the internal connectivity of the DMN and SN, respectively, and this effect decreases with cannabis abstinence treatment, with the most significant alterations occurring in the DMN (Wall et al., 2019). Moreover, research has revealed that cannabis use is

linked with an increase in functional connectivity between the SN and ECN, which correlates with the severity of cannabis use (Imperatori et al., 2020). In comparison to our previous study, node anomalies in small-world and default mode network have found in both short and long-term cannabis users, and additionally, the range of network anomalies may expand with duration of cannabis use (H. Xu et al., 2024). These findings highlight the effect of RCU on the structural organization of the brain in young adults, indicating that RCU can be detrimental to brain function, and providing valuable insights into minimizing this negative effect in RCU individuals.

However, there were some limitations in this study. First, this was a cross-sectional study, which only observed and analyzed the RCU in a certain period, and determination of the causal relationship was impossible. Second, the RCU selected for this study also combined higher levels of alcohol and tobacco use, which may also affect the cannabis use results. Third, short-term cannabis use has now been found to affect structural brain networks, which may lead to cognitive dysfunction, so a comprehensive evaluation of the effects on the brain from cannabis is also needed.

5. Conclusion

Young adults with RCU exhibited significant variations in small-world and clustering coefficients for networks constructed using CT. In addition, significant anomalies in node degree, betweenness centrality, and node efficiency were observed in the DMN, SN, and ECN. These results suggest that RCU primarily influences the triple network structure of young adults, and this negative effect of RCU on individuals should be minimized.

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CRediT authorship contribution statement

Jiahao Li: Writing – original draft, Visualization, Software, Methodology. **Hui Xu:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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References

Achard, S., & Bullmore, E. (2007). Efficiency and cost of economical brain functional networks. *PLoS Computational Biology, 3*(2), e17.

Battistella, G., Fornari, E., Annoni, J. M., Chtioui, H., Dao, K., Fabritius, M., Favrat, B., Mall, J. F., Maeder, P., & Giroud, C. (2014). Long-term effects of cannabis on brain structure. *Neuropsychopharmacology, 39*(9), 2041–2048. https://doi.org/10.1038/npp.2014.67

Bonn-Miller, M. O., Boden, M. T., Bucossi, M. M., & Babson, K. A. (2014). Self-reported cannabis use characteristics, patterns and helpfulness among medical cannabis users. *The American Journal of Drug and Alcohol Abuse, 40*(1), 23–30. https://doi.org/10.3109/00952990.2013.821477

Buckner, R. L. (2013). The brain's default network: Origins and implications for the study of psychosis. *Dialogues in clinical neuroscience, 15*(3), 351–358. https://doi.org/10.31887/DCNS.2013.15.3/rbuckner

Cottam, W. J., Iwabuchi, S. J., Drabek, M. M., Reckziegel, D., & Auer, D. P. (2018). Altered connectivity of the right anterior insula drives the pain conn ectome changes in chronic knee osteoarthritis. *Pain, 159*(5), 929–938. https://doi.org/10.1097/j.pain.0000000000001209

Davis, A. K., Lin, L. A., Ilgen, M. A., & Bohnert, K. M. (2018). Recent cannabis use among Veterans in the United States: Results from a national sample. *Addictive Behaviors, 76*, 223–228. https://doi.org/10.1016/j.addbeh.2017.08.010

De Ridder, D., Vanneste, S., Smith, M., & Adhia, D. (2022). Pain and the Triple Network Model. *Frontiers in Neurology, 13*. https://doi.org/10.3389/fneur.2022.757241

Desikan, R. S., Ségonne, F., Fischl, B., Quinn, B. T., Dickerson, B. C., Blacker, D., Buckner, R. L., Dale, A. M., Maguire, R. P., Hyman, B. T., Albert, M. S., & Killiany, R. J. (2006). An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. *Neuroimage, 31*(3), 968–980. https://doi.org/10.1016/j.neuroimage.2006.01.021

Ducharme, S., Albaugh, M. D., Nguyen, T. V., Hudziak, J. J., Mateos-Perez, J. M., Labbe, A., Evans, A. C., Karama, S., & Brain Development Cooperative, G. (2016). Trajectories of cortical thickness maturation in normal brain development–the importance of quality control procedures. *NeuroImage, 125*, 267–279. https://doi.org/10.1016/j.neuroimage.2015.10.010

Evans, A. C. (2013). Networks of anatomical covariance. *NeuroImage, 80*, 489–504. https://doi.org/10.1016/j.neuroimage.2013.05.054

Fischl, B. (2012). FreeSurfer. *Neuroimage, 62*(2), 774–781. https://doi.org/10.1016/j.neuroimage.2012.01.021

Flannery, J. S., Riedel, M. C., Salo, T., Hill-Bowen, L. D., Poudel, R., Adams, A. R., Laird, A. R., Gonzalez, R., & Sutherland, M. T. (2012). Interactive Effects of HIV Infection and Cannabis Use on Insula Subreg ion Functional Connectivity. *Journal of neuroimmune pharmacology : the official journal of the Soci ety on NeuroImmune Pharmacology, 17*(1–2), 289–304. https://doi.org/10.1007/s11481-021-10005-8

Gentili, R. J., Bradberry, T. J., Oh, H., Costanzo, M. E., Kerick, S. E., Contreras-Vidal, J. L., & Hatfield, B. D. (2015). Evolution of cerebral cortico-cortical communication during visuomotor adaptation to a cognitive-motor executive challenge. *Biological Psychology, 105*, 51–65. https://doi.org/10.1016/j.biopsycho.2014.12.003

Glasser, M. F., Sotiropoulos, S. N., Wilson, J. A., Coalson, T. S., Fischl, B., Andersson, J. L., Xu, J., Jbabdi, S., Webster, M., Polimeni, J. R., Van Essen, D. C., Jenkinson, M., & Consortium, W. U.-M. H. (2013). The minimal preprocessing pipelines for the Human Connectome Project. *Neuroimage, 80*, 105–124. https://doi.org/10.1016/j.neuroimage.2013.04.127

Gong, G., He, Y., Chen, Z. J., & Evans, A. C. (2012). Convergence and divergence of thickness correlations with diffusion connections across the human cerebral cortex. *NeuroImage, 59*(2), 1239–1248. https://doi.org/10.1016/j.neuroimage.2011.08.017

Goulden, N., Khusnulina, A., Davis, N. J., Bracewell, R. M., Bokde, A. L., McNulty, J. P., & Mullins, P. G. (2014). The salience network is responsible for switching between the default mode network and the central executive network: replication from DCM. *Neuroimage, 99*, 180–190. https://doi.org/10.1016/j.neuroimage.2014.05.052

He, Y., Chen, Z. J., & Evans, A. C. (2007). Small-world anatomical networks in the human brain revealed by cortical thickness from MRI. *Cerebral Cortex, 17*(10), 2407–2419. https://doi.org/10.1093/cercor/bhl149

Hirvonen, J., Goodwin, R. S., Li, C. T., Terry, G. E., Zoghbi, S. S., Morse, C., Pike, V. W., Volkow, N. D., Huestis, M. A., & Innis, R. B. (2012). Reversible and regionally selective downregulation of brain cannabinoi d CB1 receptors in chronic daily cannabis smokers. *Molecular psychiatry, 17*(6), 642–649. https://doi.org/10.1038/mp.2011.82

Imperatori, C., Massullo, C., Carbone, G. A., Panno, A., Giacchini, M., Capriotti, C., Lucarini, E., Ramella Zampa, B., Murillo-Rodríguez, E., Machado, S., & Farina, B. (2020). Increased resting state triple network functional connectivity in unde rgraduate problematic cannabis users: A preliminary EEG coherence study. *Brain Sciences, 10*(3), 136. https://doi.org/10.3390/brainsci10030136

Leh, S. E., Petrides, M., & Strafella, A. P. (2010). The neural circuitry of executive functions in healthy subjects and Pa rkinson's disease. *Neuropsychopharmacology, 35*(1), 70–85. https://doi.org/10.1038/npp.2009.88

Lorenzetti, V., Chye, Y., Silva, P., Solowij, N., & Roberts, C. A. (2019). Does regular cannabis use affect neuroanatomy? An updated systematic review and meta-analysis of structural neuroimaging studies. *European Archives of Psychiatry and Clinical Neuroscience, 269*(1), 59–71. https://doi.org/10.1007/s00406-019-00979-1

Ma, L., Steinberg, J. L., Bjork, J. M., Keyser-Marcus, L., Vassileva, J., Zhu, M., Ganapathy, V., Wang, Q., Boone, E. L., Ferré, S., Bickel, W. K., & Gerard Moeller, F. (2018). Fronto-striatal effective connectivity of working memory in adults wit h cannabis use disorder. *Psychiatry Research. Neuroimaging, 278*, 21–34. https://doi.org/10.1016/j.pscychresns.2018.05.010

Marcus, D. S., Harms, M. P., Snyder, A. Z., Jenkinson, M., Wilson, J. A., Glasser, M. F., Barch, D. M., Archie, K. A., Burgess, G. C., Ramaratnam, M., Hodge, M., Horton, W., Herrick, R., Olsen, T., McKay, M., House, M., Hileman, M., Reid, E., Harwell, J., & Consortium, W. U.-M. H. (2013). Human Connectome Project informatics: quality control, database servic es, and data visualization. *Neuroimage, 80*, 202–219. https://doi.org/10.1016/j.neuroimage.2013.05.077

Menon, V., & Uddin, L. Q. (2010). Saliency, switching, attention and control: A network model of insula function. *Brain Structure & Function, 214*(5–6), 655–667. https://doi.org/10.1007/s00429-010-0262-0

Mullins, M. (2013). Defining recent cannabis use analytically. *Clinical Toxicology (Philadelphia, Pa.), 61*(5), 324–325. https://doi.org/10.1080/15563650.2023.2210404

Musshoff, F., & Madea, B. (2006). Review of biologic matrices (urine, blood, hair) as indicators of rece nt or ongoing cannabis use. *Therapeutic Drug Monitoring, 28*(2), 155–163. https://doi.org/10.1097/01.ftd.0000197091.07807.22

Nestor, L. J., Behan, B., Suckling, J., & Garavan, H. (2020). Cannabis-dependent adolescents show differences in global reward-assoc iated network topology: A functional connectomics approach. *Addiction Biology, 25*(2). https://doi.org/10.1111/adb.12752

Nestor, L. J., Suckling, J., Ersche, K. D., Murphy, A., McGonigle, J., Orban, C., Paterson, L. M., Reed, L., Taylor, E., Flechais, R., Smith, D., Bullmore, E. T., Elliott, R., Deakin, B., Rabiner, I., Hughes, A. L., Sahakian, B. J., Robbins, T. W., Nutt, D. J., & Consortium, I. (2020). Disturbances across whole brain networks during reward anticipation in an abstinent addiction population. *NeuroImage: Clinical, 27*, Article 102297. https://doi.org/10.1016/j.nicl.2020.102297

Orr, C., Spechler, P., Cao, Z., Albaugh, M., Chaarani, B., Mackey, S., D'Souza, D., Allgaier, N., Banaschewski, T., Bokde, A. L. W., Bromberg, U., Büchel, C., Burke Quinlan, E., Conrod, P., Desrivières, S., Flor, H., Frouin, V., Gowland, P., Heinz, A., et al. (2019). Grey Matter Volume Differences Associated with Extremely Low Levels of Cannabis Use in Adolescence. *The Journal of Neuroscience, 39*(10), 1817–1827. https://doi.org/10.1523/JNEUROSCI.3375-17.2018

Panikratova, Y. R., Vlasova, R. M., Akhutina, T. V., Korneev, A. A., Sinitsyn, V. E., & Pechenkova, E. V. (2020). Functional connectivity of the dorsolateral prefrontal cortex contribu tes to different components of executive functions. *International Journal of Psychophysiology, 151*, 70–79. https://doi.org/10.1016/j.ijpsycho.2020.02.013

Price, J. S., McQueeny, T., Shollenbarger, S., Browning, E. L., Wieser, J., & Lisdahl, K. M. (2015). Effects of marijuana use on prefrontal and parietal volumes and cognit ion in emerging adults. *Psychopharmacology, 232*(16), 2939–2950. https://doi.org/10.1007/s00213-015-3931-0

Rubinov, M., & Sporns, O. (2010). Complex network measures of brain connectivity: Uses and interpretations. *NeuroImage, 52*(3), 1059–1069. https://doi.org/10.1016/j.neuroimage.2009.10.003

Sanabria-Diaz, G., Melie-Garcia, L., Iturria-Medina, Y., Aleman-Gomez, Y., Hernandez-Gonzalez, G., Valdes-Urrutia, L., Galan, L., & Valdes-Sosa, P. (2010). Surface area and cortical thickness descriptors reveal different attributes of the structural human brain networks. *NeuroImage, 50*(4), 1497–1510. https://doi.org/10.1016/j.neuroimage.2010.01.028

Scott, J. C., Rosen, A. F. G., Moore, T. M., Roalf, D. R., Satterthwaite, T. D., Calkins, M. E., Ruparel, K., Gur, R. E., & Gur, R. C. (2019). Cannabis use in youth is associated with limited alterations in brain structure. *Neuropsychopharmacology, 44*(8), 1362–1369. https://doi.org/10.1038/s41386-019-0347-2

Tang, V. M., Le Foll, B., Blumberger, D. M., & Voineskos, D. (2021). Repetitive Transcranial magnetic stimulation for comorbid major depres sive disorder and alcohol use disorder. *Brain Sciences, 12*(1), 48. https://doi.org/10.3390/brainsci12010048

Tao, R., Li, C., Jaffe, A. E., Shin, J. H., Deep-Soboslay, A., Yamin, R., Weinberger, D. R., Hyde, T. M., & Kleinman, J. E. (2020). Cannabinoid receptor CNR1 expression and DNA methylation in human prefrontal cortex, hippocampus and caudate in brain development and schizophrenia. *Translational Psychiatry, 10*(1), 158. https://doi.org/10.1038/s41398-020-0832-8

Taurisano, P., Antonucci, L. A., Fazio, L., Rampino, A., Romano, R., Porcelli, A., Masellis, R., Colizzi, M., Quarto, T., Torretta, S., Di Giorgio, A., Pergola, G., Bertolino, A., & Blasi, G. (2016). Prefrontal activity during working memory is modulated by the interact ion of variation in CB1 and COX2 coding genes and correlates with freq uency of cannabis use. *Cortex; A Journal Devoted to the Study of the Nervous System and Behavior, 81*, 231–238. https://doi.org/10.1016/j.cortex.2016.05.010

Van Essen, D. C., Smith, S. M., Barch, D. M., Behrens, T. E. J., Yacoub, E., Ugurbil, K., & Consortium, W. U.-M. H. (2013a). The WU-Minn human connectome project: An overview. *Neuroimage, 80*, 62–79. https://doi.org/10.1016/j.neuroimage.2013.05.041

Van Essen, D. C., Ugurbil, K., Auerbach, E., Barch, D., Behrens, T. E. J., Bucholz, R., Chang, A., Chen, L., Corbetta, M., Curtiss, S. W., Della Penna, S., Feinberg, D., Glasser, M. F., Harel, N., Heath, A. C., Larson-Prior, L., Marcus, D., Michalareas, G., Moeller, S., & Consortium, W. U.-M. H. (2012). The Human Connectome Project: a data acquisition perspective. *Neuroimage, 62*(4), 2222–2231. https://doi.org/10.1016/j.neuroimage.2012.02.018

Wall, M. B., Pope, R., Freeman, T. P., Kowalczyk, O. S., Demetriou, L., Mokrysz, C., Hindocha, C., Lawn, W., Bloomfield, M. A., Freeman, A. M., Feilding, A., Nutt, D., & Curran, H. V. (2019). Dissociable effects of cannabis with and without cannabidiol on the hu man brain's resting-state functional connectivity. *Journal of Psychopharmacology (Oxford, England), 33*(7), 822–830. https://doi.org/10.1177/0269881119841568

Weizman, L., Dayan, L., Brill, S., Nahman-Averbuch, H., Hendler, T., Jacob, G., & Sharon, H. (2018). Cannabis analgesia in chronic neuropathic pain is associated with alte red brain connectivity. *Neurology, 91*(14), e1285–e1294. https://doi.org/10.1212/WNL.0000000000006293

Winkler, A. M., Greve, D. N., Bjuland, K. J., Nichols, T. E., Sabuncu, M. R., Haberg, A. K., Skranes, J., & Rimol, L. M. (2018). Joint analysis of cortical area and thickness as a replacement for the analysis of the volume of the cerebral cortex. *Cerebral Cortex, 28*(2), 738–749. https://doi.org/10.1093/cercor/bhx308

Xu, H., Li, D., & Yin, B. (2022). Aberrant hippocampal shape development in young adults with heavy cannabis use: Evidence from a longitudinal study. *Journal of Psychiatric Research, 152*, 343–351. https://doi.org/10.1016/j.jpsychires.2022.06.037

Xu, H., Li, J., Huang, H., Yin, B., & Li, D.-D. (2024). Abnormal developmental of structural covariance networks in young adults with heavy cannabis use: A 3-year follow-up study. *Translational Psychiatry, 14*(1), 45. https://doi.org/10.1038/s41398-024-02764-8

Xu, H., Wang, X., Chen, Z., Bai, G., Yin, B., Wang, S., Sun, C., Gan, S., Wang, Z., Cao, J., Niu, X., Shao, M., Gu, C., Hu, L., Ye, L., Li, D., Yan, Z., Zhang, M., & Bai, L. (2018). Longitudinal changes of caudate-based resting state functional connectivity in mild traumatic brain injury [original Research]. *Frontiers in Neurology, 9*. https://doi.org/10.3389/fneur.2018.00467

Zehra, A., Burns, J., Liu, C. K., Manza, P., Wiers, C. E., Volkow, N. D., & Wang, G. J. (2018). Cannabis addiction and the brain: A review. *Journal of Neuroimmune Pharmacology, 13*(4), 438–452. https://doi.org/10.1007/s11481-018-9782-9

Zhou, Y., Li, R., Wang, X., Miao, H., Wei, Y., Ali, R., Qiu, B., & Li, H. (2017). Motor-related brain abnormalities in HIV-infected patients: a multimod al MRI study. *Neuroradiology, 59*(11), 1133–1142. https://doi.org/10.1007/s00234-017-1912-1