Association of Cannabis Use During Adolescence With Neurodevelopment

Matthew D. Albaugh[1], Jonatan Ottino-Gonzalez[1], Amanda Sidwell[1], Claude Lepage[2], Anthony Juliano[1], Max M. Owens[1], Bader Chaarani[1], Philip Spechler[1], Nicholas Fontaine[1], Pierre Rioux[2], Lindsay Lewis[2], Seun Jeon[2], Alan Evans[2], Deepak D'Souza[3], Rajiv Radhakrishnan[3], Alexandra Potter[1], Hugh Garavan[1], and IMAGEN

[1]Department of Psychiatry, Larner College of Medicine, University of Vermont; [2]McConnell Brain Imaging Centre, McGill University; [3]Department of Psychiatry, Yale University School of Medicine

Introduction

- Animal studies have shown that the adolescent brain is sensitive to disruptions in endocannabinoid signaling, resulting in altered neurodevelopment and lasting behavioral effects.[1]
- Despite such findings, few studies have investigated ties between cannabis use and adolescent brain development in humans.
- Here, we examined the degree to which MRI-assessed cerebral cortical thickness development was qualified by cannabis use in a large longitudinal sample of adolescents.[2]

Sample

- Neuroimaging and behavioral data were obtained from the IMAGEN study conducted across 8 European sites, which includes 2,223 adolescents recruited from schools at 14 years of age.
- We identified participants who reported being cannabis-naïve at study baseline, and had behavioral and quality-controlled neuroimaging data available at study baseline and 5-year follow-up (n = 799; 450 females, 349 males).

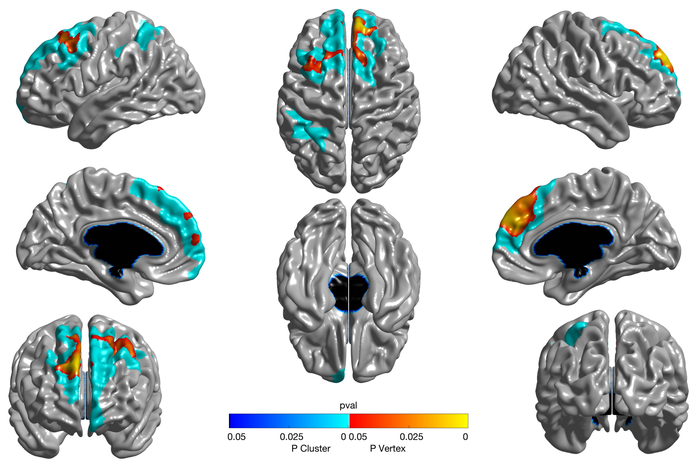
Measures

- Substance use was assessed at baseline and 5-year follow-up with the European School Survey Project on Alcohol and Drugs (ESPAD).
- The Alcohol Use Disorders Identification Test (AUDIT) is a 10-item screening tool created by the World Health Organization that assesses alcohol consumption, drinking behaviors, and alcohol-related problems. The AUDIT Alcohol Consumption scale (AUDIT-C) was used in the present study and is comprised of items on the AUDIT that explicitly assess amount and frequency of alcohol consumption.
- Quality-controlled native MR images were processed through the CIVET pipeline (version 2.1.0) using the CBRAIN platform and Compute Canada (www.computecanada.ca).
- Maps of CB1 receptor availability were generated using positron emission tomography (PET) and the reversible ligand [^{11}C]OMAR in a separate sample of 21 young adults aged 18-35.

Analyses

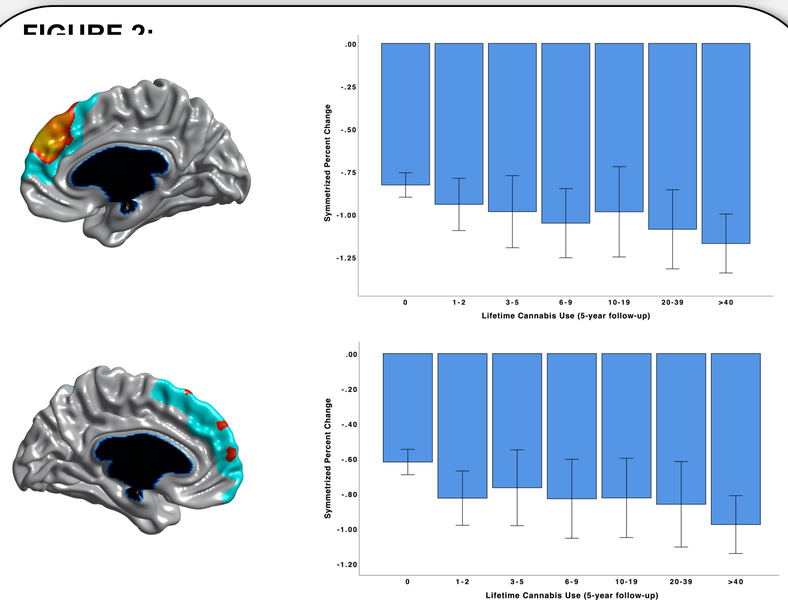
- Cortical thickness analysis was implemented using SurfStat, a toolbox created for MATLAB (The MathWorks, Inc., Natick, Massachusetts) by Dr. Keith Worsley (http://www.math.mcgill.ca/keith/surfstat/).
- Longitudinal cortical thickness analysis was conducted using linear mixed-effects models (LMMs).

FIGURE 1:



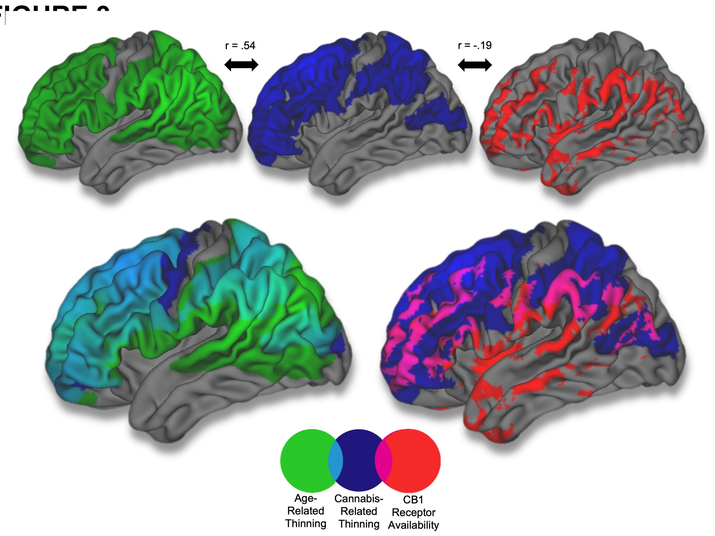
*Areas where cortical thickness is associated with Time*Cannabis interaction in a linear mixed-effects model analysis, controlling for the main effects of time, lifetime cannabis use, total brain volume, sex, handedness, AUDIT Alcohol Consumption score, and site (n = 799; 1598 MRIs). Shown at p ≤ 0.05 with a whole-brain random field theory correction. Blue shades correspond to areas significant at the cluster level and orange shades to areas significant at the vertex level.*

FIGURE 2:



cortical thickness, in millimeters per year, with respect to the mean cortical thickness across both time points) at varying levels of lifetime cannabis use (at 5-year follow-up). Top = right dorsomedial prefrontal cluster, bottom = left dorsomedial prefrontal cluster. Error bars represent 95% confidence intervals.

FIGURE 3:



Topographical overlap between age-related cortical thinning in sample (n = 799), areas in which age-related thinning was qualified by cannabis use, and PET-assessed CB1 receptor availability (collected on a separate sample of 21 healthy adults). The r values correspond to correlation coefficients between unthresholded vertex-level surface maps. Please note that thresholds have been lowered for visualization purposes. Regional [^{11}C]OMAR volume distribution (V_T) shown at > 1.4, age-related thinning map shown at t < -15, and cannabis-related thinning map shown at t < -2.

- In LMMs, subject ID was entered as a random effect in order to account for within-individual dependence. Change in lifetime cannabis use (from baseline to 5-year follow-up) was included as a time-invariant covariate.
- Age, total brain volume, sex, handedness, site, and AUDIT consumption score were controlled for in all analyses.
- To account for multiple comparisons, random field theory correction was applied to the cortical surface.

Results

- At 5-year follow-up, cross-sectional analysis revealed evidence of a dose-dependent association between lifetime cannabis use and cortical thickness (n = 799), with significant negative associations between lifetime cannabis use and thickness in prefrontal cortices.
- There were no significant associations between baseline cortical thickness and follow-up lifetime cannabis use.
- LMM analysis (799 subjects; 1598 MRIs) revealed a significant Time*Cannabis interaction, such that cannabis use was associated with accelerated age-related cortical thinning in a number of cortical regions (Figures 1 and 2).
- The unthresholded t statistic map for the Time*Cannabis interaction was significantly associated with the PET-derived map of CB1 receptor availability (r = -0.189, p < .001), indicating that cortical areas in which age-related thinning was qualified by cannabis partially overlapped with areas showing higher density of CB1Rs as indexed by [^{11}C]OMAR binding (Figure 3).
- The spatial pattern of cannabis-related cortical thinning was strongly correlated with the unthresholded t statistic map for the effect of time, indicating that, on average, cannabis-related thinning was greater in cortical regions evidencing the most significant age-related thinning in this sample (r = 0.540, p < .001) (Figure 3).

Conclusions

- Results indicate that age-related cortical thinning was associated with cannabis use in a dose-dependent fashion.
- Baseline cortical thickness was not associated with lifetime cannabis use at 5-year follow-up suggesting that the neuroanatomical differences observed at 5-year follow-up did not precede initiation of cannabis use.
- Across analyses, cannabis-related effects persisted when covarying for alcohol and nicotine use.
- Results suggest that cannabis use during adolescence is linked to altered neurodevelopment, particularly in cortices rich in CB1 receptors and undergoing the greatest age-related thickness change in middle-to-late adolescence.

REFERENCES

1. **Miller, M.L., et al. Adolescent exposure to Δ9-tetrahydrocannabinol alters the transcriptional trajectory and dendritic architecture of prefrontal pyramidal neurons. *Molecular Psychiatry* 24(4):588-600, 2018.**
2. **Albaugh, M.D., et al. Association of cannabis use during adolescence with neurodevelopment. JAMA Psychiatry. 2021 Jun 16;78(9):1-11. doi: 10.1001/jamapsychiatry.2021.1258.**