INPLASY

Cannabis use and brain development: A systematic review and meta-analysis

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ADMINISTRATIVE INFORMATION

Support - None.

Review Stage at time of this submission - The review has not yet started.

Conflicts of interest - None declared.

INPLASY registration number: INPLASY202480132

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 29 August 2024 and was last updated on 29 August 2024.

INTRODUCTION

Review question / Objective P: Cannabis users; I: Neuroimaging; C: Non-cannabis userrs; O: Alterations in brain structure; Do cannabis users demonstrate significantly different changes in brain structure and function in comparison to non-using controls?
Is there a correlation between cannabis dose/ frequency/duration of use and any structural and functional changes in the developing brain?
Do the changes observed across various neuroimaging modalities correlate with one another?

Rationale The main psychoactive compound of cannabis, Δ9-tetrahydrocannabinol (THC), interacts with the brain's endogenous cannabinoid system, binding to the type 1 cannabinoid receptor (CB1R). The endocannabinoid system plays a crucial role in regulatory and homeostatic functions. These cannabinoid receptors, particularly CB1 receptors, are densely distributed in brain regions such as the prefrontal cortex, hippocampus, amygdala, and dorsolateral prefrontal cortex.
We wish to determine the precise effect seen in each of these areas with regular cannabis use, with a view to profiling the potential manifestations of these effects in terms of cognitive function and illness outcome.
Although several reviews have investigated the impact of cannabis on brain structure and function, primarily through structural MRI, there is a pressing need for a comprehensive large-scale review evaluating all neuroimaging modalities. Notably, only one systematic review over the past decade has addressed MRS changes associated with cannabis use. Each neuroimaging modality provides nuanced and unique information regarding the profile of brain changes related to cannabis use. Therefore a broader review is crucial to advance our understanding of the multifaceted effects of cannabis on the brain.

Condition being studied The condition being studied is cannabis use.

Participants in this study will be Cannabis users vs Non/minimal ever cannabis users, aged 11-40
Forms: Cannabis will include any form of THC, CBD, synthetic cannabinoids, and means of administration will include any forms of inhalation and ingestion
Neuroimaging: structural MRI, DTI MRI, functional MRI (both resting state and task-based), MRS.

METHODS

Search strategy Initially, a systematic literature search will be conducted on the databases listed below. This search will follow the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.
Databases: PubMed, ScienceDirect, PsycINFO, Google Scholar, Embase (Cannabis OR weed OR marijuana OR tetrahydrocannabinol OR THC or cannabinoid OR CBD OR CBD-THC OR hashish) AND (MRI OR magnetic resonance imaging OR MRS or magnetic resonance spectroscopy OR DTI OR diffusion tensor imaging OR fMRI OR functional magnetic resonance imaging OR rsMRI OR resting state magnetic resonance imaging OR neuroimaging AND (brain OR hippocampus OR amygdala OR prefrontal cortex OR cerebellum OR basal ganglia).

Participant or population
Inclusion criteria
Participants:
History of cannabis use in individuals between age 11-40
Controls:
None or minimal cannabis use in lifetime

Factors included in both groups for future sub group analysis include:
other illicit substances
other psychiatric diagnoses

Exclusion criteria for participants:
Aged 41 years old
Previous history of: head trauma neurological disease intellectual disabilities pregnancy, chronic medical illness (lasting more than 1 year)
Long term medications except for prescribed psychiatric medications where a psychiatric diagnoses is present (subgroup analyses)

Exclusion criteria for controls:
Aged 41 years old
Previous history of: head trauma, neurological disease intellectual disabilities pregnancy, chronic medical illness (lasting more than 1 year)
Long term medications except for prescribed psychiatric medications where a psychiatric diagnoses is present (subgroup analyses)
Any more than minimal cannabis use in lifetime – based on a scoping review of the literature, a reasonable cut off would be 10 lifetime uses.

Intervention Forms: Cannabis will include any form of THC, CBD, synthetic cannabinoids, and means of administration will include any forms of inhalation and ingestion.
Neuroimaging: structural MRI, DTI MRI, functional MRI (both resting state and task-based), MRS.

Comparator None or minimal cannabis use in lifetime
Exclusion criteria for controls:
Aged 41 years old
Previous history of: head trauma, neurological disease intellectual disabilities pregnancy, chronic medical illness (lasting more than 1 year)
Long term medications except for prescribed psychiatric medications where a psychiatric diagnoses is present (subgroup analyses)
Any more than minimal cannabis use in lifetime – based on a scoping review of the literature, a reasonable cut off would be 10 lifetime uses.

Study designs to be included Inclusion:Any form of case-control study, randomised control trial or pre/post design case-control study which characterised level of cannabis useParticipant and control inclusion and exclusion criteria as detailed aboveNeuroimaging: structural MRI, DTI MRI, resting state functional MRI, task-based functional MRI, and MRS.Participant and control inclusion and exclusion criteria as detailed aboveNeuroimaging: structural MRI, DTI MRI, resting state functional MRI, task-based functional MRI, and MRS.Exclusion:Cohort studies which did not include controls.

Eligibility criteria Defined above.

Information sources Electronic databases as listed above.

Main outcome(s) Main outcomes: Changes in brain structure and function in cannabis users vs controls as determined by neuroimaging.
Measures of effect: cohen's d (or similar effect size) between each group for each measure below
Full Meta-analysis and meta-regression to be run on associated covariates, e.g., duration of use, co-morbid psychiatric conditions.
Data will be collected for each form of neuroimaging listed, followed by individual statistical analysis of each.

Additional outcome(s) Volume differences of specific brain areas between cannabis users and controls.
Diffusion differences of specific brain areas between cannabis users and controls.
Metabolite differences of specific brain areas between cannabis users and controls fMRI task differences between cannabis users and controls.
rsMRI differences between cannabis users and controls.

Data management Inclusion and Exclusion criteria will be defined as per above.
Four review authors screen papers by title and abstracts using Covidence. Conflicts will be settled by a fifth senior reviewer. Four authors extract the findings from each paper and place information into Excel spreadsheet. Data will be cross-checked by a fifth, senior reviewer.

Quality assessment / Risk of bias analysis The quality of the studies eligible for inclusion will be evaluated using the modified Newcastle-Ottawa Scale (mNOS) (24). Studies with NOS scores 0–3, 4–6 and 7–9 will be considered as low, moderate and high quality, respectively. Furthermore, Funnel and Galbraith plots will be formulated to quantitatively assess for publication bias.

Strategy of data synthesis Four authors extract the findings from each paper using Covidence and place information into Excel spreadsheet. Data will be cross-checked by a fifth, senior reviewer.
All statistical analyses will be conducted using SPSS v28.0 (22).
Heterogeneity will be explored using I^2 scores and visualised through Galbraith plots. Low, moderate and high heterogeneity will be indicated by an I2 score of 25, 50, 75% respectively.
Effect sizes will be calculated for structural and functional changes in cannabis users vs non-users using Cohen's D. Standard Error will also be computed.
Meta-regressions will be performed using the demographic characteristics.
In the event of systematic differences in methodology and study characteristics, a Restricted Maximum Likelihood (REML) random effects model will be used for subgroup meta-analyses. Using a 95% Confidence Interval (CI) and a significant p-value of 0.05, confidence intervals and cumulative levels of significance will also be calculated for each subgroup pooled result.

Subgroup analysis If the necessary data are available, subgroup analyses will be done for confounding factors such as substance use (other than cannabis), psychiatric comorbidities, duration of use, preferred method of use.
Age specific analysis subgroups: age 16-20, 21-25, 26-30, 31-35, 36-40.

Sensitivity analysis Modified Newcastle-Ottawa Scores will be calculated for each included study to assess quality of eligible studies. Furthermore, Funnel and Galbraith plots will be formulated to quantitatively assess for publication bias. Should systematic differences in methodology and study characteristics arise, a Restricted Maximum Likelihood (REML) random effects model will be utilised.

Language restriction English-language studies.

Country(ies) involved Ireland.

Keywords Cannabis; THC; CBD; Substance use; Neuroimaging; Magnetic resonance imaging; Diffusion tensor imaging; Magnetic resonance spectroscopy; Neurology.

Dissemination plans Apply for publication in appropriate peer-reviewed journal, e.g., Springer Brain Structure and Function Journal.

Contributions of each author
Author 1 - Michael O'Connor - Author 1 will assist in all stages of data collection and analysis, as well as drafting of the manuscript.
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