Cannabis and Health

Module 4

Lecture 2: Cannabis and the Brain Part II

Cannabis and the Brain

- Last lecture covered the effects of cannabis on gray matter and white matter morphology

- This lecture covers the functional effects of cannabis in the brain in animal and human studies

Summary of Functional Effects in Animals and Humans

- Reviews of animal and human studies (Curran et al., 2016; Panlilio et al., 2018; Zehra et al., 2018) suggest:
  - Alterations in dopamine reward circuits
  - Reductions in CB1 receptors
  - Changes in stress circuits
  - Changes in growth of dendrites
- Reviews of human fMRI studies suggest:
  - Changes in dopamine reward circuits
  - Changes in emotion regulation

Critique of Literature: Inconsistency in findings and Type I error (e.g., imaging studies)

- The animal and human literature often has contradictory findings with respect to the effects of cannabis on the brain
- In the animal studies, may be related to differences in dose, drug, route of administration, and sex differences – these vary study to study
- In human studies, likely related to inflated Type I error (when you find a difference that does not really exist) due to sheer number of statistical tests
- Also due to differences in study parameters from one study to the next

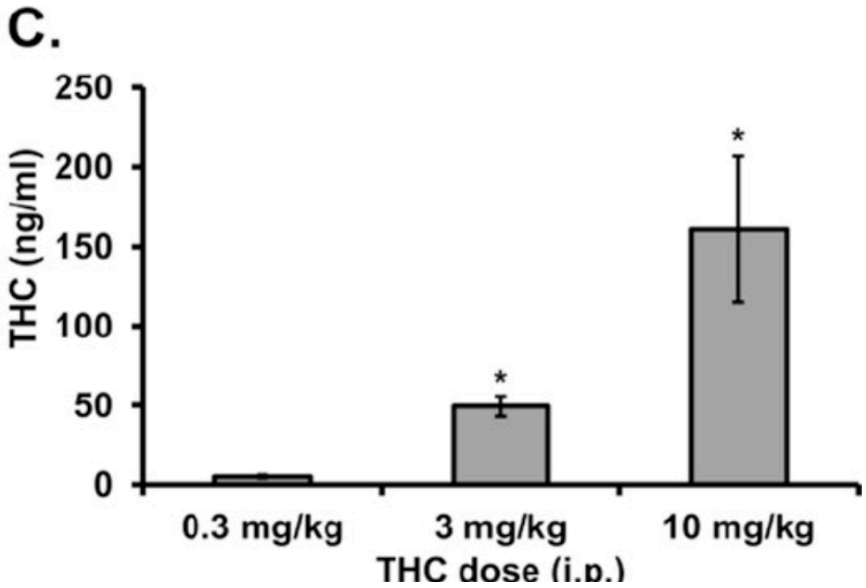
Critique of Literature: Small Sample Size

- In general, small sample sizes can lead to spurious findings – there are a lot of small neuroimaging studies and only a few large studies

- Animal studies also have small groups but control over study conditions much better

Drug, Route of Administration, and Dose

- Animals will not reliably self administer THC - a problem that has been difficult to overcome
  - This makes traditional studies of the addictive potential of cannabis to be more difficult
- Animal studies sometimes use CB1 agonist other than THC
- Route of administration also varies considerably in animals studies (injection, oral, inhaled)
- The doses used in animal studies varies dramatically from 1 mg/kg to 30+ mg/kg



Nguyen et al., 2016, Neuropharmacology

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4970926/

What does a “change” in the brain mean?

- Many of the studies that report associations between cannabis use and brain morphology or function do not include data that would help interpret the association
- Does a difference in the “shape” of the amygdala have any translation, positive or negative, in terms of behavior or cognition on a day to day basis?
  - Nobody knows
- Causation or temporal precedence not possible with human studies
  - Cannot randomly assign subjects to use THC for 10 years to find out if THC actually causes ”change” in the brain
  - Cannot prove causation - possible that differences in the brain precede cannabis use
  - Shared vulnerability factor may underlie both differences in brain and cannabis use
- Future studies like enormous NIH funded ABCD, led by NIDA, will shed light on the questions

Example 1: One joint produces change in gray matter

JNeurosci
THE JOURNAL OF NEUROSCIENCE

Research Articles: Behavioral/Cognitive

Grey Matter Volume Differences Associated with Extremely Low Levels of Cannabis Use in Adolescence

Catherine Orr, MPsych/PhD[1,2], Philip Spechler, MSci[1], Zhipeng Cao[3,4], Matthew Albaugh, PhD[1], Bader

Abstract

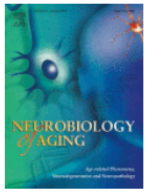
Rates of cannabis use among adolescents are high, and are increasing concurrent with changes in the legal status of marijuana and societal attitudes regarding its use. Recreational cannabis use is understudied, especially in the adolescent period when neural maturation may make users particularly vulnerable to the effects of Δ-9-tetrahydrocannabinol (THC) on brain structure. In the current study, we used voxel-based morphometry to compare grey matter volume (GMV) in 46 fourteen year old human adolescents (males and females) with just one or two instances of cannabis use and carefully matched THC-naïve controls. We identified extensive regions in the bilateral medial temporal lobes as well as the bilateral posterior cingulate, lingual gyri, and cerebellum that showed greater GMV in the cannabis users. Analysis of longitudinal data confirmed that GMV differences were unlikely to precede cannabis use. GMV in the temporal regions was associated with contemporaneous performance on the Perceptual Reasoning Index and with future generalized anxiety symptoms in the cannabis users. The distribution of GMV effects mapped onto biomarkers of the endogenous cannabinoid system providing insight into possible mechanisms for these effects.

Example 2:

ELSEVIER

Neurobiology of Aging

Volume 61, January 2018, Pages 177-186



Regular article

Reversal of age-related cognitive impairments in mice by an extremely low dose of tetrahydrocannabinol

Yosef Sarne [a], Roni Toledano [a], Lital Rachmany [a], Effrat Sasson [b], Ravid Doron [c, d]

Abstract

This study was designed to test our hypothesis that an ultra-low dose of delta-9 tetrahydrocannabinol (THC) reverses age-dependent cognitive impairments in old mice and to examine the possible biological mechanisms that underlie this behavioral effect. Old female mice aged 24 months that had been injected once with 0.002 mg/kg THC (3–4 orders of magnitudes lower than doses that induce the conventional cannabinoid effects in mice) performed significantly better than vehicle-treated old mice and performed similarly to naive young mice aged 2 months, in 6 different behavioral assays that measured various aspects of memory and learning. The beneficial effect of THC lasted for at least 7 weeks. The single injection of THC increased the level of Sirtuin1, an enzyme that has been previously shown to be involved in neuroprotection and neuroplasticity, in the hippocampus and in the frontal cortex of old mice, for at least 7 weeks. Magnetic resonance imaging demonstrated a larger volume and higher tissue density in various regions of the brain of THC-treated old mice. These findings suggest that extremely low doses of THC that are devoid of any psychotropic effect and do not induce desensitization may provide a safe and effective treatment for cognitive decline in aging humans.

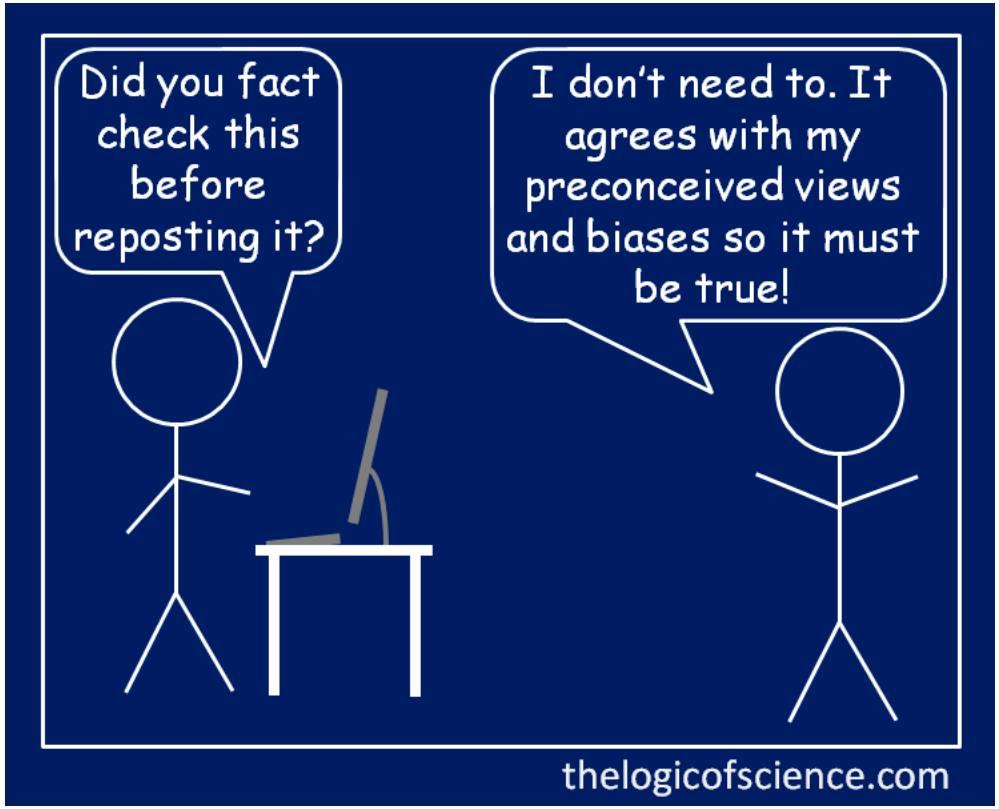
Healthy Skepticism

- The next two slides below provide an abstract from two recent studies of cannabis and the brain
- Evaluate the study linking one joint to change in brain volumes
- Evaluate study linking micro doses of THC to reversing age related declines in animals.
- Which one do you think is more credible and why?

Health Skepticism

- Important!! – How did your own confirmation bias played a role in your evaluation

- If it sounds too good to be true…



Conclusions

- Lots of studies suggest an association between acute and chronic cannabis use and measures of brain function and structure
  - Almost certainly the case the cannabis use causes some changes to the brain
  - The degree of change and more importantly the degree to which these changes may be positive or negative is not clear
  - A number of methodological issues muddy the waters

- Common sense
  - Not harmless regardless of what it does to your brain
  - Clear acute effects on cognition and learning
  - Risk profile may be dramatically different for young versus old