Effects of Cannabinoids on Verbal Learning and Memory: Relationship to Biological Sex
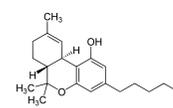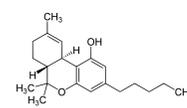
Literature Review

- Herbal cannabis (*Cannabis sativa*) is the most commonly used drug in the world
- Due to the legalization of cannabis, there has been an increase in usage among women[7] and youths[3]
- Herbal cannabis contains over 500 different cannabinoids
  - Cannabinoid: any active chemical constituents within the cannabis plant
    - Known to have significant impacts on memory[9]
      - The human brain has an endocannabinoid system that regulates synaptic transmission
    - 2 major active cannabinoids:
      - Cannabidiol (CBD)
      - Delta-9-tetrahydrocannabinol (THC) →
- Delta-tetrahydrocannabinol (THC) is known as one of the main psychoactive ingredients in herbal cannabis
  - Known to induce psychotic effects such as anxiety, feeling "high", and memory deficits[1,2,3,5,6,7,8]
  - A pure form (dronabinol) is often used during experimentation in order to keep THC effects constant
  - Oral administration: high individual variability, longer period of time before onset of effects, lower peak effects compared to inhaled and intravenous[7]
  - Past research suggests women and men experience effects differently[1,7]
    - Women tend to develop a cannabis use disorder more rapidly than men[7]
- Verbal learning and memory:
  - A subcategory of working memory that deals with encoding, consolidating, and retrieving verbal information
- Rey's Auditory Verbal Learning Task (RAVLT) ⬜ used to measure verbal learning and memory deficits
  - Procedure and Materials:
    - 2 lists of words:
      - List A (15 unrelated words that have no heavy emotional meaning)
      - List B (15 different words following the same criteria as List A)
    - Every word from List A and List B is read with an even cadence
    - Trials 1-5, Trial 7 (Short Delay Recall), and Trial 8 (Long Delay Recall) use List A
    - Trial B (performed after Trial 5) uses List B
    - Scoring: the score for each trial is the number of words recalled correctly
  - Age has been shown to be the biggest decider of RAVLT performance[4,9]
  - Gender is an inconclusive factor in RAVLT performance
    - Some literature suggests that females perform better than matched males[9] while others suggest that there is no significant difference between males and females[4]
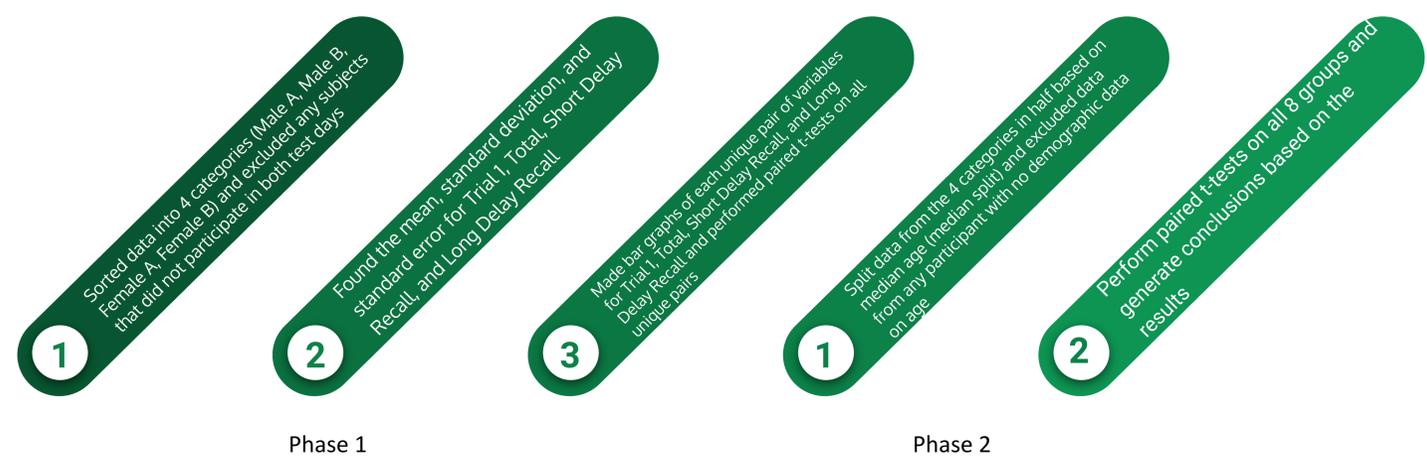
Problem Statement

The biological sex differences in THC-induced verbal learning and memory deficits are not well-categorized. The purpose of this project is to examine the acute verbal learning deficits induced by oral THC in healthy humans and analyze sex-related differences in this response.

Hypothesis

If the subjects administered THC orally, it will acutely induce verbal learning deficits measured using the RAVLT compared to placebo and this deficit will be affected by the biological sex of the participants, with women having less deficits than men.

Variables

- Independent Variable: Drug condition (placebo vs. dronabinol)
- Dependent Variable: RAVLT Performance
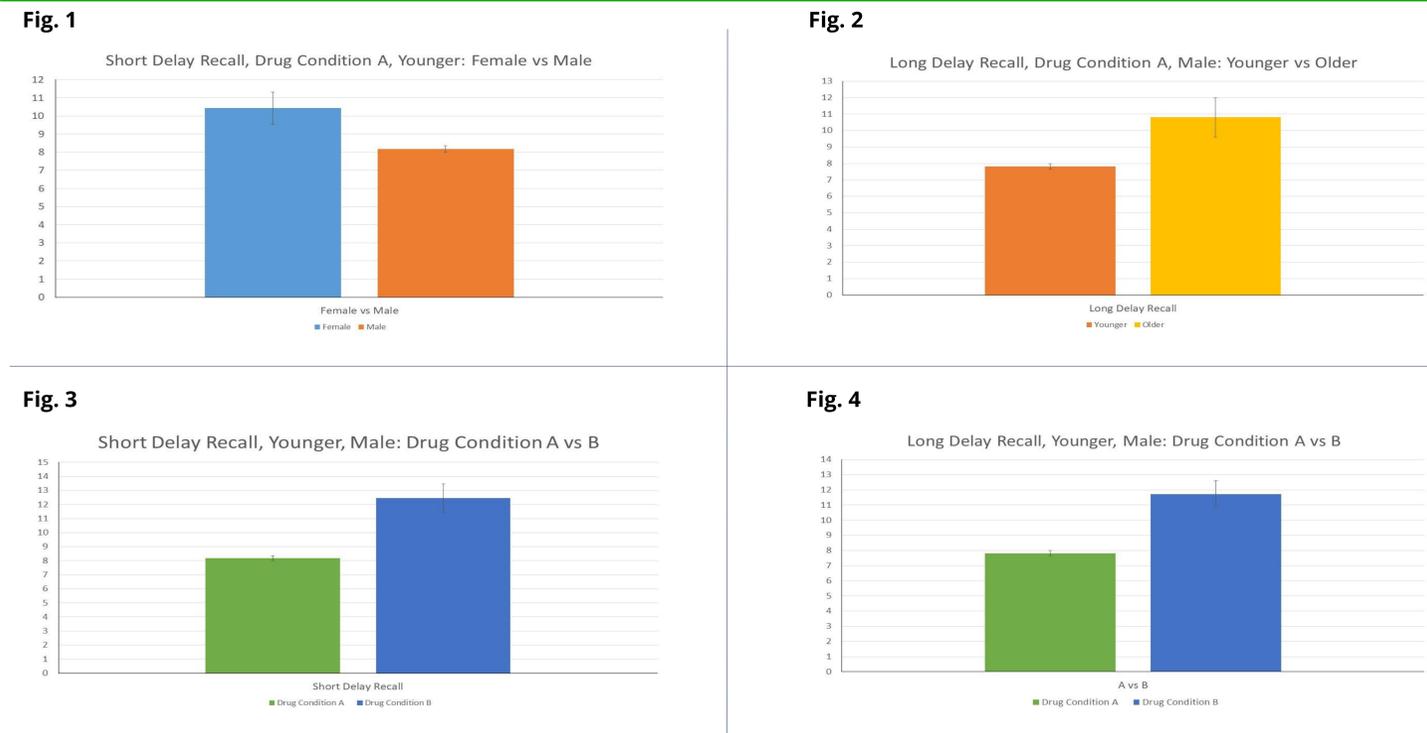
Experimental Design

Data Collection

- Data was collected from a substudy carried out by mentors Dr. Mohini Ranganathan, Dr. Patrick Skosnik, and their laboratory group
  - 2 test days with at least 3 days in between
  - Double-blind and placebo-controlled
  - Drug: 10 mg of dronabinol taken orally
  - RAVLT was administered 80 minutes after dronabinol administration
  - 54 participants, 4 excluded from data analysis for Phase 1, 6 excluded from analysis during Phase 2
- Data analysis and conclusions were made by the mentee

Data Analysis Procedure

1. Sorted data into 4 categories (Male A, Male B, Female A, Female B) and excluded any subjects that did not participate in both test days

2. Found the mean, standard deviation, and standard error for Trial I, Total, Short Delay Recall, and Long Delay Recall

3. Made bar graphs of each unique pair of variables for Trial I, Total, Short Delay Recall, and Long Delay Recall and performed paired t-tests on all unique pairs

Phase 1

1. Split data from the 4 categories in half based on median age (median split) and excluded data from any participant with no demographic data

2. Perform paired t-tests on all 8 groups and generate conclusions based on the results

Phase 2

Data and Results

Fig. 1

Short Delay Recall, Drug Condition A, Younger: Female vs Male

Female vs Male
■ Female ■ Male

Fig. 2

Long Delay Recall, Drug Condition A, Male: Younger vs Older

Long Delay Recall
■ Younger ■ Older

Fig. 3

Short Delay Recall, Younger, Male: Drug Condition A vs B

Short Delay Recall
■ Drug Condition A ■ Drug Condition B

Fig. 4

Long Delay Recall, Younger, Male: Drug Condition A vs B

A vs B
■ Drug Condition A ■ Drug Condition B

Conclusions

- Phase 1 suggested that women and men have no significant difference in RAVLT performance at placebo
  - Opposed hypothesis and most of the reviewed literature[1,8,9]
  - An RAVLT study done by Magalhães et al. (2010) supported this conclusion[4]
- Phase 1 and majority of Phase 2 suggests that the THC had no effect on both sexes for RAVLT performance
  - Possibilities:
    1. The test was done before the onset of oral THC effects
       - Oral THC is known to peak at around 120 minutes after ingestion[5]
       - This study administered the RAVLT 80 minutes after ingestion
    2. The dose of the oral THC was too low
       - unlikely because Marin-Santos et al. (2012)[5] also used 10 mg THC with peak results after 2 hours
    3. Oral THC was not a good administering method
       - There is high individual variability in effects and duration of onset due to differences in metabolism and lifestyle
       - Oral administration has lower peak effects and longer onset period compared to intravenous and inhaled THC
    4. The timing of the words read out loud during the RAVLT had some effect
       - The words were read at a slower pace than the standard because the data was collected using an EEG-adapted version of the RAVLT
    5. There was no significant difference between the performances of males and females at baseline
       - Supported by this study and Magalhães et al. (2010)[4]
       - Opposed by Bassir Nia et al. (2018)[1], Van Der Elst et al. (2005)
  - Phase 2 showed inconsistent results
    - Only four relatively random groups showed significant differences
    - Could be because of uncontrollable factors (i.e. metabolism)

Possible Future Research

- Test if administering the RAVLT 120 minutes after administration would have more significant differences in RAVLT performance induced by the oral THC
- Test if using a high dosage would induce greater THC effects on verbal learning and memory
- Test if using another route of administration (intravenous or inhaled) could induce greater THC effects and therefore have a greater effect in RAVLT performance
- Analyze whether the brain used different neuron networks under the influence of THC compared to placebo using brain imaging (EEG or fMRI)

Implications

- Adds to the growing literature on cannabinoids and their effects on cognition, especially on verbal learning and memory
- Informs both clinicians and the general public about the effects of cannabinoids

References

1. Bassir Nia, Anahita, et al. "Cannabis Use: Neurobiological, Behavioral, and Sex/Gender Considerations." *Current Behavioral Neuroscience Reports*, vol. 5, no. 4, 2018, pp. 271–280., https://doi.org/10.1007/s40473-018-0167-4.
2. Bhattacharyya, Sagnik, and Tabea Schoeler. "The Effect of Cannabis Use on Memory Function: An Update." *Substance Abuse and Rehabilitation*, 2013, p. 11., https://doi.org/10.2147/sar.s25869.
3. Jacobus, Joanna, and Susan Tapert. "Effects of Cannabis on the Adolescent Brain." *Current Pharmaceutical Design*, vol. 20, no. 13, 2014, pp. 2186–2193., https://doi.org/10.2174/13816128113199990426.
4. Magalhães, Sabrina S., and Amer C. Hamdan. "The Rey Auditory Verbal Learning Test: Normative Data for the Brazilian Population and Analysis of the Influence of Demographic Variables." *Psychology & Neuroscience*, vol. 3, no. 1, 2010, pp. 85–91., https://doi.org/10.3922/j.psns.2010.1.011.
5. Martin-Santos, R., et al. "Acute Effects of a Single, Oral Dose of D9-Tetrahydrocannabinol (THC) and Cannabidiol (CBD) Administration in Healthy Volunteers." *Current Pharmaceutical Design*, vol. 18, no. 32, 2012, pp. 4966–4979., https://doi.org/10.2174/138161212802884780.
6. Ranganathan, Mohini, et al. "Tetrahydrocannabinol (THC) Impairs Encoding but Not Retrieval of Verbal Information." *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, vol. 79, 2017, pp. 176–183., https://doi.org/10.1016/j.pnpbp.2017.06.019.
7. Ranganathan, Mohini, and Deepak Cyril D'Souza. "The Acute Effects of Cannabinoids on Memory in Humans: A Review." *Psychopharmacology*, vol. 188, no. 4, 2006, pp. 425–444., https://doi.org/10.1007/s00213-006-0508-y.
8. Ranganathan, Mohini, et al. "Gender Related Differences in the Acute Effects of Delta-9-Tetrahydrocannabinol in Healthy Humans." 29 Sept 2021. Manuscript.
9. Smith, Janette L., et al. "Verbal Learning and Memory in Cannabis and Alcohol Users: An Event-Related Potential Investigation." *Frontiers in Psychology*, vol. 8, 2017, https://doi.org/10.3389/fpsyg.2017.02129.
10. VAN DER ELST, WIM, et al. "Rey's Verbal Learning Test: Normative Data for 1855 Healthy Participants Aged 24–81 Years and the Influence of Age, Sex, Education, and Mode of Presentation." *Journal of the International Neuropsychological Society*, vol. 11, no. 3, 2005, pp. 290–302., https://doi.org/10.1017/s1355617705050344.