Identification of Δ9-tetrahydrocannabinol (THC) Impairment Using Functional Brain Imaging of Resting State Connectivity

Jodi M. Gilman, William A. Schmitt, Kevin Potter, Brian Kendzior, Gladys N. Pachas, Sarah Hickey, Michael Pascale, A. Eden Evins

Center for Addiction Medicine, Department of Psychiatry, Massachusetts General Hospital; Harvard Medical School

Abstract

The primary cannabinoid in cannabis, Δ9-tetrahydrocannabinol (THC), causes intoxication and impaired function, with implications for traffic, workplace and other situational safety risks. There are currently no evidence-based methods to detect cannabis-impaired driving, and current field sobriety tests with gold-standard, drug recognition evaluations are resource-intensive and may be prone to bias. This study evaluated the capability of a simple, portable imaging method to accurately detect individuals with THC impairment. In this study, 169 cannabis users, aged 18-55 years, underwent functional near-infrared spectroscopy (fNIRS) before and after receiving oral THC and placebo, at study visits one week apart. Impairment was defined by convergent classification by consensus clinical ratings and an algorithm based on post-dose tachycardia and self-rated “high.” Our primary outcome, PFC oxygenated hemoglobin concentration (HbO) connectivity measures, were able to predict impairment with 78% accuracy, using standard machine learning algorithms. These findings demonstrate that PFC response patterns and connectivity produce a neural signature of impairment, and that PFC signal, measured with fNIRS, can be used as a sole input to ML models to objectively determine impairment from THC intoxication at the individual level. Future work is warranted to determine the specificity of this classifier to acute THC impairment.

ClinicalTrials.gov Identifier: NCT03655717

Methods

- 169 participants with regular cannabis use were given a single dose of up to 80mg of dronabinol, an FDA-approved synthetic THC ingredient in MARINOL® Capsules or identical placebo.
- Study physicians determined the dronabinol dose based on the degree of expected tolerance, given participant’s average dose, frequency, and type of cannabis use, self-report of degree of intoxication (high) experienced with each use, history of any adverse effects experienced when using cannabis, and baseline characteristics such as participant’s sex, height, weight, BMI and blood pressure.
- Participants completed the Drug Effects Questionnaire (DEQ), a 100mm visual analogue scale, pre-dose and every 20-25 minutes post-dose to assess the extent to which participants (1) felt any THC effect(s), and (2) felt high.
- Heart rate and blood pressure measurements were collected at baseline and at 25-minute intervals after dronabinol administration.
- Participants underwent two fNIRS sessions; one before dronabinol administration (“pre-THC”), and the other at approximately two hours after dronabinol administration (“post-THC”), which is the median peak of pharmacokinetic effects of dronabinol.
- During each session, 6 minutes of resting-state functional data were collected using a continuous-wave NIRS device, in which 8 Sources and 7 detectors were placed on the forehead, resulting in 20 channels covering PFC regions.
- fNIRS analysis was conducted using the CONN toolbox (https://web.conn-toolbox.org).
- Impairment was defined by convergent classification by consensus clinical ratings and an algorithm based on post-dose tachycardia and self-rated “high,” and was compared with results of extended field sobriety tests, which were performed by certified drug recognition examiner police officers after THC or placebo.

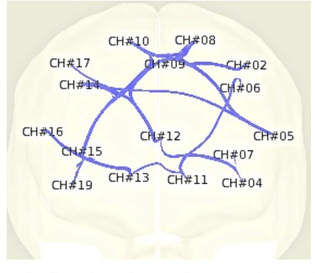
Results

Participant Characteristics

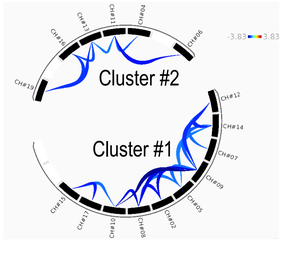
Variables	Overall	Impaired post active study drug (THC)	Not clearly impaired post active study drug (THC)	Discordant/ No valid scans
Sample size	169	80	57	32
Demographics				
Age	25.2 (6.4)	24.4 (5.3)	26.3 (7.5)	25.4 (6.6)
Sex; % Male (n)	50.9% (86)	57.5% (46)	47.4% (27)	40.6% (13)
Race				
% White (n)	67.5% (114)	68.8% (55)	70.2% (40)	59.4% (19)
% Black (n)	11.2% (19)	5% (4)	14% (8)	21.9% (7)
% Asian (n)	6.5% (11)	10% (8)	3.5% (2)	3.1% (1)
% Multi-racial (n)	7.7% (13)	10% (8)	5.3% (3)	6.2% (2)
% Other (n)	7.1% (12)	6.2% (5)	7% (4)	9.4% (3)
Ethnicity; % Hispanic (n)	20.1% (34)	25% (20)	17.5% (10)	12.5% (4)
Years of education completed	15.3 (2.1)	15.4 (2.2)	15.3 (2.1)	15 (1.8)
Cannabis use characteristics				
Age began regular use[1]	19 (3.9)	18.6 (3.6)	19.7 (4.6)	18.8 (3.6)
Weekly users; % Yes (n)	42% (71)	48.8% (39)	38.6% (22)	31.2% (10)
Daily users; % Yes (n)	56.2% (95)	51.2% (41)	56.1% (32)	68.8% (22)
Used multiple times per day; % Yes (n)	45% (76)	36.2% (29)	56.1% (32)	46.9% (15)
Urine THC-COOH (ng/mL)	221.8 (473.2)	98.1 (147.5)	456.2 (795.3)	163 (136.1)
CUDIT score	12 (5.3)	11.6 (5.2)	12.4 (5.2)	12.4 (5.7)
Psychiatric characteristics				
STAI - State (Baseline)	31.9 (6)	31.2 (5.1)	32.2 (6.2)	33 (7.7)
Lifetime depression				
% Diagnosed (n)	17.2% (29)	12.5% (10)	17.5% (10)	28.1% (9)
Lifetime anxiety				
% Diagnosed (n)	18.9% (32)	15% (12)	22.8% (13)	21.9% (7)

Comparing resting state connectivity of post-dose THC and post-dose placebo in impaired participants, we identified two clusters of decreased connectivity after THC. There were no differences in connectivity in those who were not clearly impaired.

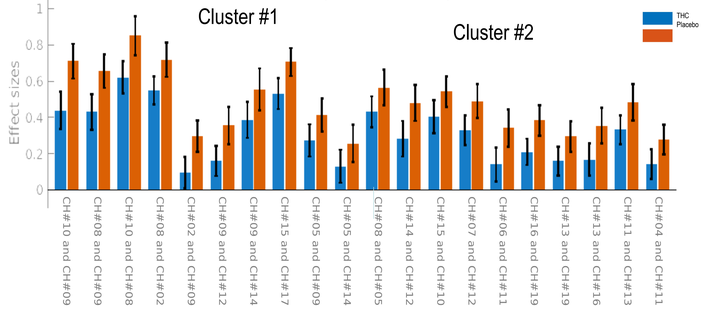
A. Schematic of the near-infrared spectroscopy (NIRS) probe array clusters



B. ROI-to-ROI connectivity: Graphical Display

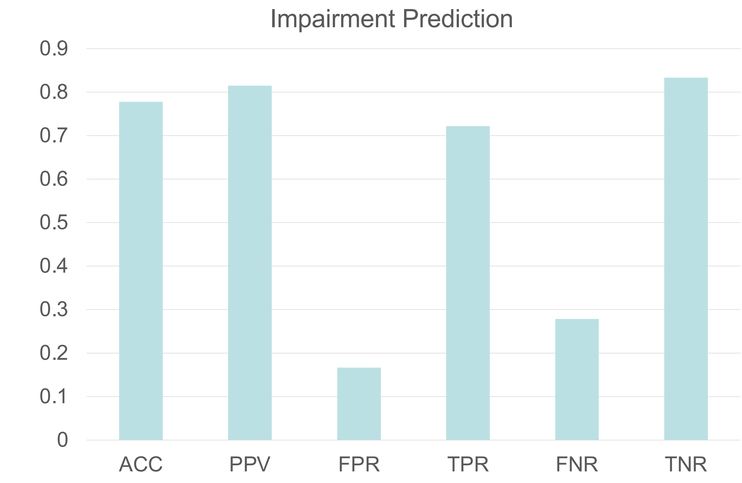


C. Resting State Connectivity of Post-dose THC and Post-dose Placebo in Impaired Participants



Results

A recurrent neural network (RNN) machine learning model, using only fNIRS data as an input, was able able to predict impairment with 78% accuracy.



This method exceeded Drug Recognition Evaluator-conducted expanded field sobriety examination (67.8% accuracy, 35.4% PPV, and 35.4% false positive rate).

Conclusions

- There is a growing public health need for an objective, reliable, unbiased method to detect impairment due to THC.
- This is not achievable with per se blood or body fluid THC or metabolite concentration cutoffs.
- Findings suggest PFC response can objectively determine who is impaired from THC intoxication, as impairment due to THC intoxication was associated with reduced PFC connectivity.
- These measures alone classified participants as impaired vs exposed but not clearly impaired with high PPV and accuracy.
- Future work is warranted to determine if observed brain signatures are specific to THC intoxication-related impairment or are a more general signature of impairment.

For more information

Contact Jodi Gilman (jgilman1@mgh.Harvard.edu)