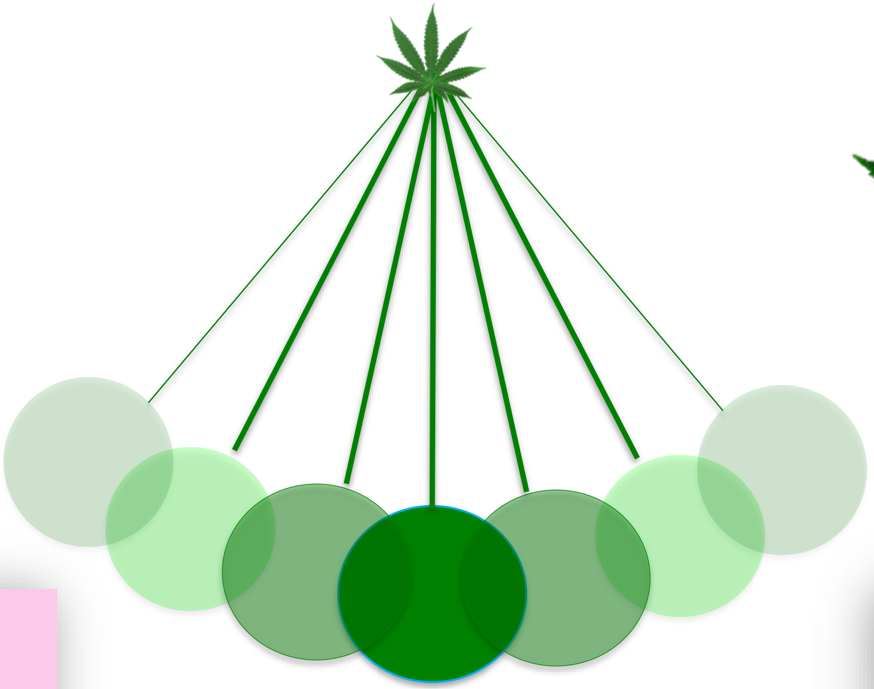
Unlocking the Biological Impact of Developmental Cannabis and Its Psychiatric Risk

Yasmin Hurd
Director, Addiction Institute of Mount Sinai
Chair of Translational Neuroscience
Icahn School of Medicine at Mount Sinai
Depts Psychiatry, Neuroscience and Pharmacological Sciences

Cannabis

Recreational



Medicinal

- No harm
- "healthy", "organic" plant
- Not addictive
- Anxiolytic
- "Wonder drug": can treat numerous conditions/disorders

- Psychopathology
  - Psychosis/schizophrenia
  - Negative affective disorders
- Anxiogenic
- Addiction risk

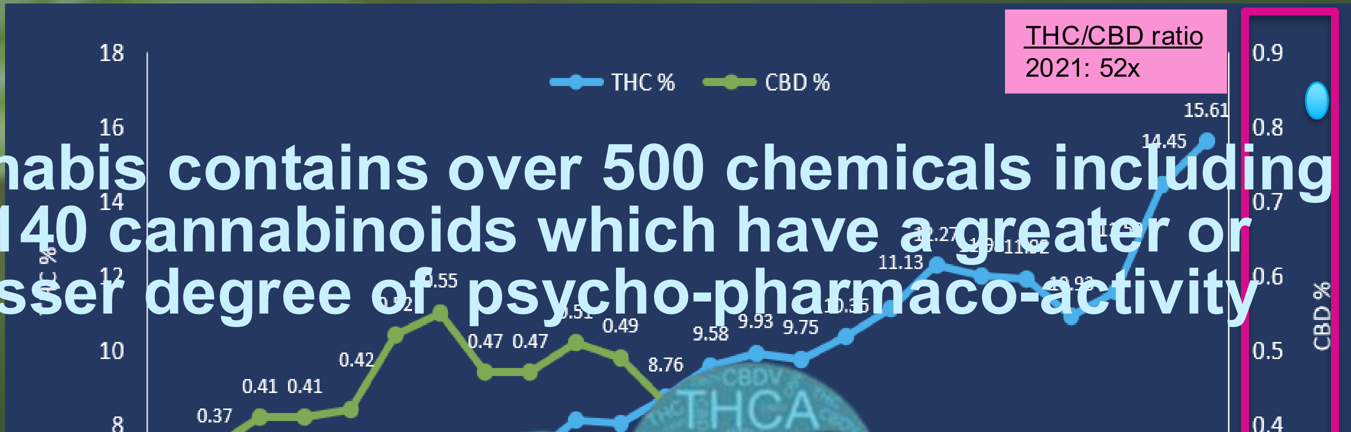
Cannabis contains over 500 chemicals including >140 cannabinoids which have a greater or lesser degree of psycho-pharmaco-activity

Complex plant

Gamma-cadinene
Eudesma-3,7(11)-diene
Gamma-elemene
Nerolidol
Cis-bergamotene
Beta-phellandrene
Beta-caryophyllene
Limonene
Trans-bergamotene
Cineol
Alpha-guaiene
Cis-ocimene
Aromadendrene
Gamma-terpinene
Alpha-humulene
Terpinolene

Alpha-2-pinene
Beta-2-pine
Myrcene
Alpha-phellandre
Delta-3-carene
Linalool
Delta-guaie
Beta-fenchol
Cis-sabinene hydrate
Camphor
Borneol
Alpha-terpineol

CANNABIS TODAY



Cannabis contains over 500 chemicals including >140 cannabinoids which have a greater or lesser degree of psycho-pharmaco-activity

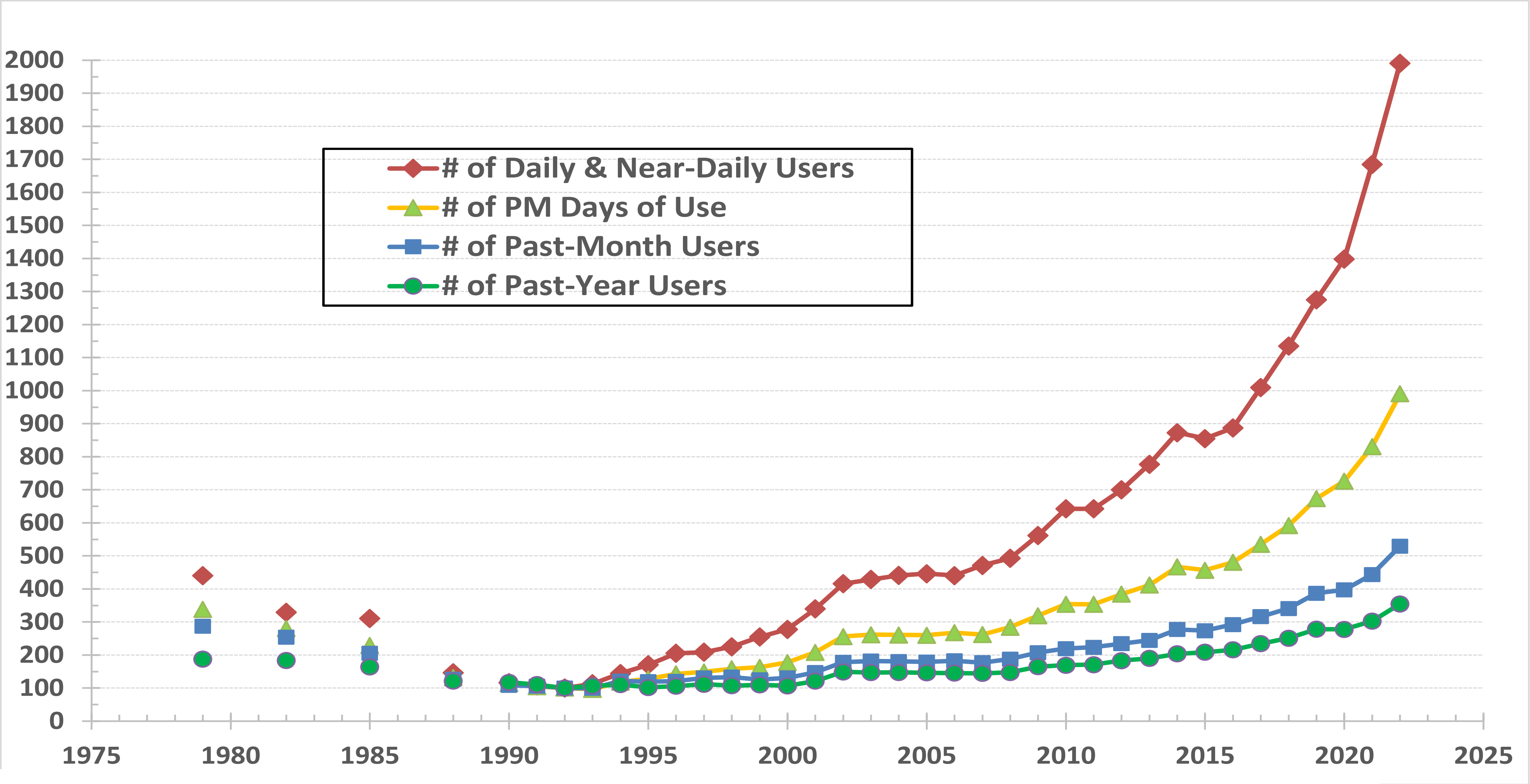
Historic **concentrated**, high **potency** Products; varied **routes** of administration

iological Psychiatry, 2016; Chandra et al., 2019

Hemp/CBD → *Chemical synthetic conversion* → **Δ⁸-THC** other THC analogs (e.g., **Δ¹⁰-TH**C and hexahydrocannabinol [**HHC**])

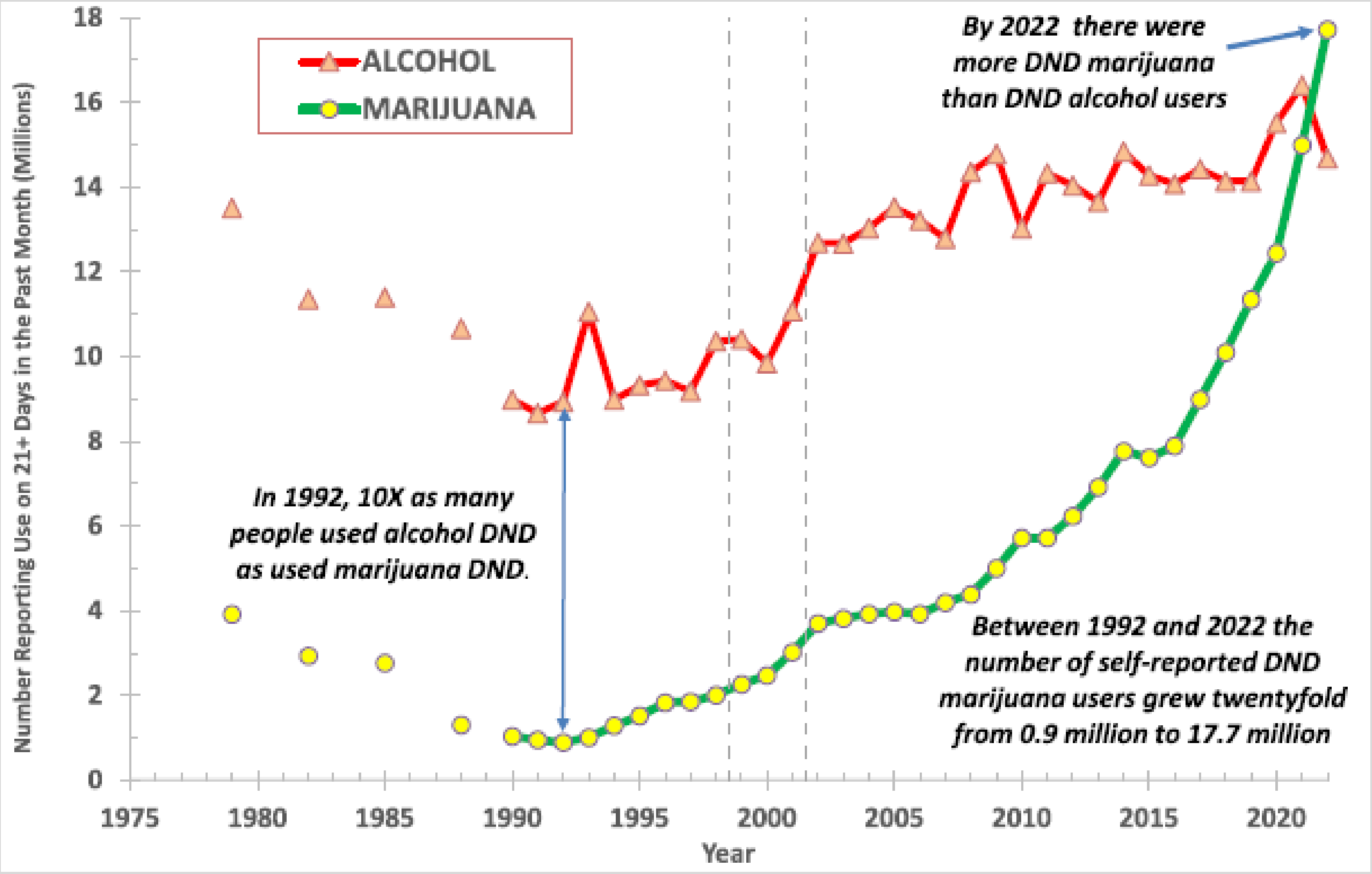
Tetrahydrocannabiphorol (**THC-P**) – rare cannabinoid (**now synthetically made**); extremely potent (>30%) **Δ⁹-THC**

Cannabis use increasing



Growth in cannabis prevalence and frequency of use reported in NSDUH since 1979 (indexed: level = 100 in 1992). NOTES: NSDUH = National Survey on Drug Use and Health; PM = past month. SOURCE: Caulkins, 2024.

People using cannabis daily/near daily now exceeds alcohol

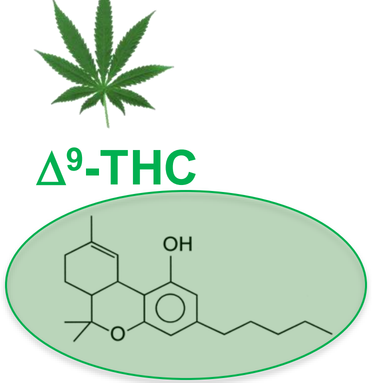


NOTES: Data presented are based on the NSDUH, which underwent methodological changes in 2020 and 2021. NSDUH = National Survey on Drug Use and Health.
SOURCE: Reproduced from Caulkins, 2024.

Complex plant

Complex endogenous biology
Complex mechanisms of action

Endocannabinoid System



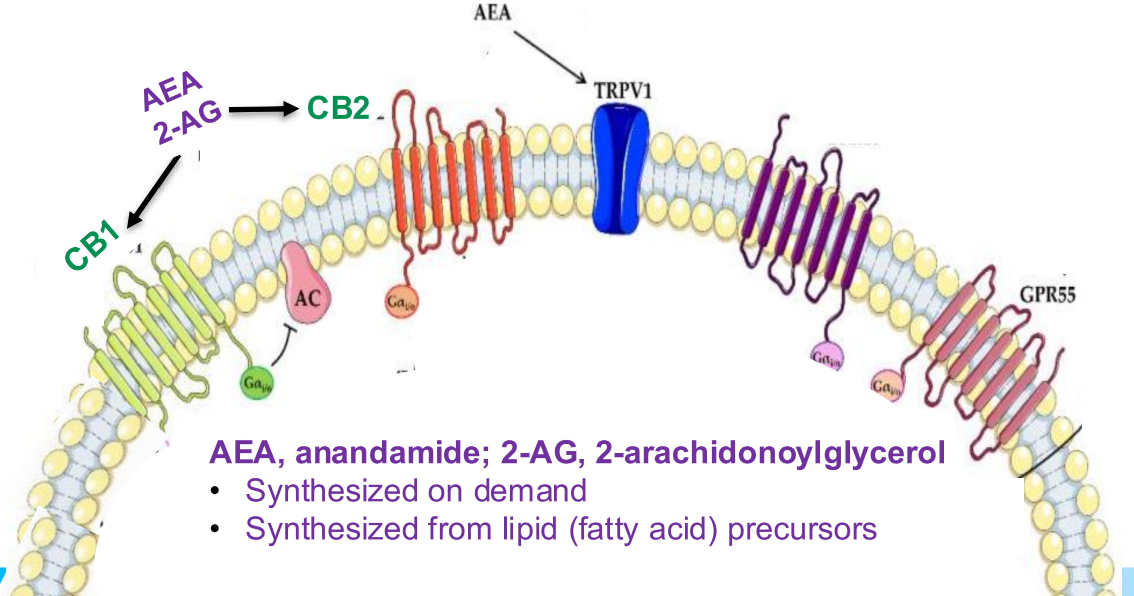
Plant-derived cannabinoids

Relatively Recent Discovery

N-arachidonoylethanolamine (anandamide) (AEA) — 1992

2-arachidonoylglycerol (2-AG) — 1995

Endogenous cannabinoids = endocannabinoids



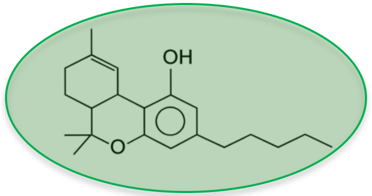
AEA, anandamide; 2-AG, 2-arachidonoylglycerol

- Synthesized on demand
- Synthesized from lipid (fatty acid) precursors

Endocannabinoid System

Endogenous cannabinoids = endocannabinoids

Δ^9-THC



Plant-derived cannabinoids

AEA, anandamide;
2-AG, 2-arachidonoylglycerol

- Synthesized on demand
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Endocannabinoid System

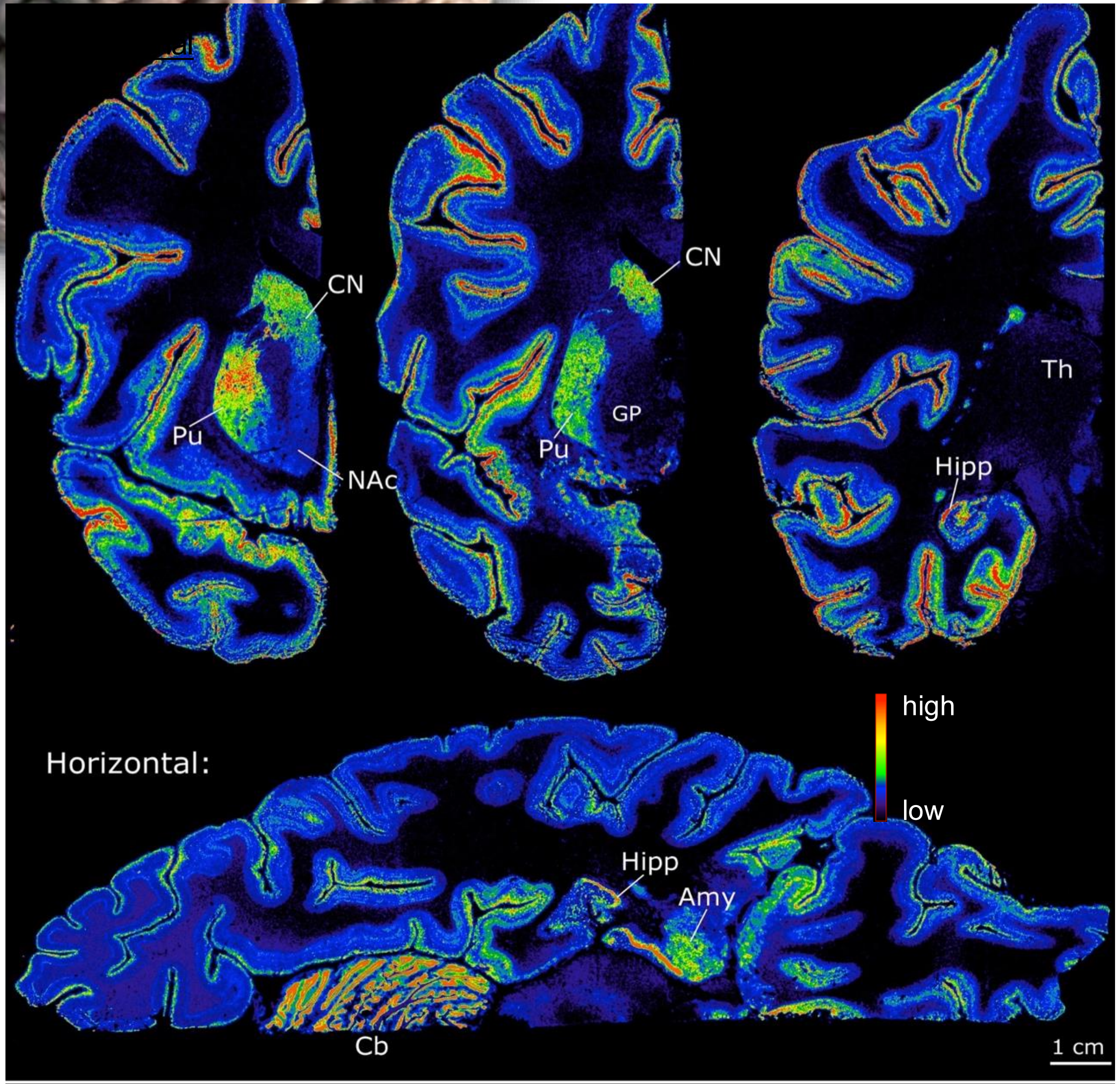
Key Modulator

CB1
CB2
GPR55
GPR35
GPR19
GPR18
TRPV1, 2
TRPV8
PPAR

AEA
2AG
FAAH
MAGL
PLC
DAGL

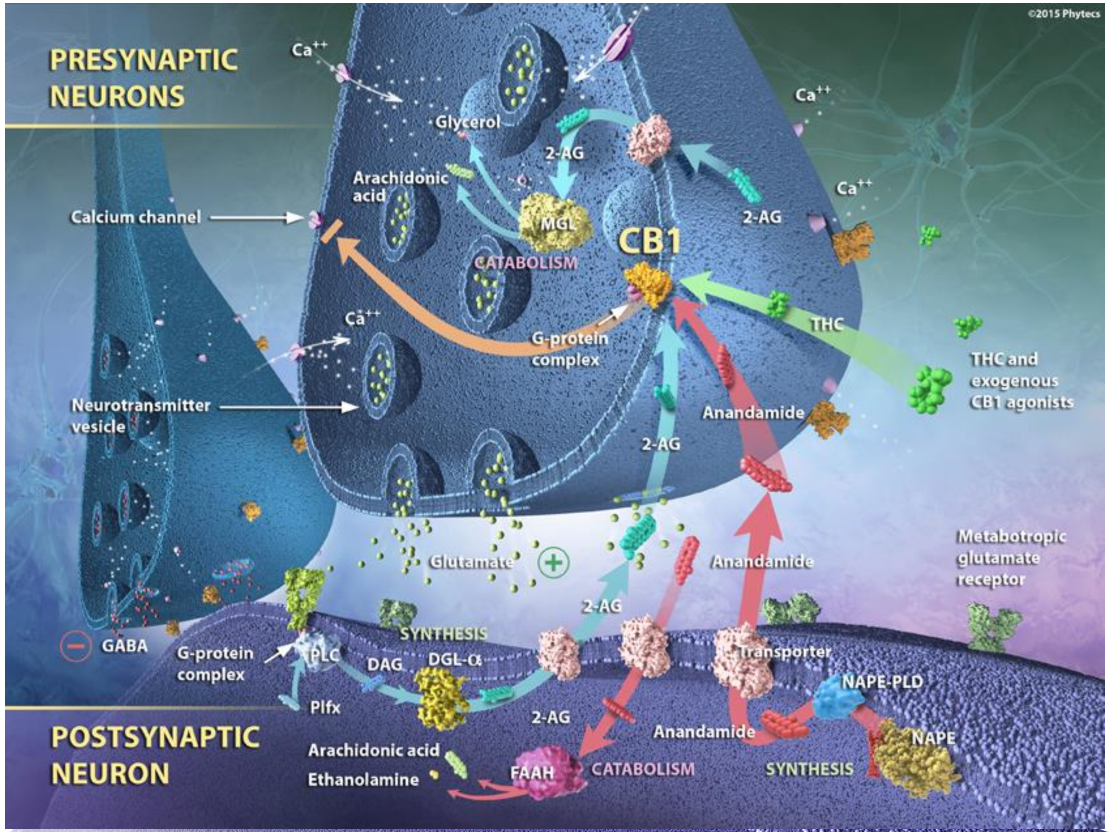
- Energy metabolism
- Appetite
- Thermoregulation
- Immune function and inflammation
- Neural development
- Learning and memory
- Pain and nociception
- Psychomotor function
- Sleep/wake cycle
- Stress and emotion regulation
- Reproduction

Endocannabinoid System



Cb, cerebellum; CN, caudate nucleus;GP, globus pallidus; Hipp, hippocampus; Pu, putamen; Th, thalamus

Widely abundant neuromodulatory system: Finetunes synaptic transmission regulating communication between cells

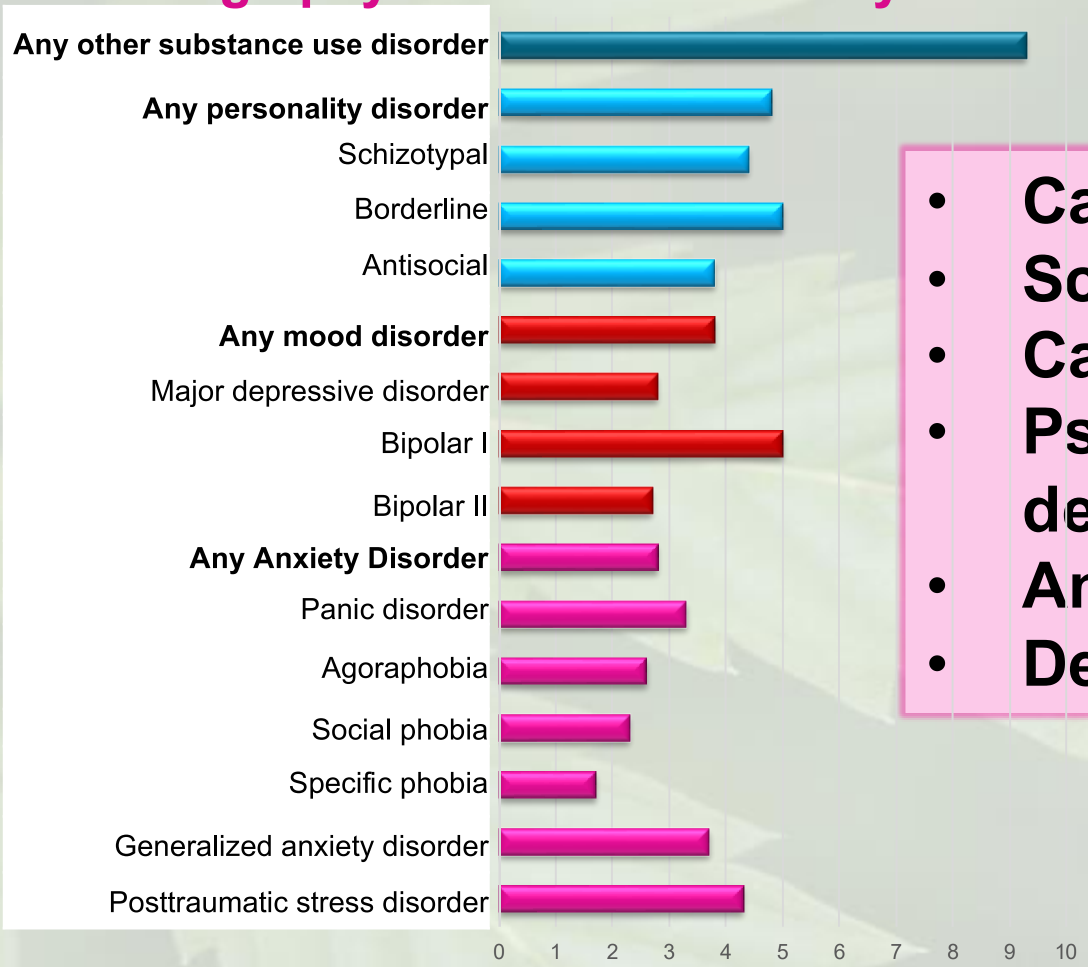


Wang et al, Neuroscience 118:681-694, 2003

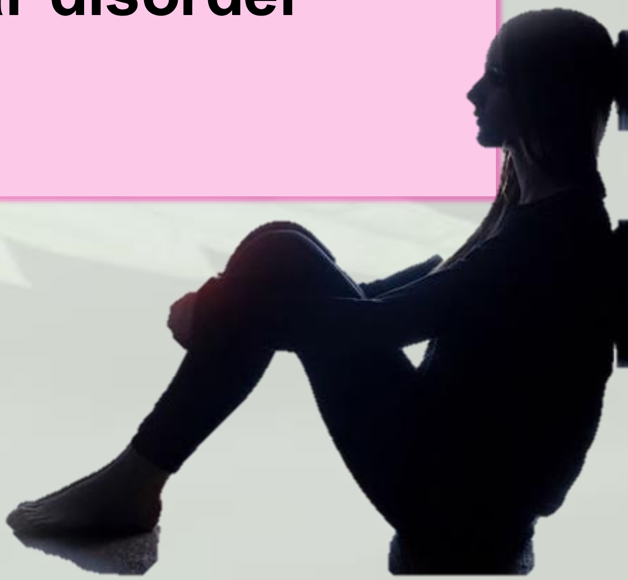
John Karapelou

Cannabis and Psychiatric Risk

High psychiatric comorbidity

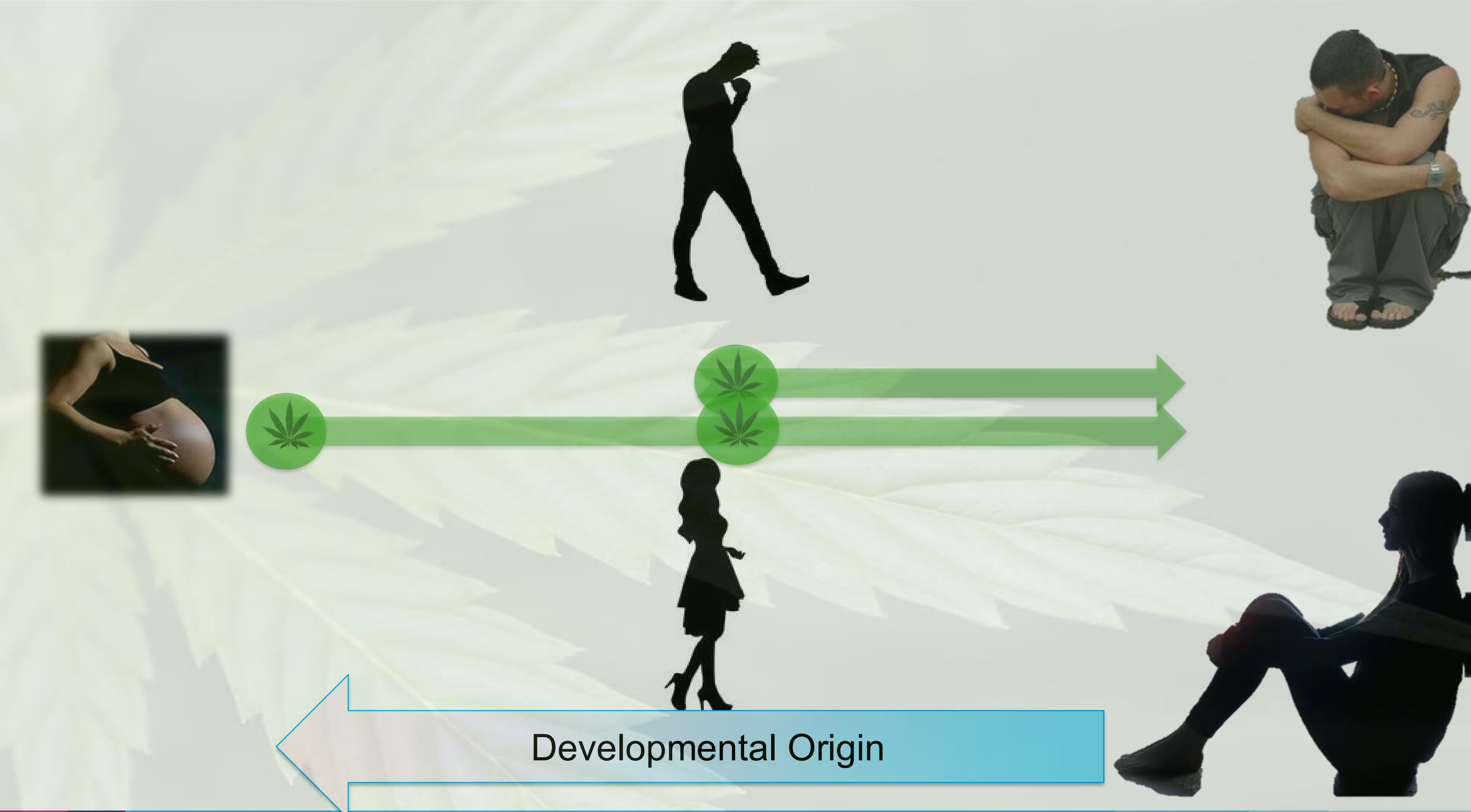


- Cannabis use disorder
- Schizophrenia
- Cannabis-induced psychosis
- Psychotic and nonpsychotic unipolar depression and bipolar disorder
- Anxiety
- Depression



Estimated past-year diagnosis of cannabis use disorder amongst cannabis users is approximately 30%

Ferland and Hurd, Nature Neuroscience, 2020


Developmental Origin

Endocannabinoid System – Critical Role in Neurodevelopmental Processes

Fetal	Infancy	Childhood	Adolescence	Young adults

Neurogenesis

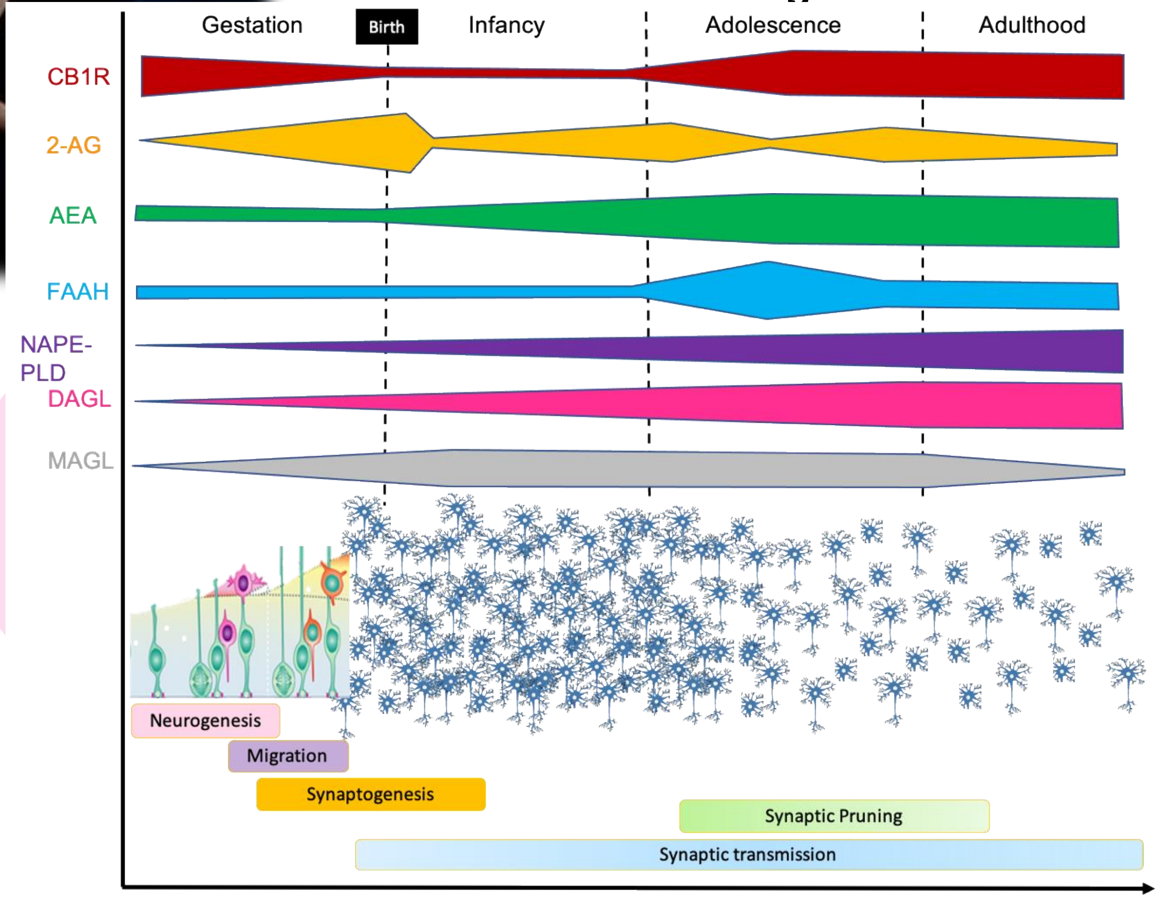
Migration

Synaptogenesis

Programmed cell death

brain

th



Fine tuning of neural circuits

Maturation of prefrontal cortex

Synaptic pruning

myelination

15.1% indoor cannabis smoking

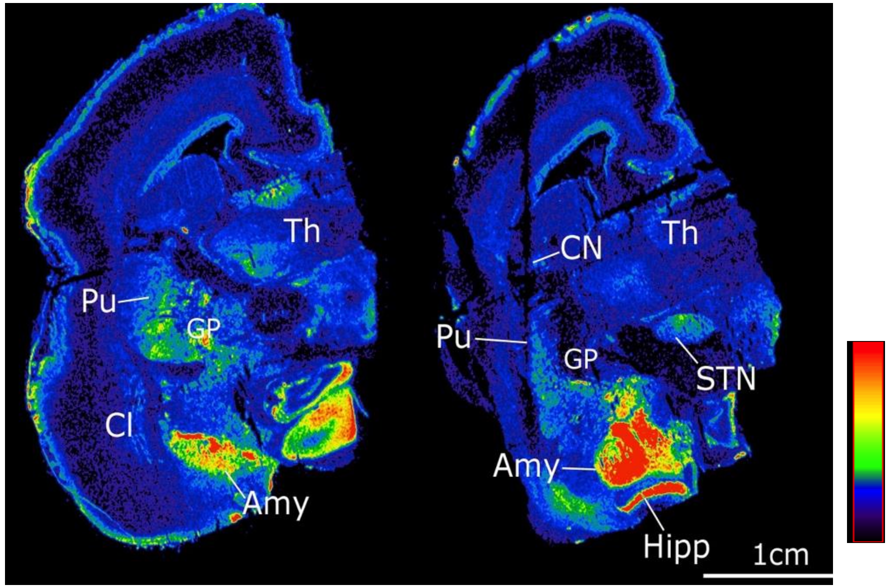
Past year cannabis use by teens:
8th graders: 11.4%
9th graders: 28%
12th graders: 35%

Bara et al., Nature Rev Neurosci, 2021

Hurd, J Clinical Invest, 2020

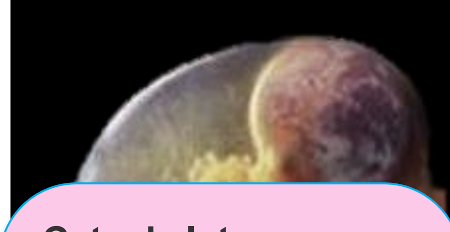
The Endocannabinoid System and Neurodevelopment

CB_1R mRNA Expression in the Human Fetal Brain



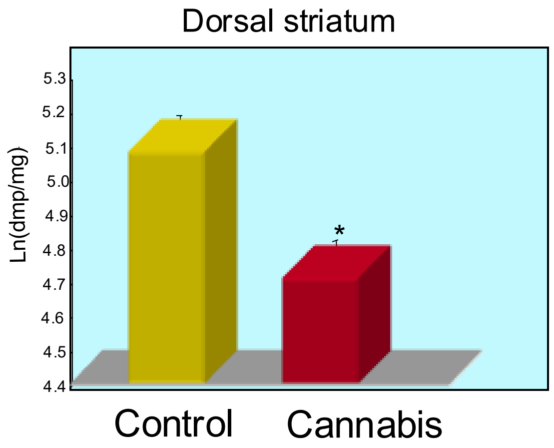
John Karap

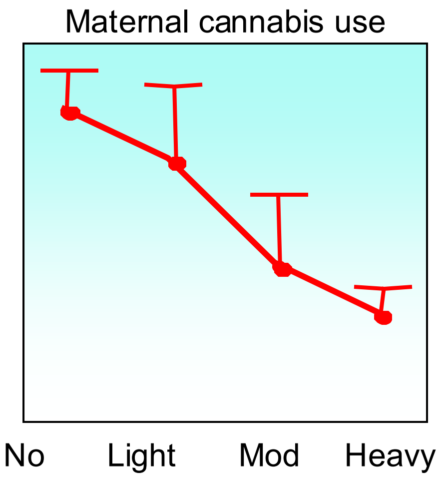
Molecular Dysregulation in the Human Fetal Brain Associated with *In Utero* Cannabis Exposure

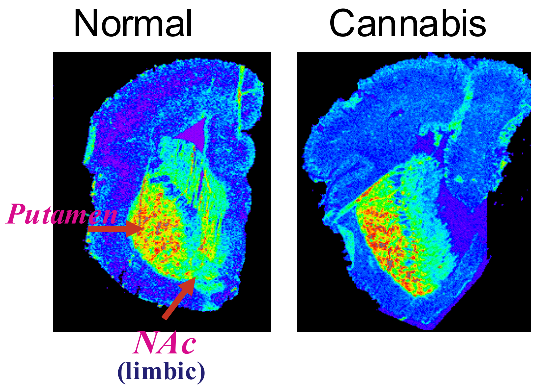


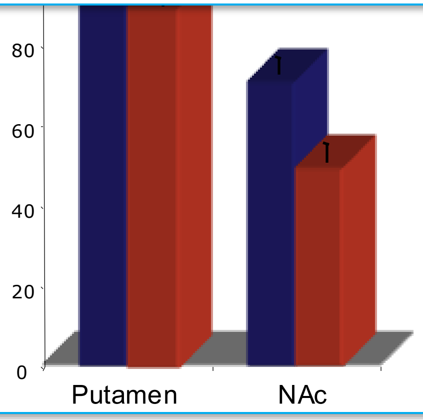
Cytoskeletal

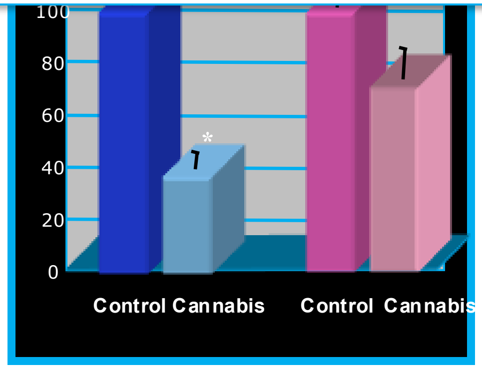
Proenkephalin: opioid neuropeptide











DiNieri et al et al. Biol Psychiatry, 2012

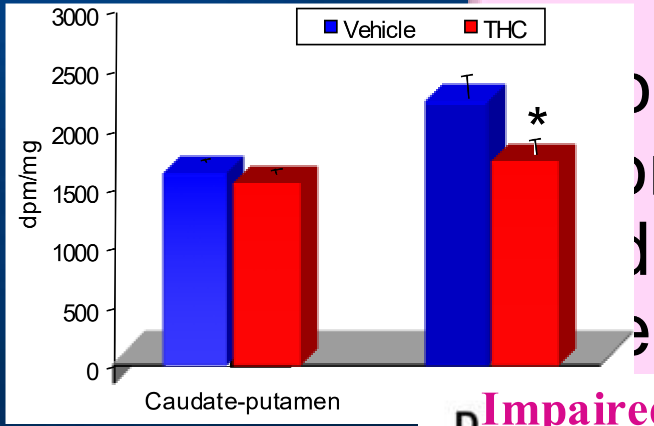
Cytoskeleton: a structure that helps cells maintain their shape and internal

Opioid neuropeptides (enkephalin): play a

Dopamine: mediates reward, goal-mediated behavior, learning, attention, memory, motor function …

- Specificity of the neurobiological findings to cannabis exposure

Dopamine D2 Gene



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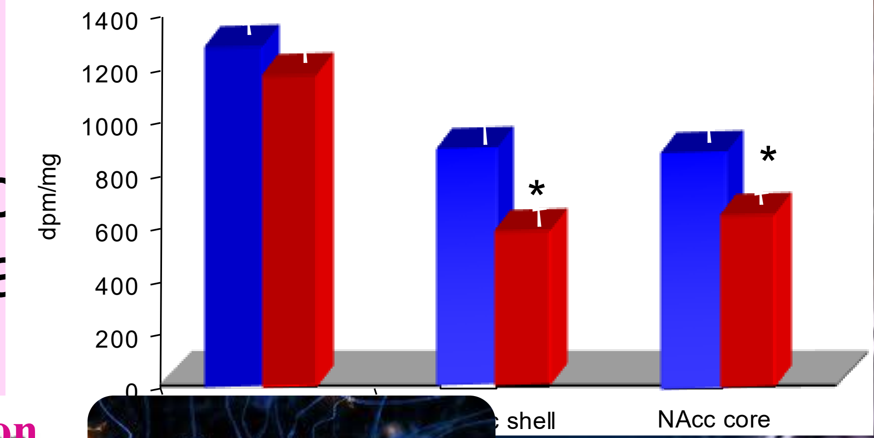
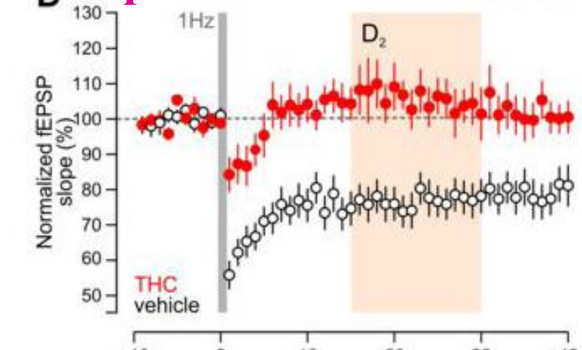


DiNieri et al., Biological Psychiatry,

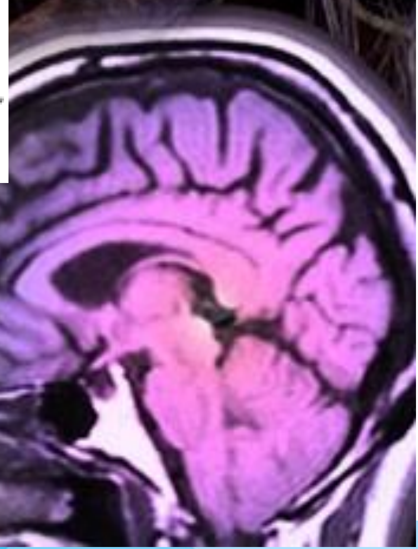
PND2 (≈ f

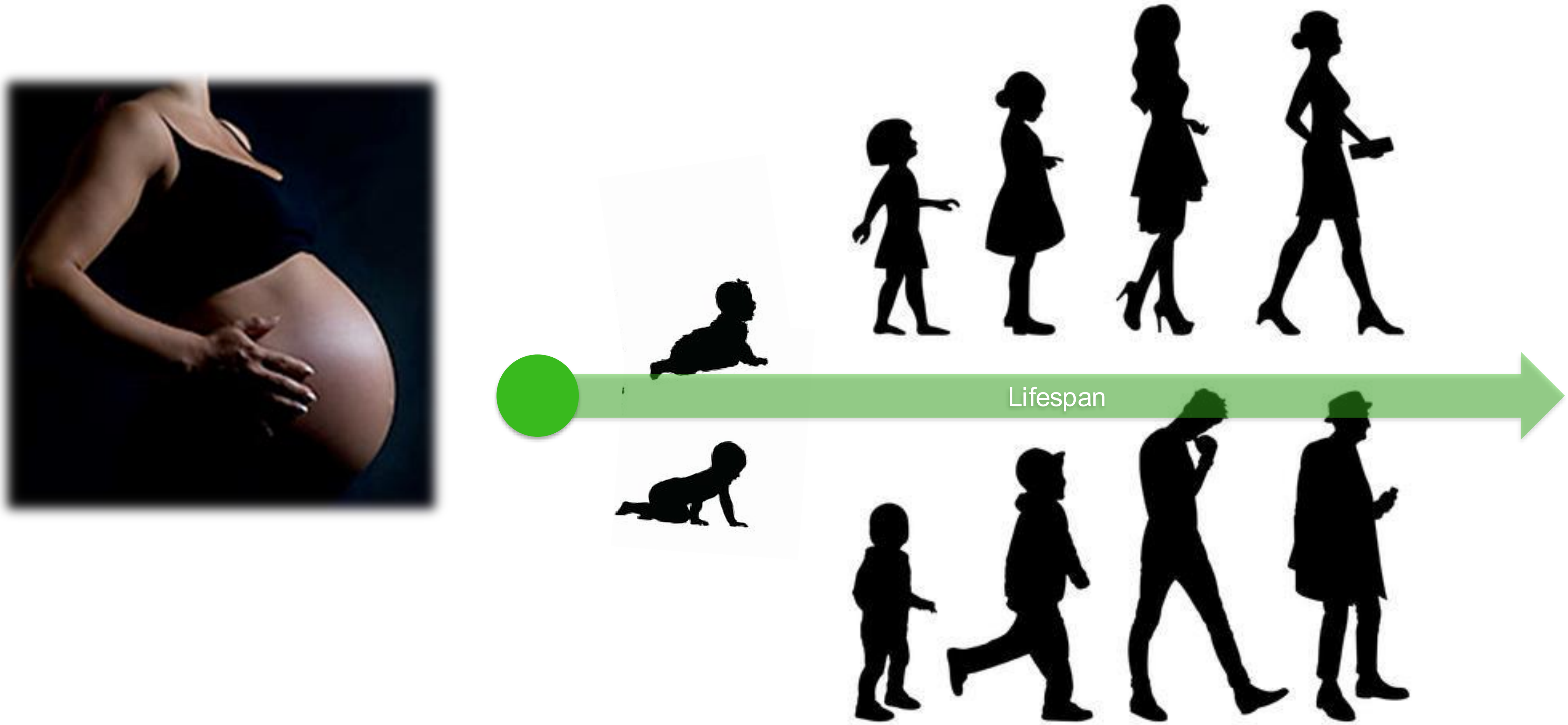
Impaired LTD induction



(≈ young adult)

Tortoriello et al., EMBO J, 2014




Lifespan

Stress (and Cannabis) in Pregnancy Project

Yoko Nomura

Pregnancy

Pre-Sandy | During-Sandy | Post-Sandy

Delivery
- Cord blood
- Placenta biopsies
- Meconium

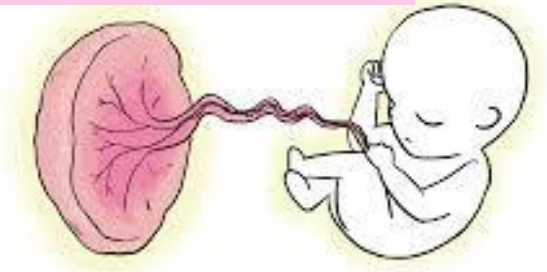
Follow-up of child from 6 months
- Physical development
- Neurobehavioral assessment/emotional/social development
- Semi-structured clinical interviews (e.g., Preschool Age Psychopathological assessment)
- Psychophysiological measures
- Maternal psychological state
- Maternal substance use
- Environmental exposure
- Biospecimens (hair, nails)

Placenta – The "Third Brain"

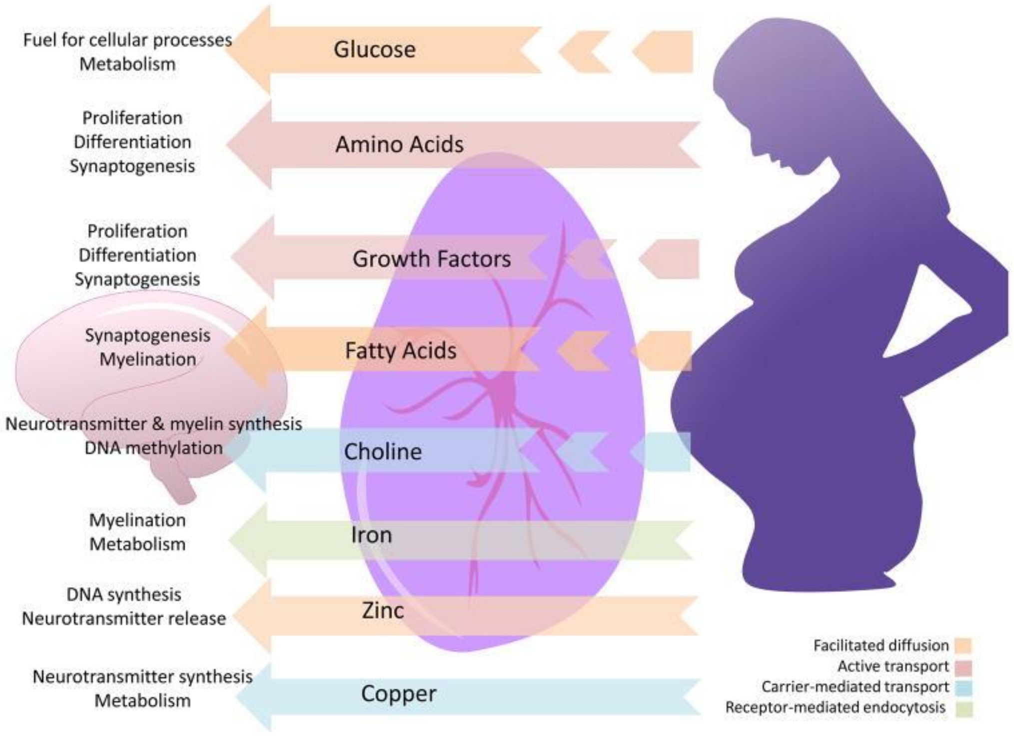
-Link between the fetal and maternal brains

Does Cannabis Impact Placental Environment?

RNA-sequencing



Placenta support fetal neurodevelopment



Placental programming is essential for neurodevelopment and aberration linked to psychiatric risk

Dysregulation of Immune Gene Expression in Placenta With Maternal Cannabis Use

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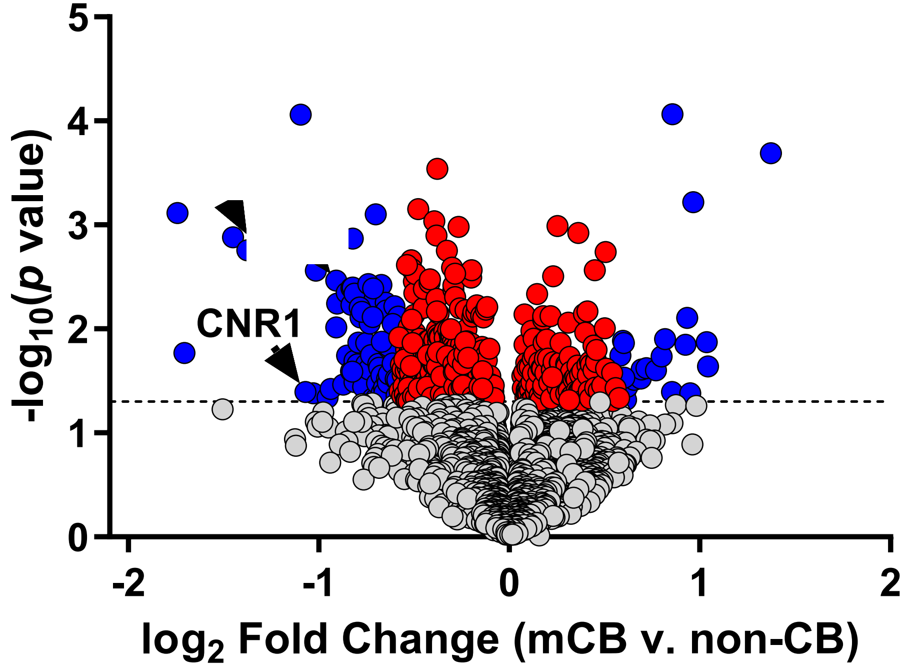
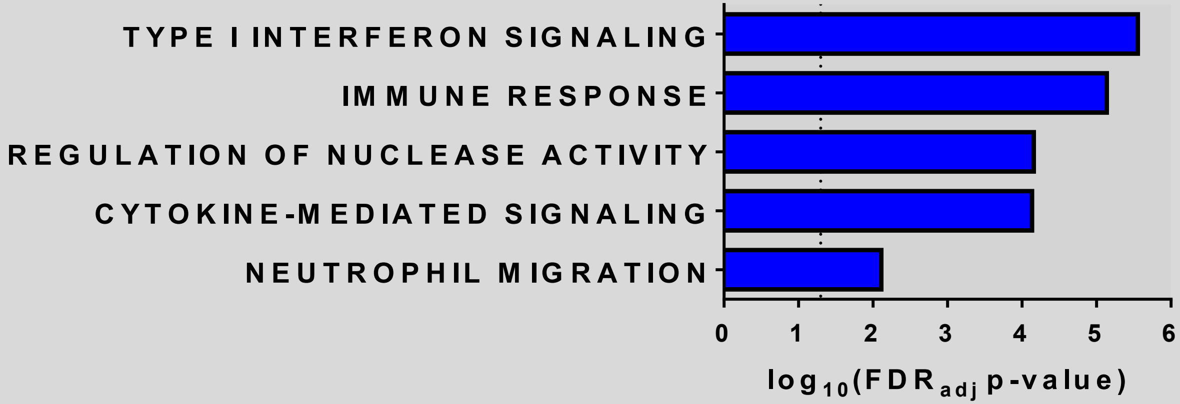
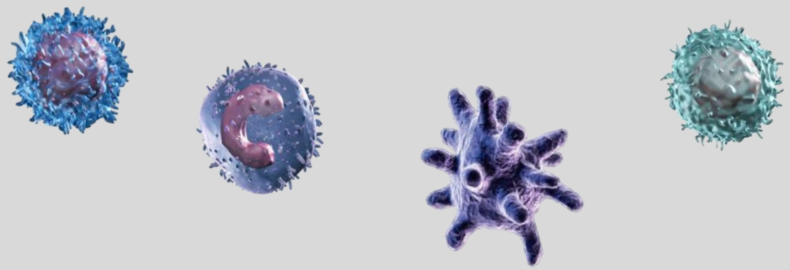






CNR1 = cannabinoid receptor type 1

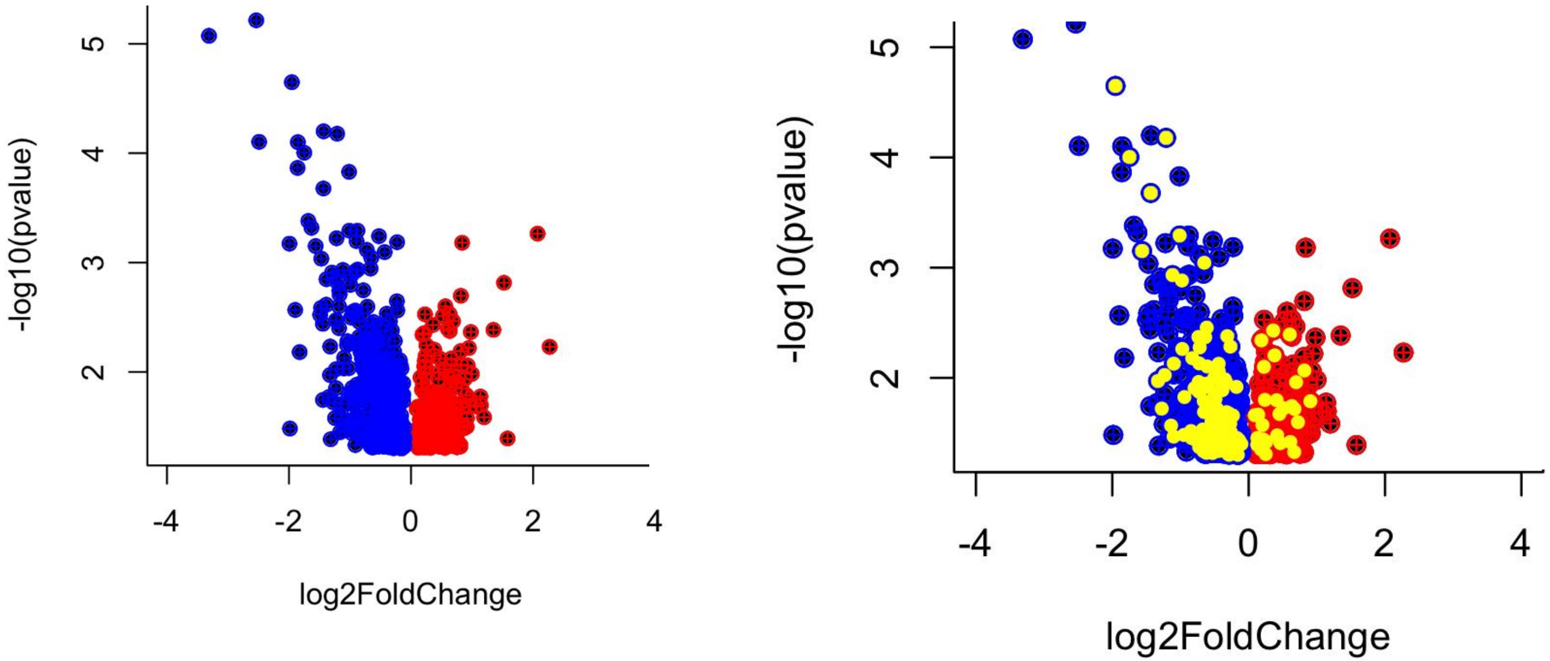
Includes several proinflammatory cytokine/chemokines (*IL1B*, *CXCL8*, *CCL2*) and enrichment for key immune function ontology such as type I interferon pathway, cytokine-mediated signaling, and neutrophil migration

Rompala, Nomura and Hurd, PNAS, 2021

Differentially Expressed Genes in the Placenta Associated with Cannabis Use

Anissa Bara

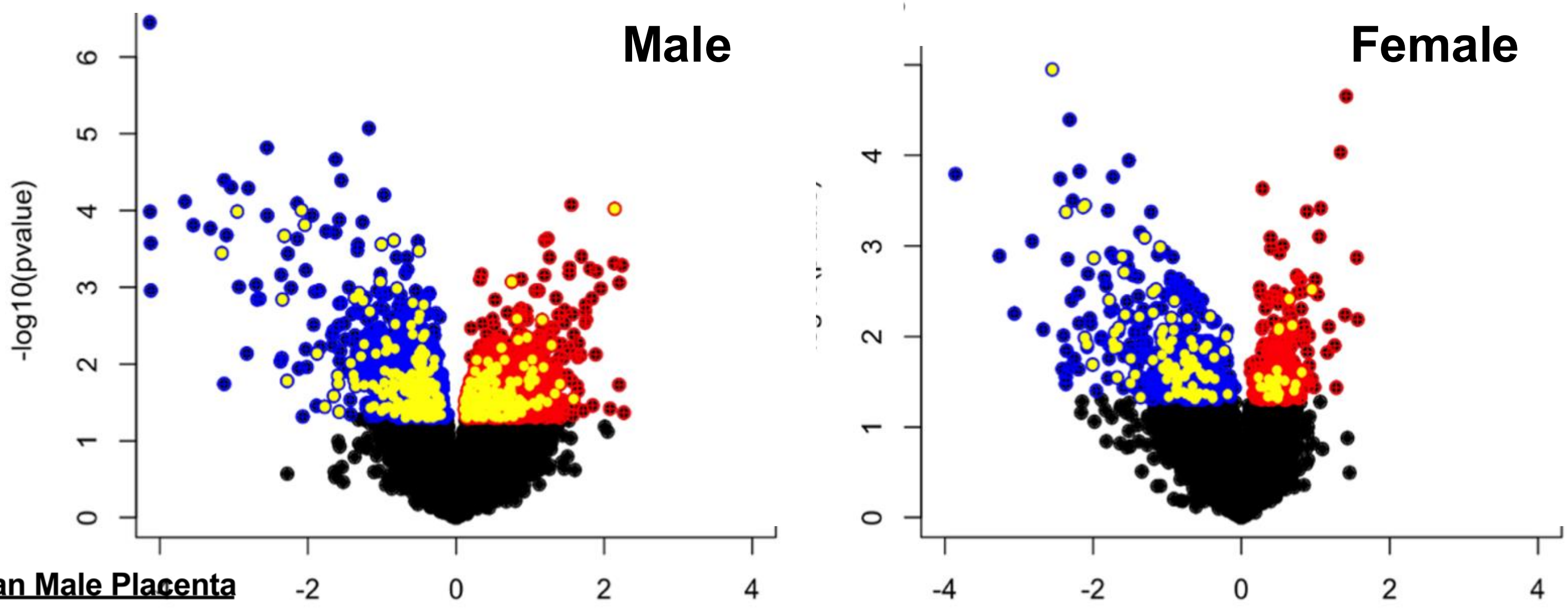
Teesta Naskar

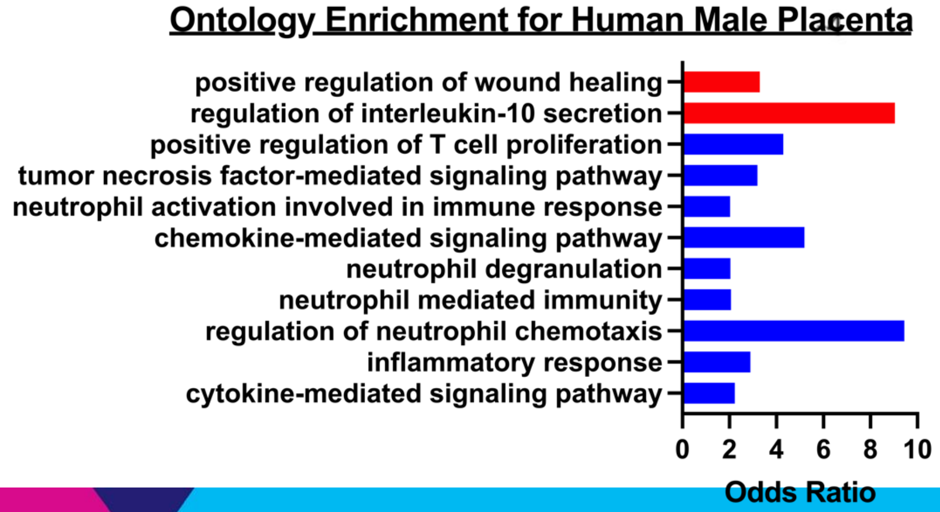


upregulated DEGs. Downregulate DEGs. Immune DEGs

Bara, Naskar et al., unpublished

Human Placenta — Sex Differences with Cannabis Exposure





Immune-related DEGs

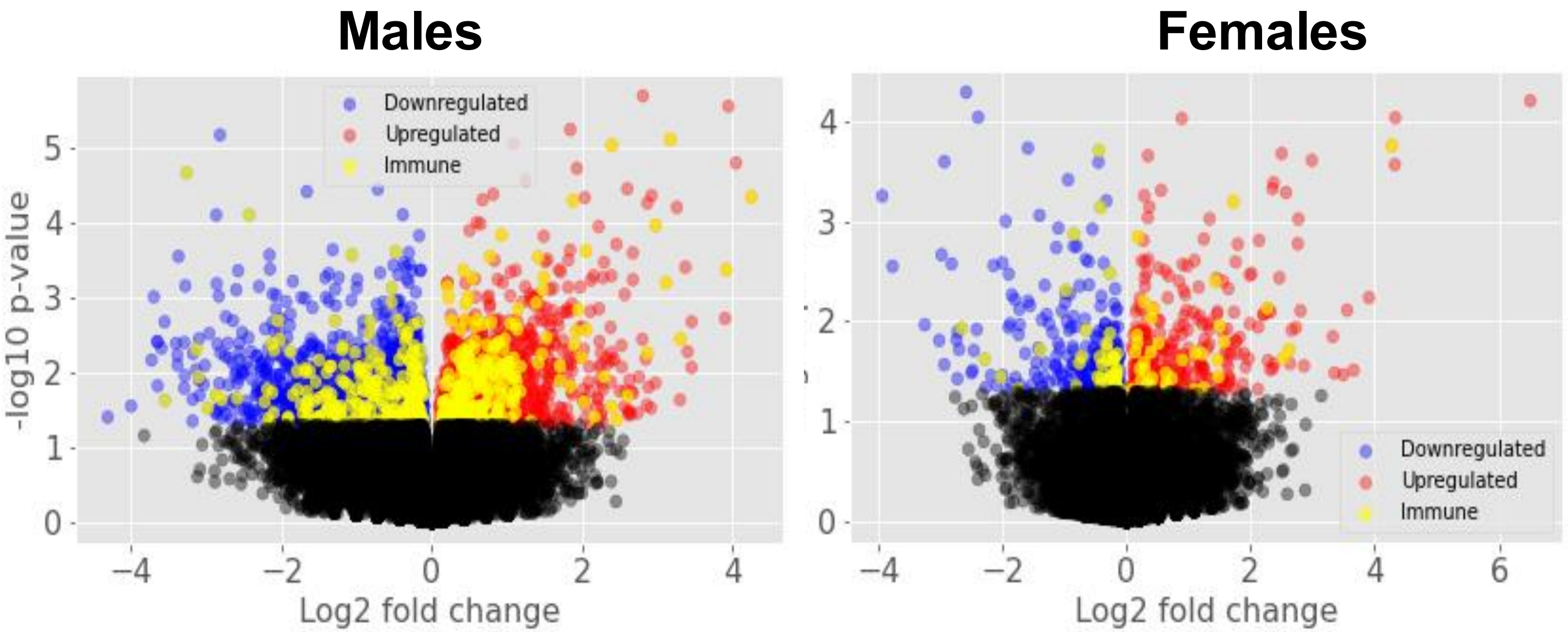
Bara, Naskar et al., unpublished

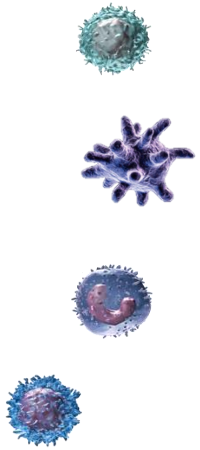
Translational Animal Model: Cannabinoid Exposure To Pregnant Dams

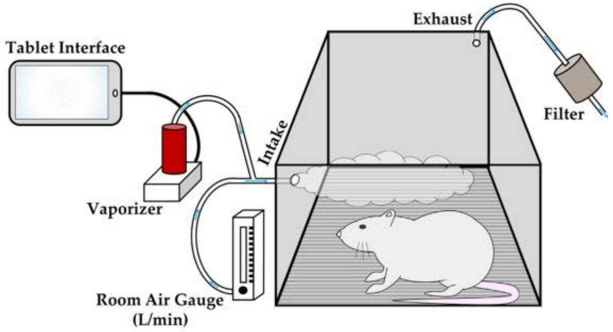
Anissa Bara

Teesta Naskar

Immune Transcriptome Dysregulation



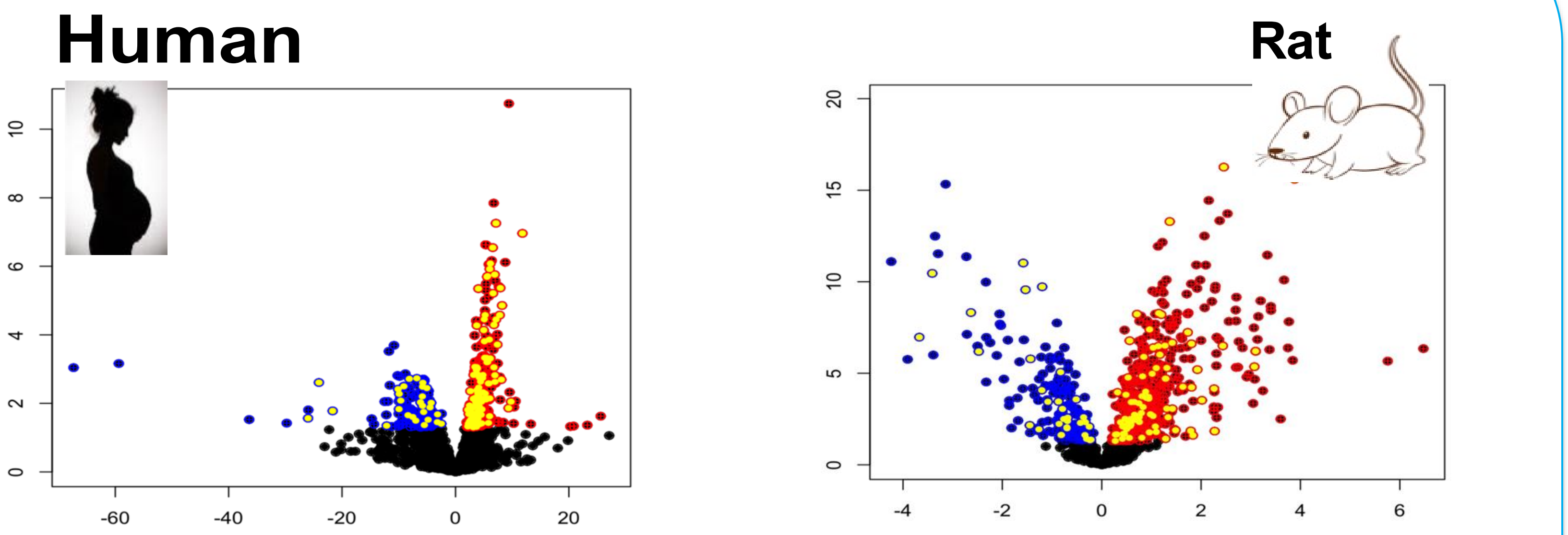


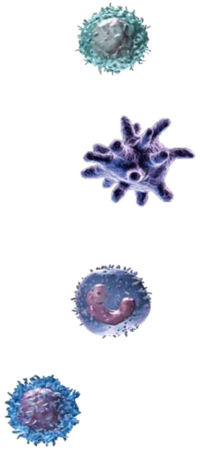


Translational vapor rat model of prenatal cannabis (THC + CBD; 10:1) exposure

Bara, Naskar et al., unpublished

Translational Animal Model: THC Exposure To Pregnant Dams Alters the Placental Immune Proteome

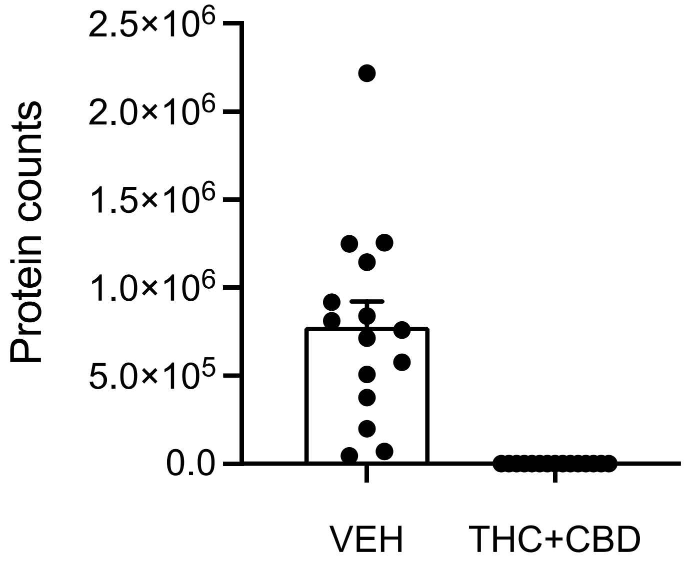


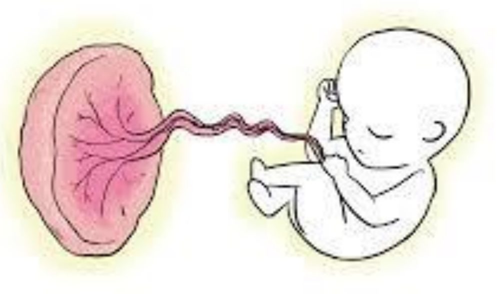


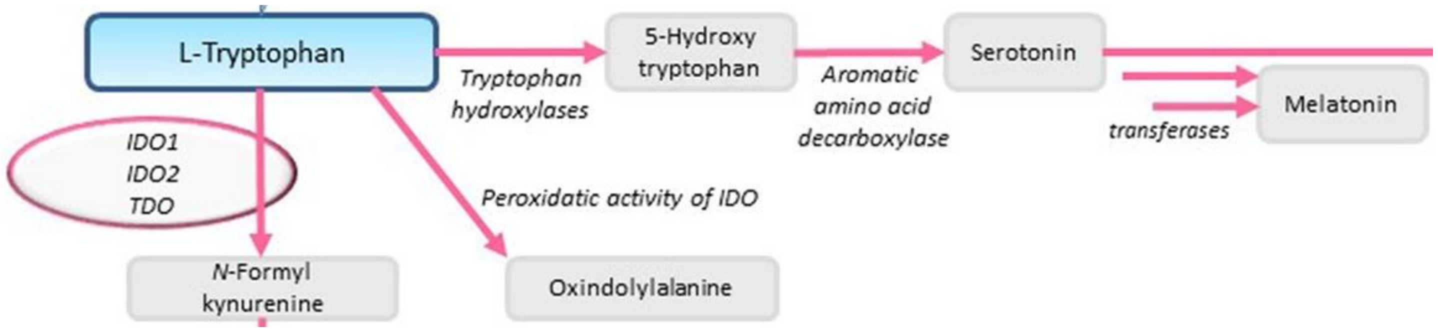
Bara, Naskar et al., unpublished

Placental Proteome

IDO1



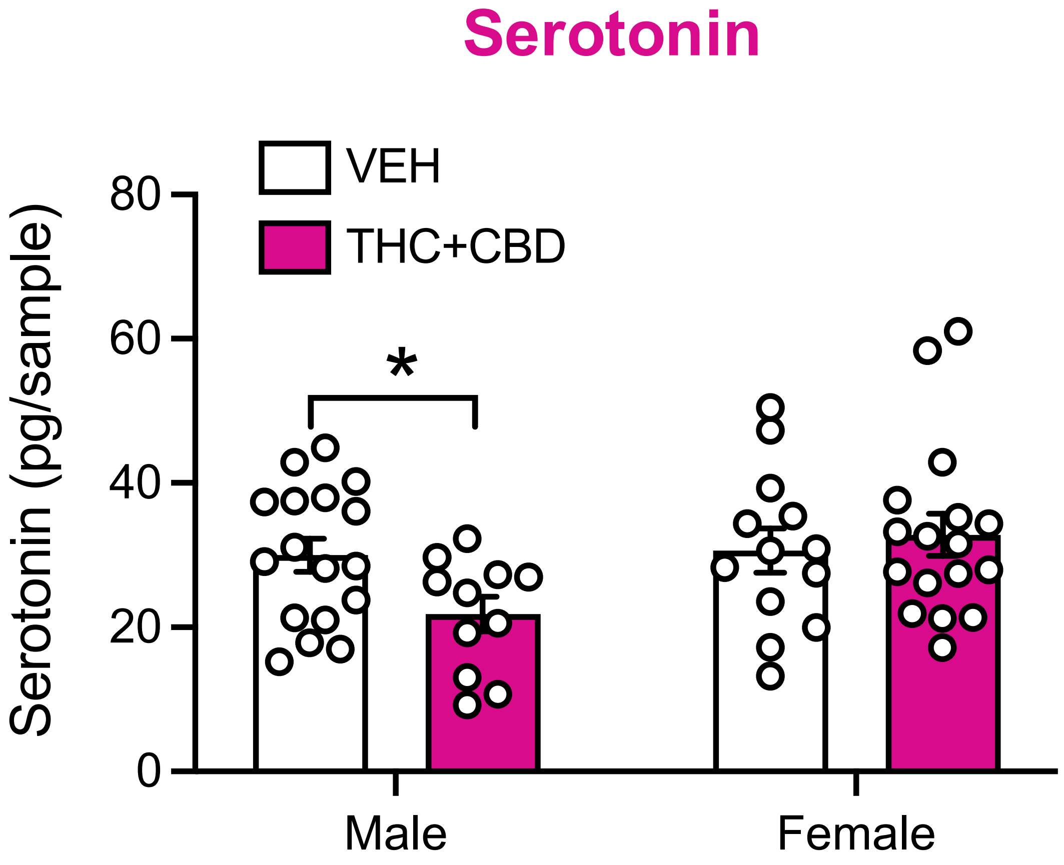




IDO1 (indoleamine 2,3-dioxygenase)

- Catalyzes the degradation of L-Tryptophan, the precursor of Serotonin and downstream to Melatonin
- Rate-limiting step of catabolism along the Kynurenine pathway
- Crucial for survival
- Produced by cells in responses of inflammation
- Crucial for Immune Suppression and Autoimmunity (protects the fetus from maternal immune rejection)
- Role in placental vascular development (formation of new placental vessels!)

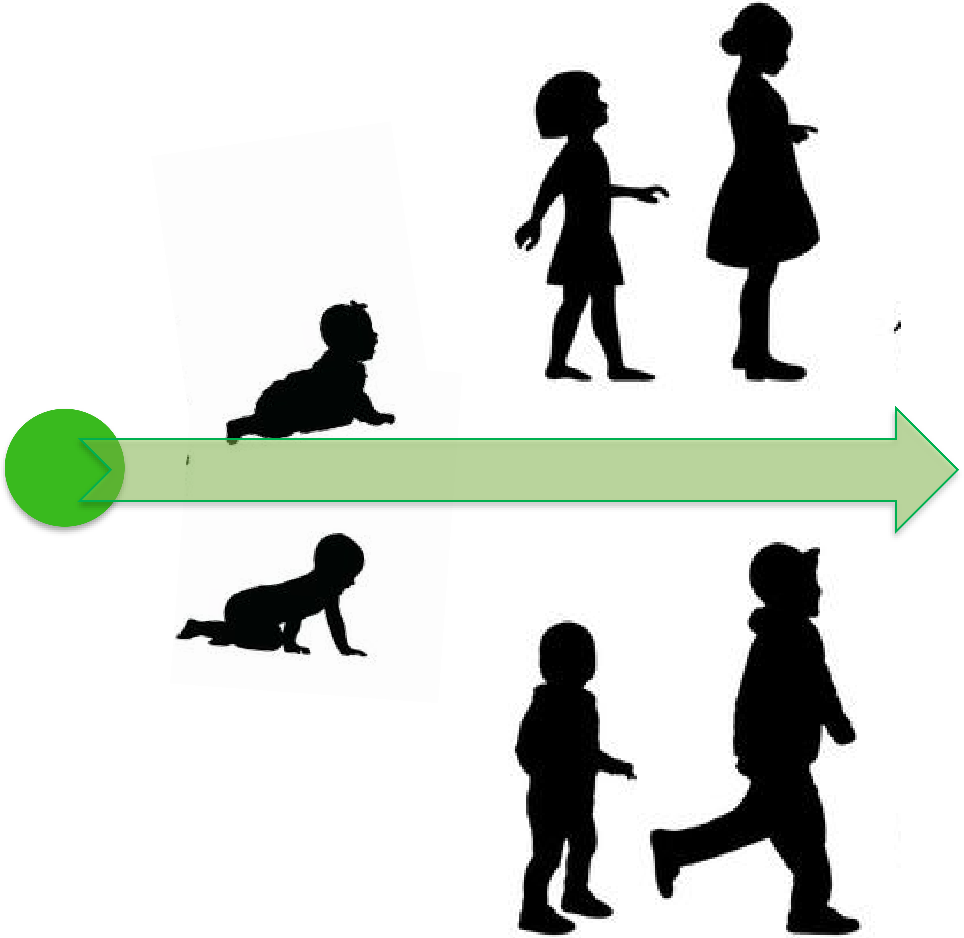
Prenatal Cannabinoid Exposure Decreases Placental Serotonin Levels in Males



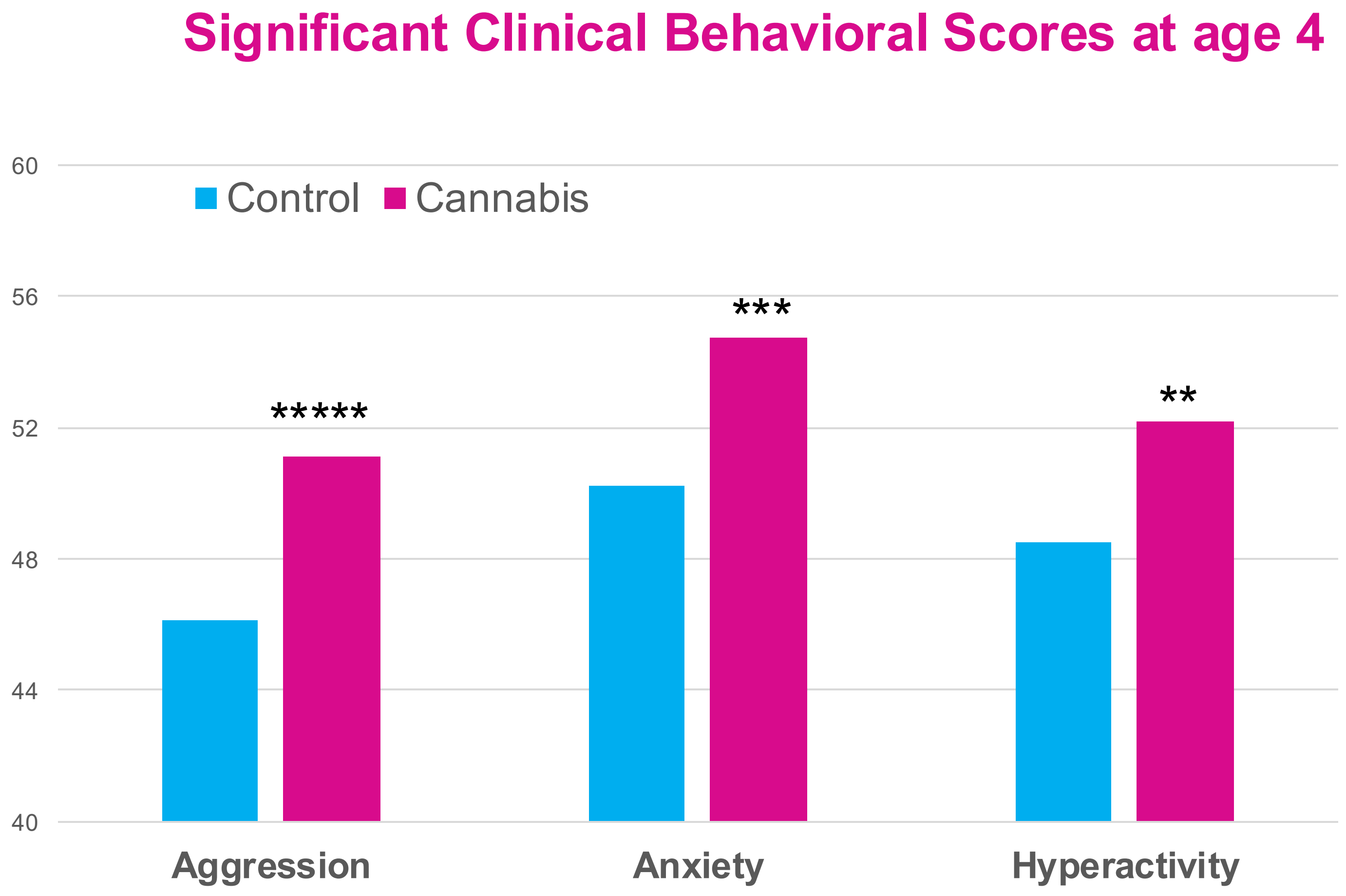
Bara et al unpublished

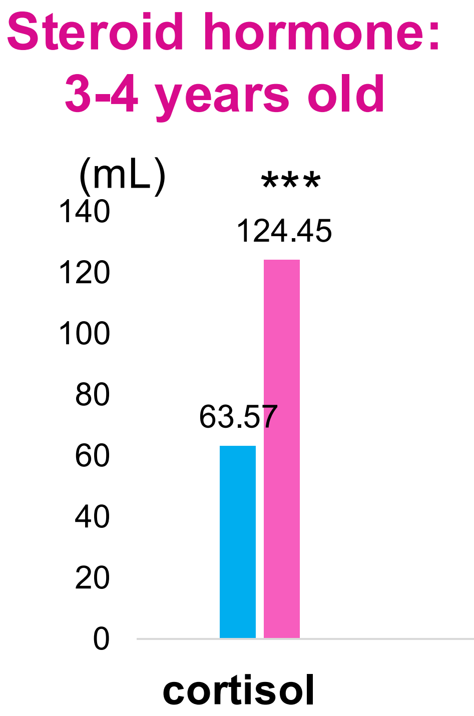
Yoko Nomura

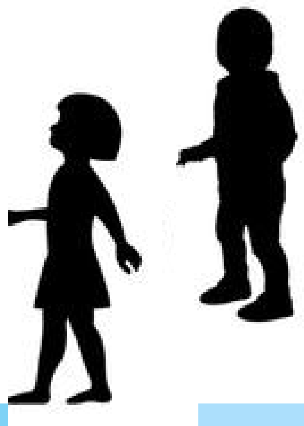
Prenatal Environment Influences Future Phenotype?



Maternal Cannabis Use in Relation to Hair Steroid Hormones And Clinical Behavior Scores in Early Childhood







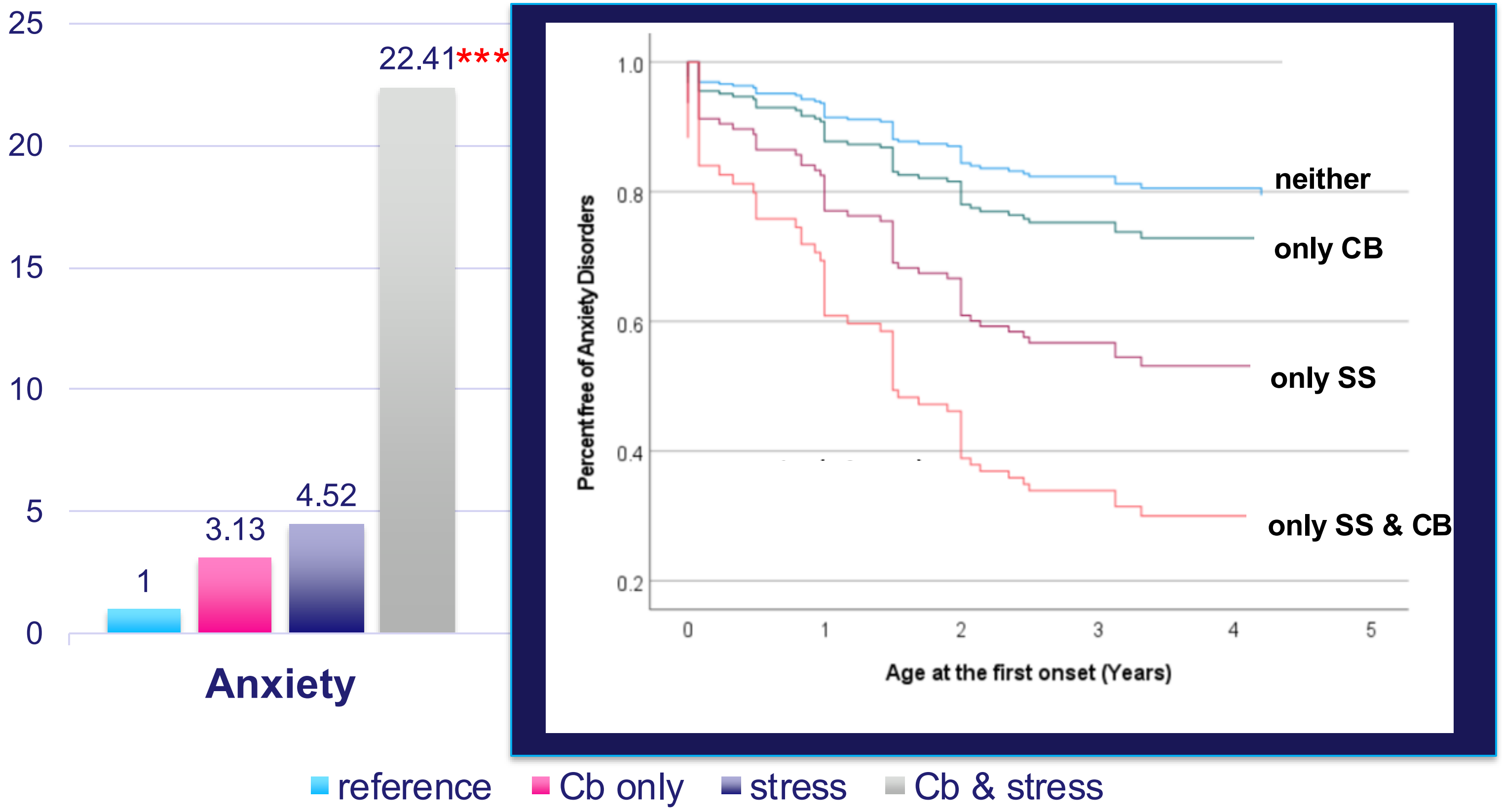
Behavioral assessment system for children (BASC-2) survey

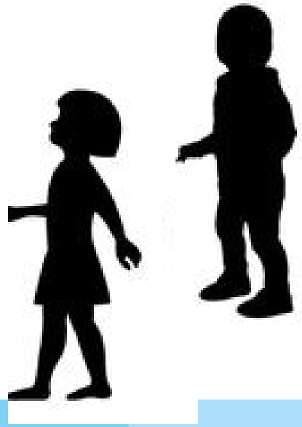
Rompala et al., PNAS 2021

Prenatal Cannabis Exposure and Stress

Synergistic Interaction

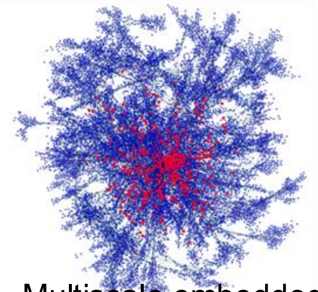
Risk (adjusted odds ratio) of clinically significant behavioral differences at age 4



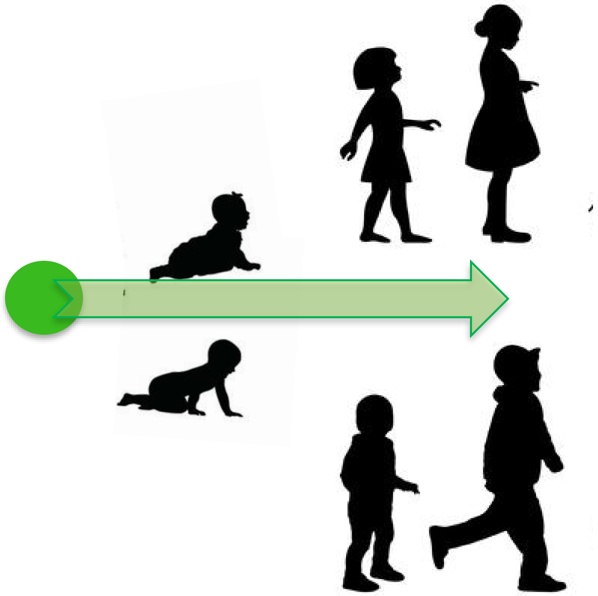


Nomura et al., BJPsych Open,, 2023

Reprogramming of Immune-Related Placental Gene Networks are Associated With At-Risk Anxiety in Early Childhood



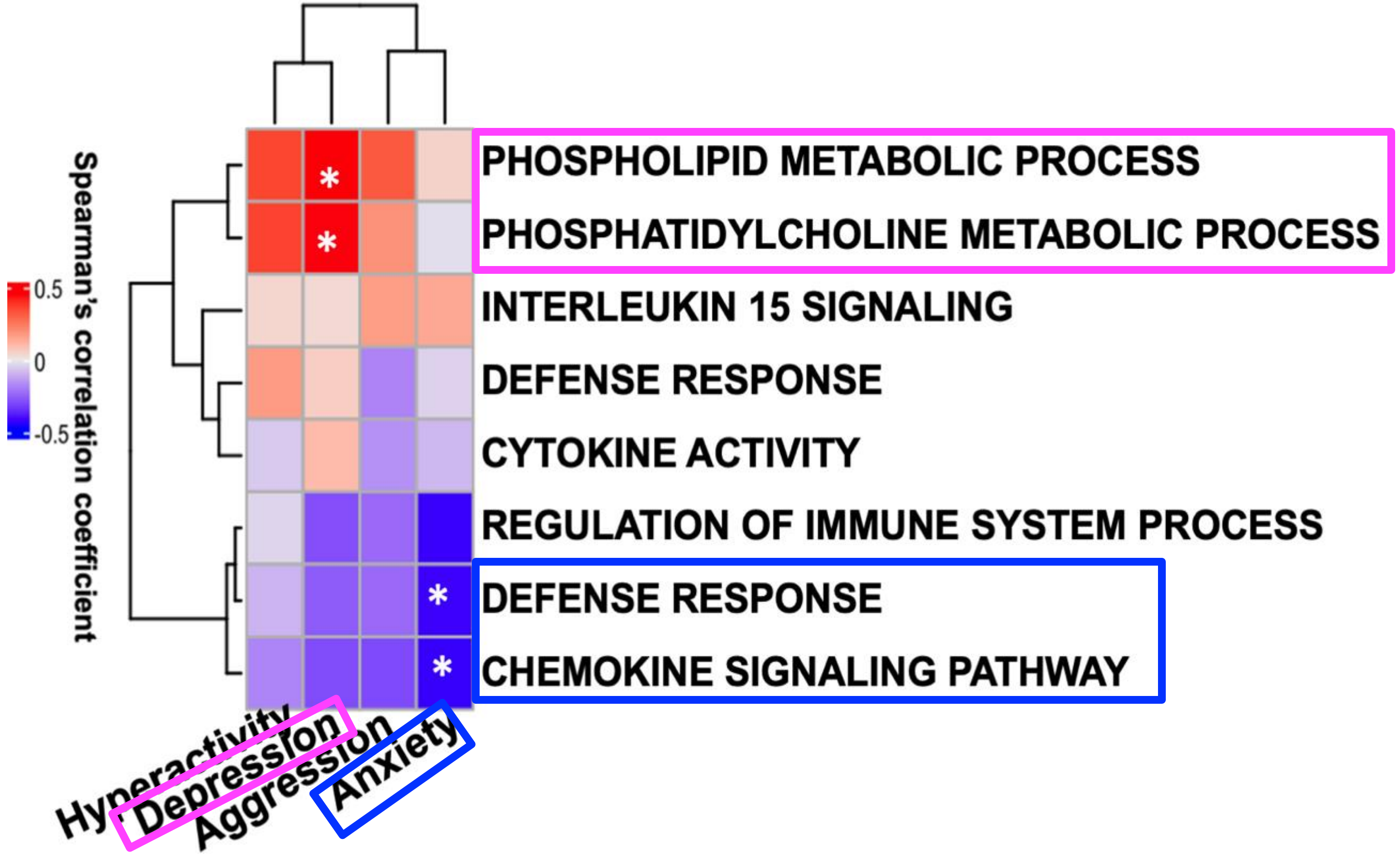
Multiscale embedded gene co-expression network Analysis: functional co-expressed gene modules



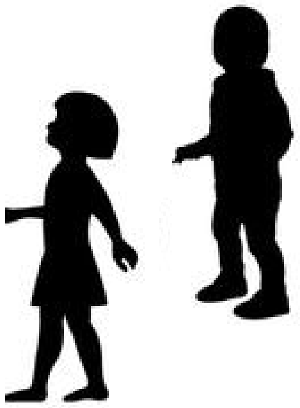
Of the differentially correlated **cytokine-related genes**, the majority significantly **correlate with anxiety** exclusively in the **maternal cannabis** group

Rompala et al., PNAS 2021

Immune-Related Placental Gene Networks are Associated with At-Risk Anxiety in Early Childhood

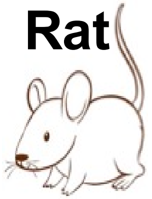


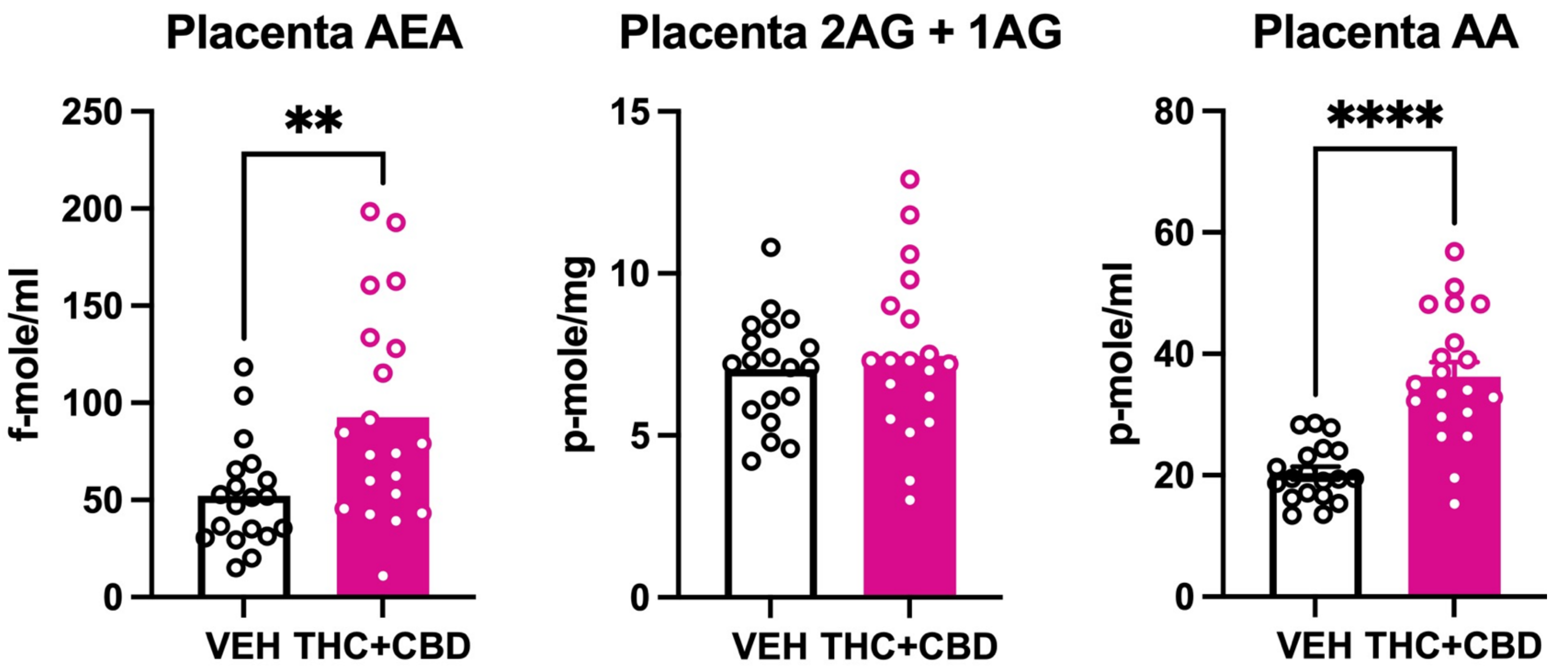
Lipid processing: energy storage, signaling, and structural components of cell membranes



Bara, Naskar et al., unpublished

THC/CBD Exposure To Pregnant Dams Alters the Placental Endocannabinoids

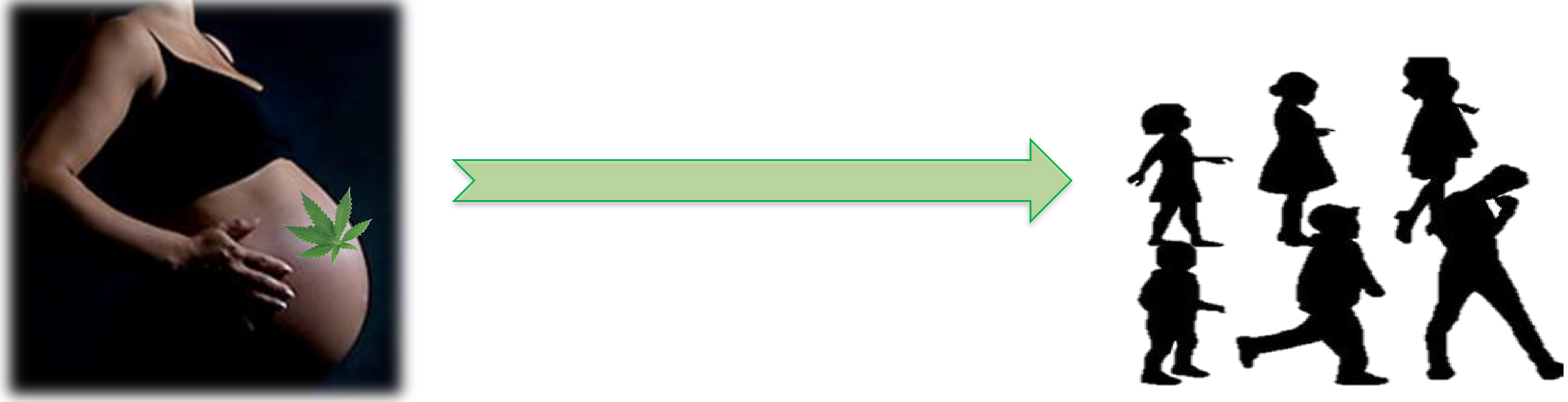




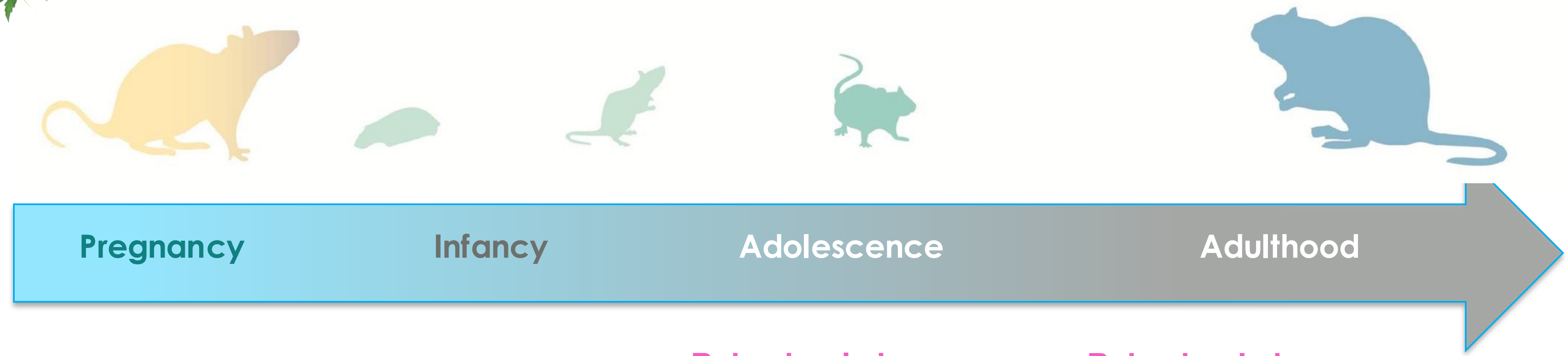
AEA, anandamide
2-AG, 2-arachidonoylglycerol;
DAGL, diacylglycerol lipase – produce 2-AG
AA, Arachidonic acid

Arachidonic acid — **substrate** for both AEA and 2-AG synthesis and AA is recycled during endocannabinoid **catabolism**.

AA also acts as a shared substrate for the eicosanoid system, which produces prostaglandins.



Prenatal THC Exposure Animal Model



Behavioral changes:
Affective behavior

Behavioral changes:
Affective behavior
Social interaction

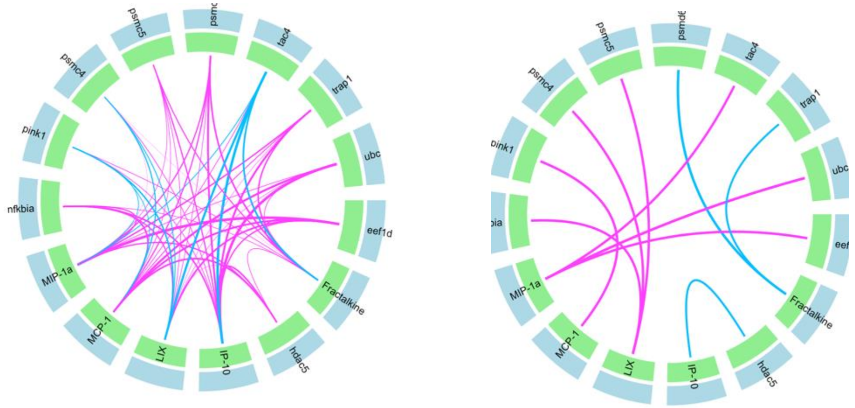
Behavioral changes:
Motivation
Depression-like phenotype
Stress sensitivity
Opioid sensitivity

Prenatal Cannabinoid Effects on Juvenile Affect and Social Behaviors

Anissa Bara

Loredana Losapio

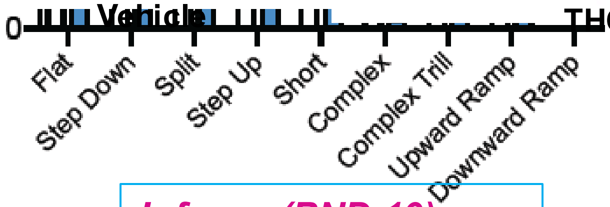
NF-kB gene expression (accumbens) and circulating cytokine levels



Vehicle

THC/CBD

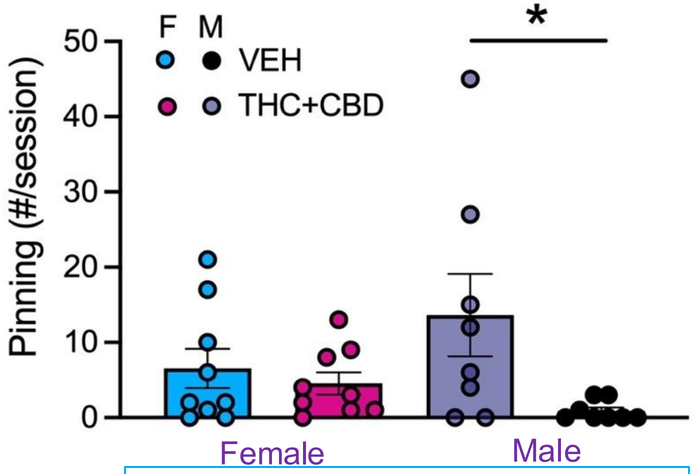
Ultrasonic vocalization



Infancy (PND 10)

- Isolation-induced Ultrasonic Volcalizations
- Social communication
- Communicative role in mother-offspring interactions
- Peak at PND10 in rats

Social play

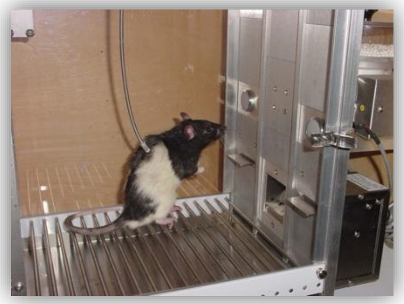


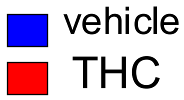
Early Adolescent (PND 22-35)

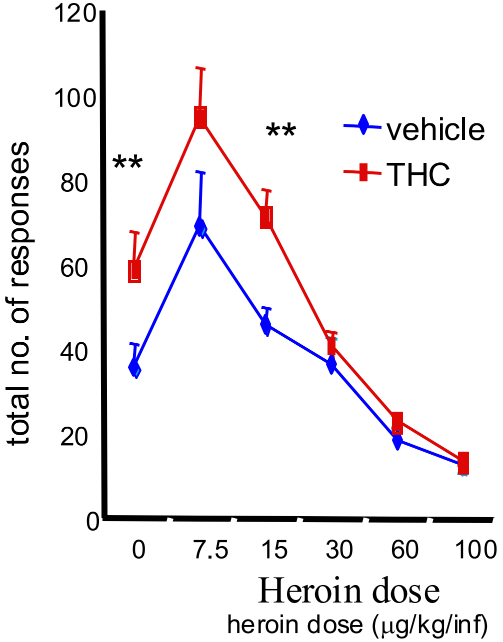
THC:CBD 10:1

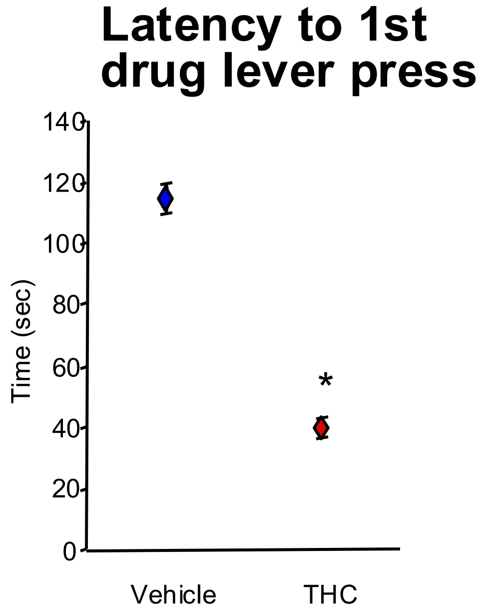
Bara et al., unpublished

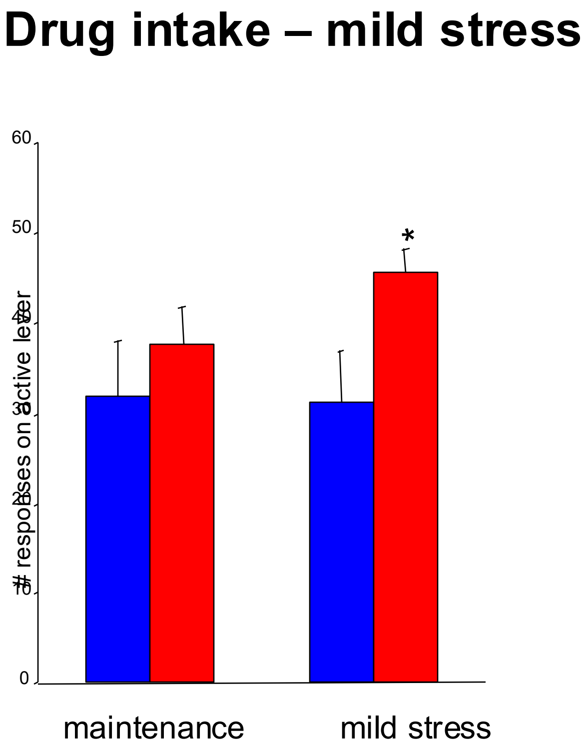
Prenatal THC Exposure Alters Sensitivity to Opioids in Adulthood

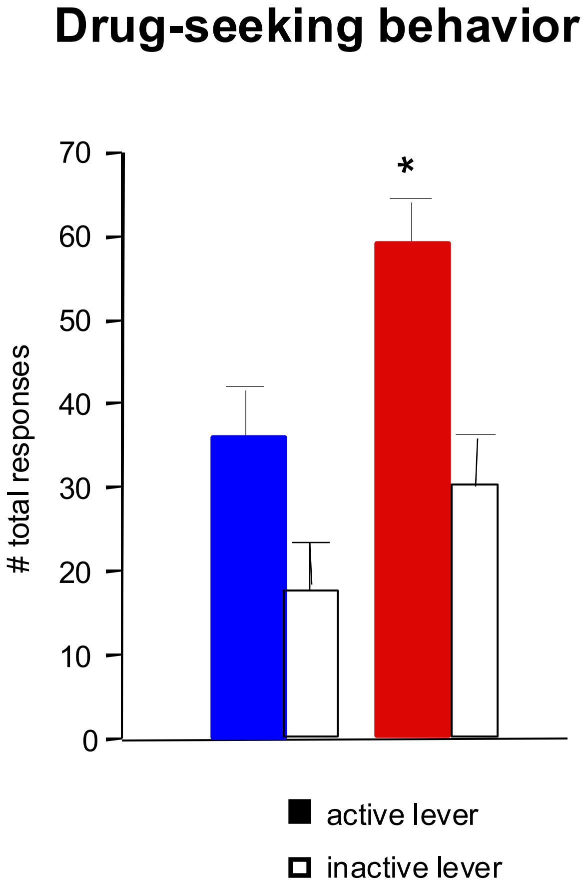












Spano et al, Biological Psychiatry, 61:554-63, 2007

Long-Term Consequences of Prenatal THC Exposure: <u>Adulthood</u>

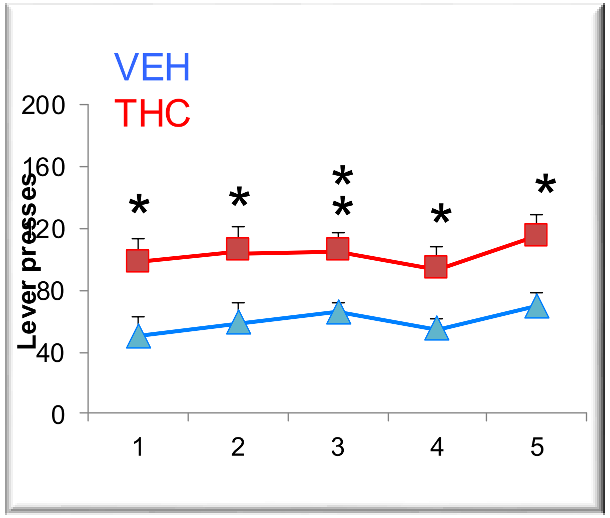
Reward: chocolate

Forced Swim Test
Behavioral despair model

Hedonic state
Sucrose preference

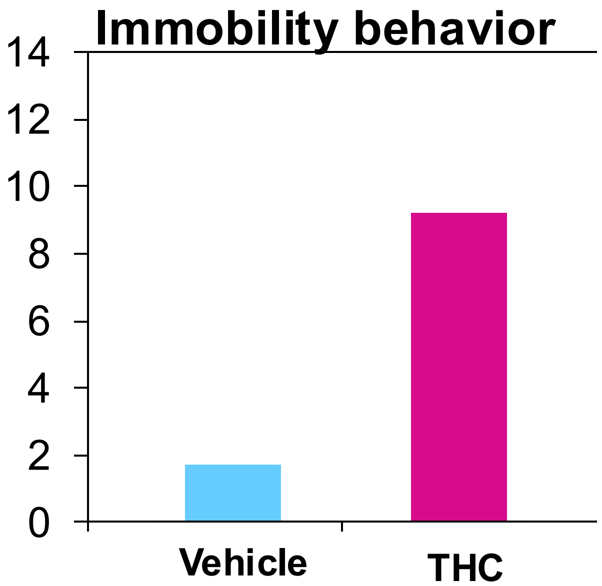
Motivation

<u>Progressive ratio behavior</u>



Increased breakpoint = increased motivation

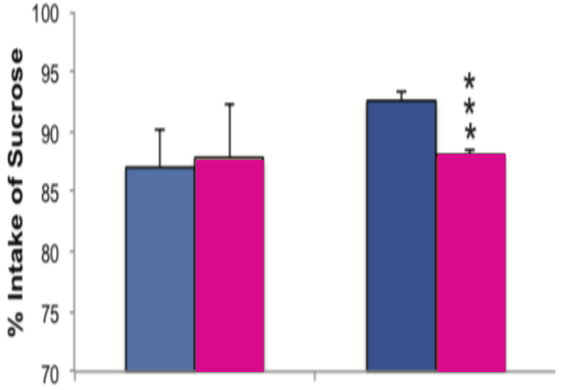
Depression-like phenotype



Hedonic state

<u>Sucrose intake</u>

VEH
THC



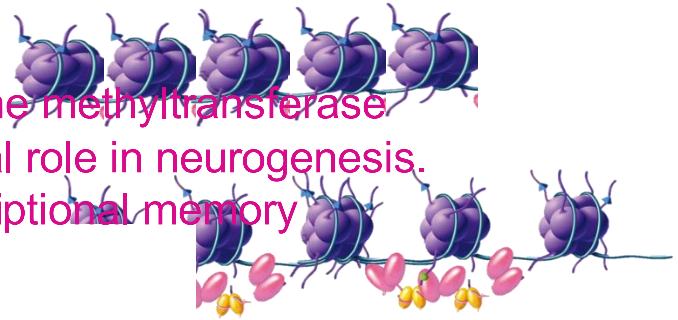
Stress - Stress +

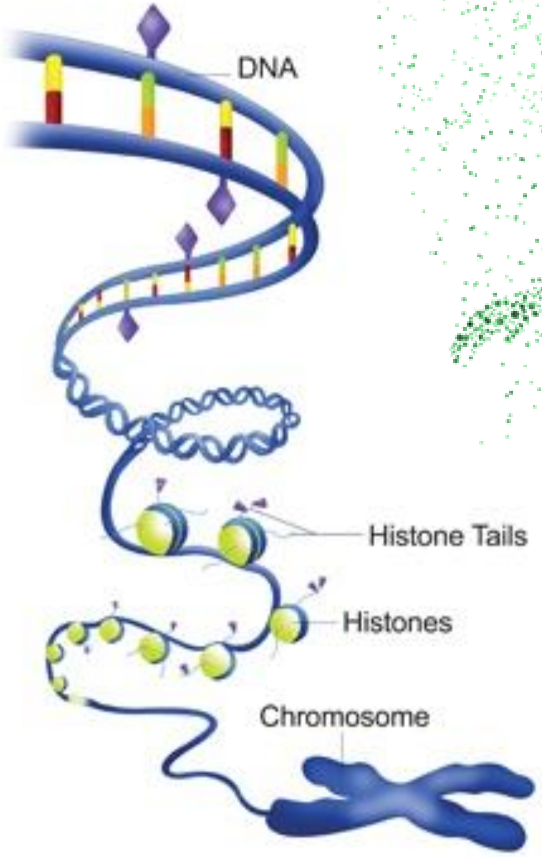
Ellis, Bara, Morris et al. Biological Psychiatry, 2021

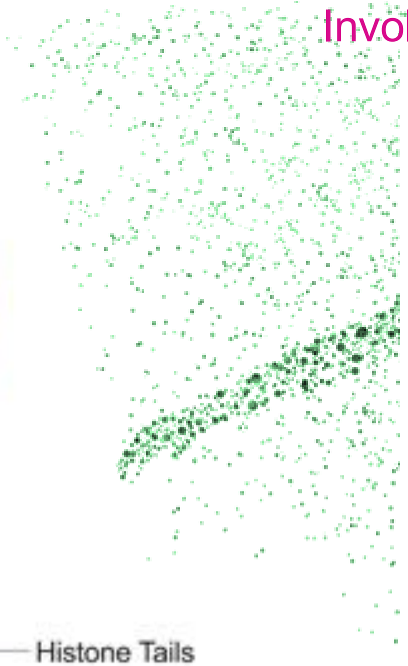
Underlying Mechanisms that Maintain *In Utero* Experiences Across Life?

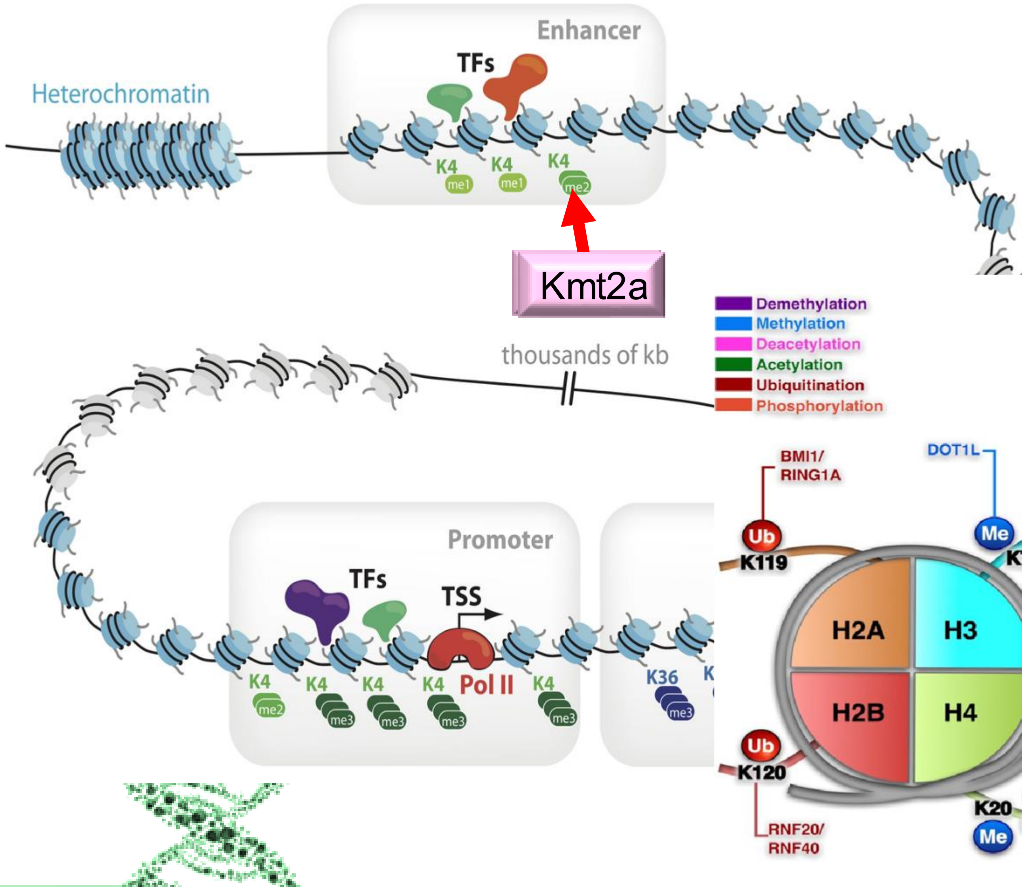
Epigenetic Mechanisms?

KMT2A/MLL1 (Mixed-Lineage Leukemia) Histone methyltransferase (mark of transcriptional activation) that plays an essential role in neurogenesis. Involved in the epigenetic maintenance of transcriptional memory



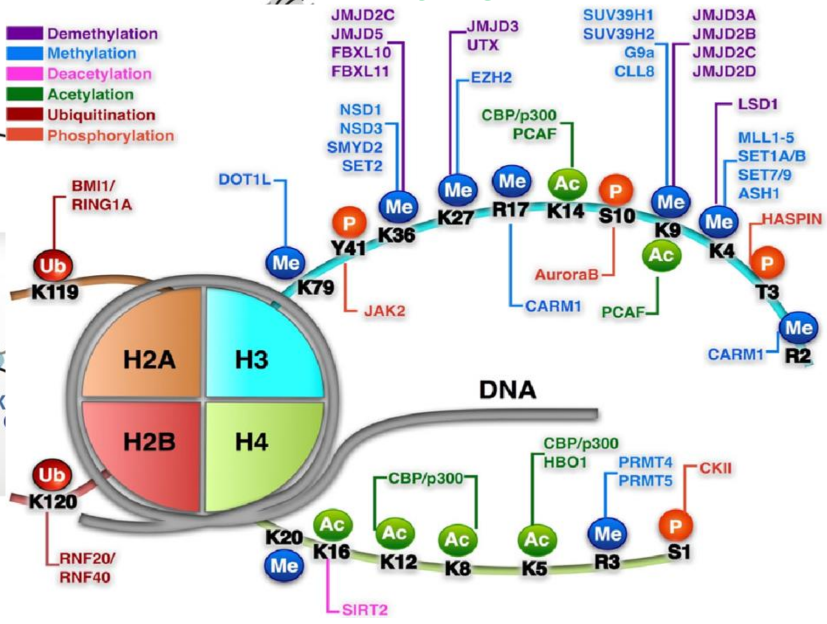






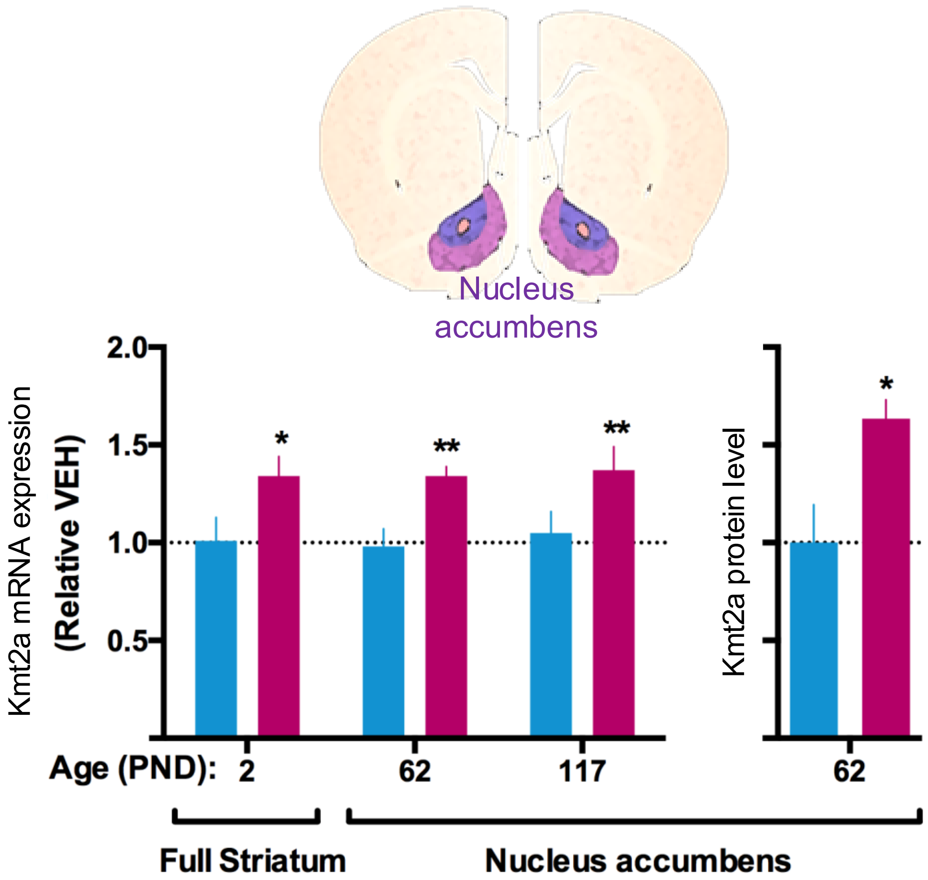
H3K4

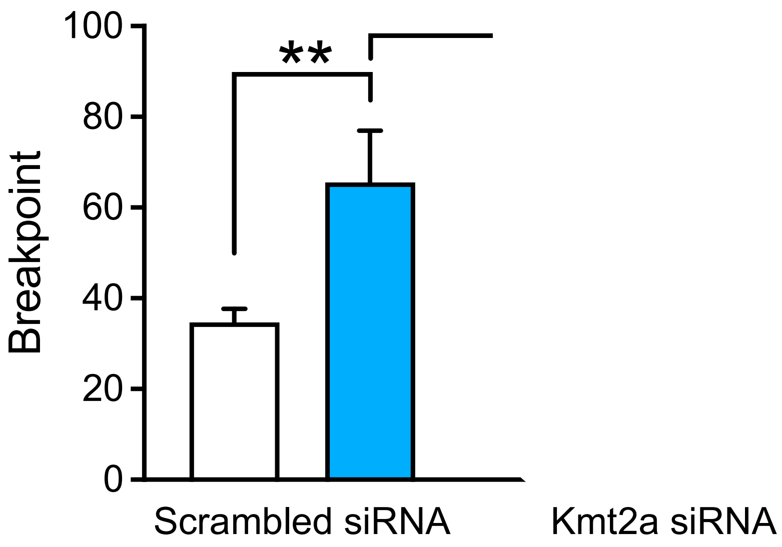
ment



Ning et al., 2016

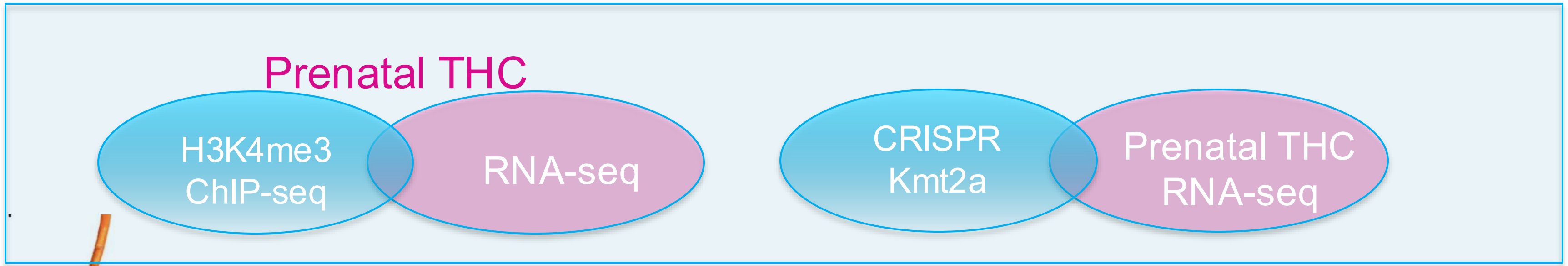
Epigenetic (Kmt2a) Perturbation *Causally* Contributes to Protracted Behavioral Effects in Adulthood due to Prenatal THC Exposure

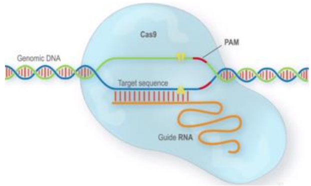


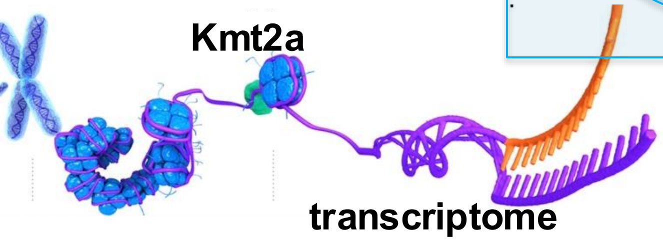


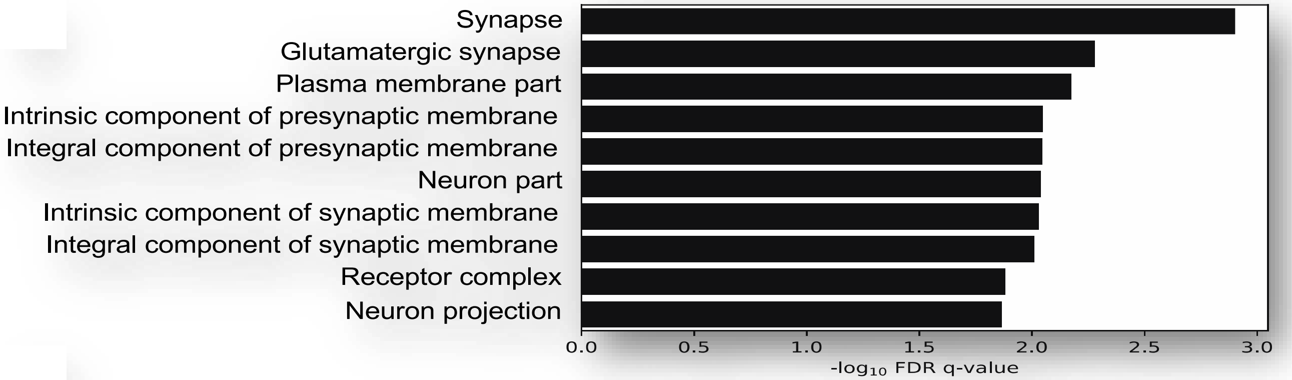
Ellis, Bara, Morris et al. Biological Psychiatry, 2022

Gene Networks Associated with Kmt2a/H3K4me4 Epigenetic Alterations and Impacted by Prenatal THC in Adulthood Relate to <u>Synaptic Plasticity</u>



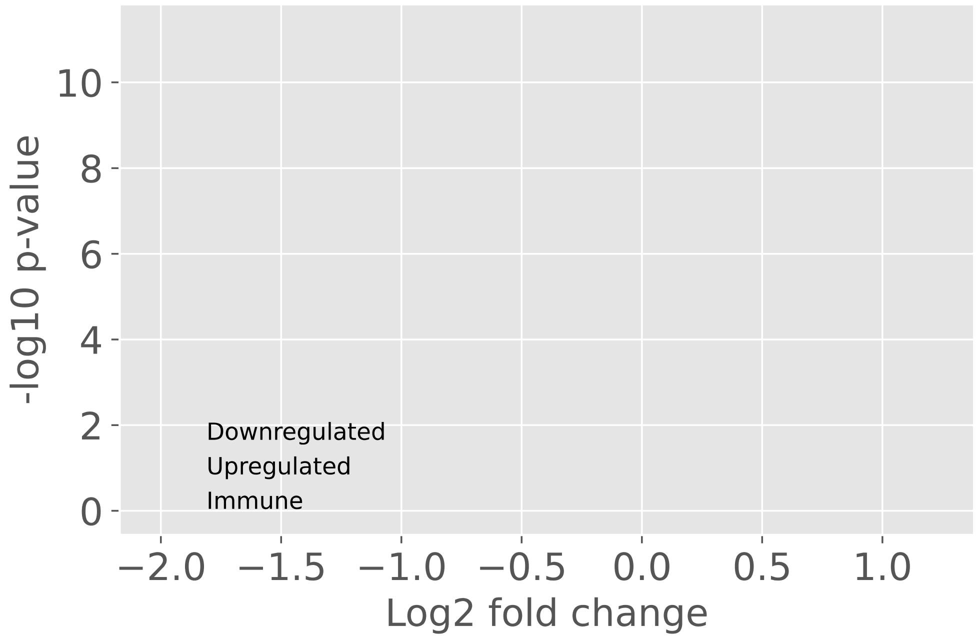


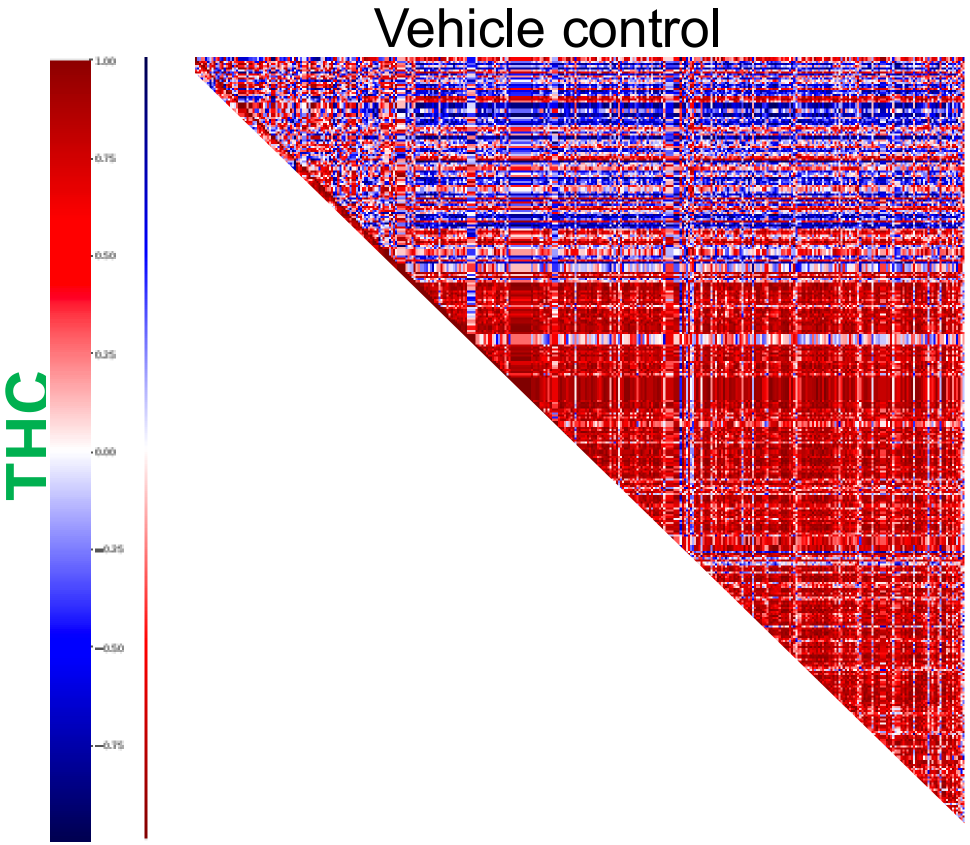




Ellis, Bara, Morris et al. Biological Psychiatry, 2021

Reorganization of Epigenetic Enrichment of Immune-Related Gene Loci in the Nucleus Accumbens of Adults with Prenatal THC Exposure





highly synchronized, positive correlations among immune-related gene loci

ADOLESCENCE

~90% of adults with substance use disorders initiate use during adolescence

Adolescent cannabis use is a critical window for Cannabis Use Disorder risk

Youth and Young Adults:

- Among individuals who used cannabis, <u>22%</u> met criteria for Cannabis Use Disorder (CUD).
- CUD was most prevalent in young adults, with the highest risk of CUD (41.1%) among the cohort of 21-year-old emerging adults.

Leung et al., Addict Behav. 2020

hildhood | Adolescence | Young adults

Migration

Synaptogenesis

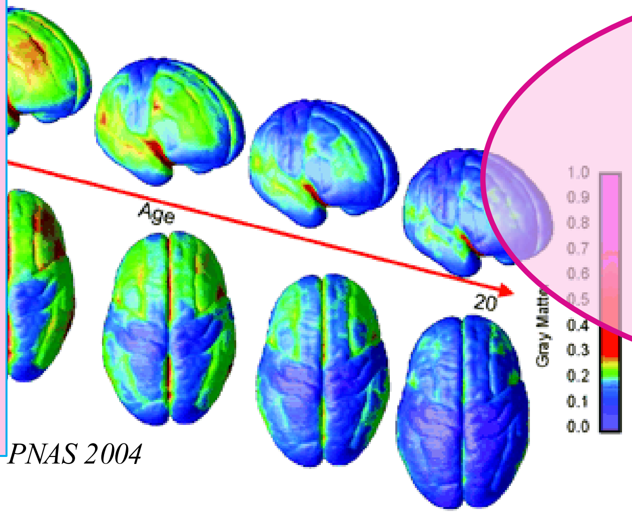
th
d brain
th

Fine tuning of neural circuits

Maturation of prefrontal cortex

Synaptic pruning

myelination



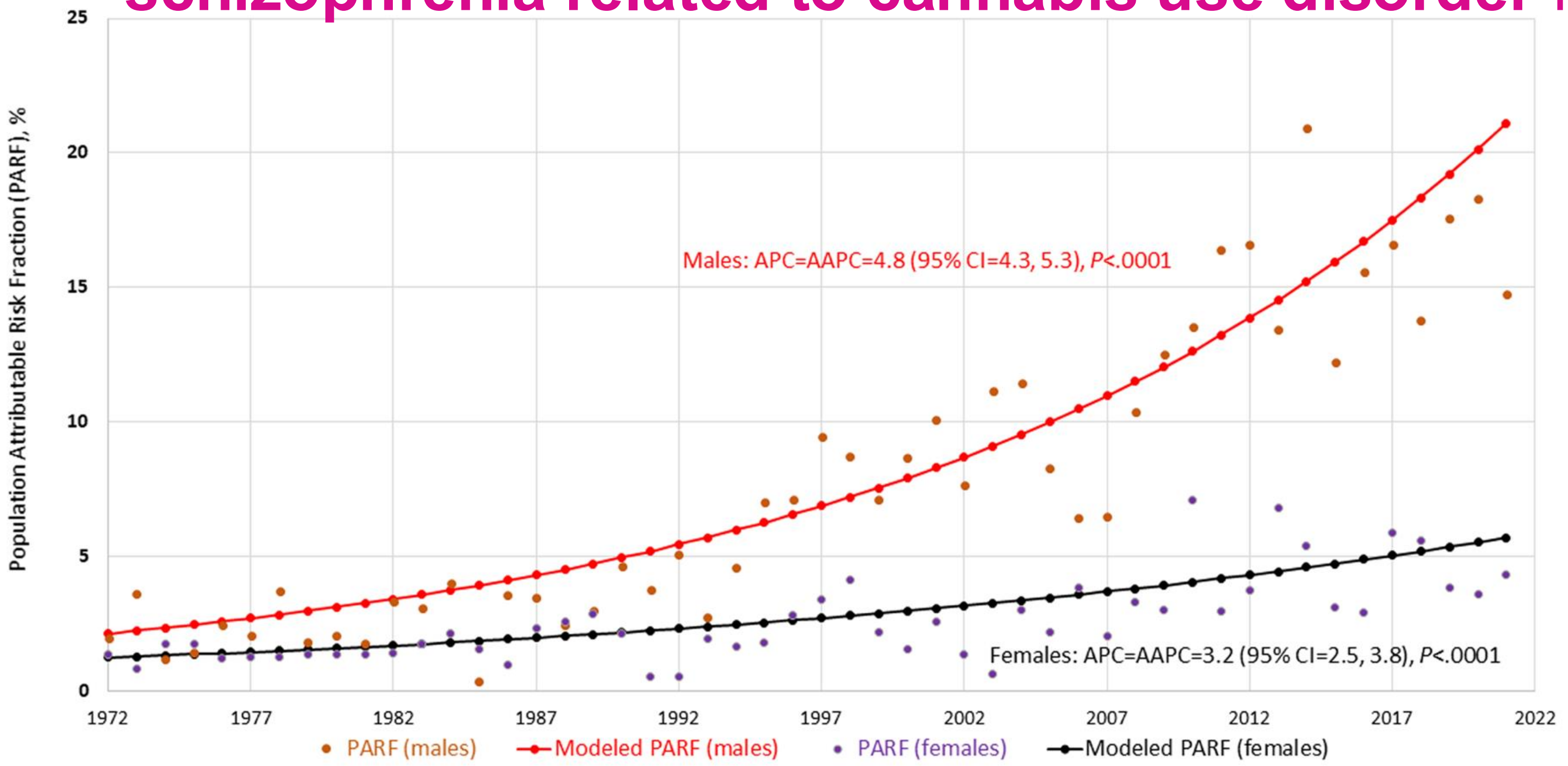
et al., PNAS 2004

Past year cannabis use by teens:
8th graders: 11.4%
9th graders: 28%
12th graders: 35%

Hurd, J Clinical Invest, 2020

Association Between Cannabis Use Disorder and Schizophrenia: *Sex and Age*

For young men aged 21-30, the proportion of **preventable cases of schizophrenia related to cannabis use disorder** may be as **high as 30%**



PARF=Population attributable risk fraction. Modeled PARF= PARF results from the selected joinpoint regression model. APC=annual percentage change. AAPC=average APC during 1972-2021. APC=AAPC: Indicate that no joinpoints were identified using Bayesian Information Criterion.

16–20-year-olds: *association between CUD and schizophrenia was* ***~2X as high for males*** *than females*

21–25-year-olds: *it was approximately* ***50% higher for males*** *than females*

>26 years old: *similar for males and females*

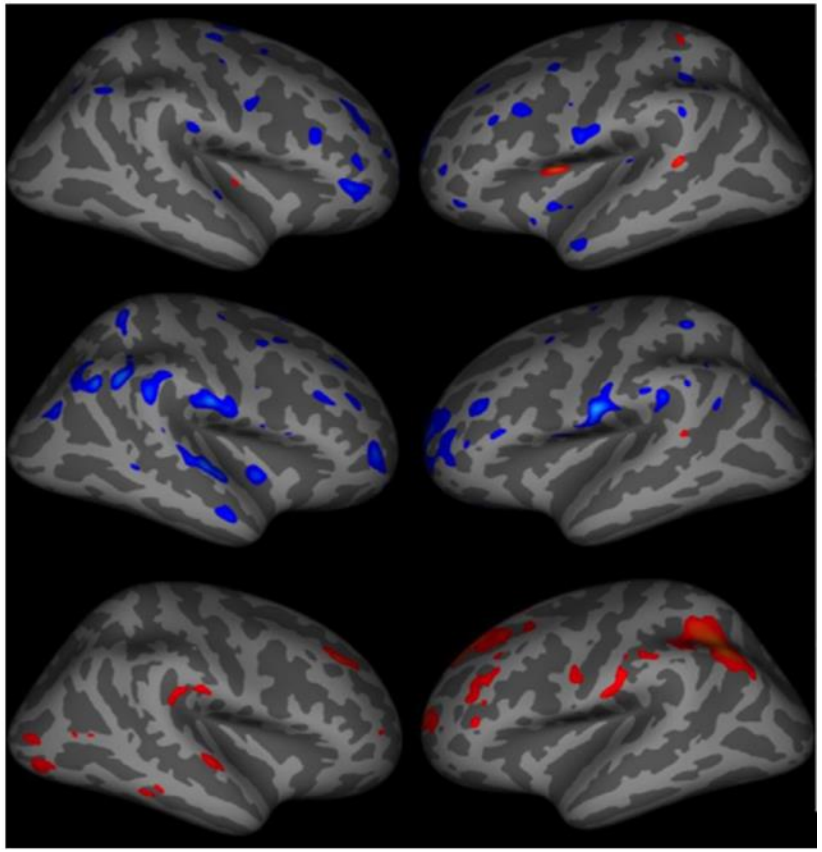
Proportion of cases of schizophrenia associated with cannabis use disorder increased 3- to 4-fold during the past 2 decades

Hjorthøj et et al, Psychol Med, 2023

The Prefrontal Cortex and Adolescent Cannabis Use

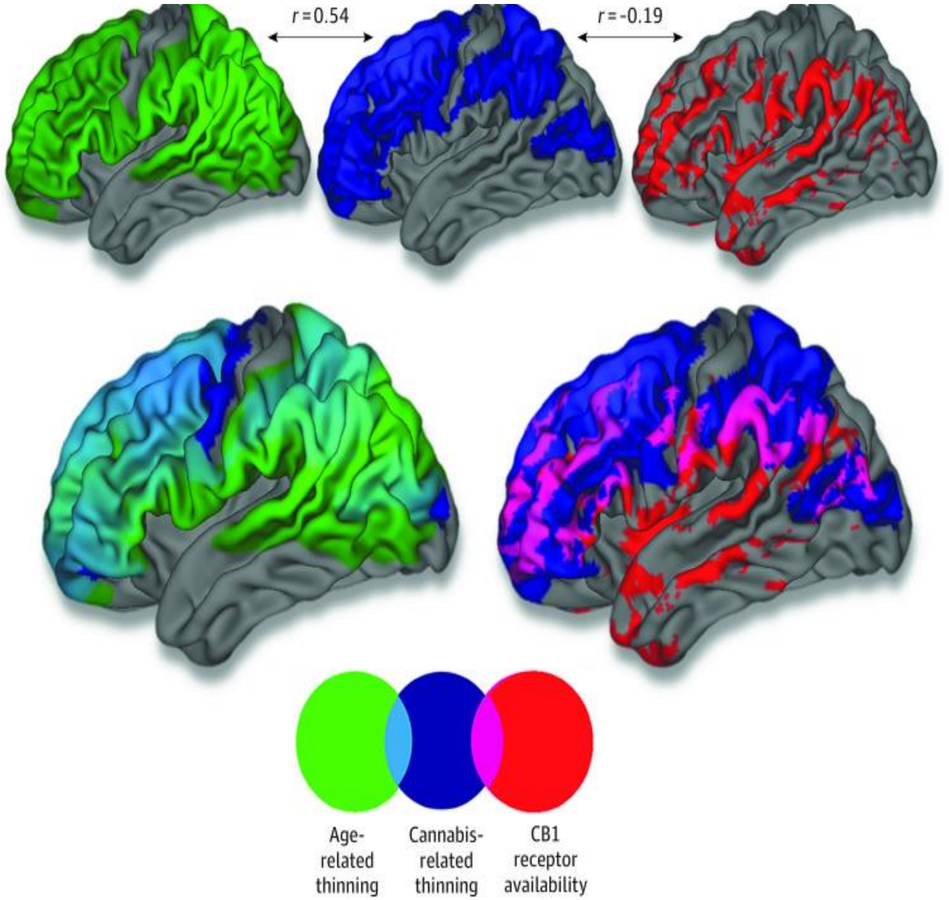
Structurally

- Alters cortical thickness
- Alters grey matter/white matter ratio
- Alters gyrification



(Filbey et al. 2015; Shollenbarger et al. 2015)

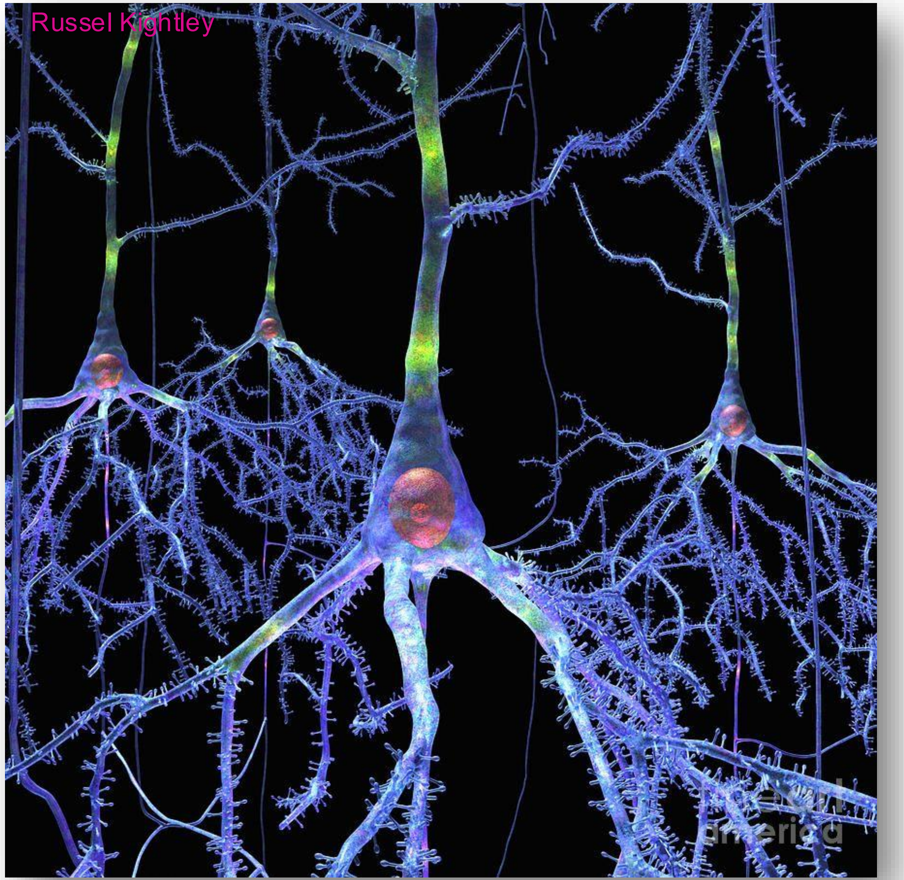
Cannabis use associated with altered cortical development, particularly in prefrontal regions rich in CB1 receptors and exhibiting protracted maturational trajectories



Accelerated cortical thinning correlated with cannabis use and impulsivity

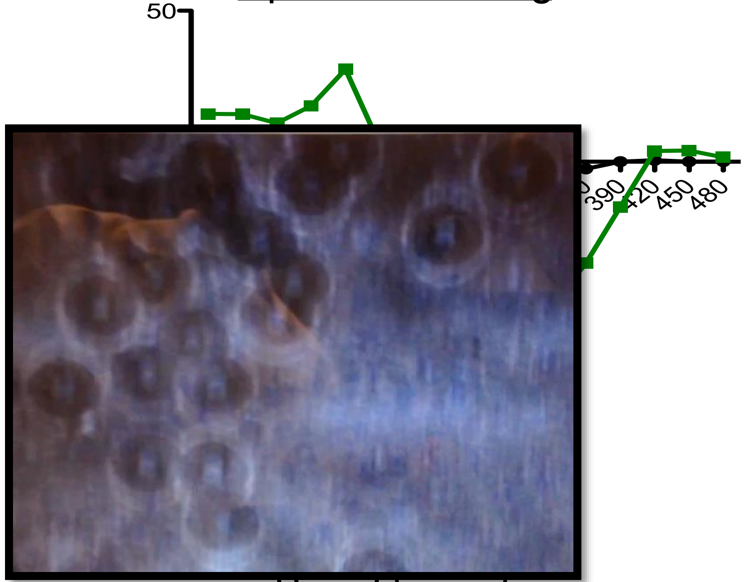
(Albaugh et al…IMAGEN., JAMA Psych, 2021)

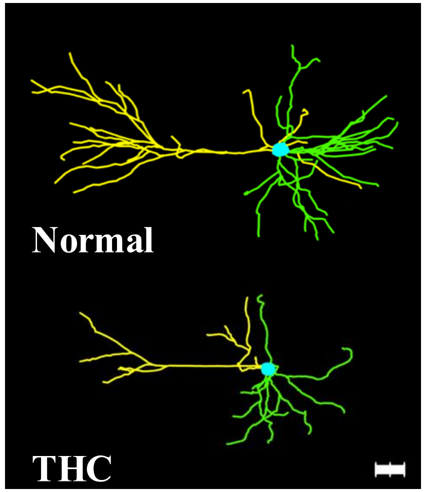
Adolescent THC Exposure: Prefrontal Cortex



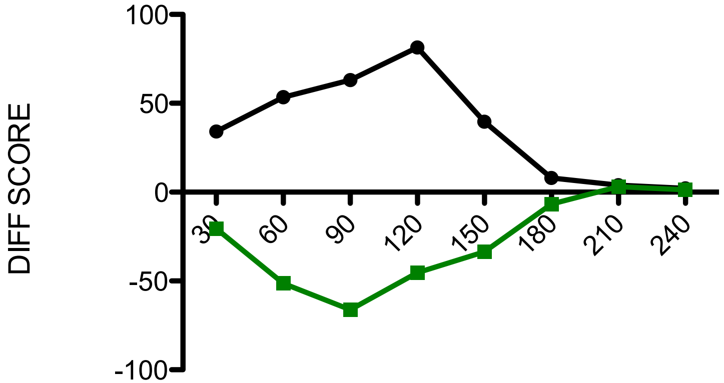
Reduced Cortical Neuronal Complexity

Apical branching





Basal branching



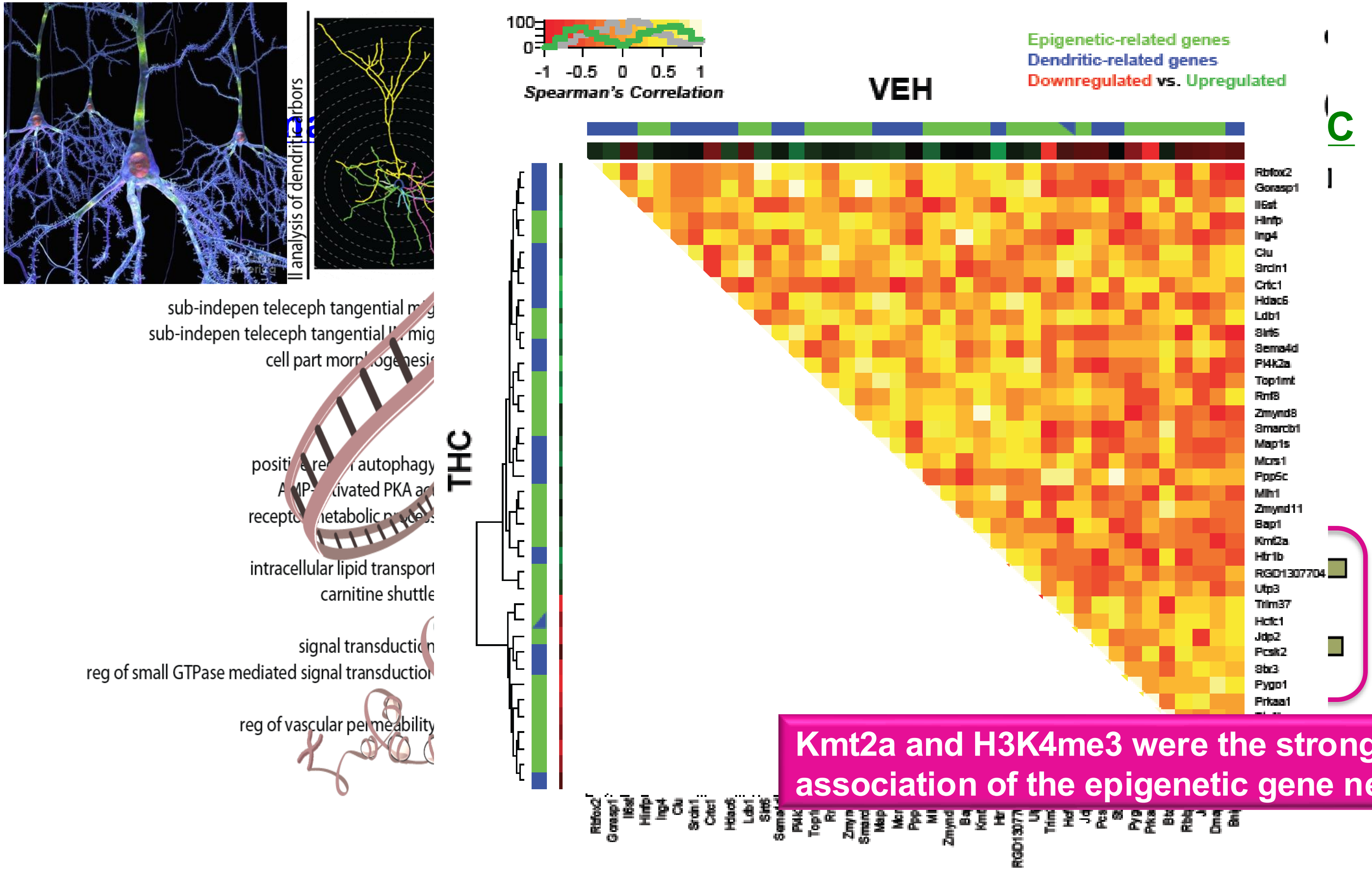
RESEMBLES STRESS MORPHOLOGICAL PHENOTYPE in PFC

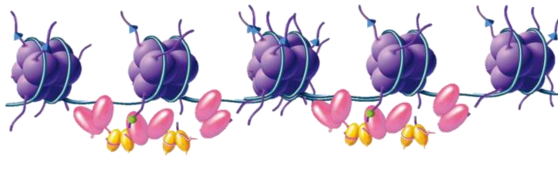
Adol THC exposure

Prelimbic (PrL) region of the Prefrontal Cortex:

- PFC subdivision during adolescence that exhibit the most pronounced developmental pruning and highest rate of spine turnover
- Layer II directly connected with amygdala, mediodorsal thalamus, nucleus accumbens

Reprogramming of the Gene Expression Landscape in Pyramidal Cortical Neurons as a Consequence of Adolescent THC Exposure

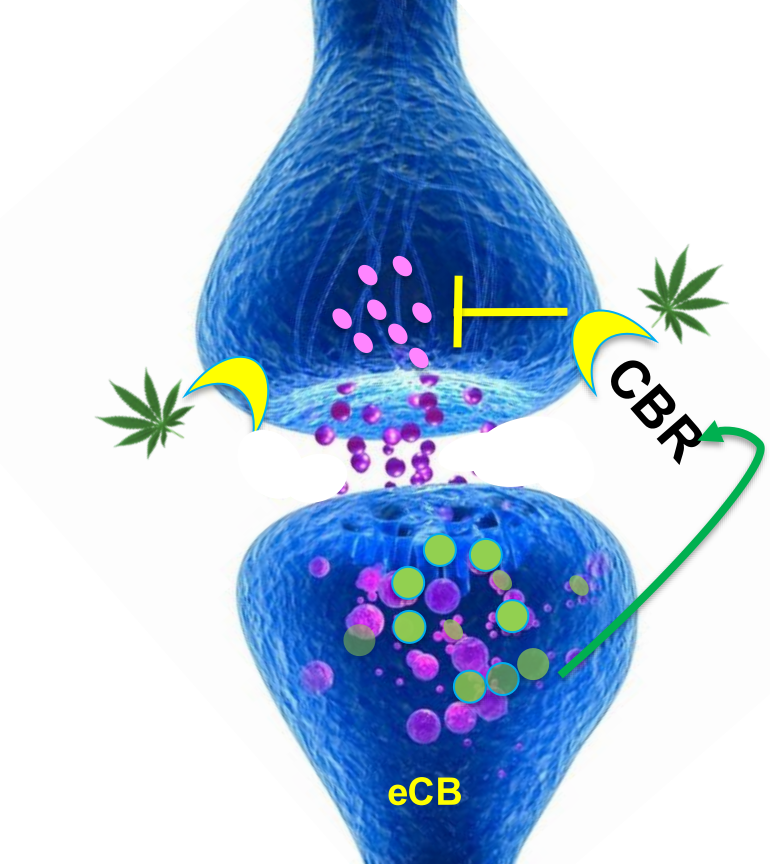




Overlap between genes differentially altered across adolescent development in THC animals and gene networks modules dysregulated in the prefrontal cortex of subjects diagnosed with schizophrenia

Kmt2a and H3K4me3 were the strongest functional association of the epigenetic gene network

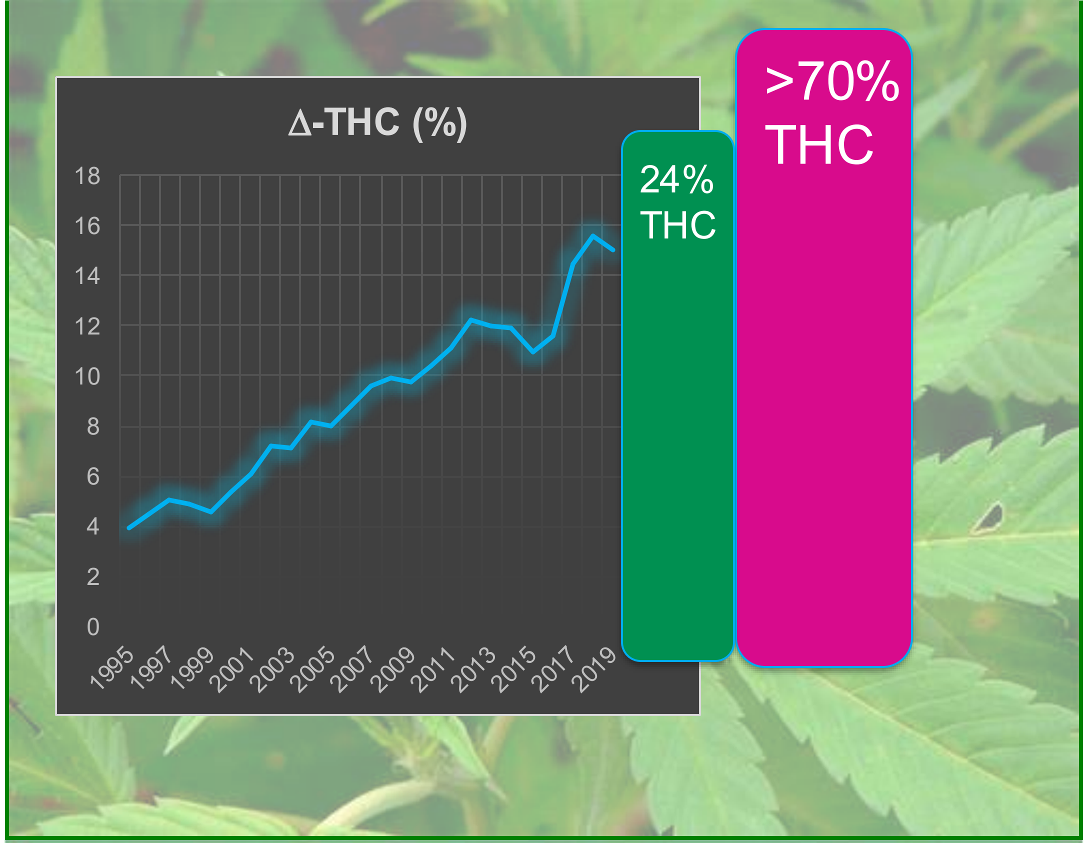
Miller et al., Molec Psychiatry, 2019



Endocannabinoid modulation

High-potency cannabis is associated with a greater risk of **psychotic symptoms, depression, anxiety, and cannabis use disorder**.

Adolescents only partially titrate their use of high-potency cannabis, which can result in the consumption of high concentrations of THC



High Potency Δ^9-THC

high-THC (low-CBD) cannabis is preferred for recreational use

eCB

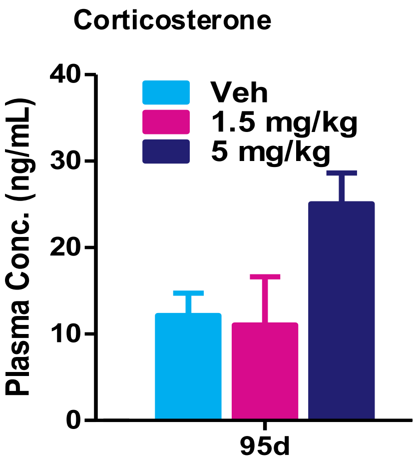
Exogenous cannabinoids

Normal synaptic regulation

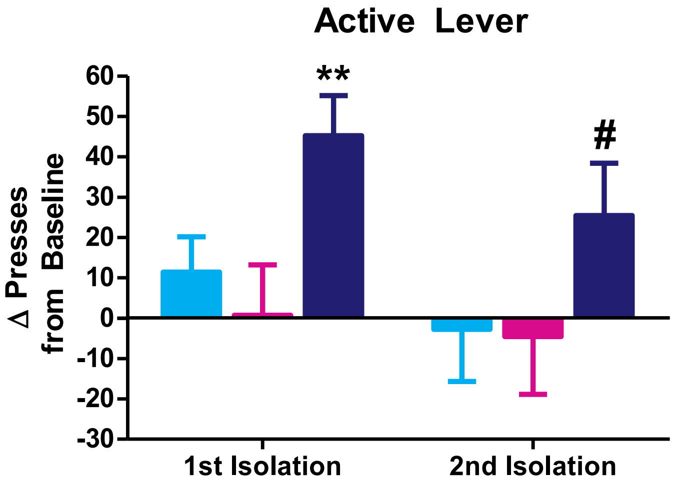
Pathological synaptic regulation

Adolescent THC Alters Stress System and Social Stress Impacts Reward Sensitivity: Dose Matters

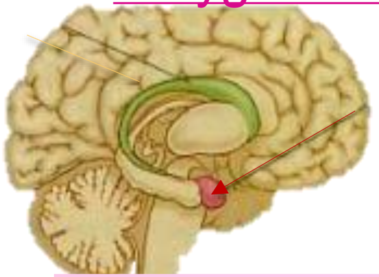
Stress hormone



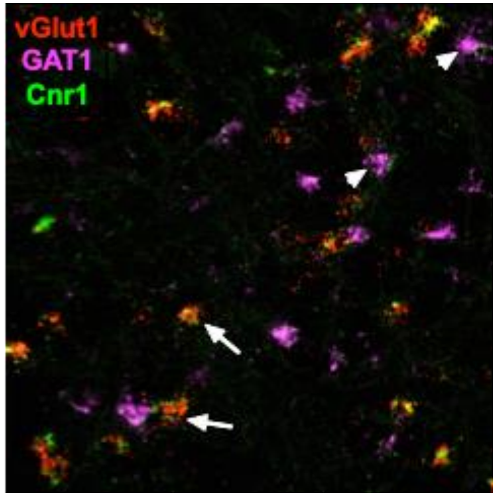
Acute isolation stress

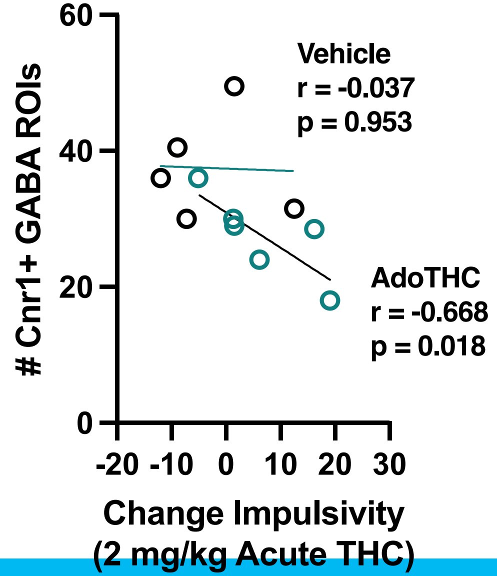


Amygdala molecular disturbances



basolateral amygdala: region critically implicated in decision making and anxiety/stress





High dose THC alters cannabinoid receptor number in the amygdala that directly relates to impulsivity

Ferland et al., JAMA Psych, 2023

Cannabis and Decision-Making Behavior

Decision making is a critical cognitive facet implicated in psychopathologies, especially addiction

Decision-making in Human Cannabis Users

ych, 2023

Re-Exposure to THC in Adulthood As a Consequence of Prior Exposure to THC During Adolescence

Adolescent THC exposure

Adult acute THC Challenge

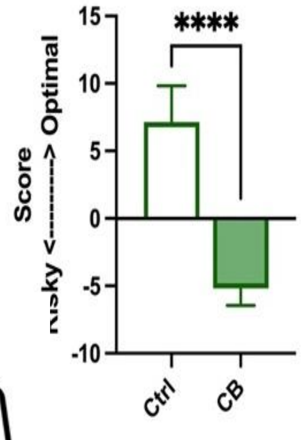
Decision-Making Behavior

Ferland et al., JAMA Psych, 2022

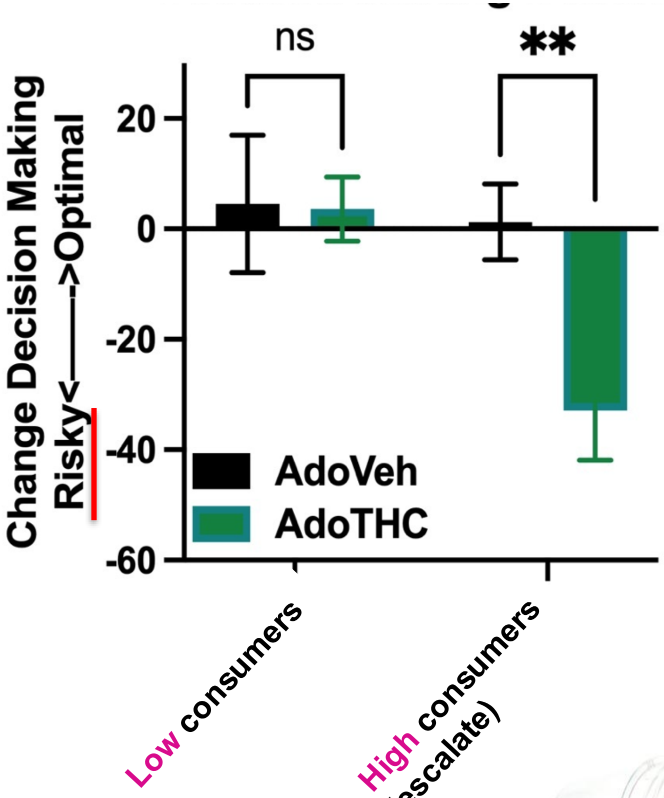
Re-Exposure to THC in Adulthood After Adolescent THC Exposure

Self-Administration

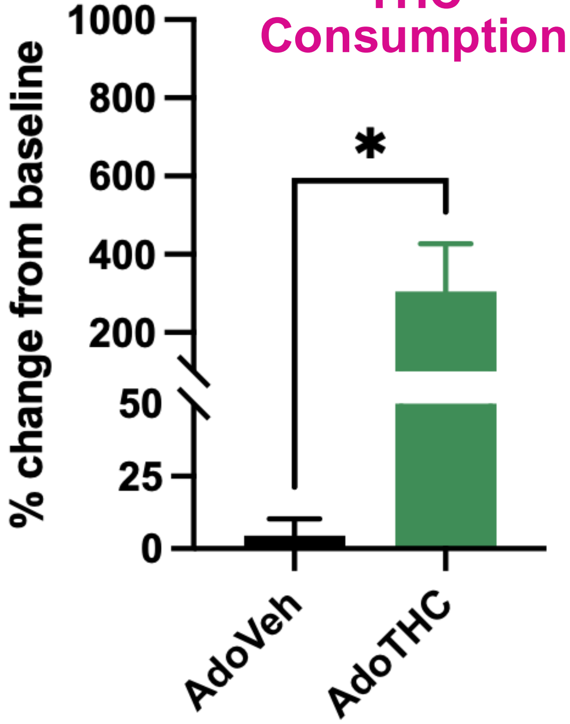
Human cannabis use disorder



Edible THC-Induced Decision-Making Deficits



Stress-Induced THC Consumption

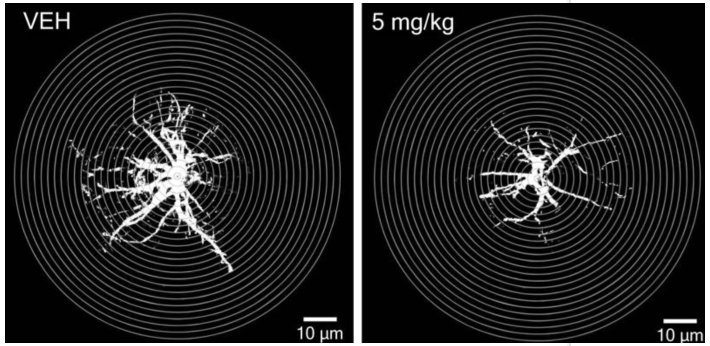


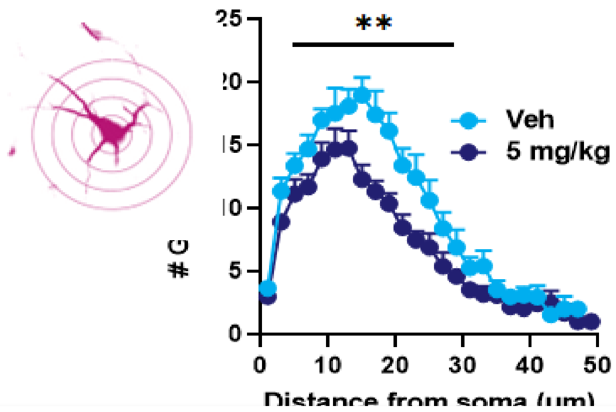
Ferland et al., JAMA Psych, 2023

Ferland, unpublished

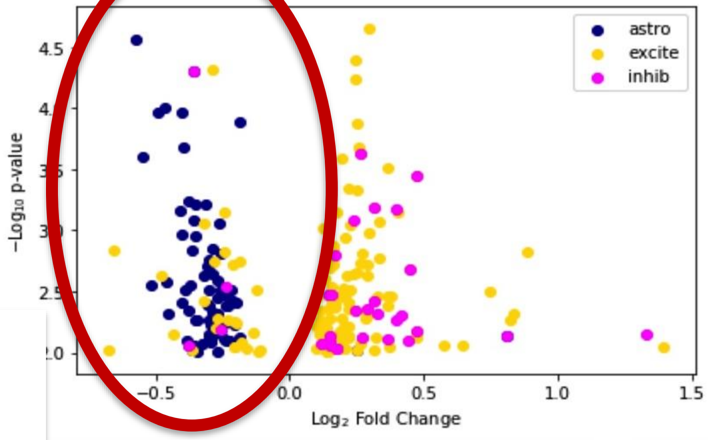
Neurobiological Underpinnings

High THC Dose — Stress Sensitivity and Astrocyte-Related Perturbation

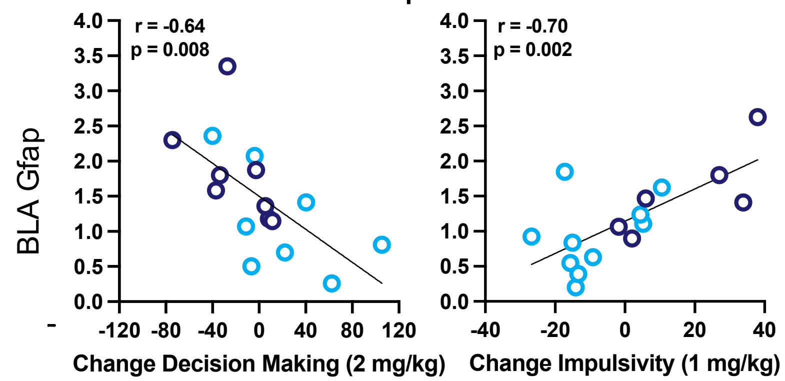


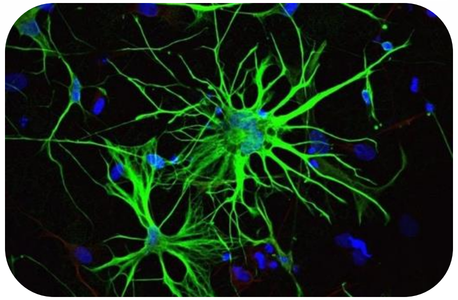


High dose THC + Stress induce marked perturbation of astrocytes in the amygdala



THC-induced alterations of astrocytes within the amygdala directly relate to <u>risky decision-making and impulsivity</u>



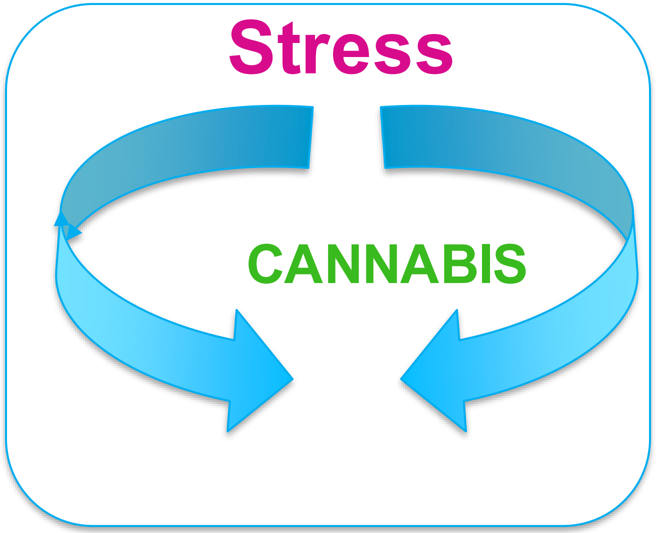


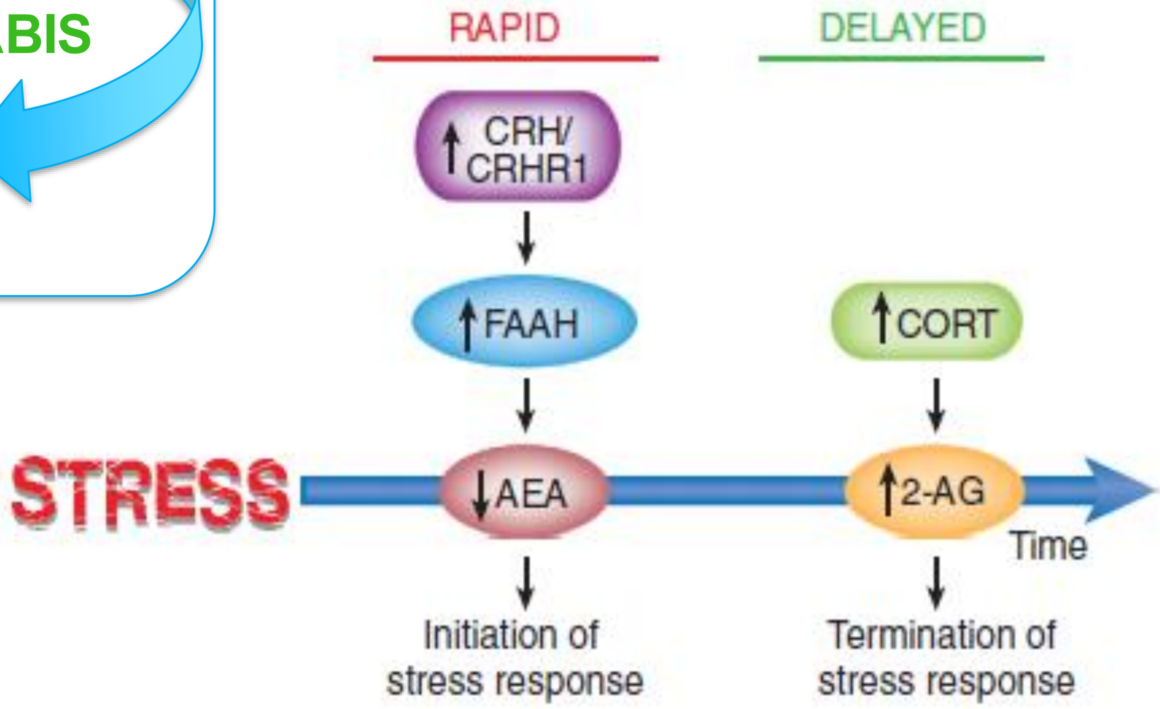
Astrocytes – critical regulation of neuronal function

Stress resulted in ~400% increase in the number of DEGs vs. non-stressed conditions

Ferland et al., Molecular Psychiatry, 2023
Ferland et al., JAMA Psychiatry, 2023

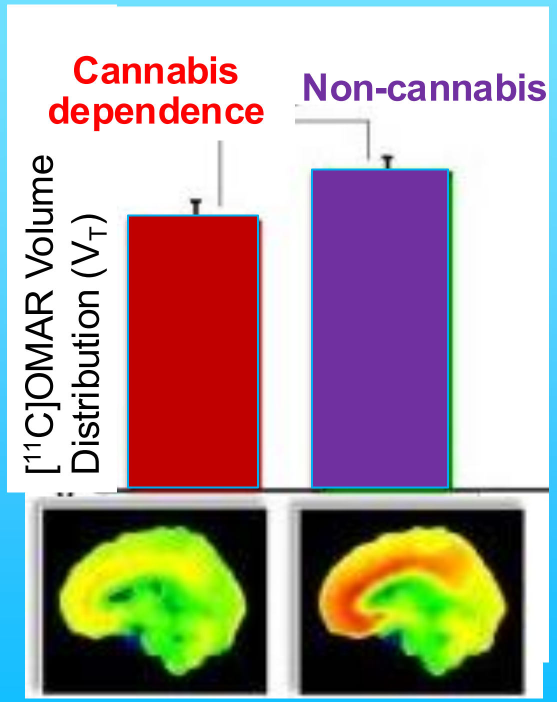
Endocannabinoid System → Inhibit Stress Response





Morena et al., 2015

Cannabinoid Receptor Availability



D'Souza et al., Biol. Psych, 2017

Frequent Cannabis use

⇩

Decreased levels of AEA and 2AG

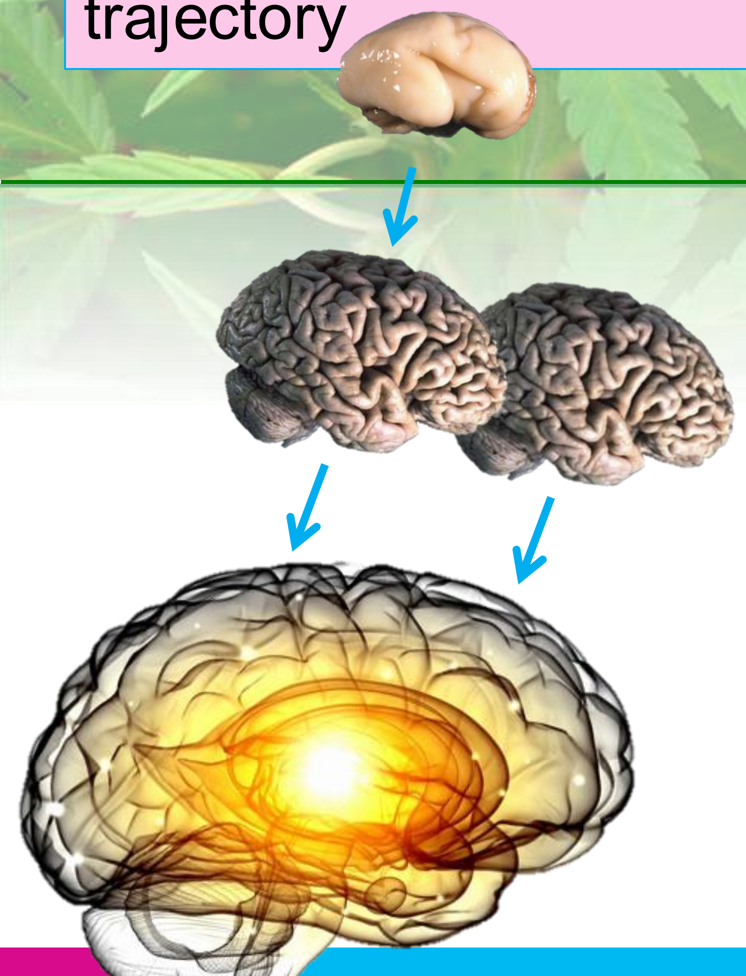
Receptor Down regulation

⇩

Poor response to stress

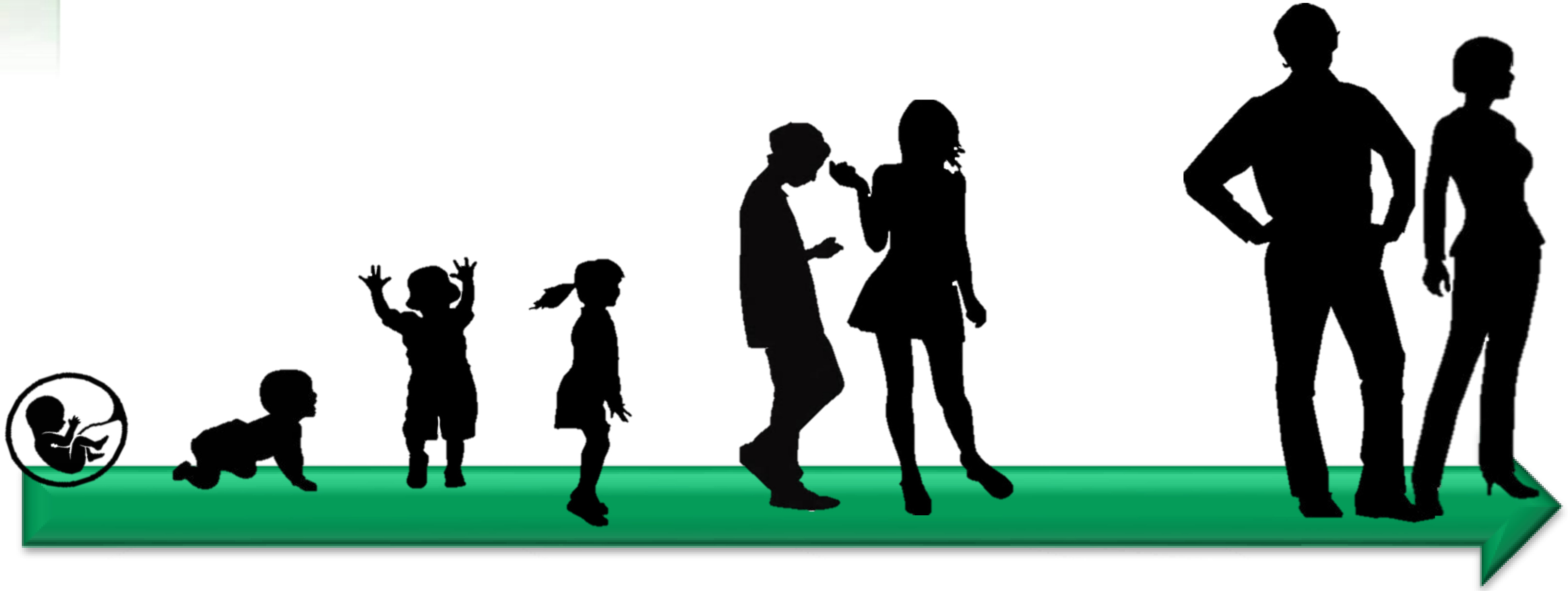
With frequent use of cannabis, there is a loss of the normal inner 'brake'

The **plasticity** of the developing brain also offers windows of opportunity for prevention and early intervention to change that trajectory

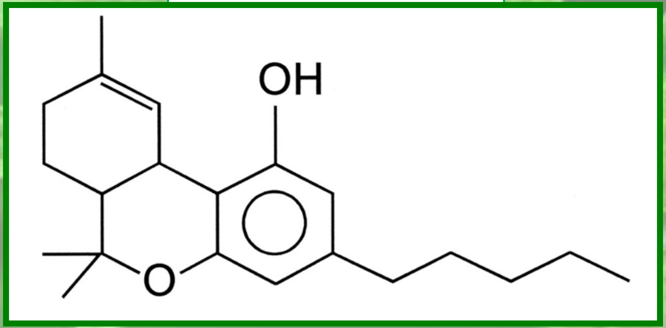


Developmental Cannabis Exposure

Potency matters
Early use matters
Frequency of use matters
Biological sex matters (but gap closing)
Behavioral traits/psychiatric comorbidity matters
Stress matters
Environment matters
Cannabinoid matters……

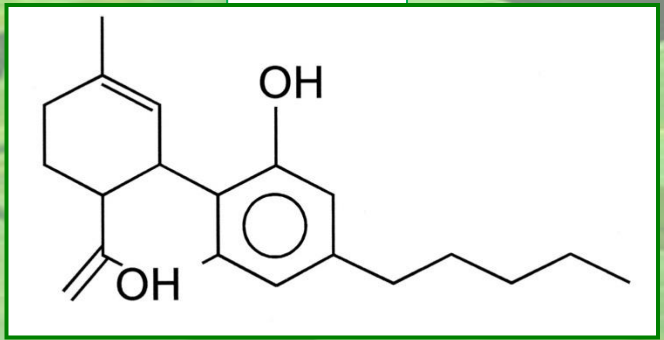


Δ^9-THC



Δ^9-tetrahydrocannabinol

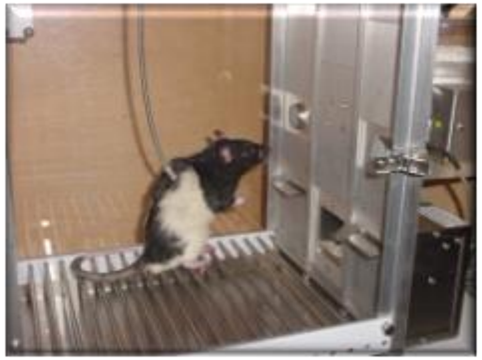
CBD



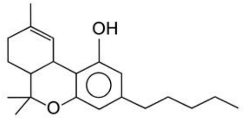
Cannabidiol

Cannabis contains over 500 chemicals including >140 cannabinoids which have a greater or lesser degree of psycho-pharmaco-activity

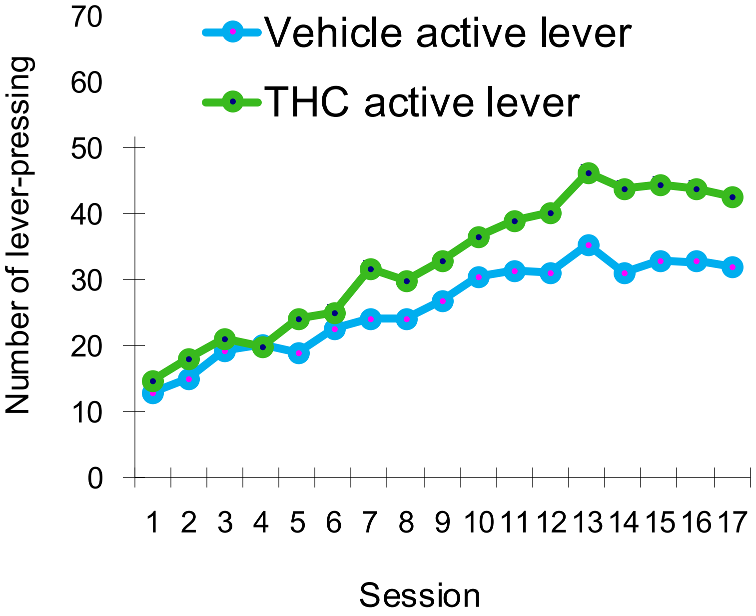
Distinct Effects of THC and CBD On Heroin Vulnerability



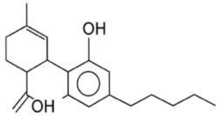
Δ^9-THC



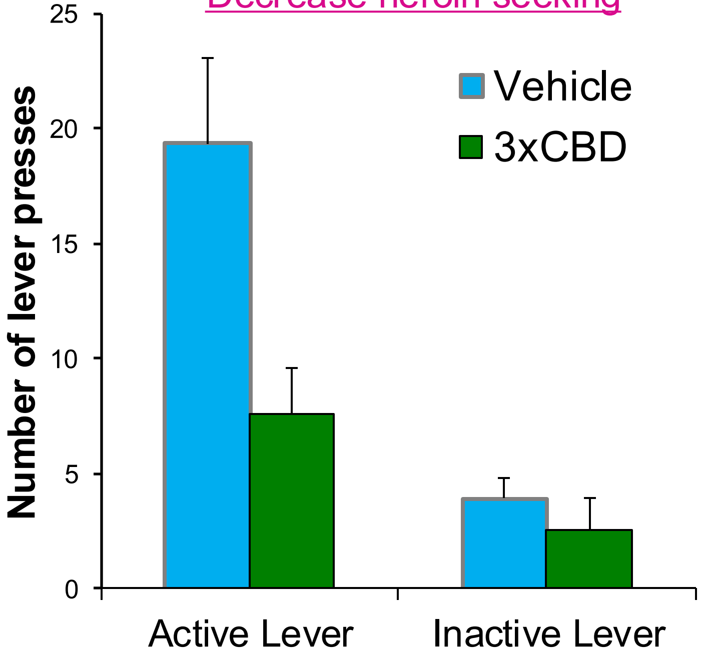
Enhance heroin self-adminstration



CBD



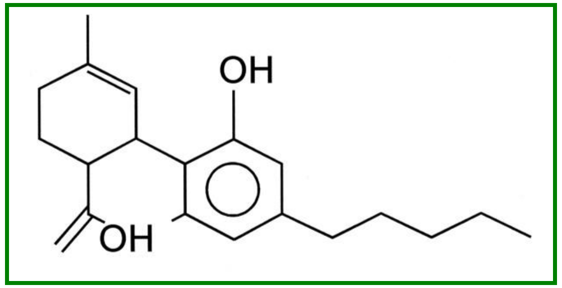
Decrease heroin seeking



Ren et al., J Neuroscience, 2009

Cannabidiol as Potential Treatment Intervention for Opioid Relapse: Double-Blinded Placebo Control Study

Double-blind, Randomized, Placebo-Controlled: Participants with Opioid Use Disorder

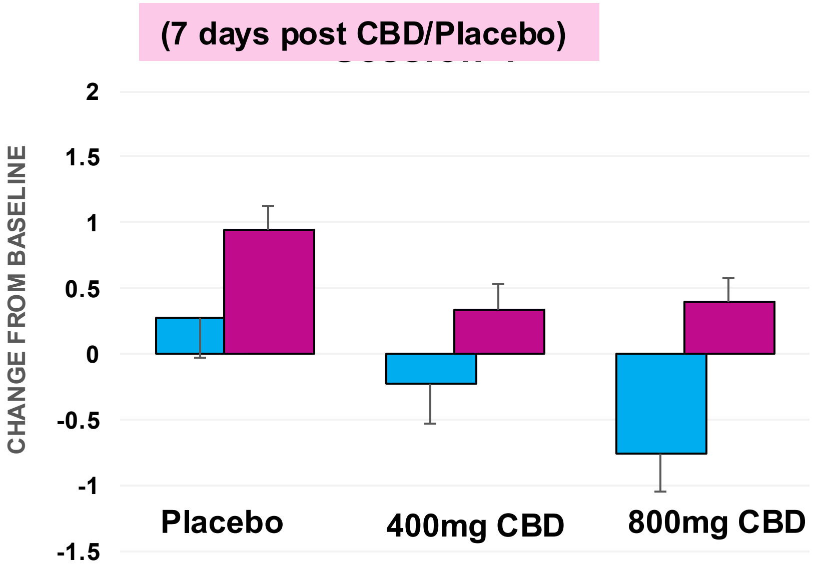


Prescreen tests	Session 1	Session 2	Session 3	Session 4
	Day 1	Day 2	Day 3	Day 10
	•CBD/PI •Cue tests	•Cue tests •CBD/PI	•CBD/PI •Cognitive tests	•Cue tests

CBD: 400 and 800 mg
Placebo

Cue-Induced Effects: Craving

VAS-C

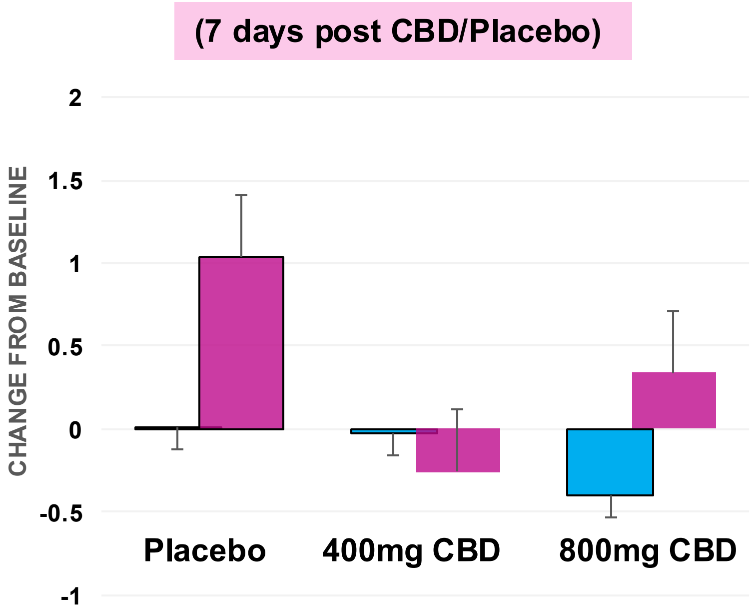


VAS, Visual analog scale

Hurd et al., Am J Psychiatry, 2019

Cue-Induced Effects: Anxiety

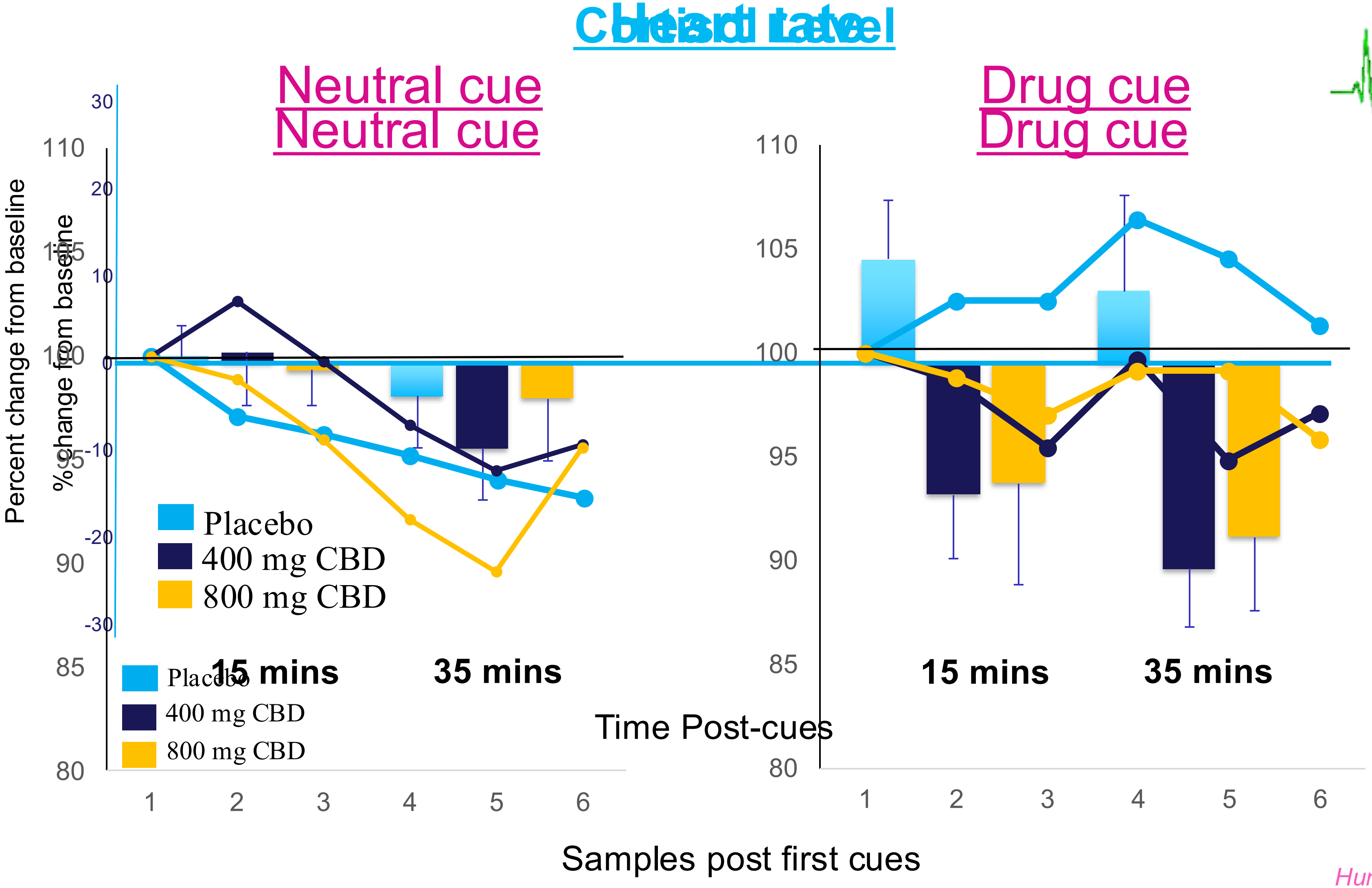
VAS-A

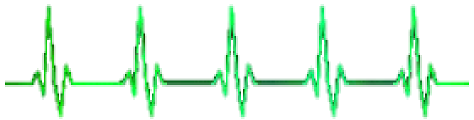


VAS, Visual analog scale

Hurd et al., Am J Psychiatry, 2019

CBD Reduces Cue-induced Physiological Measures of Stress





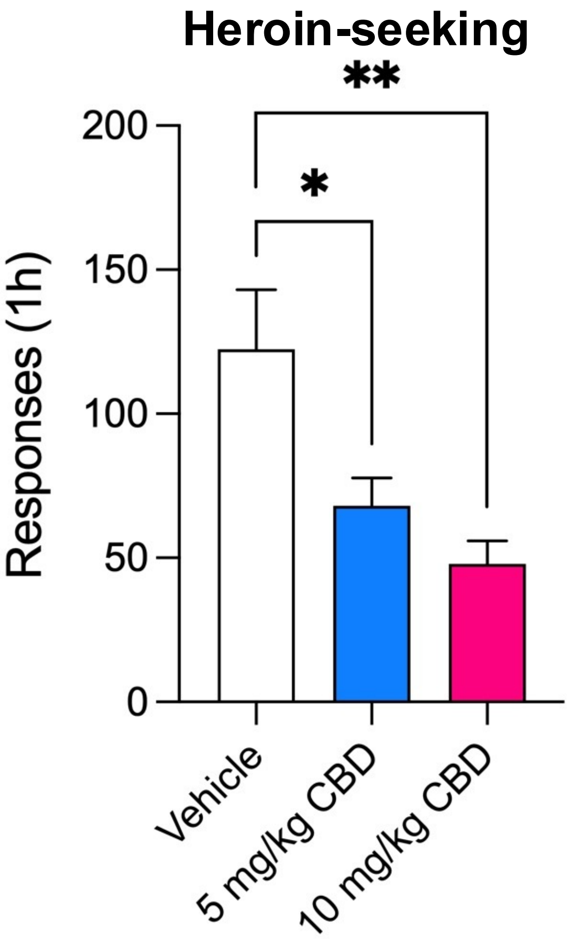
Hurd et al., Am J Psychiatry, 2019

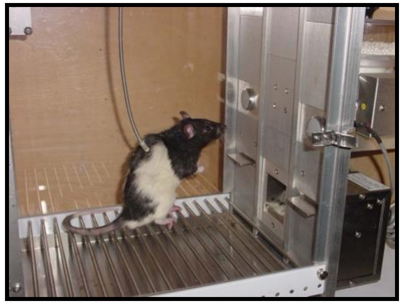
CBD Reduces Cue-Induced Drug-Seeking and Anxiety-like Behavior

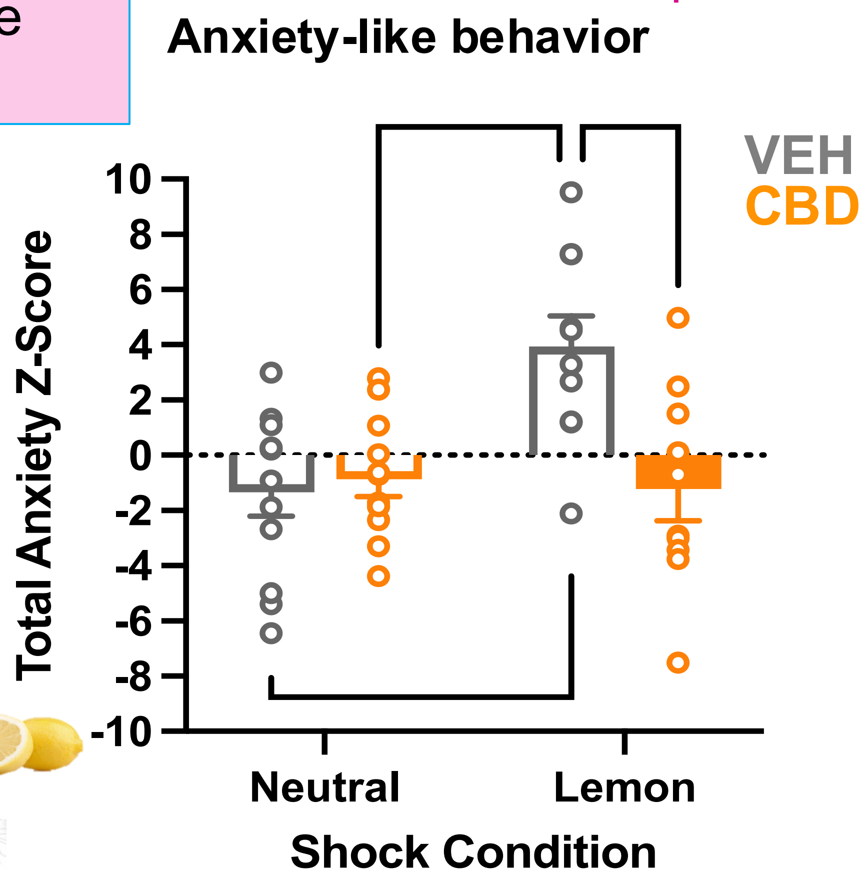
Alex Chisholm

Jacqueline Ferland

CBD did not affect behavior in animals exposed to neutral cue or encoding of the cue behavioral response.







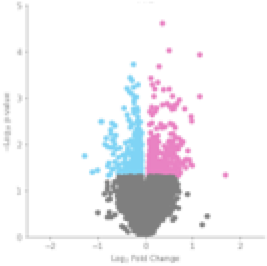
Chisholm et al., unpublished

Ferland et al., Mol Psychiatry, 2025

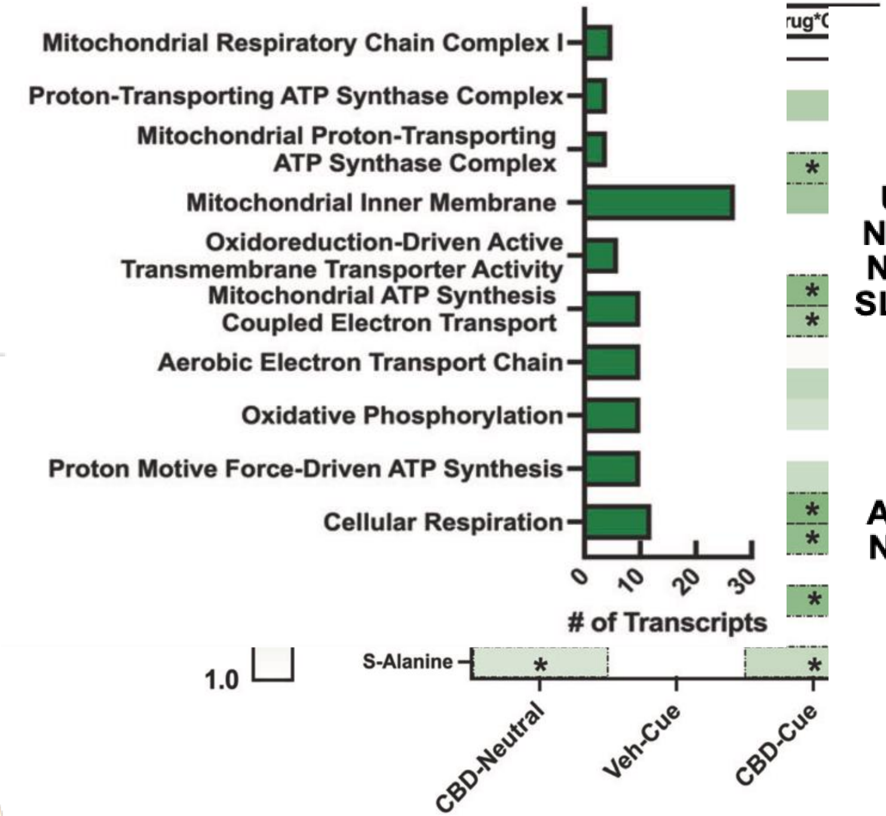
CBD Normalizes or Reverses Neural Networks in the Accumbens Altered by Anxiety Phenotypes

Katie Lynch

Jacqueline Ferland

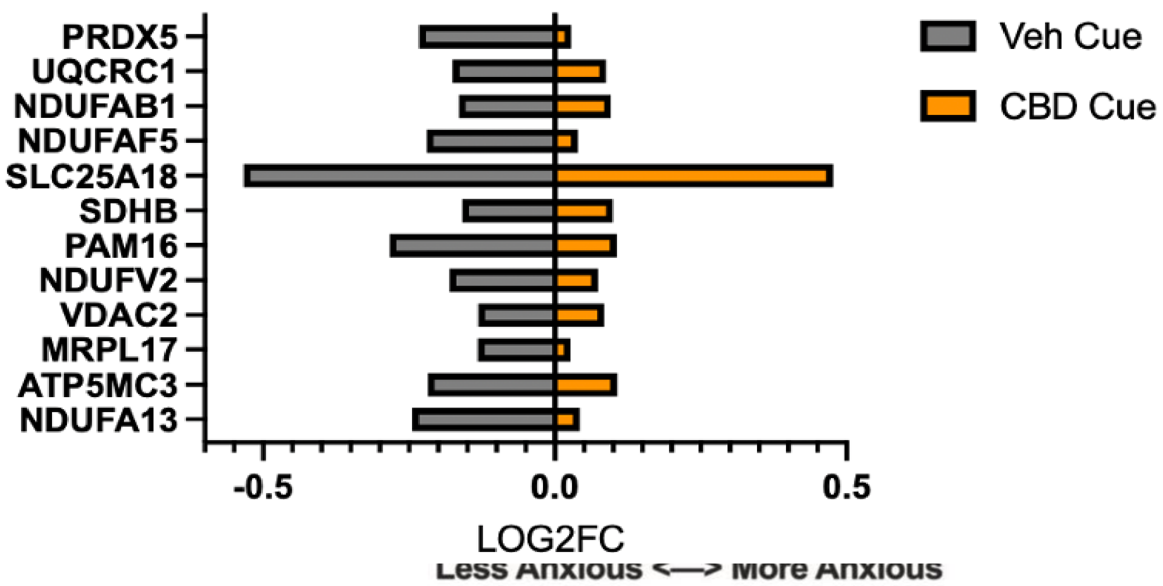


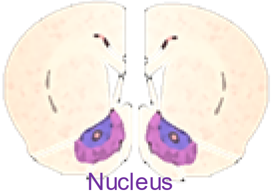
Anxiety-Related c1_5 Network Ontology Enrichment



Lipidomics

Mitochondrial Respiration Transcripts





Nucleus accumbens

Gene modules that correlated with anxiety-like behavior involved mitochondria function

Ferland et al., Mol Psychiatry, 2025

CBD Normalizes or Reverses Neural Networks in the Accumbens Altered by Heroin-Seeking and Anxiety Phenotypes

Alex Chisholm

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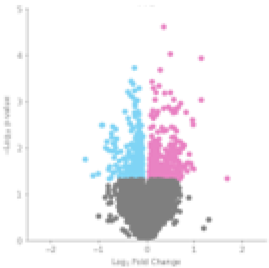


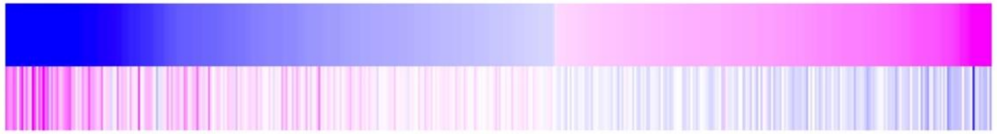
Heroin seeking

Anxiety

Heroin

Veh

CBD

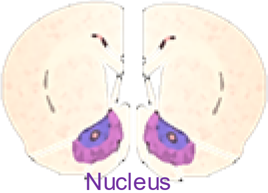


Anxiety

Veh

CBD

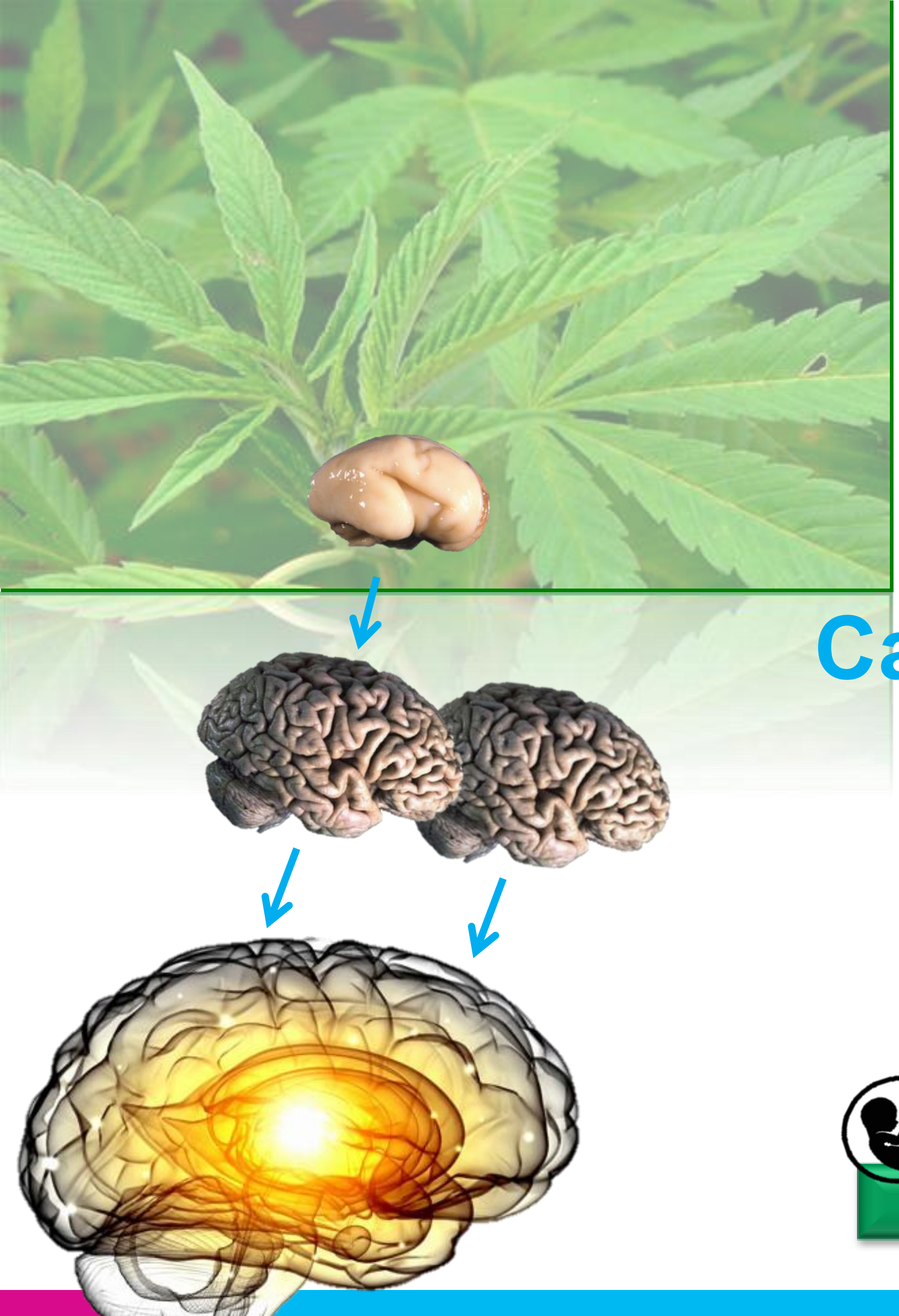
RNA-sequencing

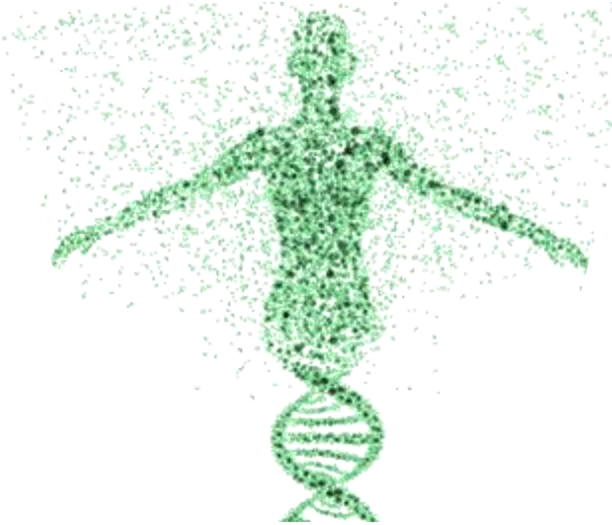


Shared genes/biological processes

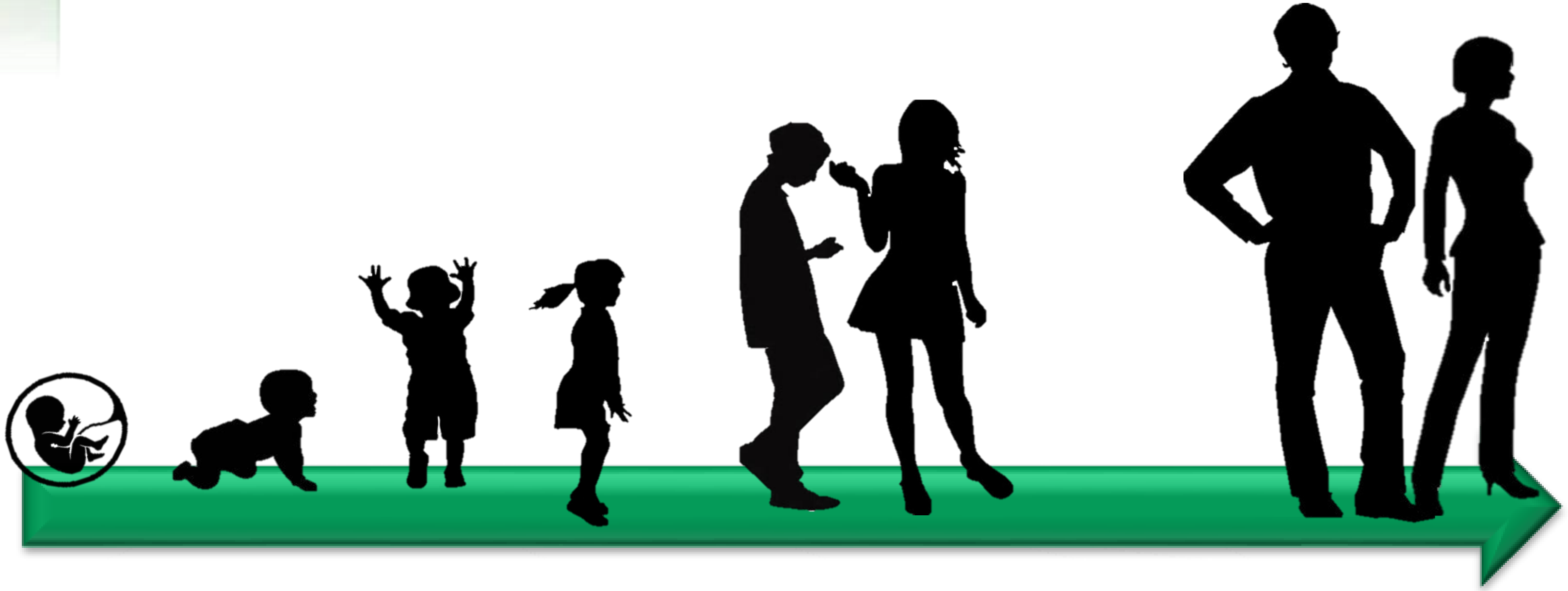
Chisholm et al., unpublished

Ferland et al., unpublished





Cannabis = Cannabinoid Exposure




NIDA
Clinical Research Team
Alex Chisholm
Teesta Naskar
Konrad Drabowski
Diana Municchi
Jacqueline Ferland
Yoko Nomura
Jeremy Sherman
Kion Winston
Katie Lynch
Andre Toussaint
Chinara Tate
Jasper Van Oort
Gabrielle Zbaeren
Pavan Poojar
Joseph Landry
James Callens
Pamela Comlan
Daniel Garcia
Maria Purcell
Chris Kudrich
Marjory Paul
Burooj Mahmood
George Gardne
(Maria) Eli Savoia
Adam Dawoud
Sam Cartwright
Alfonso Brea Guerrero
Hanish Kodali
Ashanta Carter
Jenee Wilson
Olusegun (Sheg
Akinwolere