



*“L’esposizione prenatale al THC
induce endofenotipi simil-
psichiatrici nella prole”*

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DEGLI STUDI
DI CAGLIARI



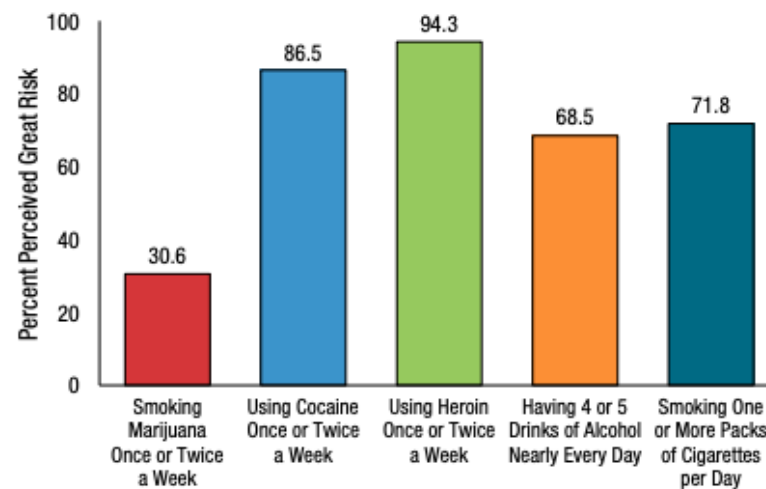
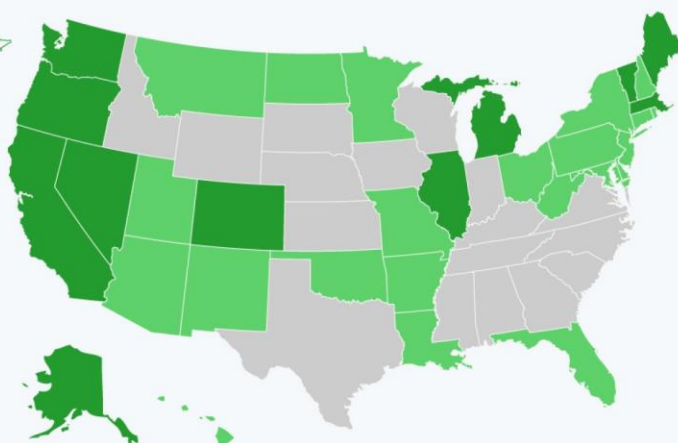
Which States Have Legalized Marijuana?

Laws on recreational and medical marijuana use in the U.S.*

■ Legalized for recreational & medical use ■ Medical use only

Legalized recreational marijuana

Alaska
California
Colorado
District of Columbia
Illinois
Maine
Massachusetts
Michigan
Nevada
Oregon
Vermont
Washington



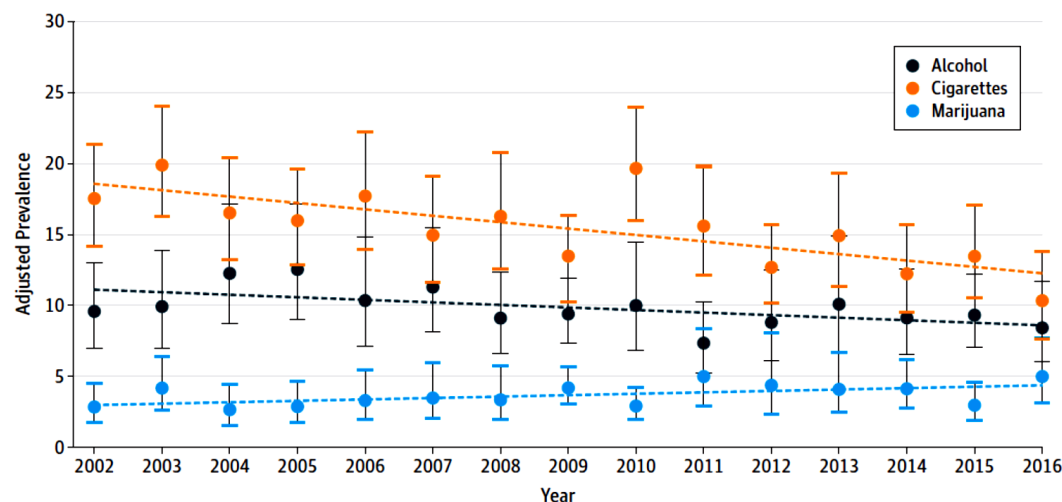
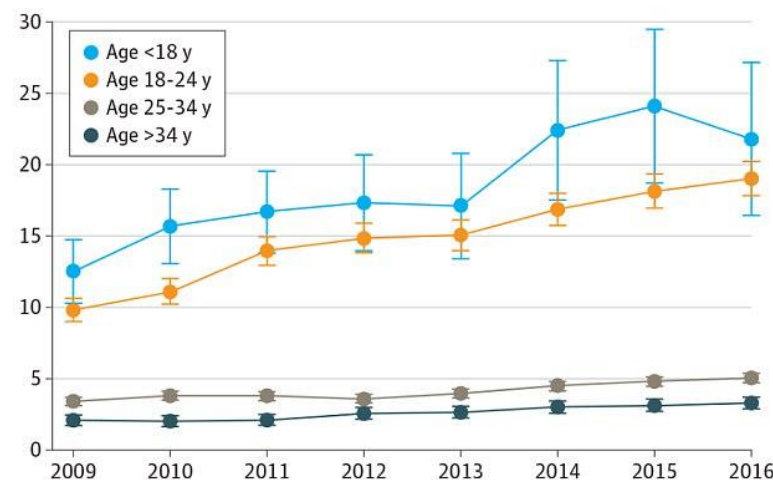
National Survey on Drug Use and Health (December 20, 2019)



- ✓ Cannabis use **increased** among pregnant women in the United States
- ✓ Differently from alcohol and tobacco, prenatal cannabis use **has not decreased**



Agrawal et al., 2019, *JAMA pediatrics*;
Young-Wolf et al. *JAMA*, 2019; Brown
et al., 2017, *JAMA*



- ✓ Most of cannabis dispensaries (including medical) recommends (on personal opinion) cannabis products for morning sickness during pregnancy

Obstet Gynecol. 2018 June ; 131(6): 1031–1038. doi:10.1097/AOG.0000000000002619.

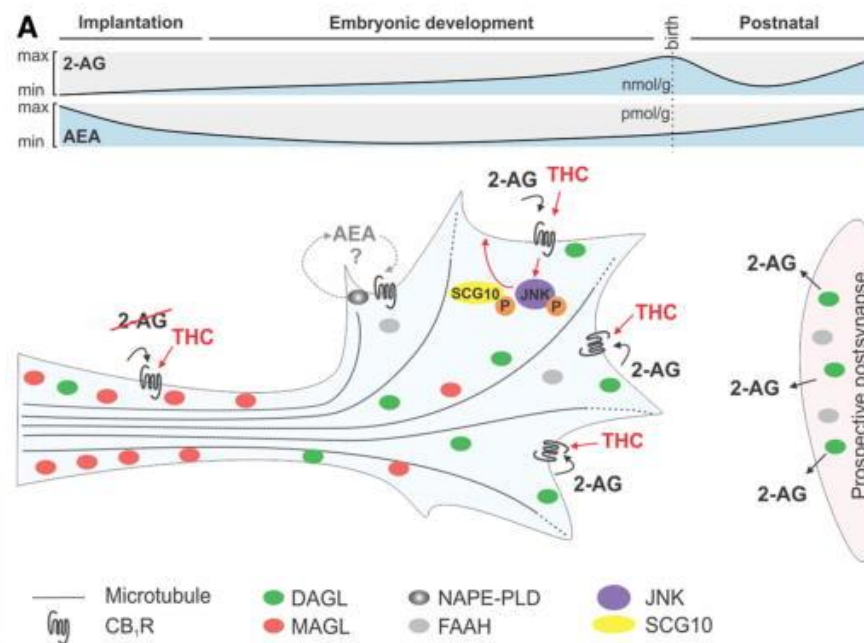
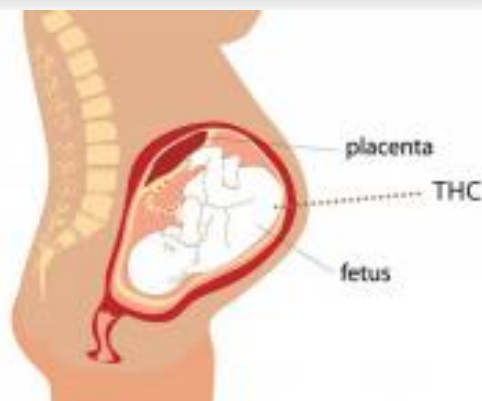
Recommendations From Cannabis Dispensaries About First-Trimester Cannabis Use

Betsy Dickson, MD¹, Chanel Mansfield, MPH¹, Maryam Guiahi, MD, MSc¹, Amanda A. Allshouse, MS², Laura M. Borgelt, PharmD¹, Jeanelle Sheeder, PhD¹, Robert M. Silver, MD³ and Torri D. Metz, MD, MS^{1,4}

Results: of the 400 dispensaries contacted, The majority, 69% recommended treatment of morning sickness with cannabis products



- ✓ CB1R are present at the earliest phases of pregnancy and involved in embryo implantation, embryonic growth and neuronal development
- ✓ Within the CNS They play a crucial role in dictating the phenotypic differentiation of neurons and control the establishment of synaptic communication



Belue et al., *Neurotoxicology and Teratology*
1995; Harkany et al., 2007, *TIPS*

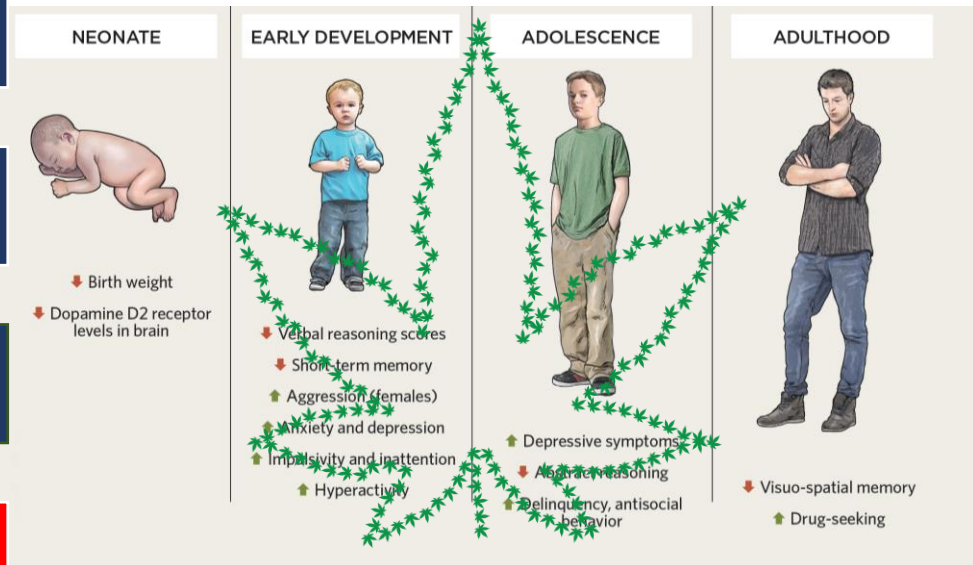
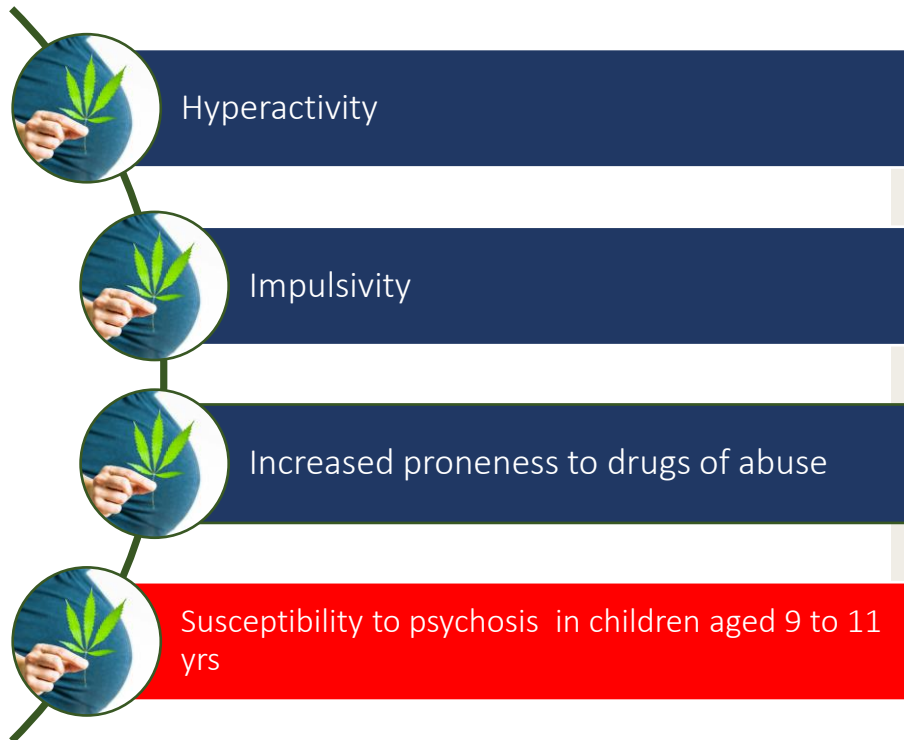
Cannabis and the Developing Brain: Insights into Its Long-Lasting Effects

Yasmin L. Hurd, Olivier J. Manzoni, Mikhail V. Pletnikov, Francis S. Lee, Sagnik Bhattacharyya, and Miriam Melis

Journal of Neuroscience 16 October 2019, 39 (42) 8250-8258; DOI: <https://doi.org/10.1523/JNEUROSCI.1165-19.2019>

JNeurosci
THE JOURNAL OF NEUROSCIENCE

- ✓ The importance of EC signaling during neuronal development is underscored by 4 longitudinal studies long-term effects on maternal cannabis use in humans



(Fine et al., 2019, 2020; JAMA; Boljuis, 2018, ACTA PS)

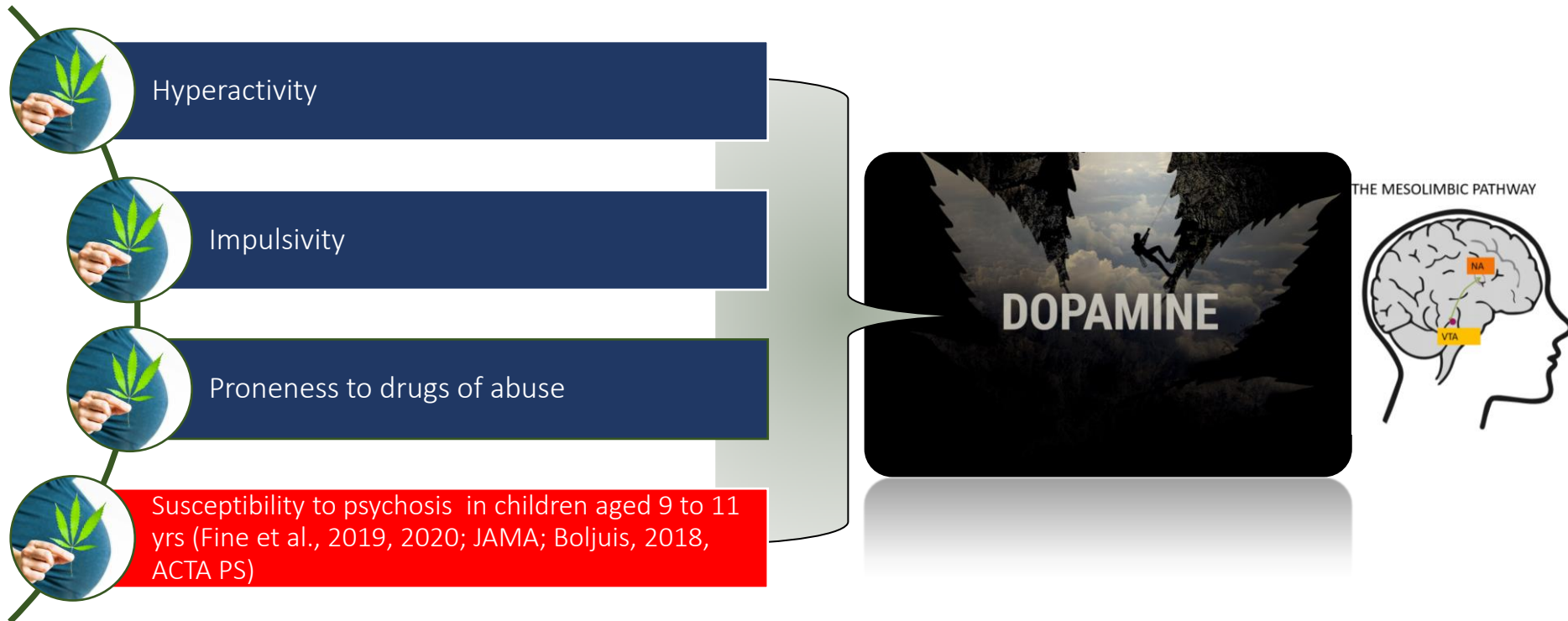
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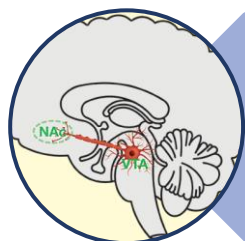
✓ All these neuropsychiatric outcomes are tied to a dysfunction of dopaminergic signaling



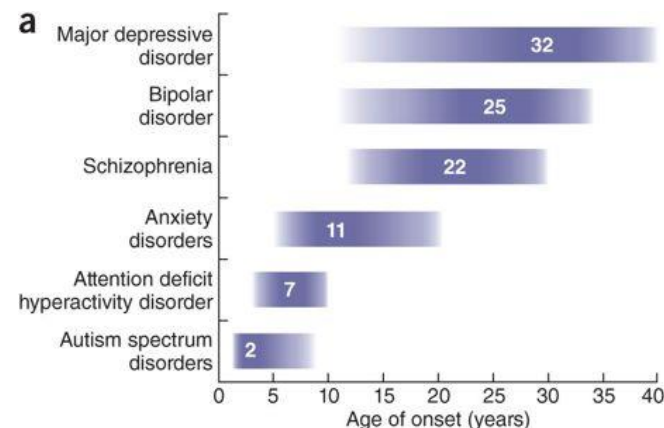
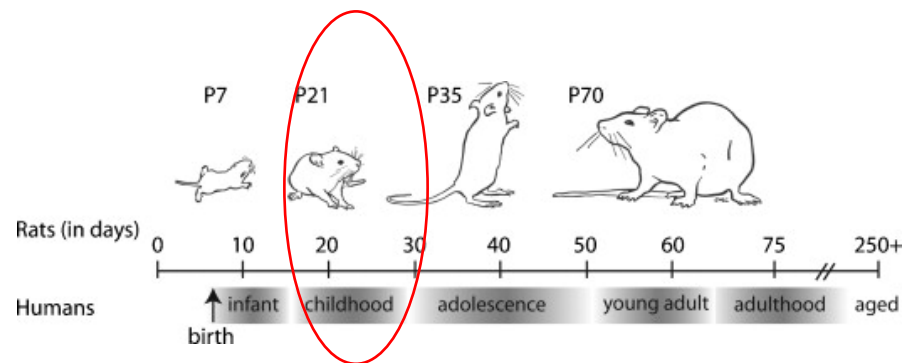
Aims of the study



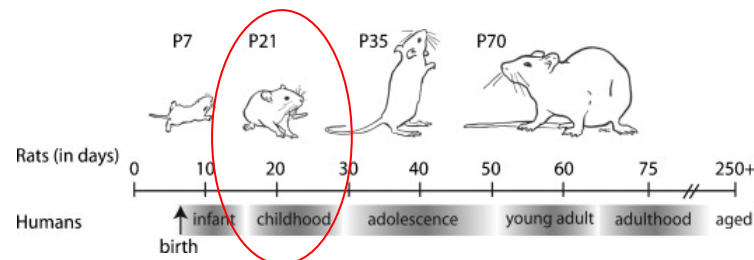
To characterize neurobehavioral endophenotypes of PCE offspring



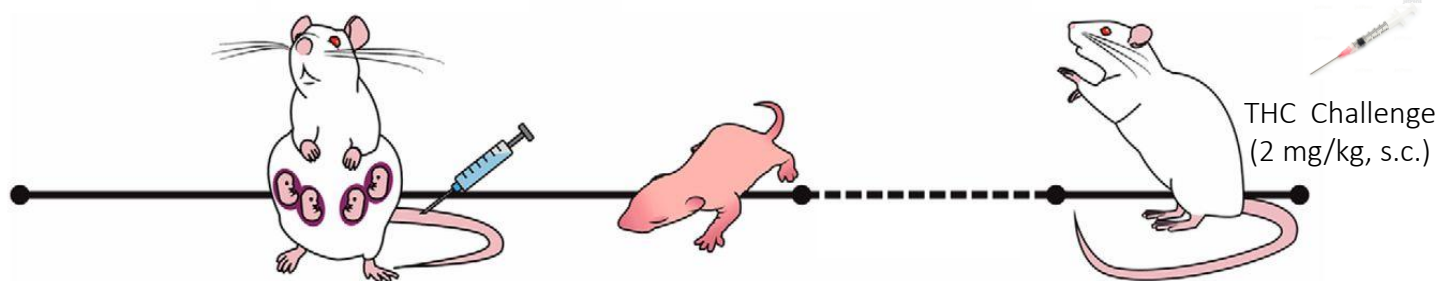
To investigate dopamine neurons excitability and transmission of the mesolimbic system



Experimental Design



A GD0 Start of pregnancy GD5-GND-20 Maternal treatment PND1/PND21 Maternal Behavior PND15-PND28 In vivo and ex-vivo analyses

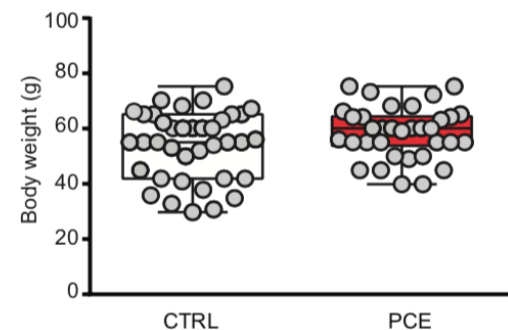
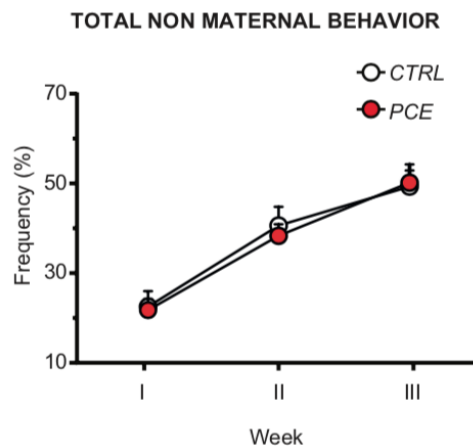
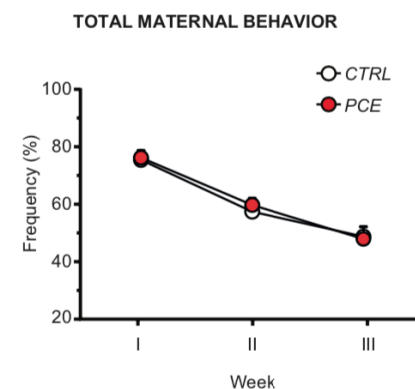
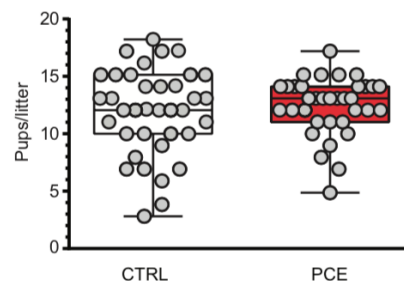
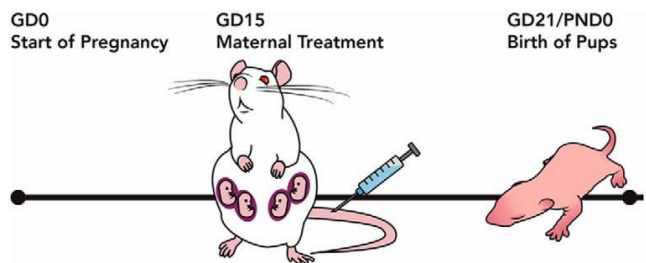


Prenatal THC exposure
(2 mg/kg, subcutaneously, once daily)




- ✓ DA-dependent behavior (PPI/OF/Bridge)
- ✓ Electrophysiological recordings in the VTA
- ✓ Neurochemical DA measures in Nac
- ✓ Immunostaining, confocal and Super Resolution microscopy

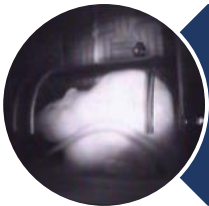
THC does not modify maternal behavior



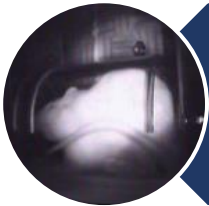
THC challenge induces psychotic-like (endo)phenotypes



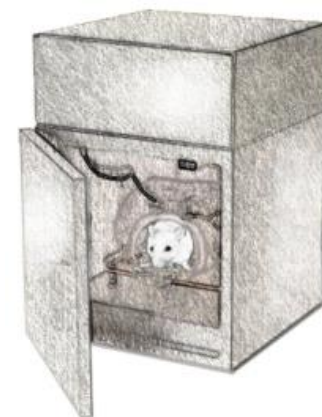
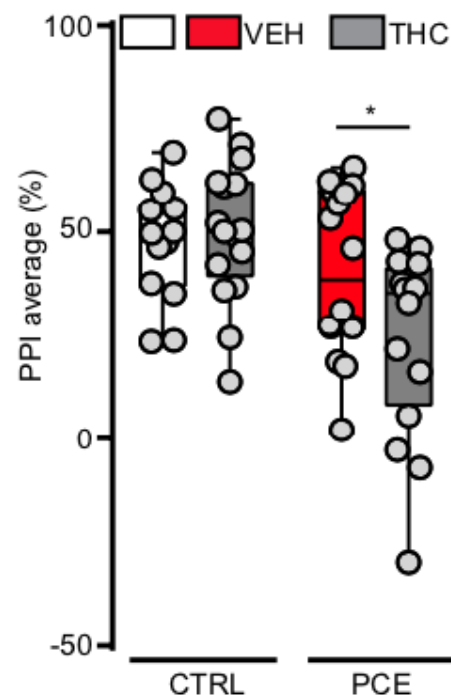
Deficits of PPI are observed in patients affected by schizophrenia
(Face Validity)



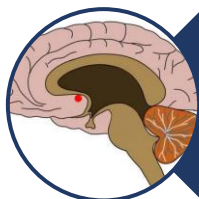
The brain structures regulate PPI overlap with the neurobiology of this disease
(Construct Validity)



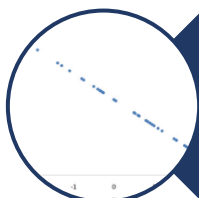
PPI loss can be reversed by antipsychotics
(Predictive Validity)



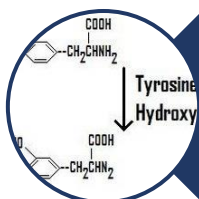
PPI deficits induced by THC are DA-dependent



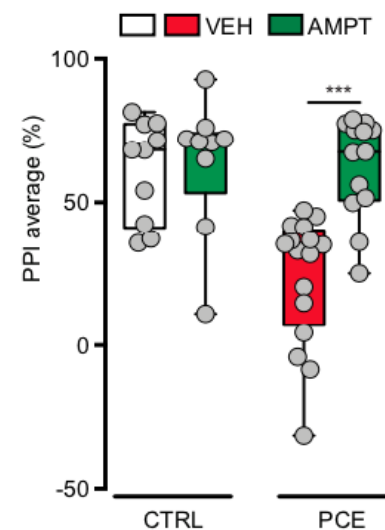
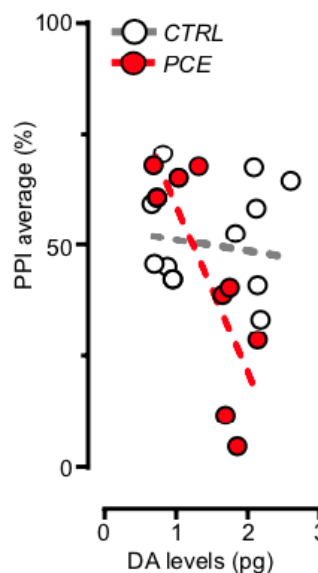
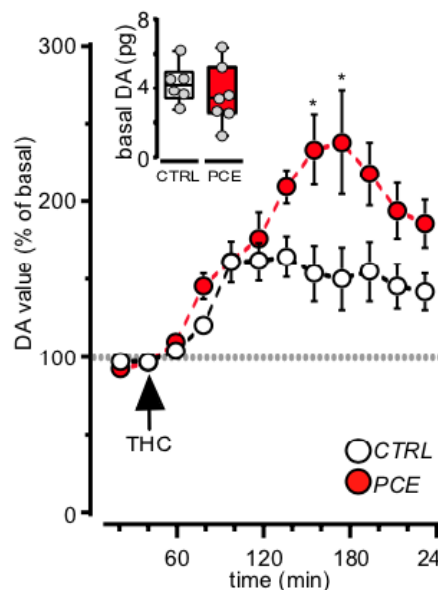
THC elicits larger DA increase in the nAcc



Accumbal DA levels inversely correlate with PPI values



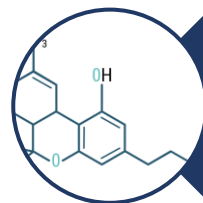
AMPT reverses PPI deficits



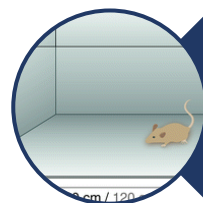
THC challenge induces hyperlocomotion



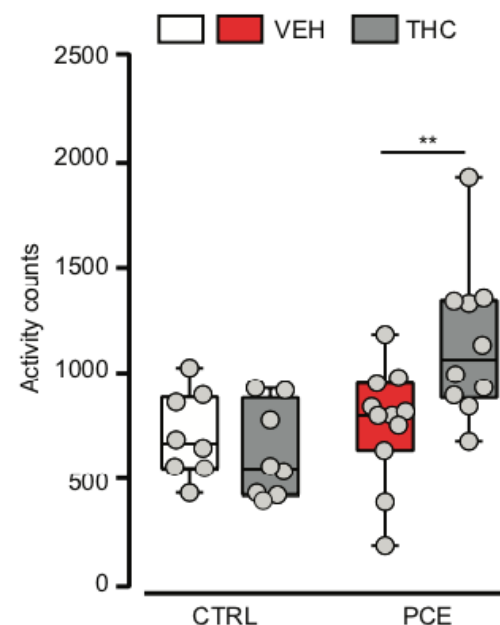
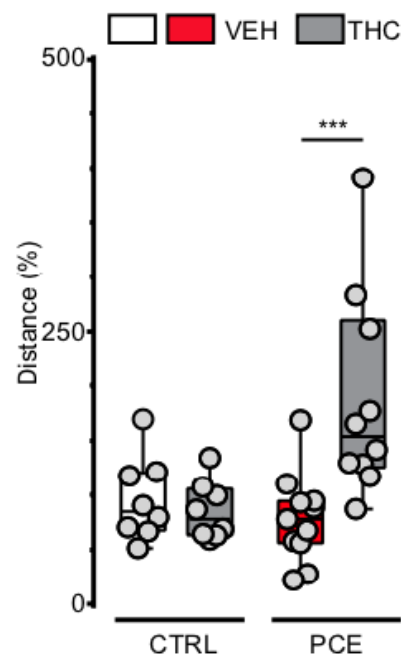
No differences are observed between progenies



THC does not modify motor function in CTRL group

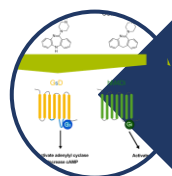


THC elicits hyperlocomotion in PCE offspring

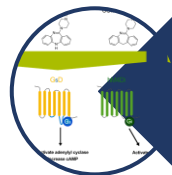




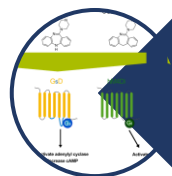
THC-induced hyperlocomotion is VTA-dependent



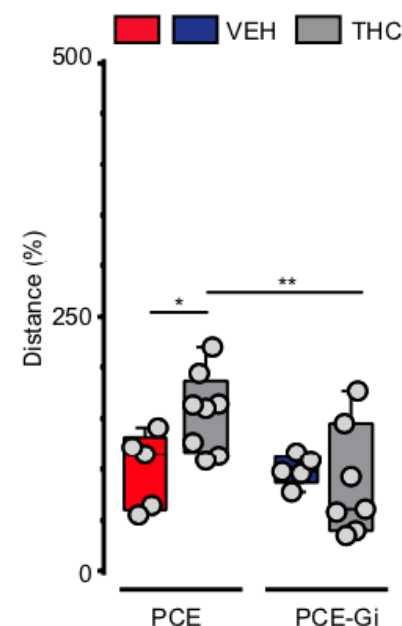
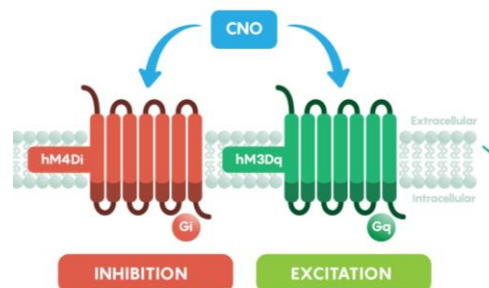
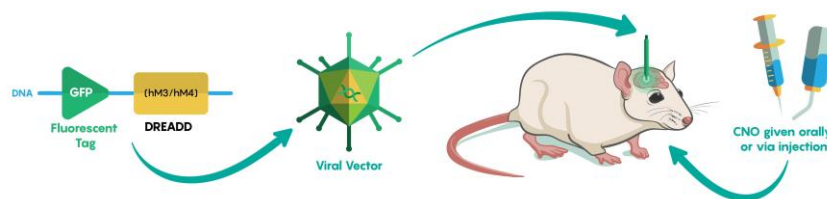
DREADD (designer receptors exclusively activated by designer drugs)



Gi-coupled hM4Di susceptible to CNO

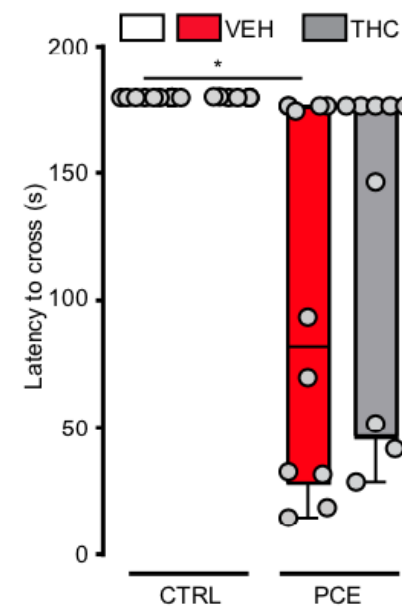
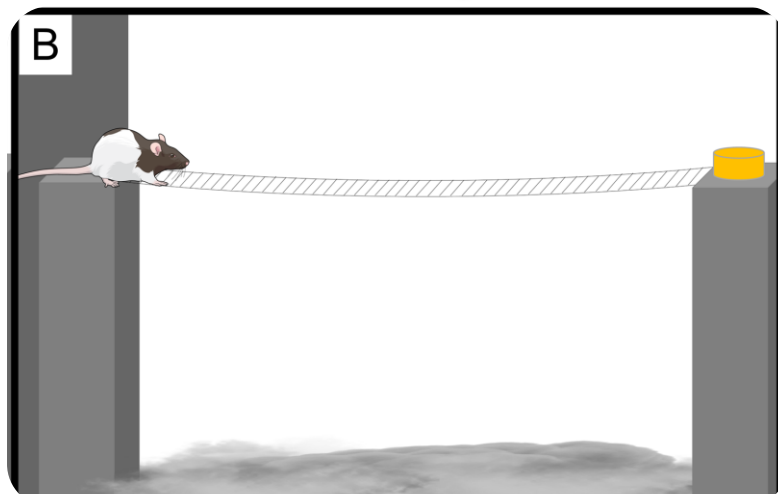


Stimulation counteracts the paradoxical hyperlocomotion elicited by THC in PCE offspring



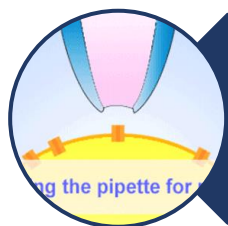
PCE offspring exhibits risk-taking behaviors

Wire Beam Bridge Test

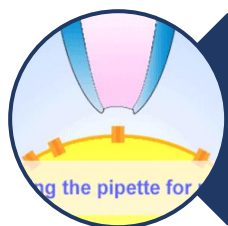




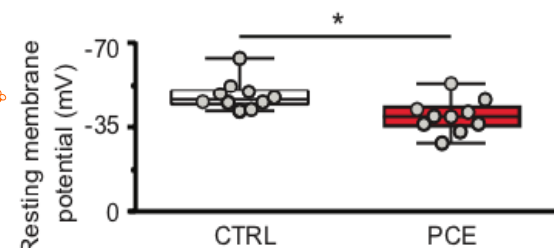
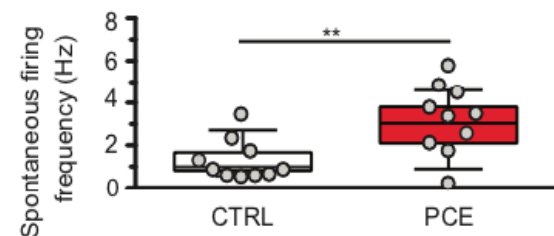
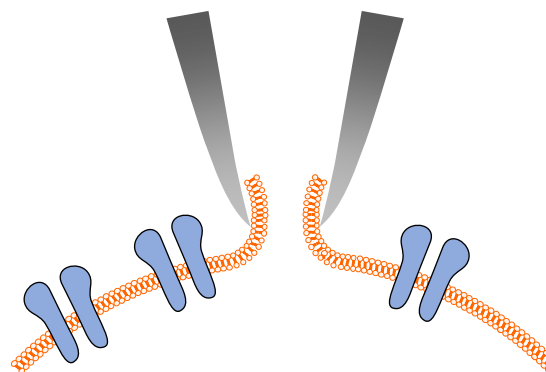
PCE-DA cells are spontaneously more active



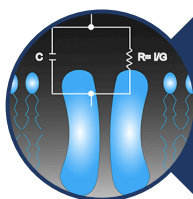
PCE DA neurons spontaneously fired at higher frequency



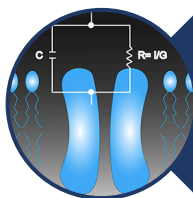
They displayed depolarized resting membrane potentials



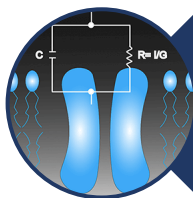
PCE increases DA neuron excitability



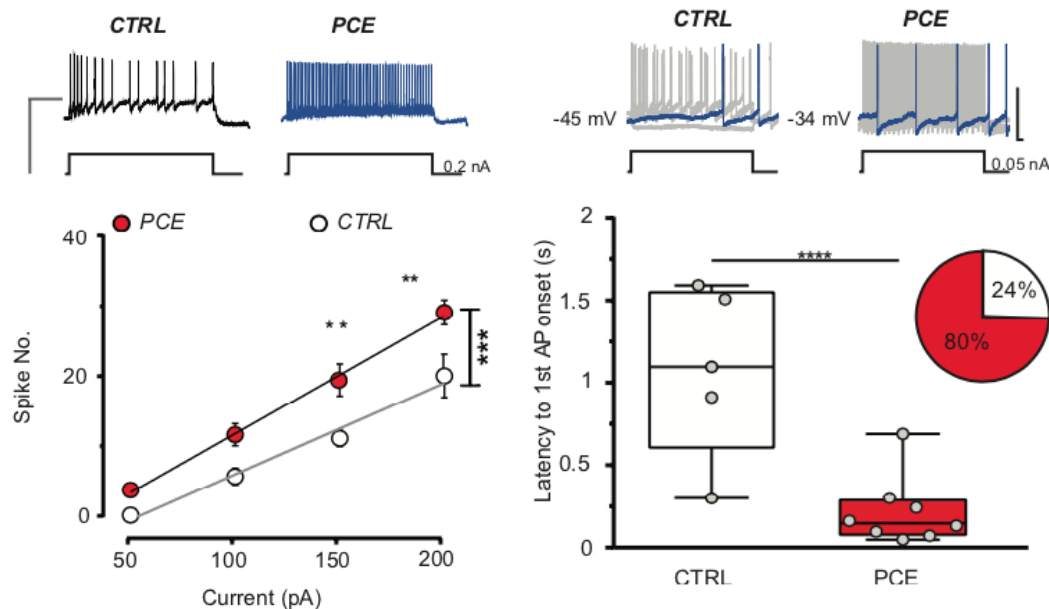
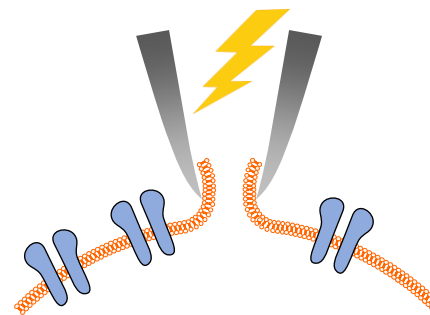
High maximum spiking frequencies in response to somatically injected currents



Reduced latency to action potential onset, which is the time needed for the first spike appearance in response to the smallest current injection



A larger proportion of PCE DA neurons fired action potentials



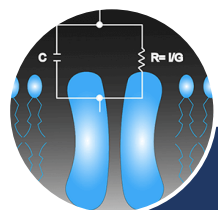


PCE modify DA cell response to THC

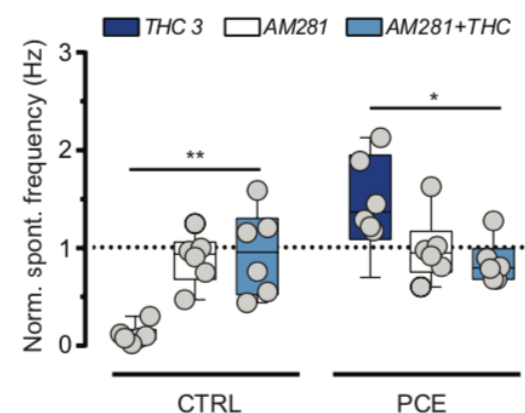
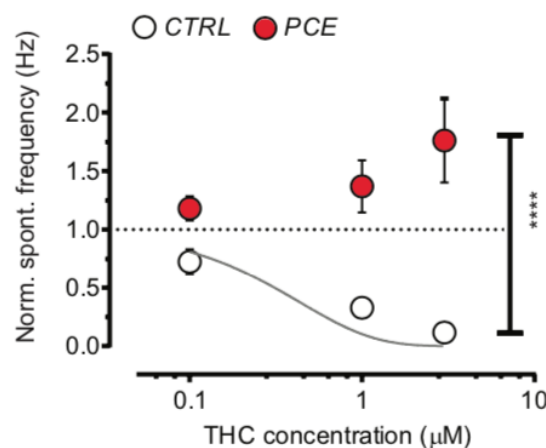
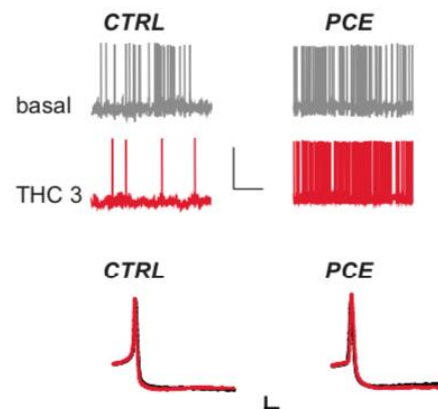
Activity



Spontaneous



Evoked

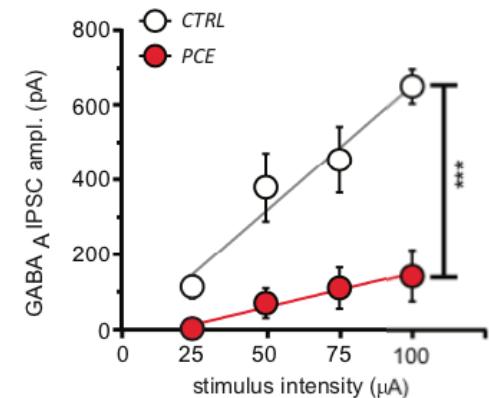
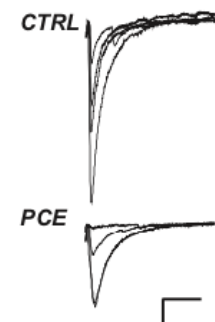
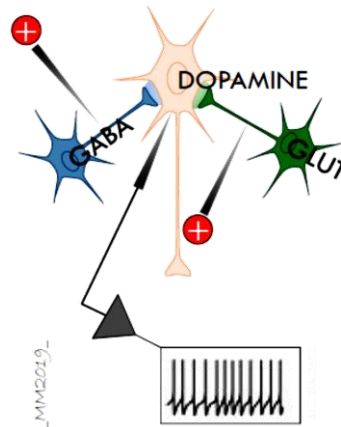
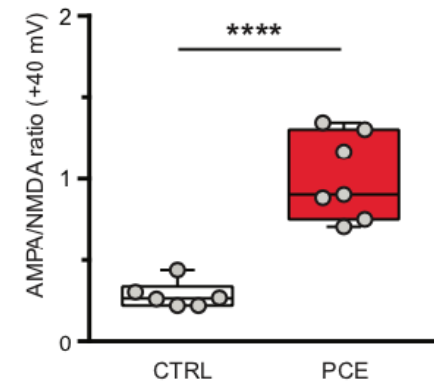
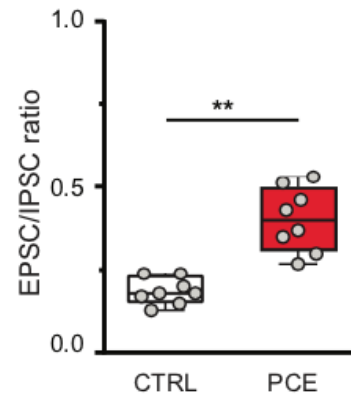
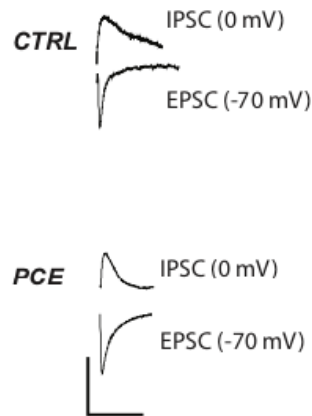


PCE biases the synaptic properties of DA neurons

Increase the excitation-to-inhibition ratio of DA neurons

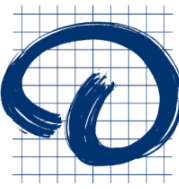
Increase the AMPA/NMDA ratio, the maturation of AMPA

A substantial decrease in synaptic inhibitor responses of VTA dopamine cells

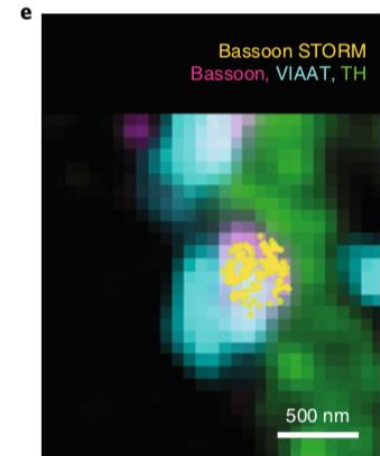
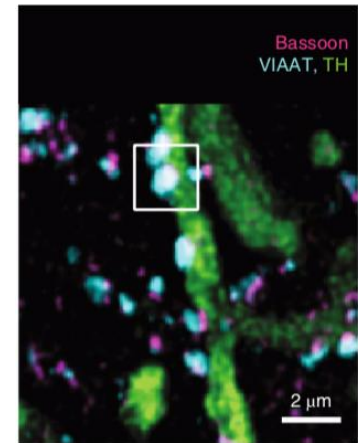
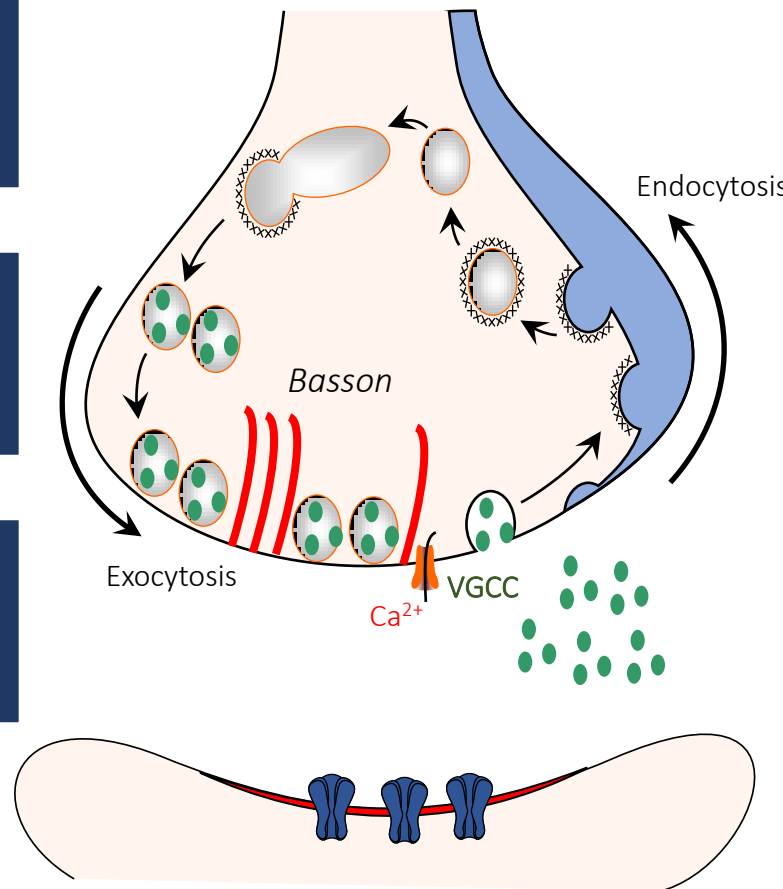
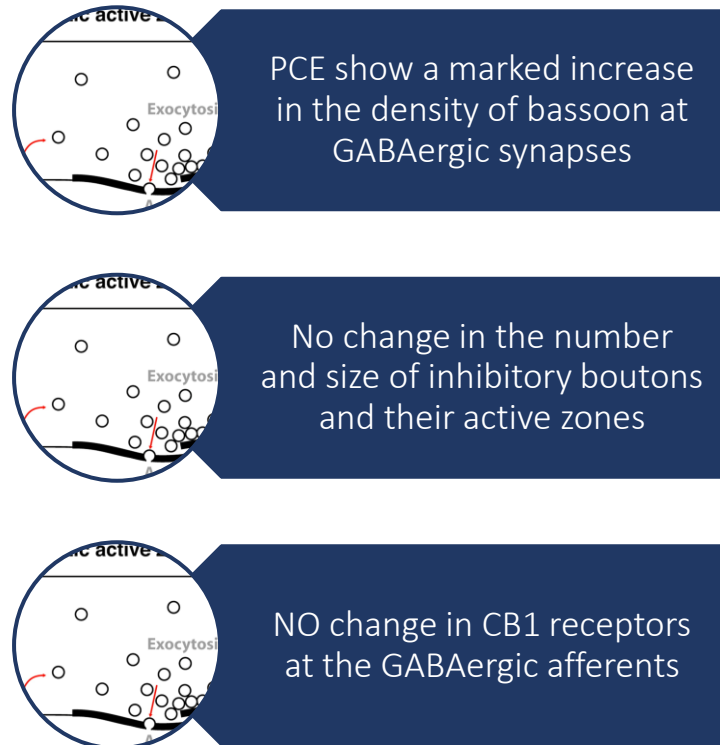




PCE increases Basson density at the inhibitory synapses

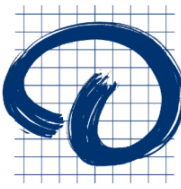


Confocal and Stochastic Optical Reconstruction Microscopy (STORM)

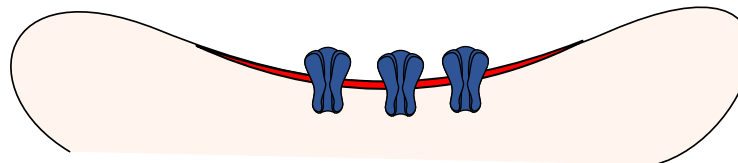
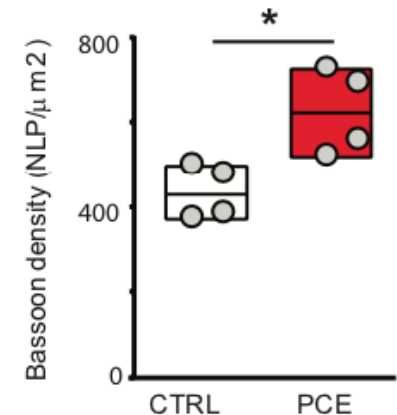
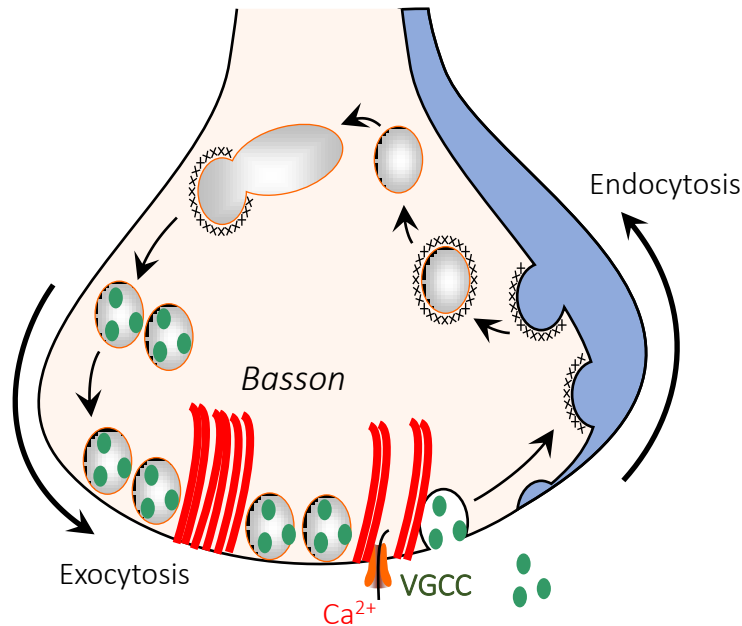
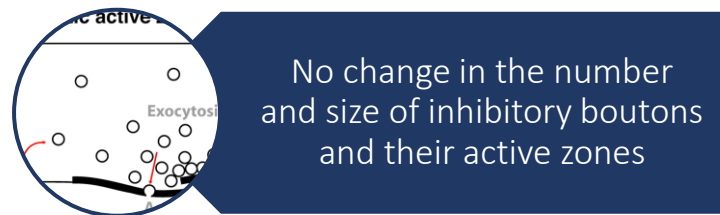
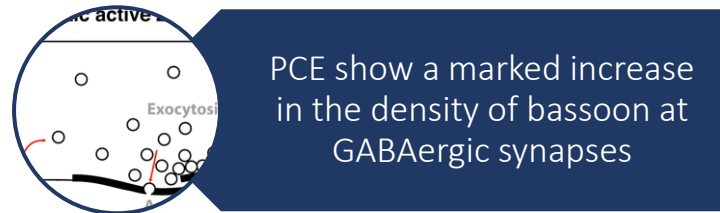




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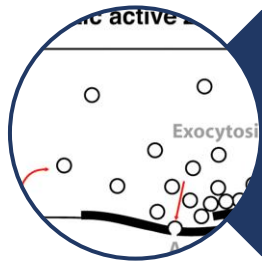


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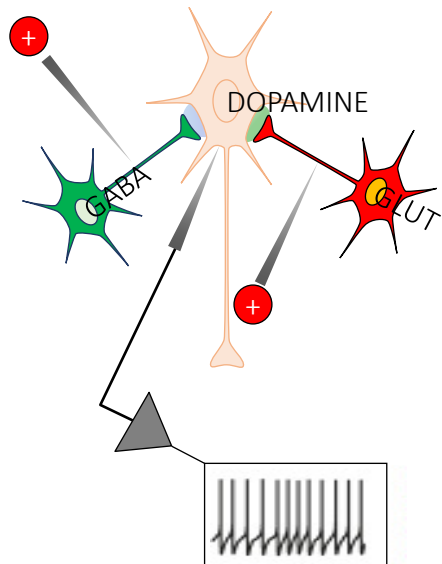


PCE leads to a polarity switch in LFS-induced plasticity

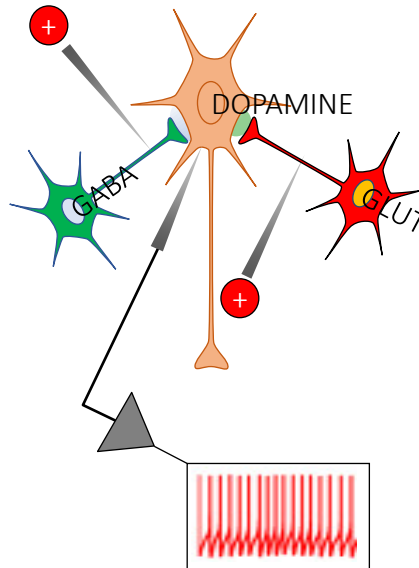


Pairing low-frequency presynaptic stimulation (LFS; 1Hz) with postsynaptic membrane depolarization (-40mV) results in a marked LTP than LTD

CONTROL

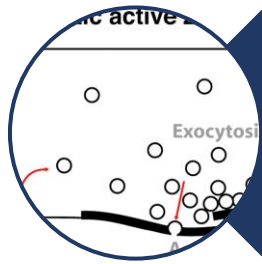


PCE



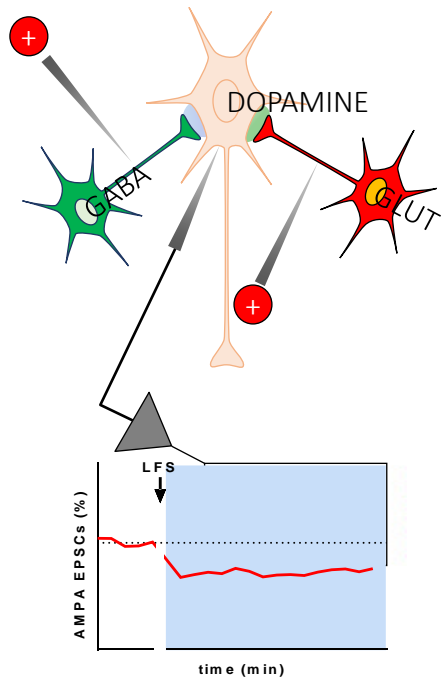


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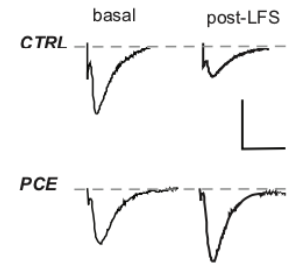
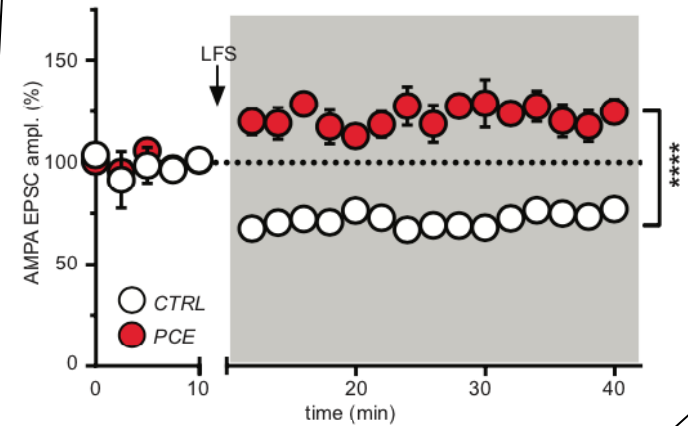
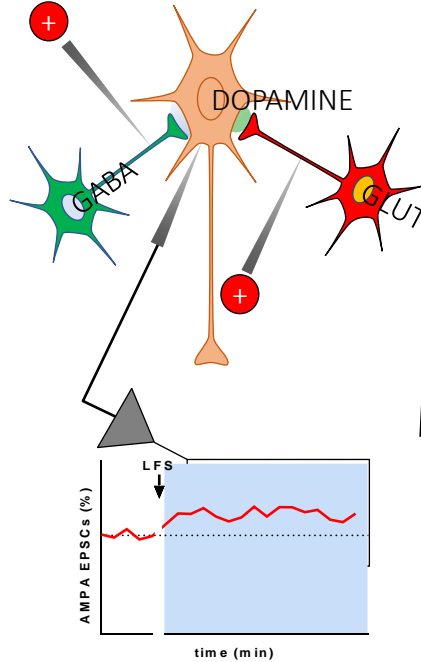


Pairing low-frequency presynaptic stimulation (LFS; 1Hz) with postsynaptic membrane depolarization (-40mV) results in a marked LTP than LTD

CONTROL



PCE



My Submissions

frontiers in Behavioral Neuroscience

In Independent Review
Mini Review

Sex differences in the outcome of offspring prenatally exposed to drugs of abuse

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Associate Editor:

Gregg Stanwood



Frontiers in Behavioral Neuroscience
Emotion Regulation and Processing

Under revision...



HOW WE SEE COLORS

WOMEN



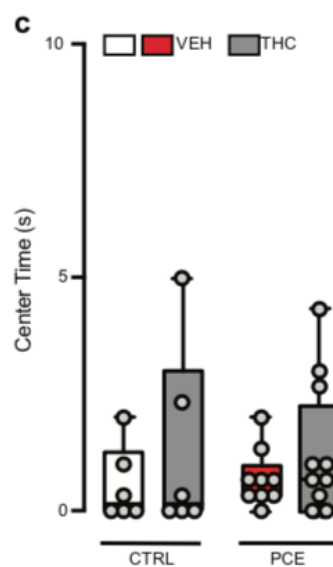
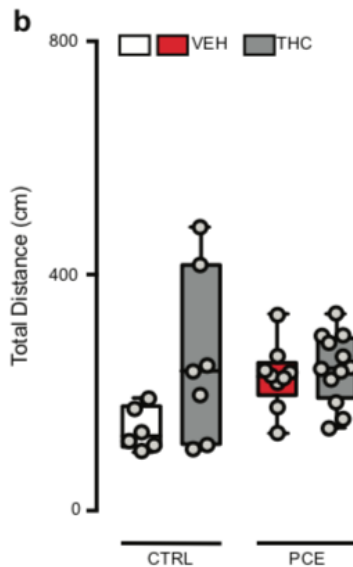
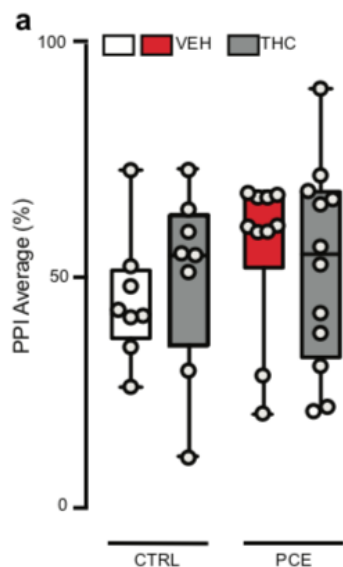
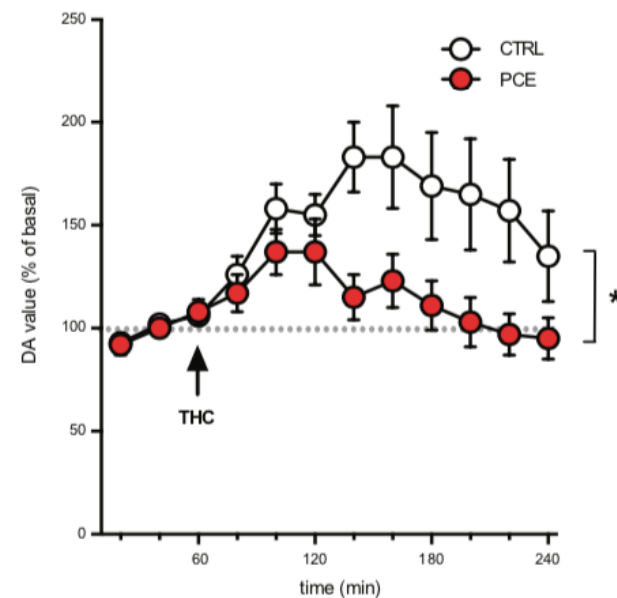
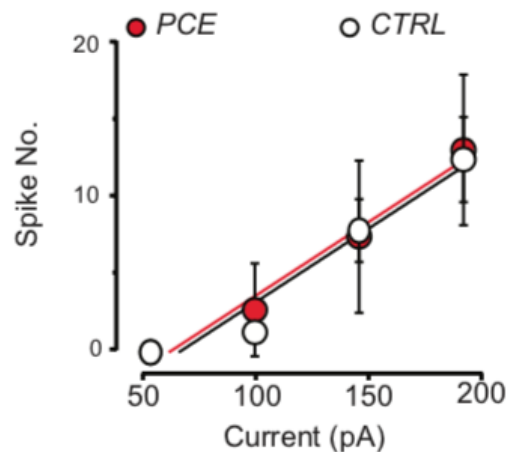
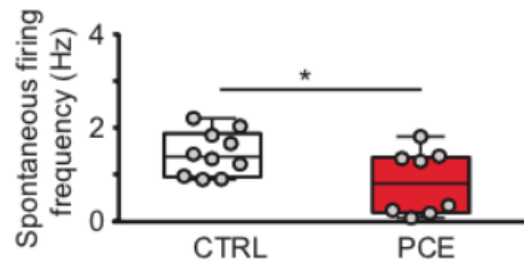
MEN



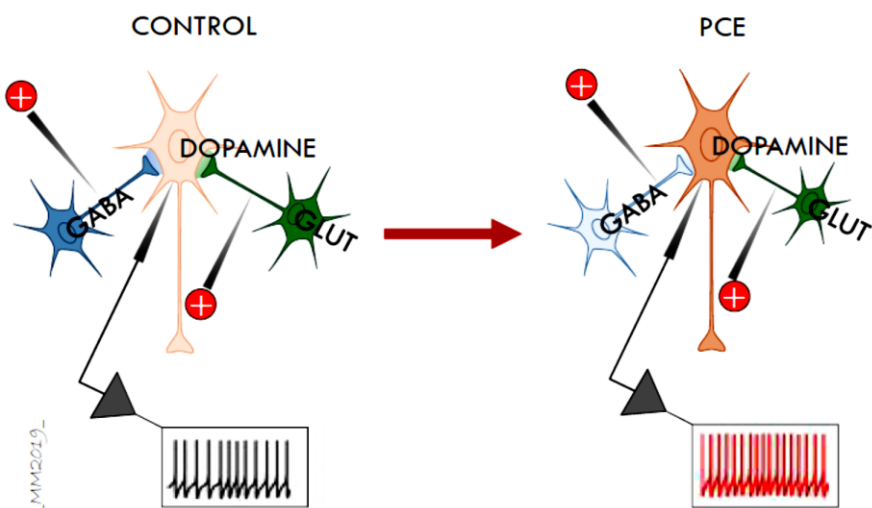
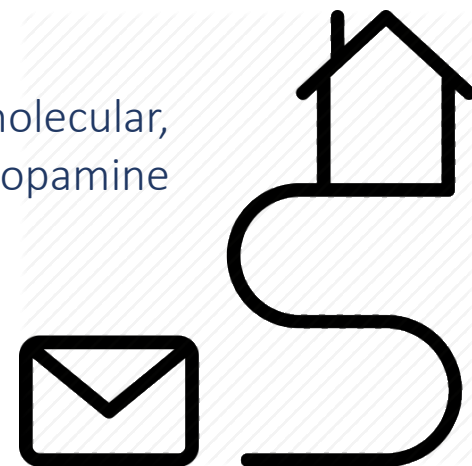
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|--------------|---|--------|
| SCARLET | ● | RED |
| DARK RED | ● | |
| WINE RED | ● | |
| PLUM | ● | VIOLET |
| EGGPLANT | ● | |
| GRAPE | ● | |
| PURPLE | ● | |
| LAVENDER | ● | PINK |
| CARNATION | ● | |
| STRAWBERRY | ● | |
| FUCHSIA | ● | ORANGE |
| SALMON | ● | |
| ORANGE | ● | |
| MELON | ● | YELLOW |
| YELLOW | ● | |
| LEMON | ● | GREEN |
| LIME | ● | |
| FRESH GRASS | ● | |
| GREEN | ● | |
| DARK GREEN | ● | BLUE |
| MOSS | ● | |
| GREEN-YELLOW | ● | |
| SEA GREEN | ● | BLUE |
| BLUE-GREEN | ● | |
| SKY BLUE | ● | |
| TURQUOISE | ● | |

BRIGHTSIDE.ME

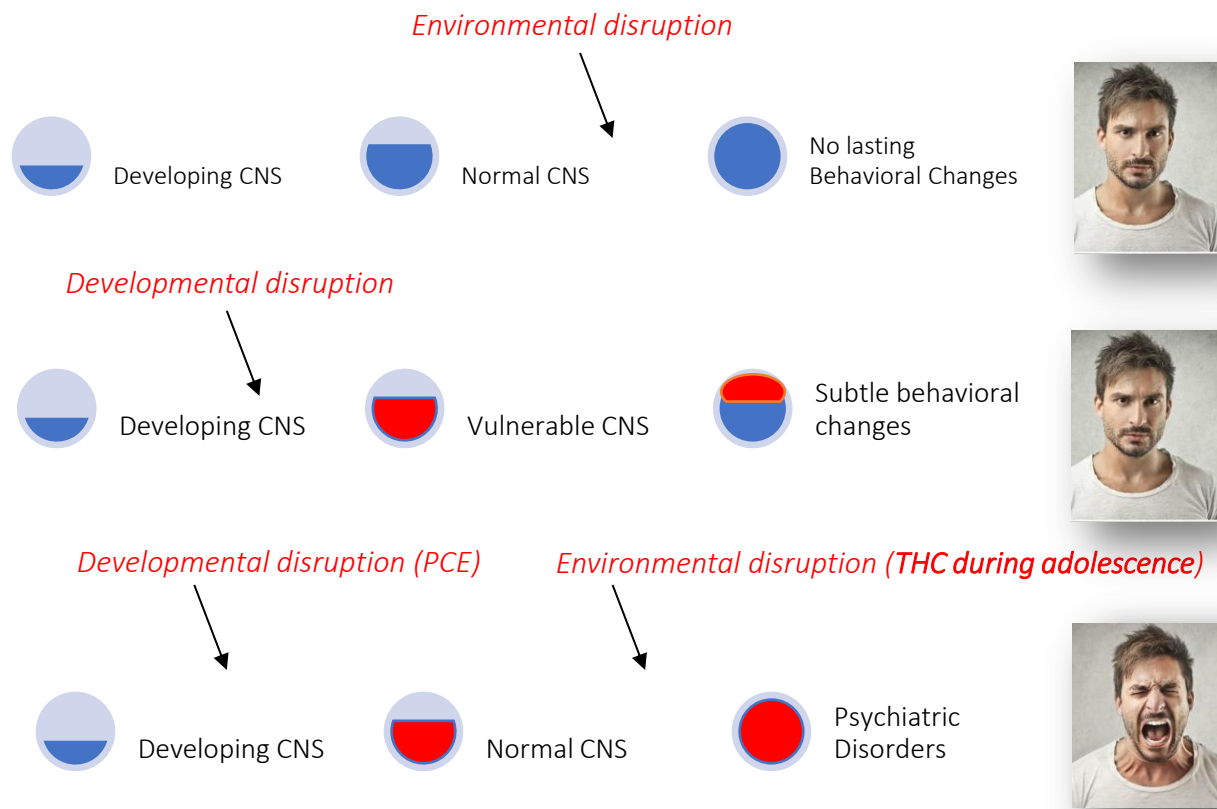
TURQUOISE ●
SKY BLUE ●
BLUE-GREEN ●
SEA GREEN ●
GREEN-YELLOW ●
MOSS ●
DARK GREEN ●
GREEN ●
FRESH GRASS ●
LIME ●
LEMON ●
YELLOW ●
MELON ●
ORANGE ●
SALMON ●
FUCHSIA ●
STRAWBERRY ●
CARNATION ●
LAVENDER ●
PURPLE ●
GRAPE ●
EGGPLANT ●
PLUM ●
WINE RED ●
DARK RED ●
SCARLET ●



- ✓ Prenatal THC exposure induces (sex-dependent) multifaceted molecular, cellular and synaptic adaptations that converge into an **aberrant** dopamine function and psychotic-like phenotypes in juvenile rat offspring

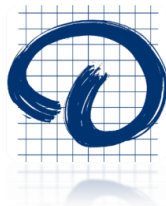


- ✓ This **hyper-excitable phenotype**, an underlying clinical feature of diverse mental diseases, may fall into the “two-hit” hypothesis of psychiatric disorders, in which **PCE may act as a first hit** that leads to a “silent” endophenotype and **THC** as second environmental insult that triggers psychotic manifestation in progenies





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DEGLI STUDI
DI CAGLIARI



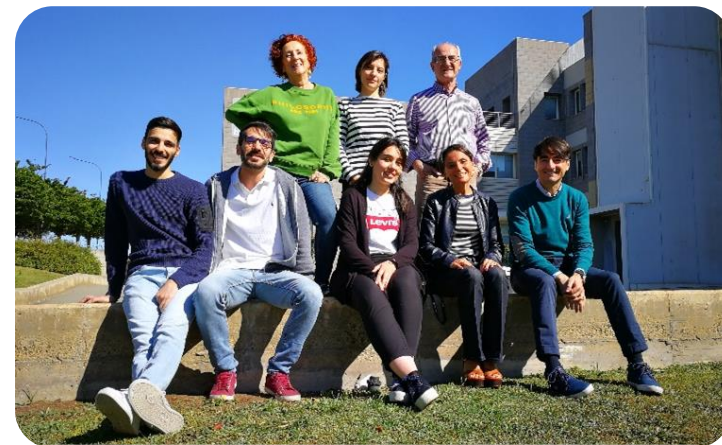
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Thank you!!!