5-HT2A agonists and LSD in mental disorders

Gabriella Gobbi, MD, PhD

Dept. of Psychiatry, McGill University
McGill University Health Center
Montréal, Québec
Canada

Conflict of Interest Disclosures

AUTHORS

☐ 1. The authors do not have any potential conflicts of interest to disclose, **OR**

☒ 2. The authors wish to disclose the following potential conflicts of interest:

Type of Potential Conflict	Details of Potential Conflict
Grant/Research Support	MESI, CIHR, FRQS, CFI, MUHC, CQDM
Consultant	EISAI, DIAMOND THERAPEUTICS
Speakers' Bureaus	
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Other	Patent inventor WO/2007/079593, Founder of Cosmas Therapeutics Inc

☐ 3. The material presented in this lecture has no relationship with any of these potential conflicts, **OR**

☒ 4. This talk presents material that is related to one or more of these potential conflicts, and the following objective references are provided as support for this lecture:

Objectives

- Explain the mechanism of action of LSD
- Explain the potential use of LSD in mental disorders

TWO CLASSES OF HALLUCINOGENS (from the ‘60)

1)Psychedelics or classical serotonergic hallucinogens

2)Dissociative anaesthetics (NMDA)

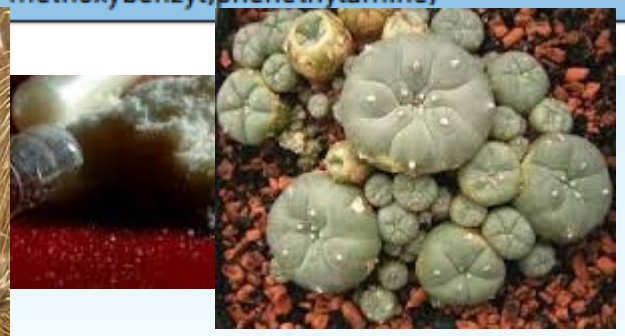
Table 1. Classical hallucinogens divided into the three biochemical classes of tryptamines, lysergamines and phenethylamines. Psilocin, DMT and mescaline are naturally occurring, the rest are synthetic: this table is illustrative, and other compounds have been discovered.

Tryptamines	Lysergamines	Phenethylamines
Psilocin	**LSD** (lysergic acid diethylamide)	**Mescaline**
DMT (*N*,*N*-dimethyltryptamine)	**LSP** (lysergic acid 3-pentylamide)	**DOI** (2,5-dimethoxy-4-iodoamphetamine)
5-MeO-DMT (5-methoxy-*N*,*N*-dimethyltryptamine)	**ETH-LAD** (6-ethyl-6-*nor*-lysergic acid diethylamide)	**DOB** (dimethoxybromoamphetamine)
DET (*N*,*N*-diethyltryptamine)	**AL-LAD** (6-allyl-6-*nor*-lysergic acid diethylamide)	**2C-B** (4-bromo-2,5-dimethoxyphenethylamine)
5-MeO-DALT (*N*,*N*-diallyl-5-methoxytryptamine)	**ALD-52** (*N*-acetyl-LSD)	**2C-E** (2,5-dimethoxy-4-ethylphenethylamine)
		25I-NBOMe (4-iodo-2,5-dimethoxy-N-(2-methoxybenzyl)phenethylamine)

Psilocin and Psilocybin mushrooms

LSD

Synthesized from Ergot



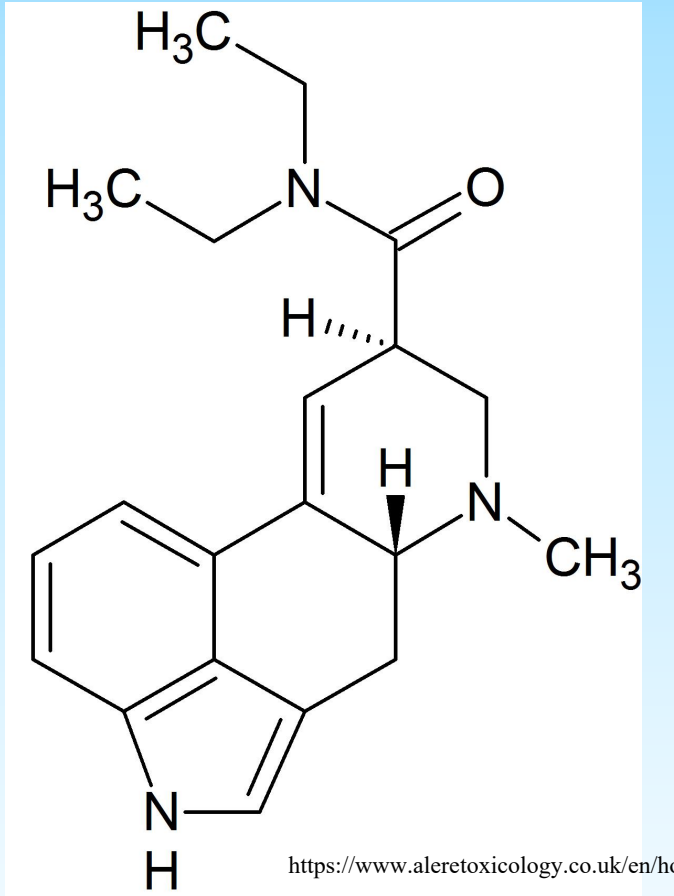
Mescaline

Extracted from Peyote

LSD - History

- Synthesized in 1938 by Albert Hoffman

- LSD research focused on:
  - Anxiety associated with terminal illness
  - Depression
  - Addiction
  - As a model of acute psychosis

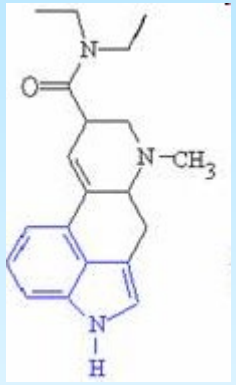


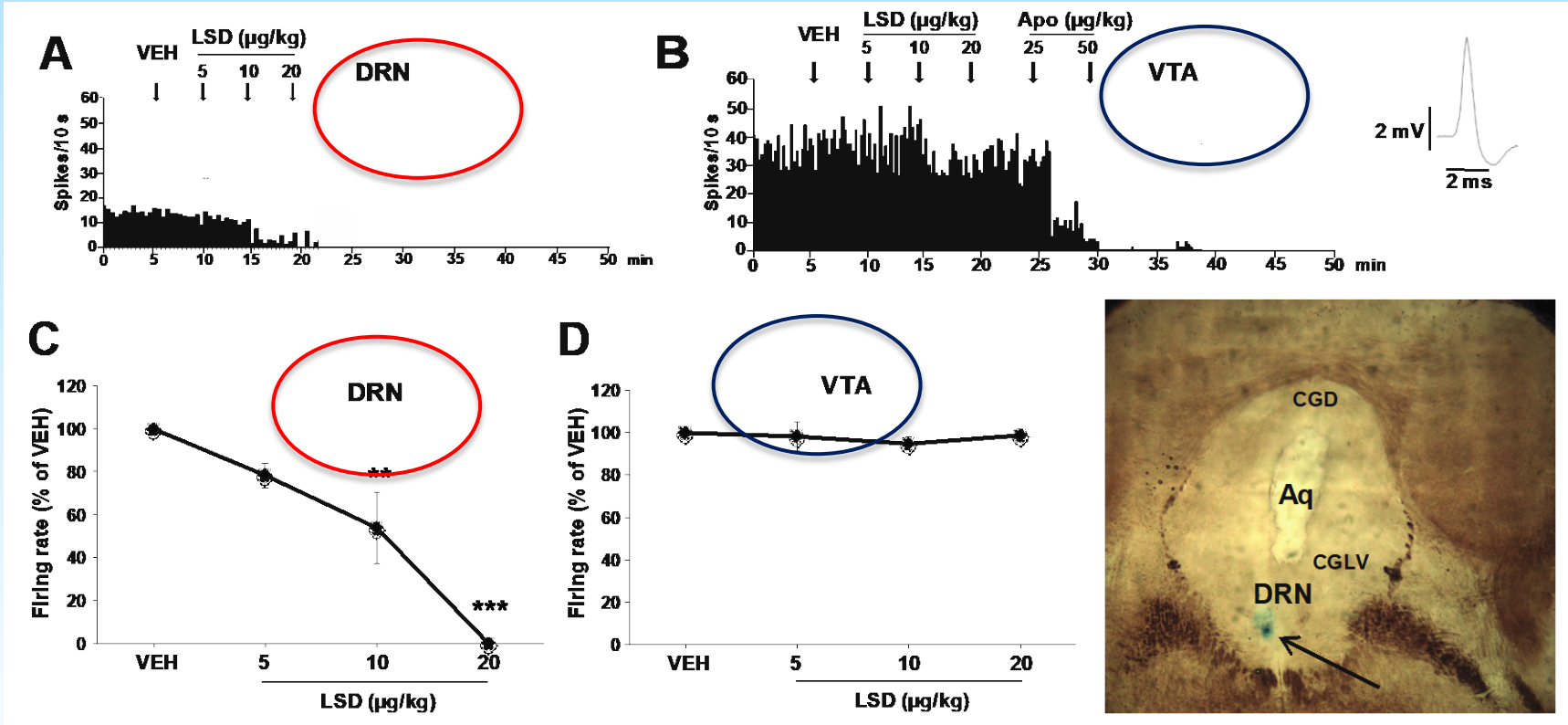
https://www.aleretoxicology.co.uk/en/home/support/drugs-library/lsd.html

Passie, et al. (2008). *CNS neuroscience & therapeutics*

LSD: effects of 5-HT and DA neurons

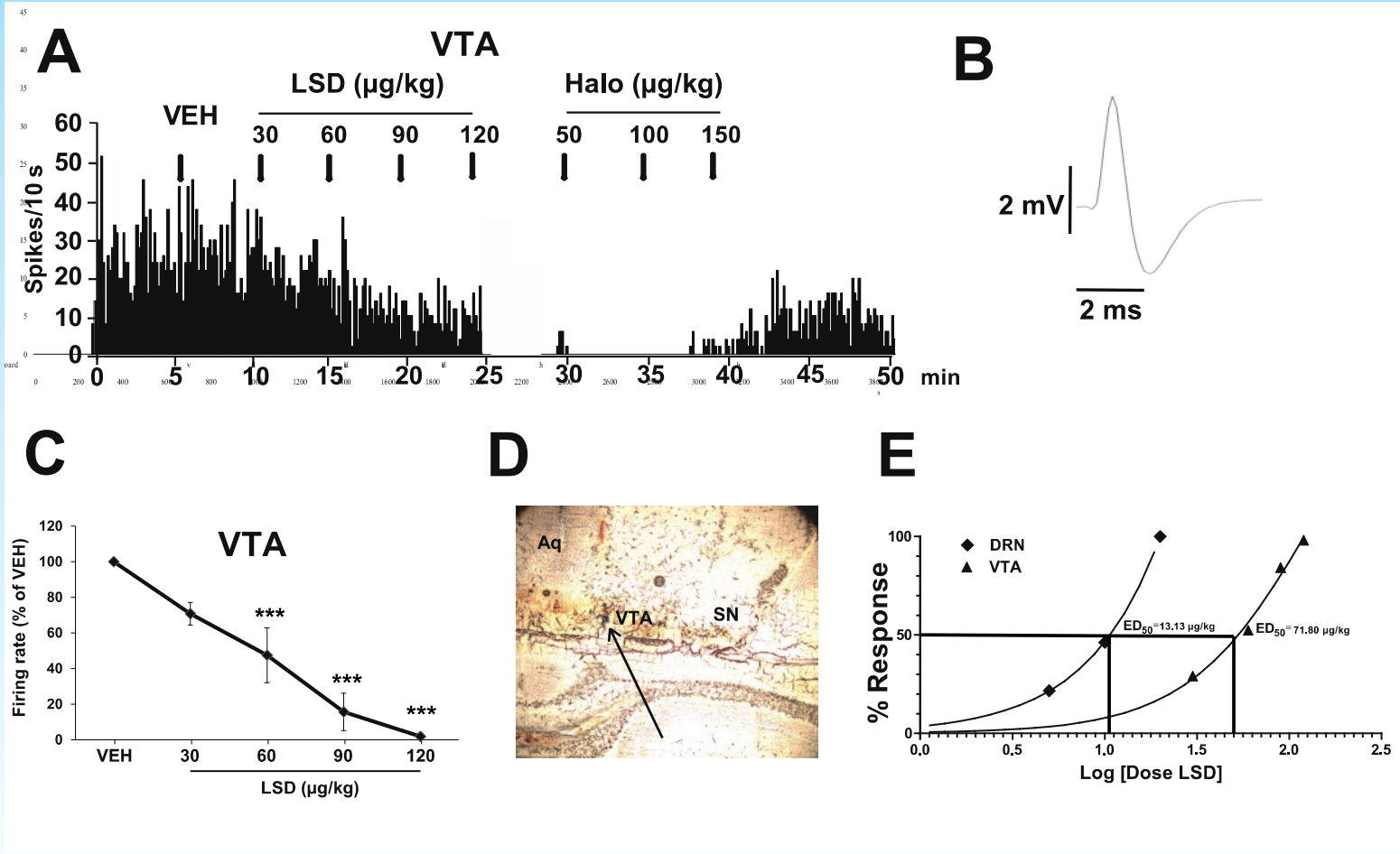
Low doses of LSD (5-20 µg/kg, i.v.) decreased 5-HT neurons of the DRN, but not DA neurons of the VTA





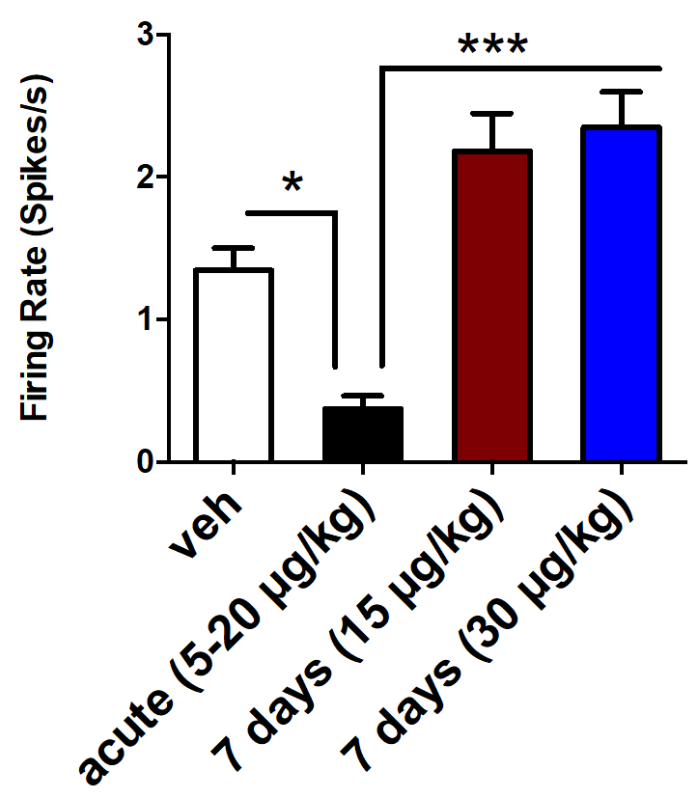
De Gregorio et al., Pharmacol Res., 2016

High doses of LSD (60-120 µg/kg, i.v.) decreased VTA DA neurons

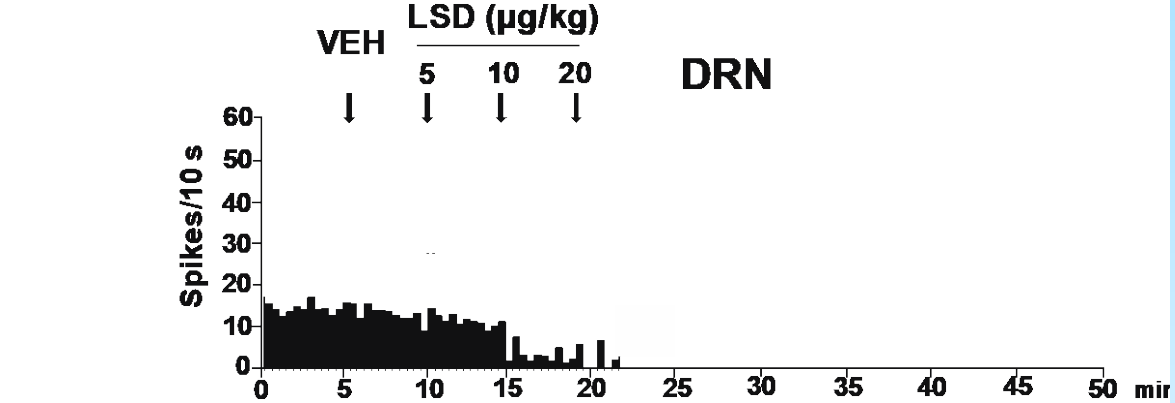


De Gregorio et al., Pharmacol Res., 2016

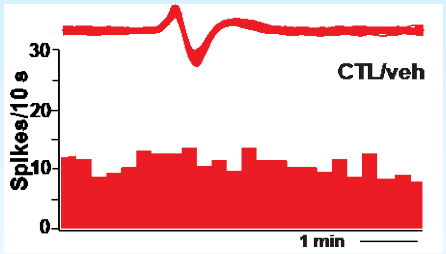
Long-term treatment with microdoses of LSD enhances 5-HT firing activity

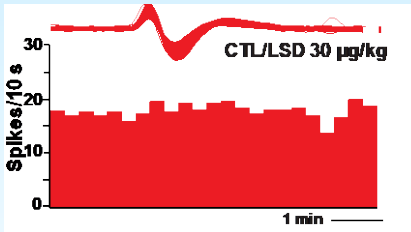


ACUTE TREATMENT



REPEATED TREATMENT



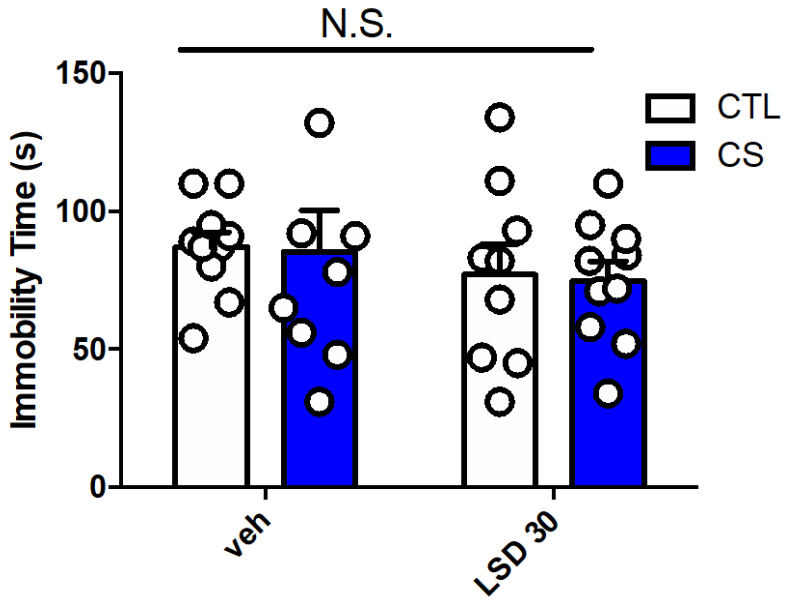


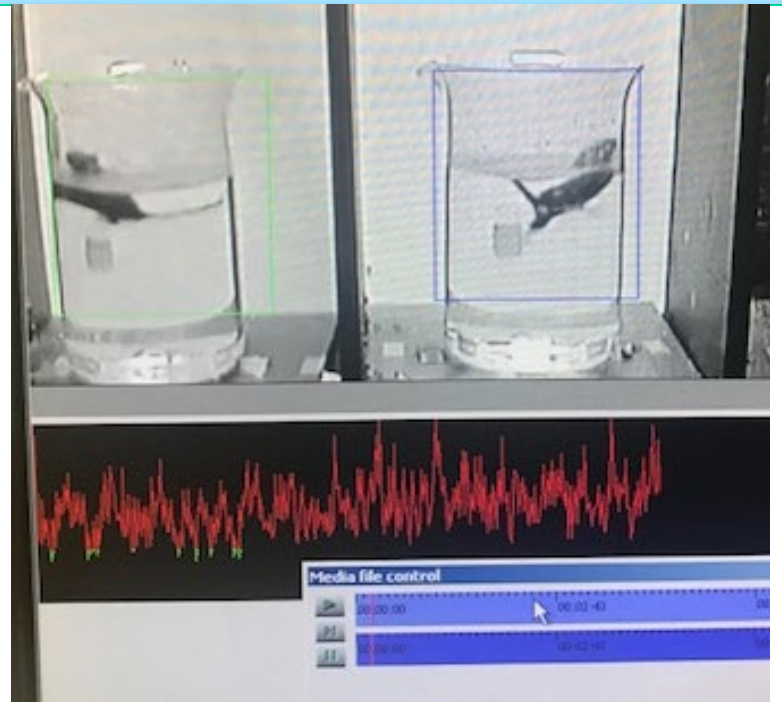
Unpublished results

Experimental Timeline

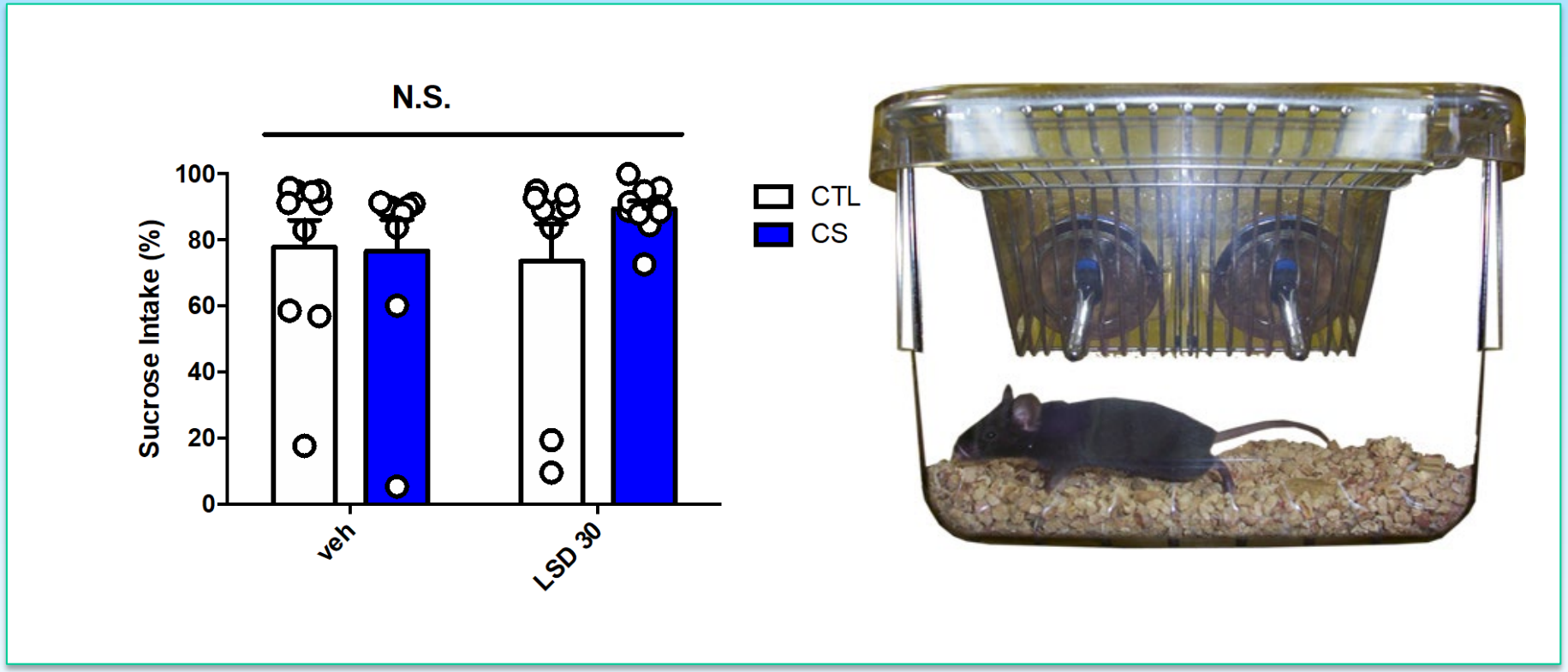
De Gregorio et al., PNAS, 2021

LSD did not affect the immobility time in the Forced Swim Test (FST) (30 μg/kg, i.p., 7 days) for depression

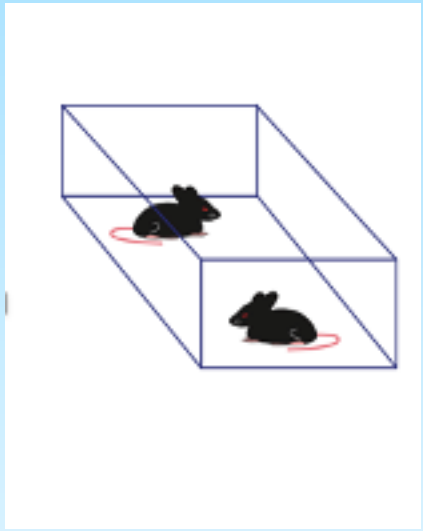




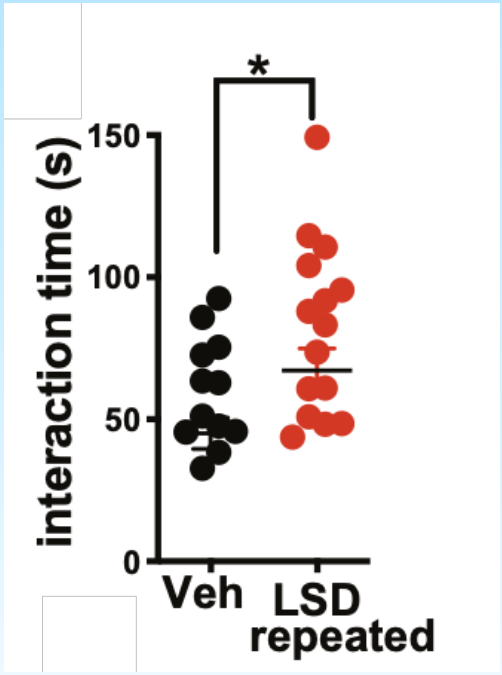
LSD did not affect the sucrose intake in the sucrose preference test (SPT) for anhedonia



LSD enhances social behavior in Direct Social Interaction Test

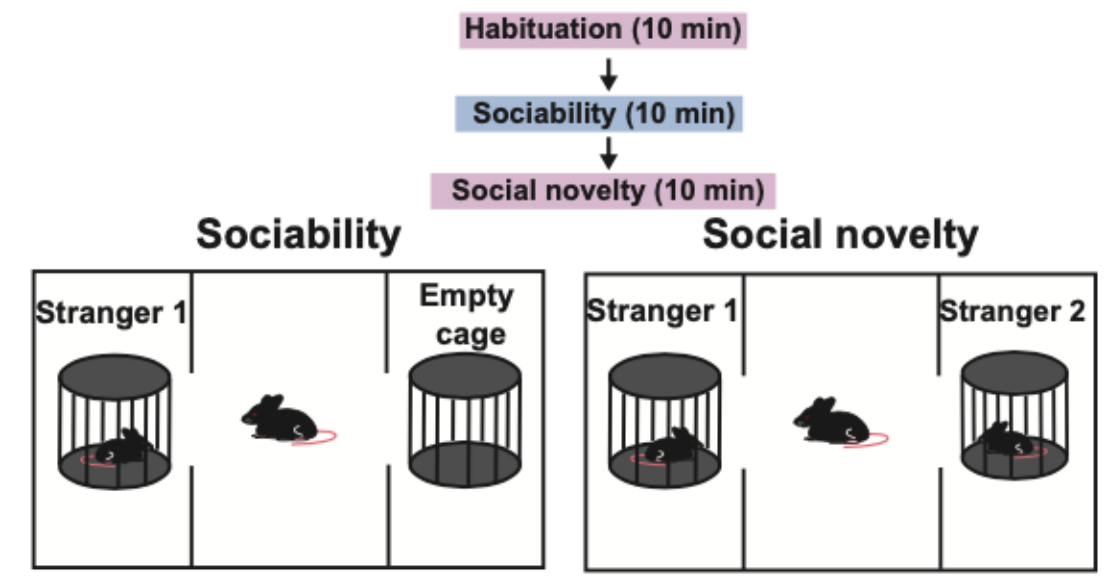


Repeated LSD

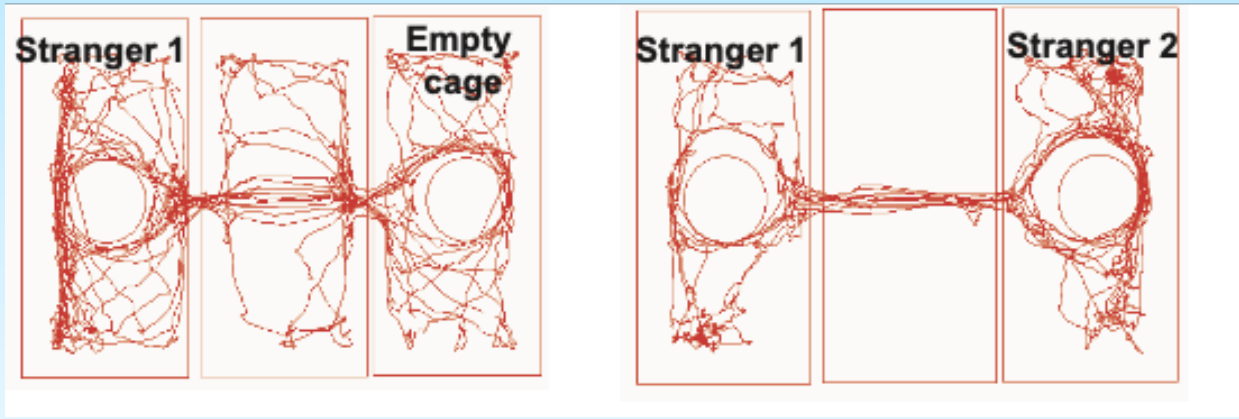


De Gregorio et al., PNAS, 2021

Three Chambers Sociability Test

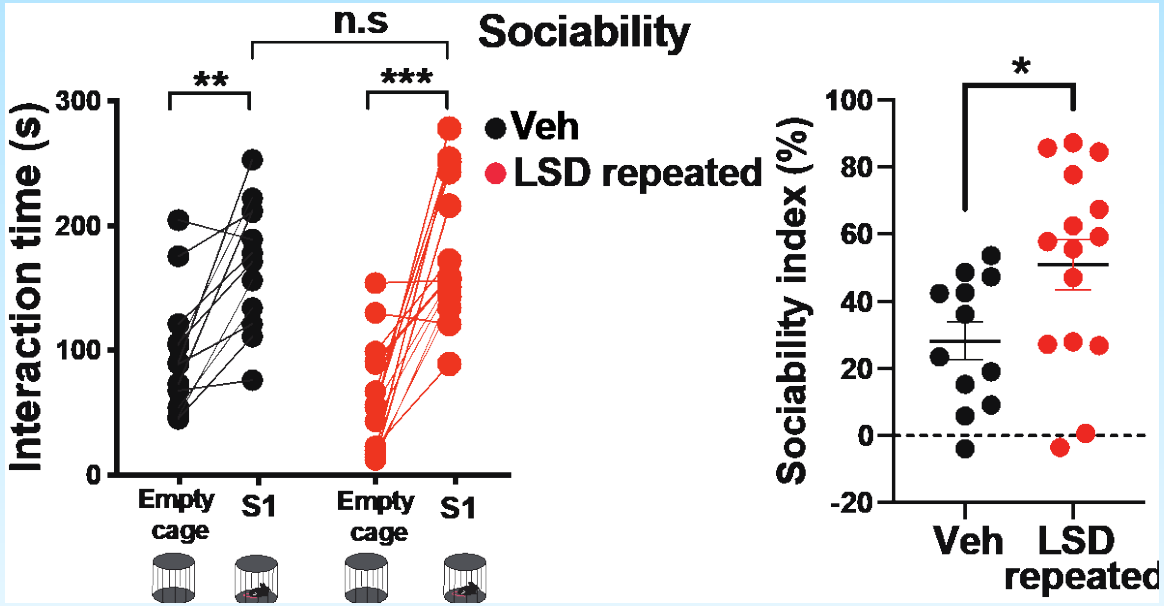


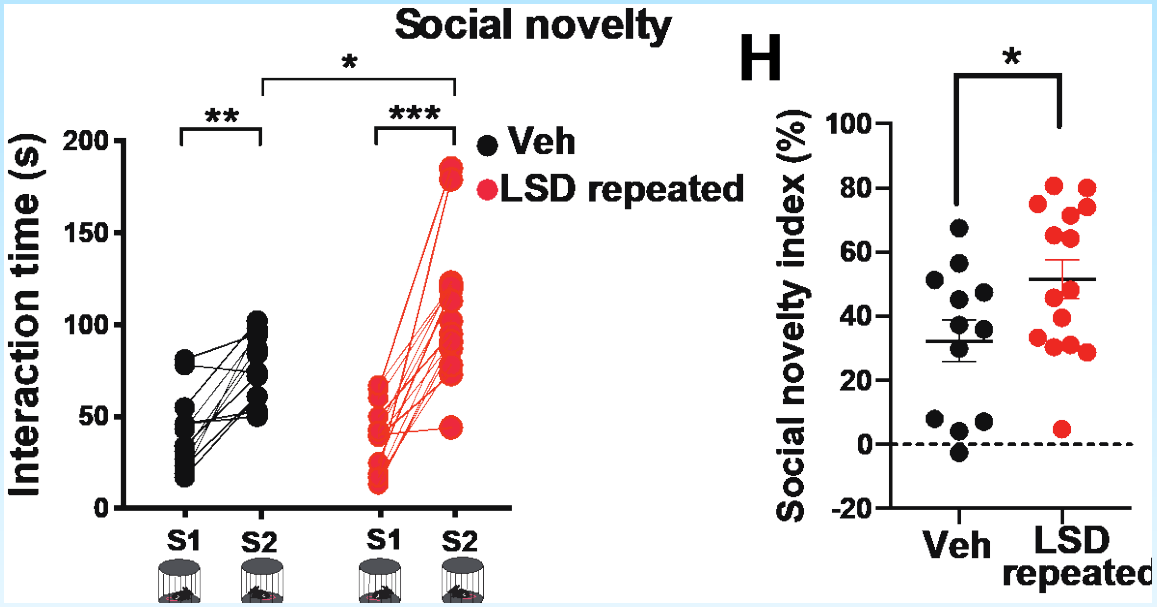
Standard results:



De Gregorio et al., PNAS, 2021

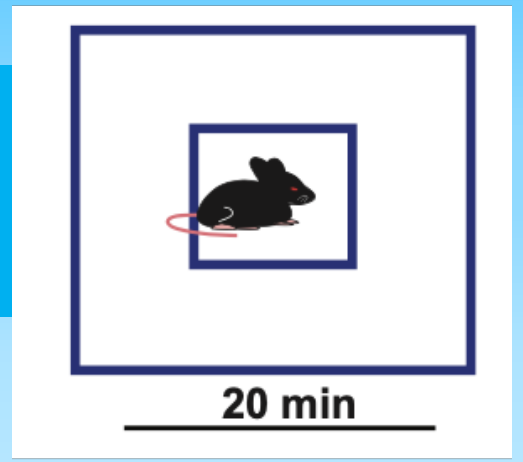
LSD enhances Social behavior in the Three Chambers Sociability Test

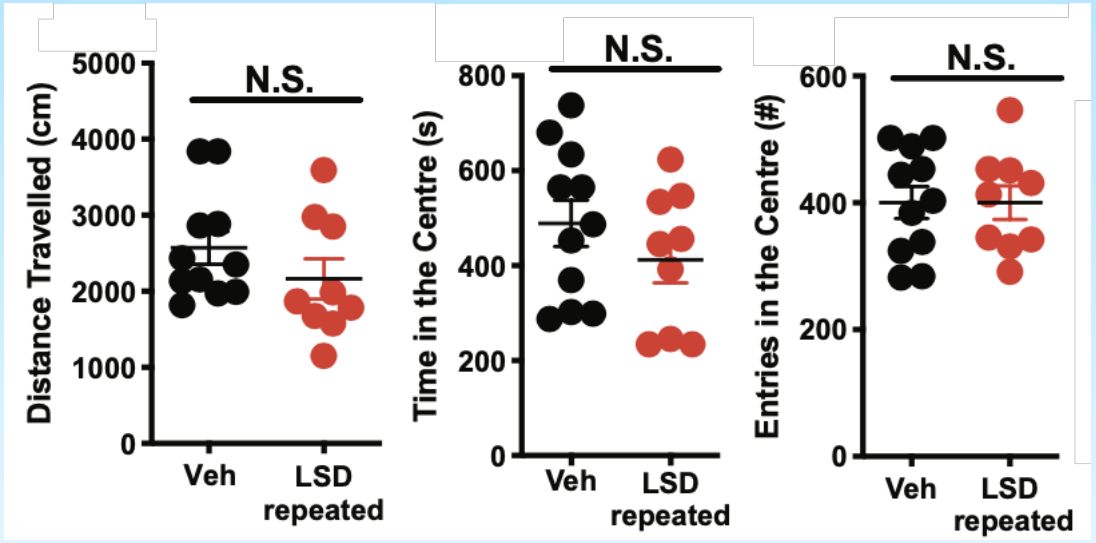


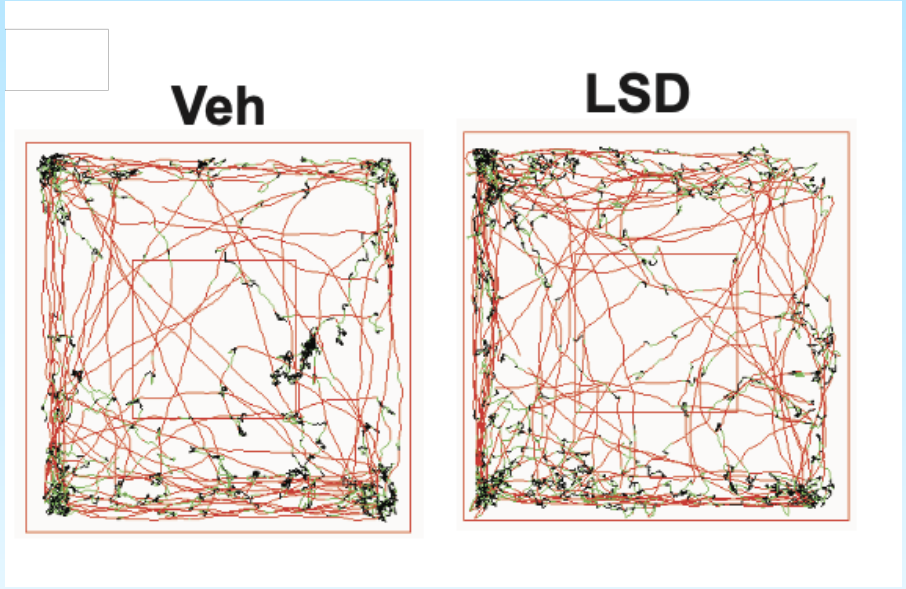


De Gregorio et al., PNAS, 2021

Open-Field Test: LSD has not effect on locomotion







De Gregorio et al., PNAS, 2021

Social Behavior Results

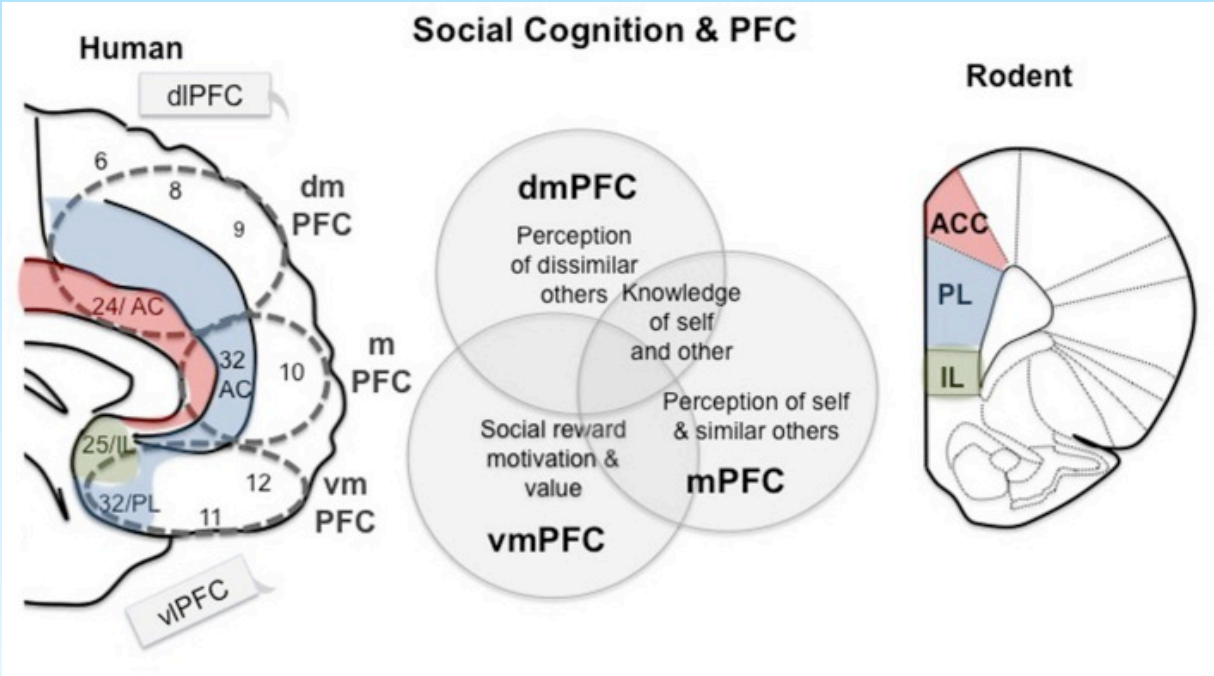
Repeated, low dose LSD (30µg/kg i.p.):

- Increases social interaction
- Increases preference for a social stimulus
- Increases preference for social novelty

What is the neural basis of these changes in behavior?

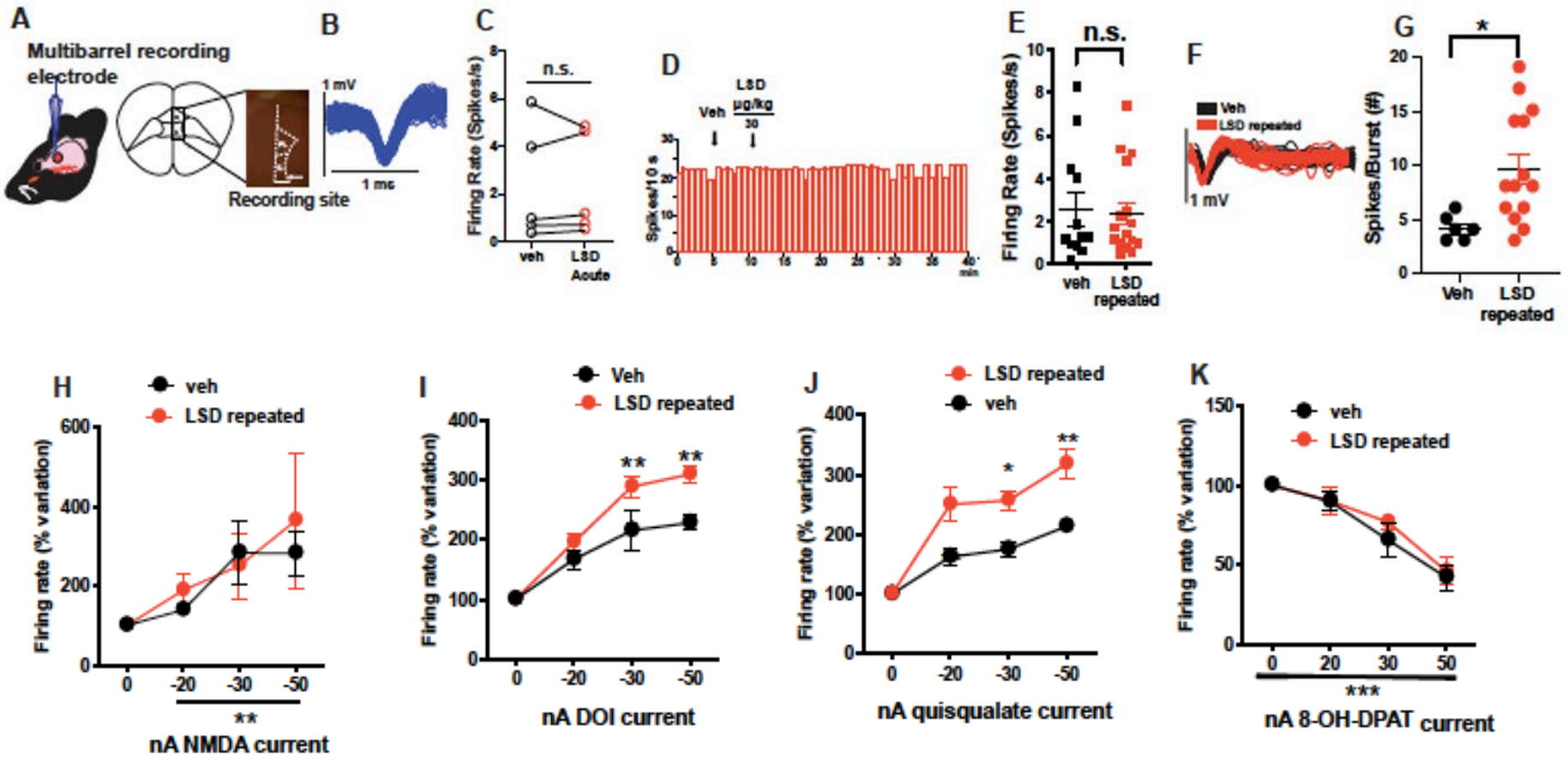
Medial Prefrontal Cortex (mPFC)

- High 5-HT2a expression
- Social cognition
- Implication of mPFC in Autism spectrum Disorder



Bicks et al., 2015

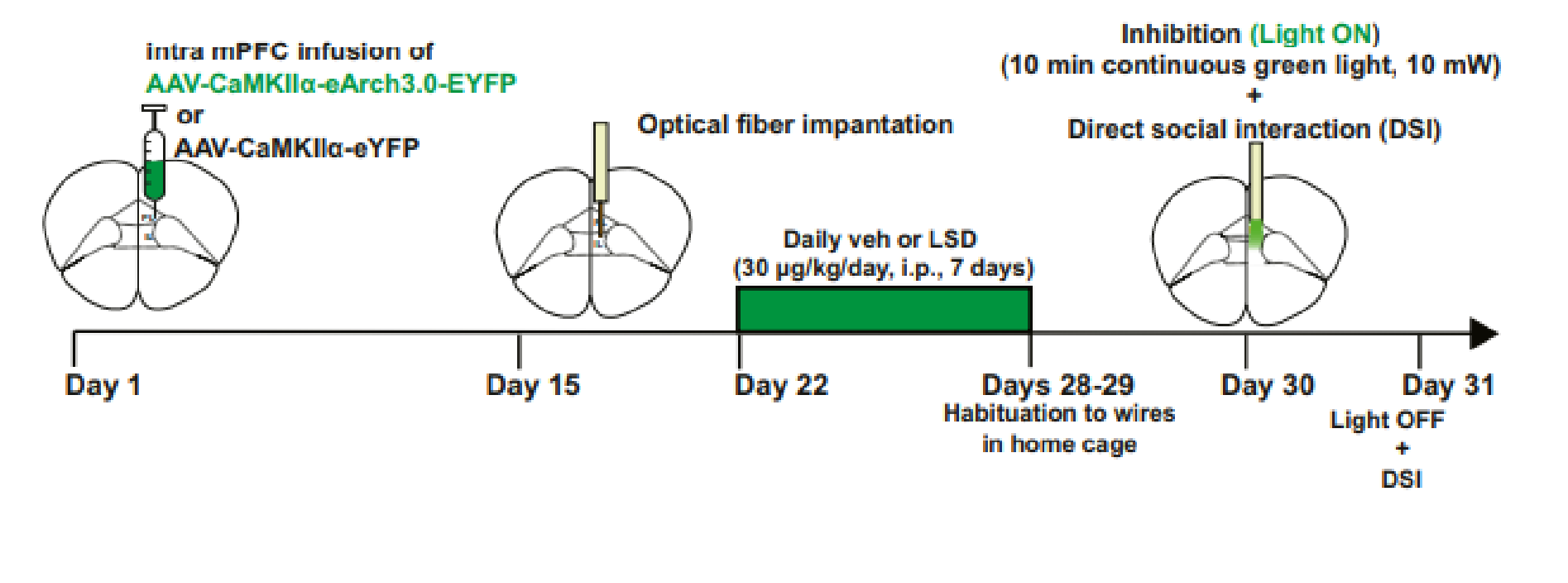
LSD potentiates AMPA and 5-HT2A responses, but not NMDA or 5-HT1A responses in mPFC



De Gregorio et al., PNAS, 2021

Optogenetics: photoinhibition of excitatory neurons in mPFC

Experimental timeline:



De Gregorio et al., 2021

Optogenetic Photoinhibition of excitatory neurons in mPFC nullifies the prosocial effects of the LSD

Social behavior with mPFC inhibition

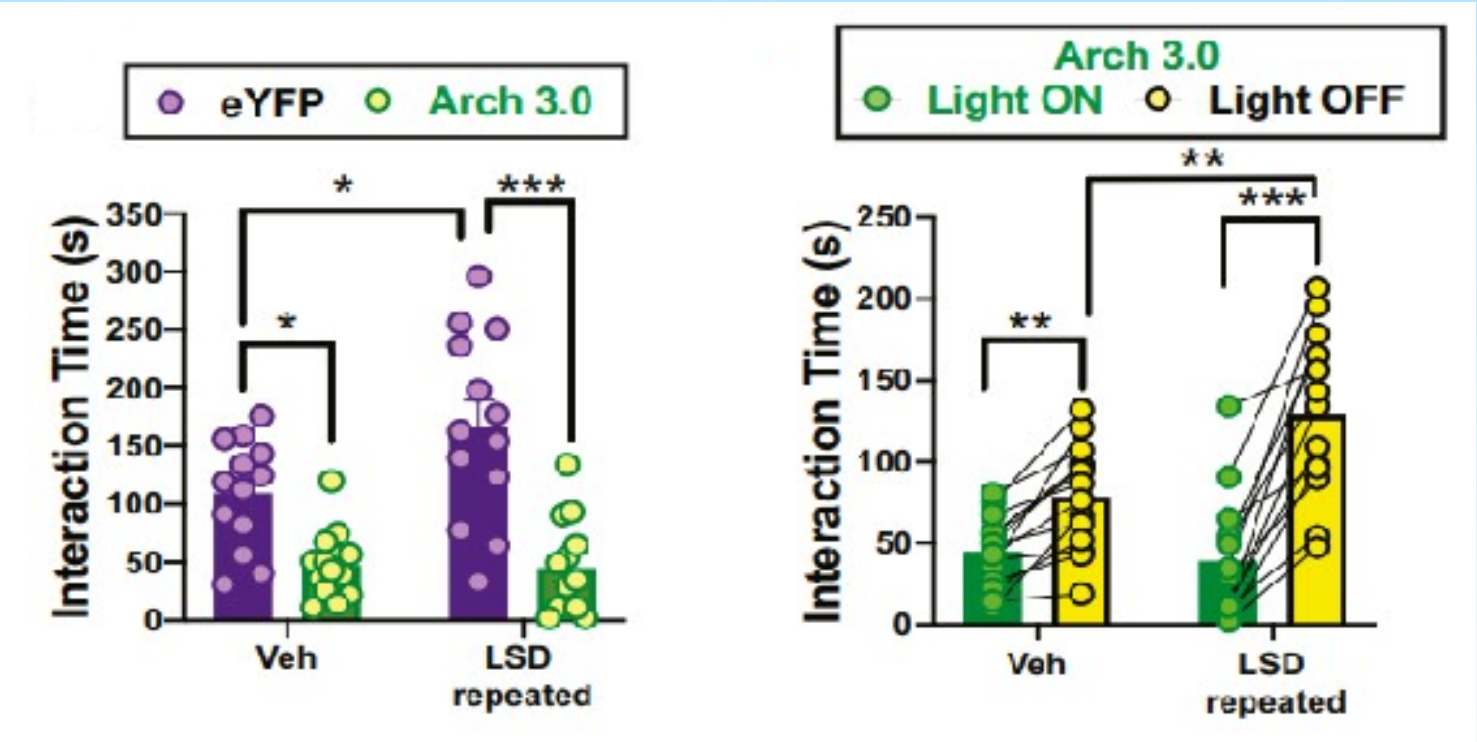
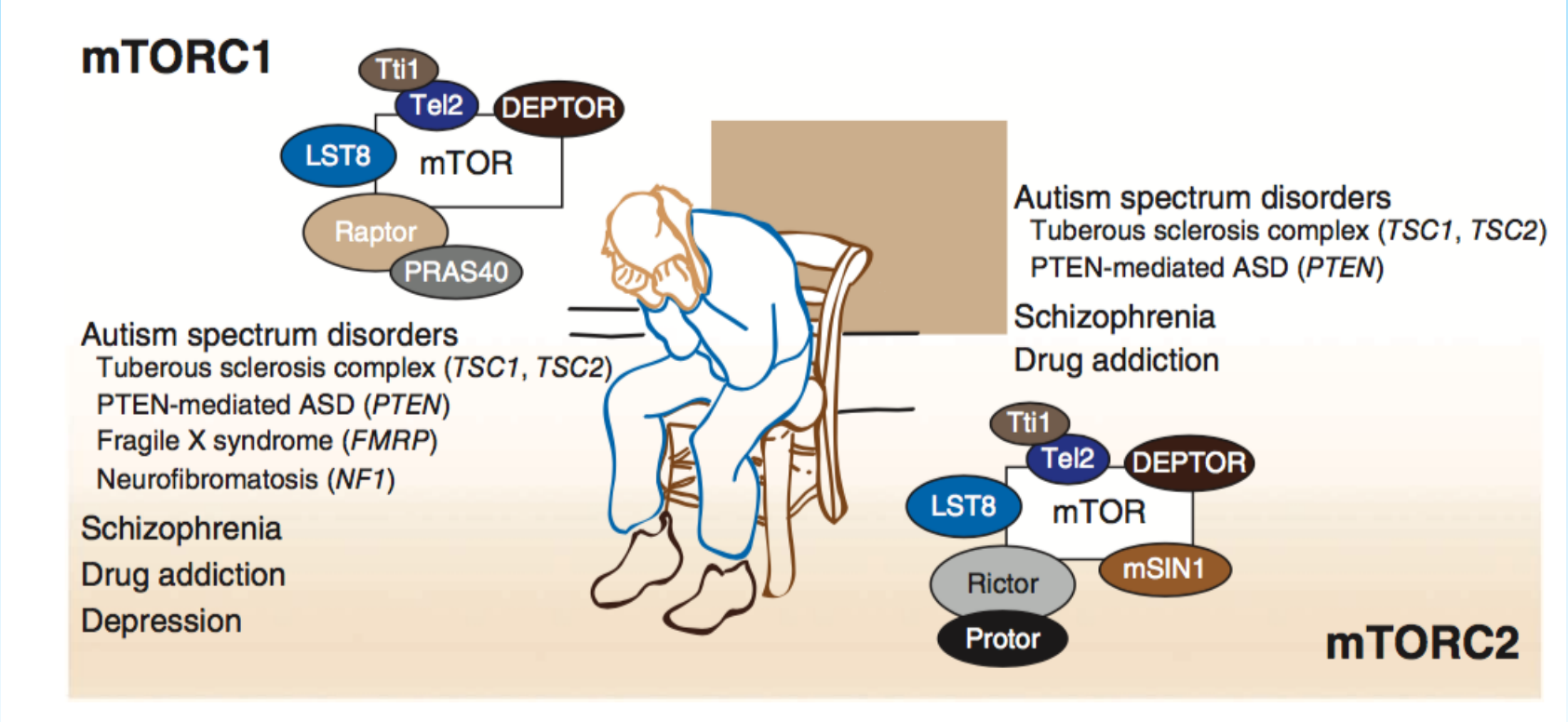


Photo-inhibition: Decrease sociability and LSD fails to increase sociability

Photo-inhibition: 24 hours later, with light OFF: LSD works

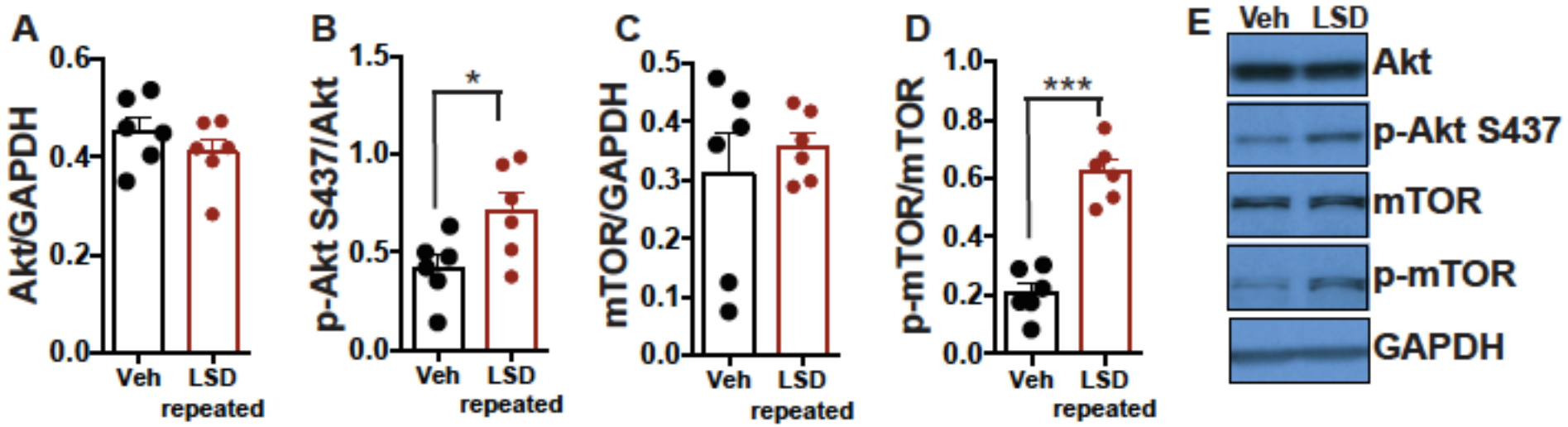
De Gregorio et al., PNAS, 2021

Potential molecular pathways: mTOR1



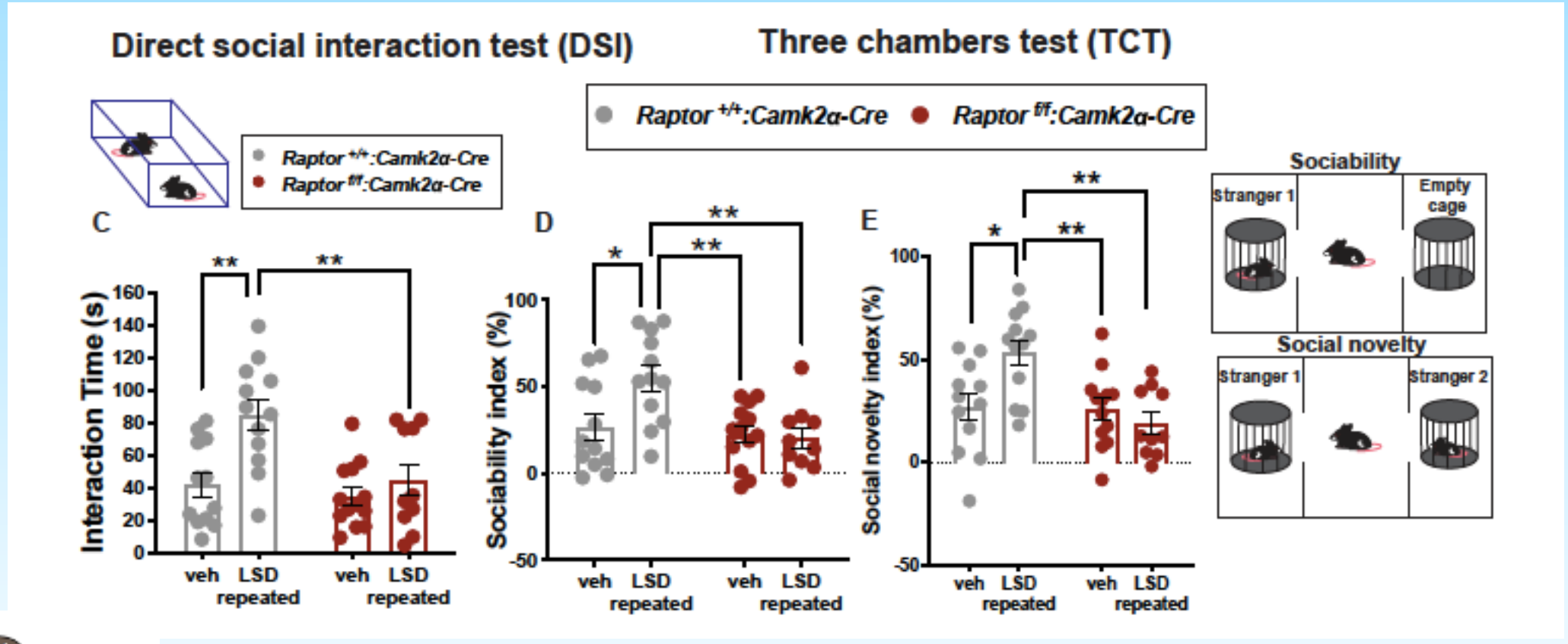
Costa-Mattioli and Monteggia 2013, Nat Neurosci

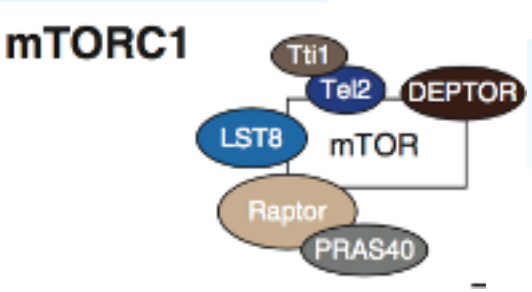
LSD increases Akt and mTOR phosphorylation in mPFC



De Gregorio et al., PNAS, 2021

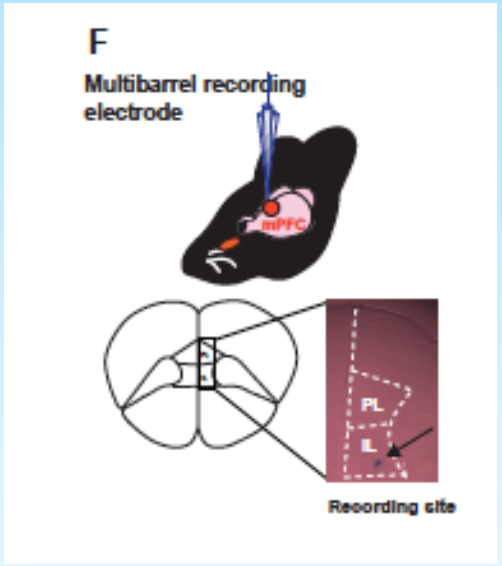
Intact mTOR complex in the excitatory neurons is necessary for the prosocial effect of LSD



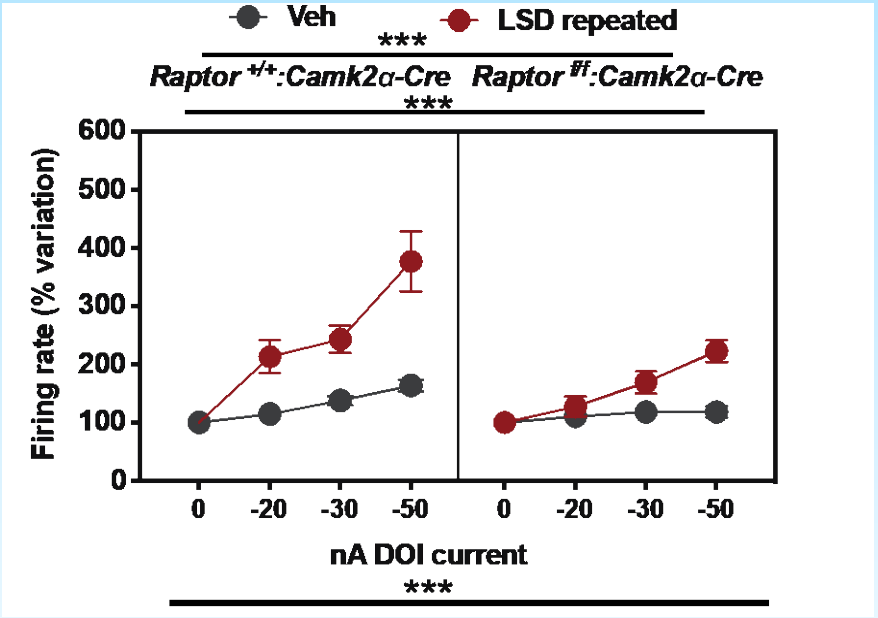


De Gregorio et al., PNAS, 2021

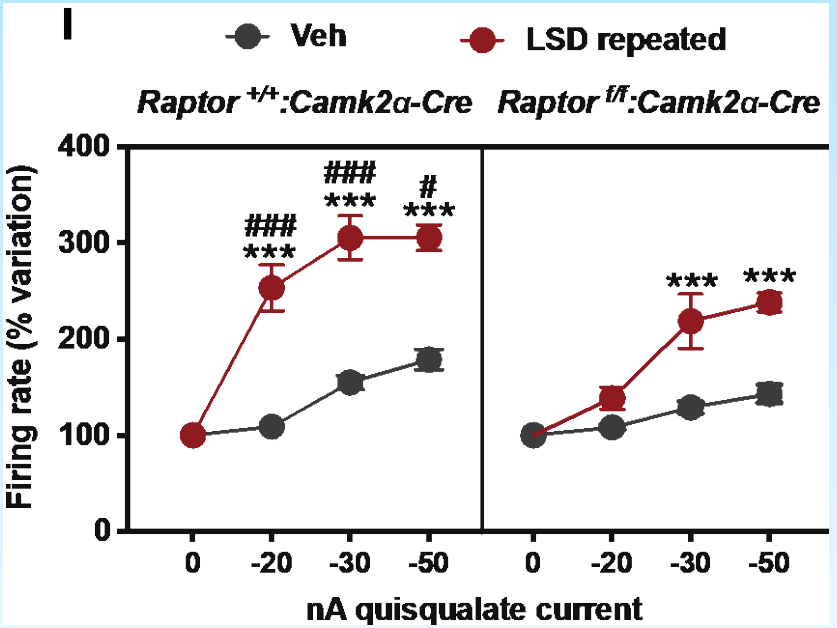
Intact mTOR complex is necessary for the prosocial effect of LSD and also the potentiation of the 5-HT2A and AMPA receptors

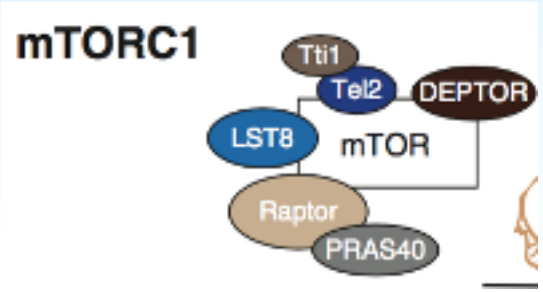


5-HT2A



AMPA





De Gregorio et al., PNAS, 2021

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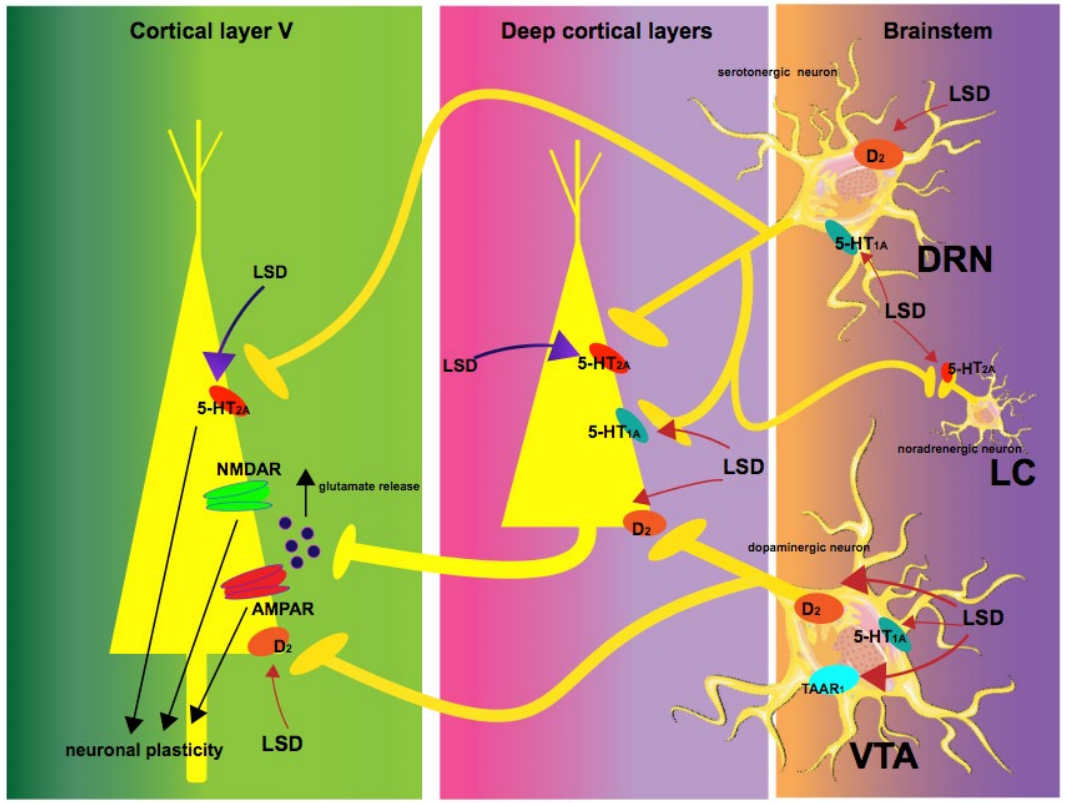
LSD and its Pathways for mental health therapeutics

LSD → 5-HT2A → AMPA → mTOR glutamatergic mPFC



Modified after
Vollenweider and Kometer
Nat Rev Neurosci, 2010

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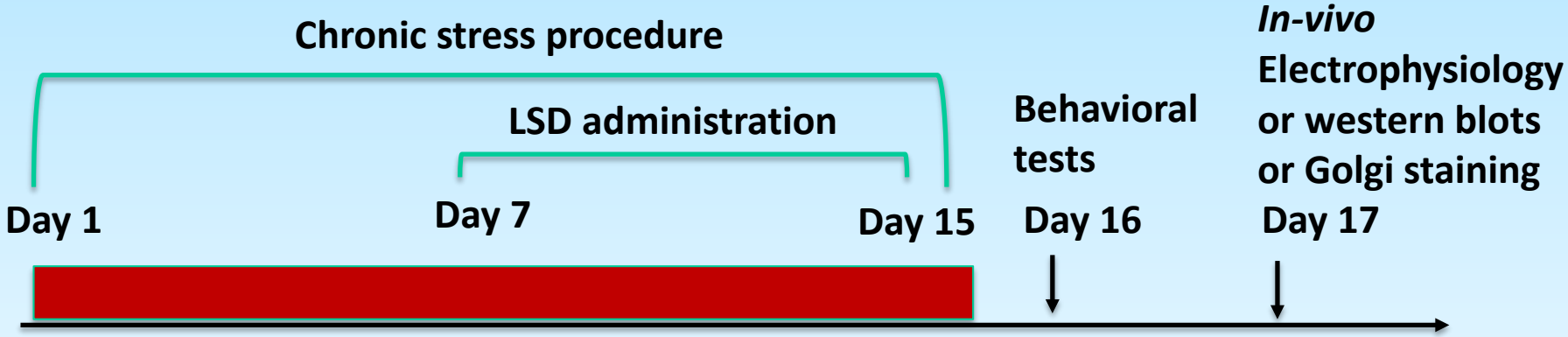
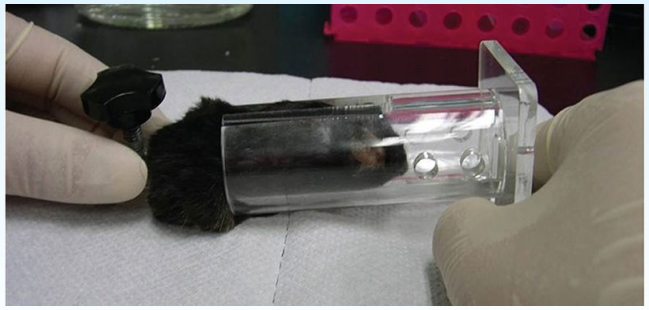
Test the effectiveness of short-term treatment (7 days) of low doses of LSD (5, 15 and 30 µg/kg per day, i.p.) to prevent anxiety-like behaviour and depressive-like behaviour induced by 15 days Chronic Stress Restrainer

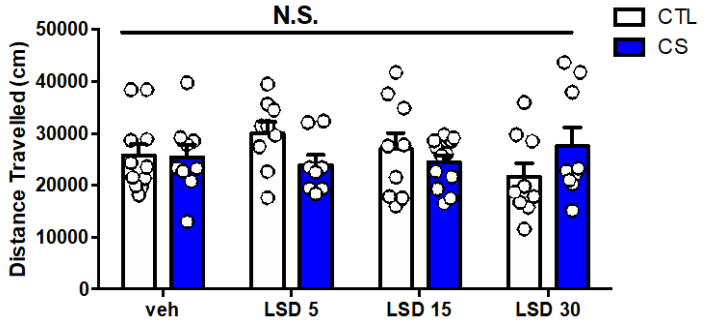


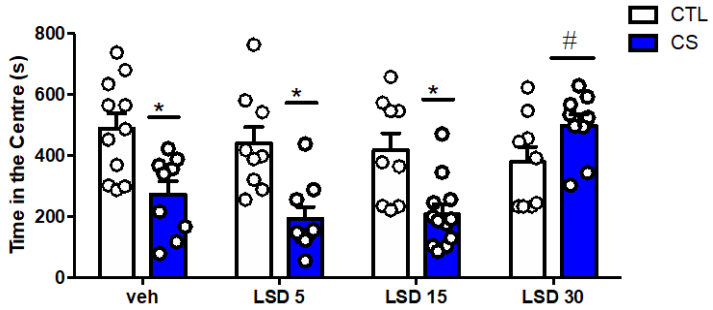


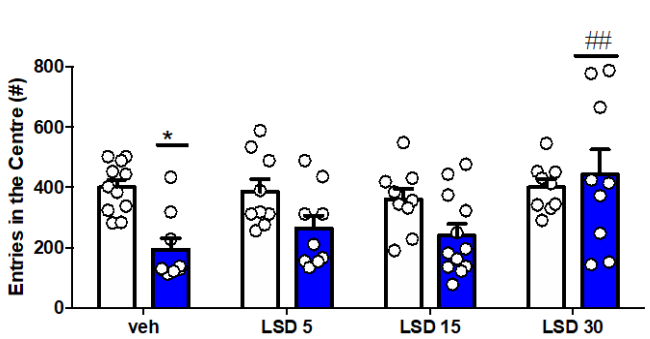
2 hours per day, 15 days

Modified protocol from *Qin et al., 2015, Neuron*

Repeated administration of LSD ameliorates anxiety-like phenotype (thigmotaxis) in the Open Field Test (OFT) (30 µg/kg, i.p., 7 days) induced by 15 days of chronic stress



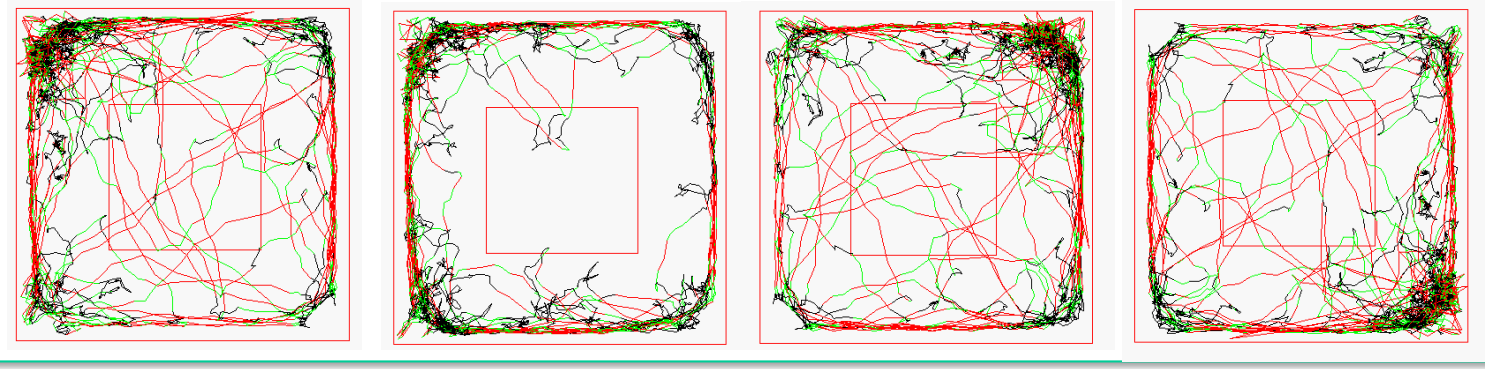




* vs CTL/veh

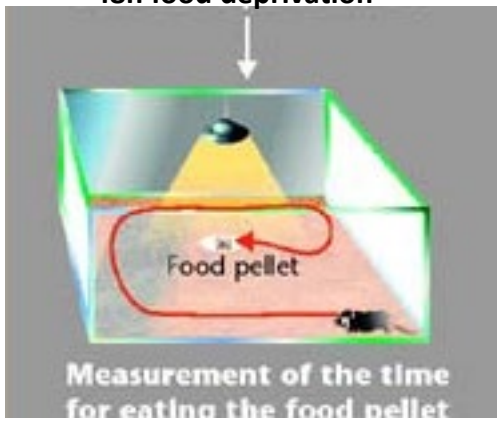
\# vs CS/veh

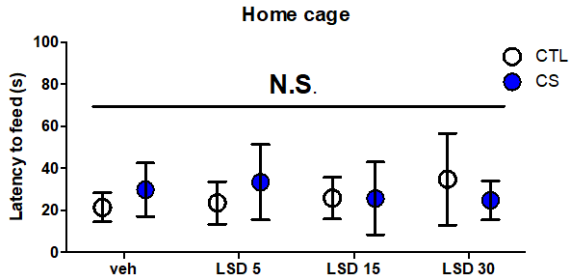
CTL/veh CS/veh CTL/LSD 30 CS/LSD 30



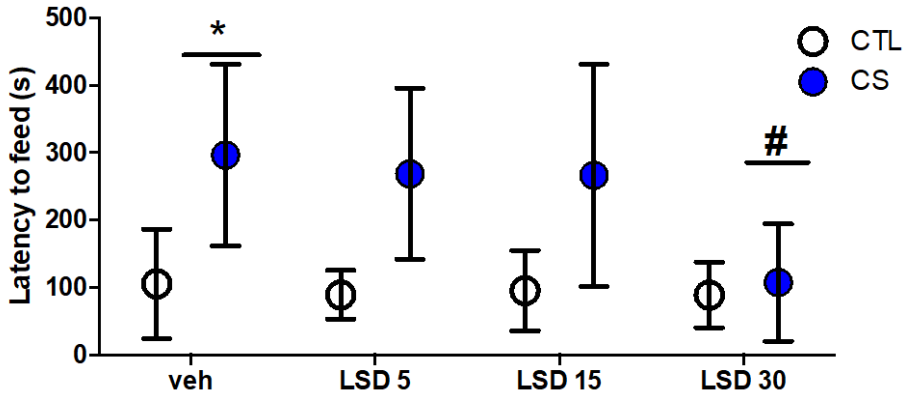
Repeated administration of LSD normalizes the latency to feed in Novelty Suppressed Feeding Test (NSFT) (30 µg/kg, i.p., 7 days), which was increased after 15 days of chronic stress

48h food deprivation





Novel Environment



* vs CTL/veh

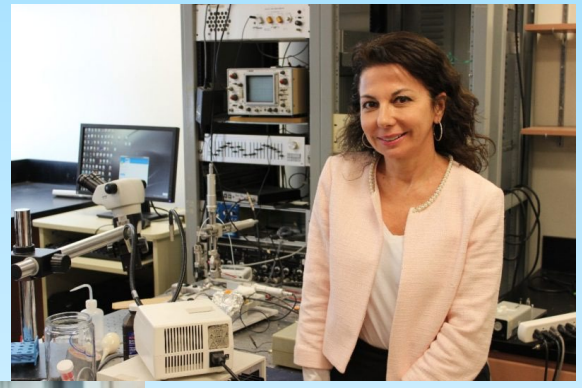
\# vs CS/veh

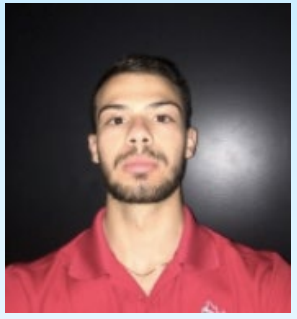
Conclusions

1. Repeated LSD administration (30ug/kg, for 7 days) enhances sociability
2. This regimen of LSD increases mPFC bursting, but not firing activity
3. Photo-inhibiting of excitatory mPFC neurons impairs social behavior and blocks LSD's pro-social effects
4. mTOR1 complex in glutamatergic neurons is essential for the prosocial effects of LSD and for its activity on AMPA and 5-HT2A receptors.
5. LSD has anti-depressant-like properties only in stressed animals
6. LSD for social anxiety? Autism? Depression?

Acknowledgment

Neurobiological Psychiatry Unit





Gabriella Gobbi
Danilo De Gregorio
Antonio Inserra
Tommy Markoupolos
Justine Enns,
Martha Lopez-Canul
Nicolas Nuñez
Youssef-El-Rahimy,

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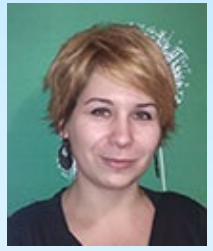
Argel Aguilar Valles
Anmol Nagpal



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