



Psychedelics: Overview on state of knowledge on molecular mechanism of action

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Forum on
NEUROSCIENCE and
NERVOUS SYSTEM DISORDERS

Exploring Psychedelics and Entactogens as Treatments for Psychiatric Disorders:
A Workshop

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	
Speakers' Bureaus	
Financial support	DIAMOND THERAPEUTICS, AURORA, DELMAR
Other	Patents inventor use LSD licensed to Diamond Therapeutics , inventor on melatonin MT2 agonist, 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: patent inventor

Objectives

- What is the effect of LSD in social behavior, anxiety and consciousness?
- What is the mechanism of action underlying these effects?

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SCIENCES
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MEDICINE

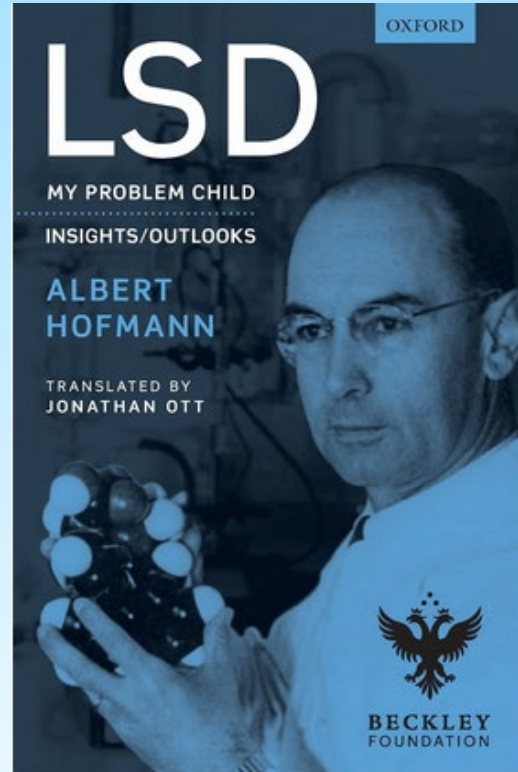
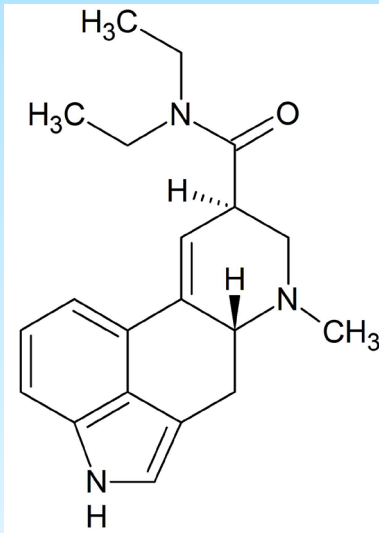


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Lysergic acid diethylamide (LSD)

History and Clinical evidence



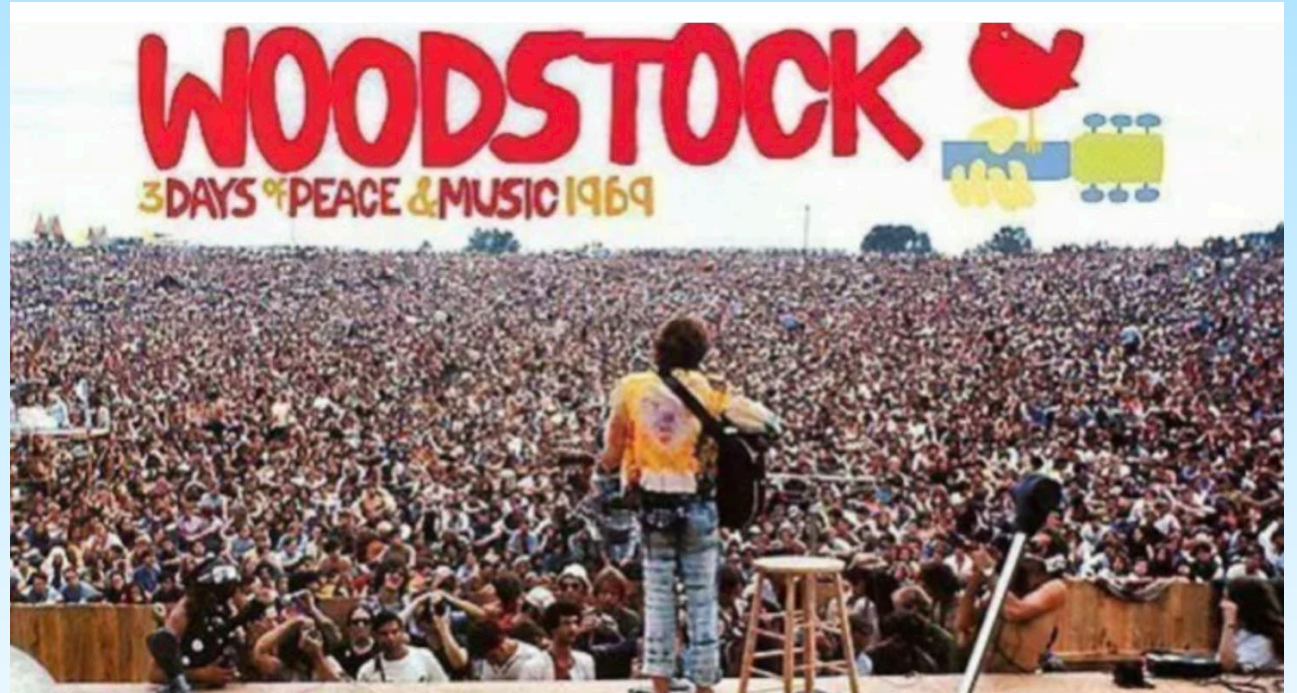
Effects of LSD

- LSD increases empathy
- LSD enhances social behavior
- and feeling of togetherness
- LSD decreases anxiety
- LSD decrease alcohol intake

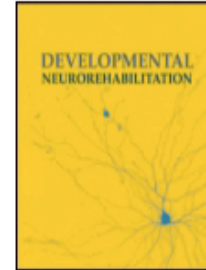
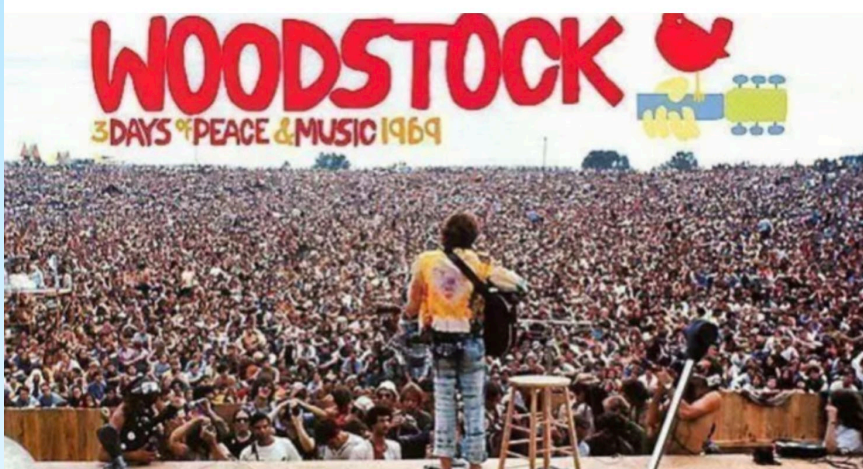
- Synthesized in 1938 by Albert Hoffman
- From lysergic acid in the ergot fungus

LSD in preclinical models

- Social Behavior ?
- Anxiety ?
- Depression ?



LSD –Facilitator of Social behavior, effects on ASD



Developmental Neurorehabilitation



ISSN: 1751-8423 (Print) 1751-8431 (Online) Journal homepage: <https://www.tandfonline.com/loi/ipdr20>

Flashback to the 1960s: LSD in the treatment of autism

Jeff Sigafoos, Vanessa A. Green, Chaturi Edrisinha & Giulio E. Lancioni



MINI REVIEW
published: XX XX 2021
doi: 10.3389/fphar.2021.749068



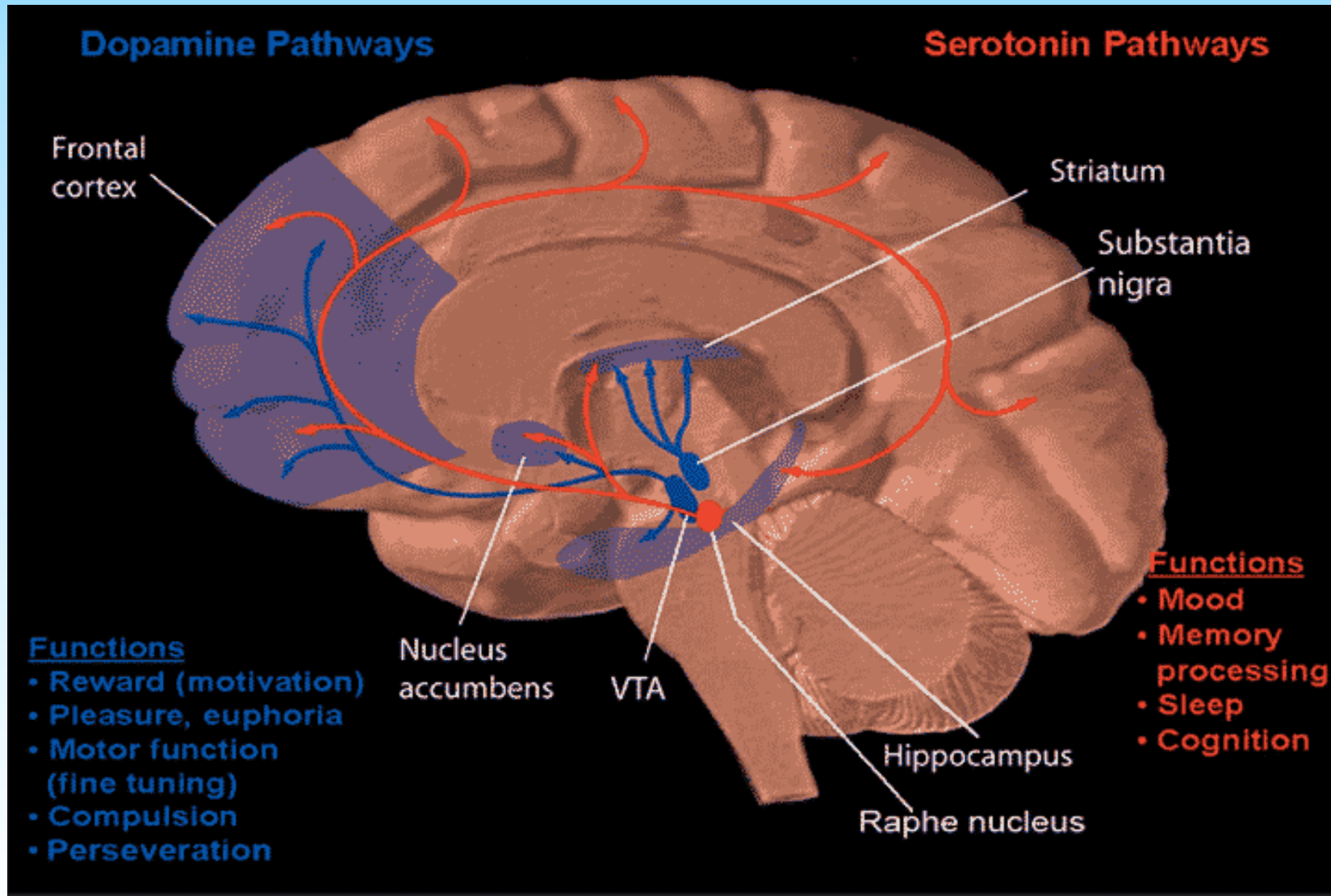
Evaluating the Potential Use of Serotonergic Psychedelics in Autism Spectrum Disorder

Athanasios Markopoulos¹, Antonio Inserra¹, Danilo De Gregorio^{1†} and Gabriella Gobbi^{1,2*}

[†]Neurobiological Psychiatry Unit, Department of Psychiatry, McGill University, Montreal, QC, Canada, ²McGill University Health Centre, McGill University, Montreal, QC, Canada

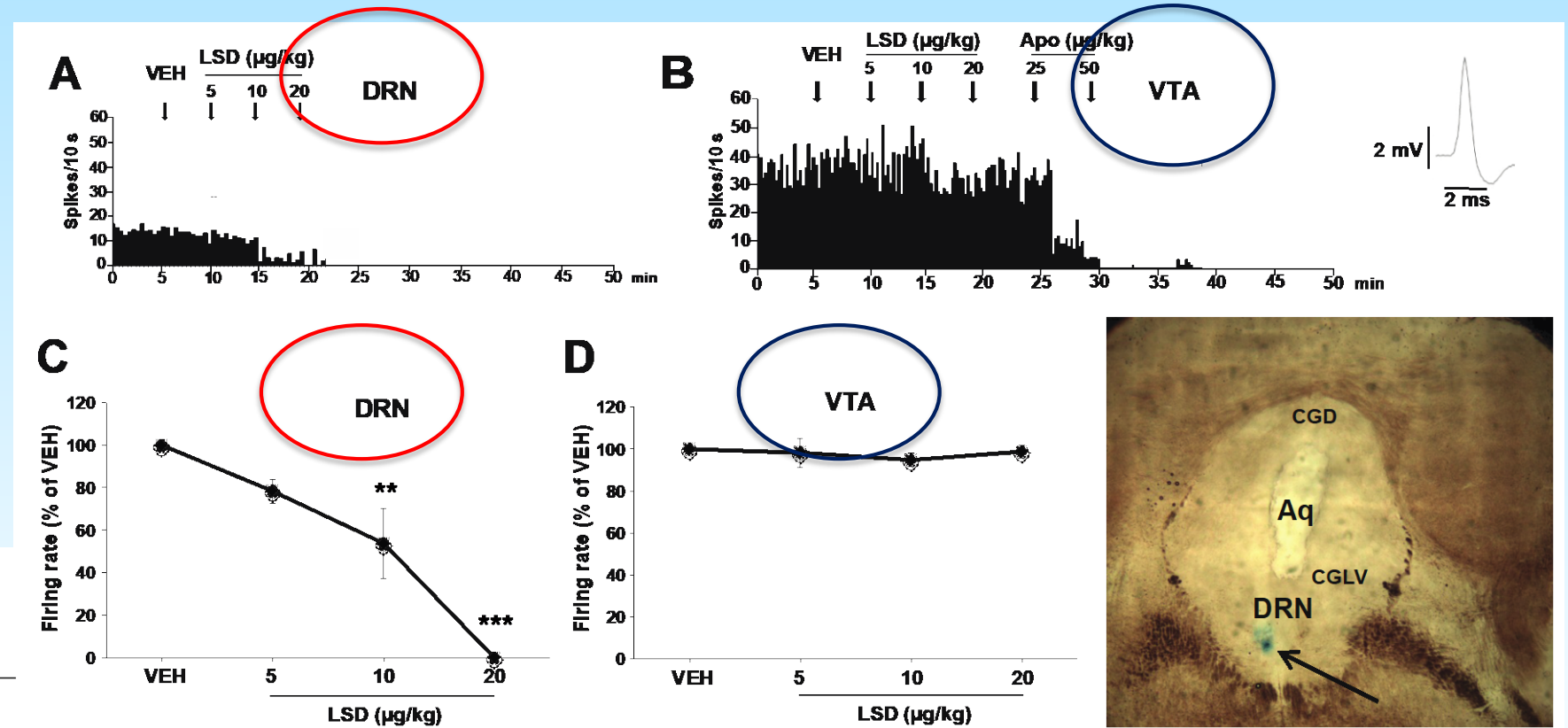
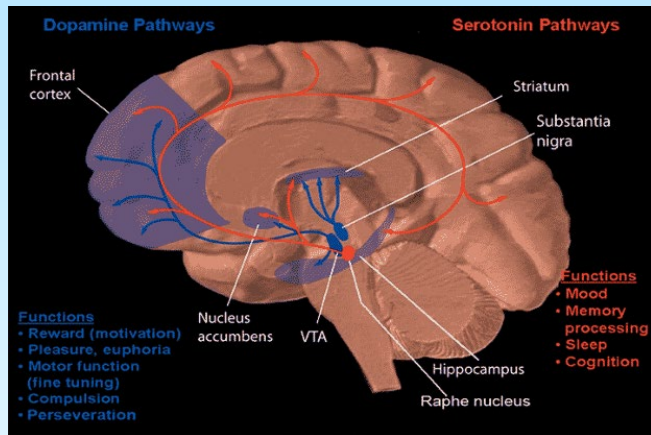
LSD: a question of doses
Low or High?

LSD micro-doses vs full doses: the 5-HT vs DA dilemma



LSD low doses vs full doses: the 5-HT vs DA dilemma

Low doses of LSD (5-20 $\mu\text{g/kg}$, i.v.) decreased 5-HT neurons of the DRN, but not DA neurons of the VTA in rat



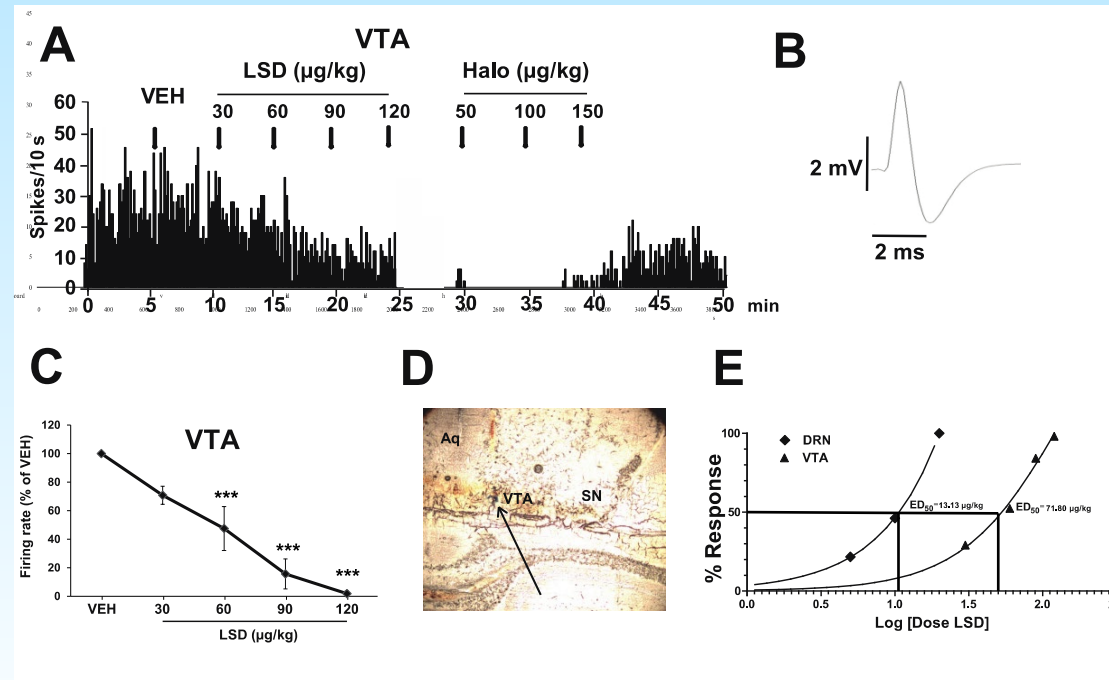
Science
AAAS

Lysergic Acid Diethylamide: Sensitive Neuronal Units in the Midbrain Raphe
Author(s): George K. Aghajanian, Warren E. Foote and Michael H. Sheard
Source: *Science*, Aug. 16, 1968, New Series, Vol. 161, No. 3842 (Aug. 16, 1968), pp. 706-708
Published by: American Association for the Advancement of Science
Stable URL: <https://www.jstor.org/stable/1725847>

De Gregorio et al., Pharmacol Res., 2016

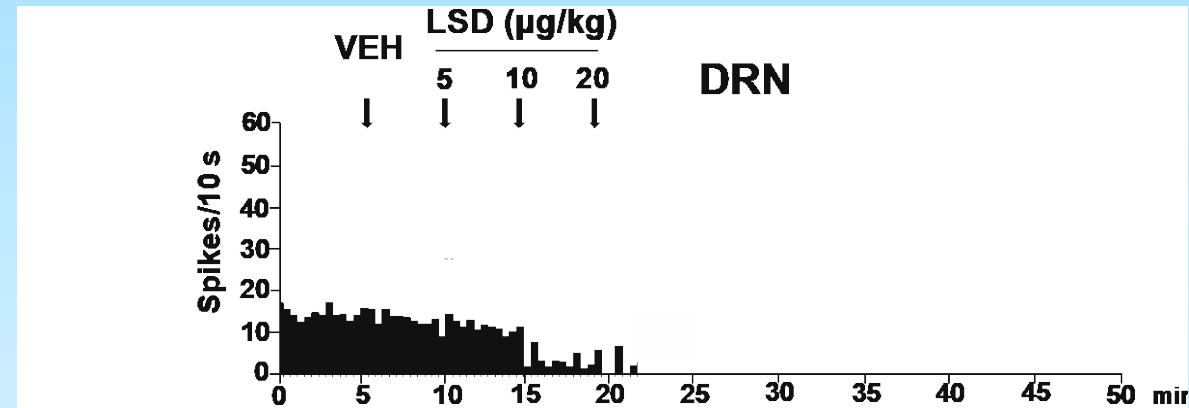
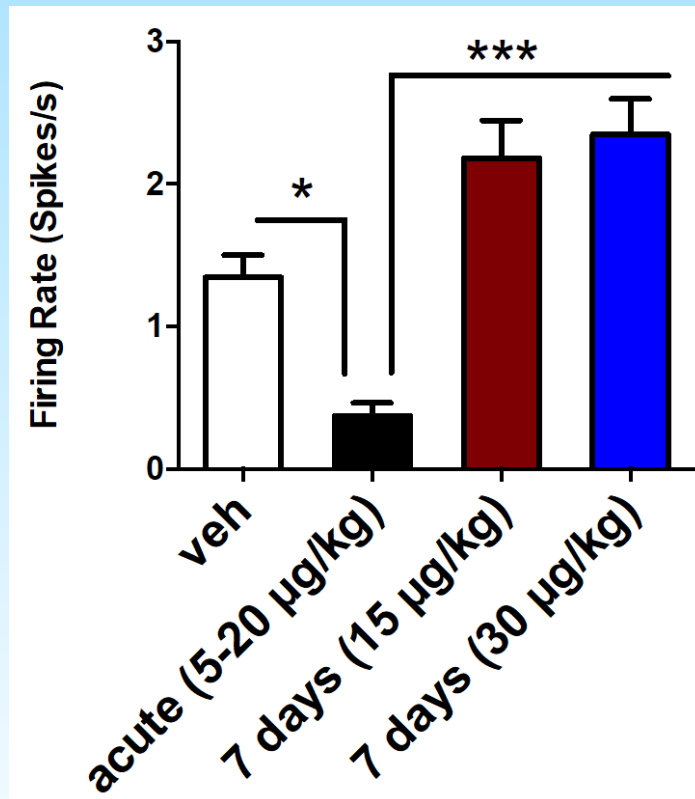
LSD “micro-doses” vs full doses: the 5-HT vs DA dilemma

**Low doses of LSD (5-20 $\mu\text{g/kg}$, i.v.) decreased 5-HT neurons of the DRN,
Only high doses (60-120 $\mu\text{g/kg}$, i.v.) activates DA neurons of the VTA**

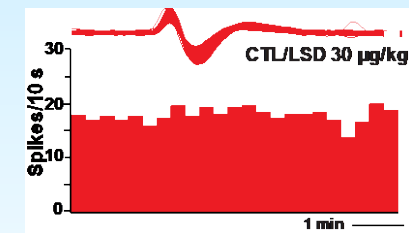
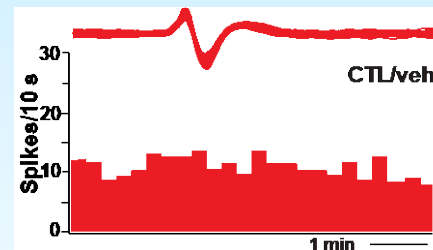


Repeated treatment with LOW doses of LSD (15-30 $\mu\text{g/kg}$ for 7 days) enhances 5-HT firing activity

ACUTE TREATMENT



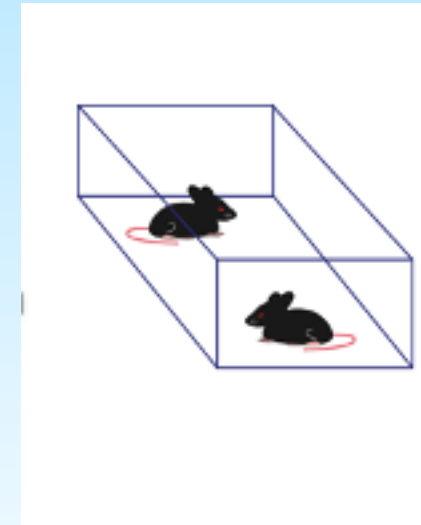
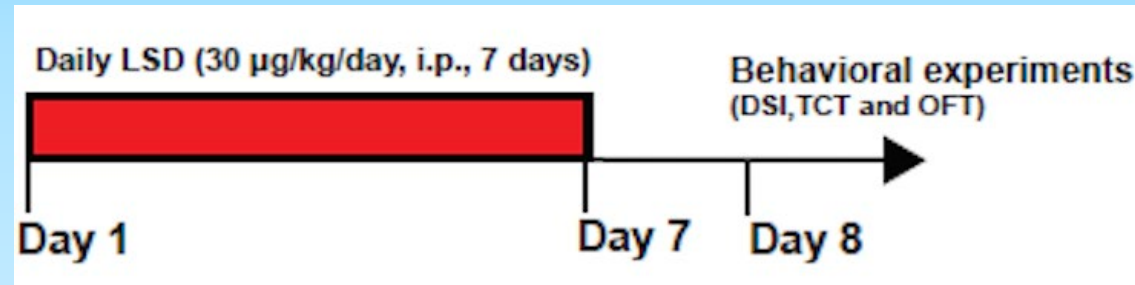
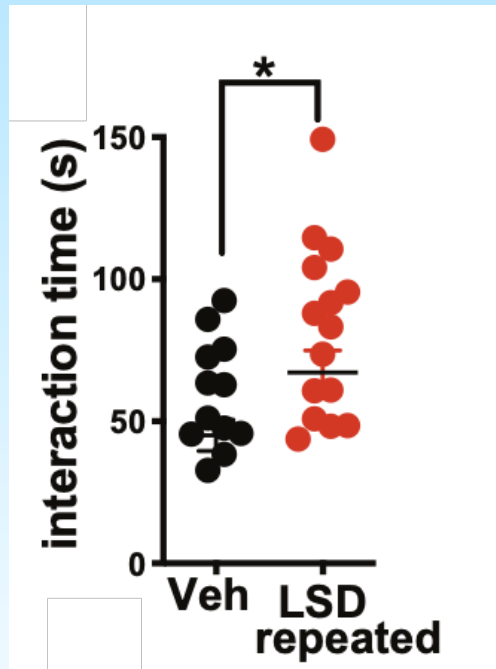
REPEATED TREATMENT



LSD in social behavior

Repeated LSD (30 $\mu\text{g/kg/day}$ for 7 days) enhances social behavior in Direct Social Interaction Test

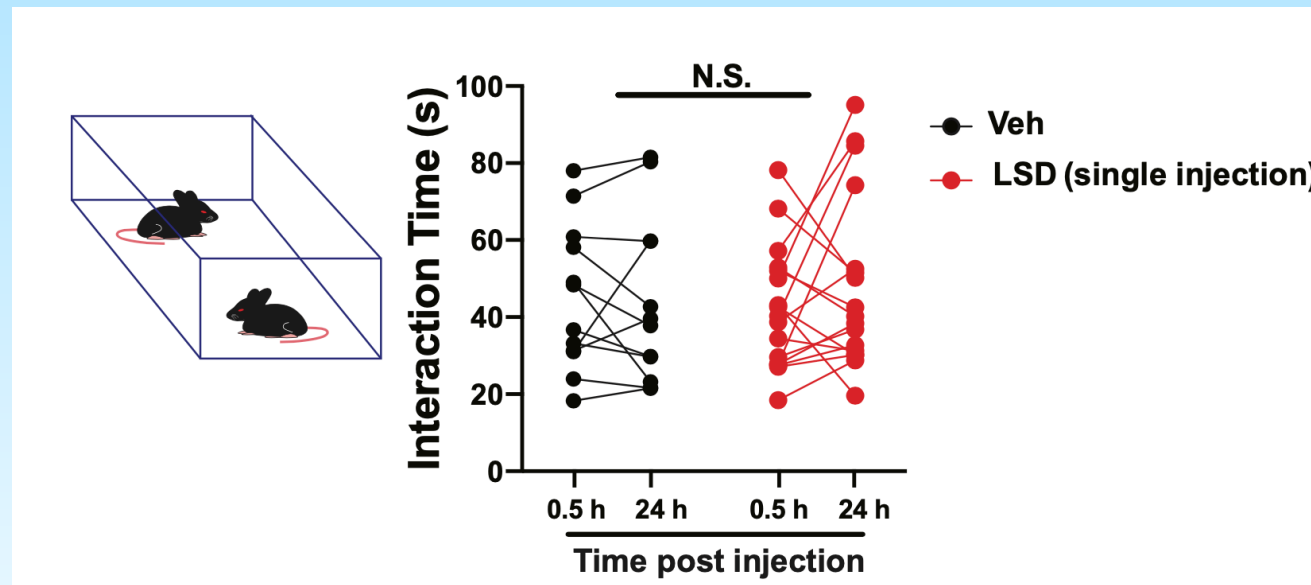
Repeated LSD



De Gregorio et al., PNAS, 2021

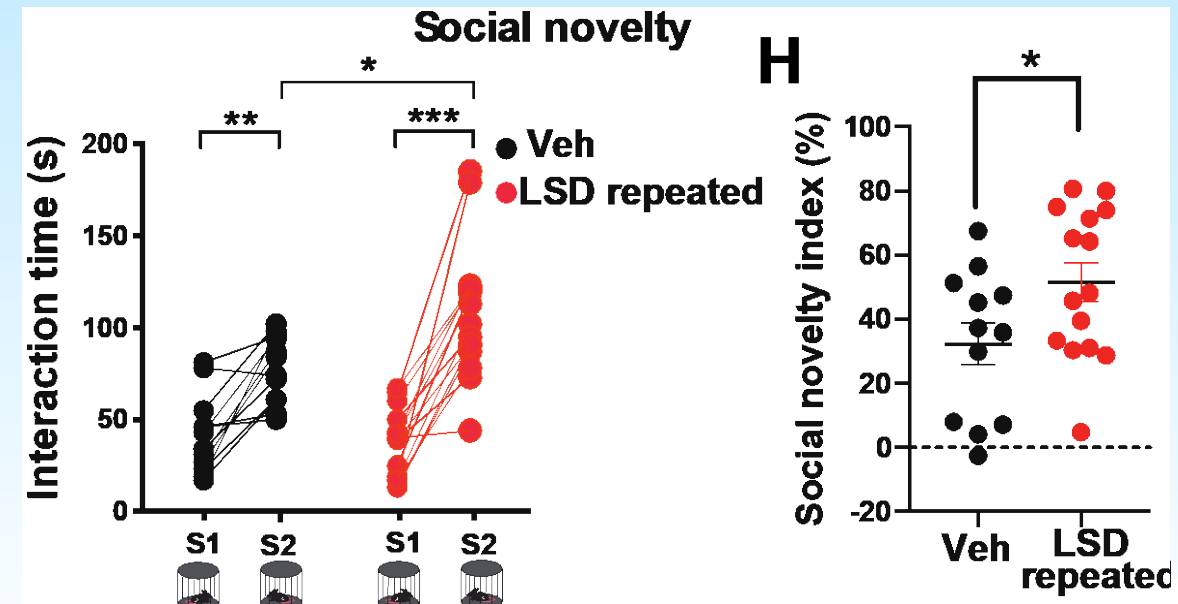
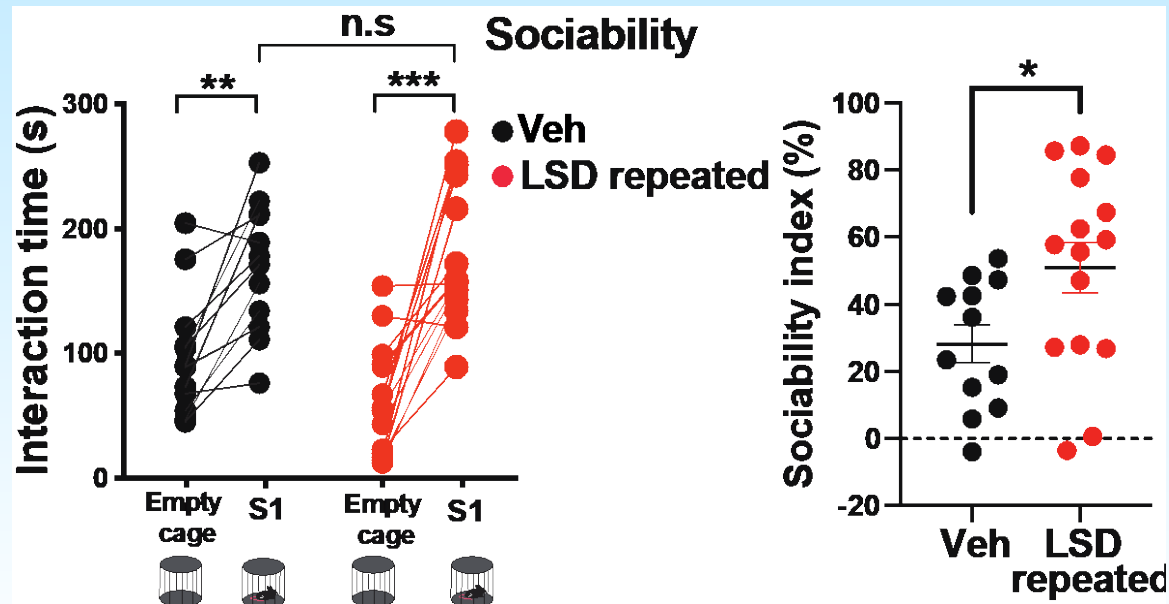
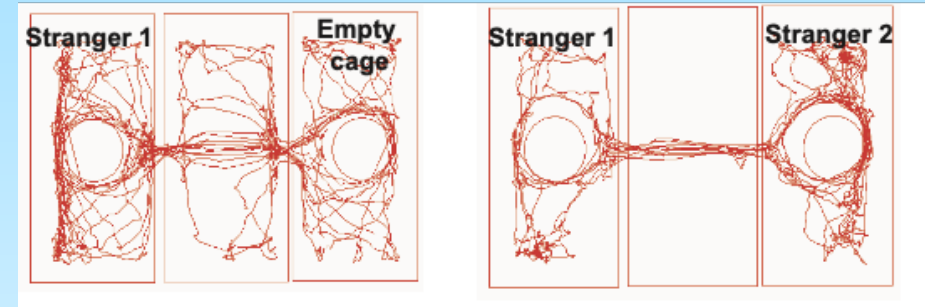
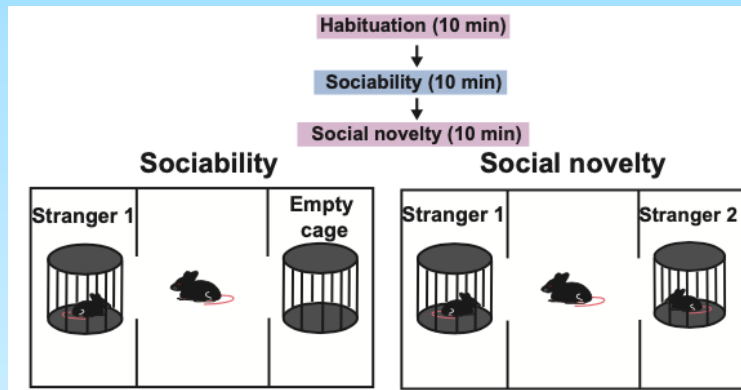
Acute low dose of LSD (30 $\mu\text{g/kg}$) does not enhance social behavior in Direct Social Interaction Test

Acute LSD



De Gregorio et al., PNAS, 2021

Repeated LSD (30 $\mu\text{g/kg/day}$ for 7 days) enhances Social behavior in the Three Chambers Sociability Test



De Gregorio et al., PNAS, 2021

Social Behavior Results

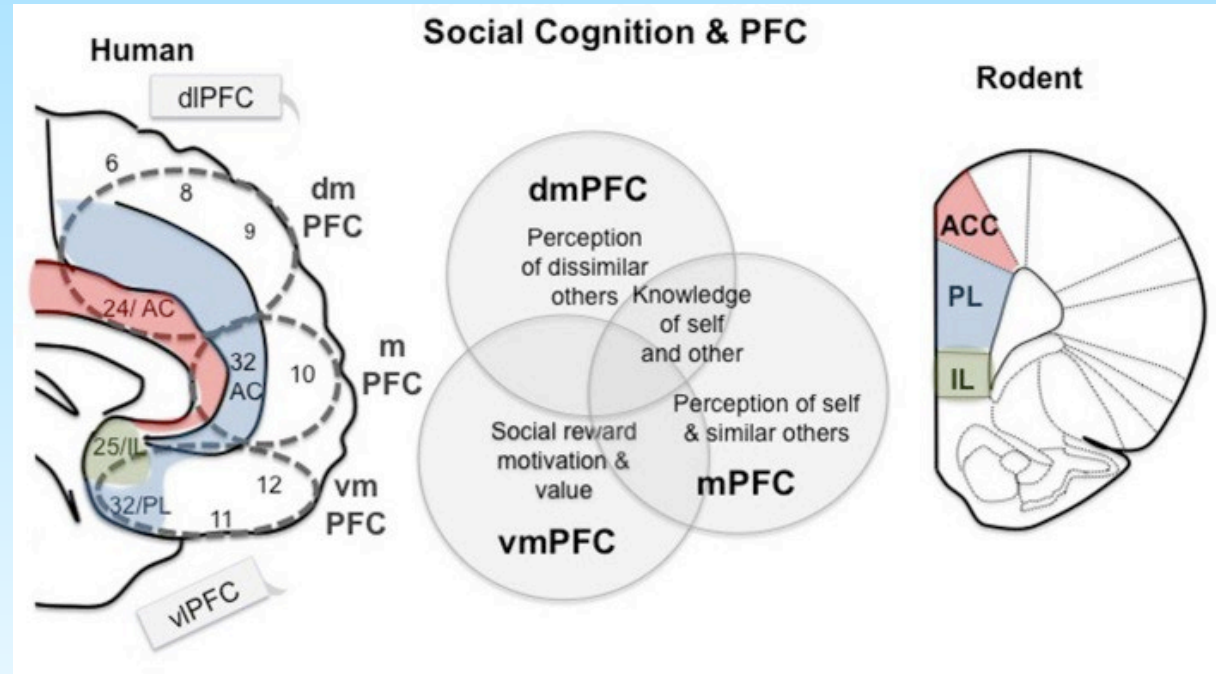
Repeated, low dose LSD (30µg/kg/day for 7 days):

- Increases social interaction
- Increases preference for a social stimulus
- Increases preference for social novelty
- Increases 5-HT firing activity

What is the neural basis of these changes in behavior?

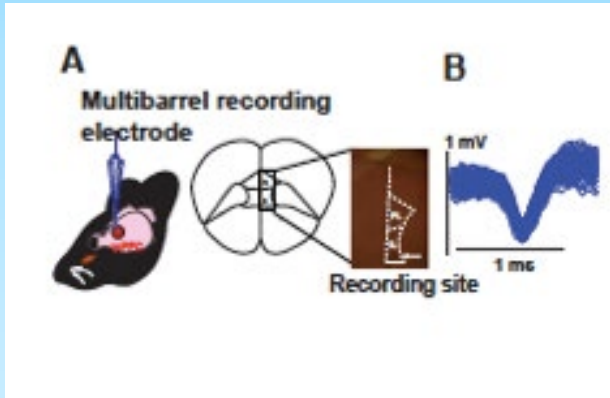
Medial Prefrontal Cortex (mPFC)

- Social cognition
- Implication of mPFC in Autism spectrum Disorder
- High 5-HT_{2A} receptor expression

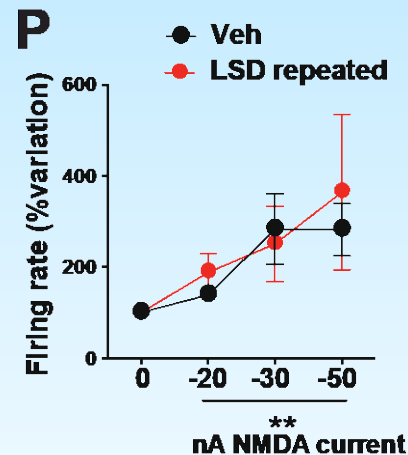


Bicks et al., Front. Psychology 2015

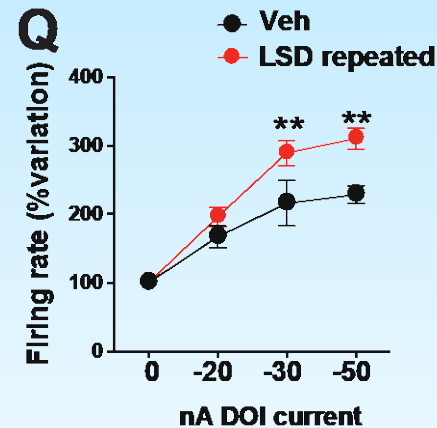
Repeated LSD (30 $\mu\text{g/kg}$) potentiates AMPA and 5-HT_{2A} responses, but not NMDA or 5-HT_{1A} responses in mPFC



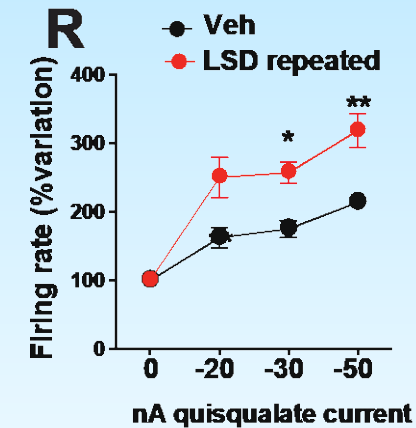
NMDA



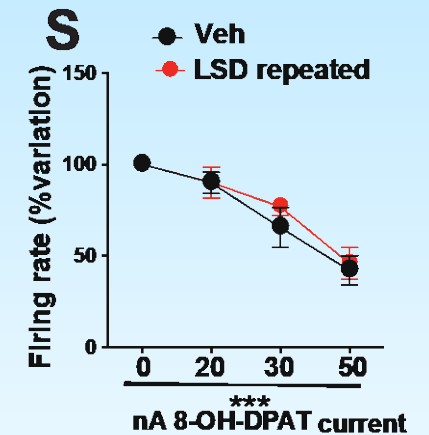
5-HT_{2A}



AMPA



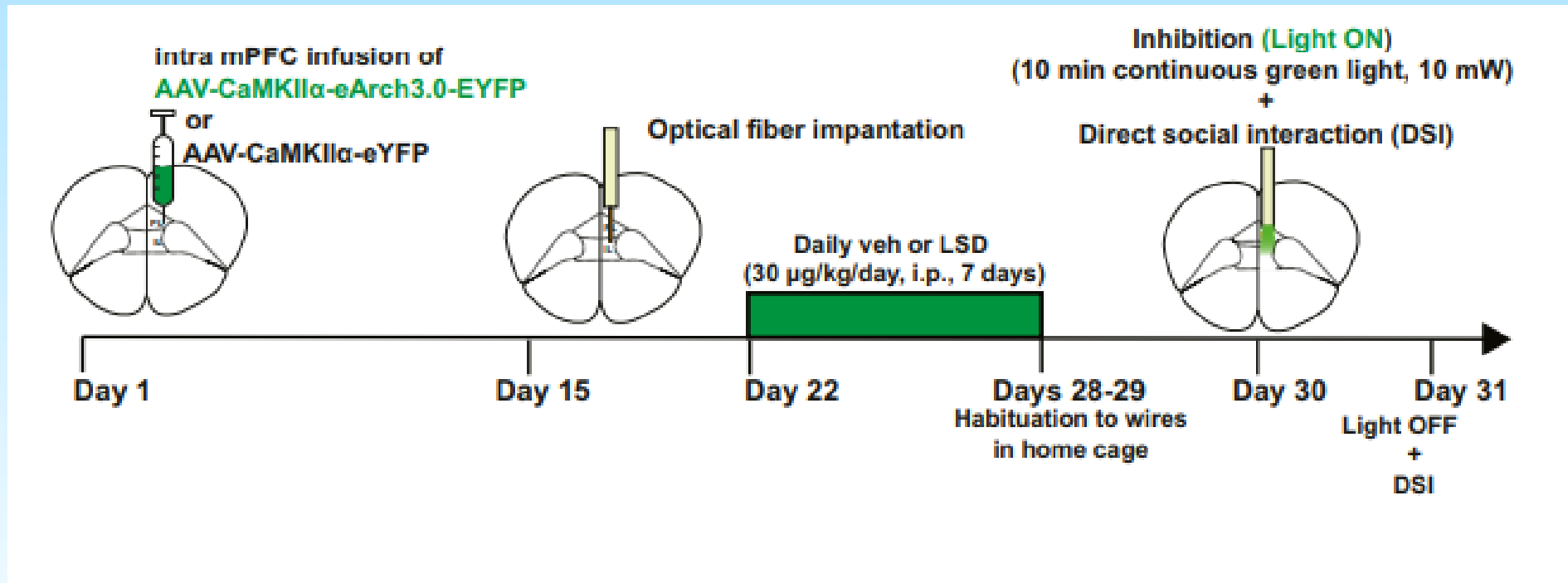
5-HT_{1A}



De Gregorio et al., PNAS, 2021

Optogenetics: photoinhibition of excitatory neurons in mPFC

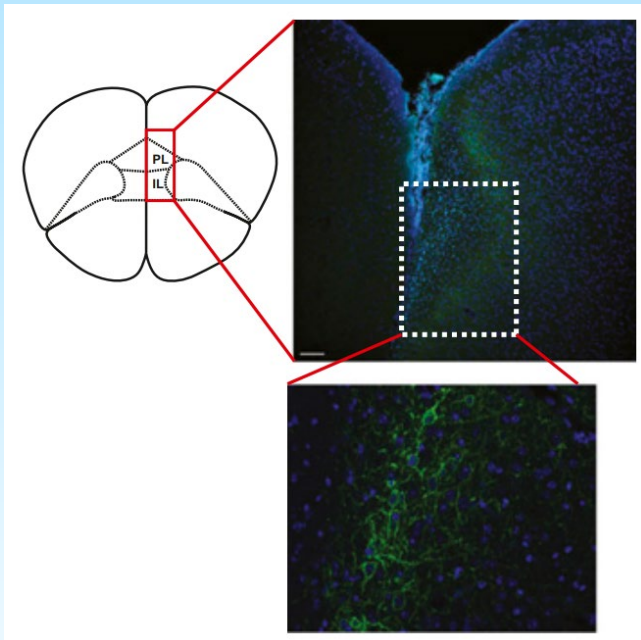
Experimental timeline:



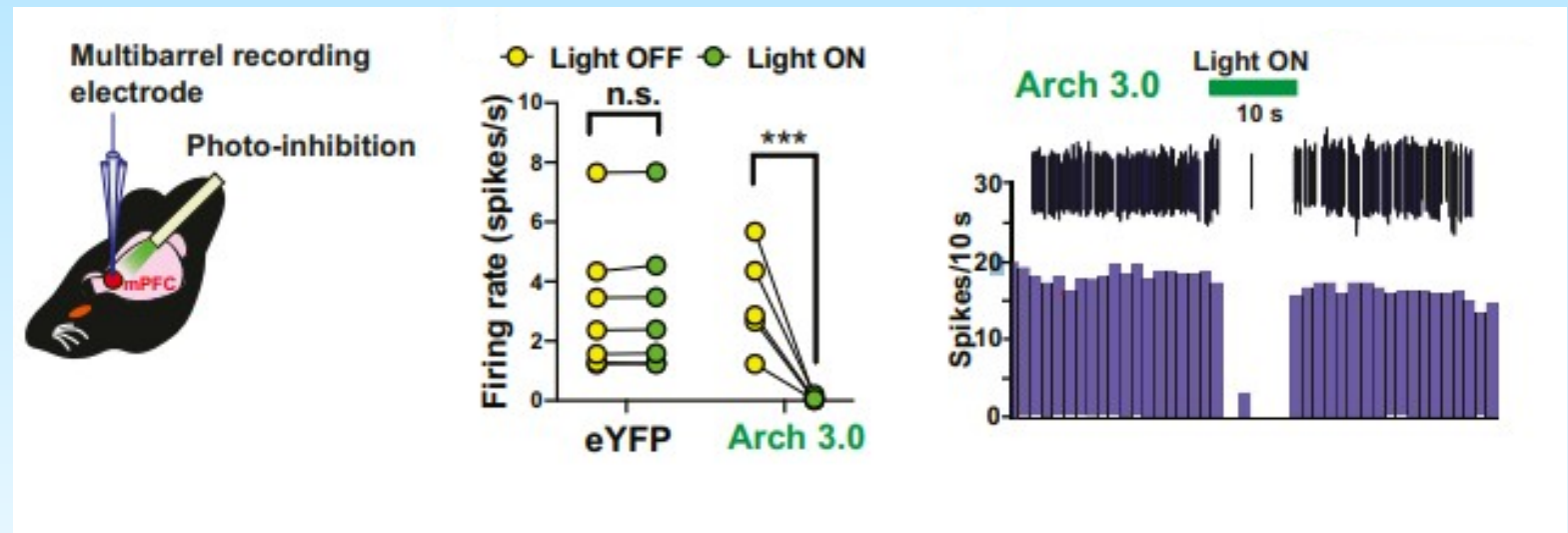
De Gregorio et al., 2021

Optogenetic Photoinhibition of excitatory neurons in mPFC: Inhibition of PFC glutamatergic neurons

Histological verification



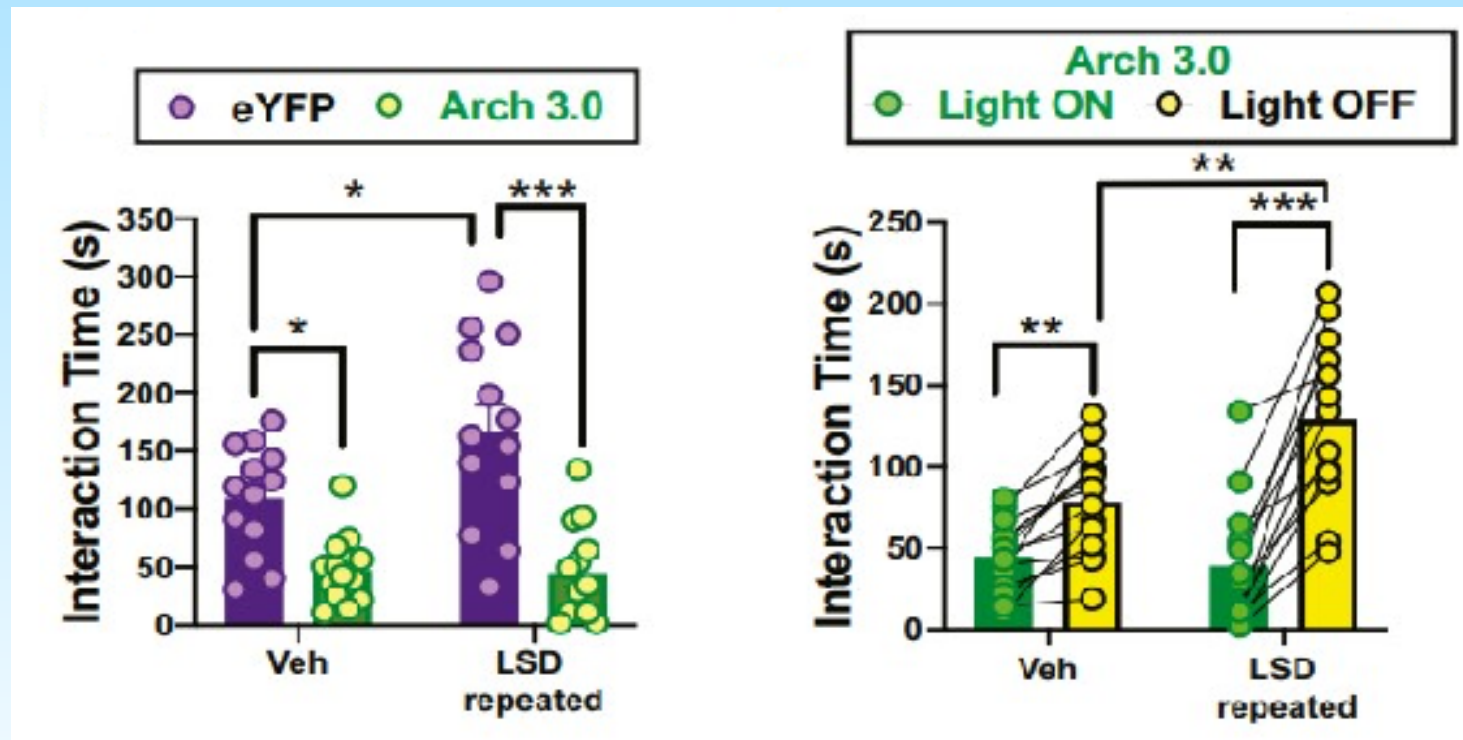
Electrophysiological verification



De Gregorio et al., PNAS, 2021

Optogenetic Photoinhibition of excitatory neurons in mPFC decreases social behavior and nullifies the prosocial effects of the LSD

Social behavior with mPFC inhibition



eYFP:
Enhanced yellow
fluorescent
protein,
Fluoresces
yellow/green
light

Arch 3.0:
Archaerhodopsin 3.0,
Inhibitory
photosensitize ion
channel

Photo-inhibition:
Decrease sociability in veh animals
and LSD fails to increase
sociability

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

De Gregorio et al., PNAS, 2021

LSD needs 5-HT_{2A} and AMPA activation as well as
intact mPFC glutamatergic neurons
for social behavior promotion



mTOR1 : Protein Kinase regulating cellular process

mTOR and fast-acting antidepressant ketamine



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Science. Author manuscript; available in PMC 2011 June 16.

Published in final edited form as:

Science. 2010 August 20; 329(5994): 959–964. doi:10.1126/science.1190287.

mTOR-dependent synapse formation underlies the rapid antidepressant effects of NMDA antagonists

Nanxin Li, Boyoung Lee, Rong-Jian Liu, Mounira Banasr, Jason M. Dwyer, Masaaki Iwata, Xiao-Yuan Li, George Aghajanian, and Ronald S. Duman

Laboratory of Molecular Psychiatry, Center for Genes and Behavior, Departments of Psychiatry and Neurobiology, Yale University School of Medicine, 34 Park Street, New Haven, CT 06508, USA

European Psychiatry 29 (2014) 419–423



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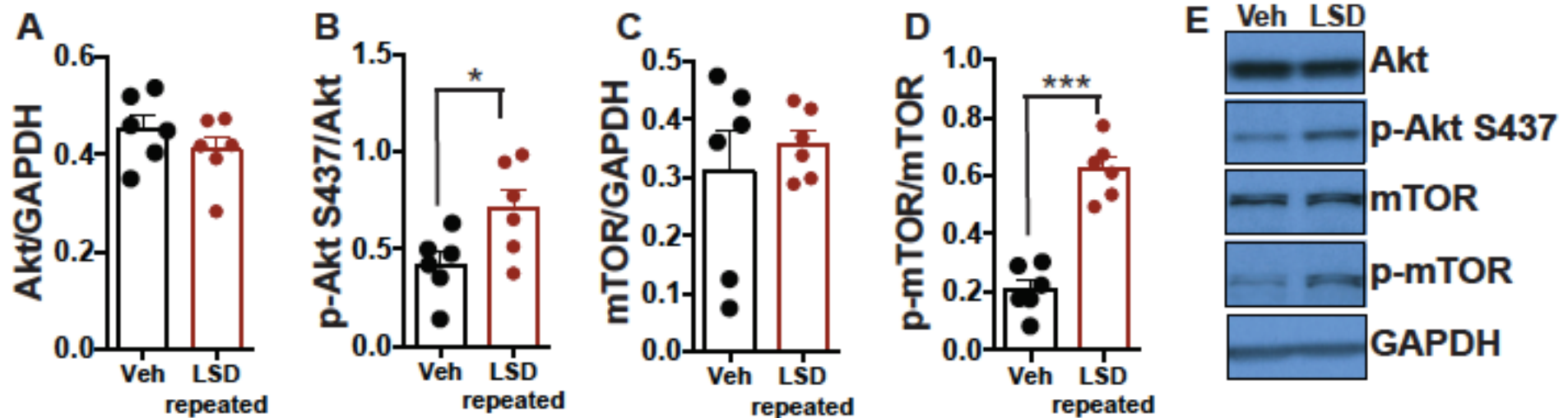
Original article

Ketamine-induced antidepressant effects are associated with AMPA receptors-mediated upregulation of mTOR and BDNF in rat hippocampus and prefrontal cortex

W. Zhou¹, N. Wang¹, C. Yang, X.-M. Li, Z.-Q. Zhou^{**}, J.-J. Yang^{*}

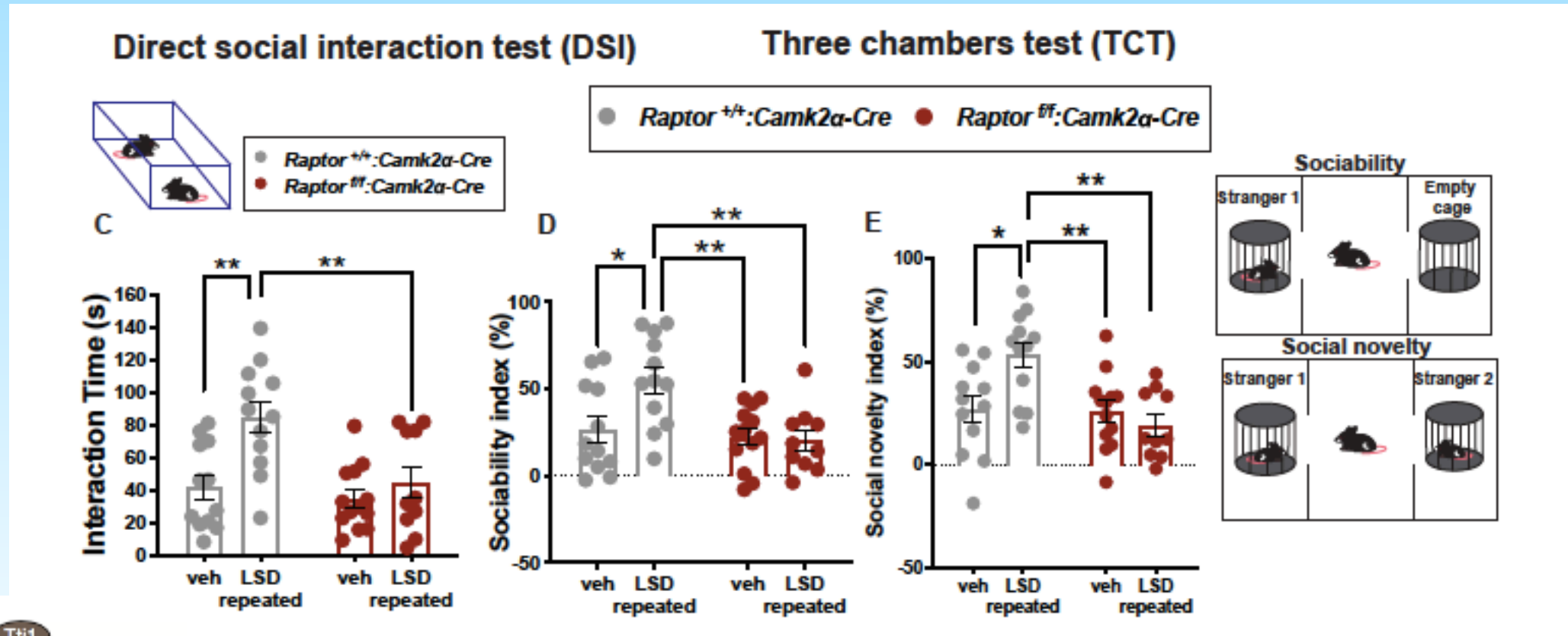
Department of Anesthesiology, School of Medicine, Jinling Hospital, Nanjing University, No. 305, East Zhongshan Road, Nanjing 210002, China

Repeated LSD increases Akt and mTOR phosphorylation in mPFC

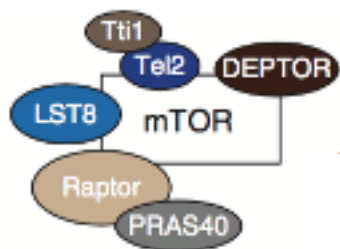


De Gregorio et al., PNAS, 2021

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



mTORC1



De Gregorio et al., PNAS, 2021

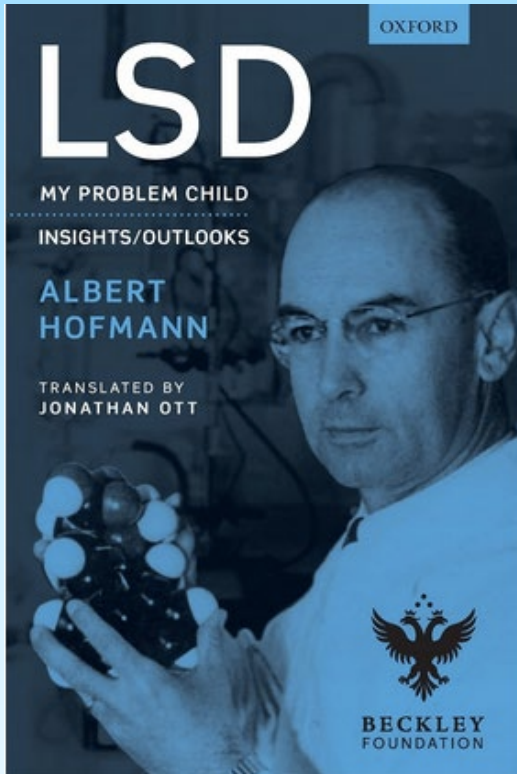
LSD requires intact mPFC and mTOR



LSD in anxiety

Lysergic acid diethylamide (LSD)

ANXIETY



LSD-assisted psychotherapy for anxiety associated with a life-threatening disease: A qualitative study of acute and sustained subjective effects

Peter Gasser¹, Katharina Kirchner² and Torsten Passie³

Psychopharm

Journal of Psychopharmacology
2015, Vol. 29(1) 57–68
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DOI: 10.1177/0269881114555249
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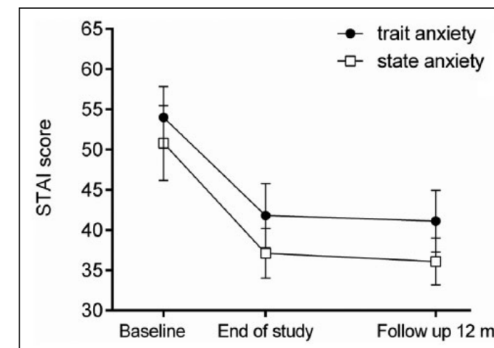
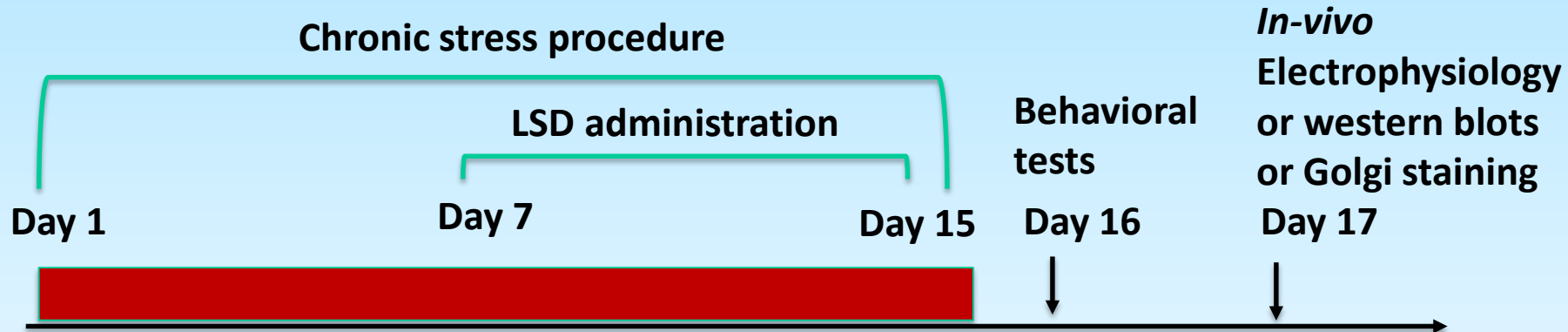


Figure 2. LTFU results of STAI state and trait scores.
STAI measurements, max. score 80 points in each branch trait anxiety and state anxiety), 20 items 4-points Likert scale). $N=9$, i.e. all participants who received two full-dose LSD sessions. Data are mean \pm SEM.

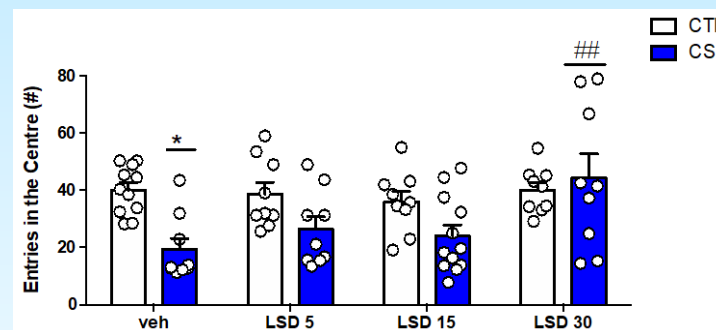
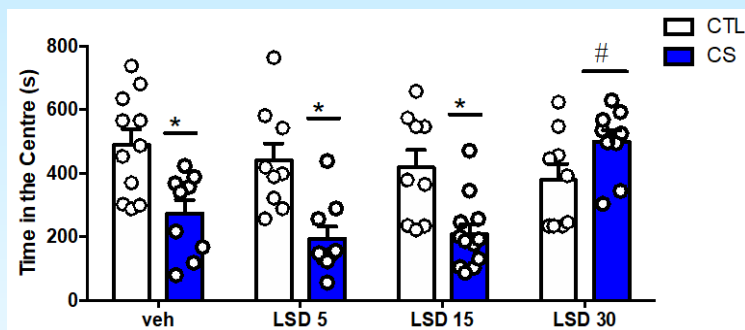
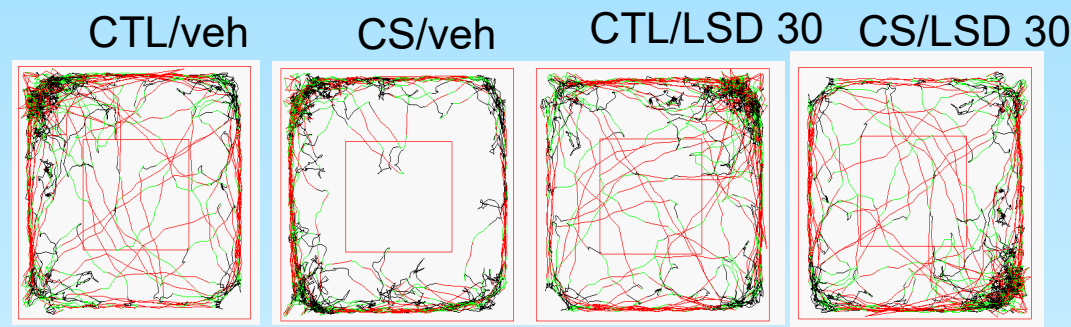
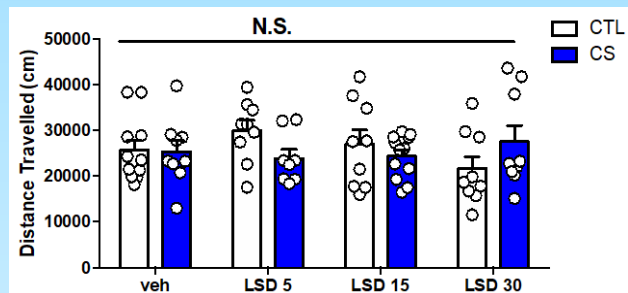
LSD for prevention of stress symptoms in mice

Test the effectiveness of short-term treatment (7 days) of low doses of LSD (5, 15 and 30 $\mu\text{g}/\text{kg}$ 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 LSD prevents stress-induced anxiety in Open Field Test

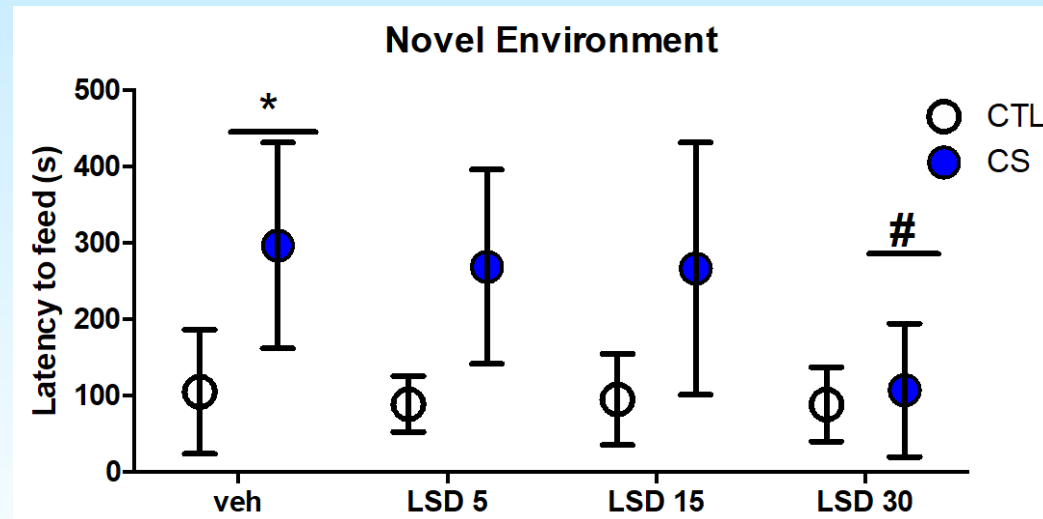
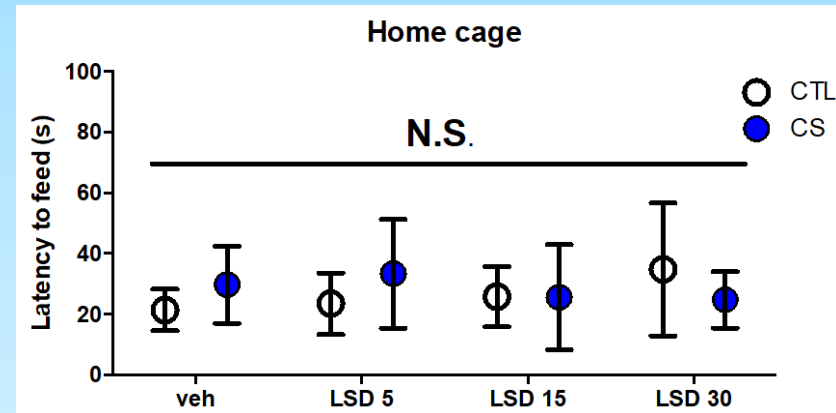
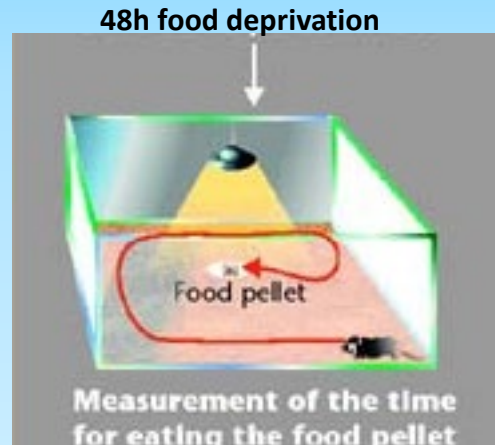


* vs CTL/veh

vs CS/veh

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

Repeated LSD prevents stress-induced anxiety in the Novelty Suppressed Feeding Test



* vs CTL/veh

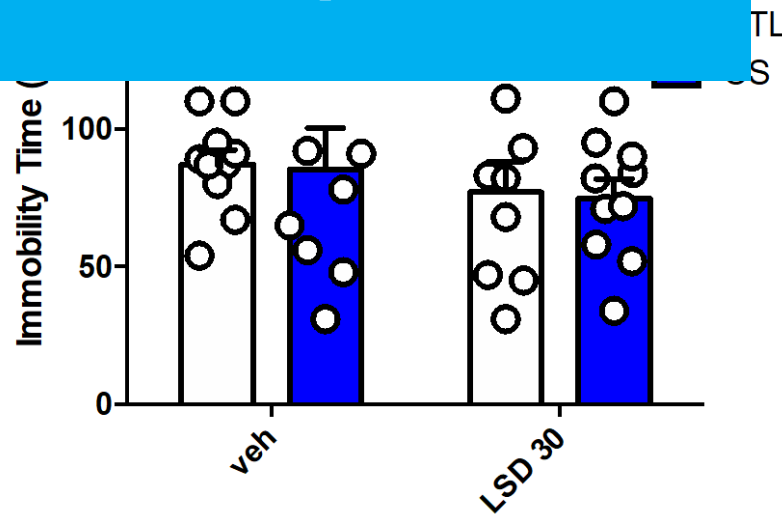
vs CS/veh

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

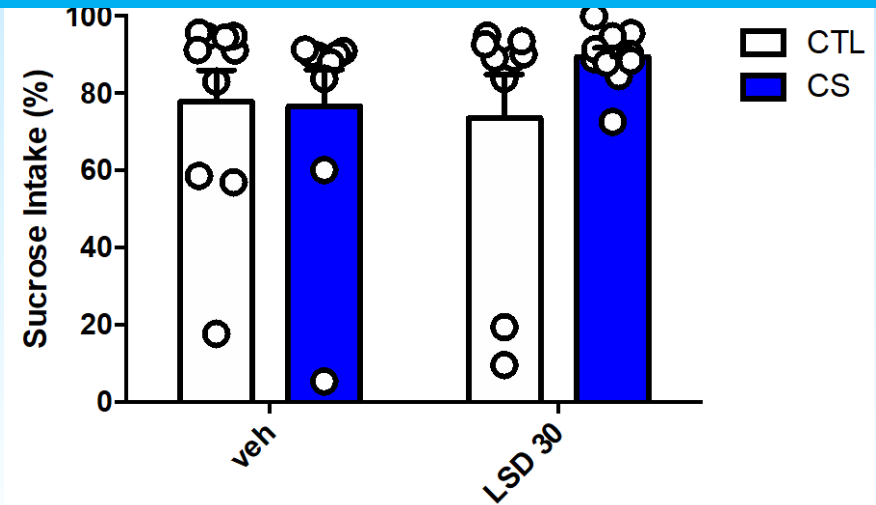
Chronic restraint stress as well as LSD (30 μ g/kg, i.p., 7 days) have no effects on depressive-like behavior



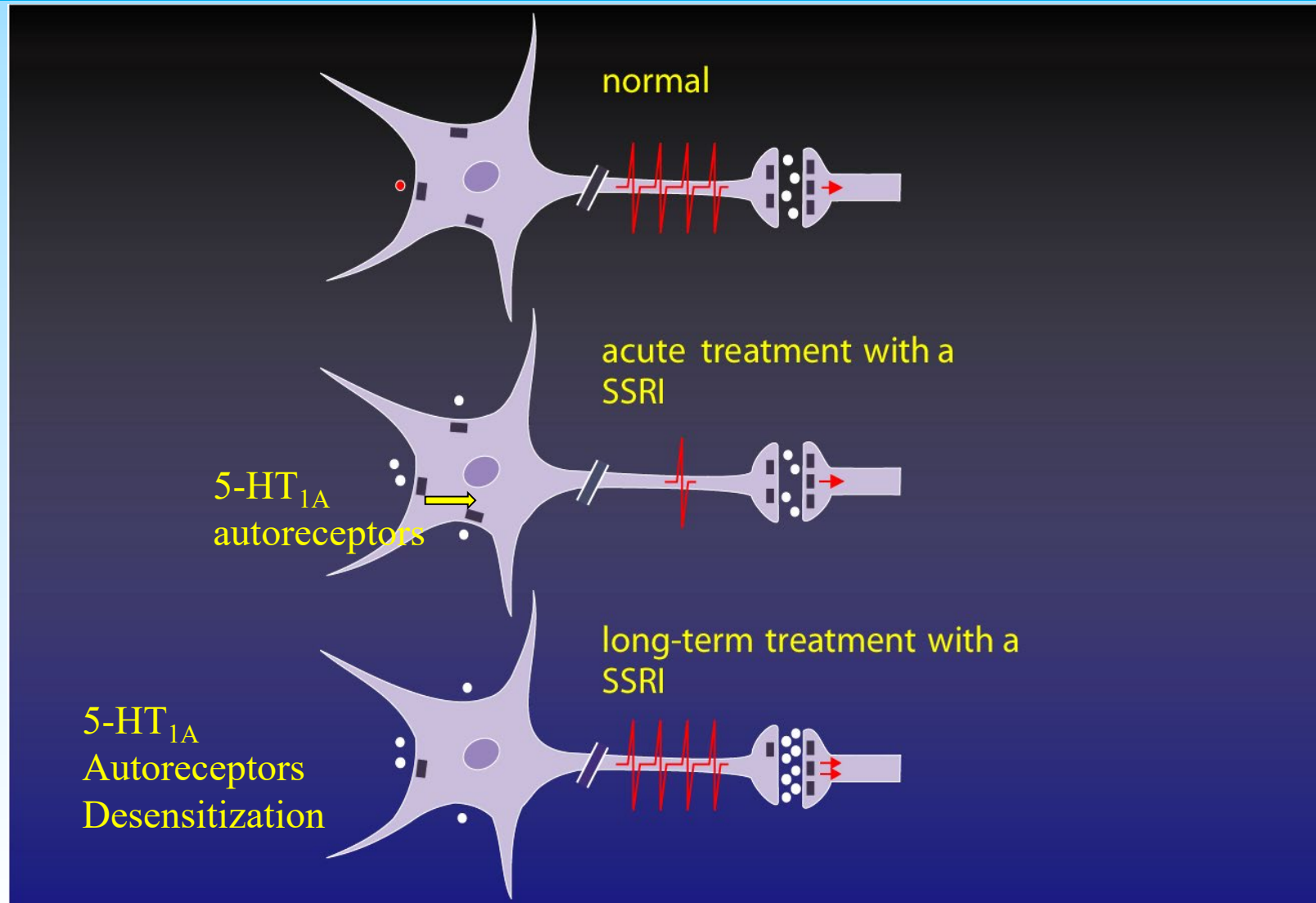
LSD did not affect the immobility time in the Forced Swim Test (FST) for depression



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



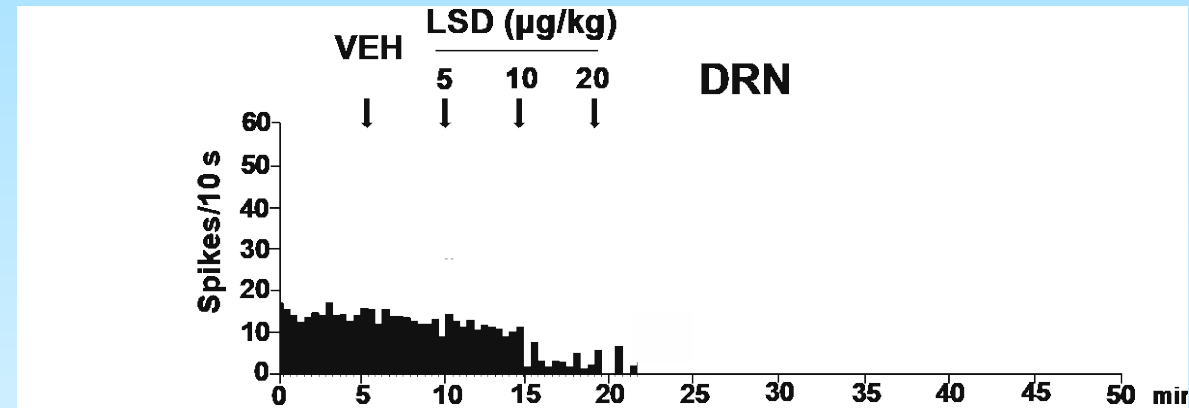
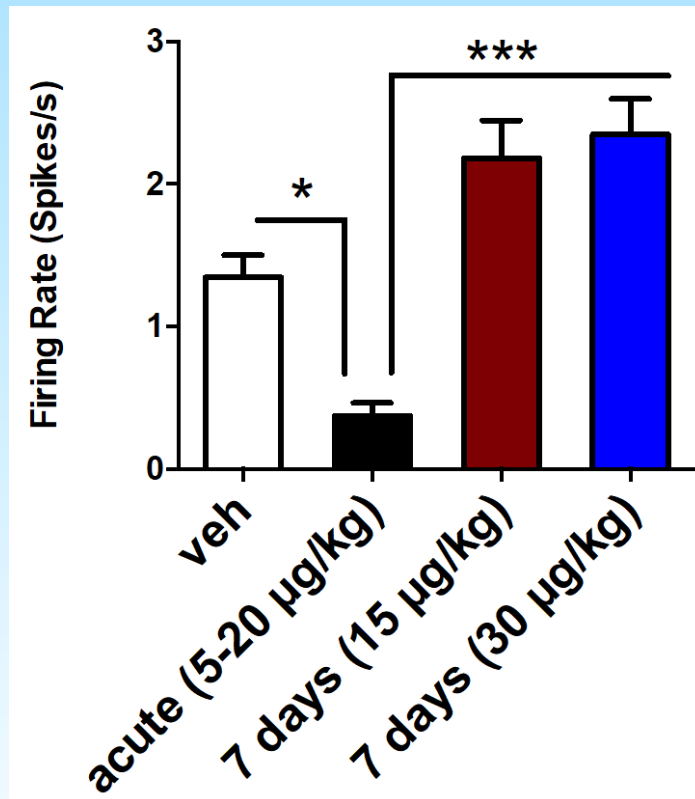
Mechanism of actions of SSRIs: 5-HT_{1A} receptor desensitization



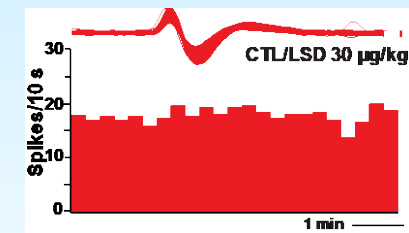
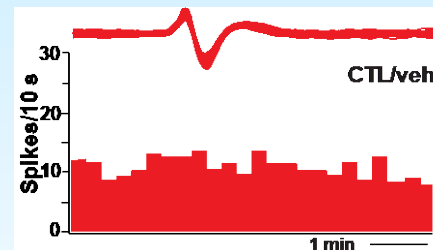
*Blier and De Montigny,
Neuropsychopharmacology,
1999*

Repeated treatment with LOW doses of LSD (15-30 $\mu\text{g/kg}$ for 7 days) enhances 5-HT firing activity

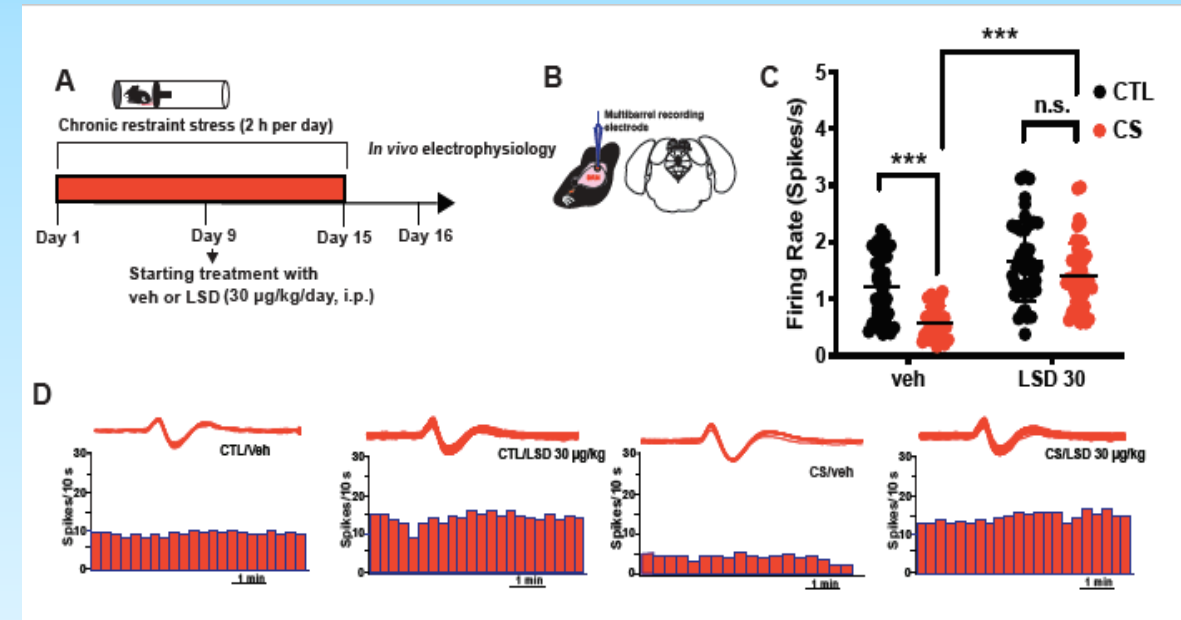
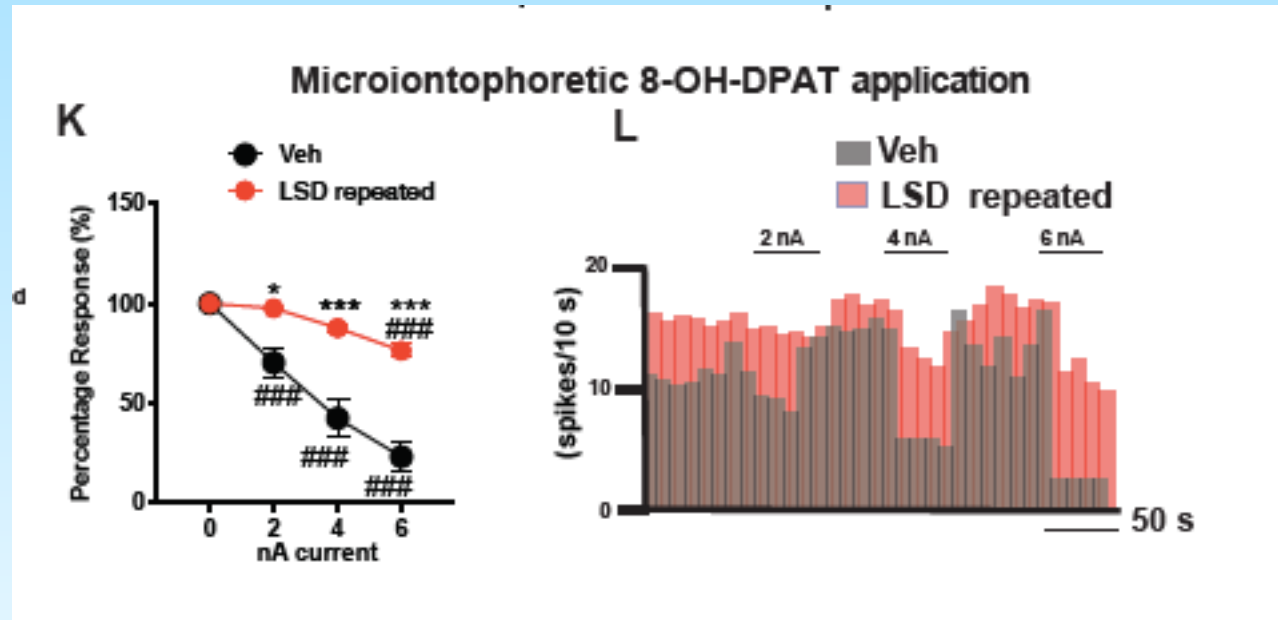
ACUTE TREATMENT



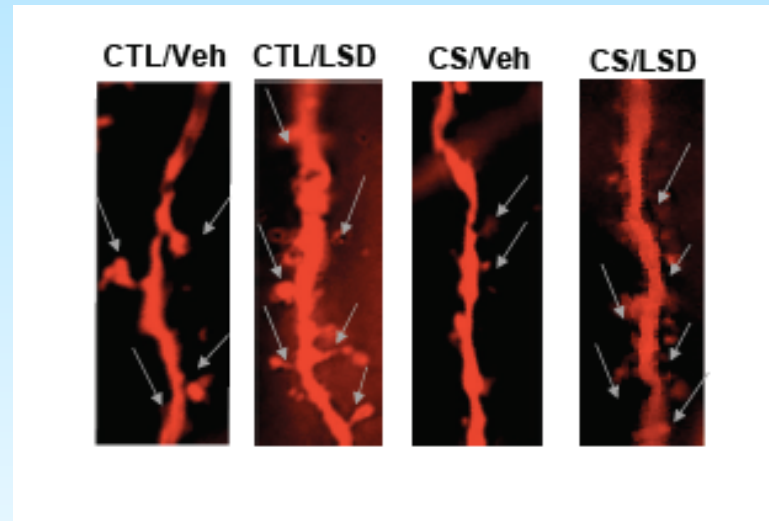
REPEATED TREATMENT



Repeated LSD treatment restores 5-HT firing activity after stress, by a desensitization of the 5-HT_{1A} autoreceptors



Repeated LSD treatment restores spines loss after stress

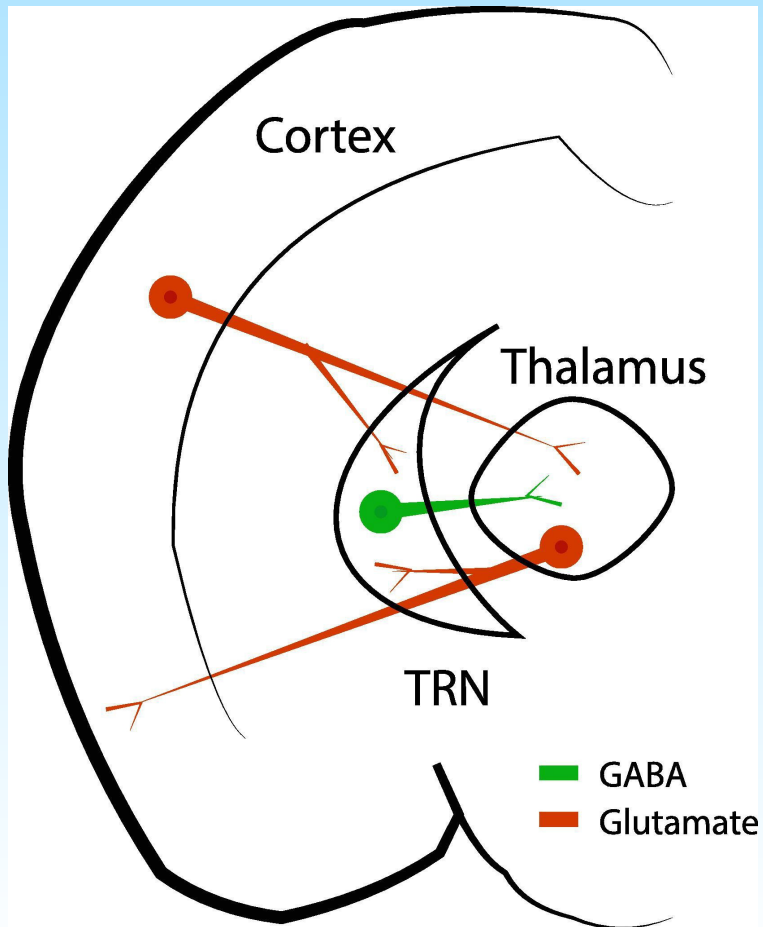


Conclusions: LSD in Social Behavior and Anxiety

1. Repeated LSD administration (30 μ g /kg, for 7 days) enhances sociability
2. Photo-inhibiting of excitatory mPFC neurons impairs social behavior and blocks LSD's pro-social effects
3. mTOR1 complex in glutamatergic neurons is essential for the prosocial effects of LSD and for its activity on AMPA and 5-HT_{2A} receptors.
4. LSD has anti-anxiety-like properties only in stressed animals
5. LSD similarly to SSRIs, restore 5-HT firing activity after stress through a 5-HT_{1A} autoreceptor desensitization.

LSD in consciousness and vigilance state

Psychedelics and cortico-thalamo-cortical pathways and reticular thalamus nuclei (TRN)



The Reticular thalamic nucleus or thalamic reticular nucleus (TRN) is implicated in:

- Vigilance
- Sleep (slow waves sleep)

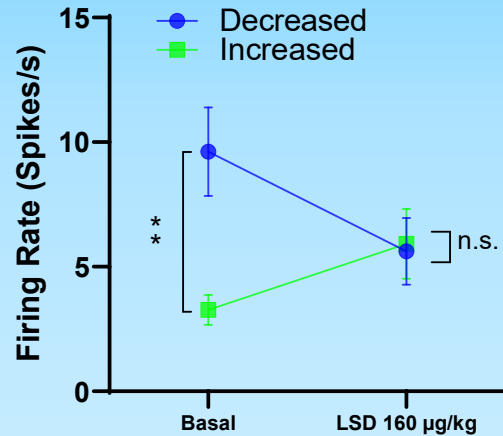
Impairment of TRN in:

- Autism
- Schizophrenia

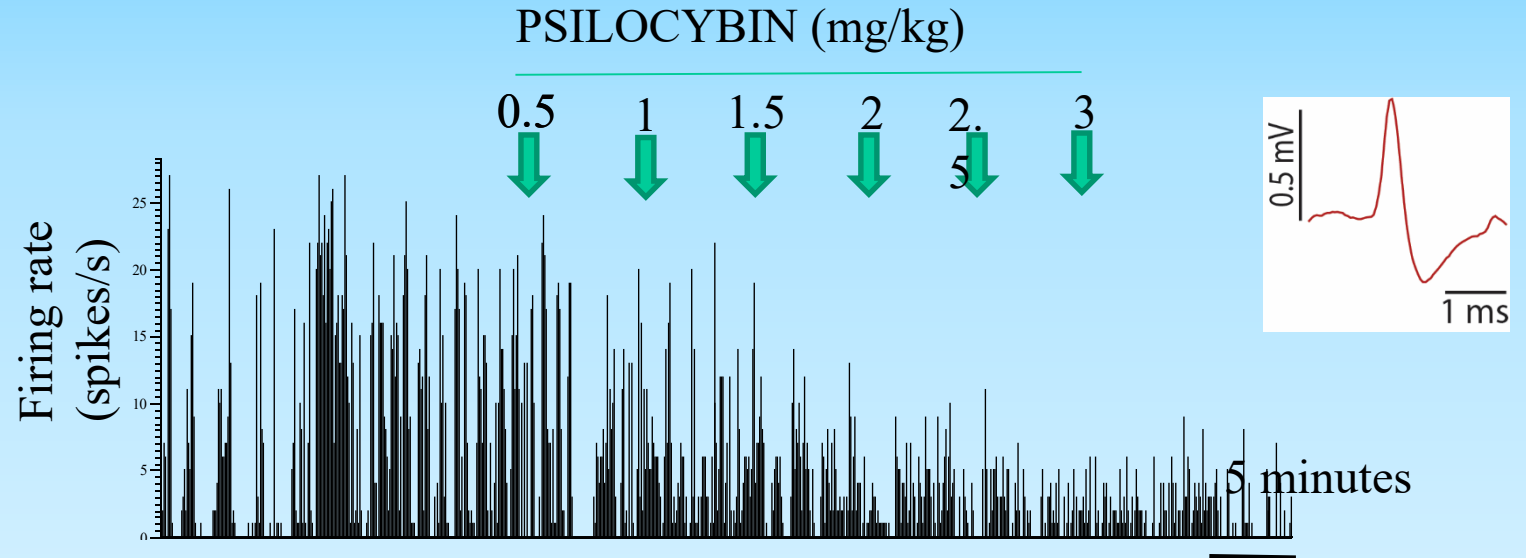
Are thalamo-cortical connections altered by psychedelics and responsible of ego-dissolution?

Psychedelics and GABAergic neurons of reticular thalamus

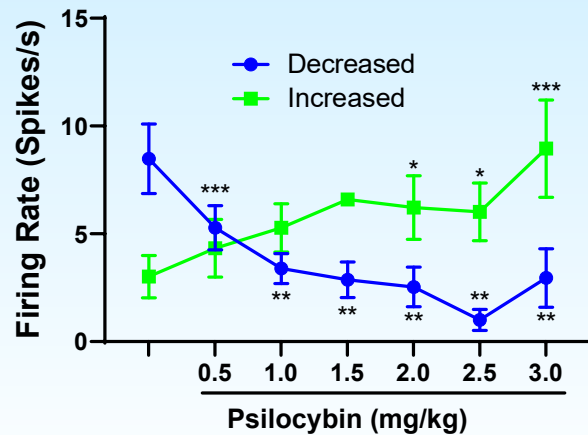
LSD



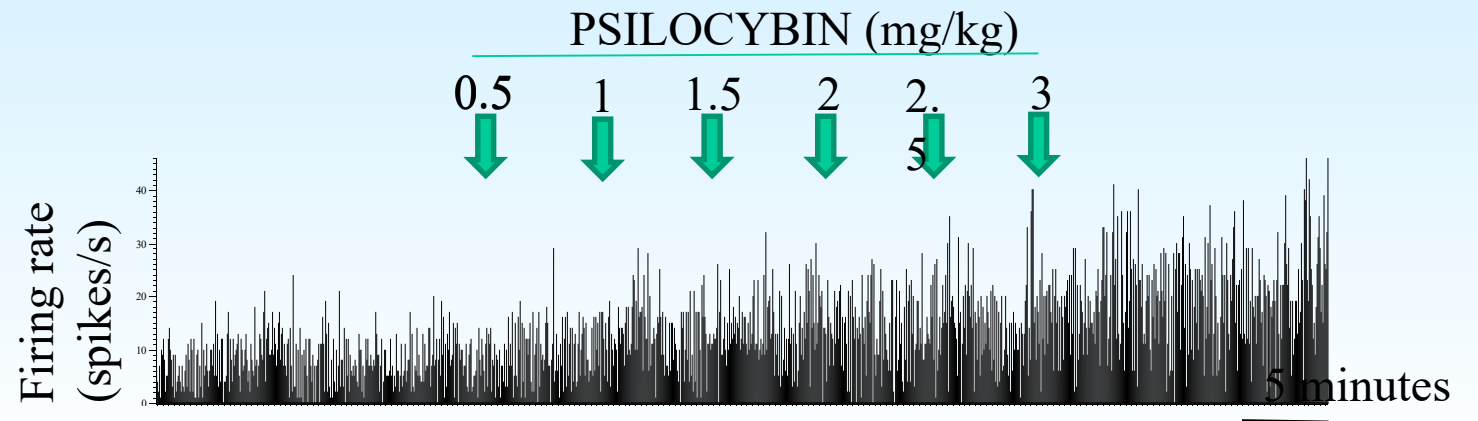
Inserra et al, 2021, *J. Psychopharm.*



PSILOCYBIN



Inserra et al, *In Preparation*



Translating preclinical data into clinical trials

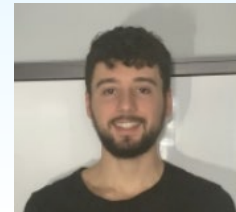
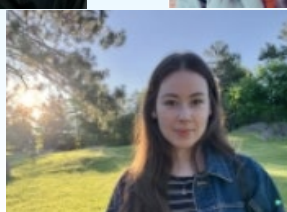
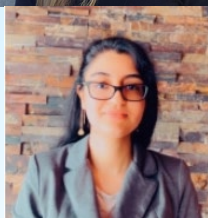
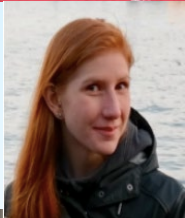
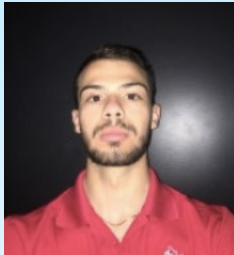
- Repeated doses of LSD for social anxiety
- Repeated doses of LSD for Autism Spectrum Disorder
- Repeated doses of LSD for generalized anxiety
- LSD even at low-doses modulates thalamo-cortex-thalamic circuits (Inserra et al., 2021; *J Psychopharm.*), which are involved in consciousness and self-awareness, they must be used in association with psychotherapy.

Acknowledgment

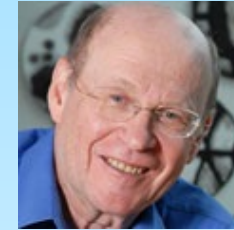
Neurobiological Psychiatry Unit



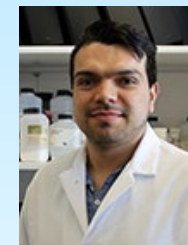
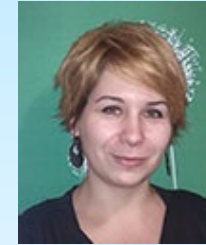
Gabriella Gobbi
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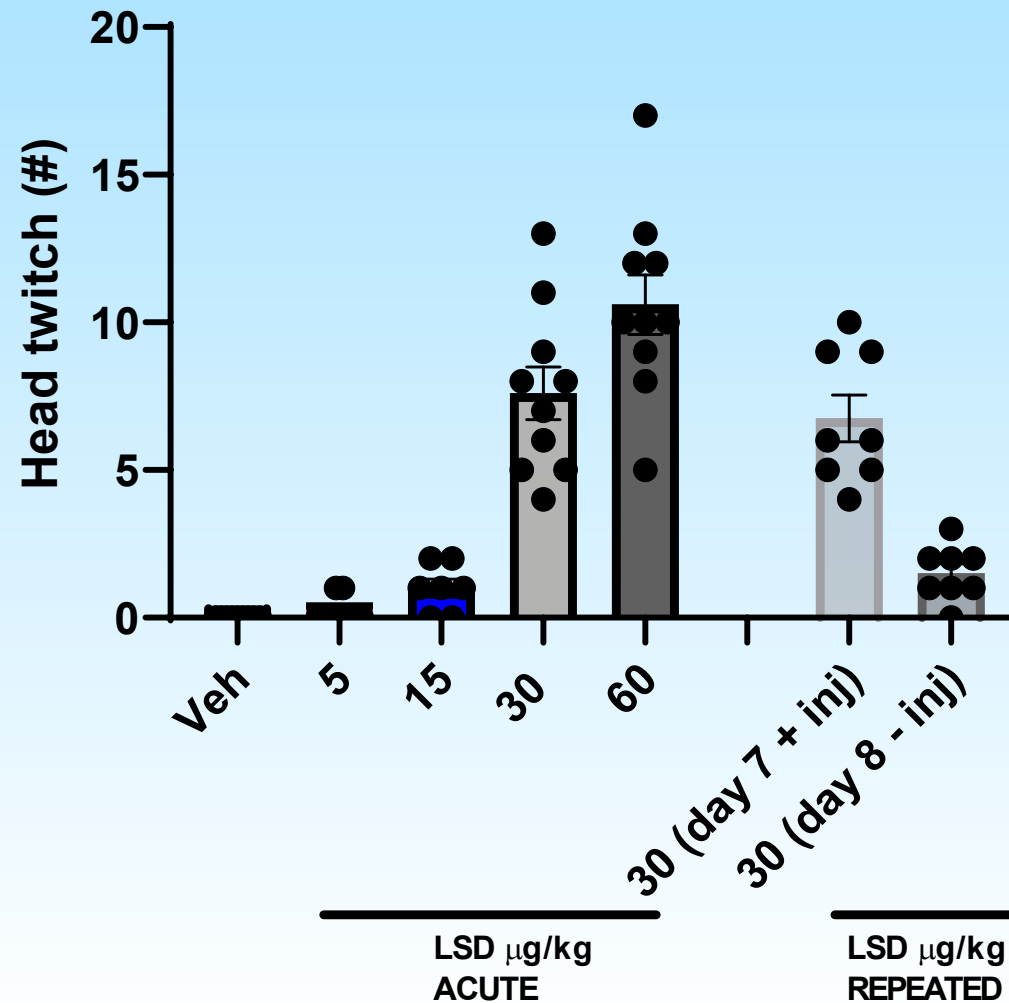


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Head Twitch Responses (HTR) = hallucinogenic potential of the 5-HT_{2A} receptor agonists



Unpublished results



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Characterization of the head-twitch response induced by hallucinogens in mice: detection of the behavior based on the dynamics of head movement

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