University of Zurich[UZH]

Psychiatrische Universitätsklinik Zürich

Psychoaktive Substanzen – Neue Therapieformen in der Psychiatrie?

Katrin Preller, PhD

PUK, 17. November 2023

Psychoactive Substances

Psilocybin

preferential **5-HT2A** and **5-HT1A** agonist

LSD

stimulates **serotonin** and **dopamine** receptors

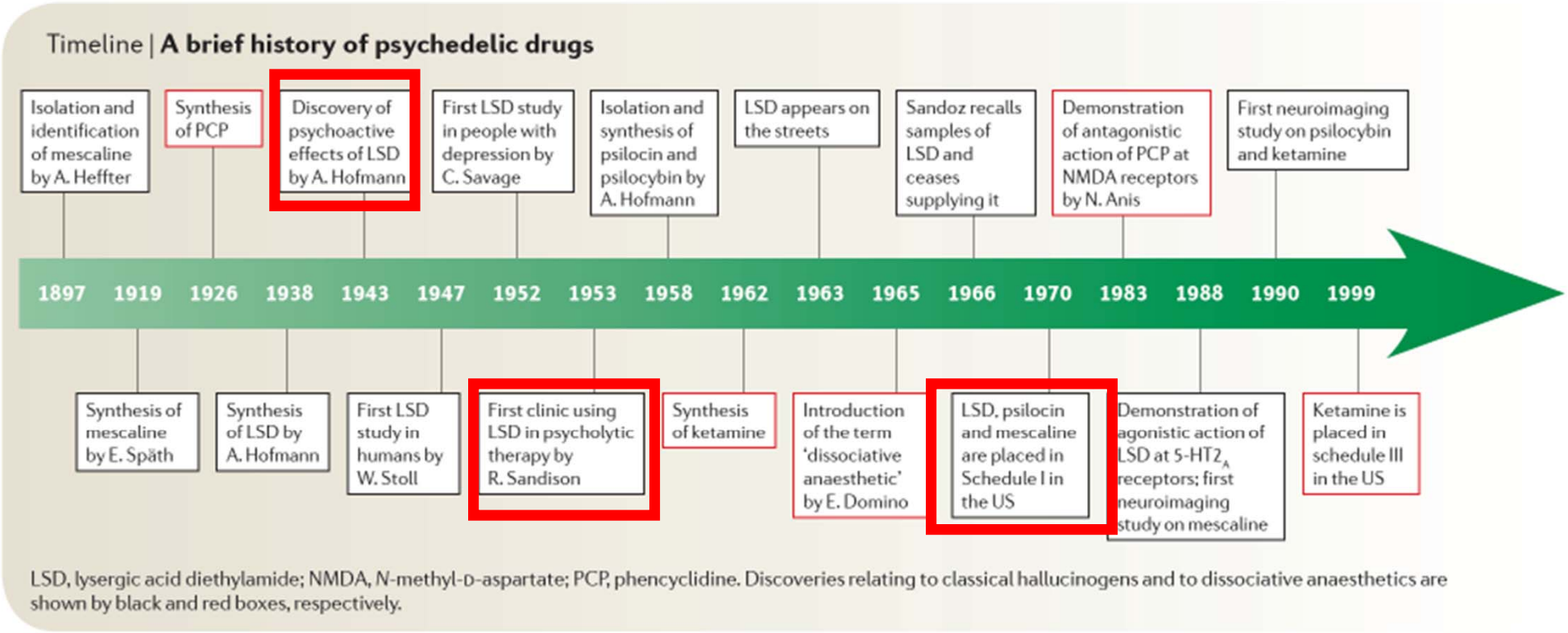
MDMA

serotonin, **norepinephrine** and **dopamine** releaser

Ketamine

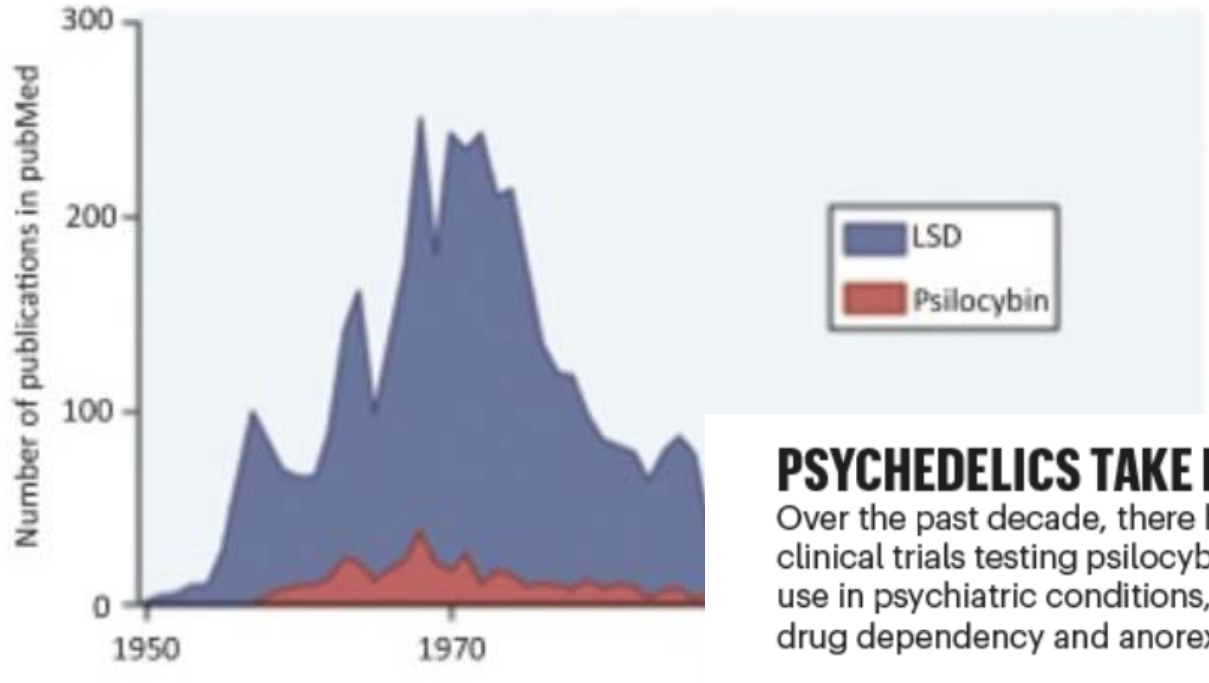
NMDA receptor antagonist

A brief history of Research on Psychedelics

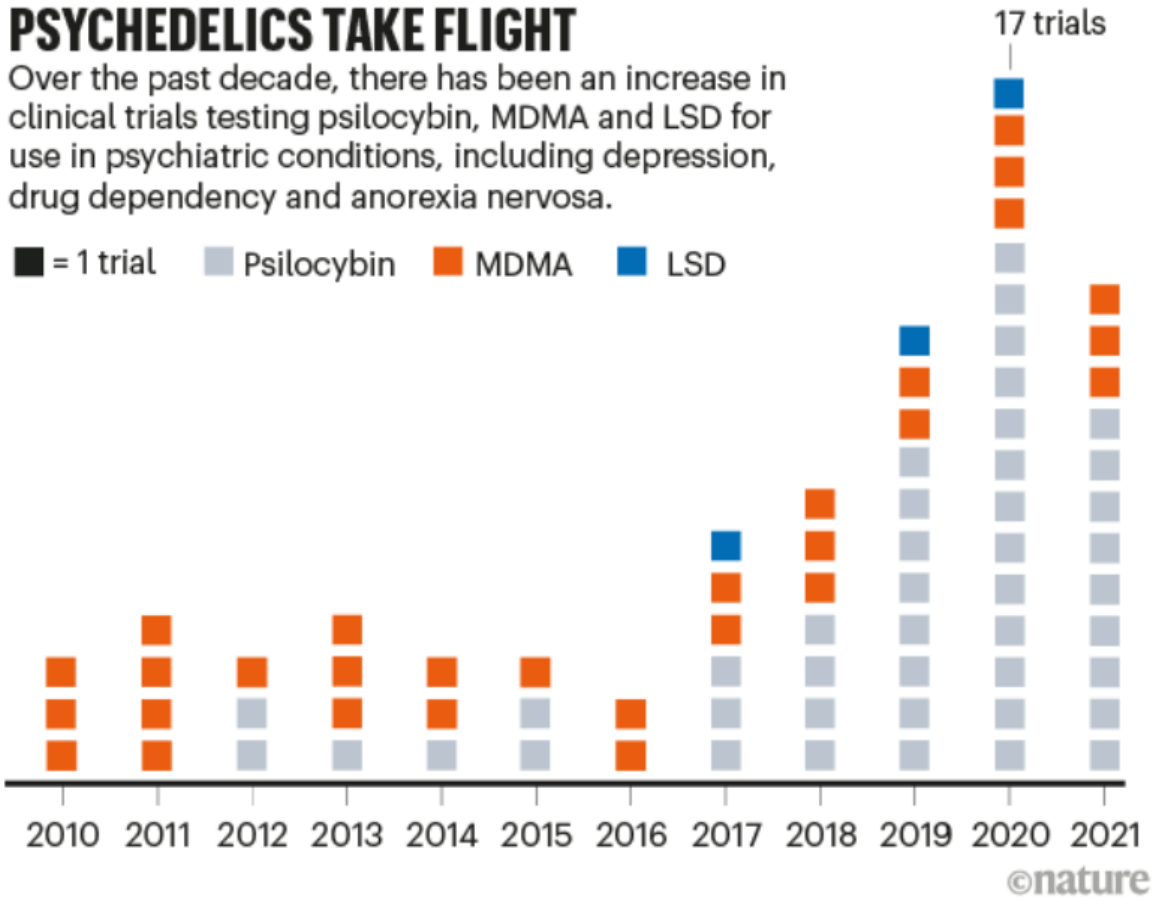


Vollenweider & Kometer, 2010

A brief history of Research on Psychedelics

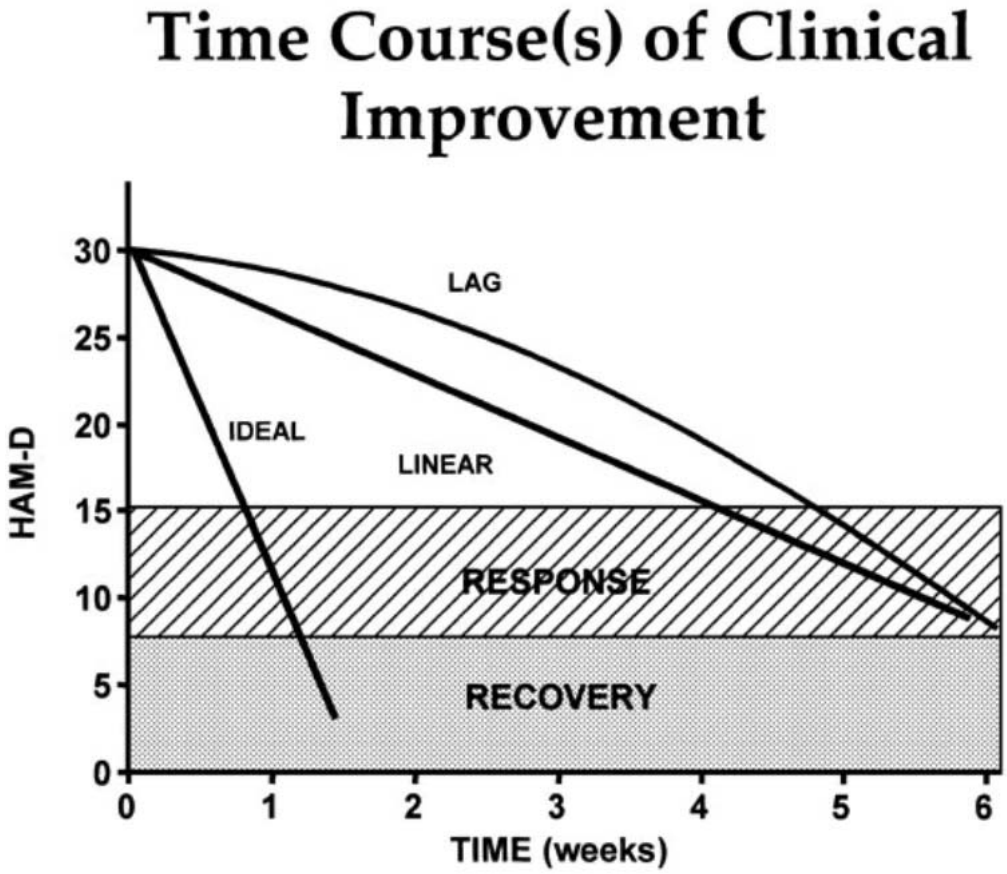


Kyzar et al., 2017



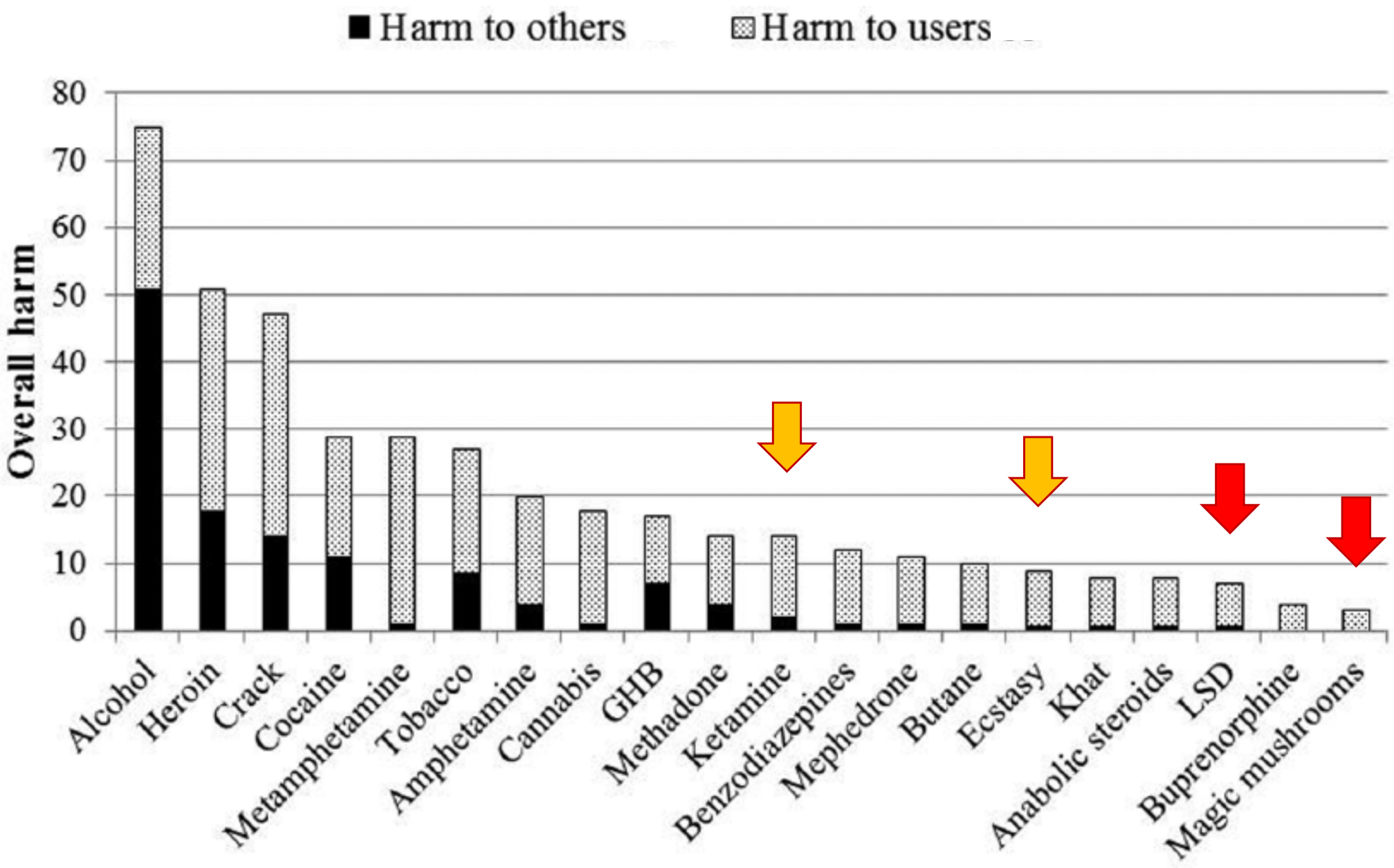
Problems with current treatments for psychiatric disorders

- Significant side effects
- Chronic administration
- Moderate response rates
- Delay in onset of effects



Frazer et al., 2002

Harm Potential



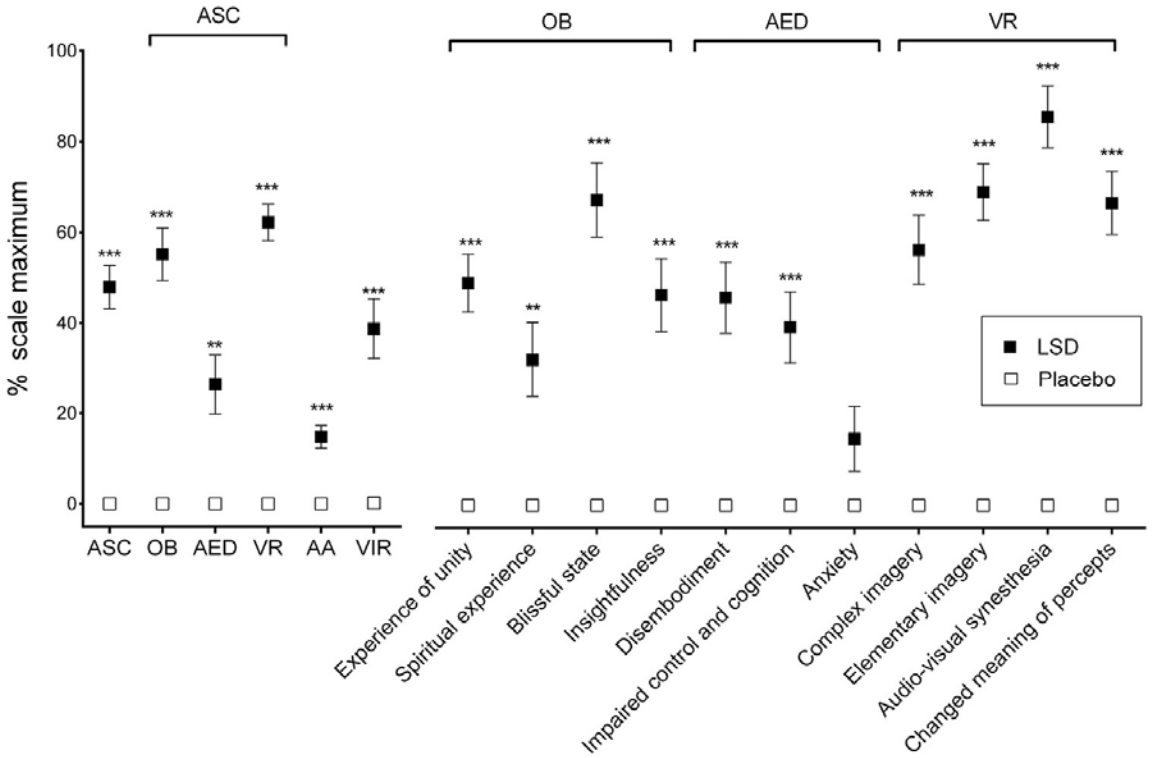
van Amsterdam et al., 2015

Subjective Effects of LSD and Psilocybin

by Candace Lewis

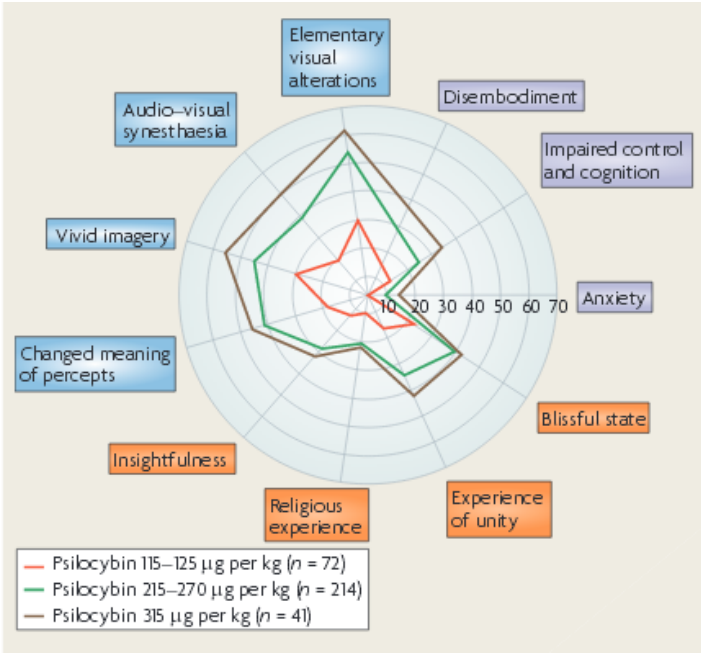
Subjective Effects of LSD and Psilocybin

A



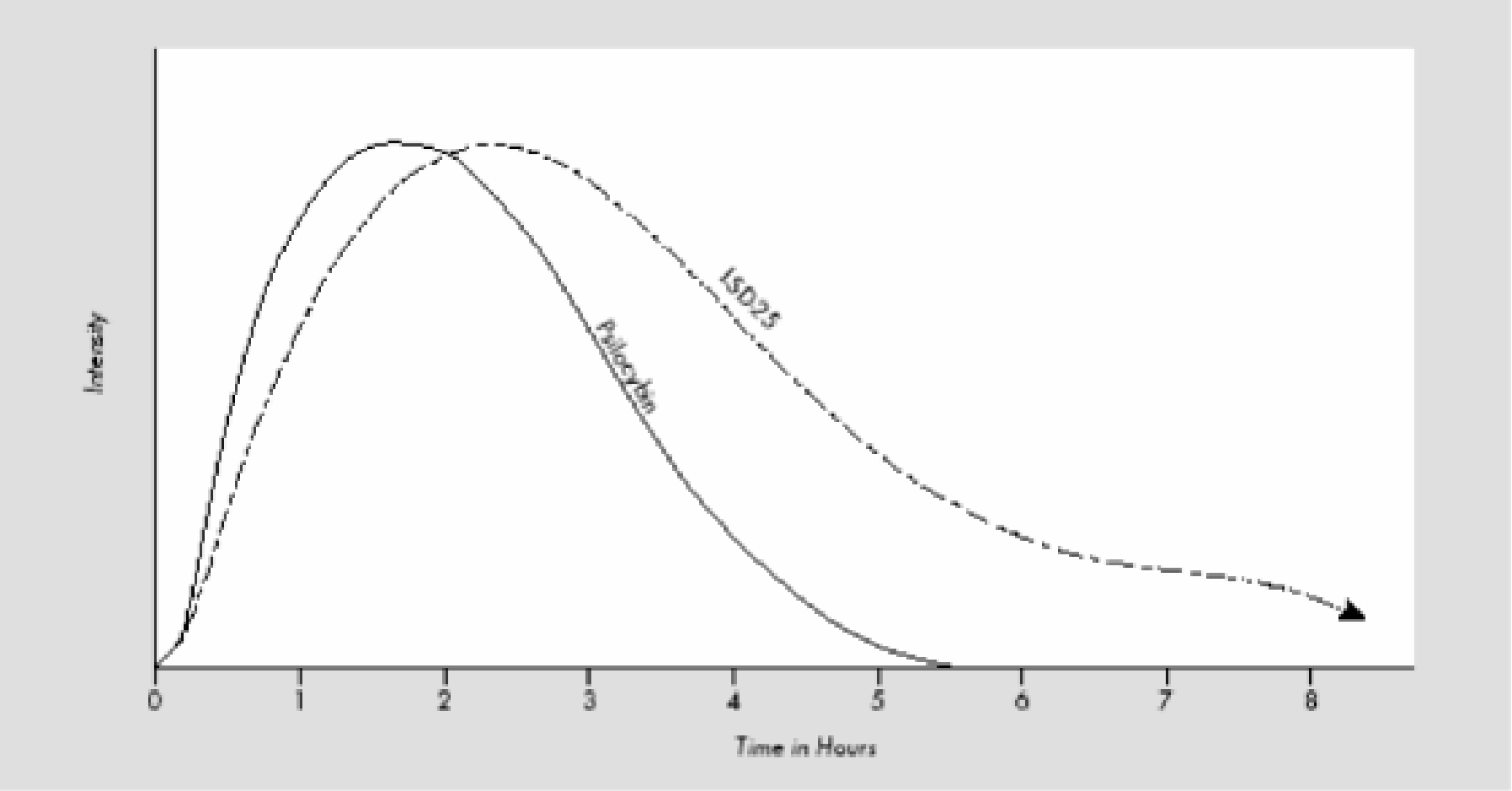
Subjective effects of LSD. From: Schmidt et al., 2015

B



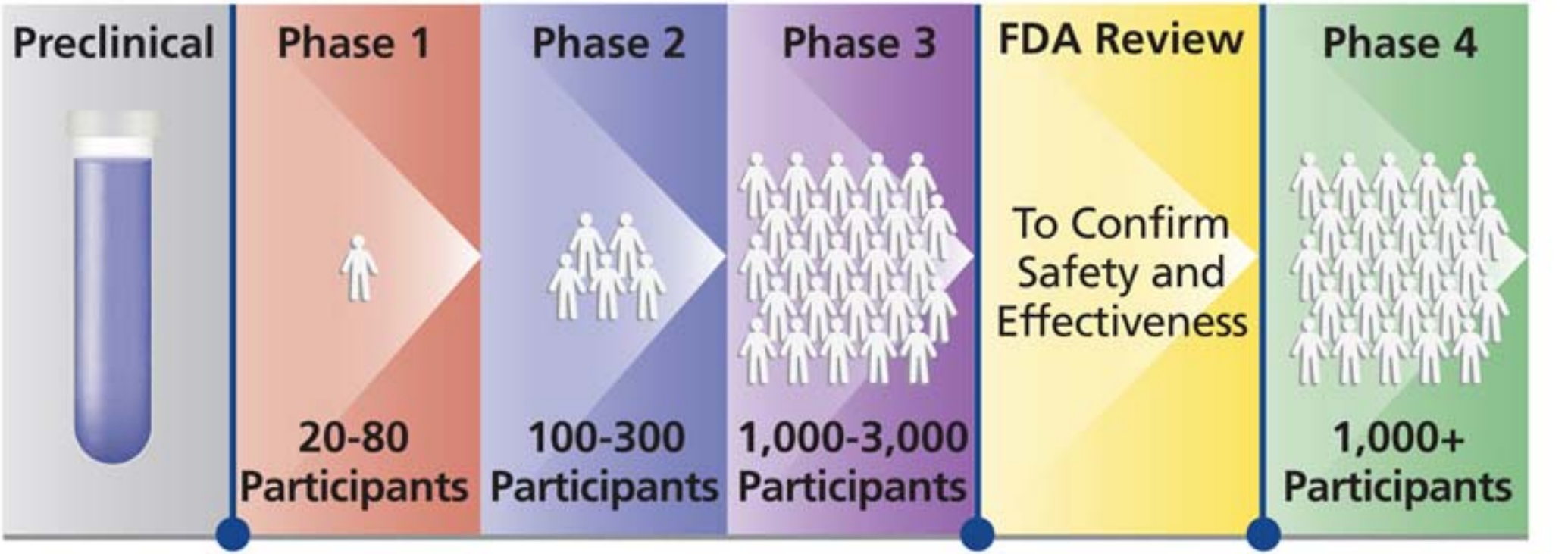
Subjective effects of psilocybin. From: Vollenweider & Kometer, 2010

Duration of Effects (LSD & Psilocybin)



Course of subjective effects of LSD p.o. compared to the hallucinogen psilocybin.
From: Passie, 2008

Where are we?



Psilocybin MDMA

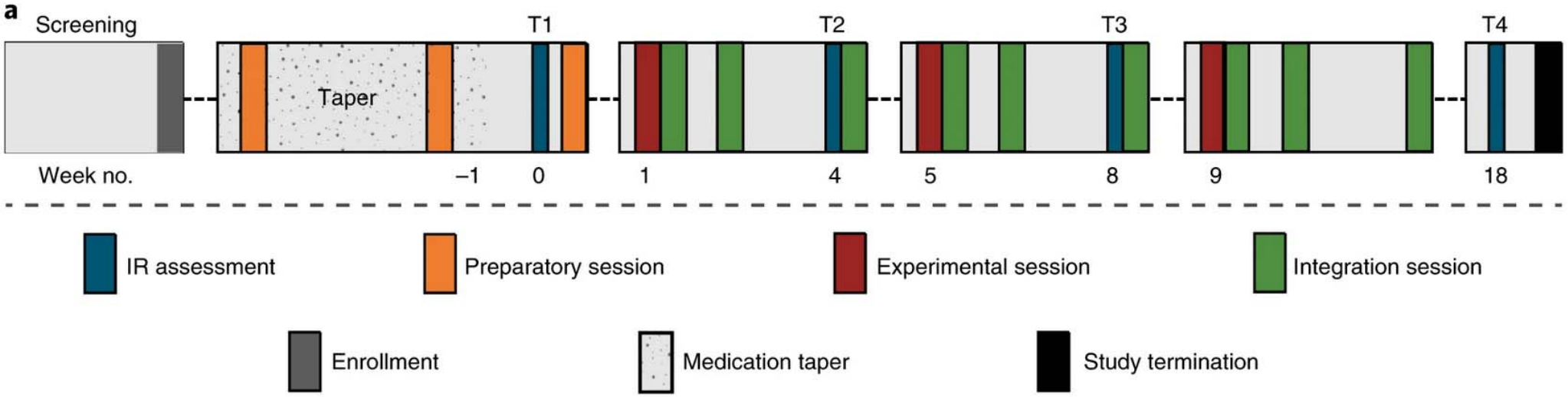
Ketamine (Spravato)

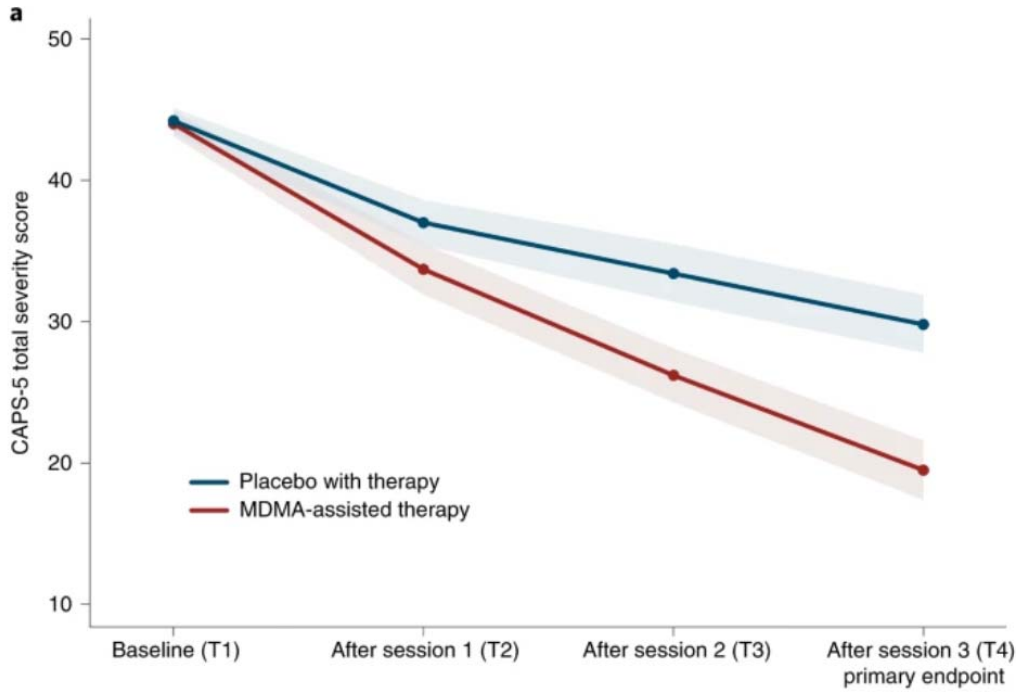
Modern Studies Testing the Efficacy of Psychedelics

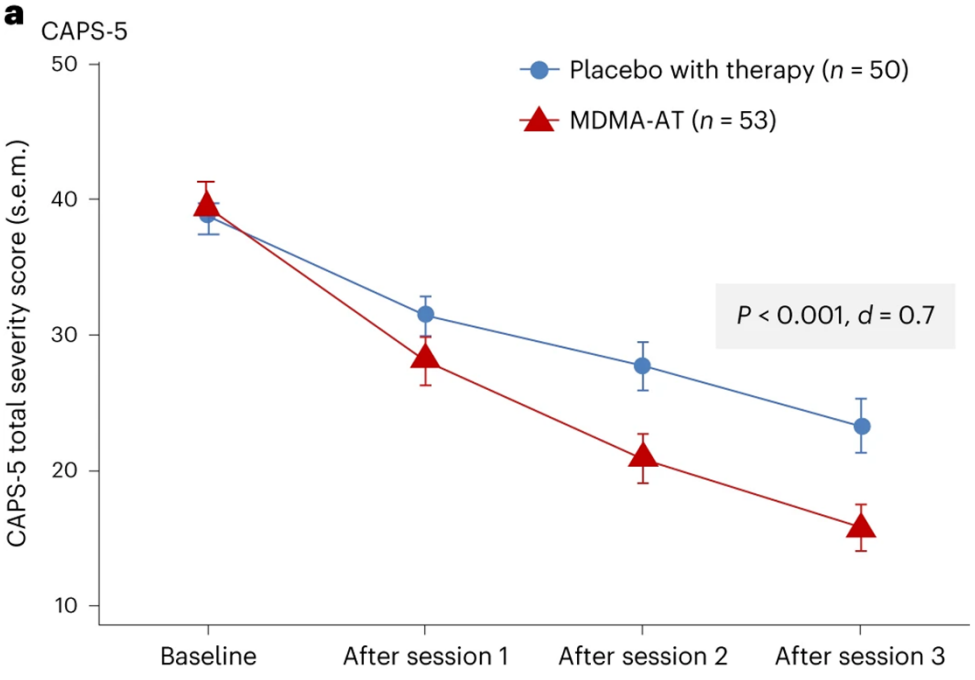
- Limited, supervised administrations
- Rapidly acting
- Long-lasting effect
- Good safety profile
- In synergy with psychotherapy

https://filtermag.org/uk-psychedelic-therapy/

MDMA – PTSD Phase III

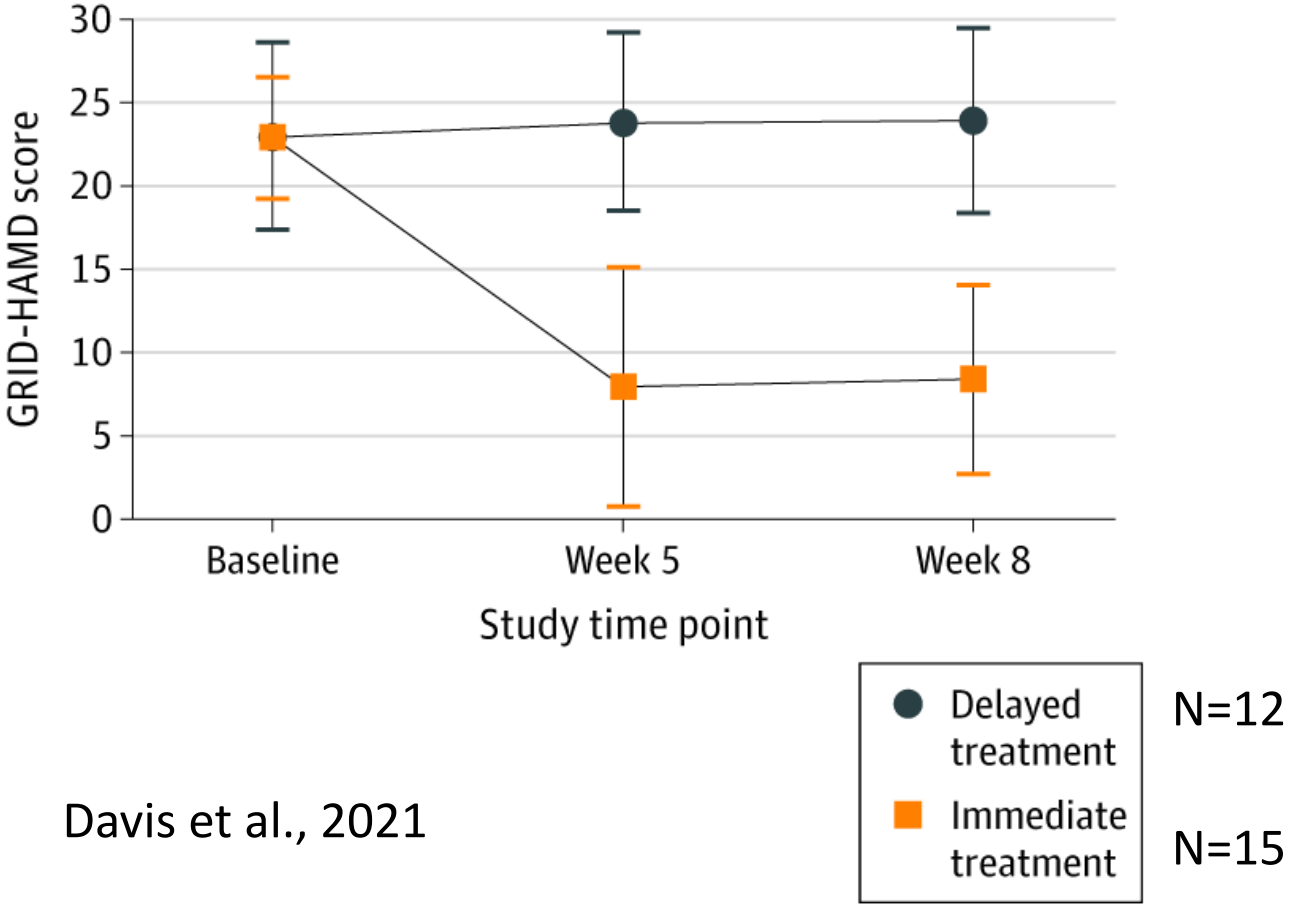




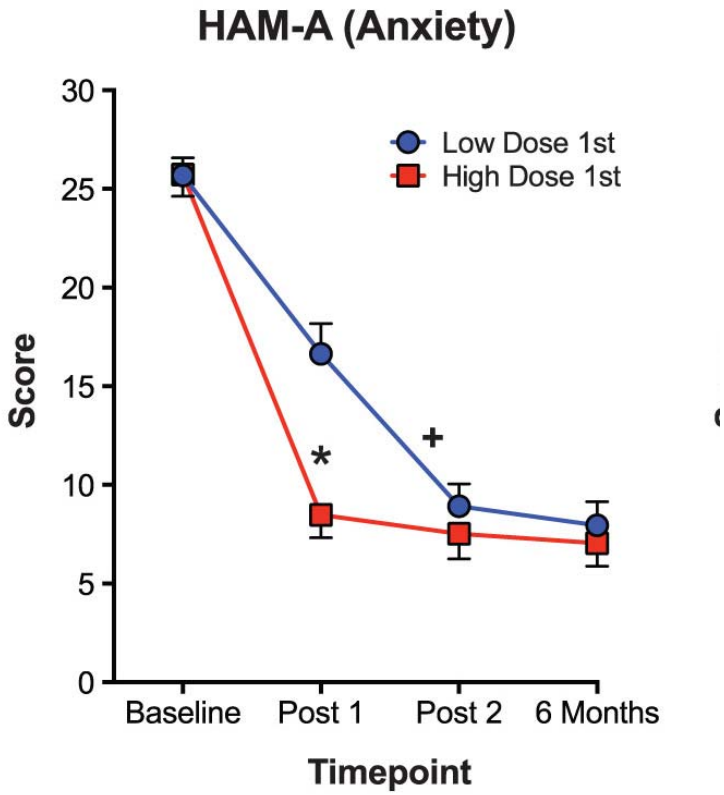


Mitchell et al., 2021, 2023

Psilocybin – Depression, Anxiety Phase II



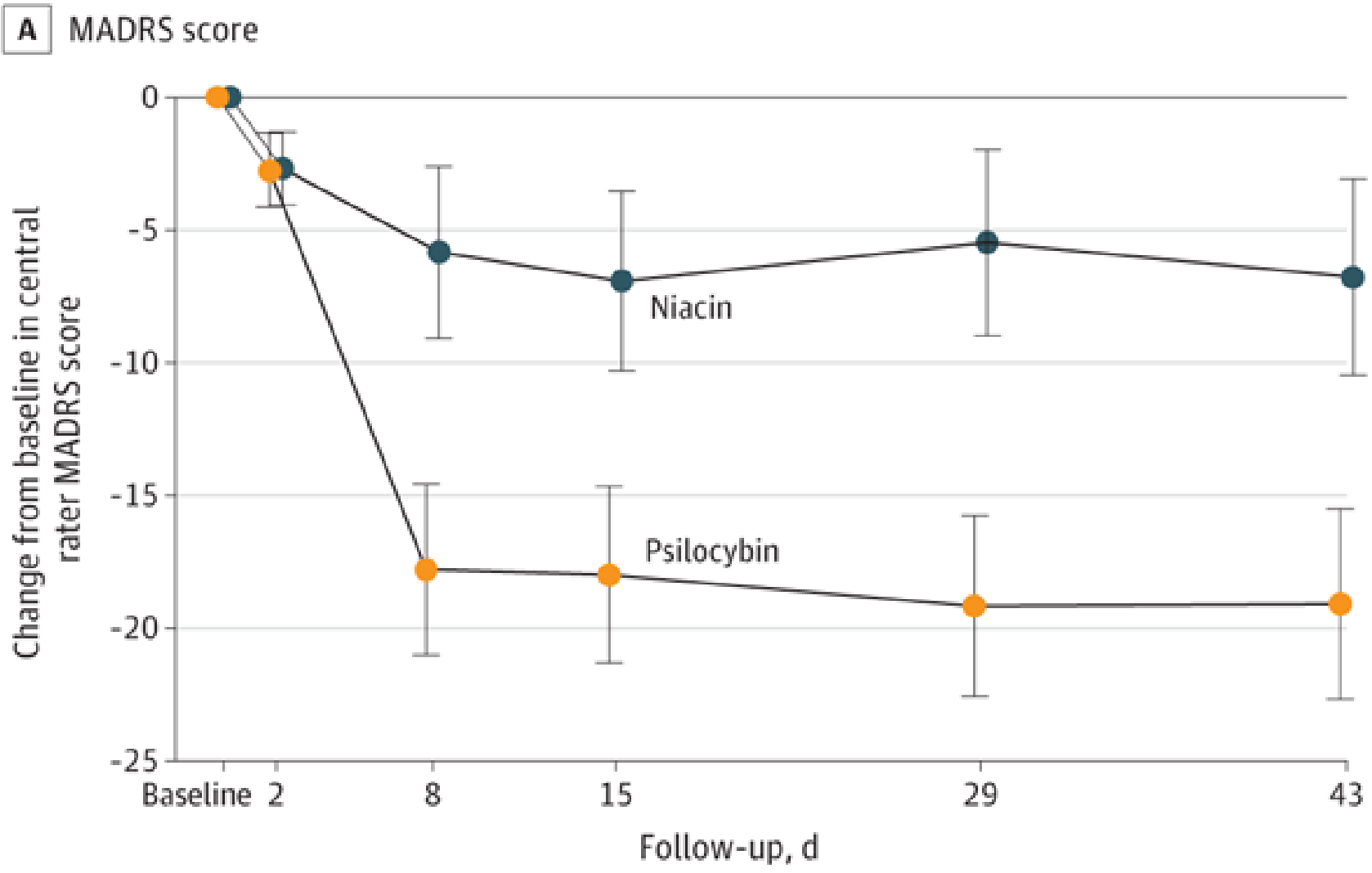
Davis et al., 2021



Griffiths et al., 2016

Session 1: 20 mg/70 kg; Session 2: 30 mg/70 kg

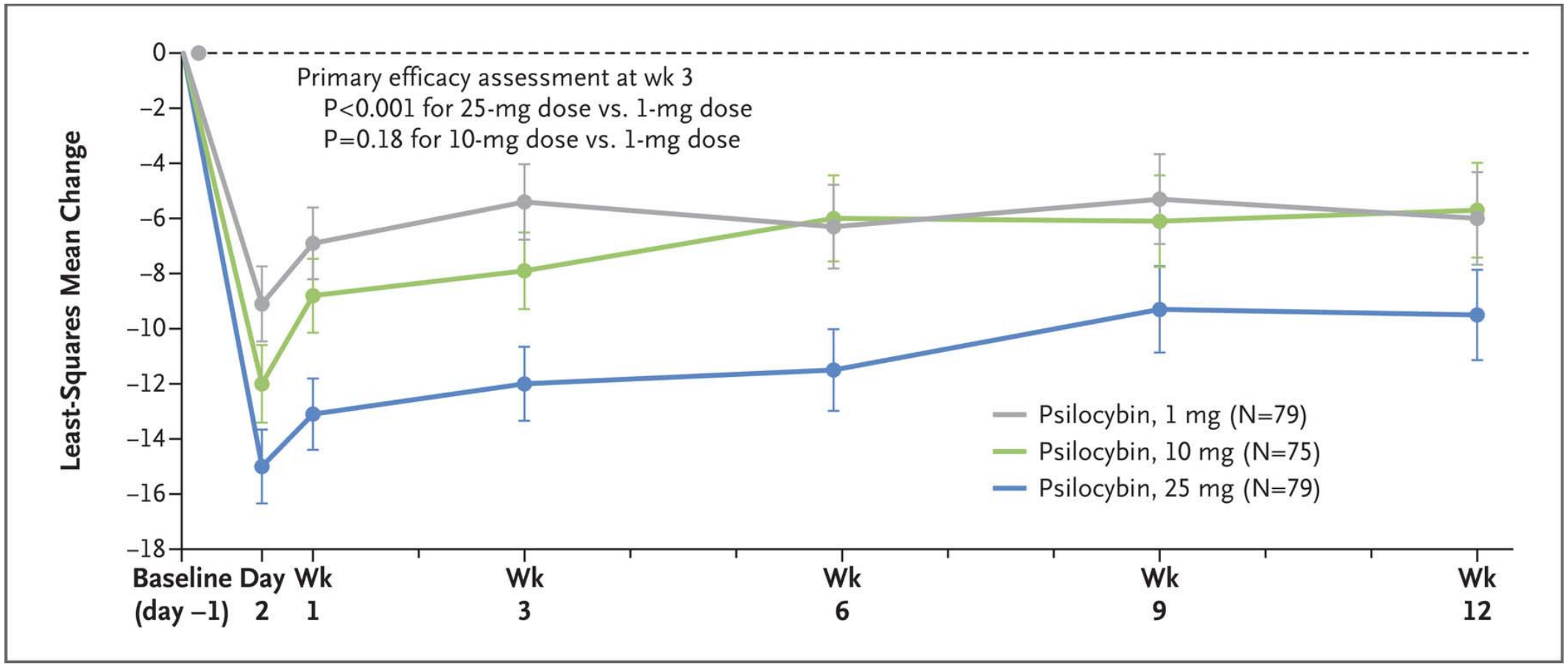
Psilocybin – Depression: Single Administration



25mg

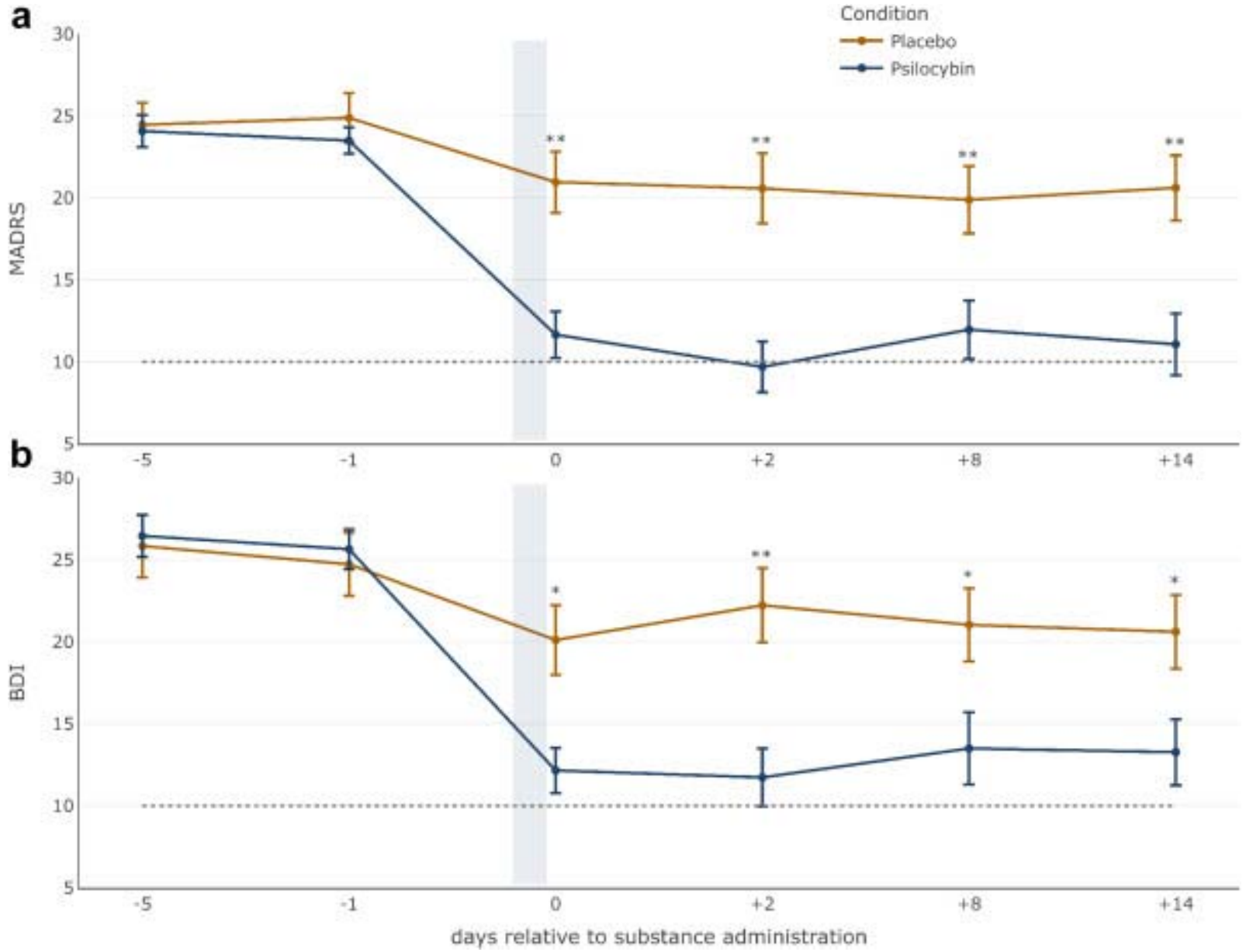
Raison et al., 2023

Psilocybin – Depression: Single Administration



Goodwin et al., 2022

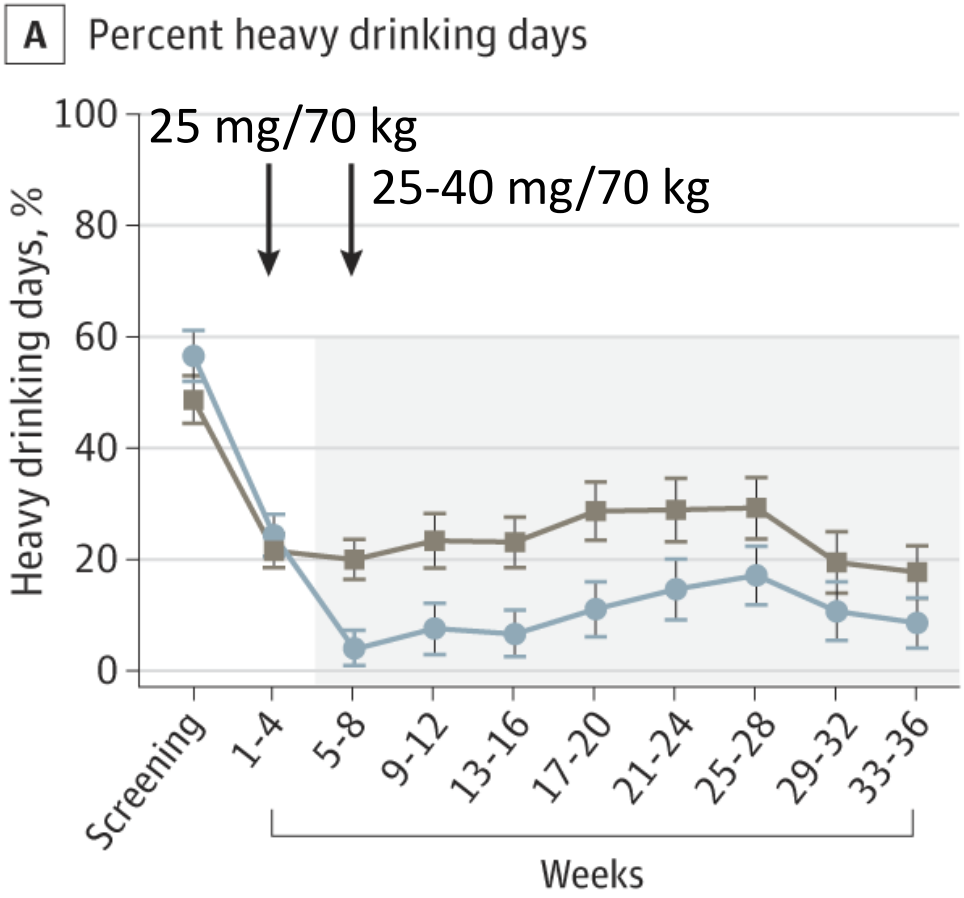
Psilocybin – Depression: Single Administration, lower dose



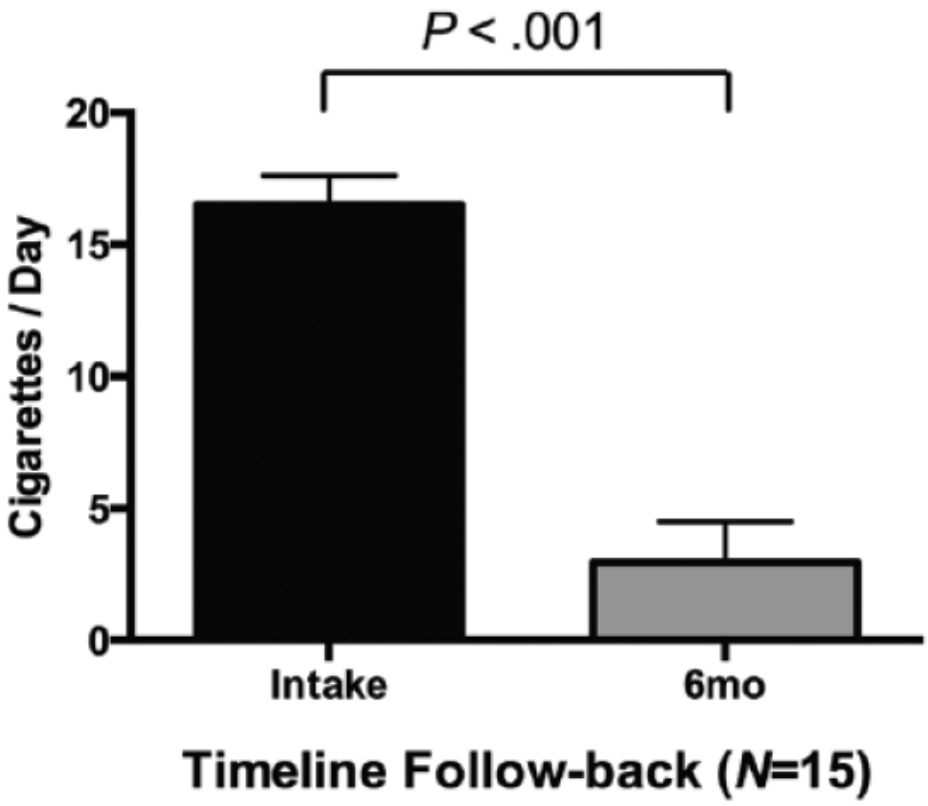
Von Rotz et al., 2023

Psilocybin – Addiction Phase II

Alcohol



Tobacco



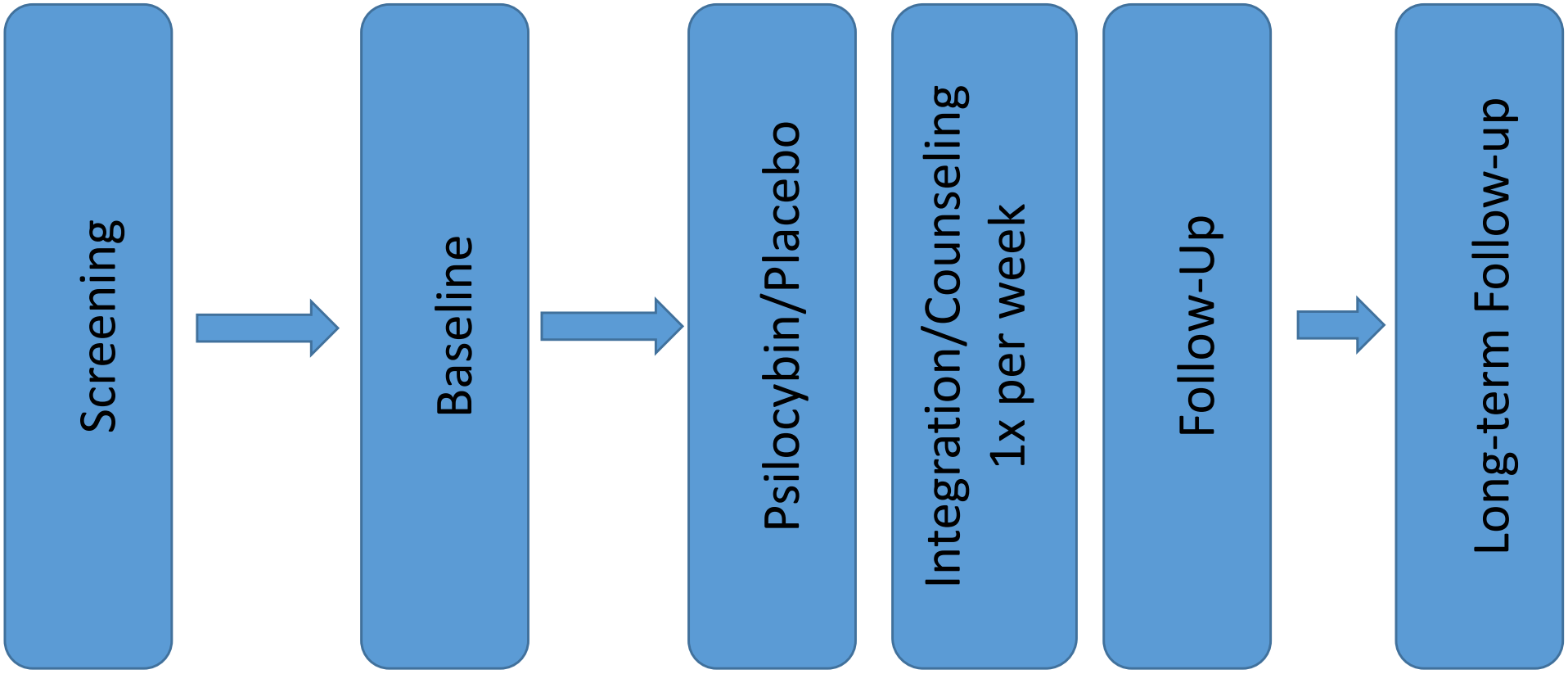
N=93

Bogenschutz et al., 2022

Johnson et al., 2014

Psilocybin for Relapse Prevention

60 Participants: 30x Psilocybin, 30x Placebo



Adverse events: Goodwin et al, 2022

Table 3. Adverse Events Reported on Day 1, from Day 2 up to Week 3, and after Week 3 up to Week 12 (Safety Population).*

Adverse Event	Psilocybin, 25 mg (N=79)	Psilocybin, 10 mg (N=75)	Psilocybin, 1 mg (N=79)
		number (percent)	
Day 1			
Any adverse event	48 (61)	35 (47)	30 (38)
Any severe adverse event	3 (4)	6 (8)	1 (1)
Adverse events occurring in ≥5% of participants in any group			
Headache	19 (24)	11 (15)	13 (16)
Nausea	17 (22)	5 (7)	1 (1)
Euphoric mood	4 (5)	5 (7)	3 (4)
Fatigue	5 (6)	2 (3)	4 (5)
Insomnia	2 (3)	3 (4)	5 (6)
Anxiety	3 (4)	6 (8)	0
Mood altered	4 (5)	3 (4)	0
Dizziness	5 (6)	1 (1)	0
Paresthesia	2 (3)	4 (5)	0
Abnormal thinking	0	4 (5)	0
Any serious adverse event	0	0	0

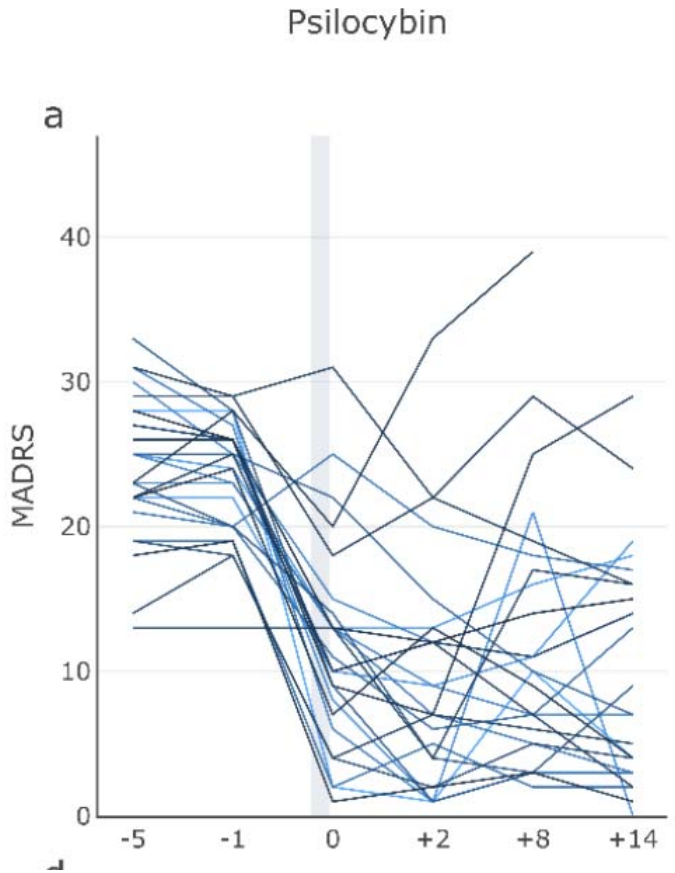
Adverse events: Goodwin et al, 2022

Adverse Event	Psilocybin, 25 mg (N=79)	Psilocybin, 10 mg (N=75)	Psilocybin, 1 mg (N=79)
		number (percent)	
Day 2 up to wk 3			
Any adverse event	44 (56)	36 (48)	35 (44)
Any severe adverse event	7 (9)	5 (7)	1 (1)
Adverse events occurring in ≥5% of participants in any group			
Headache	9 (11)	5 (7)	9 (11)
Insomnia	4 (5)	5 (7)	8 (10)
Anxiety	4 (5)	6 (8)	3 (4)
Fatigue	6 (8)	2 (3)	3 (4)
Suicidal ideation	5 (6)	4 (5)	2 (3)
Depression	3 (4)	3 (4)	4 (5)
Mood altered	4 (5)	0	1 (1)
Any serious adverse event	4 (5)	4 (5)	0
Suicidal ideation	2 (3)	2 (3)	0
Intentional self-injury	2 (3)	1 (1)	0
Hospitalization	0	1 (1)	0

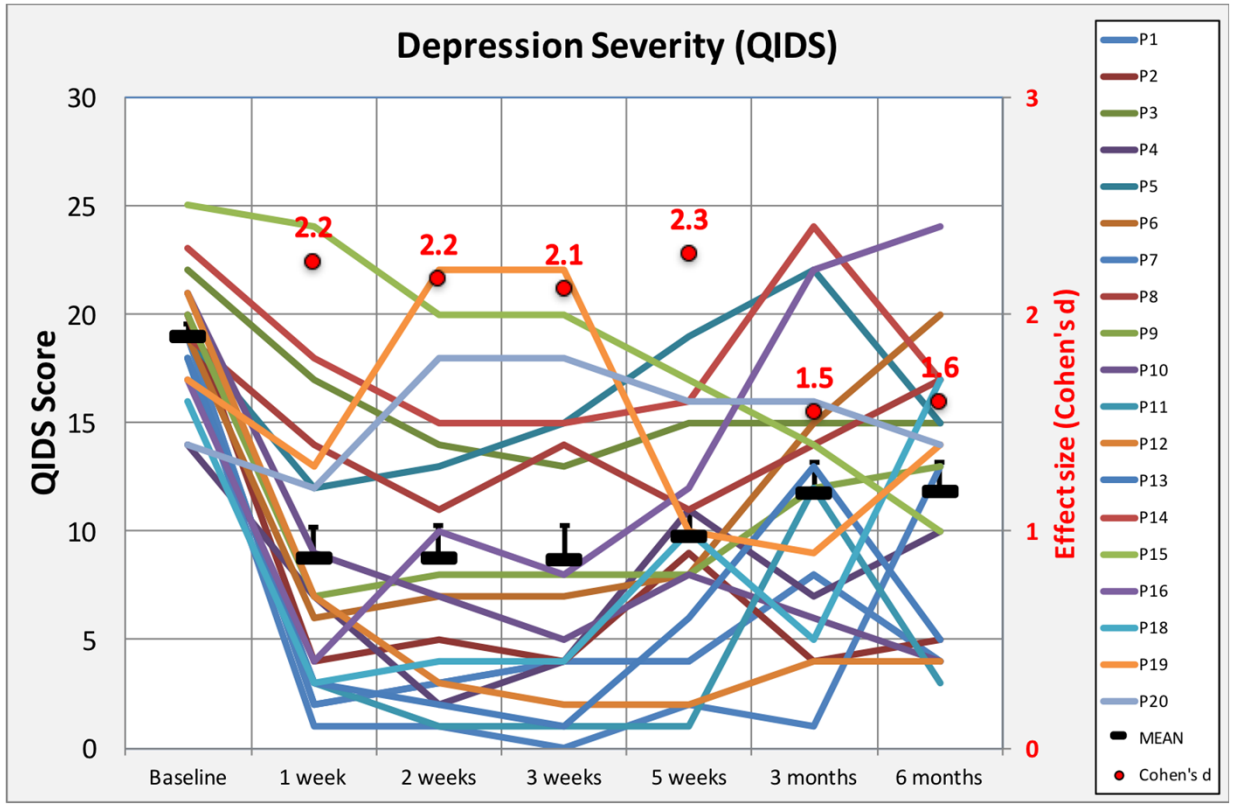
Adverse events: Goodwin et al, 2022

Adverse Event	Psilocybin, 25 mg (N=79)	Psilocybin, 10 mg (N=75)	Psilocybin, 1 mg (N=79)
		number (percent)	
After wk 3 up to wk 12			
Any adverse event	23 (29)	24 (32)	24 (30)
Any severe adverse event	2 (3)	3 (4)	0
Adverse events occurring in ≥5% of participants in any group			
Headache	3 (4)	2 (3)	6 (8)
Any serious adverse event	4 (5)	3 (4)	1 (1)
Suicidal behavior	3 (4)	0	0

Inter-individual heterogeneity in clinical data



Von Rotz et al., 2023



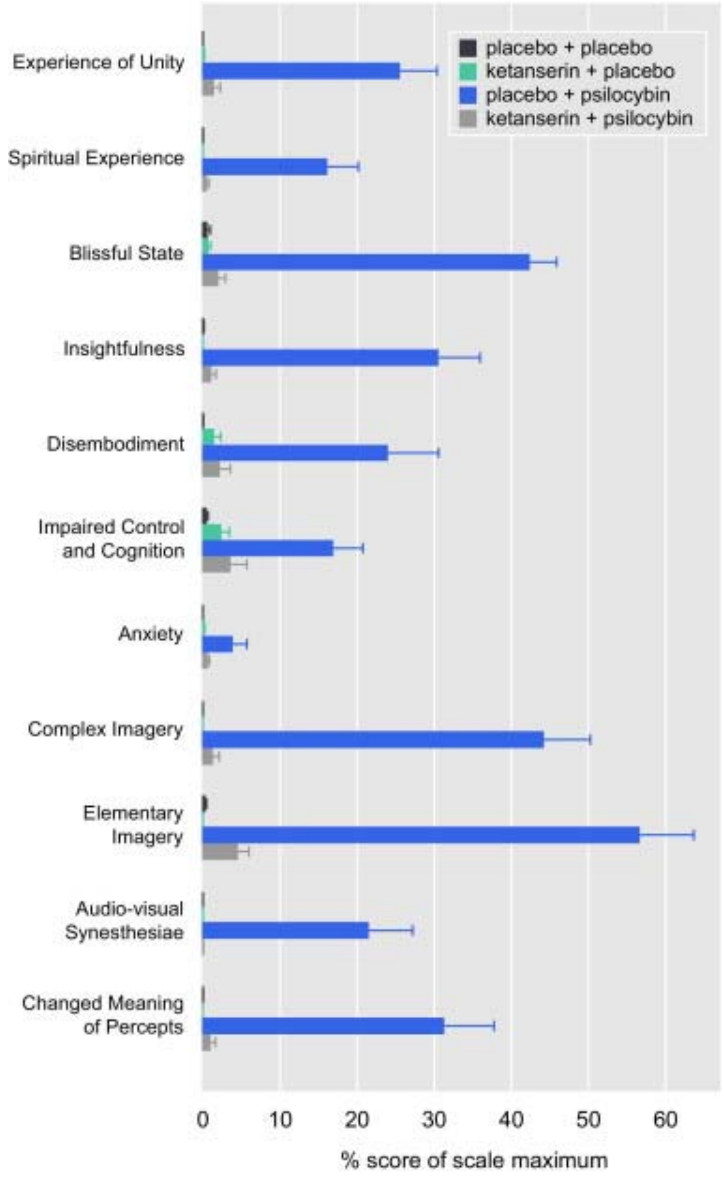
Carhart-Harris et al., 2018

Understanding the mechanisms of action is important!

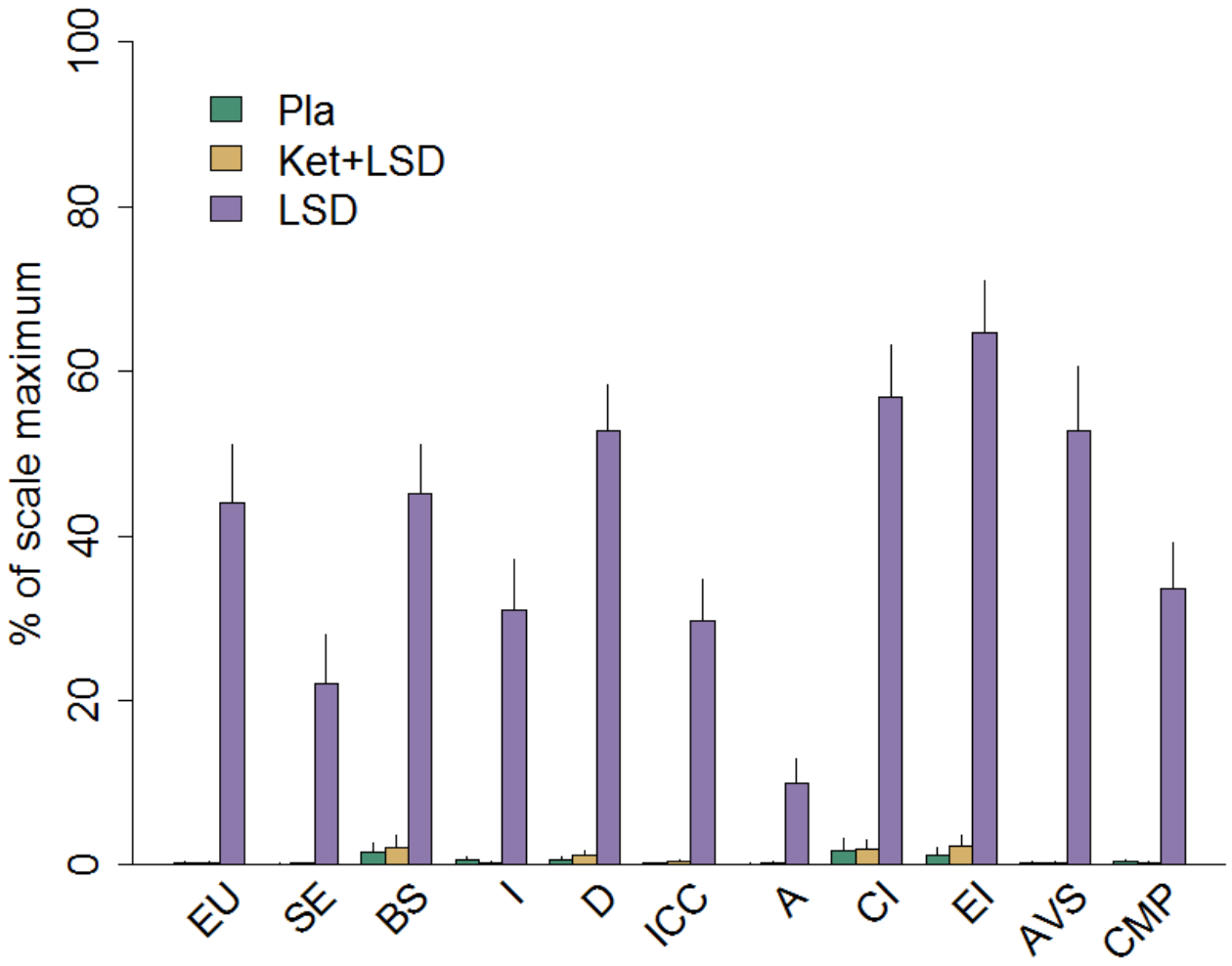
The Neurobiology of Psychedelics

Ketanserin blocks Subjective Effects

Psilocybin



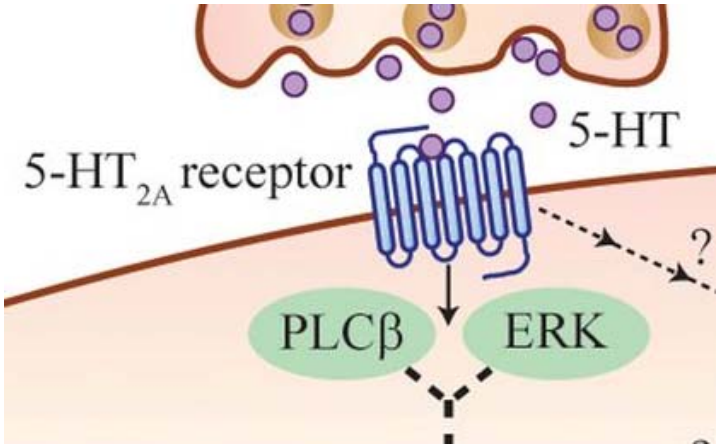
LSD



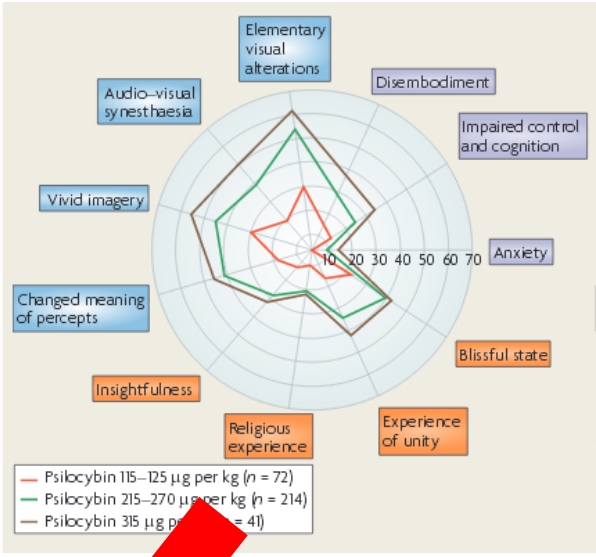
Kometer et al., 2012

Preller et al., 2018

From Receptors to Clinical Effects



?



?

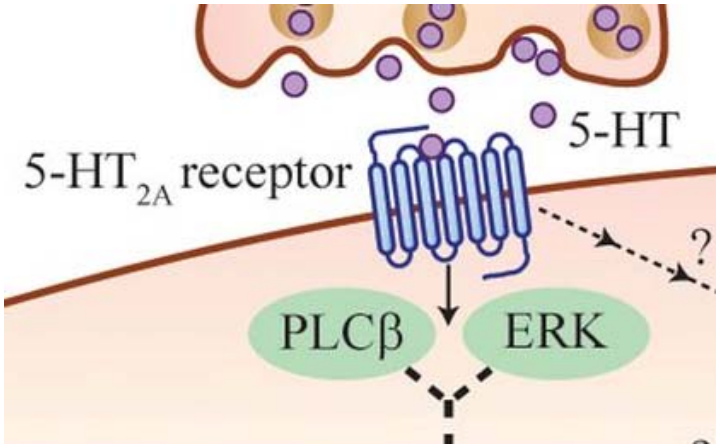
?

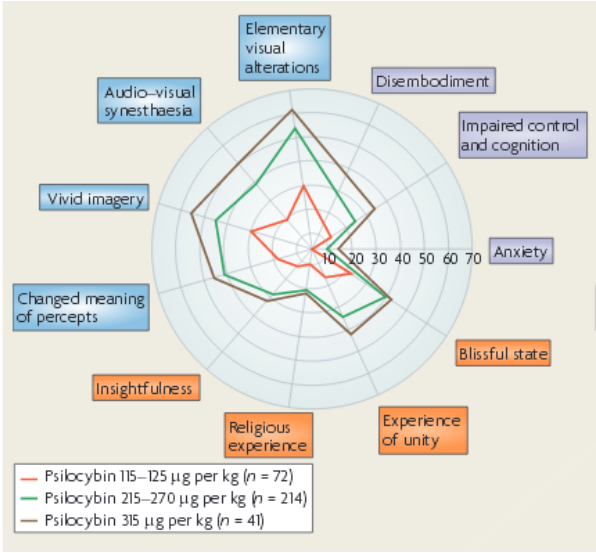
JAMA Psychiatry | Original Investigation

Effects of Psilocybin-Assisted Therapy on Major Depressive Disorder
A Randomized Clinical Trial

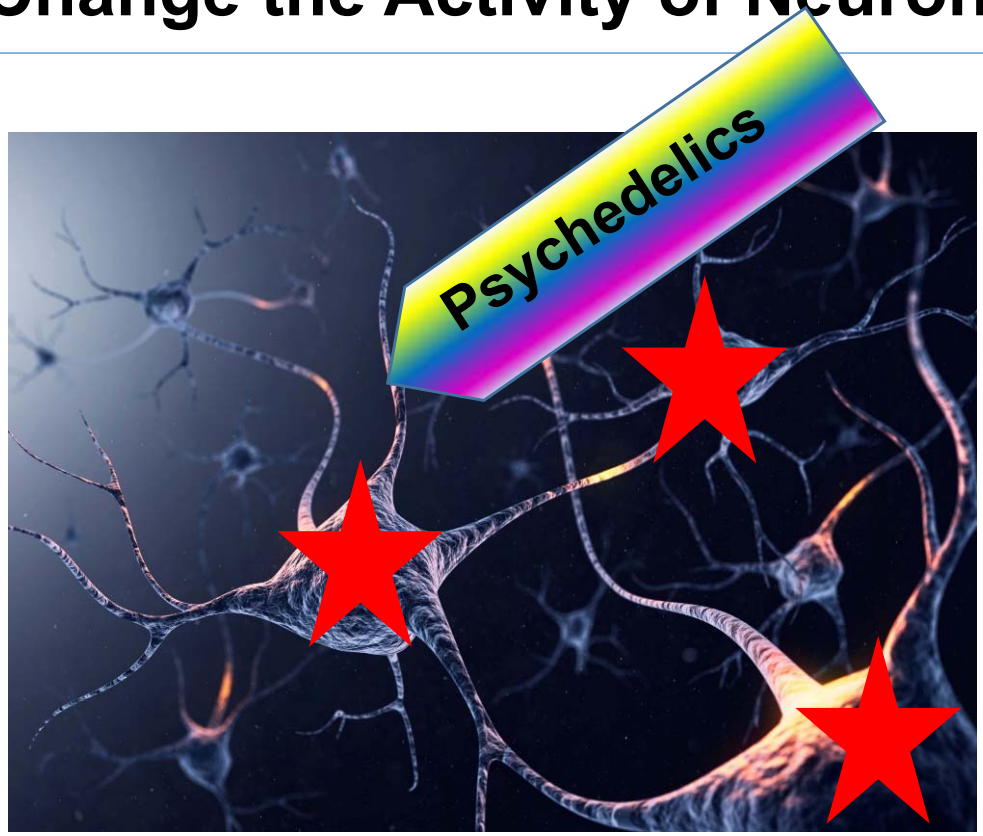
Alan K. Davis, PhD; Frederick S. Barrett, PhD; Darrick G. May, MD; Mary P. Cosimano, MSW; Nathan D. Sepeda, BS; Matthew W. Johnson, PhD; Patrick H. Finan, PhD; Roland R. Griffiths, PhD

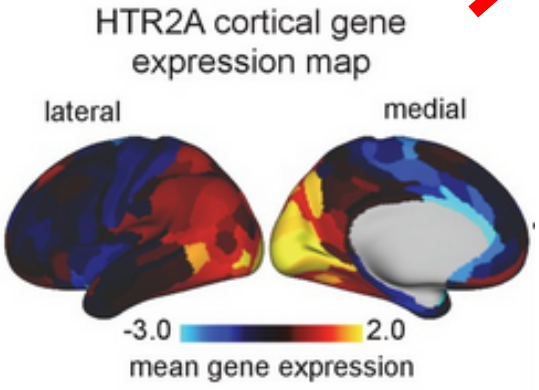
From Receptors to Clinical Effects

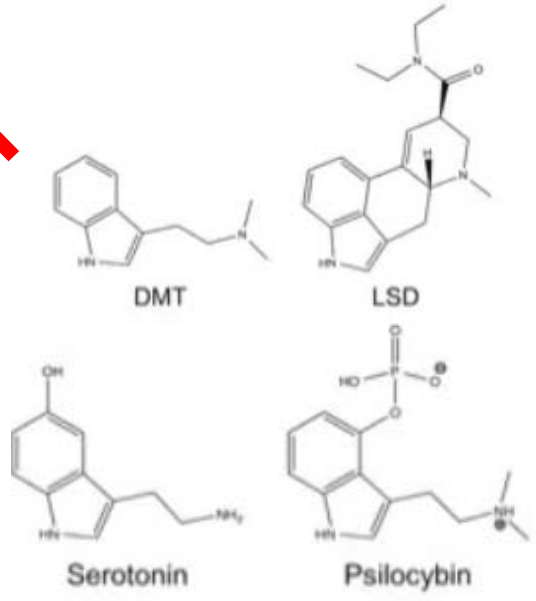




Psychedelics Change the Activity of Neurons

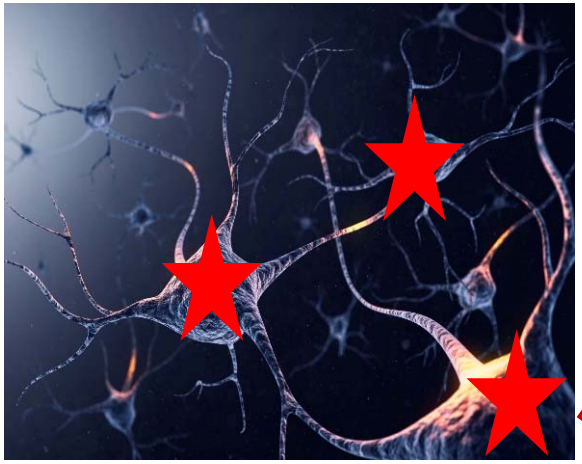


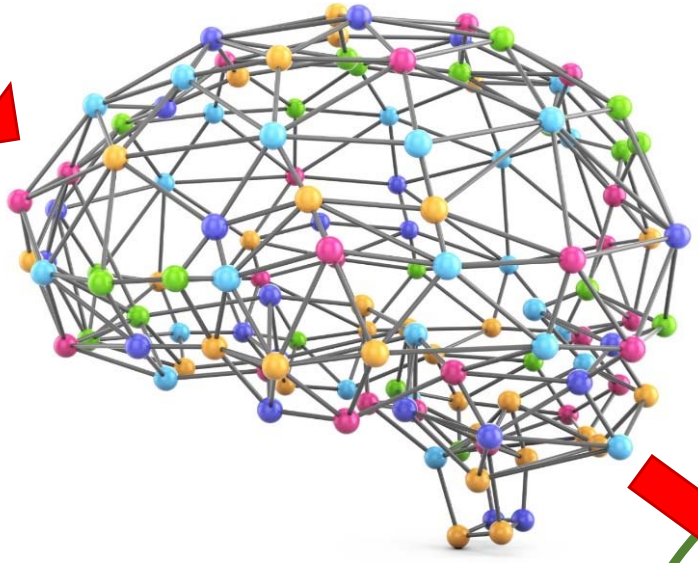


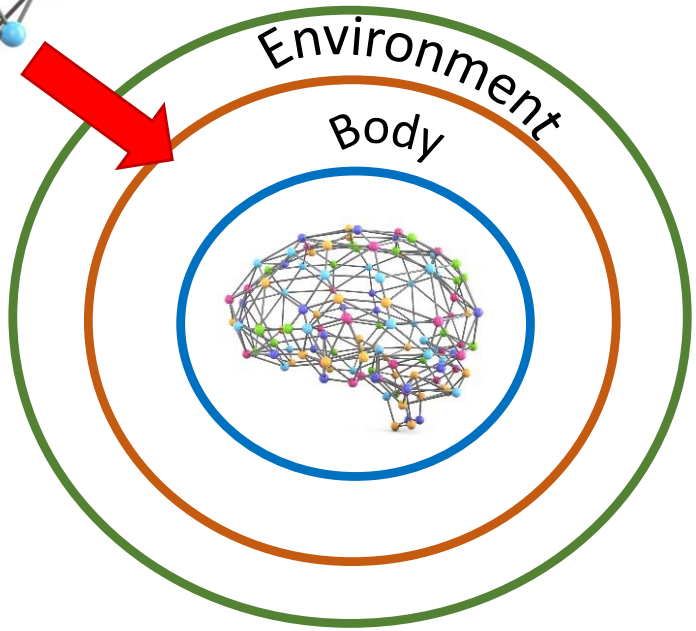


Preller et al. 2018

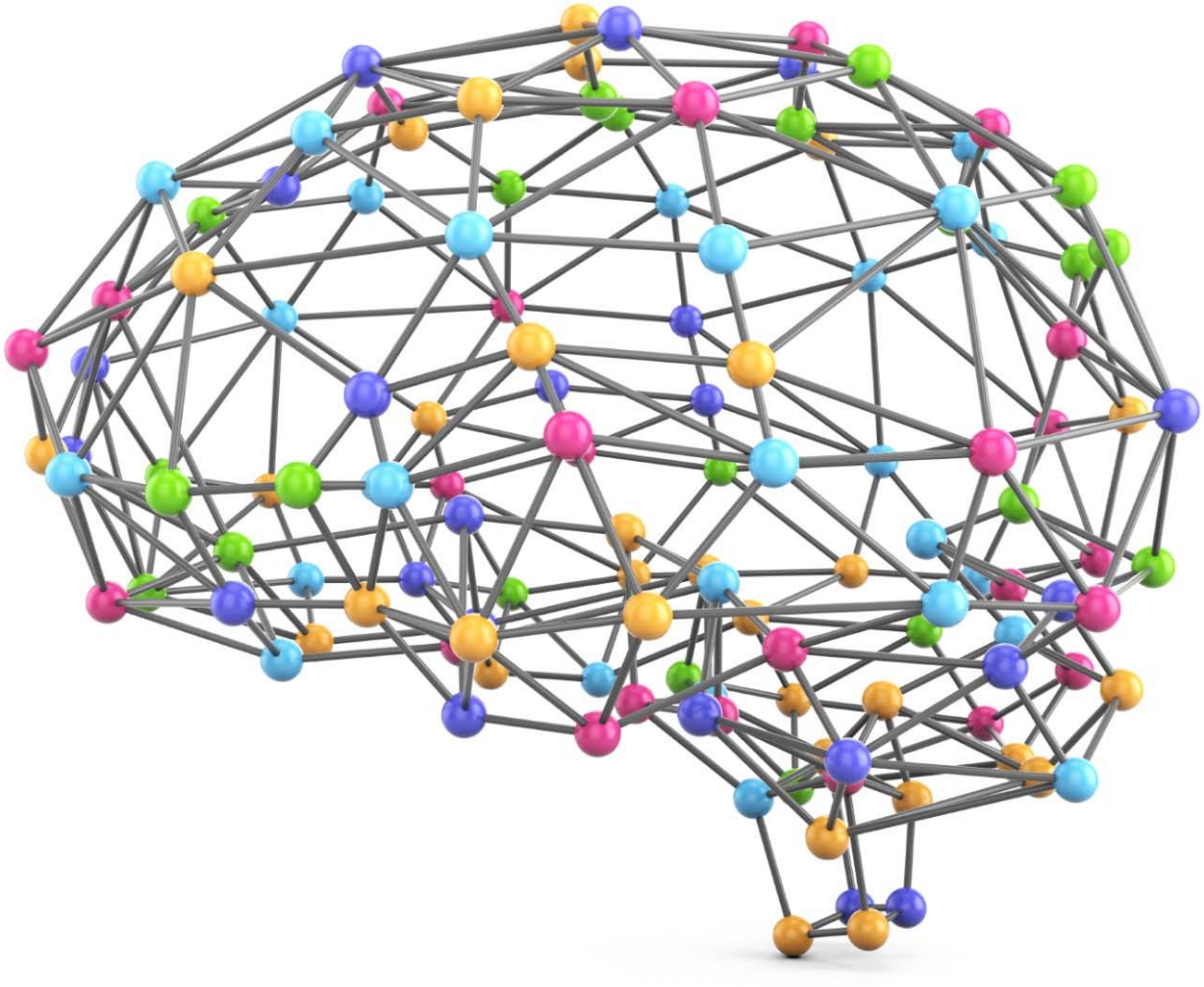
From Neurons to Interactions with the Environment



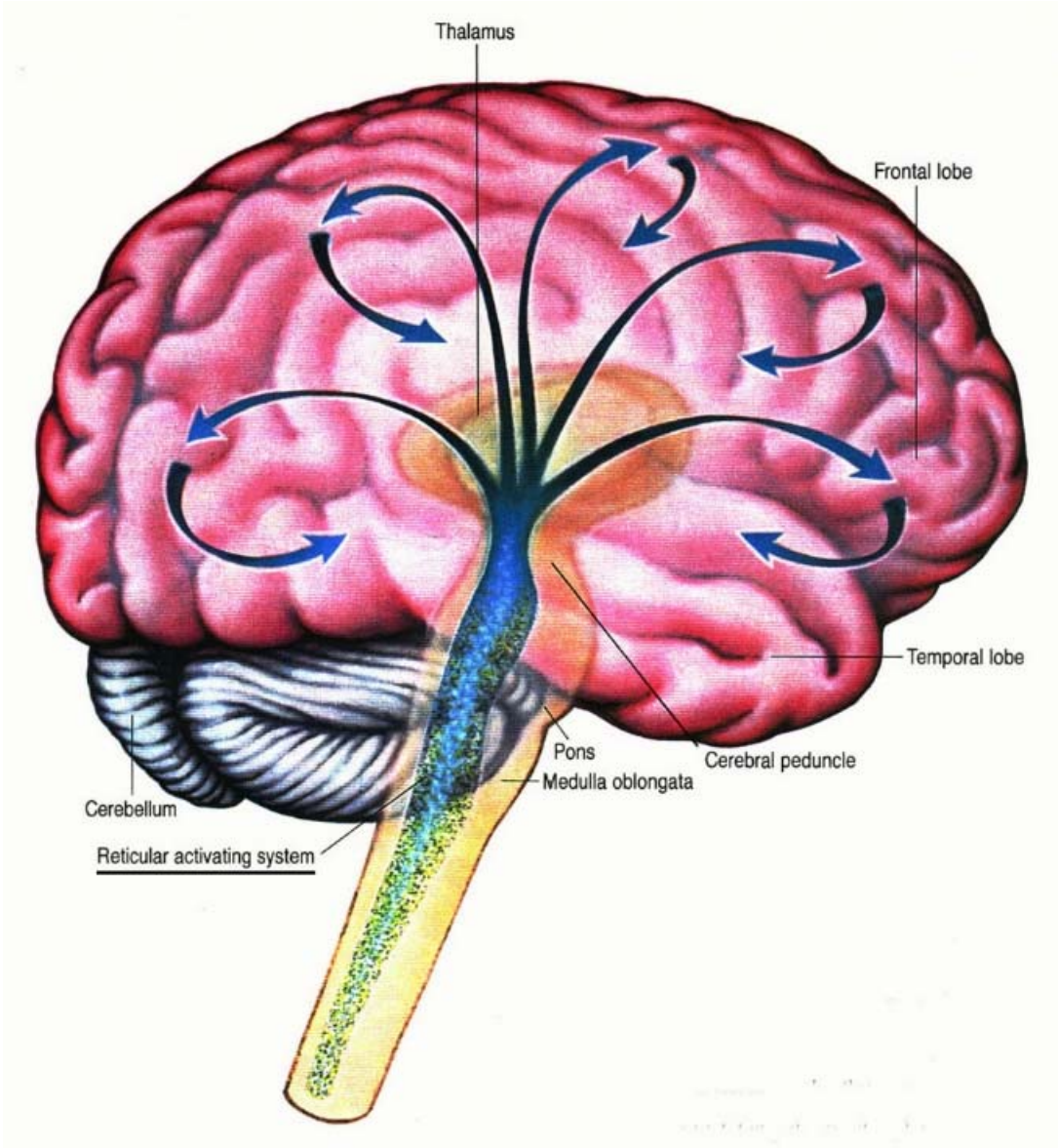




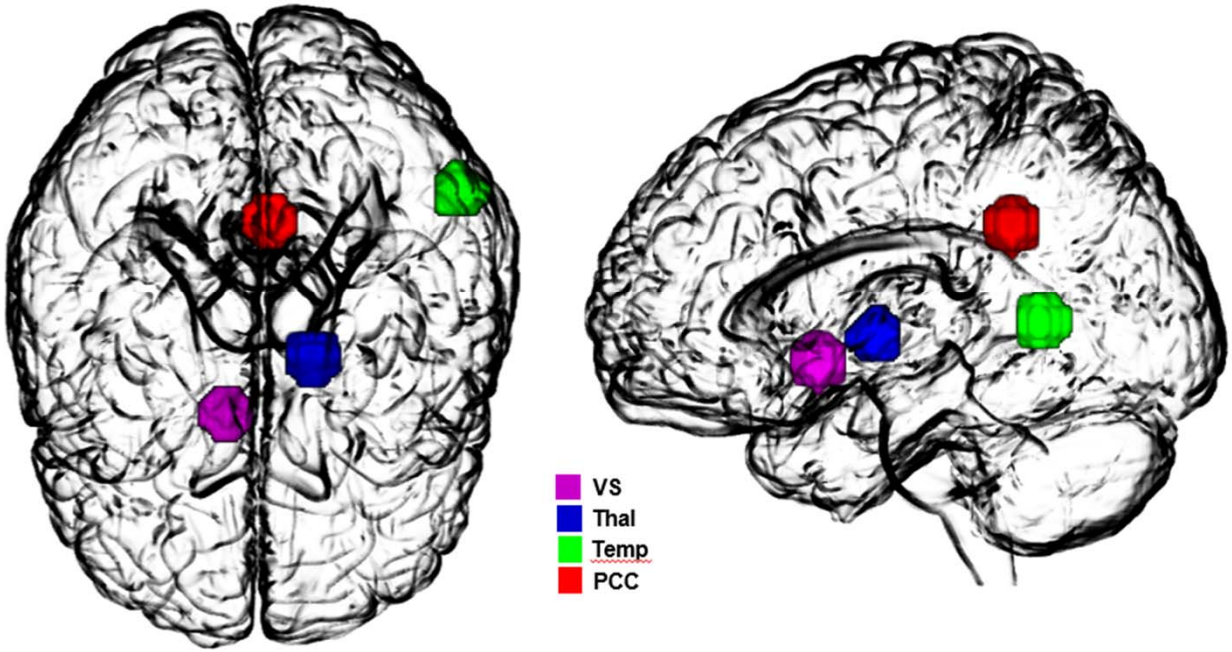
Modulation of Brain Connectivity



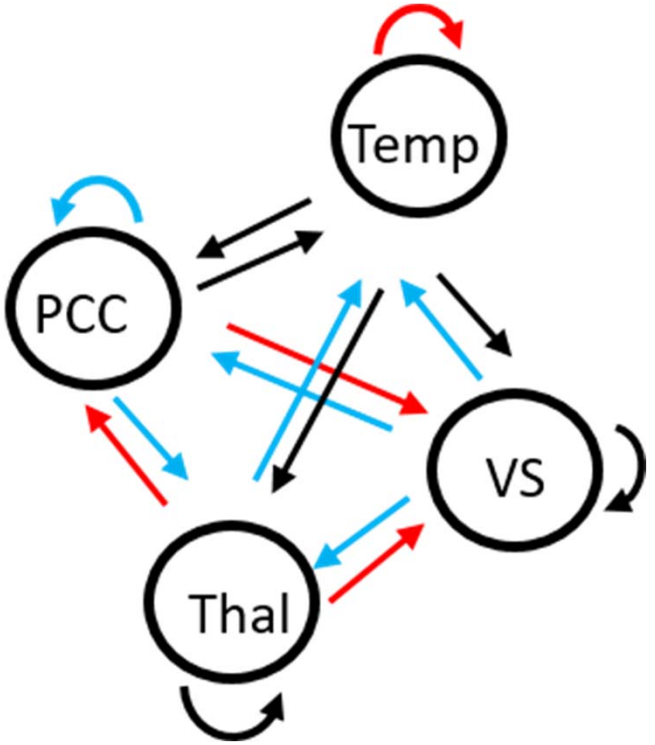
The Thalamic Filter Model



Thalamic Connectivity under LSD



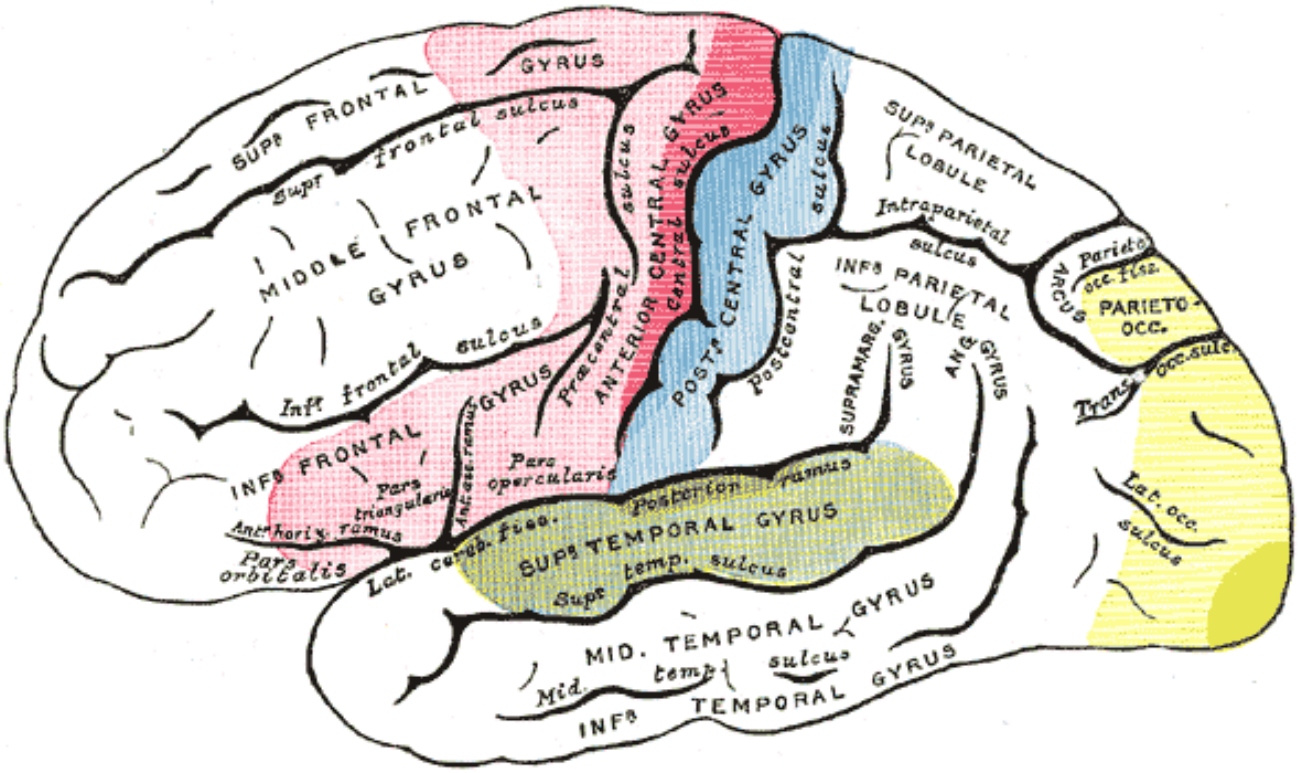
LSD-Placebo



red: increased effective connectivity
blue: decreased effective connectivity

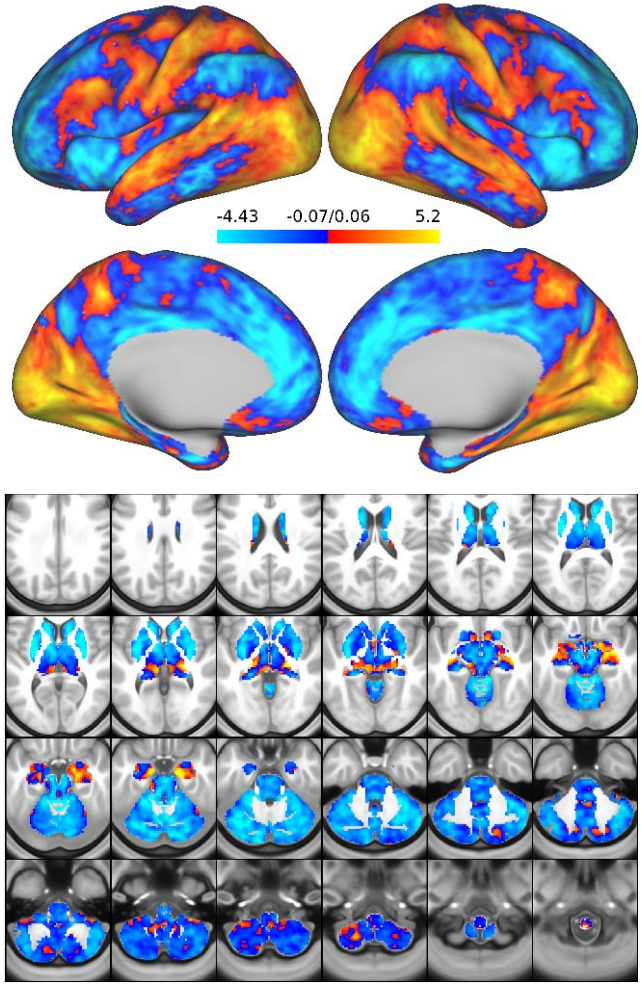
Preller er al., 2019, PNAS

What about the Cortex?



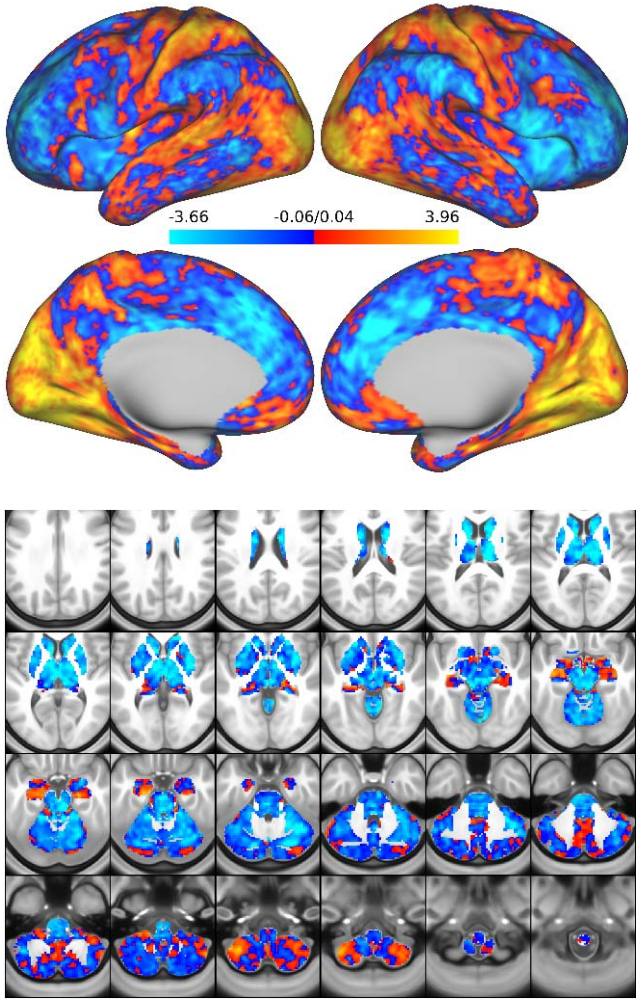
Changes in GBC are similar under LSD and Psilocybin

LSD vs. Placebo



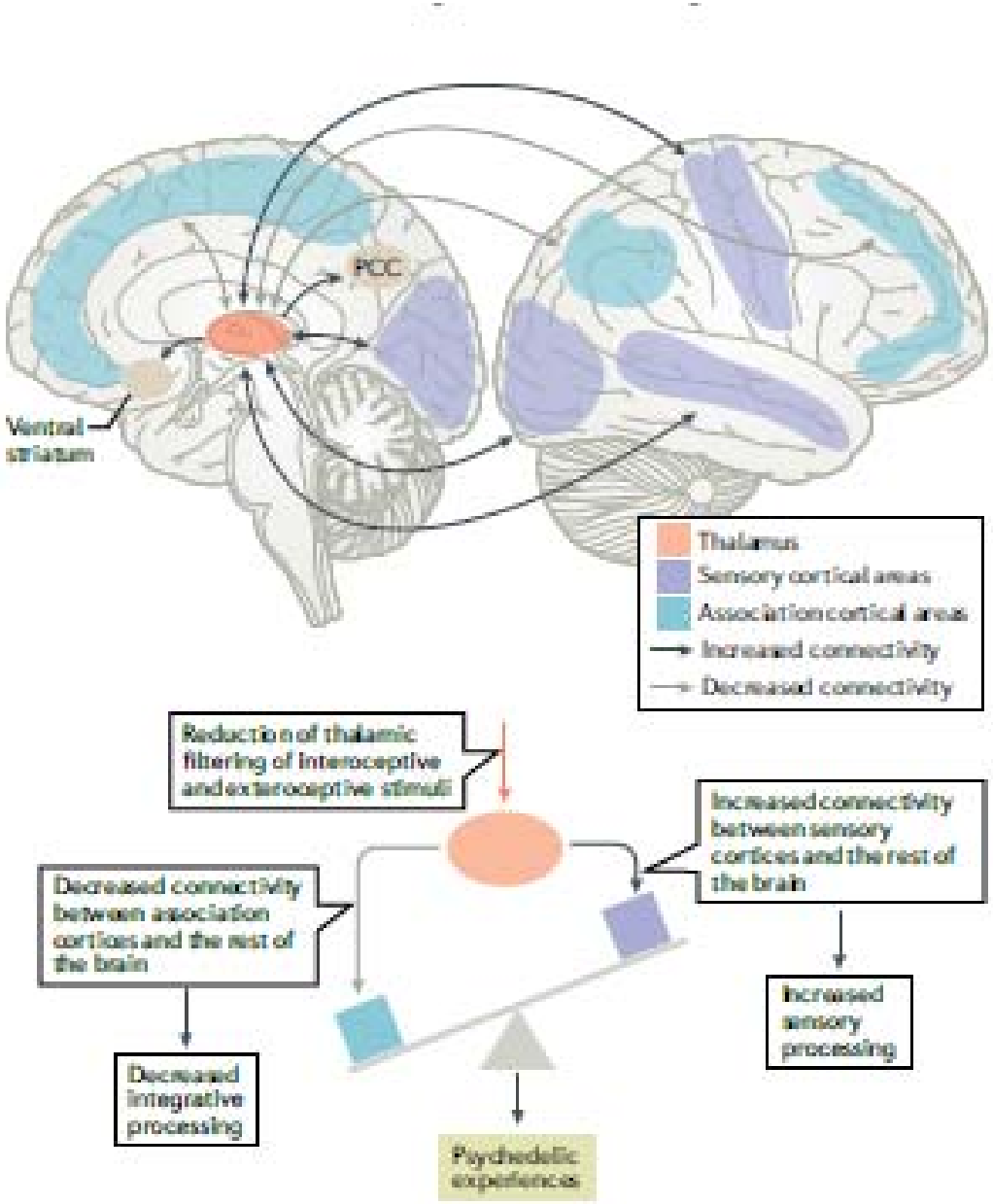
≈

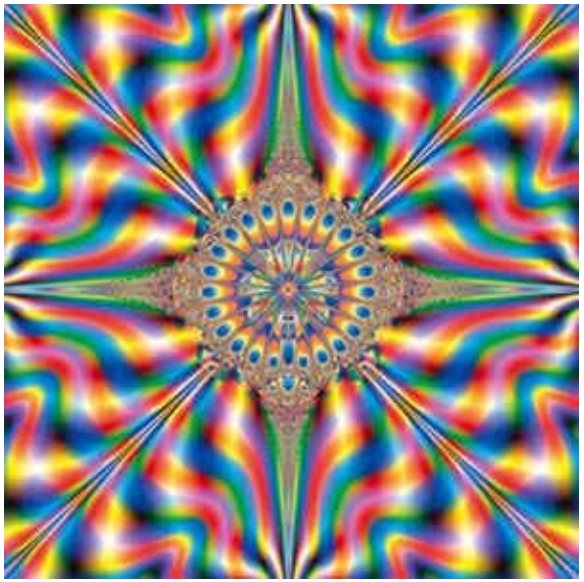
Psilocybin vs. Placebo



Preller et al., 2020; Preller at al., 2018

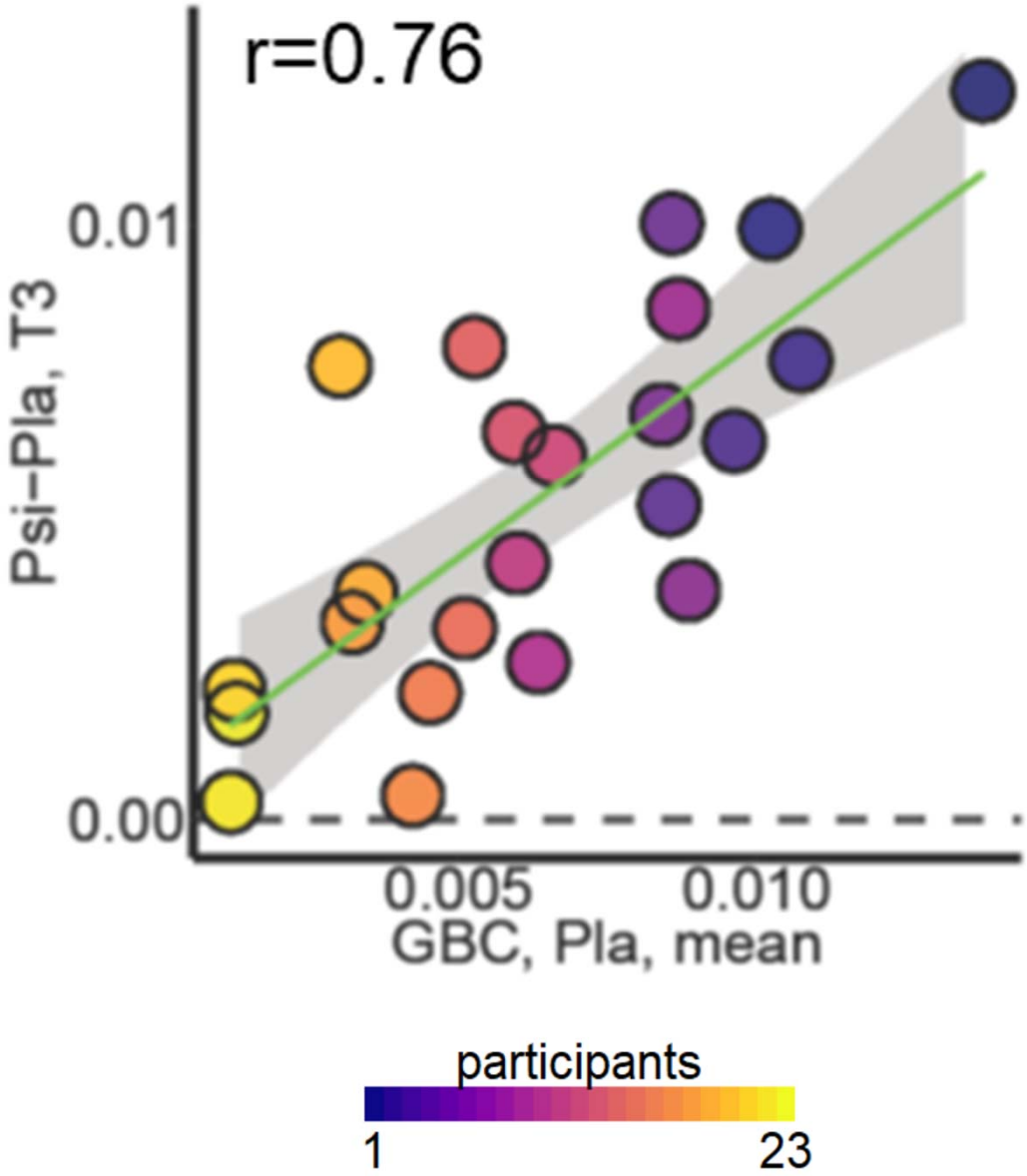
Dysbalance between Sensory Processing and Integration





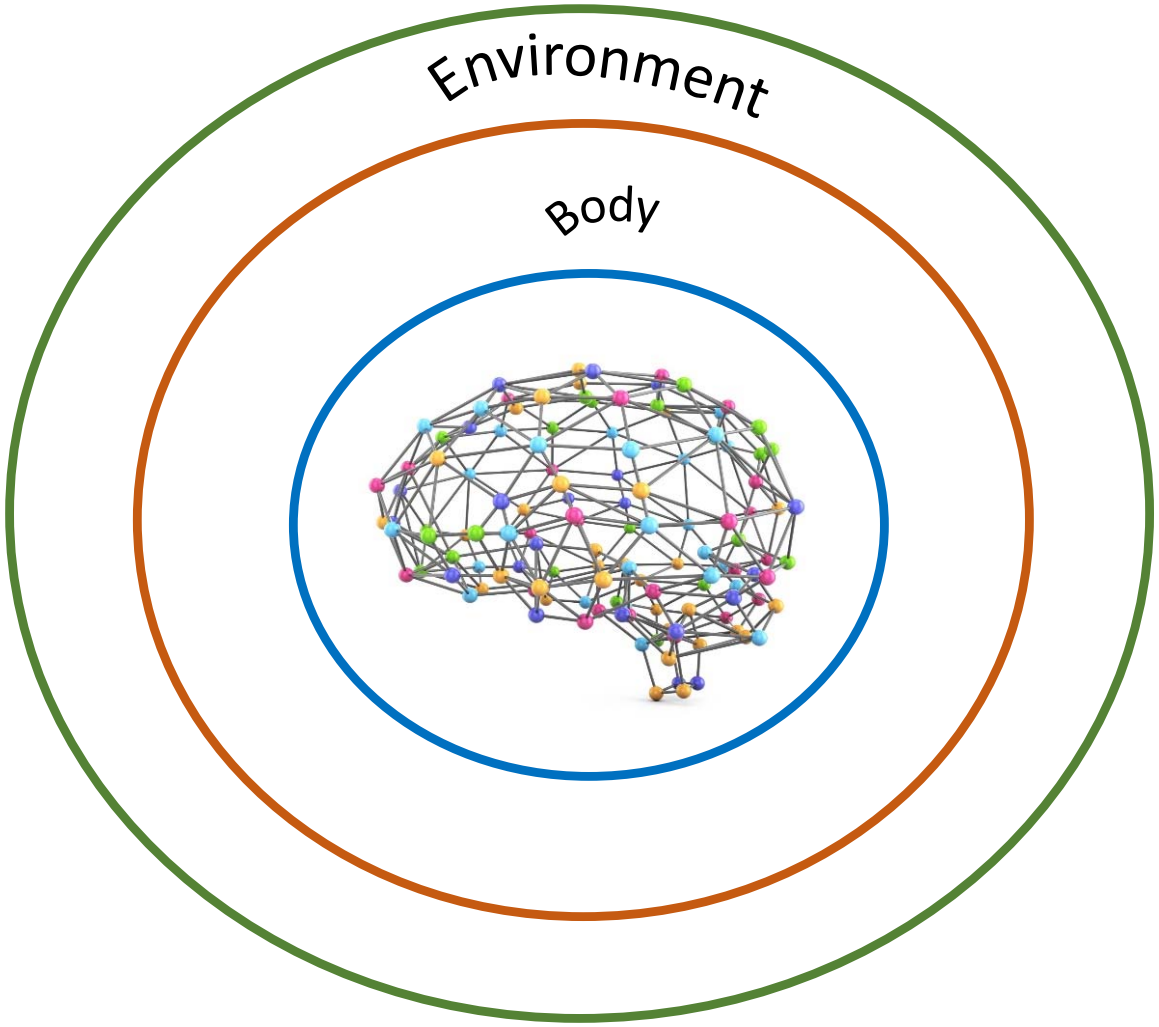
Vollenweider & Preller, 2020, NRN

Baseline Connectivity Correlates with Magnitude of Psilocybin Effects

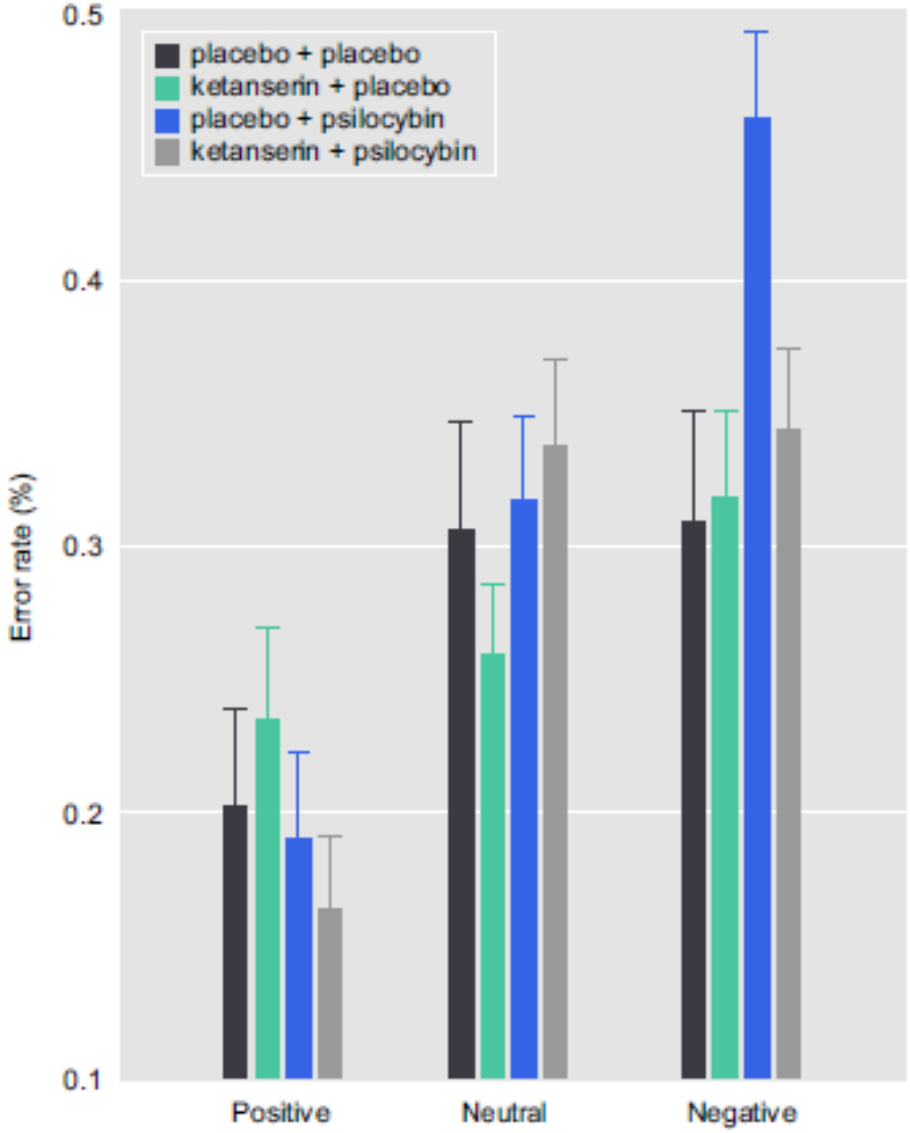


Preller et al., 2020

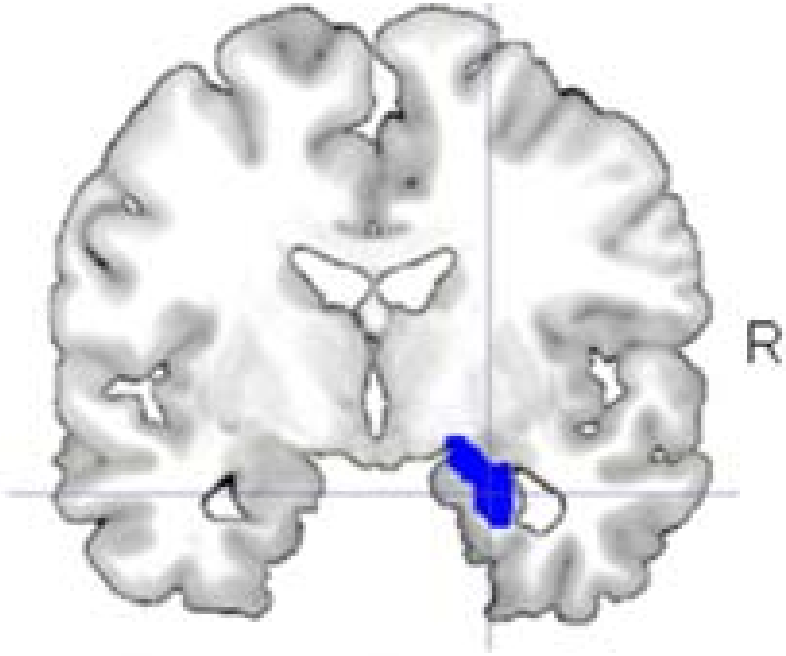
Interaction between Brain and Environment



Reduced Reactivity to Negative Stimuli



Kometer et al., 2012, BPS

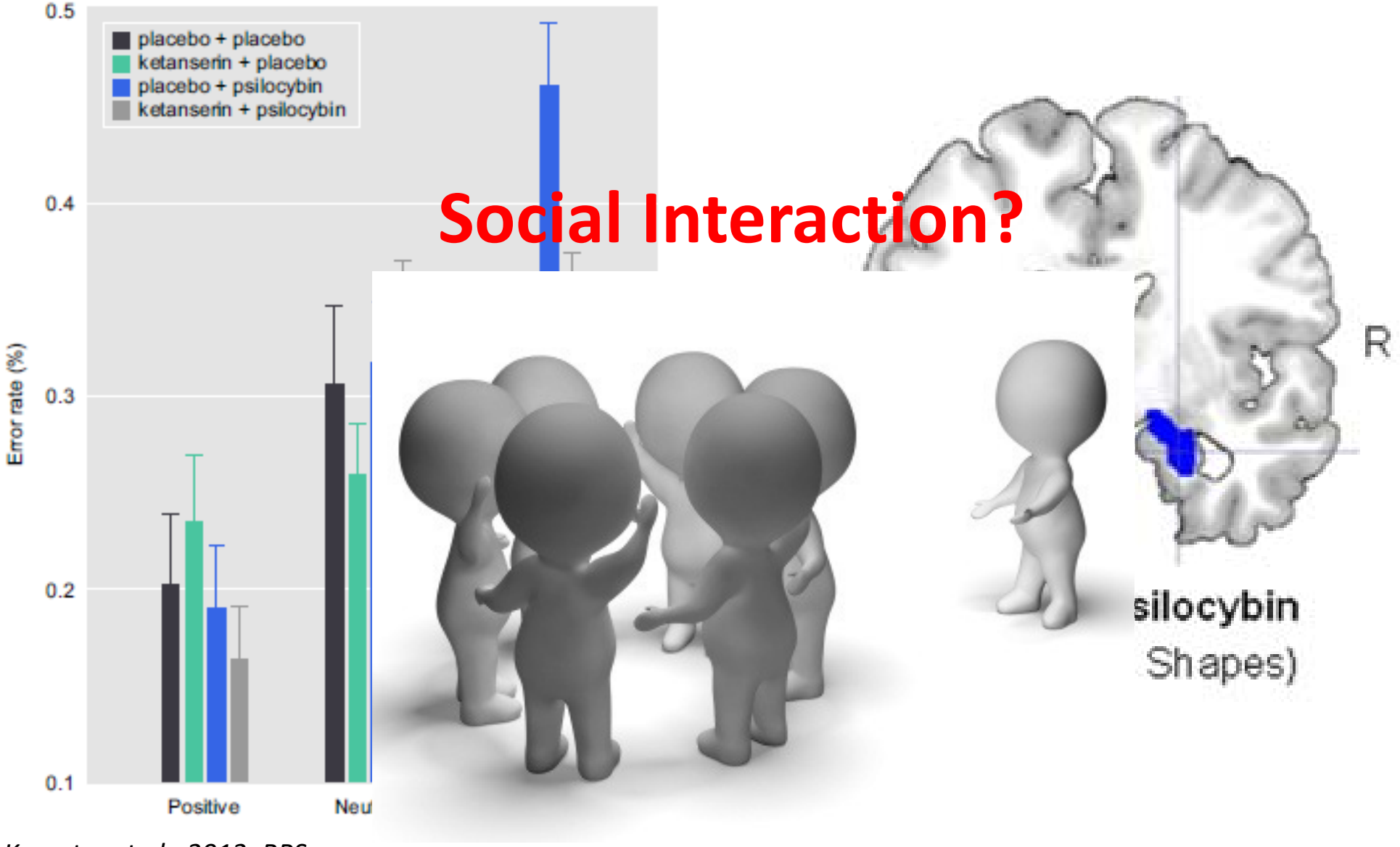


Placebo > Psilocybin

Negative (vs Shapes)

Krähenmann et al., 2014, BPS

Reduced Reactivity to Negative Stimuli



Kometer et al., 2012, BPS

Krähenmann et al., 2014, BPS

Social Exclusion Task

Cyberball

You are connected

Michael

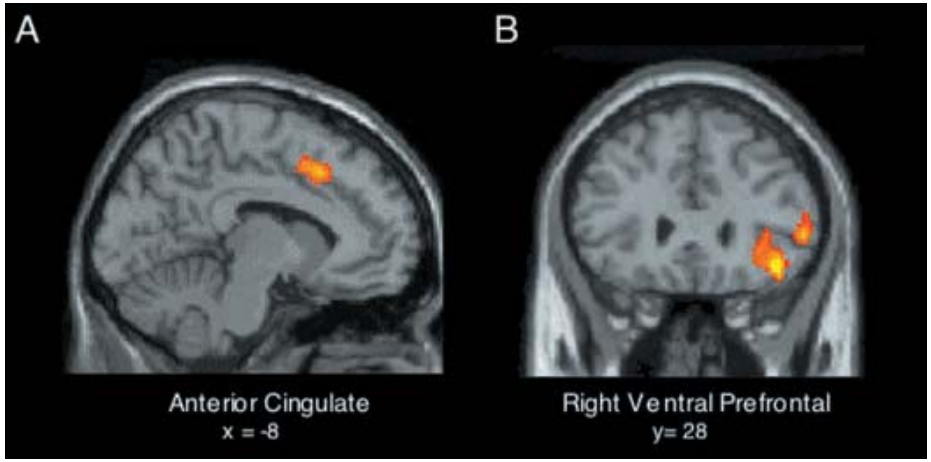
Sara

participant's name

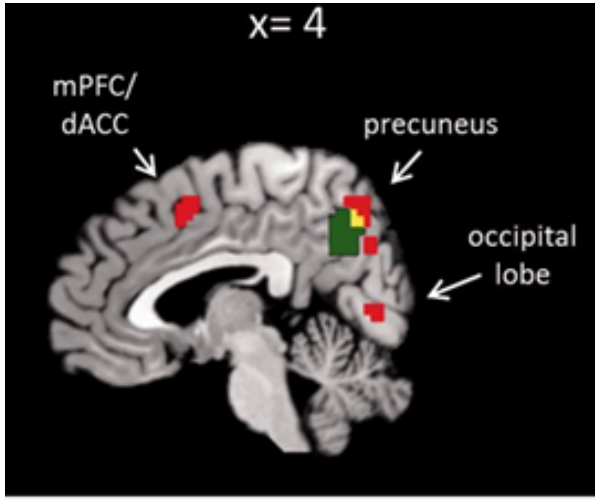
participant's

photo

Social Exclusion Task



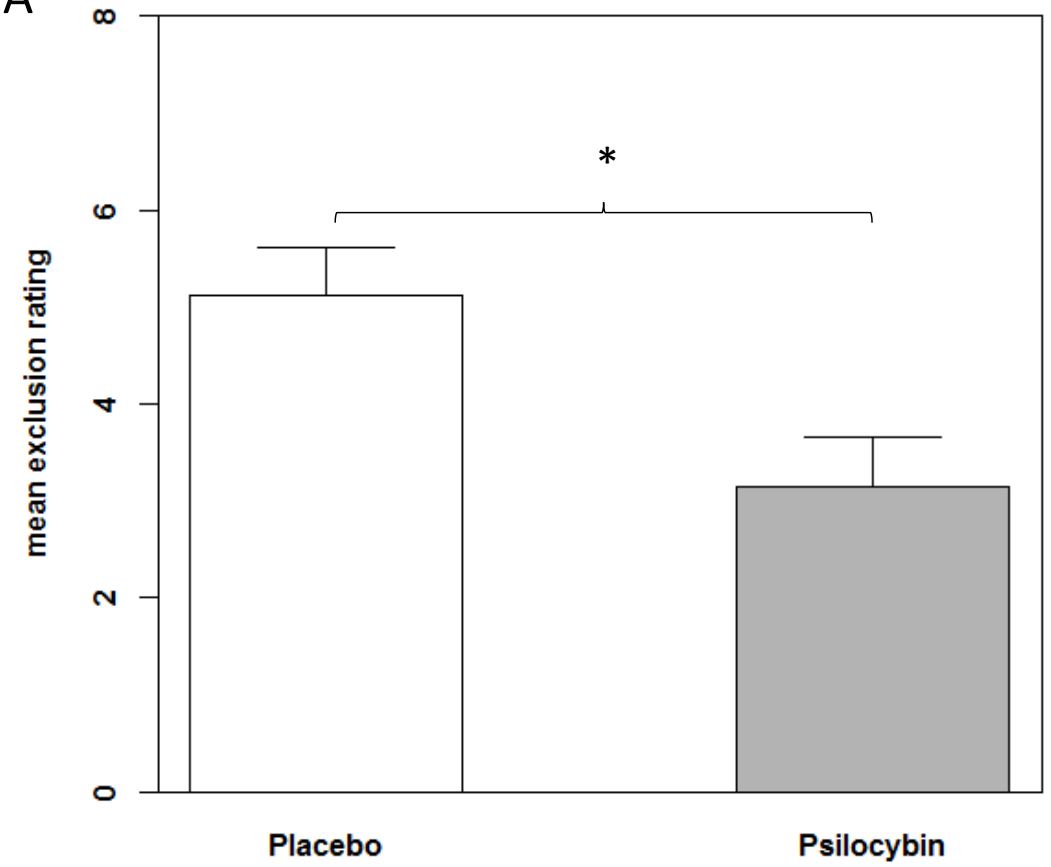
„Social Pain“ in normal waking states
Eisenberger, Science, 2003



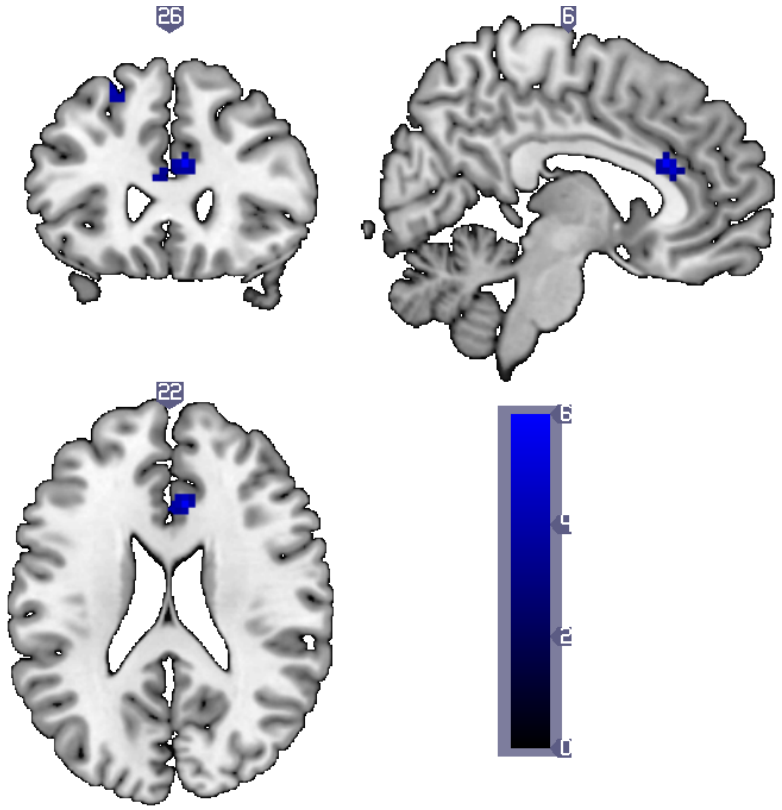
Red: increased reaction in Borderline Personality Disorder patients
Domsalla, 2013, SCAN

Psilocybin Reduces Social Exclusion Processing

A

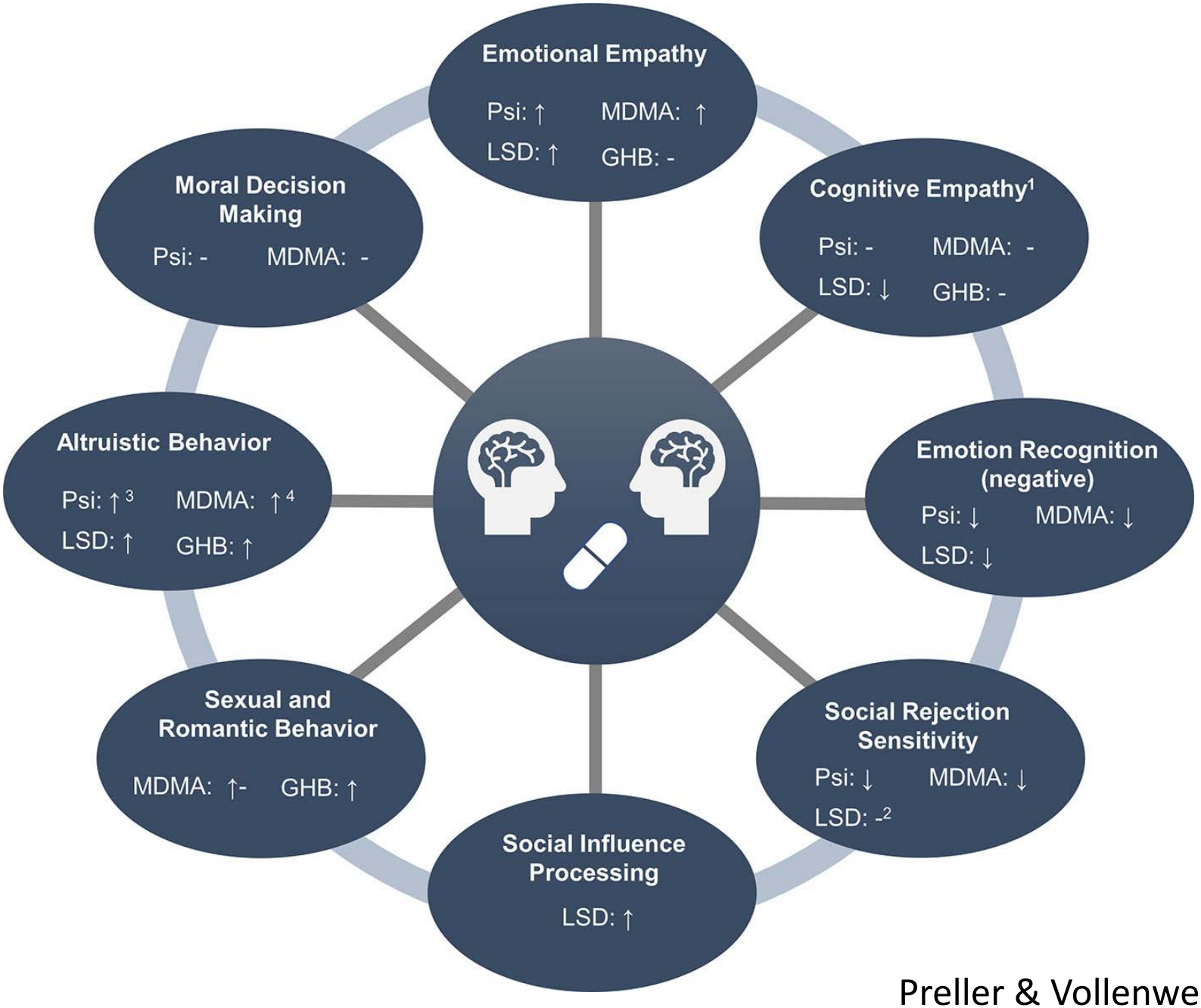


B



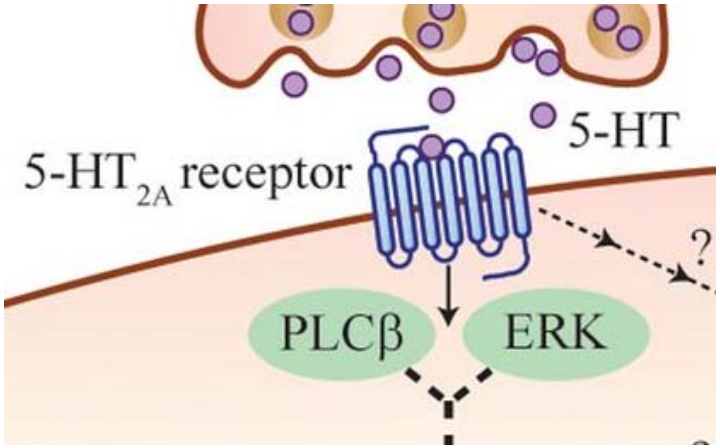
Preller et al., PNAS, 2016

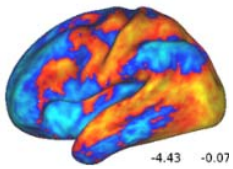
Modulation of Social Cognition via Psychedelics and Entactogens

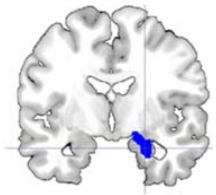


Preller & Vollenweider, 2019

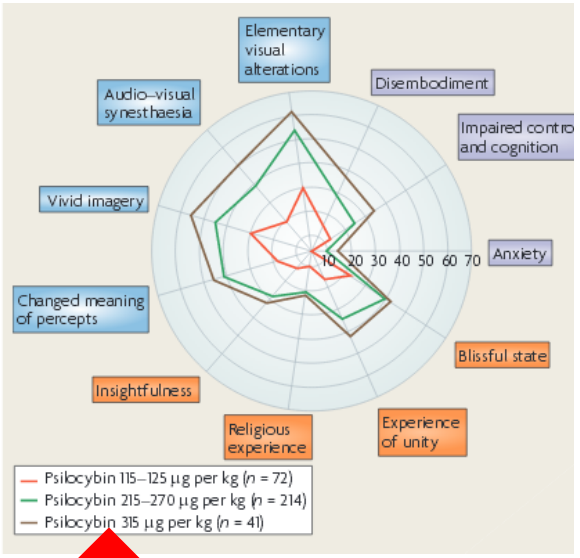
From Receptors to Clinical Effects







!



?

?

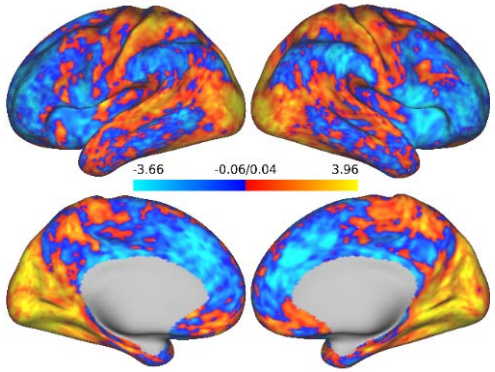
JAMA Psychiatry | Original Investigation

Effects of Psilocybin-Assisted Therapy on Major Depressive Disorder
A Randomized Clinical Trial

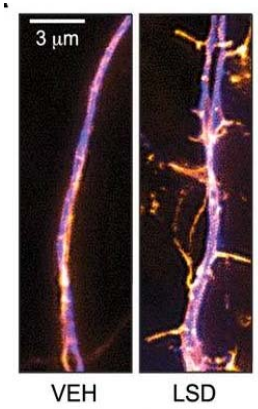
Alan K. Davis, PhD; Frederick S. Barrett, PhD; Darrick G. May, MD; Mary P. Cosimano, MSW; Nathan D. Sepeda, BS; Matthew W. Johnson, PhD; Patrick H. Finan, PhD; Roland R. Griffiths, PhD

Possible Mechanisms of Action

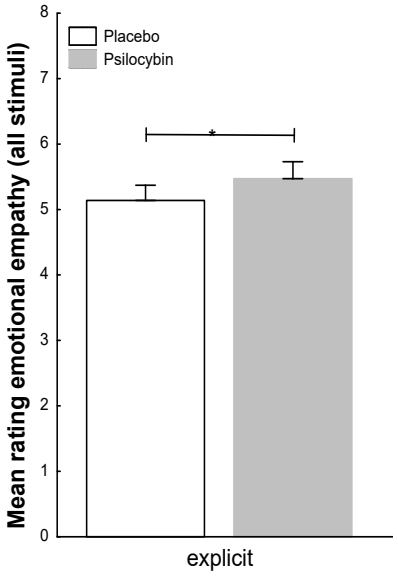
- Alterations in the 5-HT2A receptor system
- Induced Neuroplasticity
- Neuroinflammation
- Epigenetics
- Alterations in Brain Networks
- Alterations in Reward/Emotion Processing
- Increased Insight in Dysfunctional Behavior
- Increased Social Connectedness



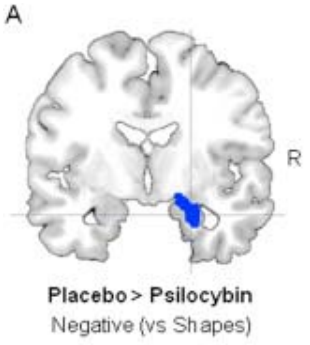
Preller et al.,2020



Ly et al., 2018



Pokorny et al., 2017



Kraehenmann et al., 2015

Conclusions

- Psychedelic-assisted therapy may be a promising new treatment model
- They have a rapid onset, long-lasting effects, and good safety profile
- Dealing with an altered state requires training on the therapist side
- Larger, well-controlled studies are needed to show efficacy
- Mechanisms need to be investigated

Usona Institute
Swiss Neuromatrix Foundation
FNSNF Schweizerischer Nationalfonds zur Förderung der wissenschaftlichen Forschung
Heffter Research Institute — Research at the Frontiers of the Mind

Thank you!

Psychiatrische Universitätsklinik Zürich:
Franz Vollenweider
Erich Seifritz
Patricia Dürler
Philipp Stämpfli
Marcus Herdener
Thomas Pokorny
Sara Romer
Nathalie Rieser
Flora Moujaes

University College London:
Karl Friston
Peter Zeidman
Adeel Razi

Yale University:
Alan Anticevic
John Murray
John Krystal
Joshua Burt
Ji Lisa Jie

MPI of Psychiatry Munich:
Leonhard Schilbach