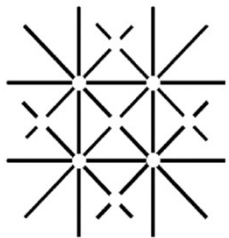


# Psychedelika: von der Droge zum Medikament

Matthias E. Liechi  
Clinical Pharmacology University  
Hospital Basel  
Switzerland

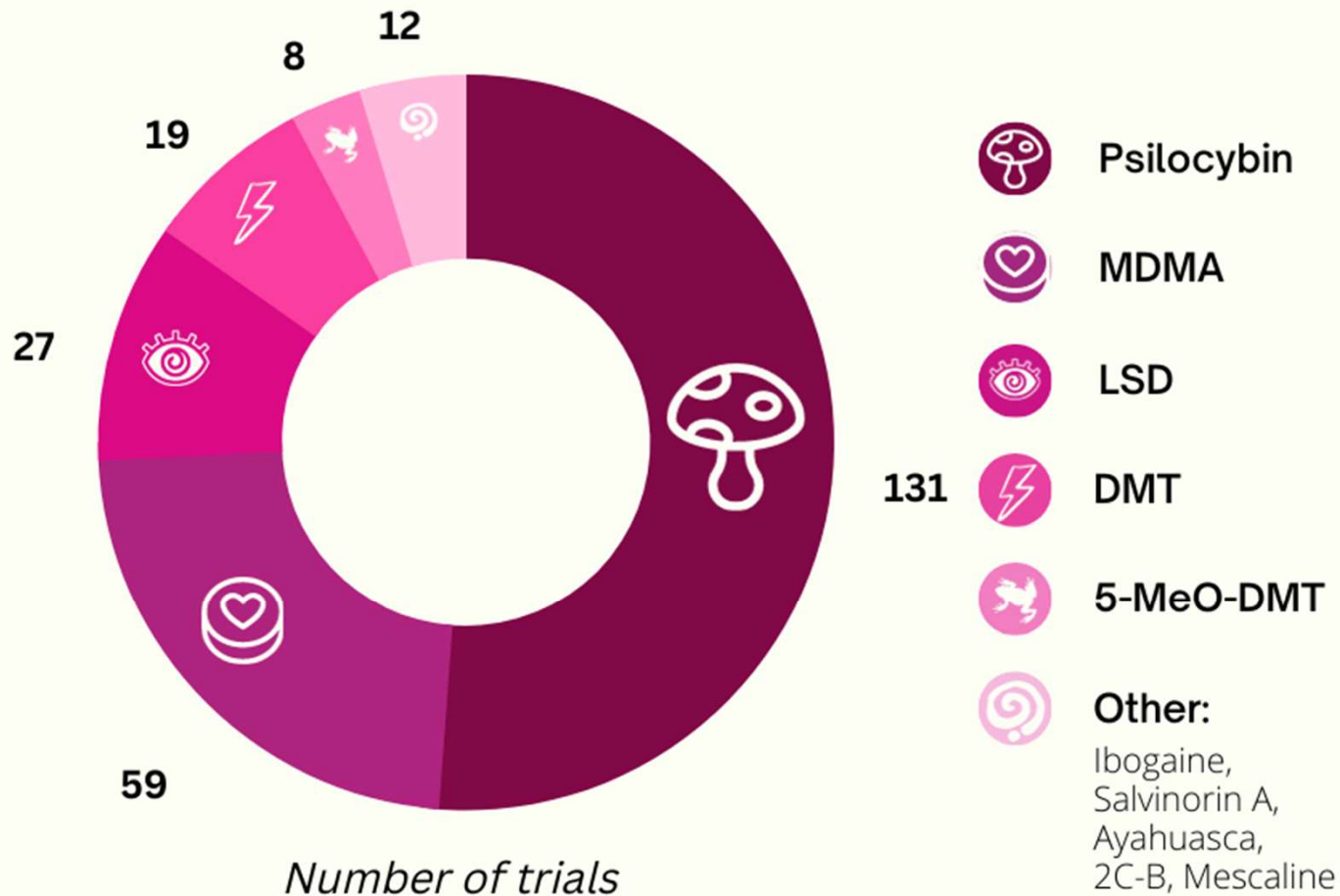


Uni Basel

Quadrimed Crans-Montana 26.1.2023

 Universitätsspital  
Basel

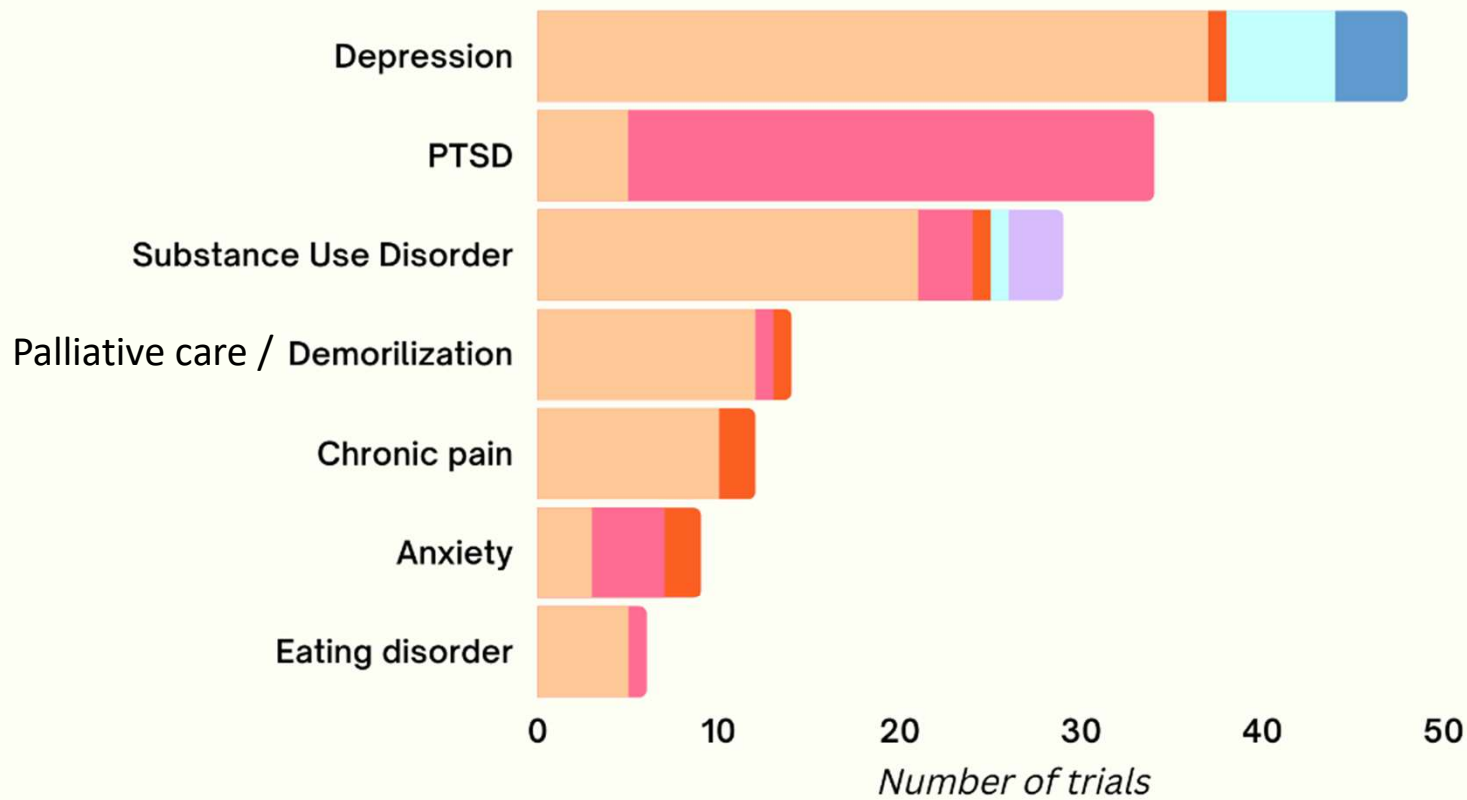
# Psychedelic Clinical Trials



[www.clinicaltrials.gov](http://www.clinicaltrials.gov), Oct 2023

From PSYLO PTY LTD

# Conditions being investigated



 Psilocybin  MDMA  LSD  DMT  5-MeO-DMT  Ibogaine

[www.clinicaltrials.gov](http://www.clinicaltrials.gov), Oct 2023

From PSYLO PTY LTD



## Why psychedelics?



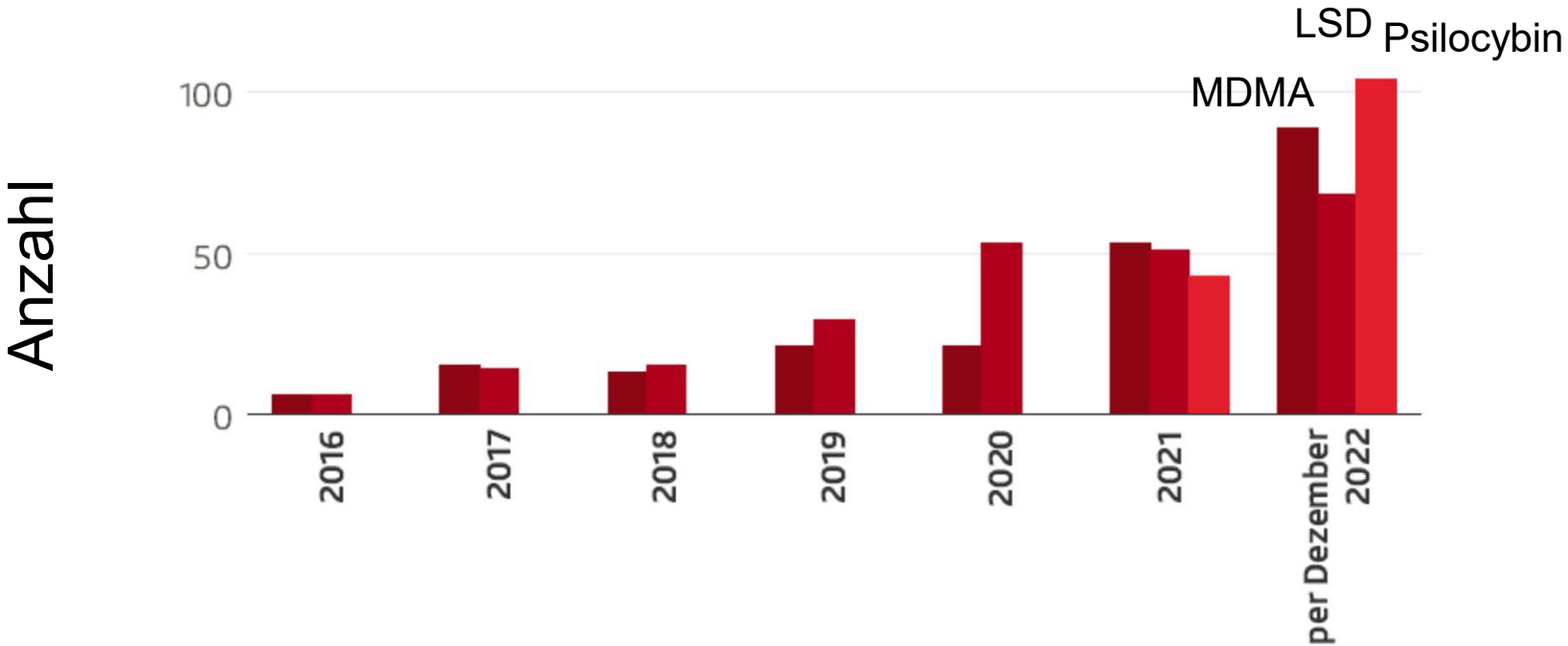
**Spravato**<sup>™</sup>  
(esketamine)   
nasal spray



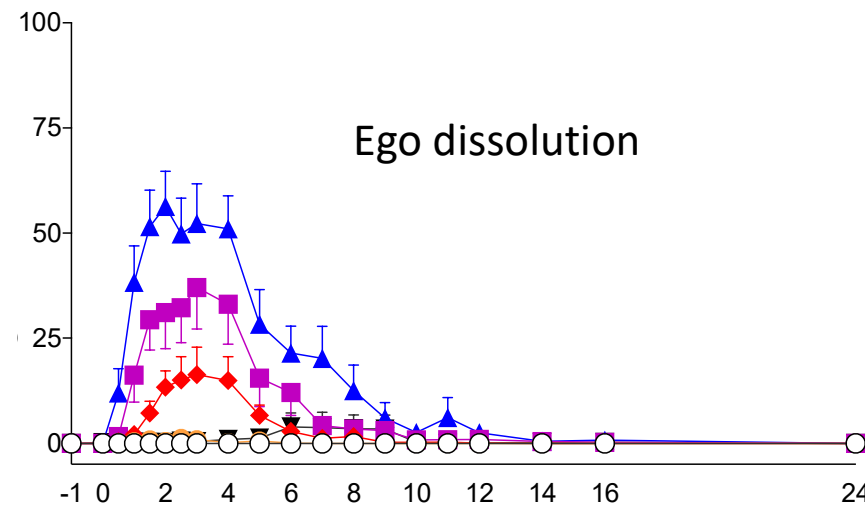
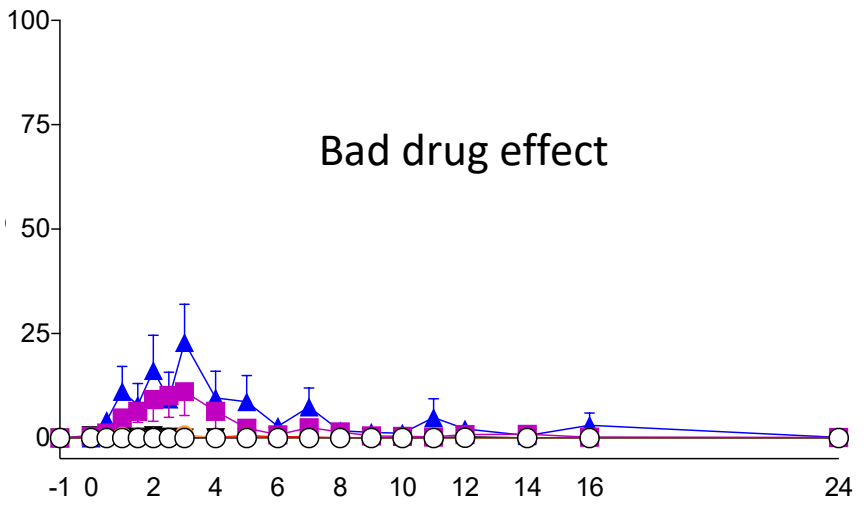
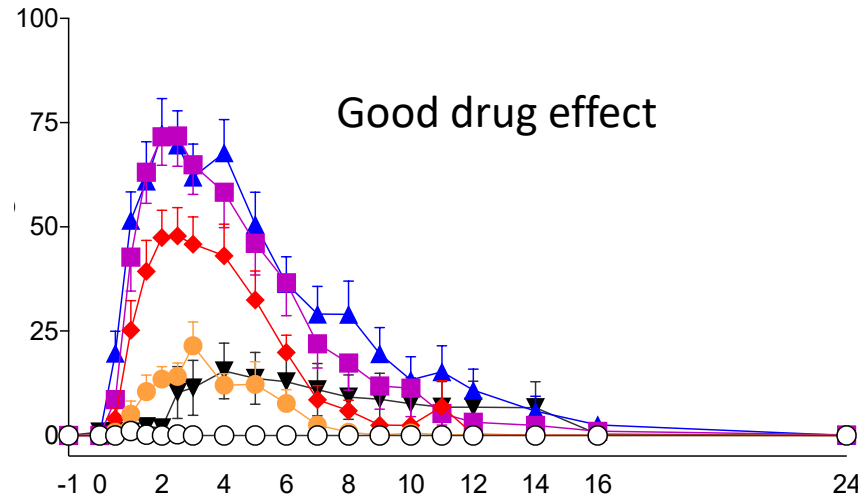
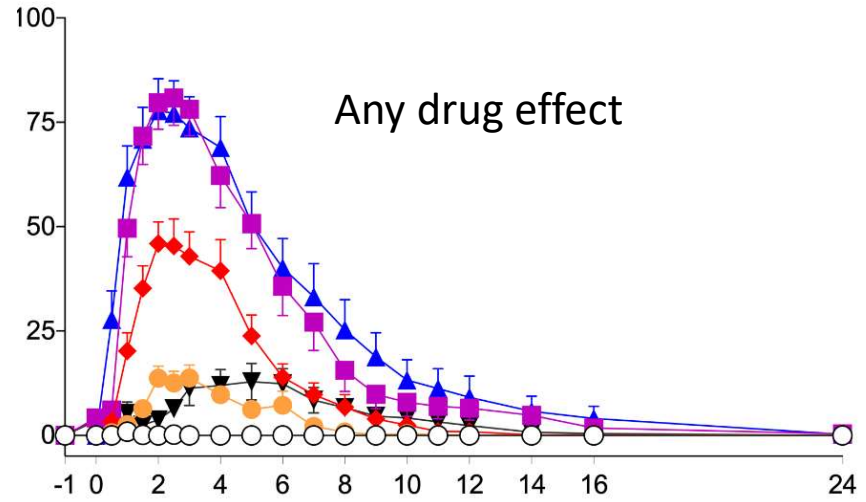
- Little innovation & low efficacy of classic antidepressants
- Ketamine acts rapidly but not sustained
- Electroconvulsive therapy acts rapidly but low acceptance
- Psychedelics act rapidly and sustained according to first studies
- Legalization/commercialization of (medical) cannabis as pathfinder



# BAG Ausnahmebewilligungen für die beschränkte medizinische Anwendung

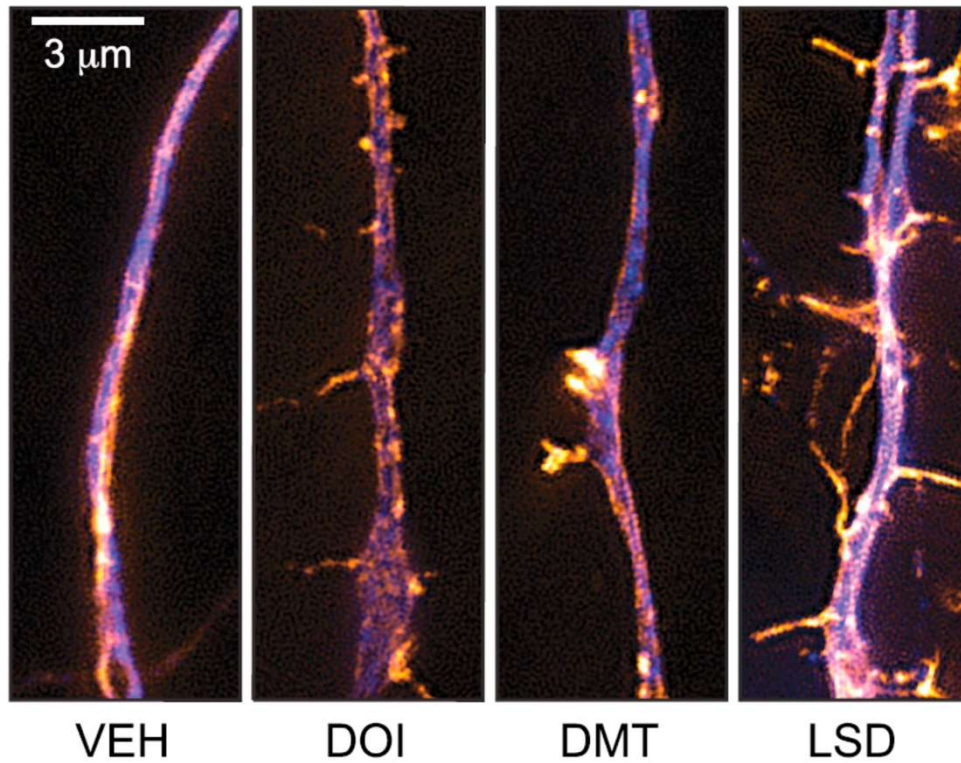


# Mode of action? 5-HT<sub>2A</sub> antagonist prevents LSD effect



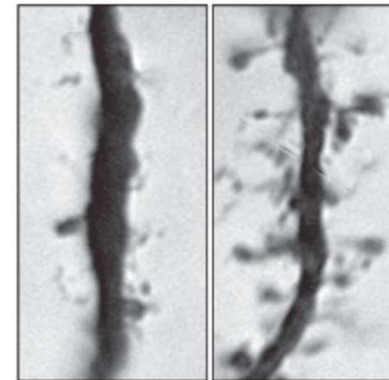
N=16, Mean+SEM

## Psychedelics promote spinogenesis



Rat cortical neuron cultures: Spine density ↑

Apical Dendrites



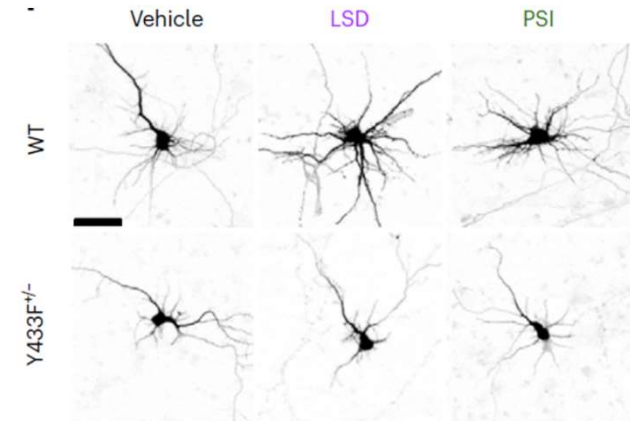
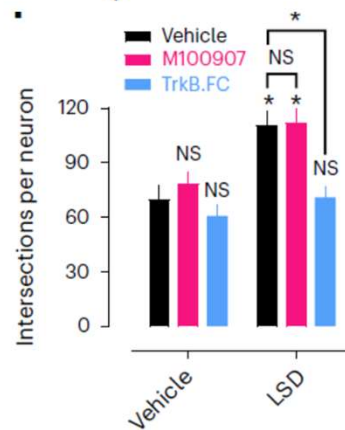
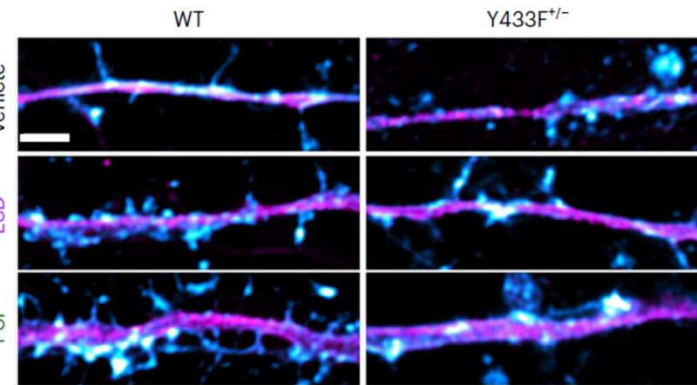
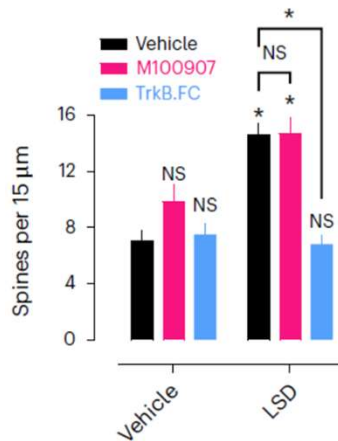
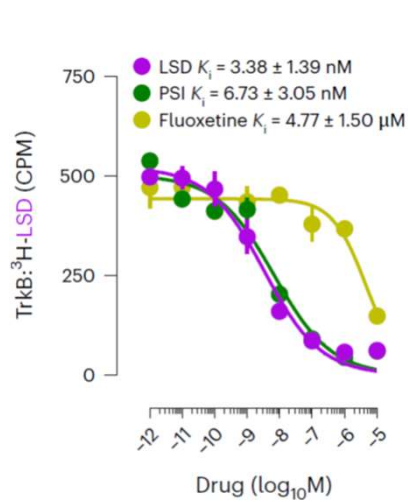
VEH

DMT

Rat PFC pyramidal neurons: Spine density ↑

Ly et al. 2018, Cell Reports 23; 3170-82

# Psychedelics promote plasticity by directly binding to BDNF receptor TrkB

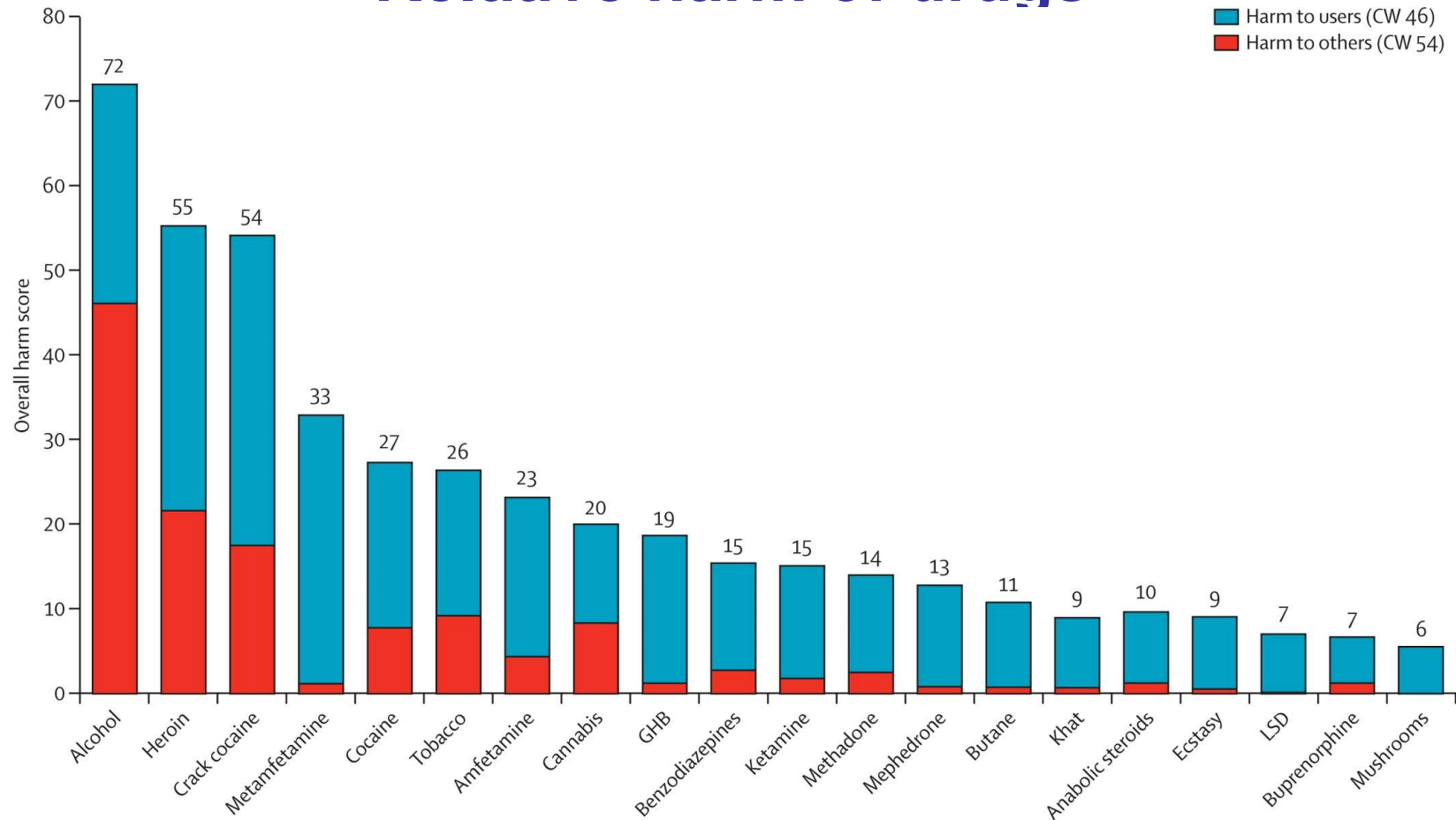


LSD and psilocybin bind to TrkB, the receptor for BDNF with 1000-fold higher affinities than those of other antidepressants.

Psychedelic-induced neuroplasticity depends on TrkB and BDNF, but not 5-HT<sub>2A</sub> activation



# Relative harm of drugs



Nutt et al 2010: Lancet 376: 1558-1565

# Psychedelics not linked to mental health problems or suicidal behavior: A population study

## Serious psychological distress

K6-scale

## Mental health treatment

Inpatient

Outpatient

Medication

Needed but did not receive

## Suicidal

Thought about killing self

Planned to kill self

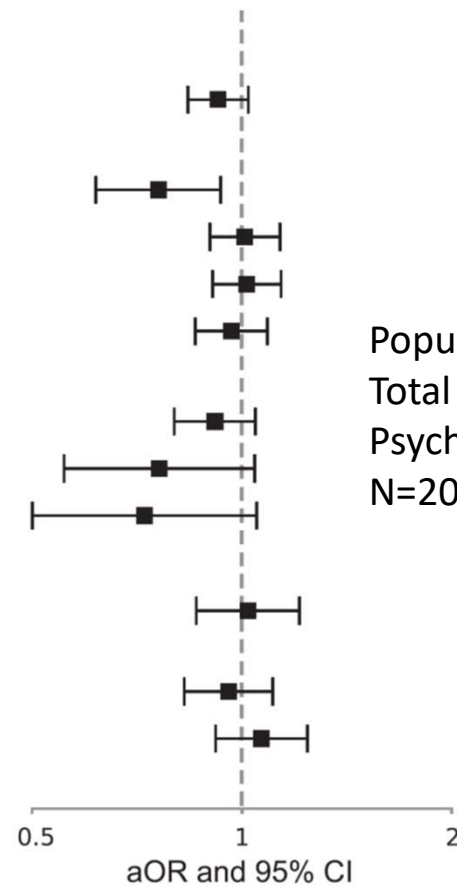
Attempted to kill self

## Depression and anxiety

Symptoms of major depressive episode

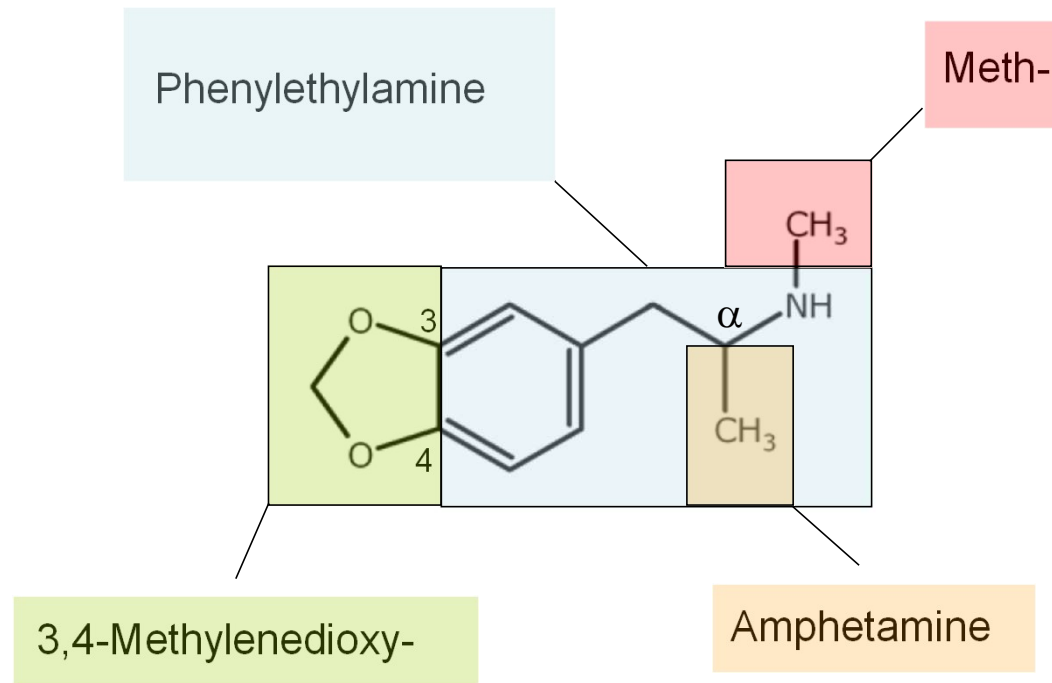
Diagnosis of depression

Diagnosis of anxiety disorder

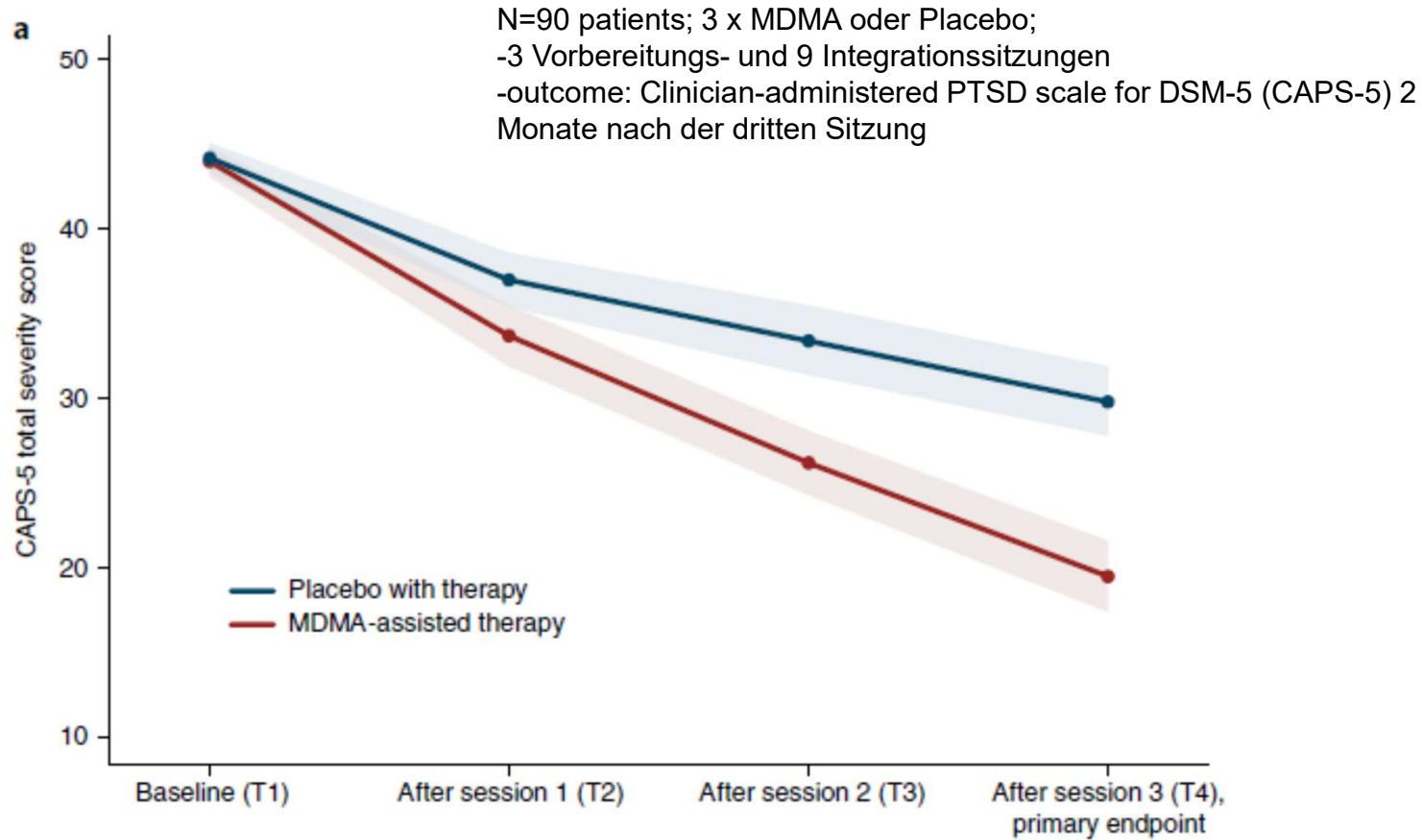


Population study in US;  
Total N=135'000  
Psychedelic user  
N=20'000

# 3,4-Methylenedioxyamphetamine (MDMA)



## MDMA reduces PTSD symptoms in phase 3 study

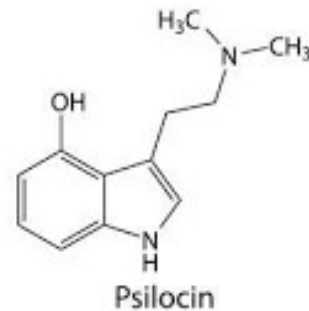
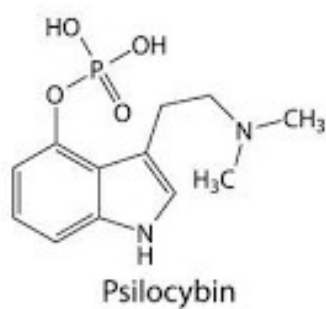


# Psilocybin

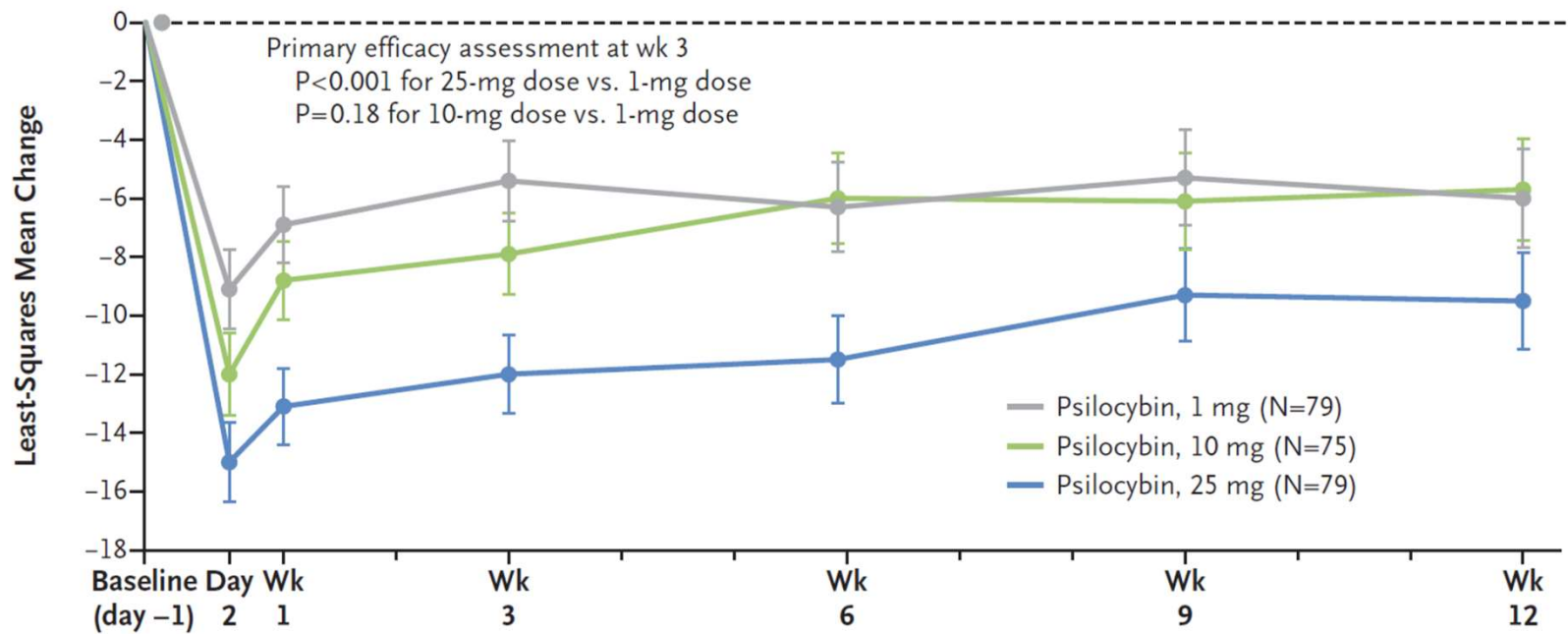
- 1958 erstmals in Basel aus *psilocybe mexicana* (ψιλός *kybē*; *Zauberpilz*) extrahiert und auch synthetisch hergestellt
- Das heute am häufigsten in Patienten untersuchte Psychedelikum



*Psilocybe mexicana*



# Single-Dose Psilocybin for a Treatment-Resistant Episode of Major Depression



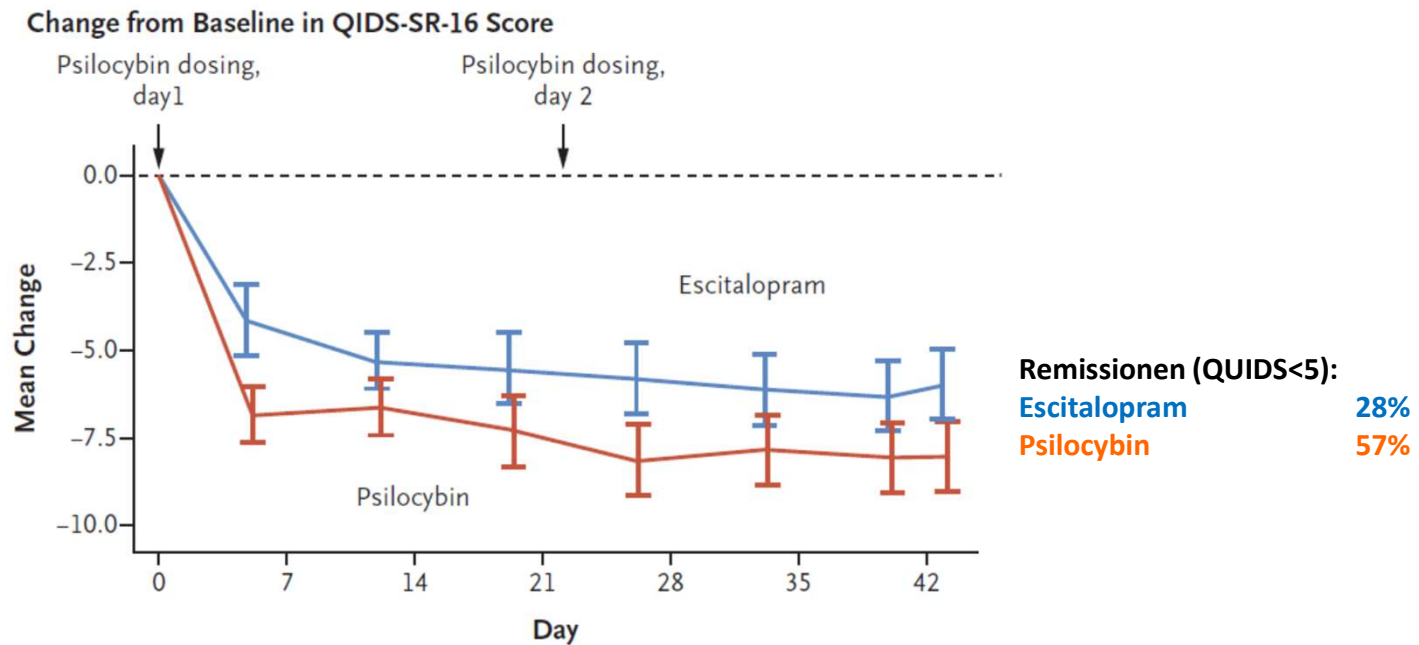
N=233; Psilocybin 25 mg vs. 10 mg vs. 1 mg

N Engl J Med 2022;387:1637-48.



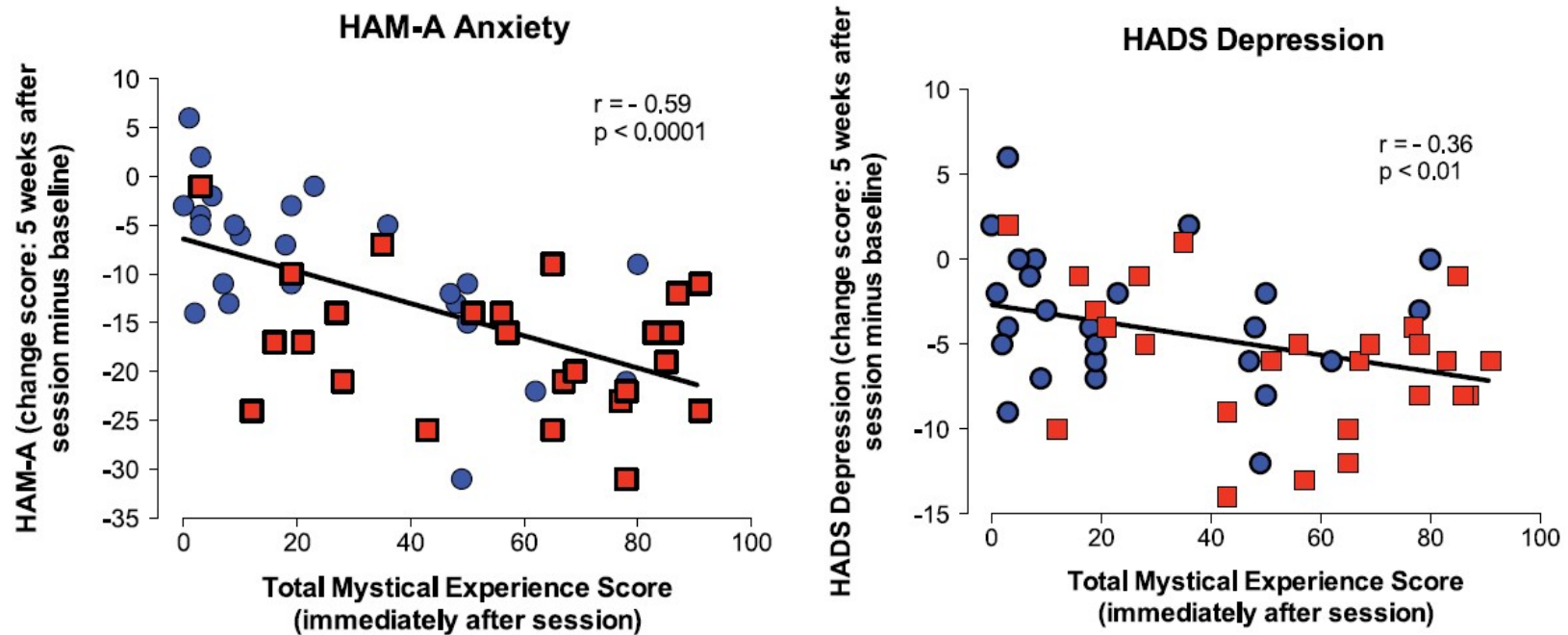
The NEW ENGLAND  
JOURNAL of MEDICINE

# Psilocybin versus Escitalopram for Depression



RCT, major depression, N=59, two doses of psilocybin 25 mg or two doses of psilocybin 1 mg plus daily escitalopram, Quick Inventory of Depressive Symptomatology at 6 wks

# Acute experience associated with long-term effects



51 cancer patients with depression/anxiety; 1/3 or 22/30 mg/70 kg of **psilocybin**, cross-over at 5 wks.

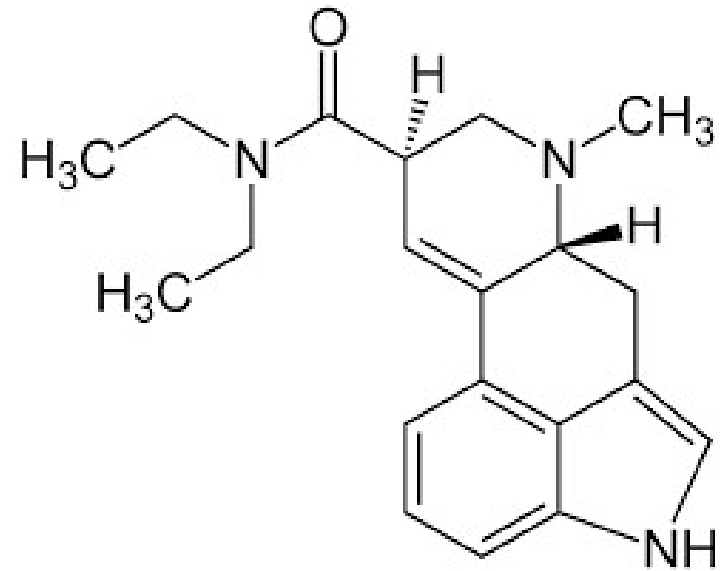
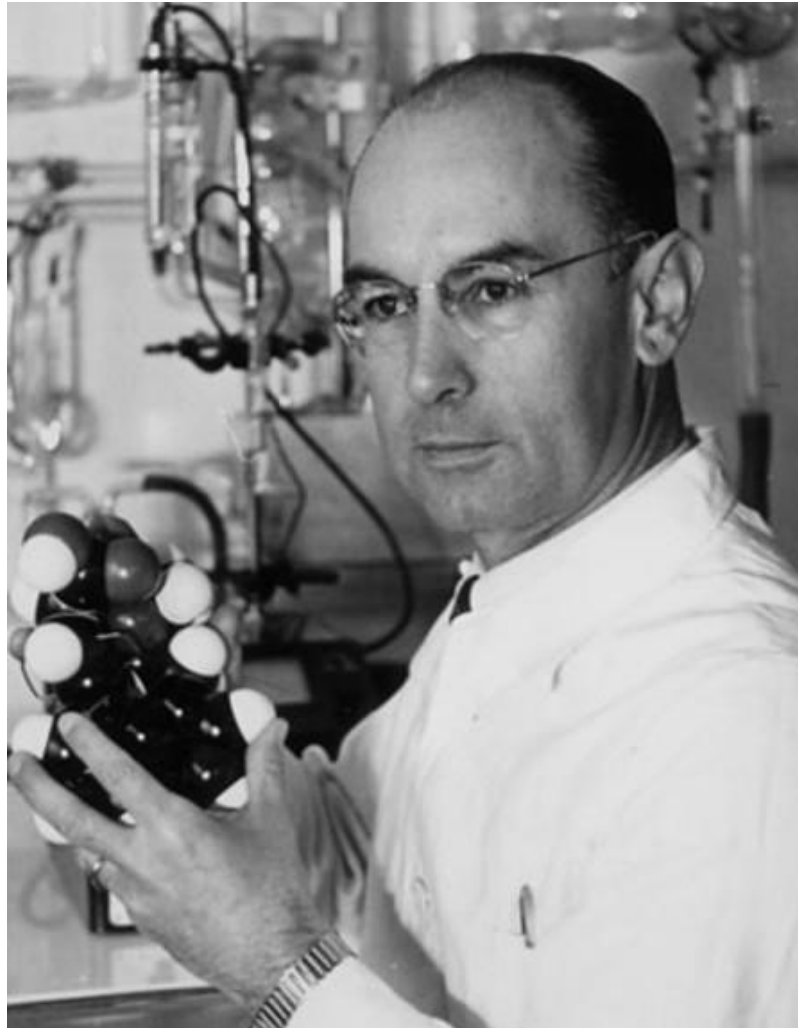


# Elements of mystical-type experiences

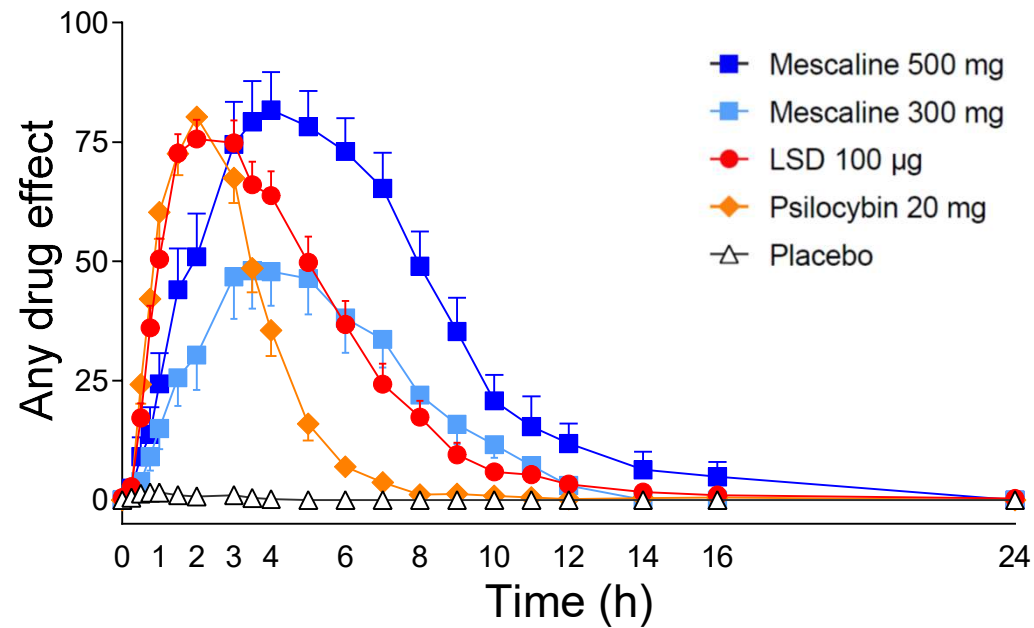
## MEQ 30 subscale items

- **mystical**
  - Unity of inside/outside, sacral, insight, lack of body, lack of border, part of something bigger, pure being, all one, *connectedness*
- **Positive mood**
  - peace, quiet, joy, bliss
- **Transcendence of time/space**
  - timeless
- **Ineffability**
  - Not to be described by words, awe, incomprehensible, amazing, humility, eternity, great

# LSD

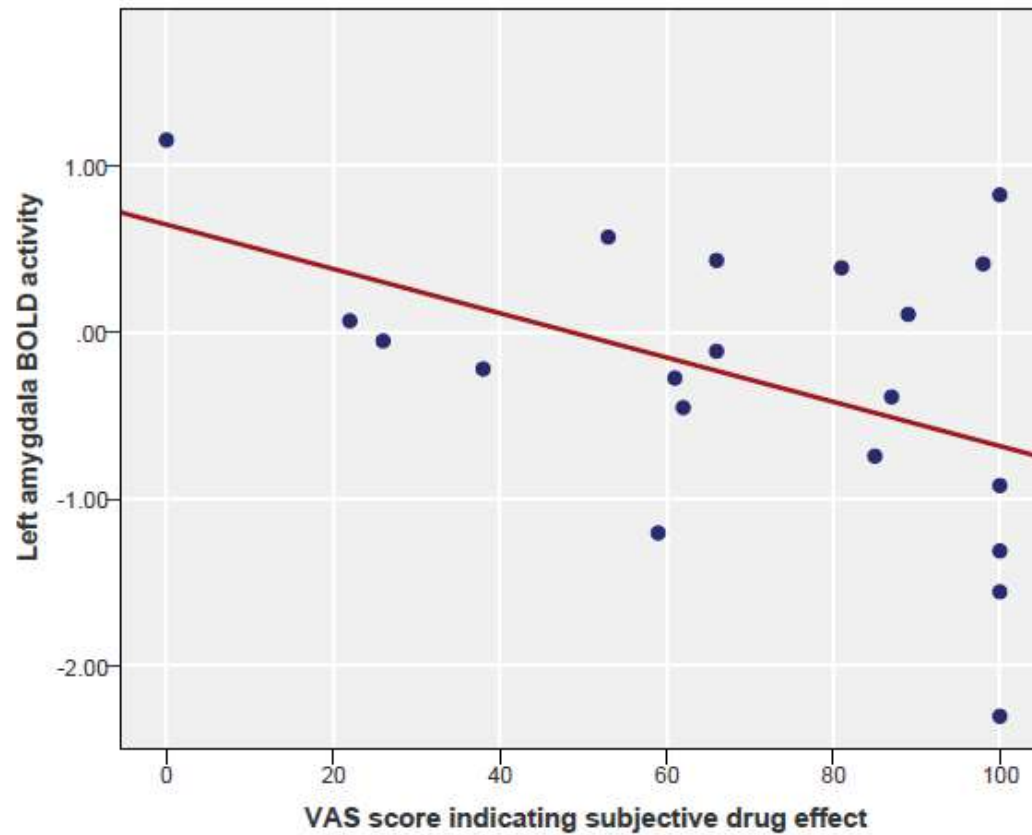
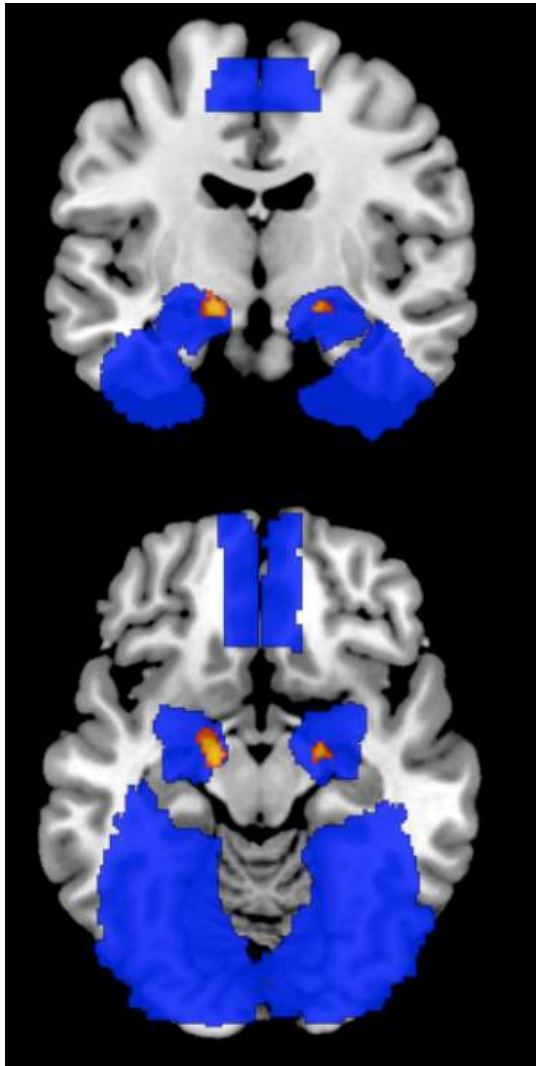


## Equivalent doses of different psychedelics



N=32, mean+SEM

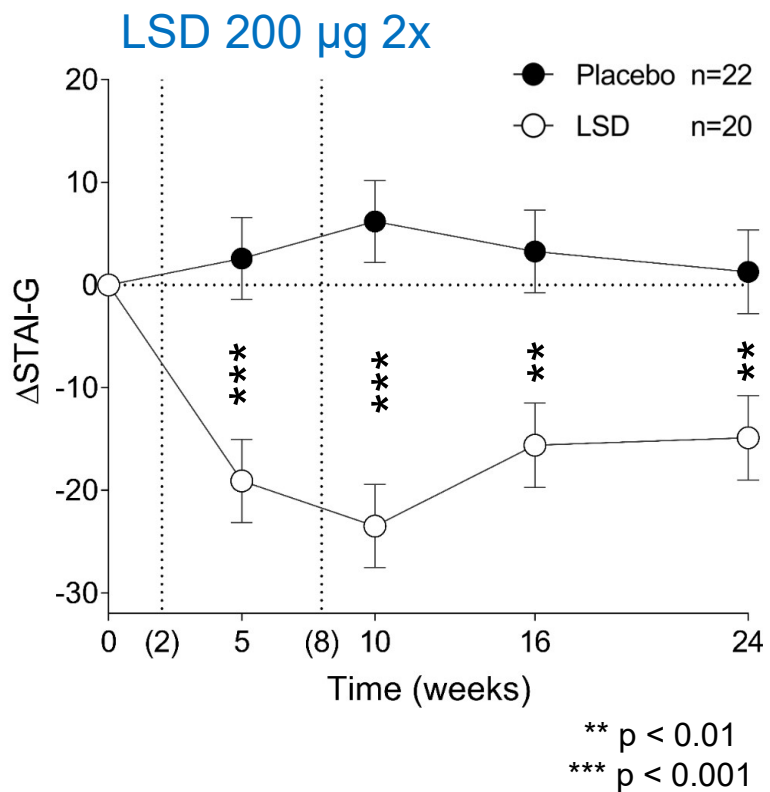
## LSD reduces amygdala BOLD response to fear



N=24, placebo-controlled administration of 100  $\mu$ g LSD

Müller et al. 2017 *Translational Psychiatry* 7: e1084

# LSD reduziert die Angst bei Patienten mit Angststörung rasch und anhaltend



- **Rapid, long-lasting and significant reductions in anxiety at 16 weeks post-treatment in LSD group**

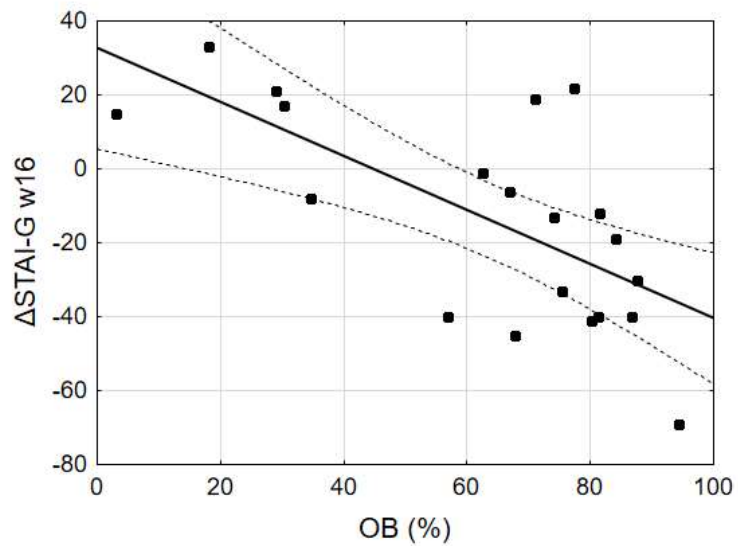
- Mean change from baseline difference = -16.2  
95% confidence interval [CI] = -27.8 to -4.5  
 $p = 0.007$

- **Clinical response ( $\geq 30\%$  reduction of STAI-G scores):**

- 65% in LSD group vs 9% in placebo group  
( $p = 0.003$ )

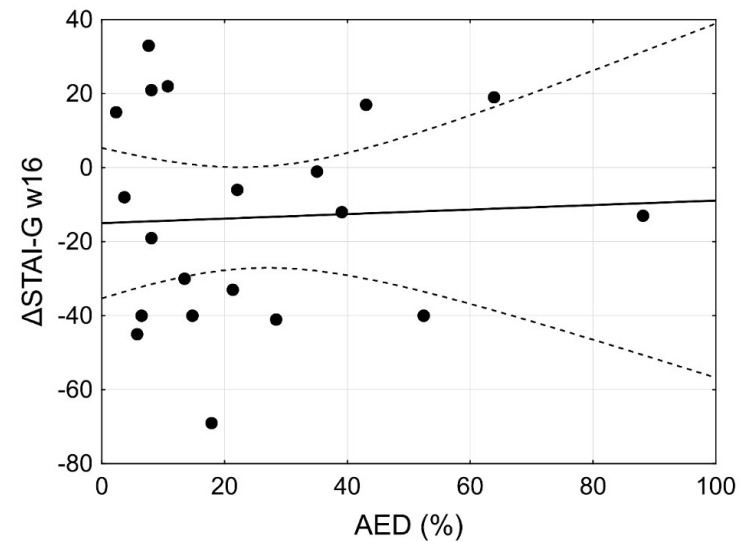
# Akute Wirkung korreliert mit Therapieeffekt

Positive Wirkung



$$r = -0.67, p = 0.001^{**}$$

Negative Wirkung



$$r = 0.05, p = 0.8$$

n=20

Holze et al 2023 Biol Psych 93:215-223

# Safety

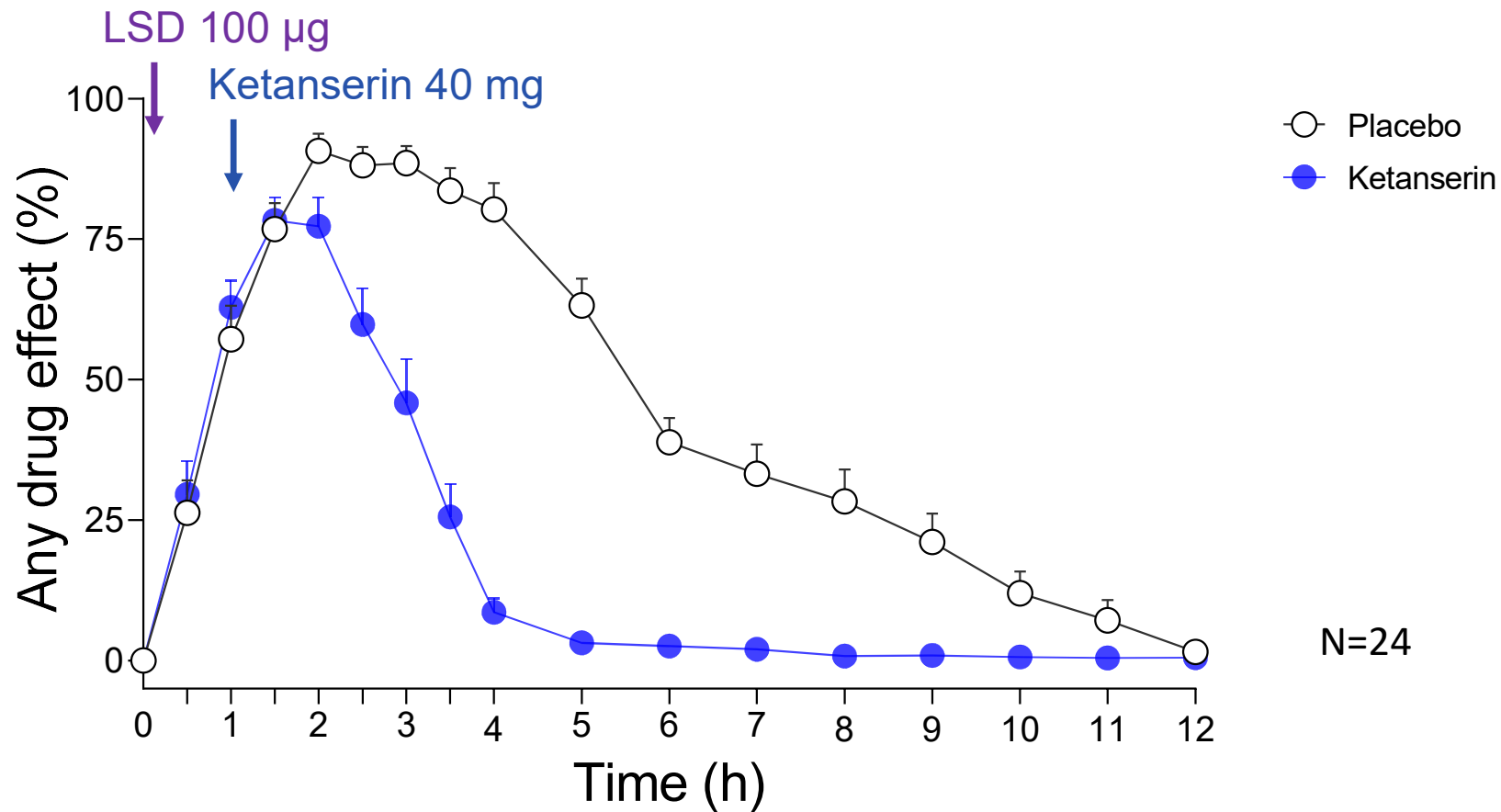
## Treatment-related events

- Untoward effects during treatment sessions
  - Nausea (10%)
  - Anxiety (7%)
  - Headache (2%)
- Serious adverse events
  - 1 x **acute transient anxiety** and delusions
    - Treated with lorazepam and olanzapine
      - second LSD dose reduced to 100 µg

## Non-treatment-related events

- Adverse events during entire study duration:
  - Total: 229, similar in placebo and LSD condition
  - Most frequently: headache, nausea, dizziness, difficulty concentrating, common cold, insomnia
- Serious adverse events
  - Total: 8
  - Mostly due to underlying illness (cancer patients)

# The 5-HT<sub>2A</sub> receptor antagonist Ketanserin reverses the acute LSD response



Becker et al. 2022 Int J Neuropsychopharmacol doi: 10.1093/ijnp/pyac075



# Acute cardiovascular safety of LSD

Cardiostimulant effects in **healthy subjects** after LSD 100 µg (N=45) or 200 µg (N=32), (50% female, mean age [range] = 30 [25-60]):

	100 µg LSD	200 µg LSD	125 mg MDMA	
<b>Systolic BP</b>				
>140	53%	59%	90%	of subjects
>160	9%	6%	38%	of subjects
>180	0%	0%	5%	of subjects
max.	173 mm Hg	170 mm Hg	196 mm Hg	
<b>Heart rate</b>				
>100 (%)	20%	25%	33%	of subjects
max.	118 bpm	121 bpm	145 bpm	
<b>Body temp.</b>				
>38° C	7%	34%	24%	of subjects
max.	38.4° C	38.8° C	39.1° C	

# Acute cardiovascular safety of psilocybin

Cardiostimulant effects in **healthy subjects** after LSD 100 µg (N=45) or Psilocybin 20 mg (N=33):

	<b>100 µg LSD</b>	<b>20 mg Psilocybin</b>	
<b>Systolic BP</b>			
>140	53%	52%	of subjects
>160	9%	6%	of subjects
>180	0%	0%	of subjects
max.	173 mm Hg	170 mm Hg	
<b>Heart rate</b>			
>100 (%)	<b>20%</b>	<b>3%</b>	of subjects
max.	118 bpm	114 bpm	
<b>Body temp.</b>			
>38° C	7%	9%	of subjects
max.	38.4° C	39.0° C	

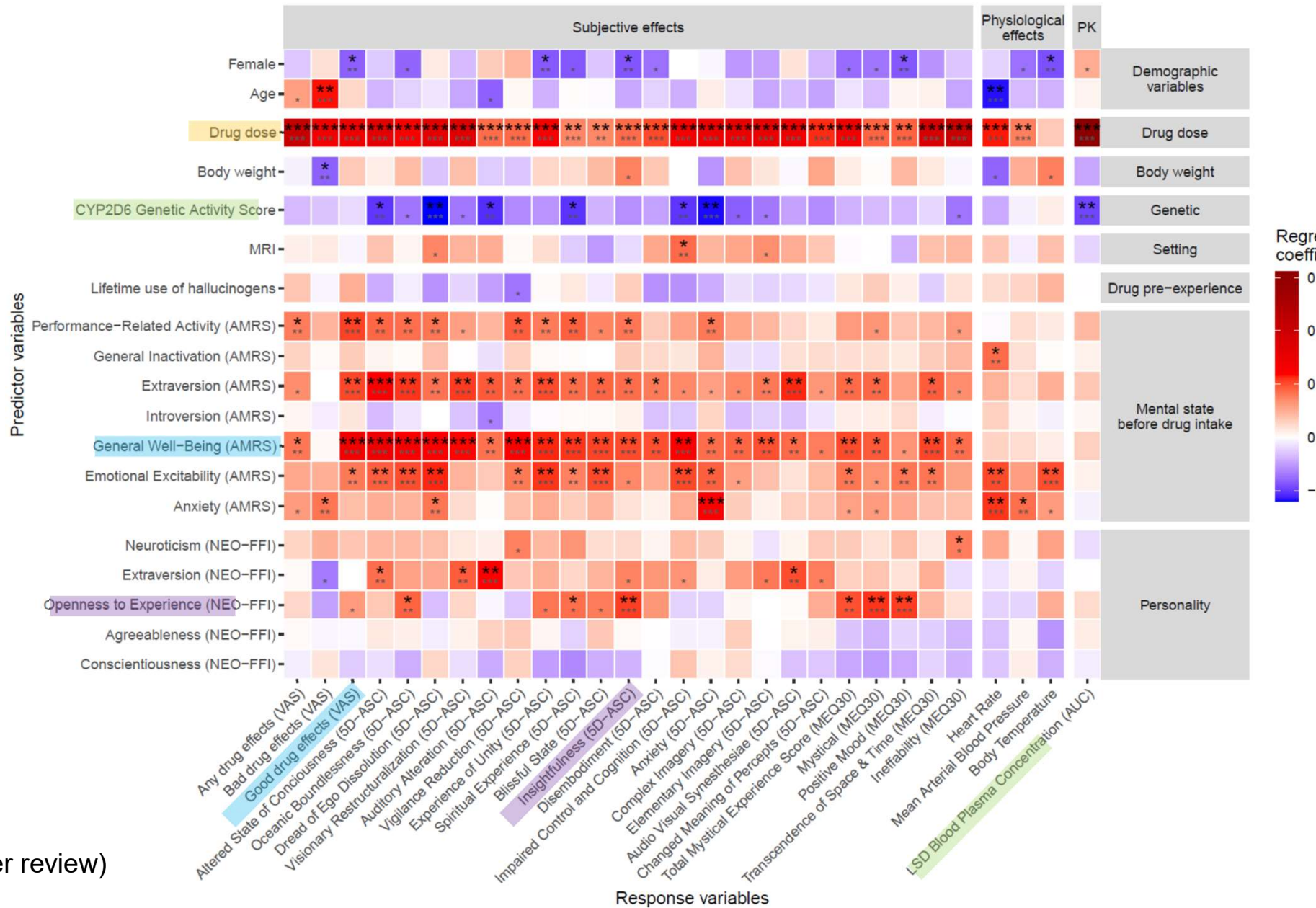
# Influence of set and setting

-LSD 25-200 µg  
 -Healthy subjects  
 -N=213

## Relevant predictors:

-drug dose  
 -personality  
 -current mood  
 (sex, body weight and prior experience have no influence)

Vizeli et al. 2024 (under review)

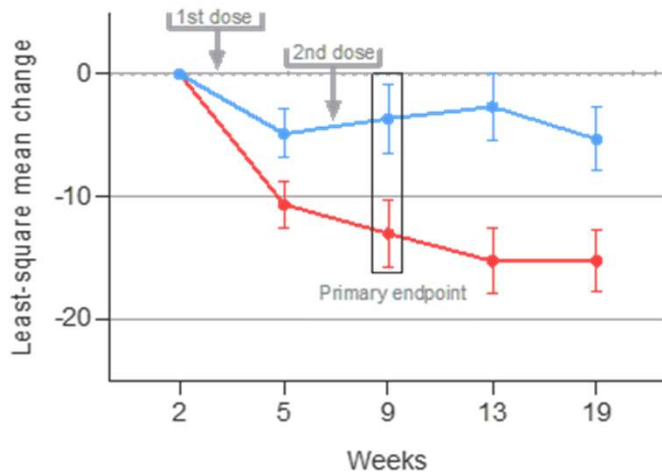


# LSD in Depression

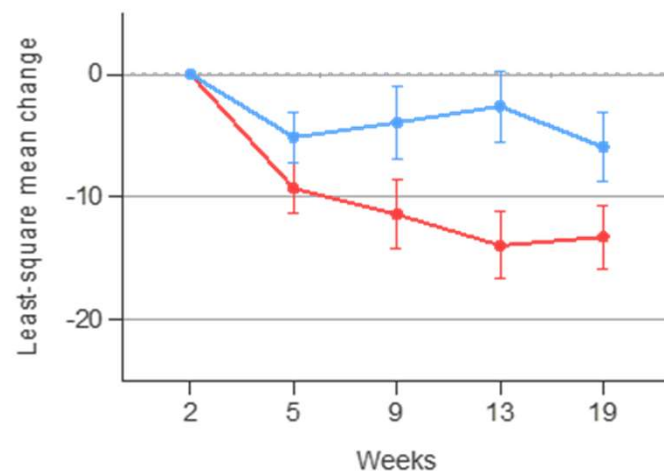
● Low dose 25 + 25  $\mu\text{g}$   
● High dose 100+200  $\mu\text{g}$

N=30/group,  
 Mean + SEM

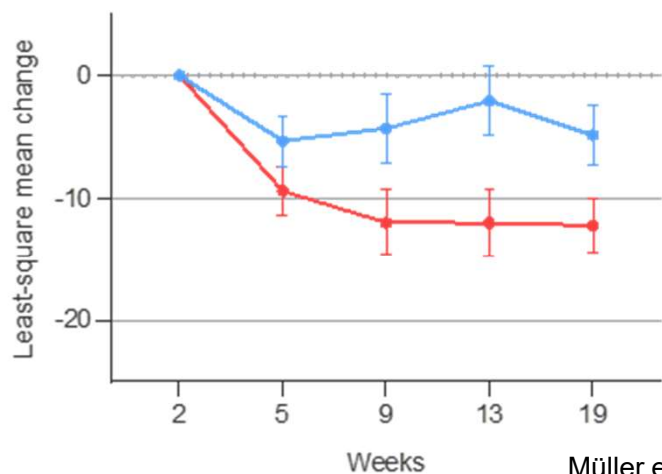
Depression clinician-rated (IDS-C)



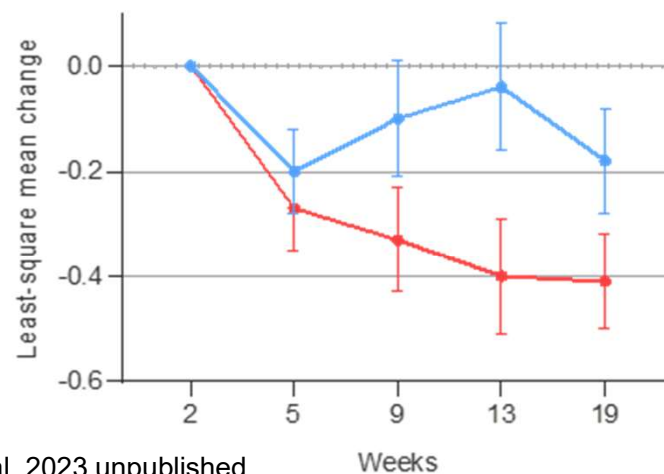
Depression self-rated (IDS-SR)



Beck Depression Inventory

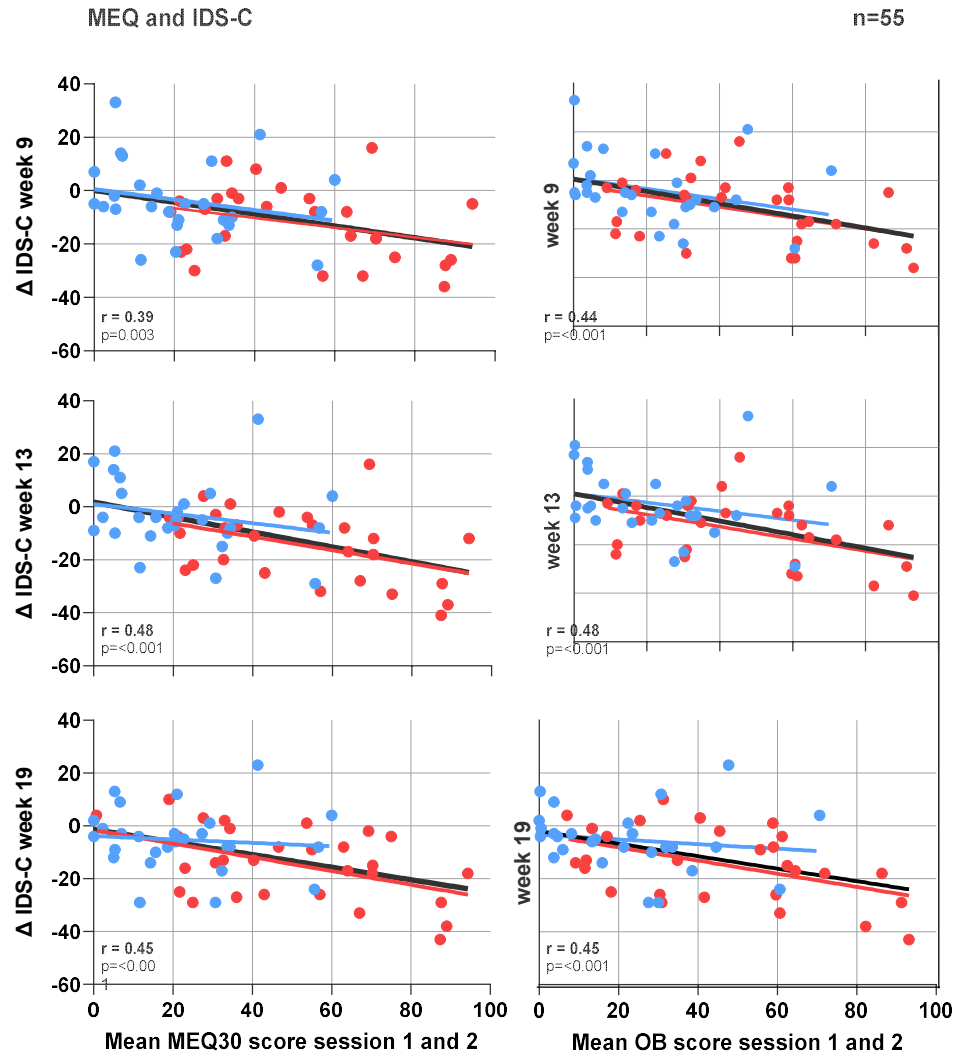


Symptom Checklist-90 global severity index



Müller et al. 2023 unpublished

# Acute effects correlate with outcome in both dose groups



● Low-dose group  
● High-dose group

25 + 25  $\mu$ g

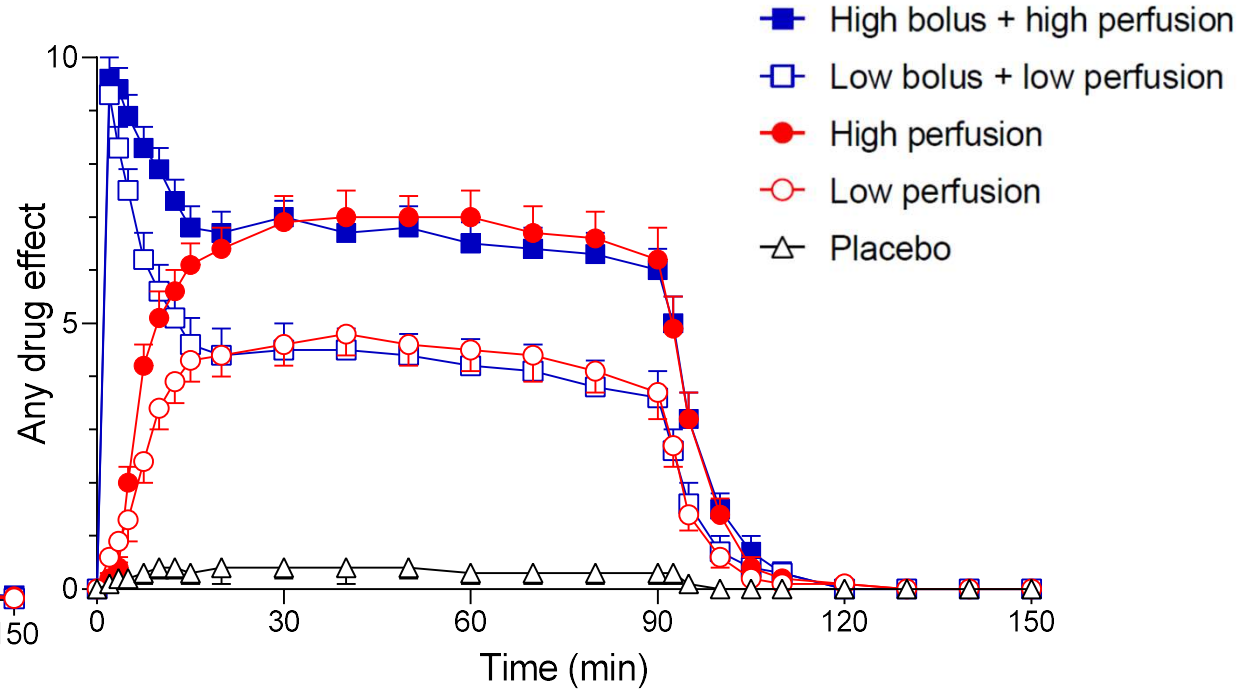
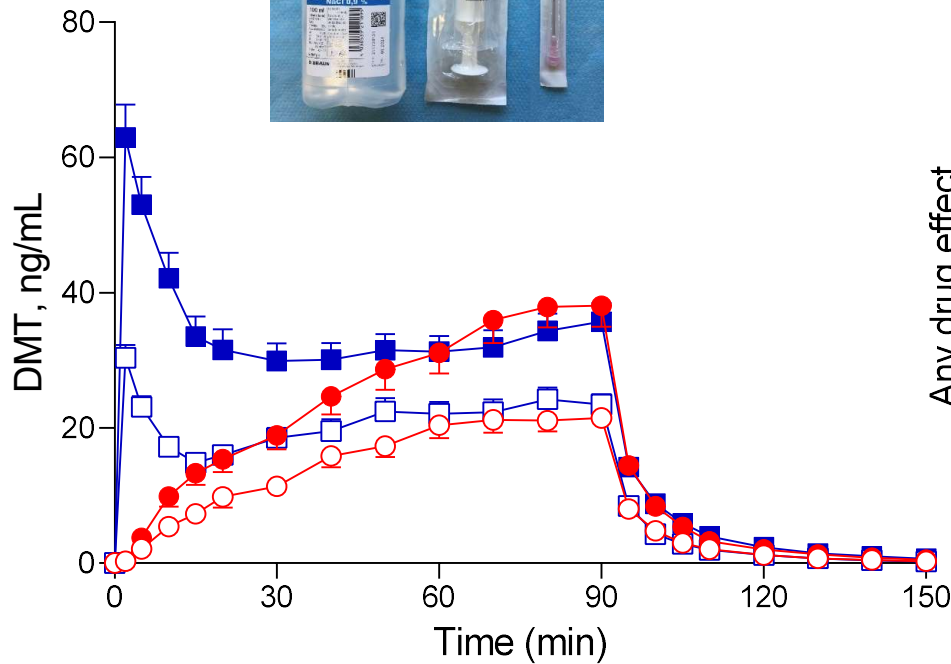
100+200  $\mu$ g

N=30/group,

Mean + SEM

Müller et al. 2023 unpublished

# DMT IV bolus/perfusion



IV Bolus DMT 15 or 25 mg; IV Perfusion DMT 0.6 or 1 mg/min; data are mean and SEM in 30 subjects in for each dose; mean elimination half-life = 5-6 min (clinically-relevant early elimination; 0-15 min)

# Open Questions

- Wirksamkeit in grossen Studien?
- Wirksamkeit in Praxis?
- Rolle von Psychotherapie (psychologischem Support)?
- Qualifikation der Behandler?
- Vergütung?