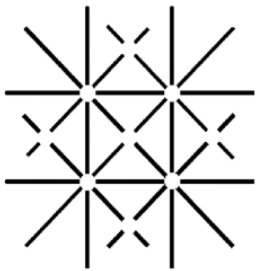


# Psychedelika als Medikamente: aktueller Stand

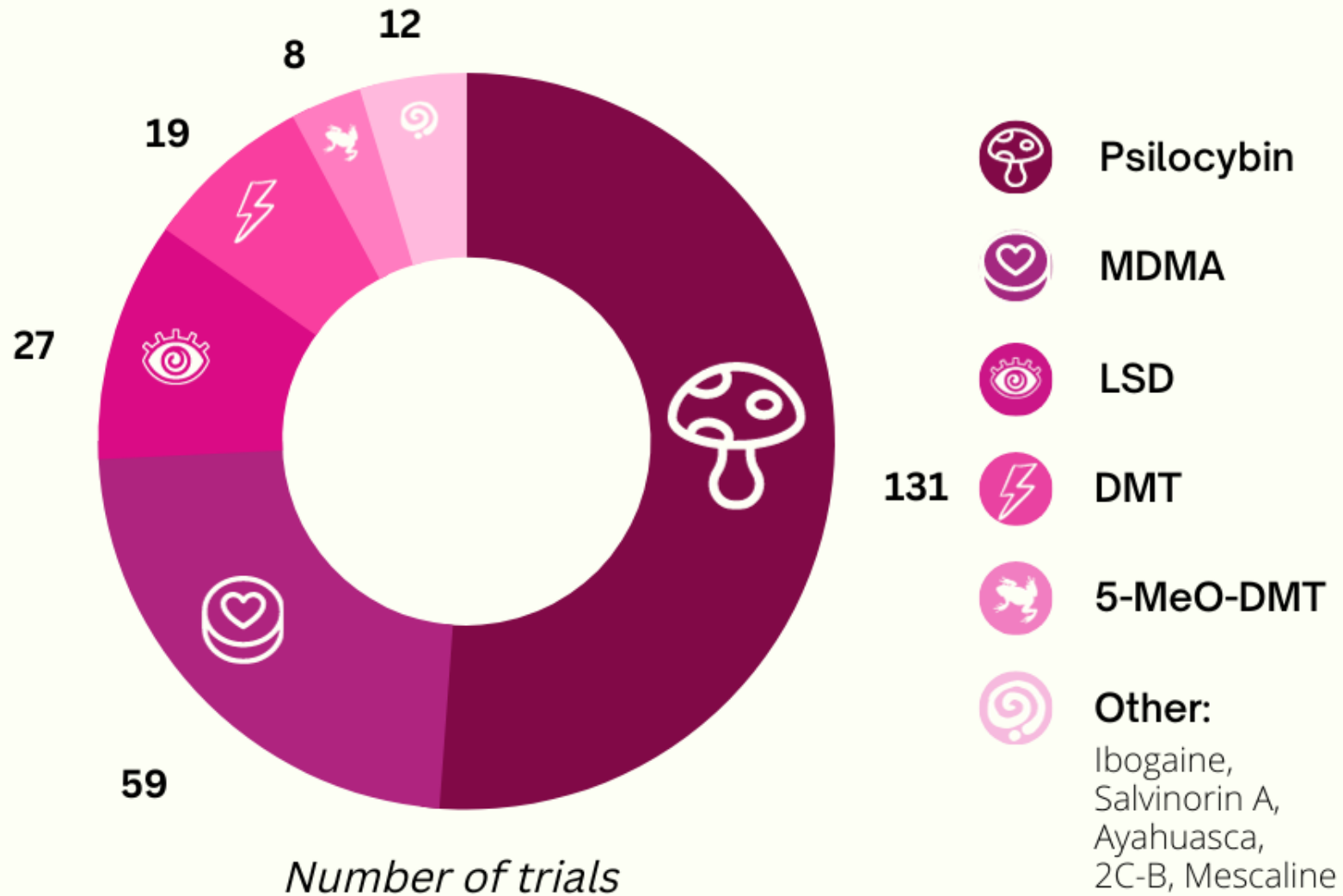
Matthias E. Liechti  
Clinical Pharmacology University  
Hospital Basel  
Switzerland



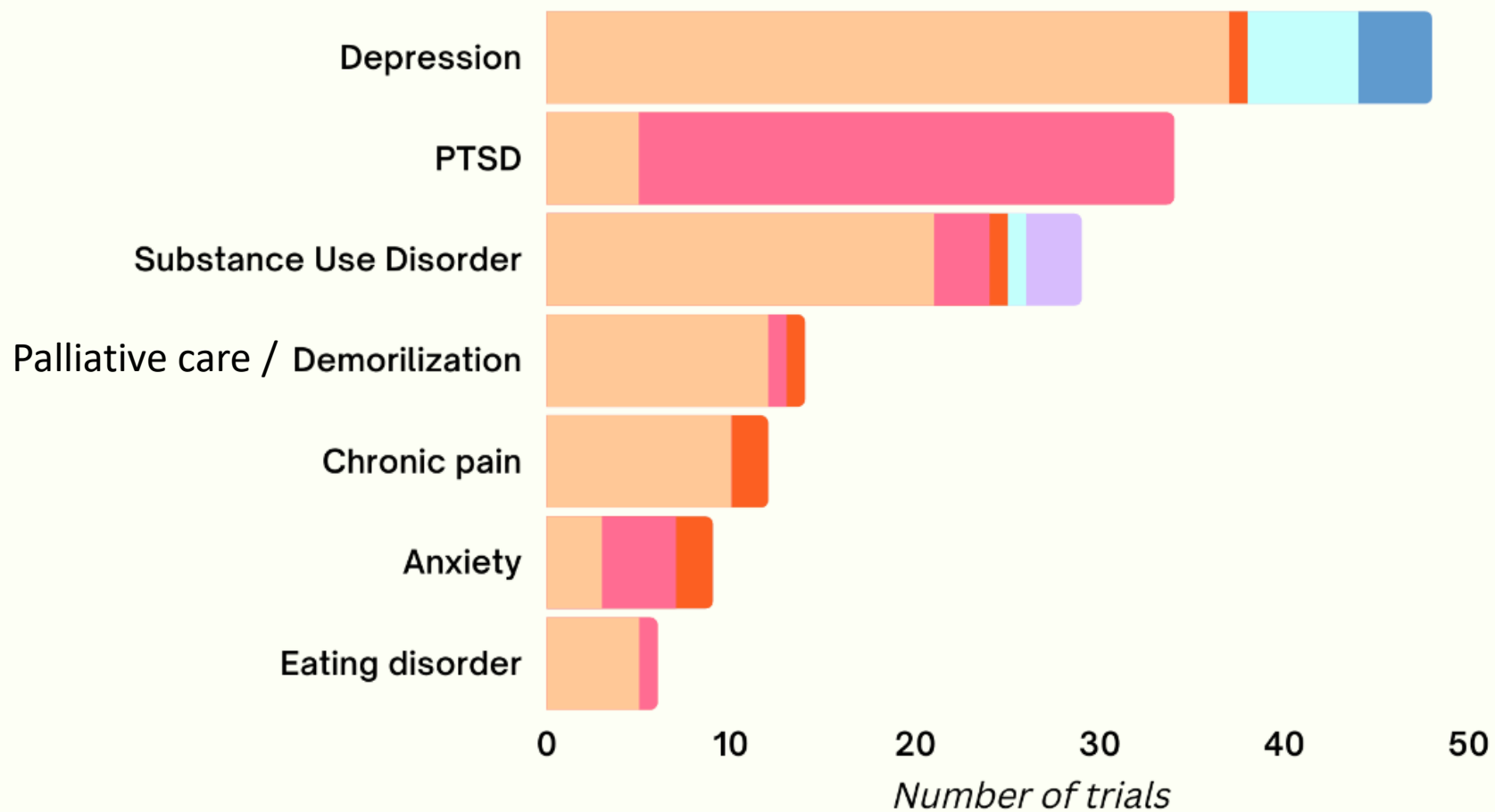
Uni Basel

Pharmazeutische Gesellschaft Basel, 30.11.2023

# Psychedelic Clinical Trials



# Conditions being investigated





# Why psychedelics?



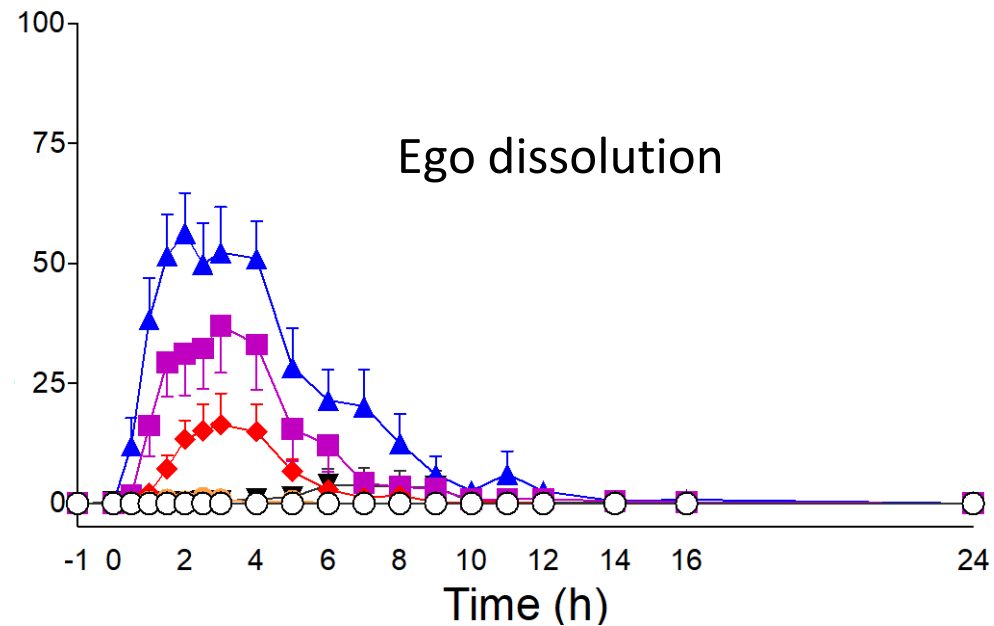
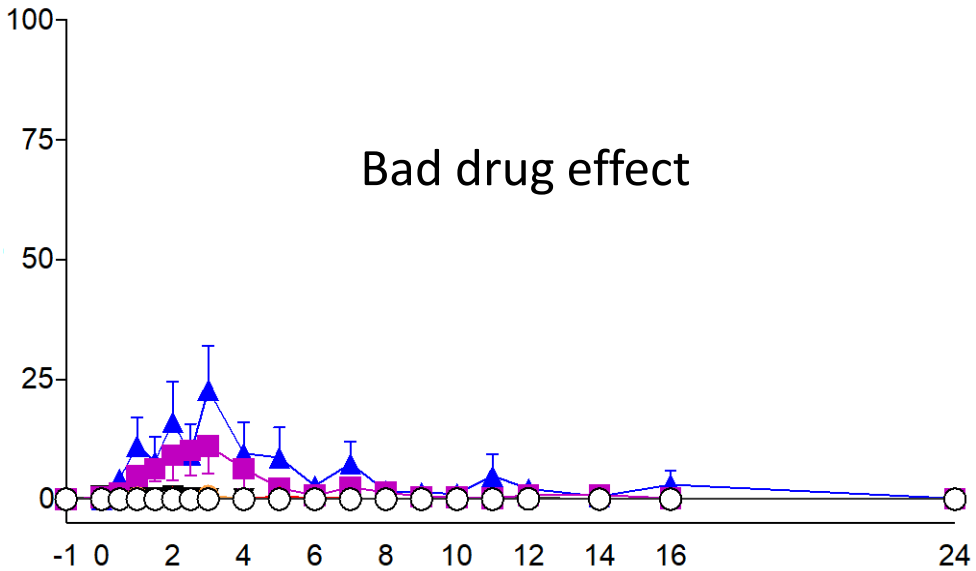
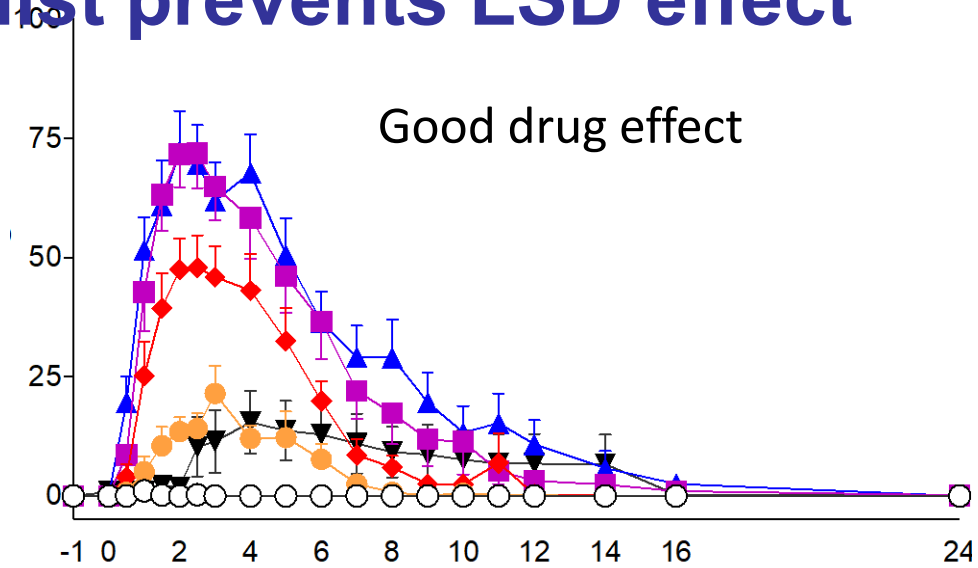
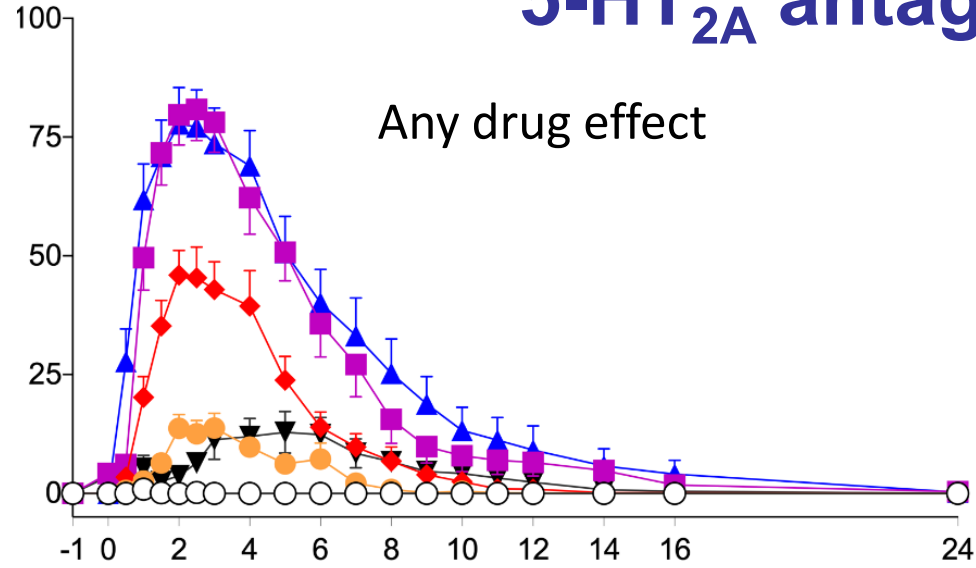
**Spravato™**  
(esketamine) (C)  
nasal spray



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

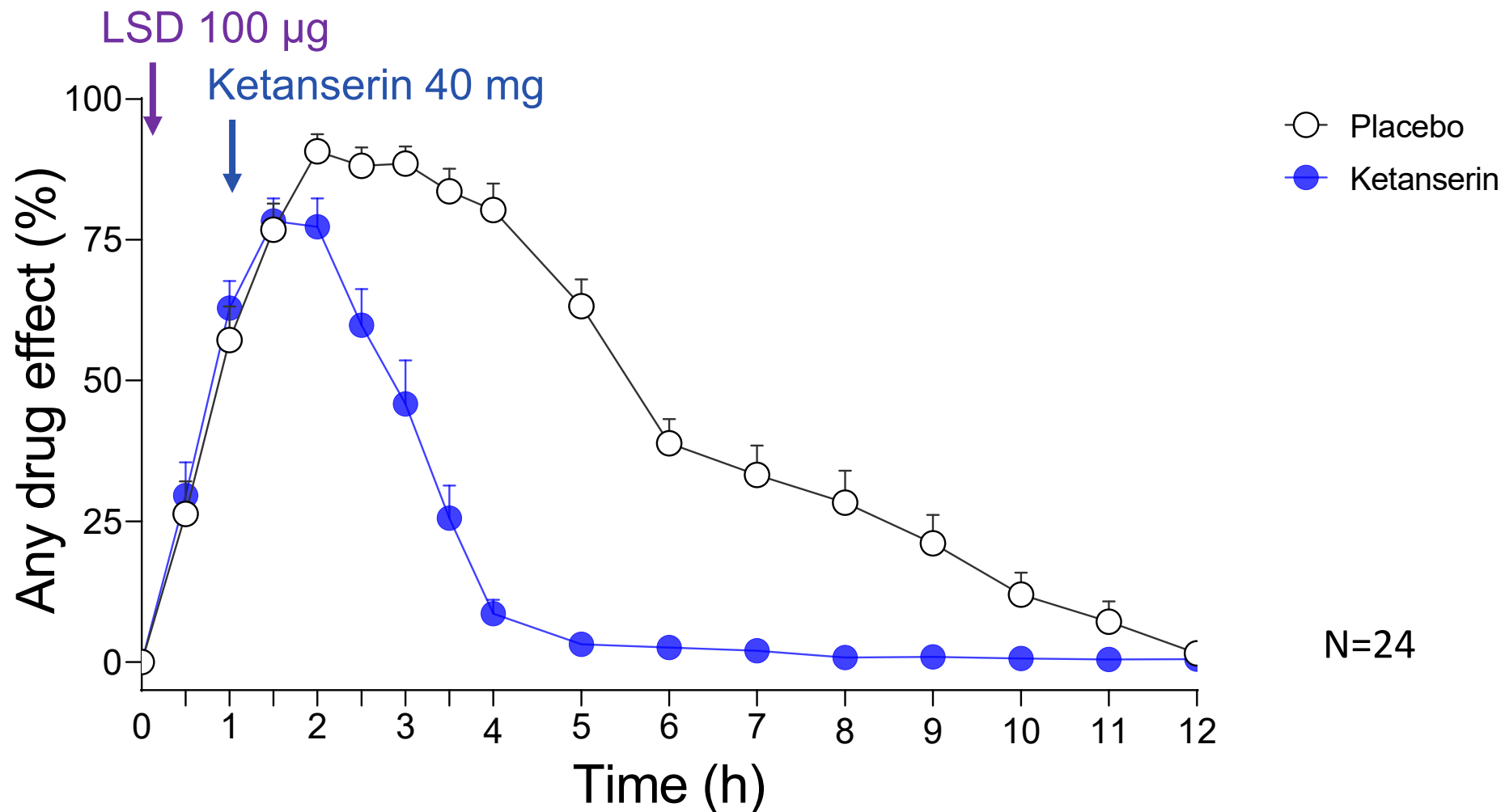


# Mode of action? 5-HT<sub>2A</sub> antagonist prevents LSD effect

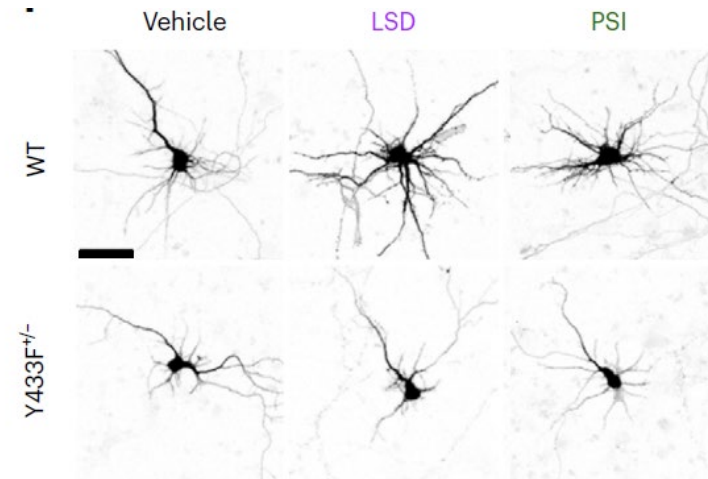
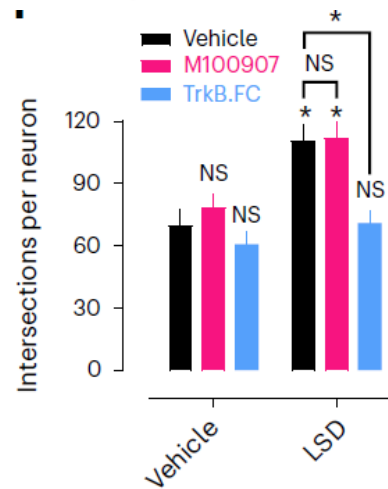
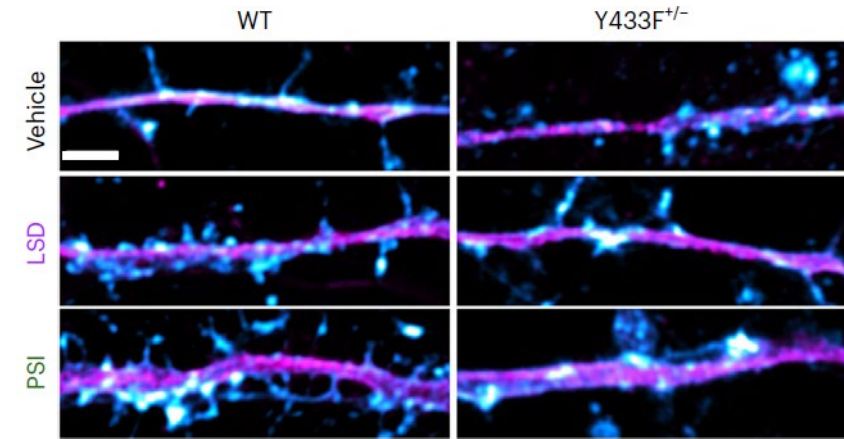
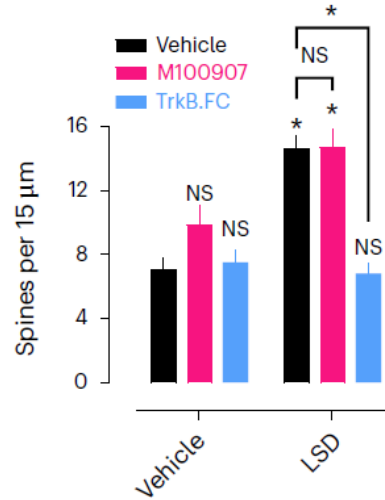
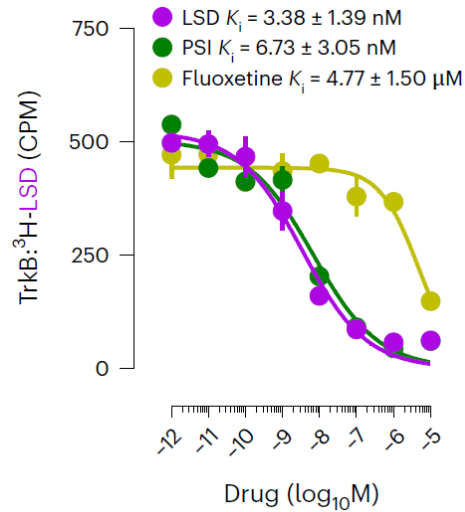


N=16, Mean+SEM

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



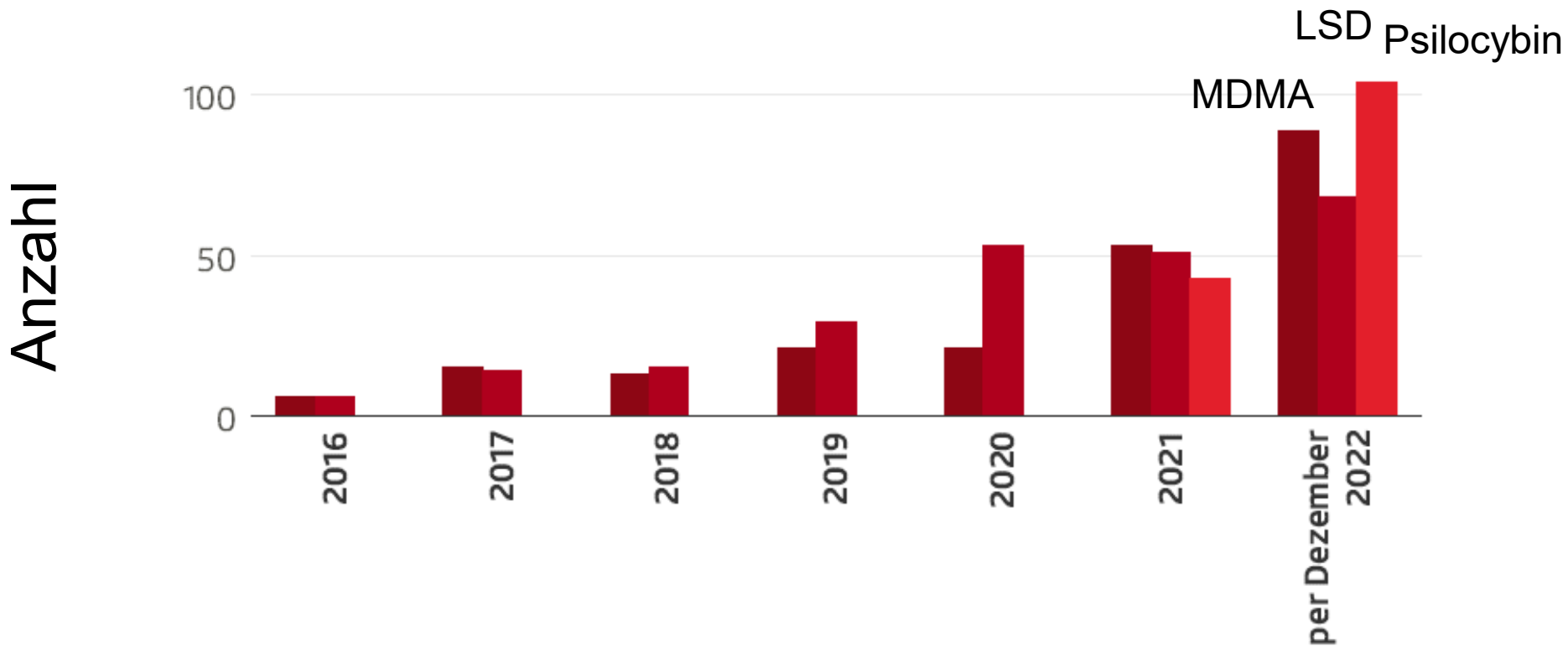
# Psychedelics promote plasticity by directly binding to BDNF receptor TrkB



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

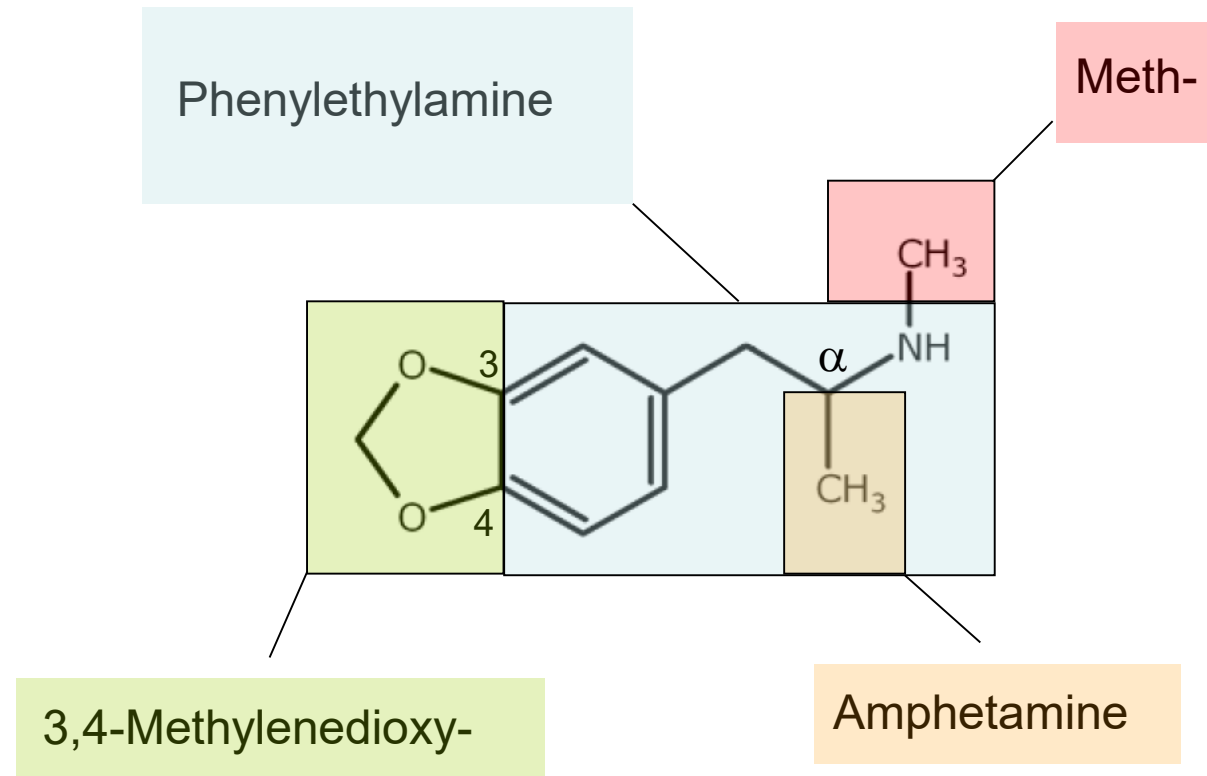
Psychedelic-induced neuroplasticity depends on TrkB and BDNF, but not 5-HT<sub>2A</sub> activation

# BAG Ausnahmewilligungen für die beschränkte medizinische Anwendung

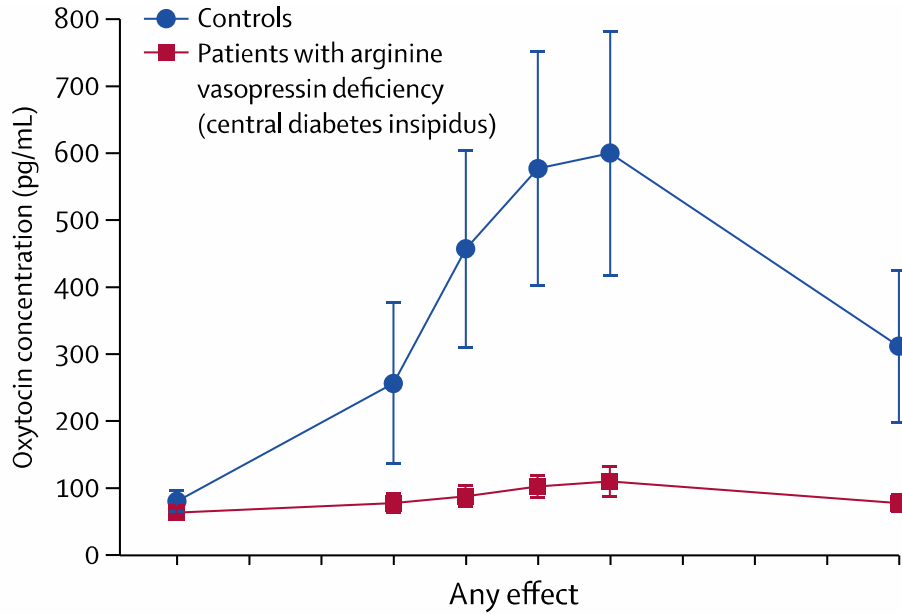




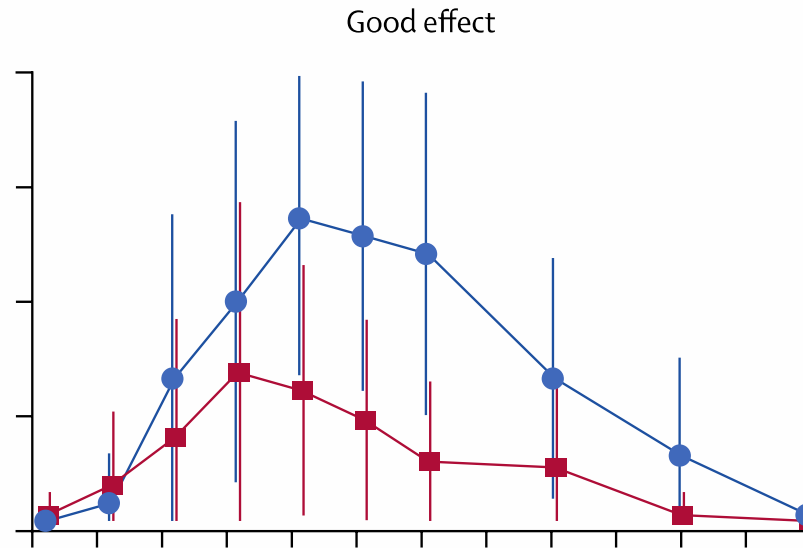
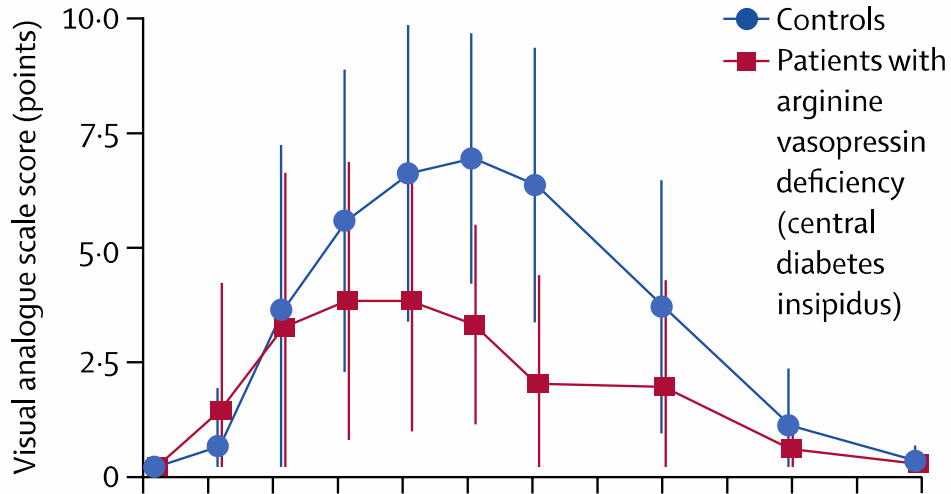
# 3,4-Methylenedioxyamphetamine (MDMA)



# Oxytocin in response to MDMA in diabetes insipidus



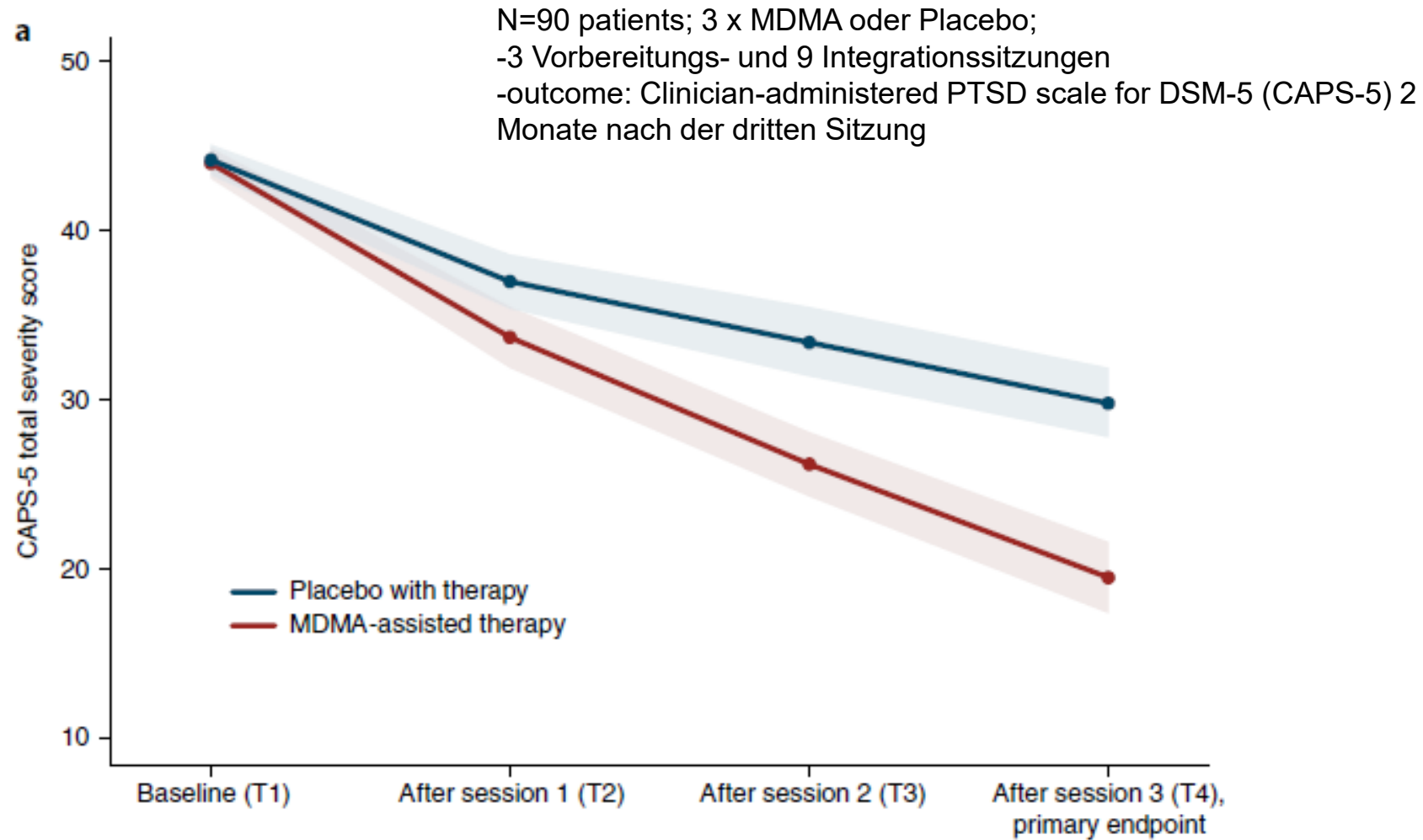
1. MDMA test to reveal oxytocin deficiency in diabetes insipidus patients
2. MDMA effect partly depends on oxytocin



N=15/group

*Lancet Diabetes Endocrinol*  
2023; 11: 454-64

# MDMA reduces PTSD symptoms in phase 3 study

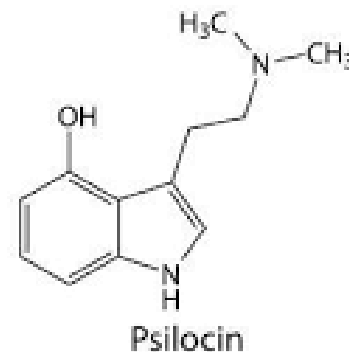
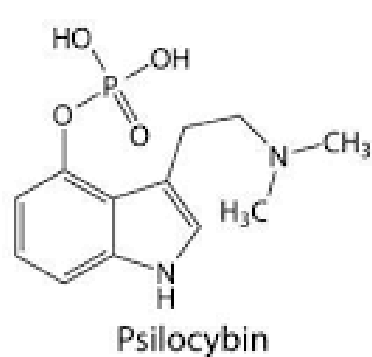


# Psilocybin

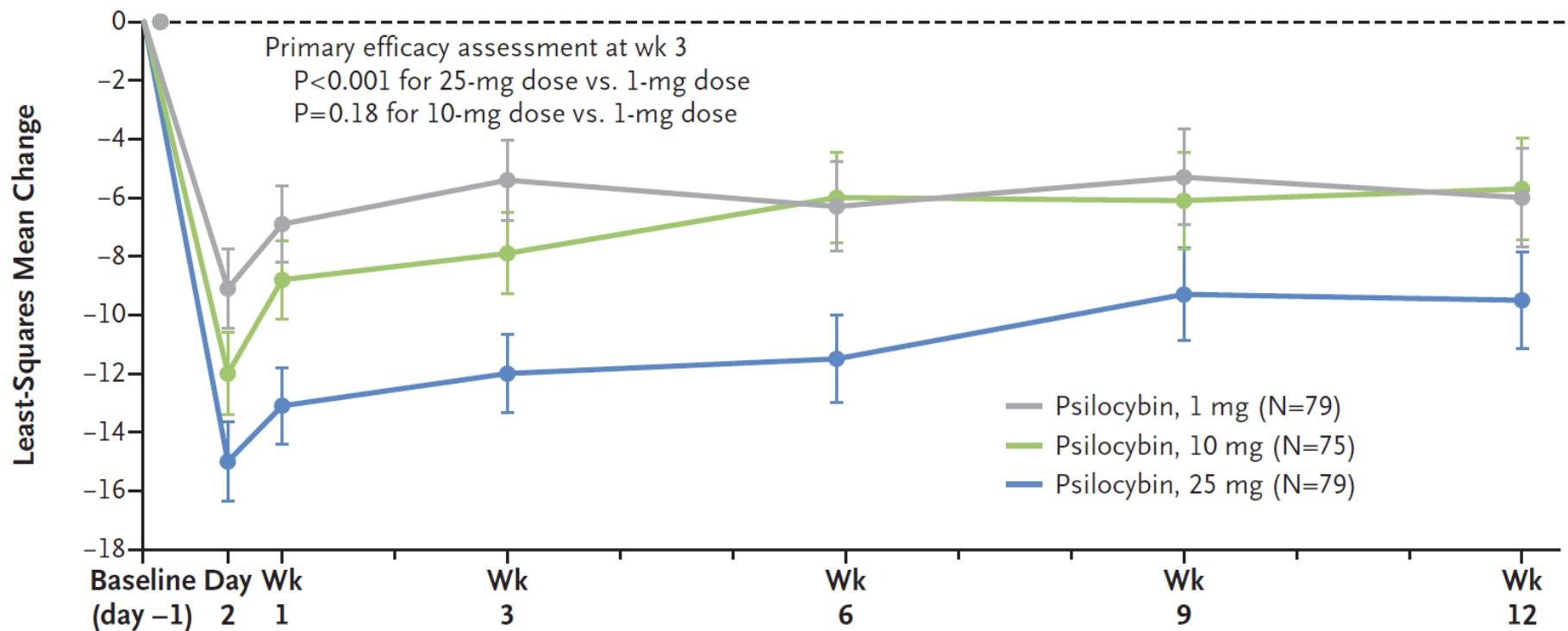
- 1958 erstmals in Basel aus *psilocybe mexicana* (ψιλός *kybē*; *Zauberpilz*) extrahiert und auch synthetisch hergestellt
- Das heute am häufigsten in Patienten untersuchte Psychedelikum



*Psilocybe mexicana*



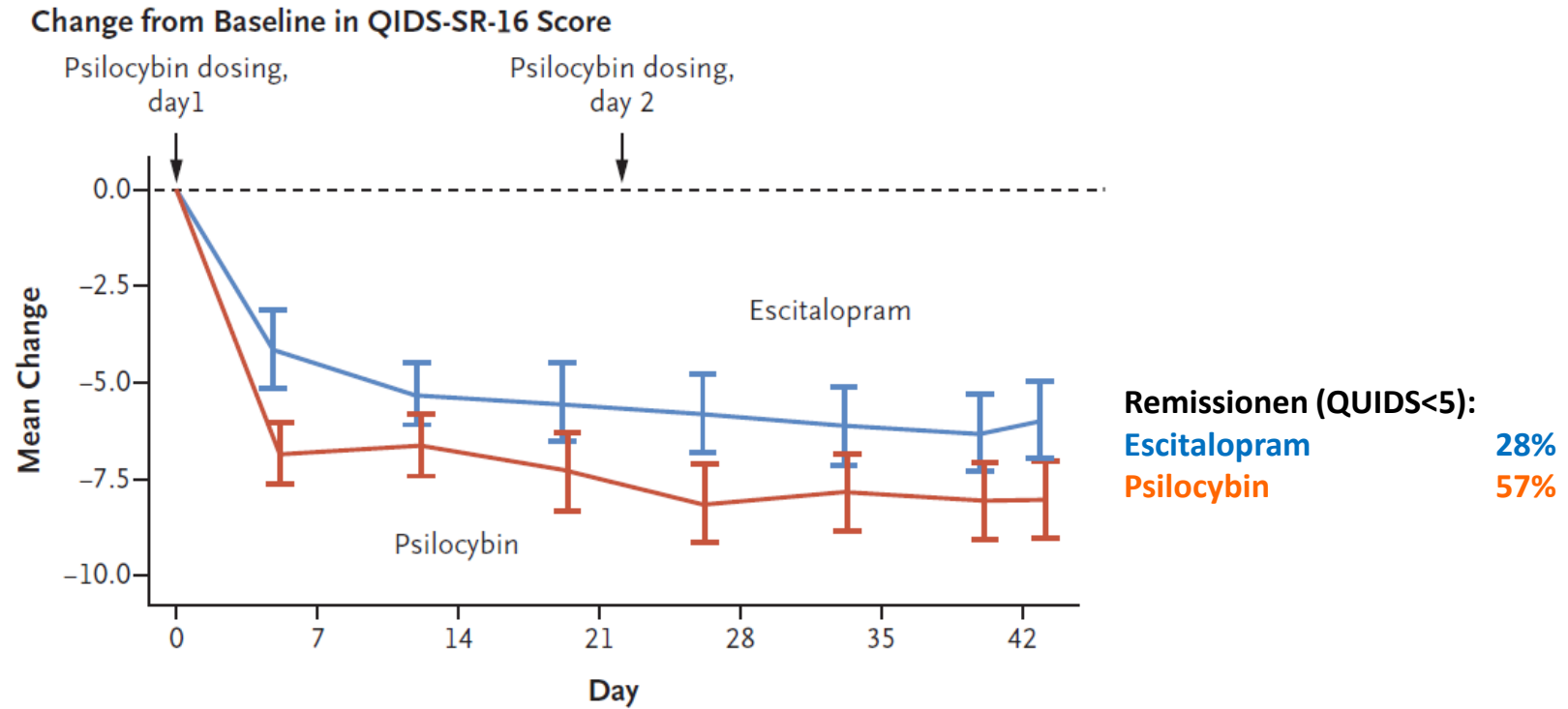
# Single-Dose Psilocybin for a Treatment-Resistant Episode of Major Depression



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

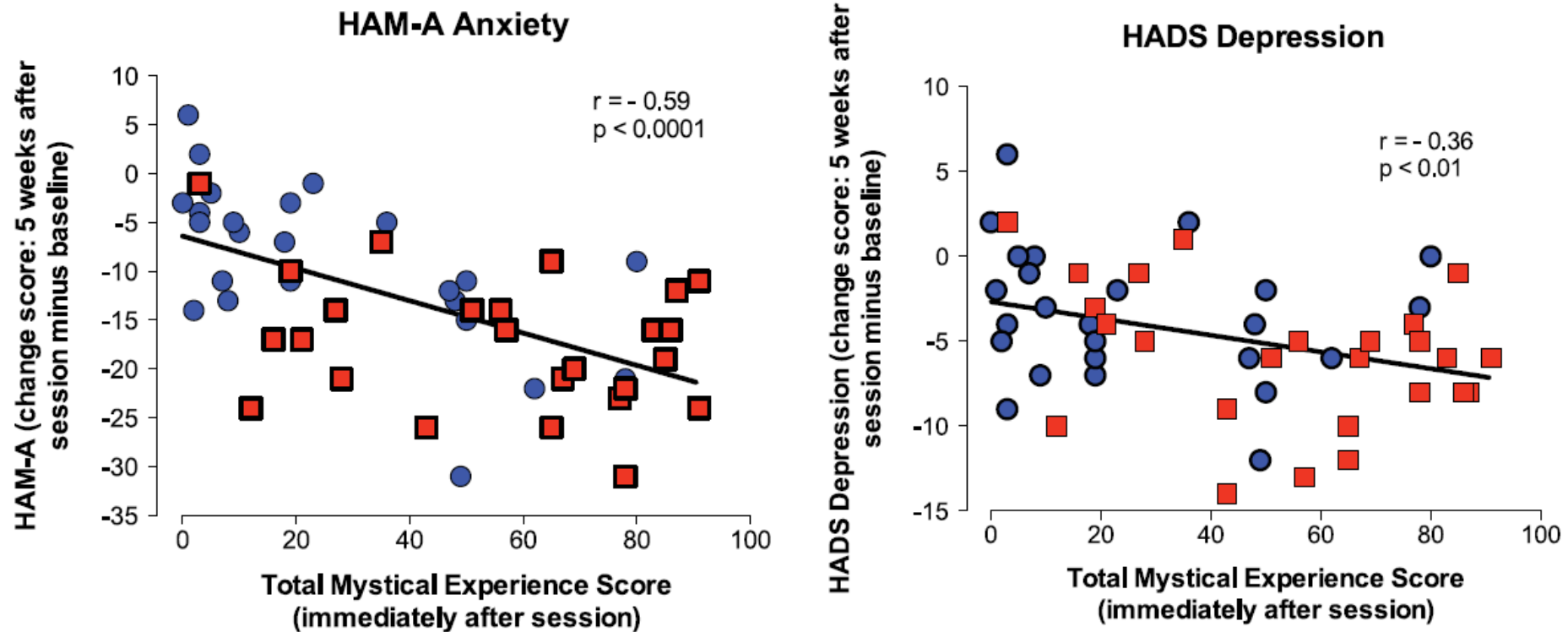
N Engl J Med 2022;387:1637-48.

# 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

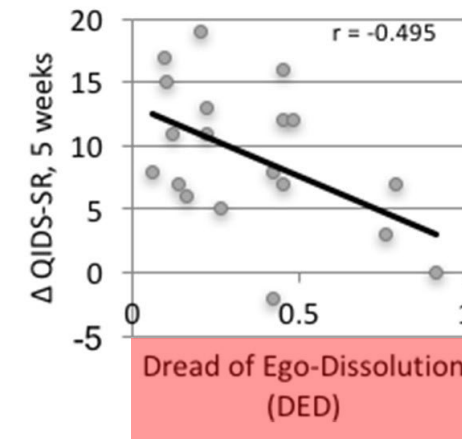
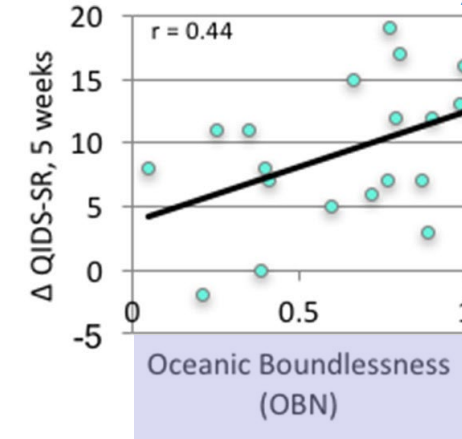
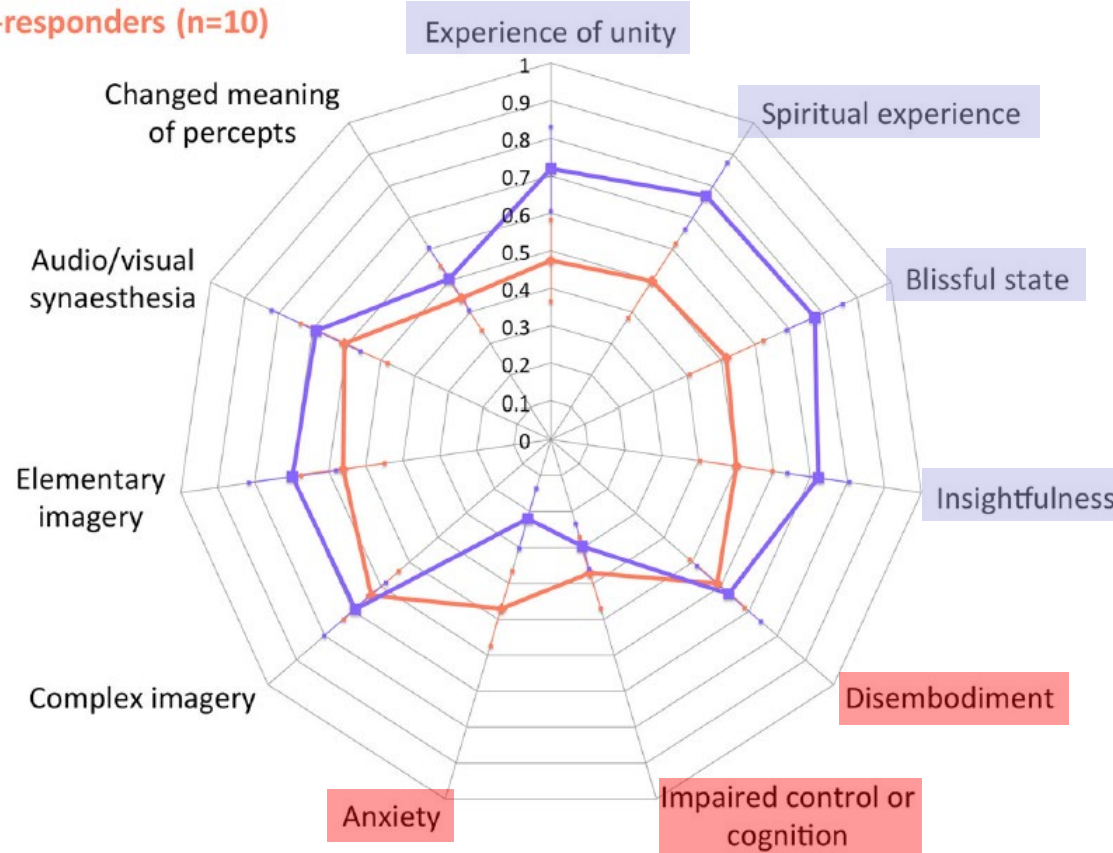


# Acute experience predicted therapeutic efficacy

Responders (n=9)

Non-responders (n=10)

## 5D-ASC (5 dimensions of altered states of consciousness)



20 TRD patients, 10 and 25 mg **psilocybin**, peak experience: 5D-ASC; long-term effect: QIDS: Quick Inventory of Depressive Symptoms at 5 wks; response: 50% score reduction

# Blissful State

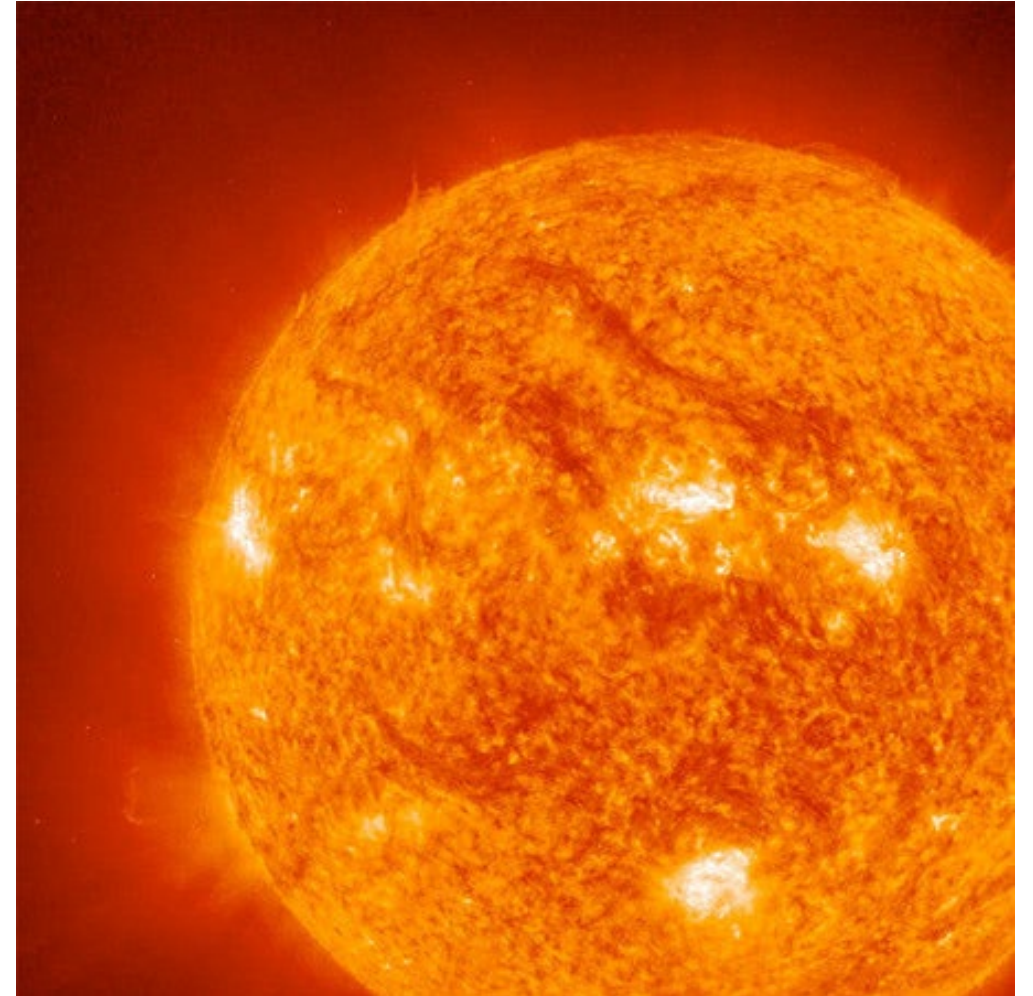
- I enjoyed boundless pleasure
- I experienced a profound peace in myself
- I experienced an all-embracing love

# Audio-Visual Synesthesiae

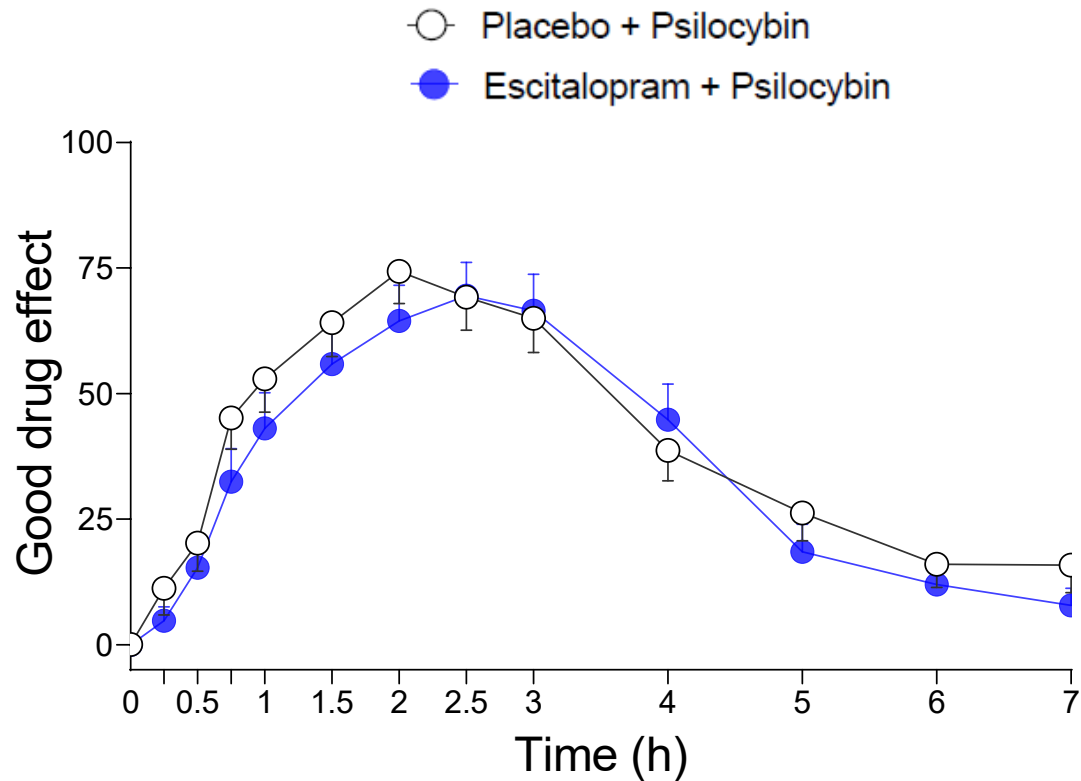
- Noises seemed to influence what I saw
- The shape of things seemed to change by sound and noises
- The colors of things seemed to be changed by sound and noises

# Therapeutic Dimensions

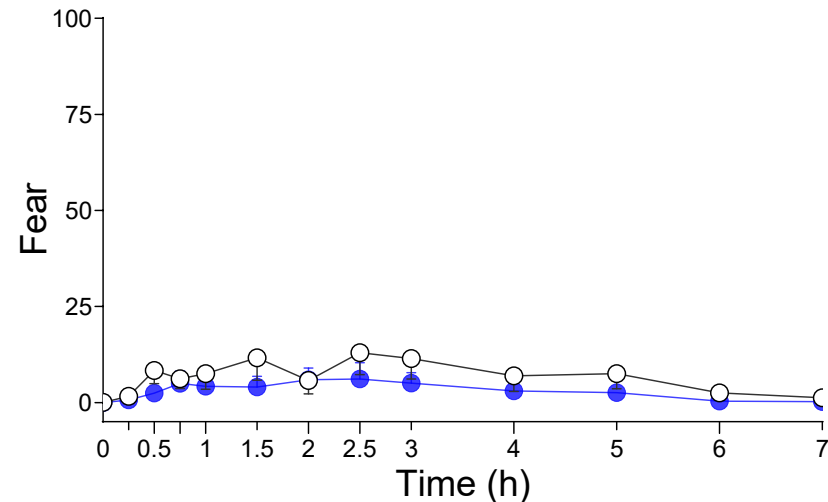
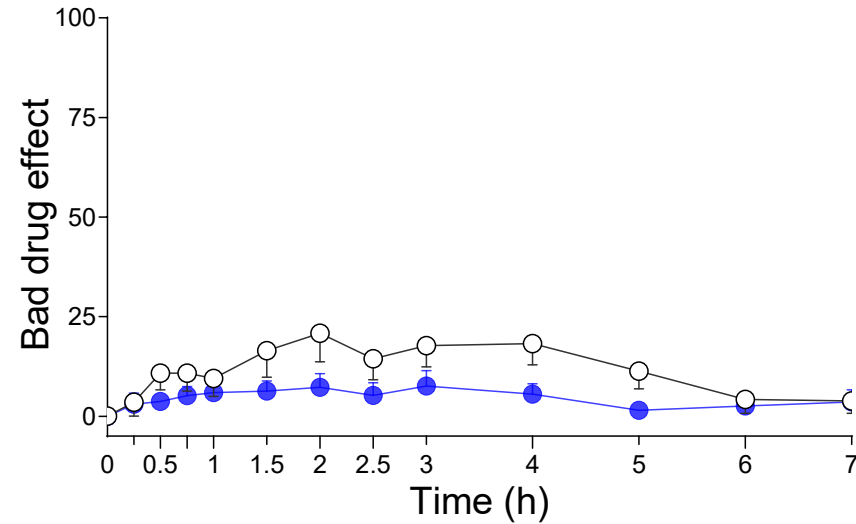
- Meaningfulness
- Connectedness
- Reductions in defensiveness
- Acceptance / *Helioscope*
- Therapeutic Alliance
- Authenticity



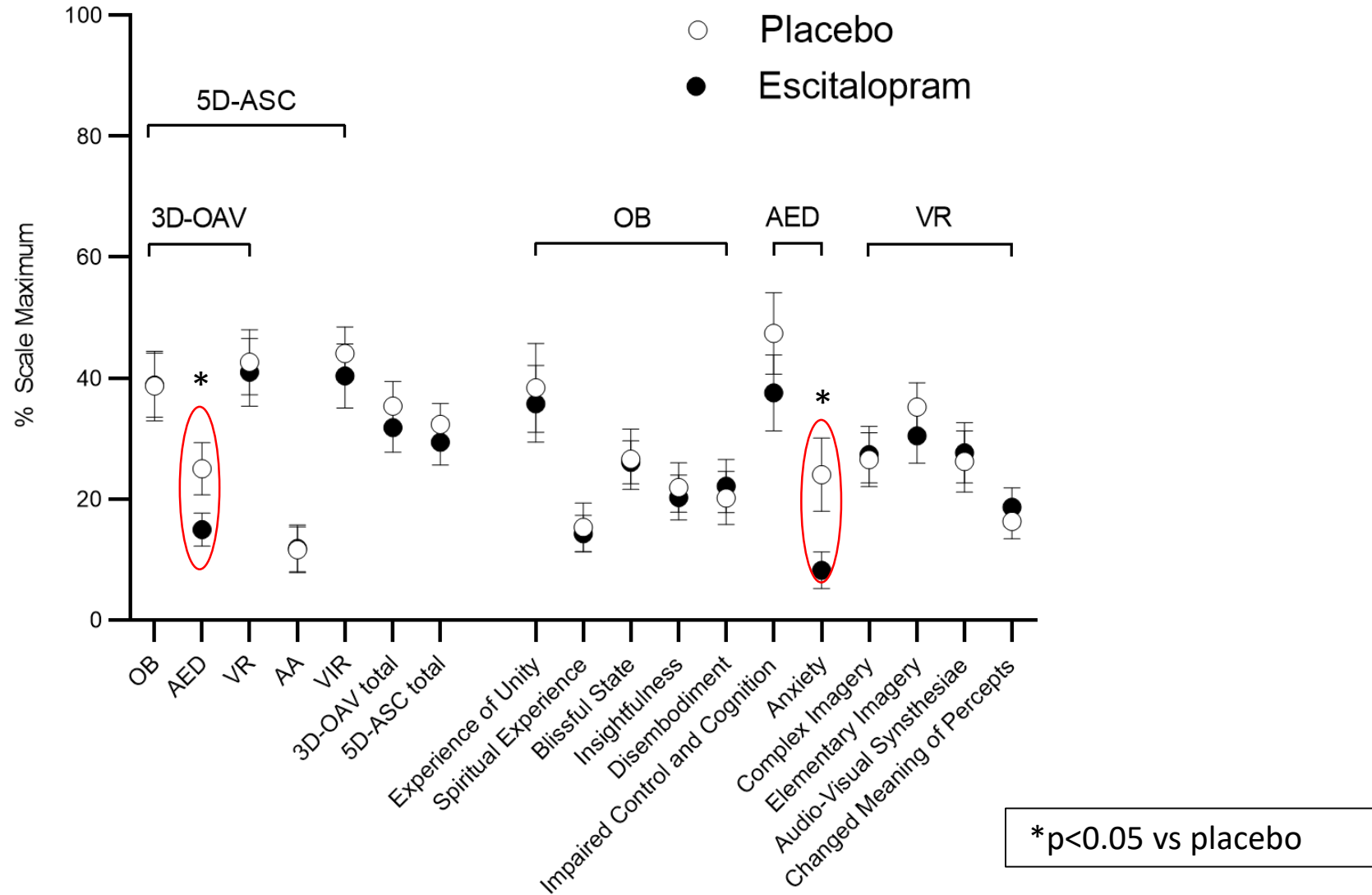
# Escitalopram reduced acute bad but not good drug effects of psilocybin





Escitalopram 10 mg/day for 7 days followed by 20 mg/day for another 7 days and psilocybin 25 mg on day 14



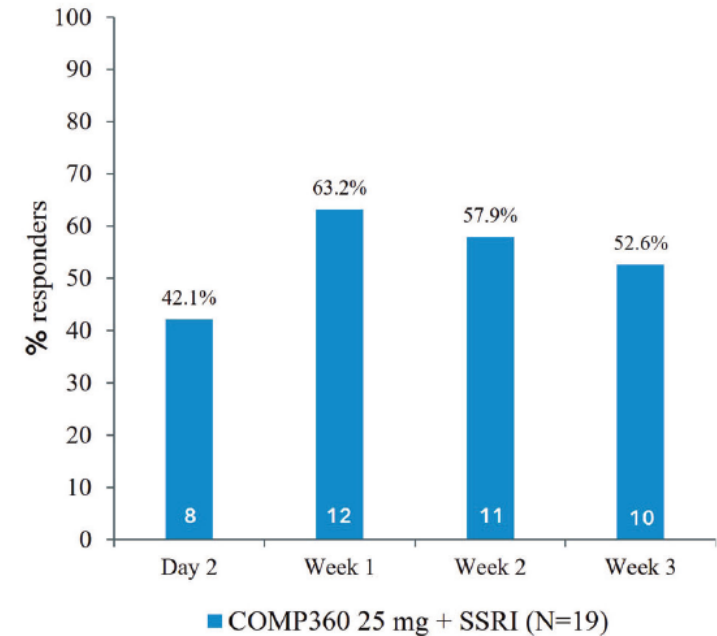
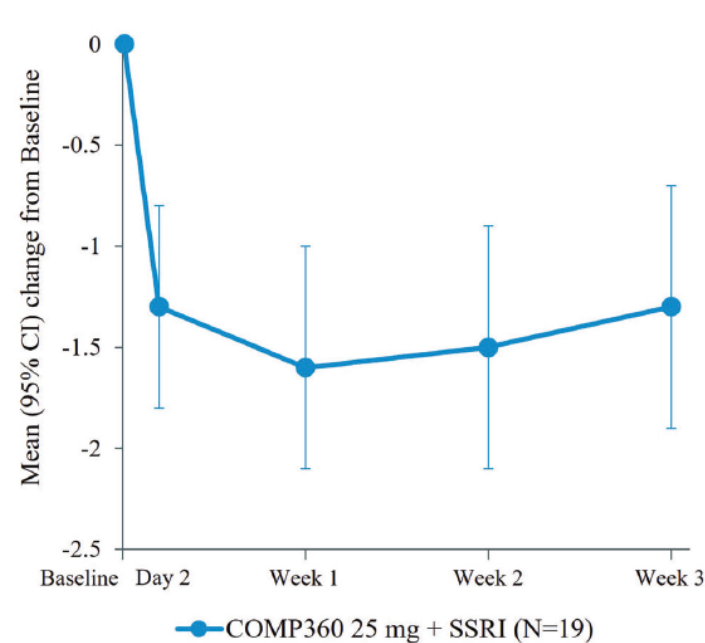
# Escitalopram reduced anxiety but not the overall psychedelic response to psilocybin



# Psilocybin for treatment resistant depression in patients taking a concomitant SSRI medication

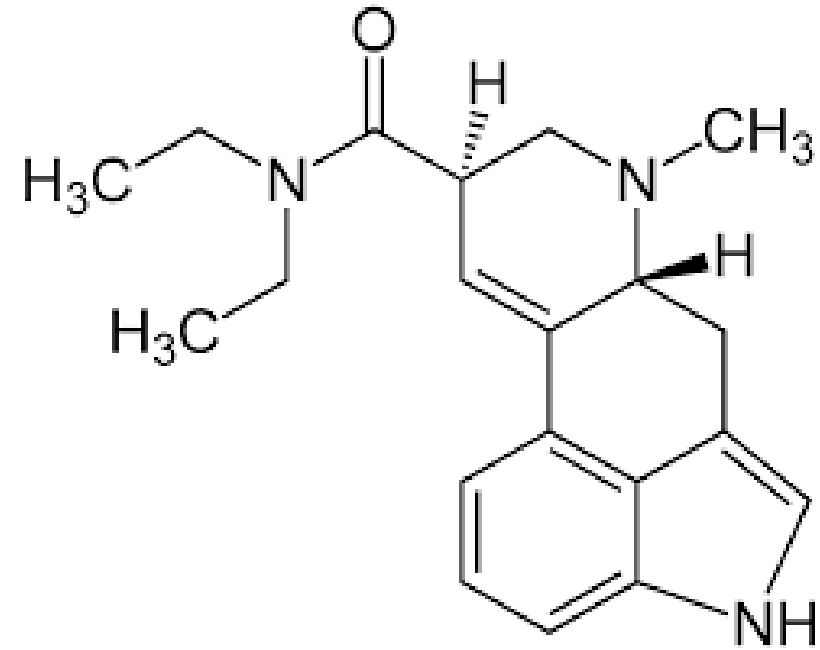
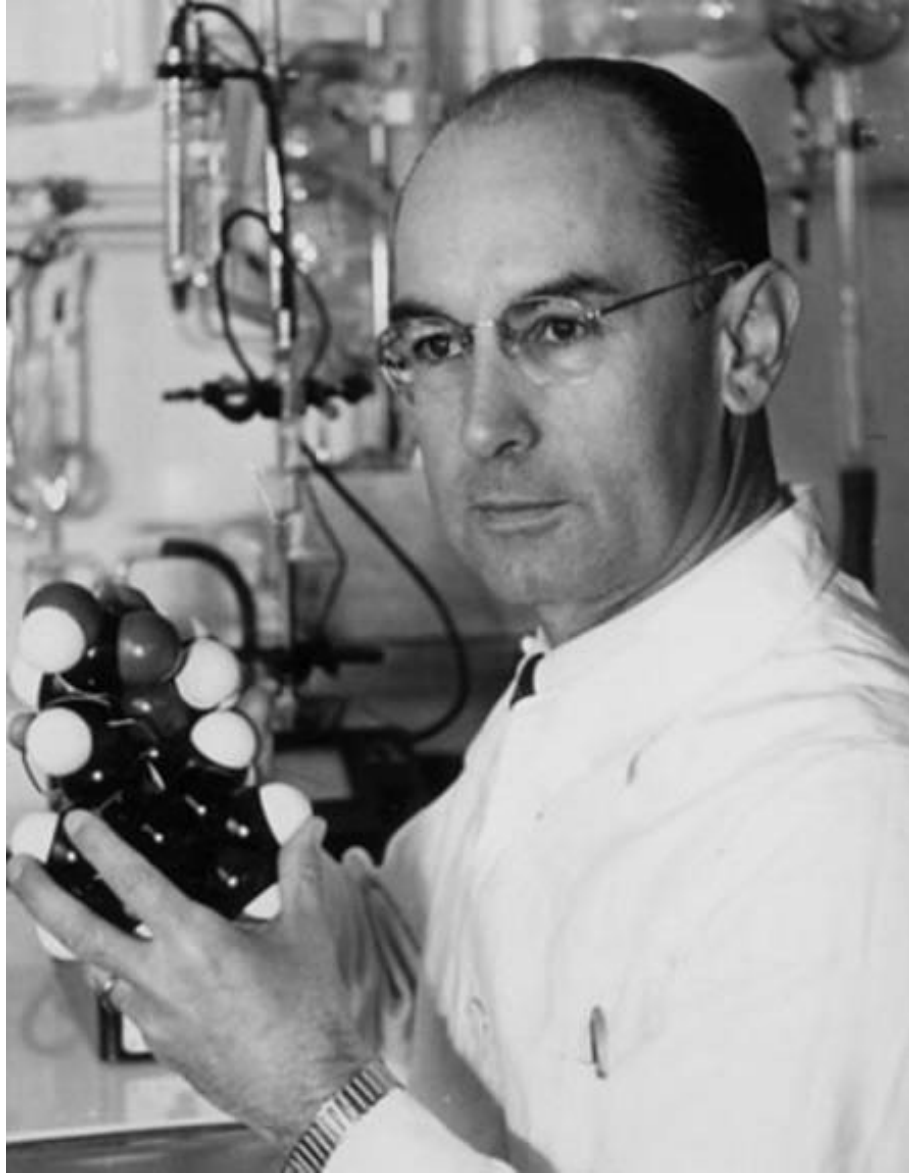
Guy M. Goodwin<sup>1</sup>✉, Megan Croal<sup>1</sup>, David Feifel<sup>2</sup>, John R. Kelly<sup>3</sup>, Lindsey Marwood<sup>1</sup> , Sunil Mistry<sup>1</sup>, Veronica O'Keane<sup>3</sup>, Stephanie Knatz Peck<sup>4</sup> , Hollie Simmons<sup>1</sup>, Claudia Sisa<sup>1</sup>, Susan C. Stansfield<sup>1</sup>, Joyce Tsai<sup>1</sup>, Sam Williams<sup>1</sup> and Ekaterina Malievskaia<sup>1</sup>

-19 patients with depression with ongoing SSRI treatment (mean duration: 15 months)  
25 mg of psilocybin add on  
-Good therapeutic response with no evidence



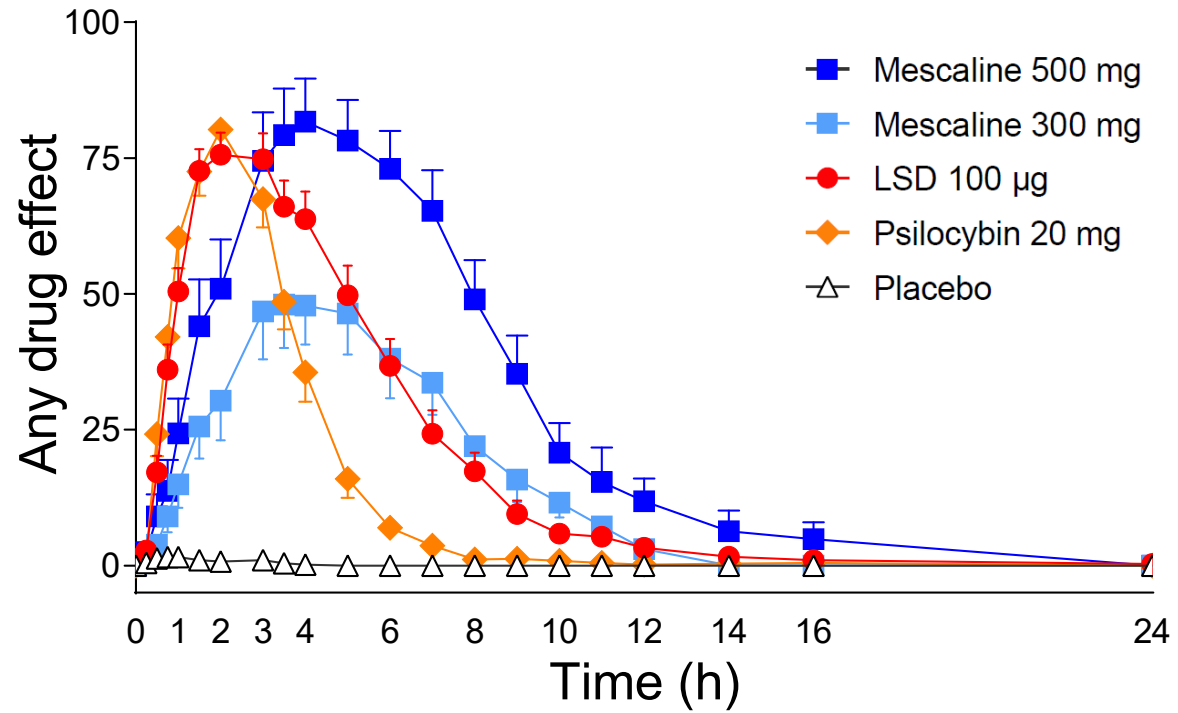


# LSD



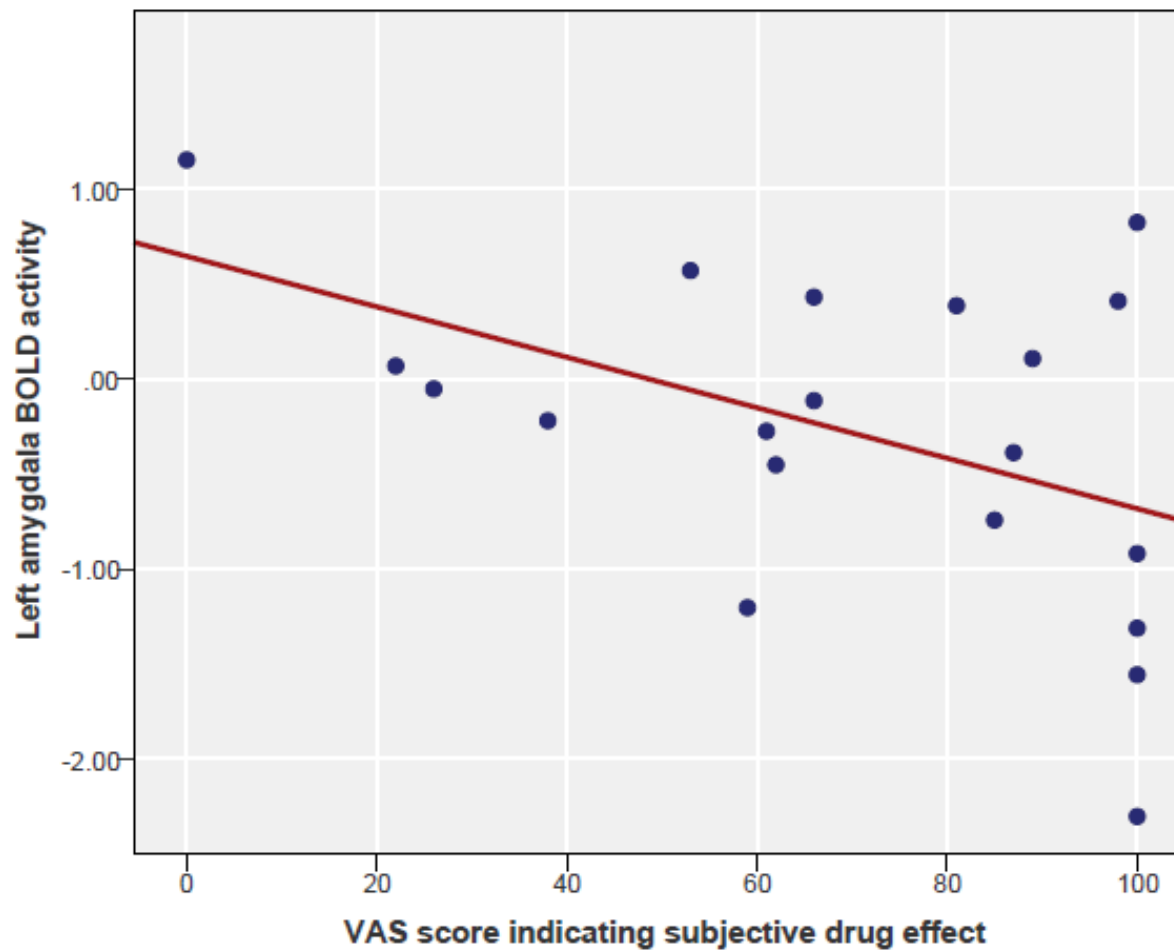
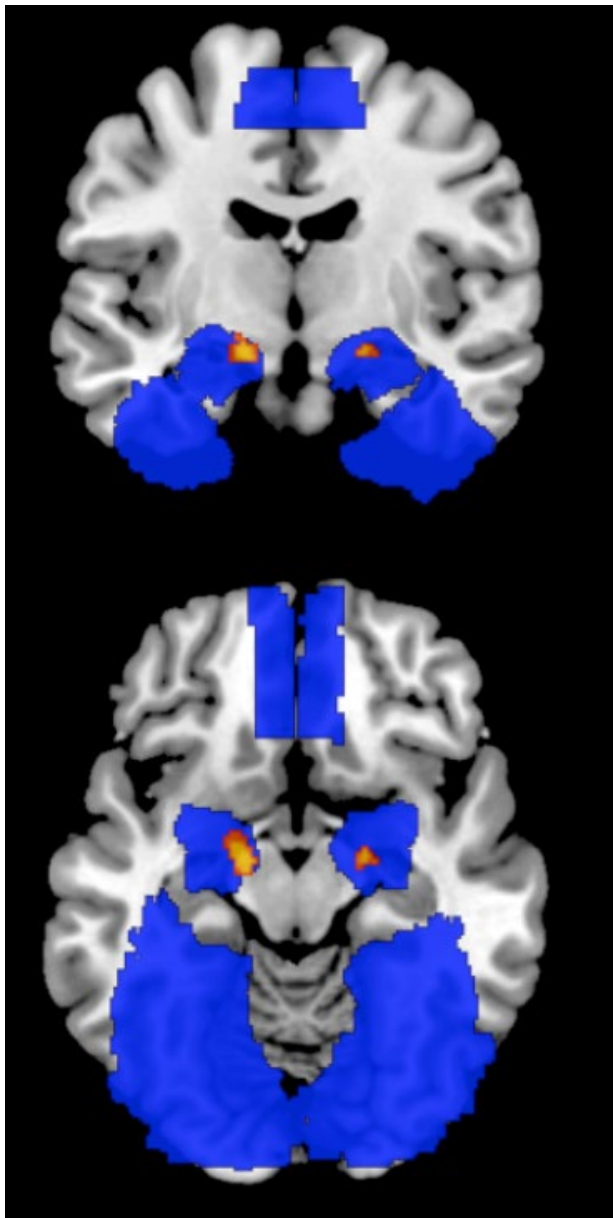


# Equivalent doses of different psychedelics



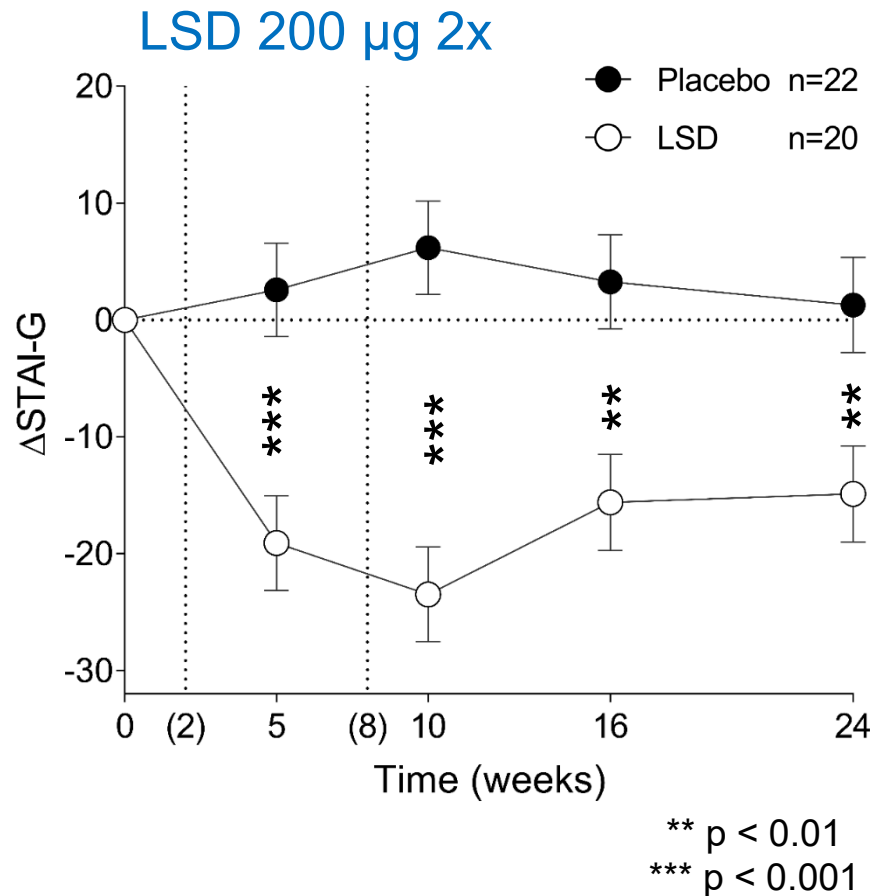
N=32, mean+SEM

# LSD reduces amygdala BOLD response to fear



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

# 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**

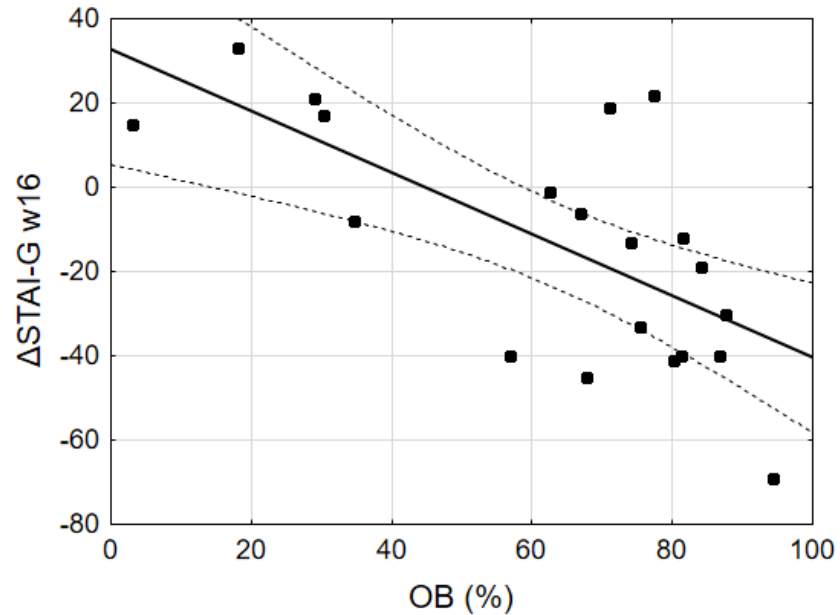
- Mean change from baseline difference = -16.2  
95% confidence interval [CI] = -27.8 to -4.5  
 $p = 0.007$

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

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

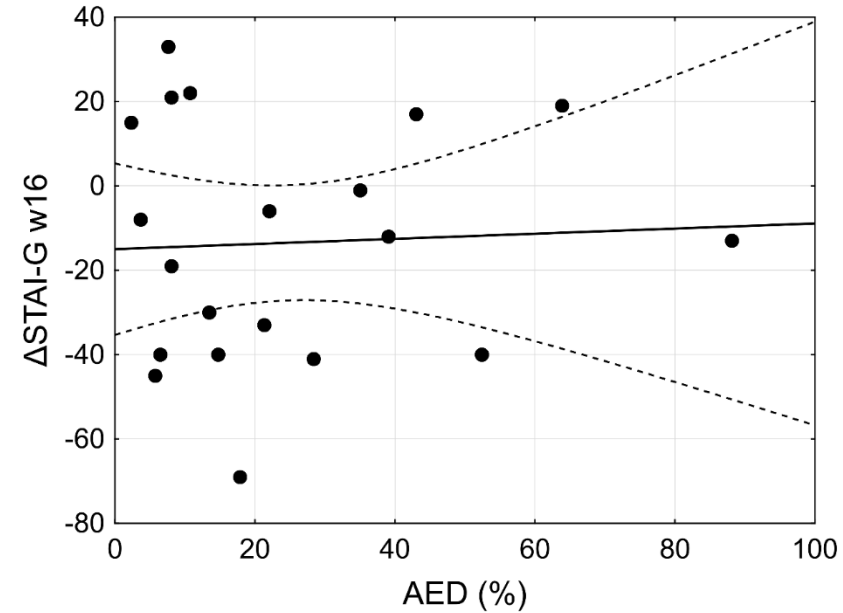
# Akute Wirkung korreliert mit Therapieeffekt

Positive Wirkung



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

Negative Wirkung



$$r = 0.05, p = 0.8$$

n=20

## Treatment-related events

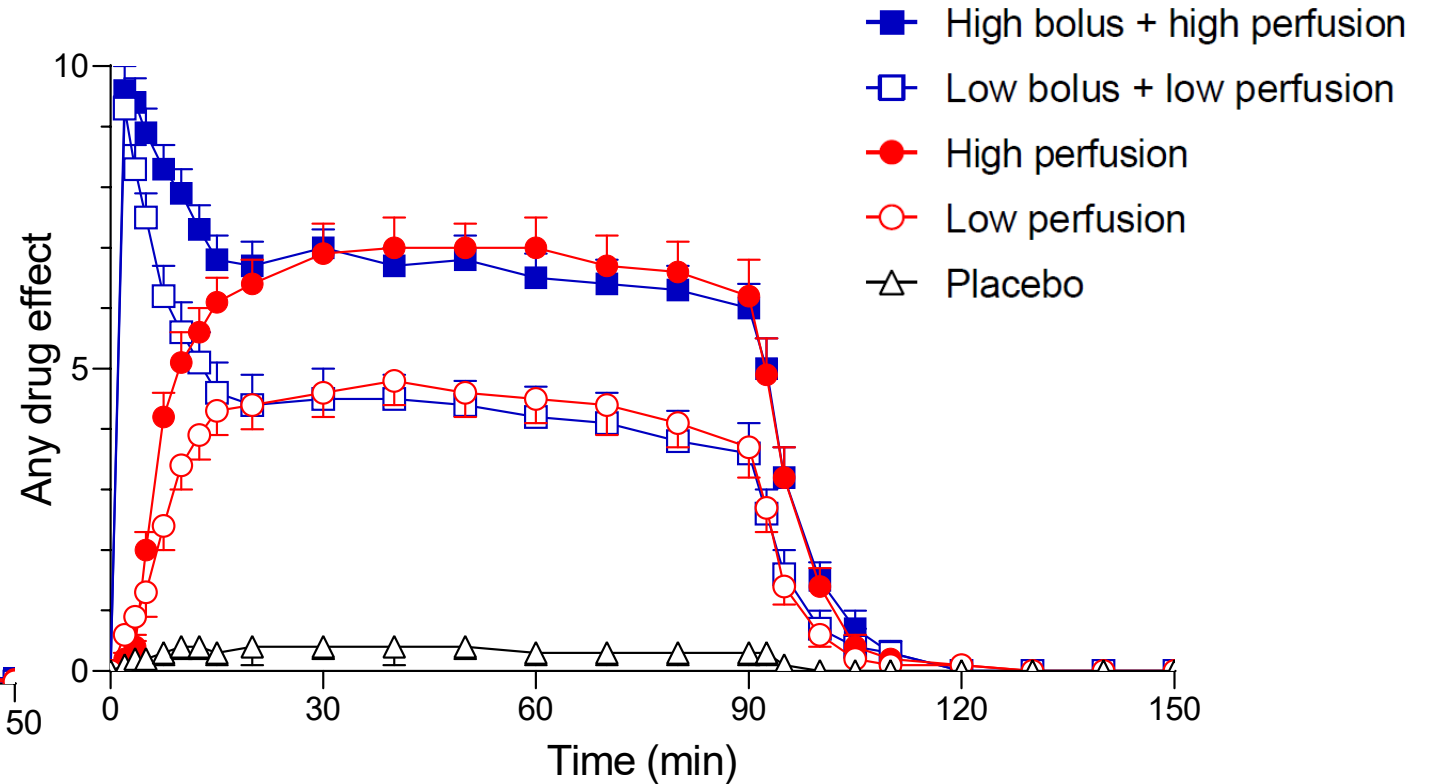
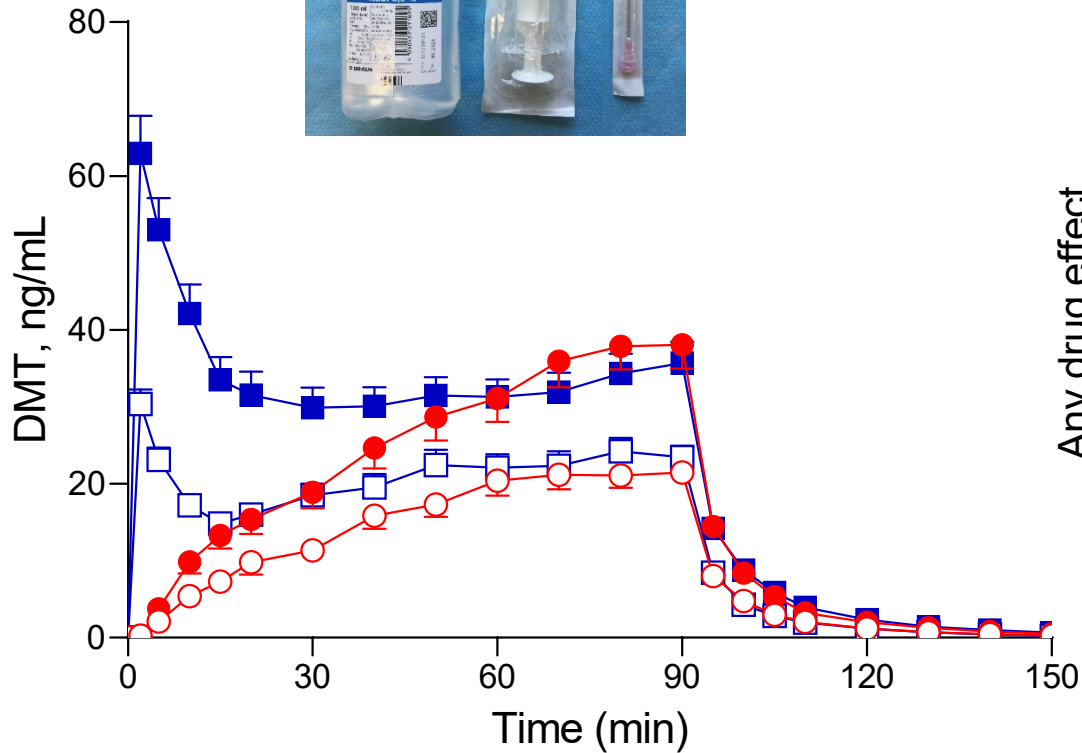
- Untoward effects during treatment sessions
  - Nausea (10%)
  - Anxiety (7%)
  - Headache (2%)
- Serious adverse events
  - 1 x acute transient anxiety and delusions
    - Treated with lorazepam and olanzapine
      - second LSD dose reduced to 100 µg

## 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)

n=44

# 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)