Klinische Pharmakologie verschiedener Psychedelika

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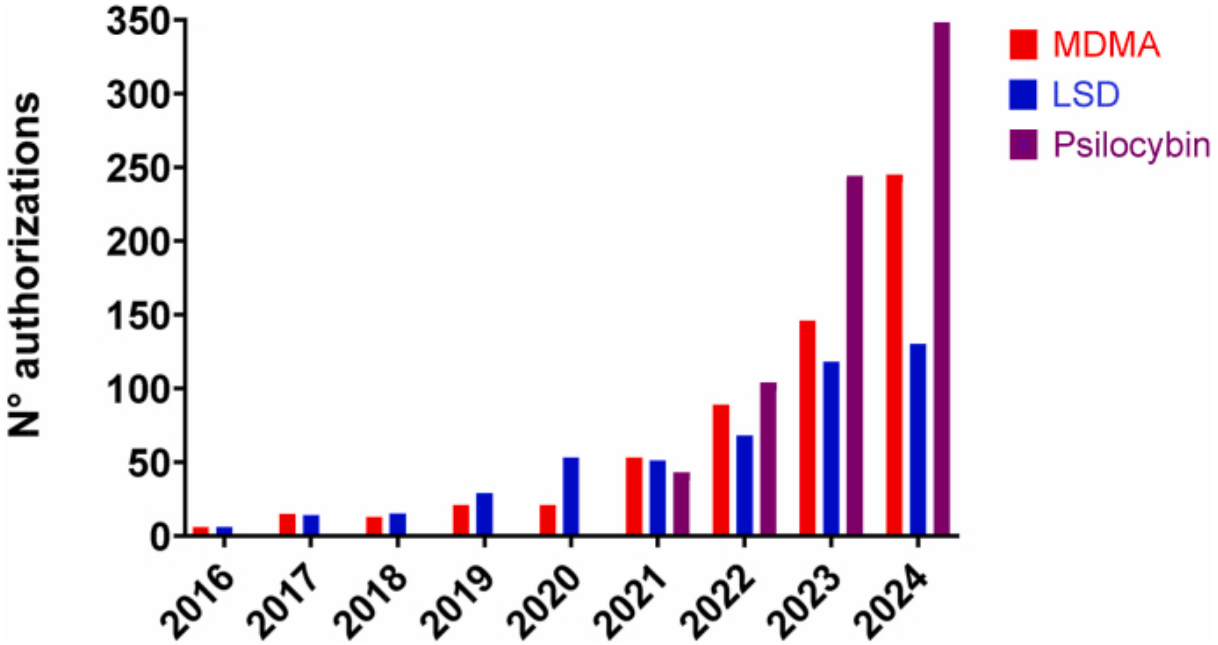
01

Swiss Limited Use Programm

Swiss Limited Use Program
(100 physicians treat 1000 patients per year)



Liechti et al. 2025 *Neuroscience Applied*

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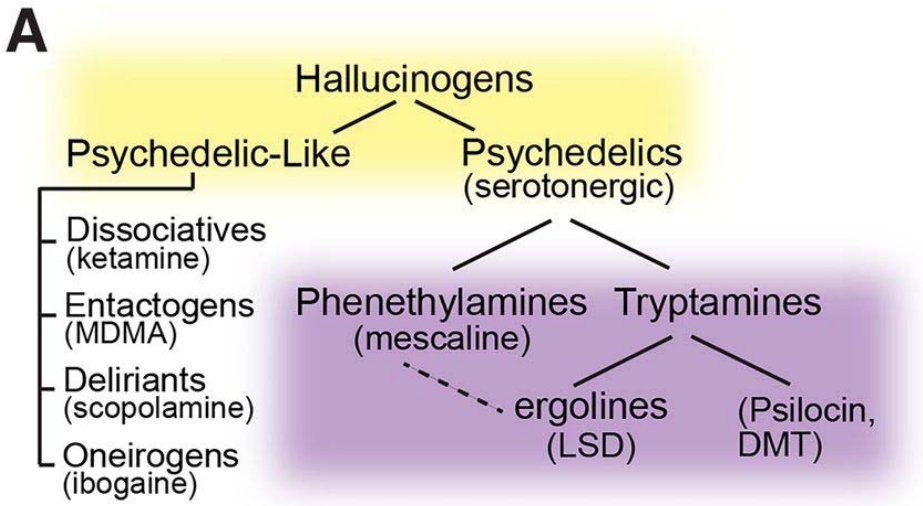
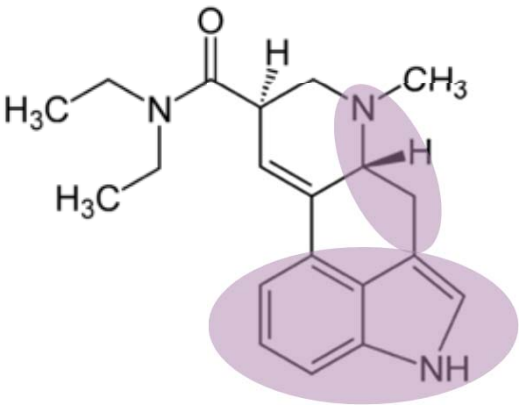
02
Background

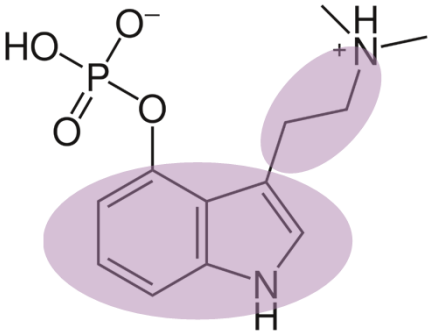
Pharmacology



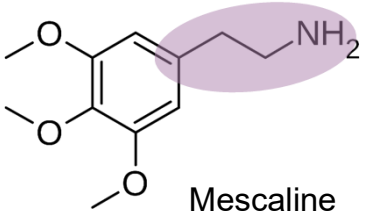
Grieco et al. 2022 *J Neurosci*



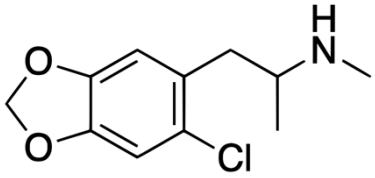
Lysergic acid diethylamide (LSD)



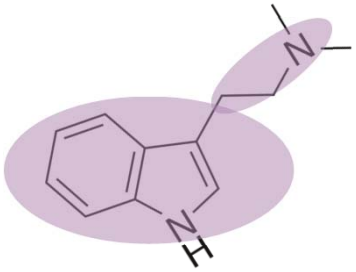
Psilocybin



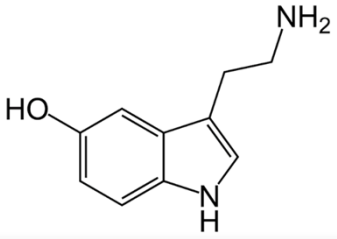
Mescaline



MDMA



DMT



Serotonin (5-HT)

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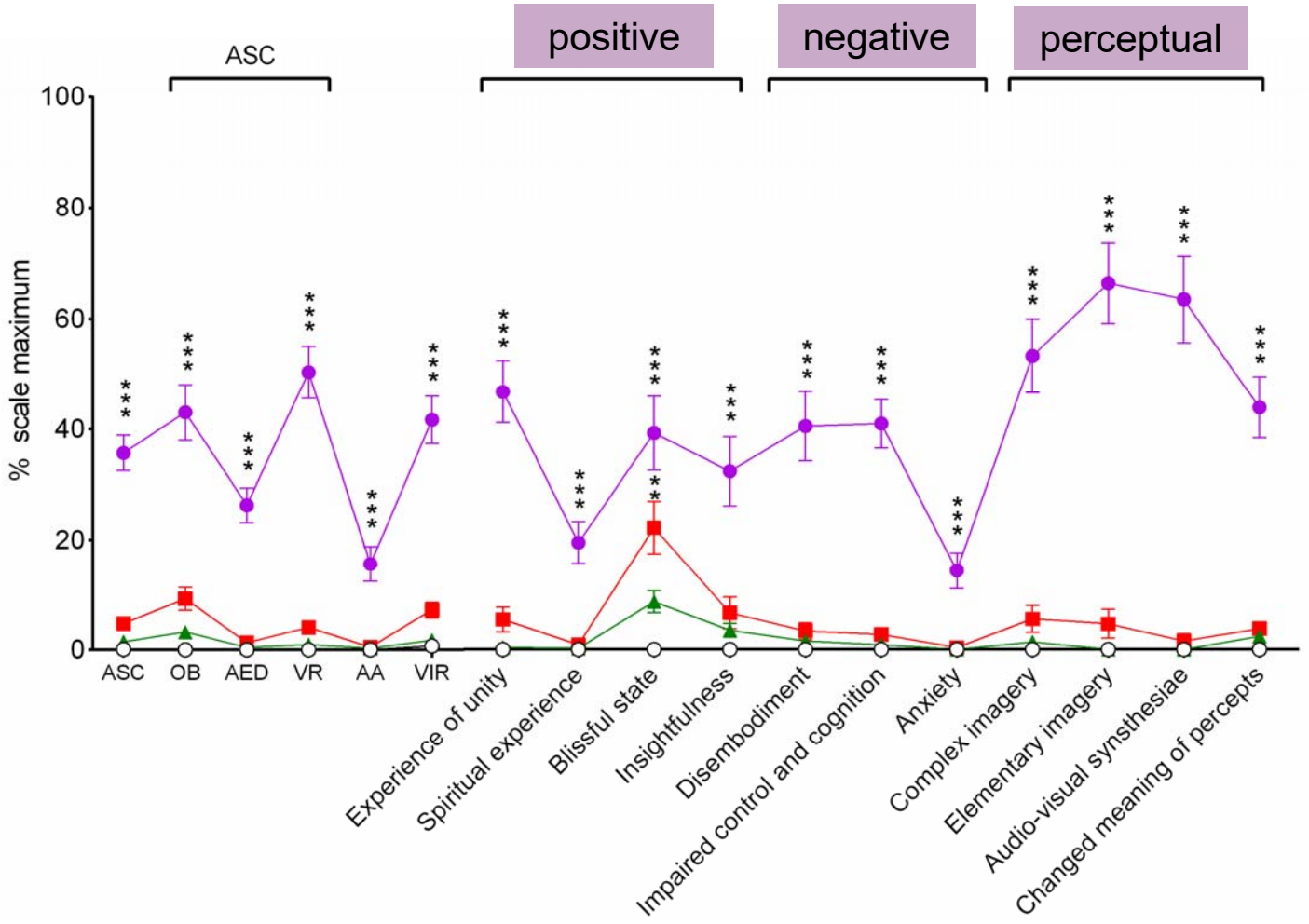
Psychedelics produce complex alterations in state of consciousness



Mean ± SEM
n=28

MDMA
LSD
Amphetamine
Placebo

*** p<0.001

** p<0.01
Compared with placebo

Holze et al. 2020 *Neuropsychopharmacology*

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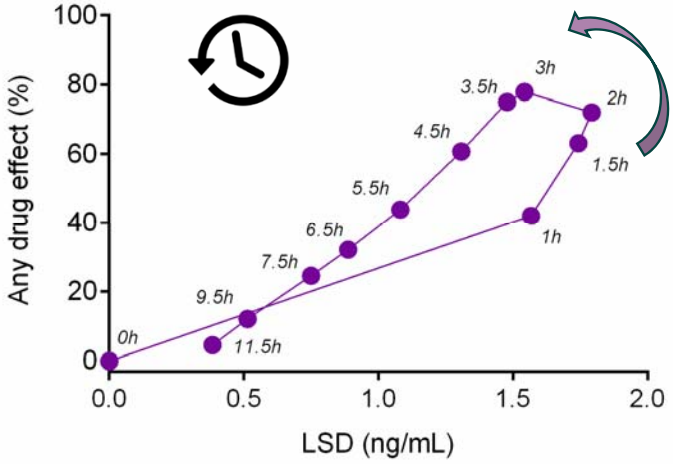
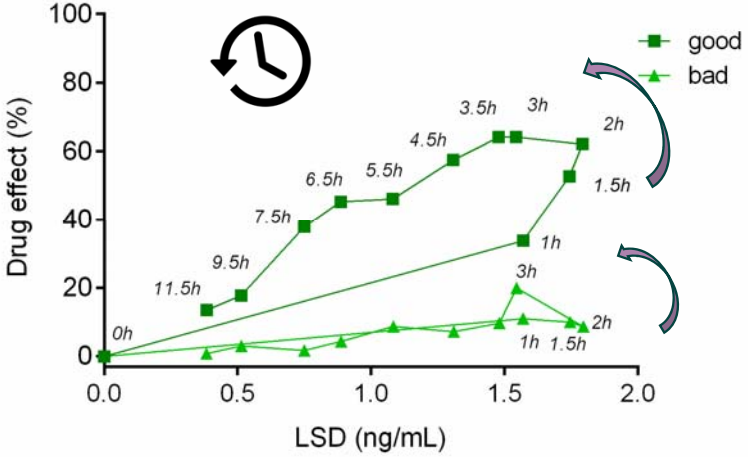
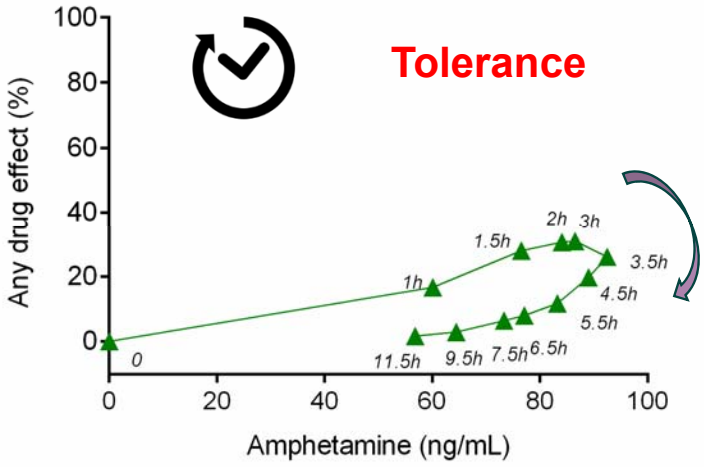
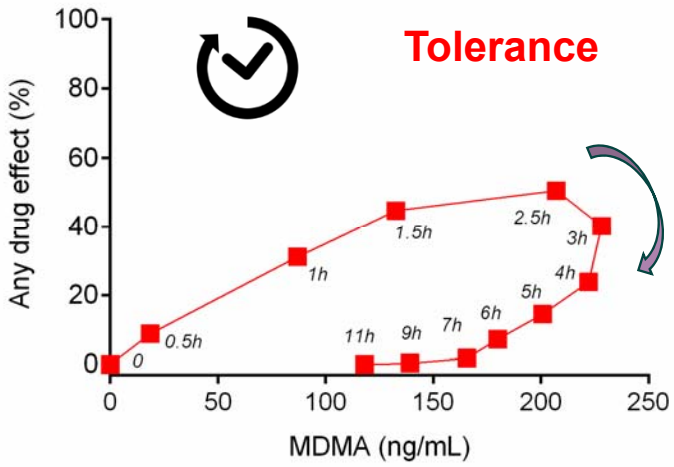
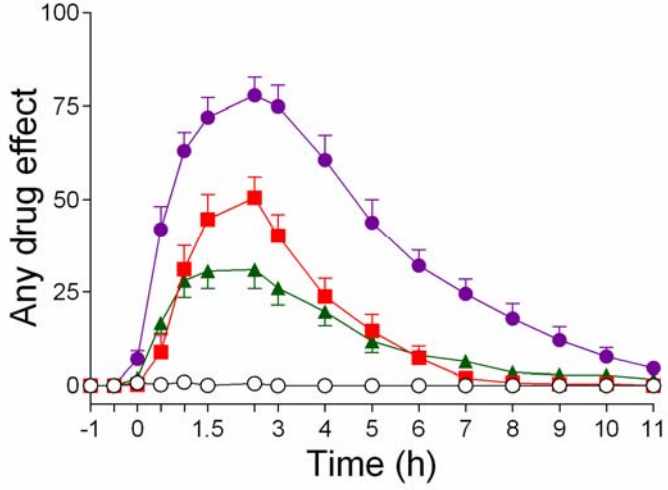
LSD exhibits **no** acute Tolerance





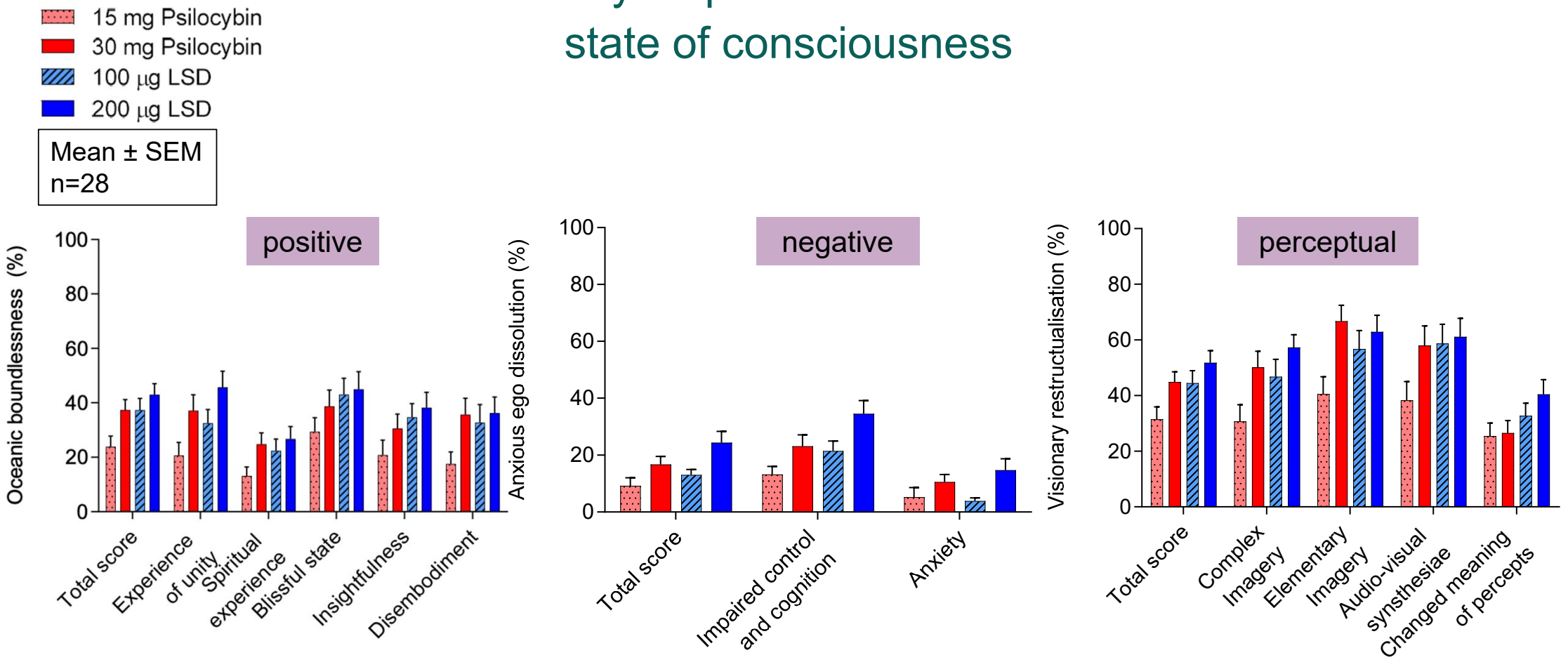






Basel

LSD and Psilocybin produce similar alterations in state of consciousness



Holze et al. 2022 *Neuropsychopharmacology*

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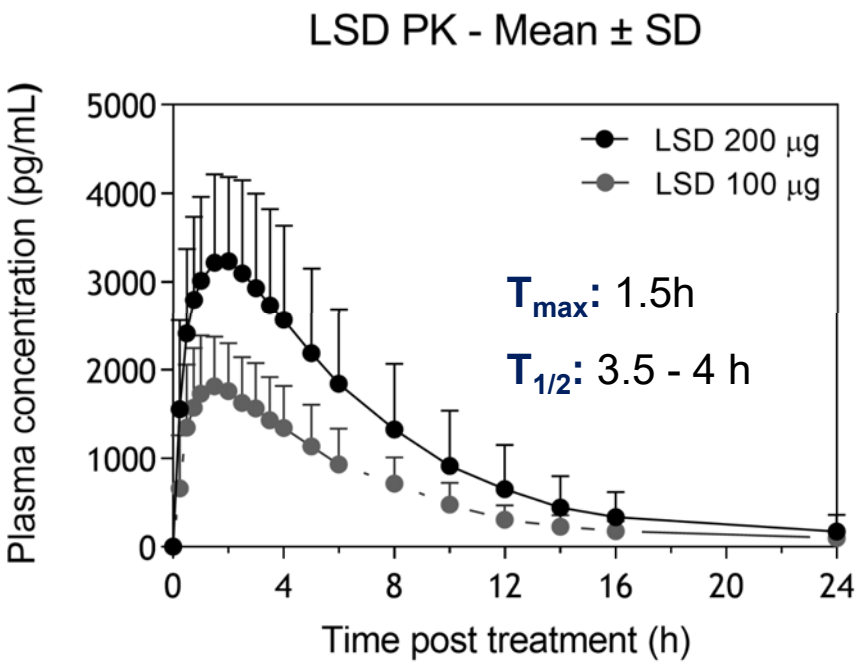
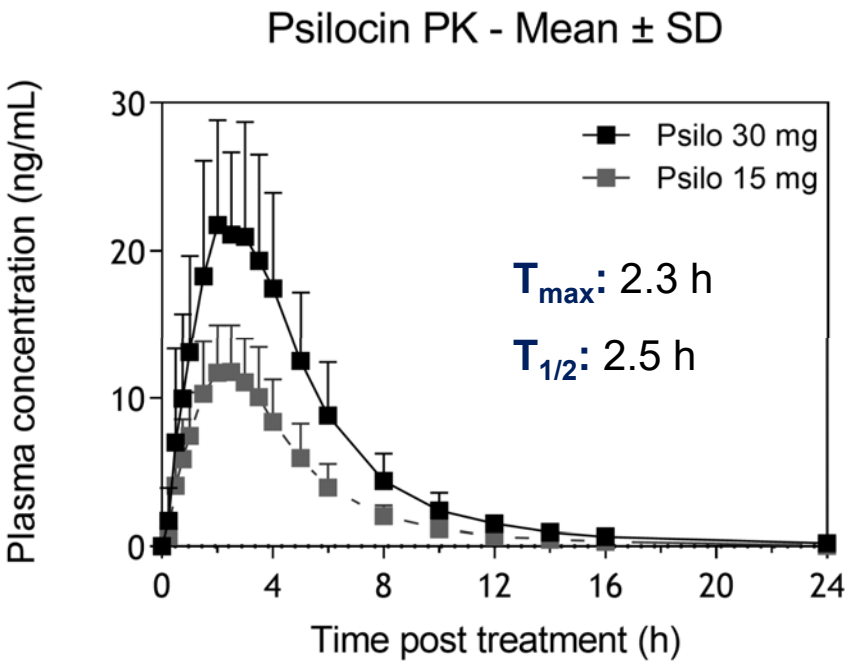
Effect durations

Effect	15 mg Psilocybin	30 mg Psilocybin	100 µg LSD	200 µg LSD
Time to onset (h)	0.8 ± 0.3 (0.3 - 1.5)	0.8 ± 0.4 (0.1 - 1.8)	0.6 ± 0.2 (0.3 - 1.0)	0.4 ± 0.2 (0.2 - 0.8)
Time to offset (h)	6.4 ± 2.1 (3.7 - 11)	7.3 ± 2.3 (4.2 - 12)	10 ± 3.1 (6.3 - 8.8)	11 ± 3.6 (5.8 - 20)
Time to maximal effect (h)	2.1 ± 0.5 (1.5 - 3.4)	2.3 ± 0.8 (0.5 - 3.3)	2.5 ± 0.5 (1.8 - 2.4)	2.2 ± 0.6 (1.2 - 3.9)
Effect duration (h)	5.6 ± 2.2 (2.5 - 10)	6.5 ± 2.4 (3.7 - 12)	9.3 ± 3.2 (5.7 - 17)	11 ± 3.7 (5.4 - 20)
Maximal effect (%)	58 ± 25 (13 - 98)	80 ± 18 (43 - 100)	77 ± 18 (33 - 100)	87 ± 13 (46 - 100)

Holze et al. 2022 *Neuropsychopharmacology*

Pharmacokinetics LSD vs. psilocybin





Holze et al. 2022 *Neuropsychopharmacology*

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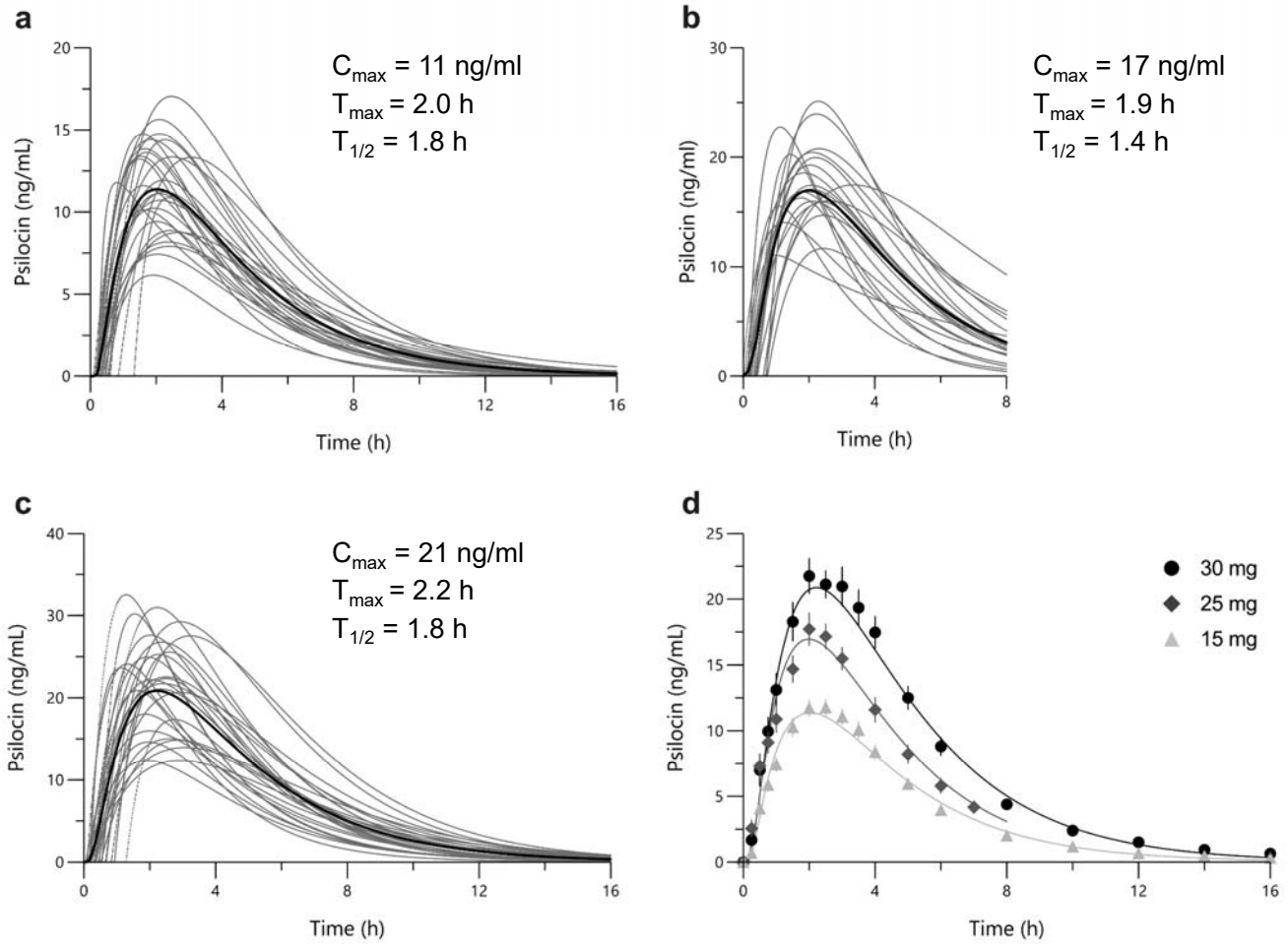
Psilocin Pharmacokinetics



a. 15 mg (n=28)
b. 25 mg (n=22)
c. 30 mg (n=28)
d. observed vs. predicted data

Mean marked in bold

- Dose-proportional
- No correlation between plasma concentration and body weight

Holze et al. 2022 *Clin Pharm Ther*

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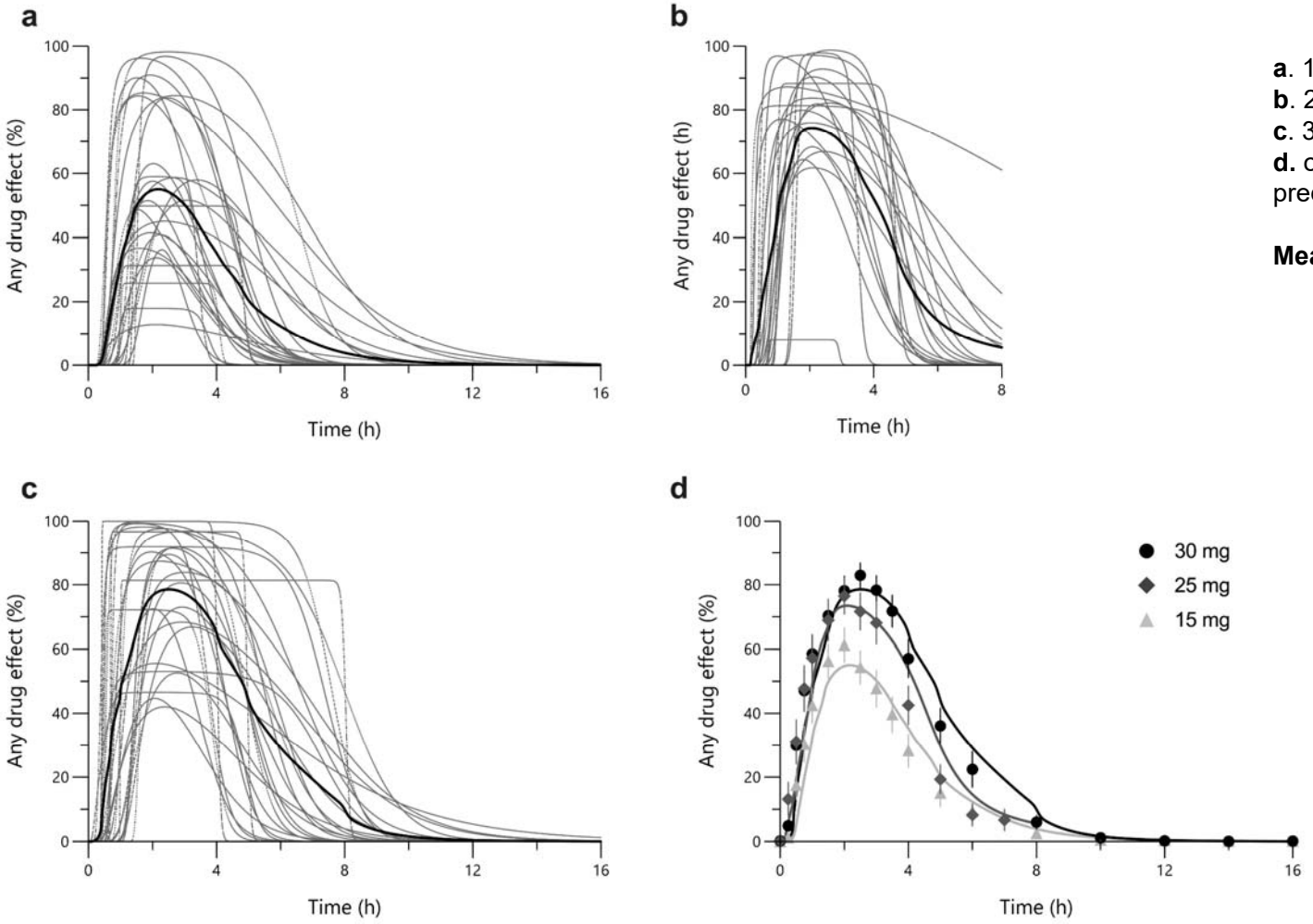
Psilocybin «Any drug effect» PK-PK model



a. 15 mg (n=28)
b. 25 mg (n=22)
c. 30 mg (n=28)
d. observed vs. predicted data

Mean marked in bold

Holze et al. 2022 *Clin Pharm Ther*

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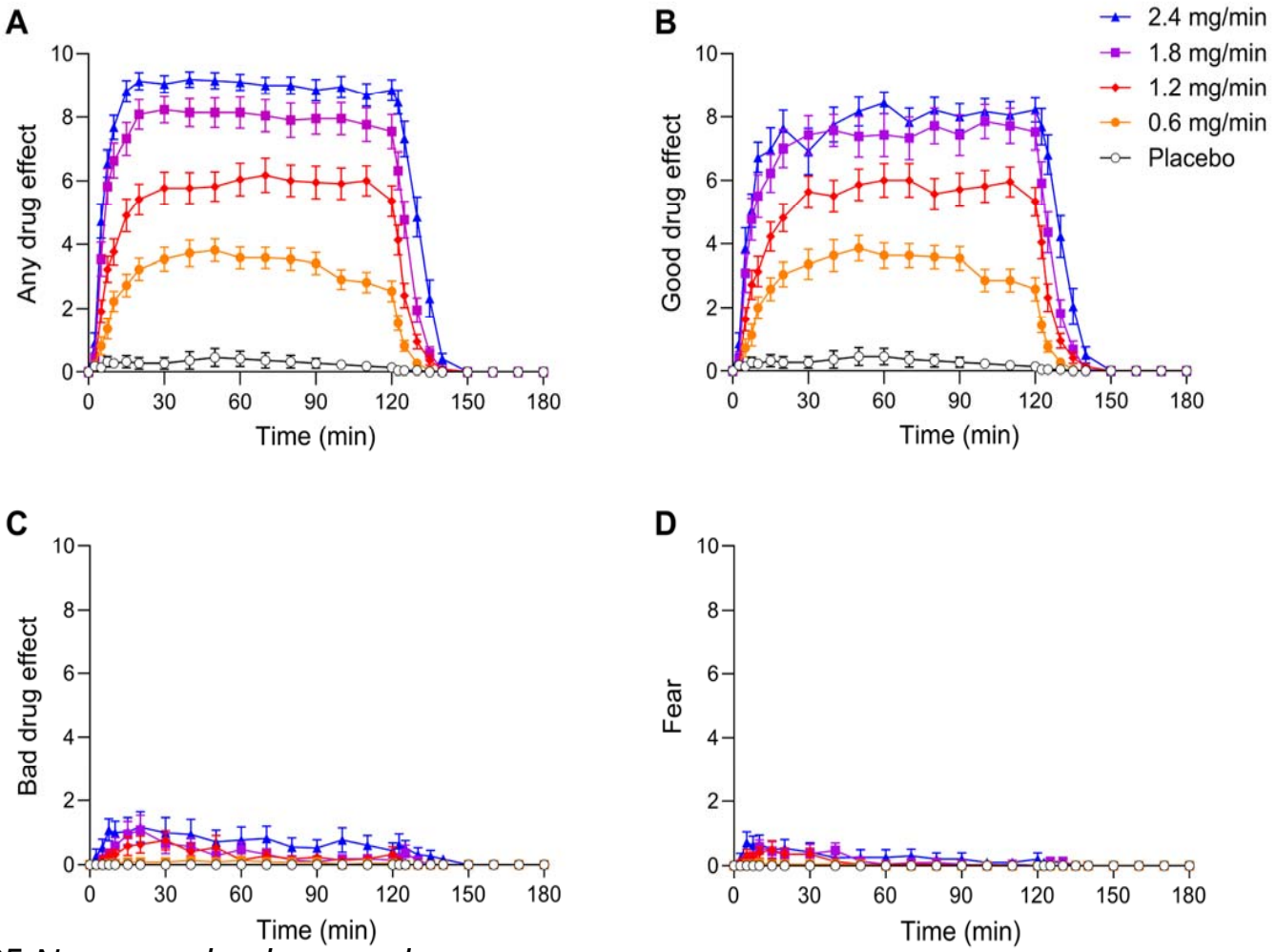
DMT-Infusion Dose Response Study



Erne, Vogt et al. 2025 *Neuropsychopharmacology*

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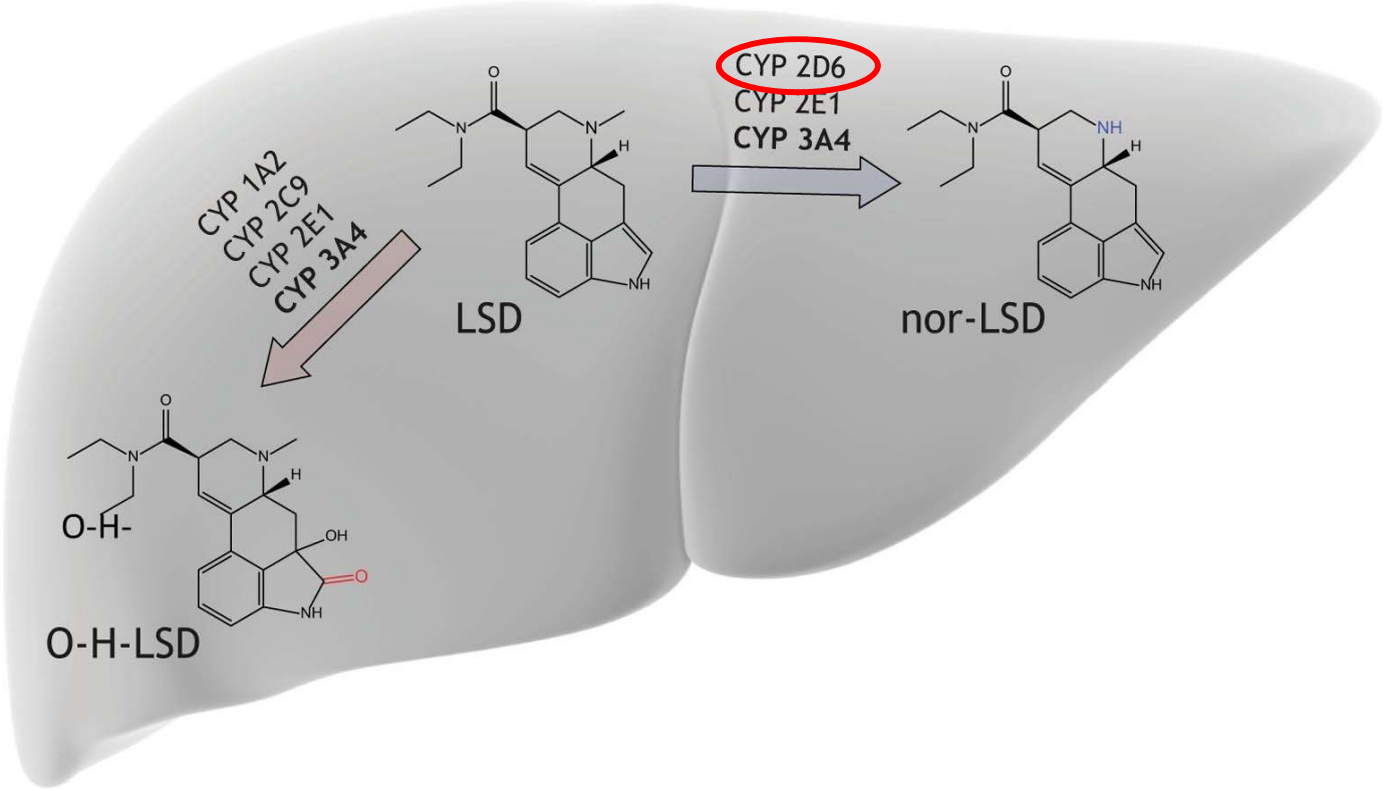
03

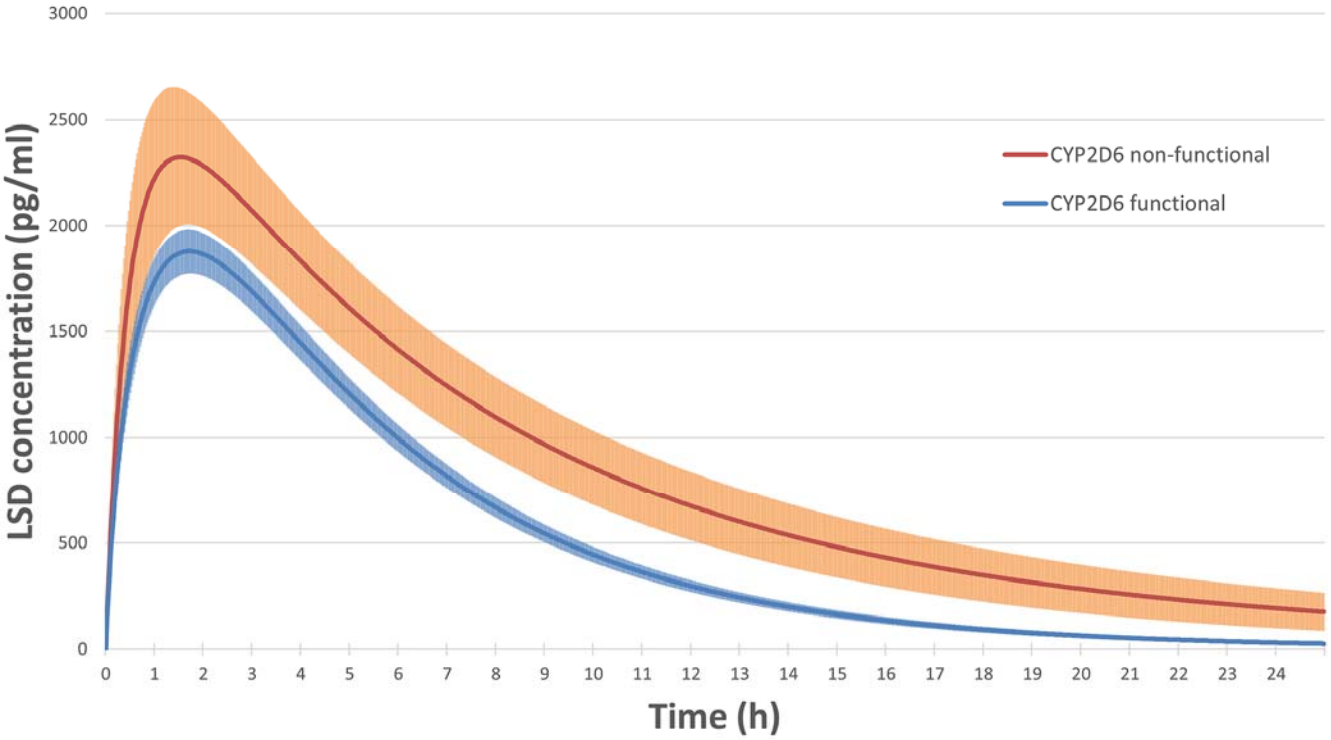
Interactions – from in vitro to in vivo

Cytochrome P450 enzymes contribute to the metabolism of LSD to nor-LSD and 2-oxo-3-hydroxy-LSD: Implications for clinical LSD use



Luethi et al. 2019 *Biochemical Pharmacology*

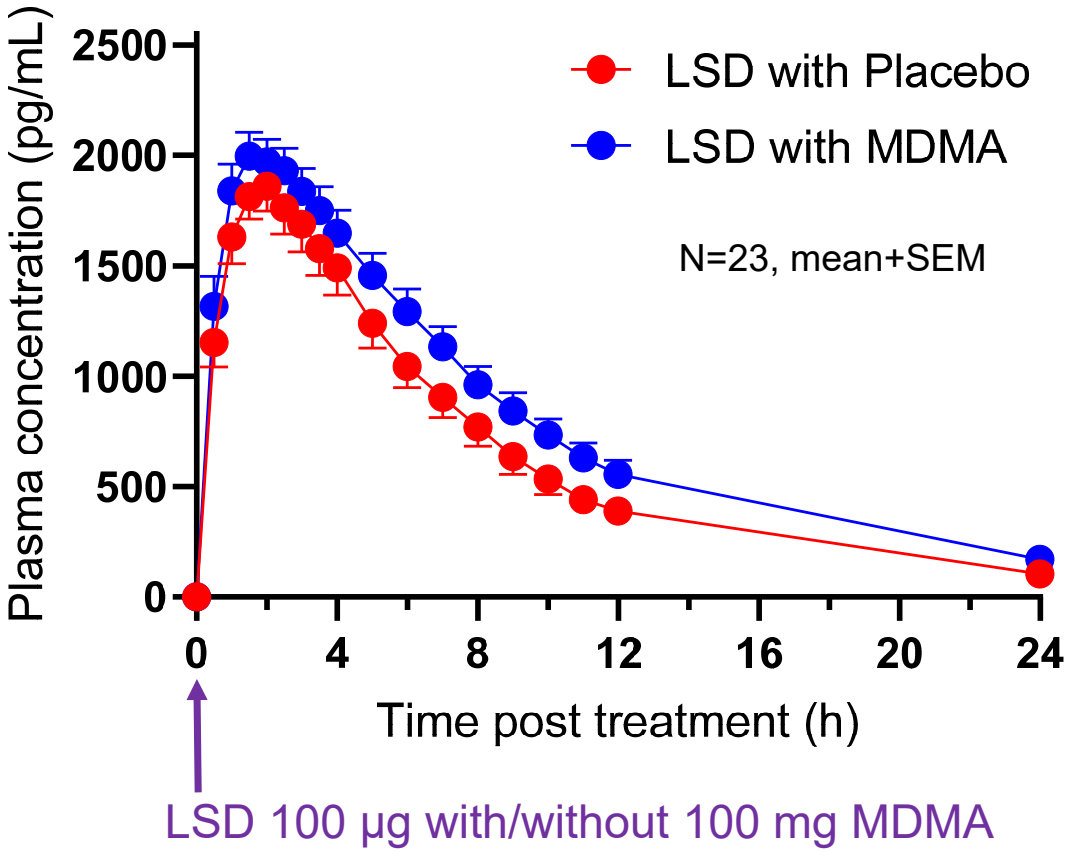
Genetic influence of CYP2D6 on pharmacokinetics and acute subjective effects



	non-f	func
$T_{1/2}$ (h)	**7.5**	**4.1*** **
Duration (h)	**11.8**	**8.9***

Vizeli et al. 2021 *Scientific reports*

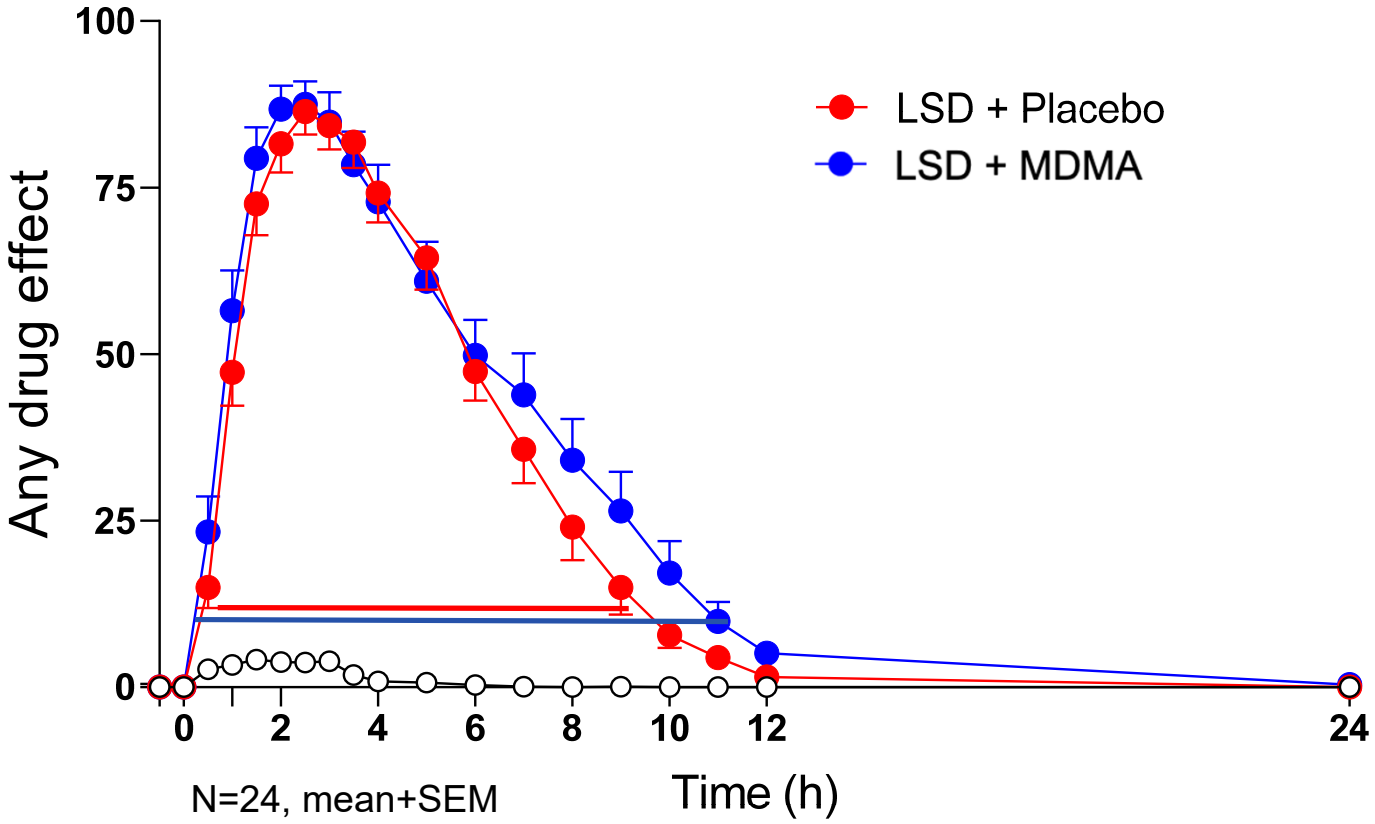
MDMA (CYP2D6 inhibitor) increases LSD concentrations



PK parameter	LSD	LSD+MDMA
C_{max} (ng/mL)	1.9	2.1
AUC_{inf} (ngh/mL)	14	19
$T_{1/2}$ (h)	**3.9**	**5.2**

Straumann et al. 2023 *Neuropsychopharmacology*

MDMA prolongs LSD effect duration



Duration [mean (SD)]

LSD	LSD+MDMA
8.4 (1.9) h	9.9 (3.8) h

Straumann et al. 2023 *Neuropsychopharmacology*

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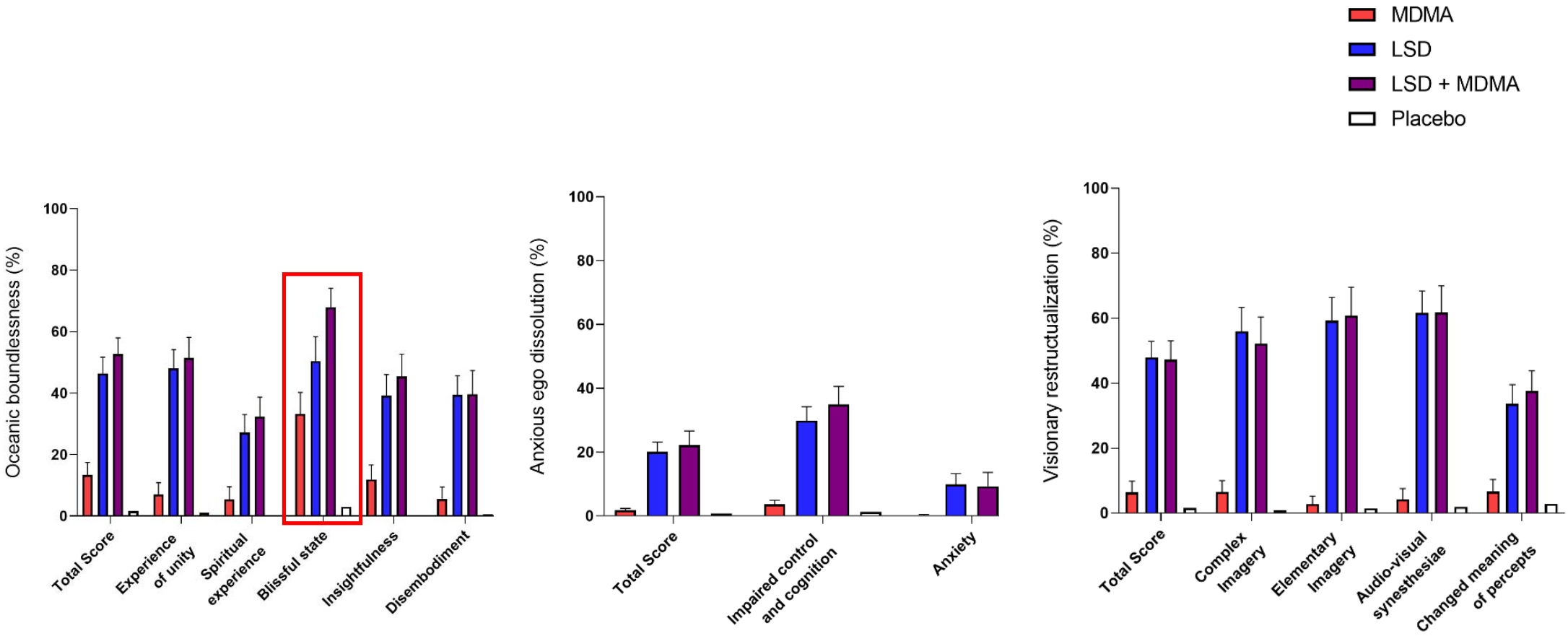
Changes in State of Consciousness – LSD+MDMA



Straumann et al. 2023 *Neuropsychopharmacology*

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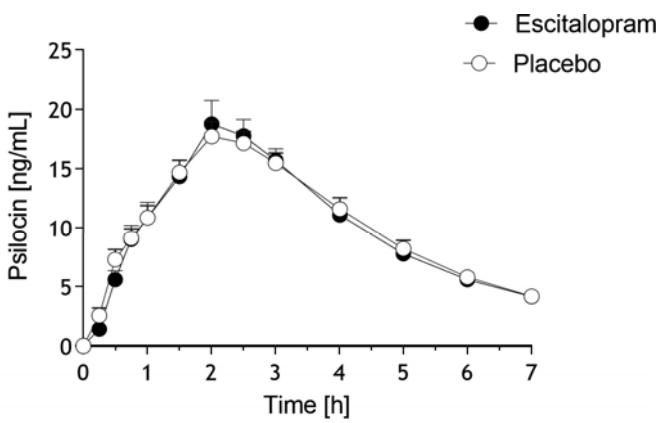
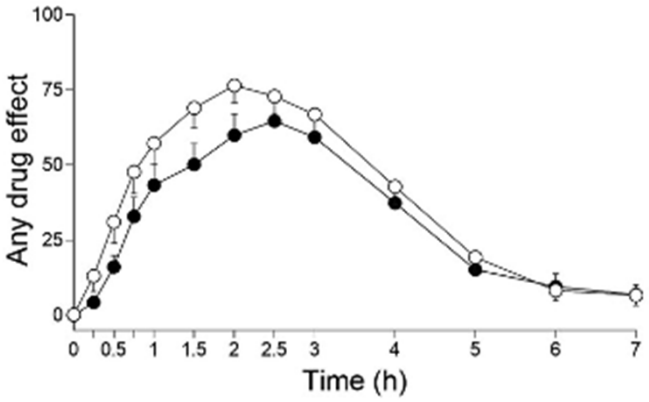
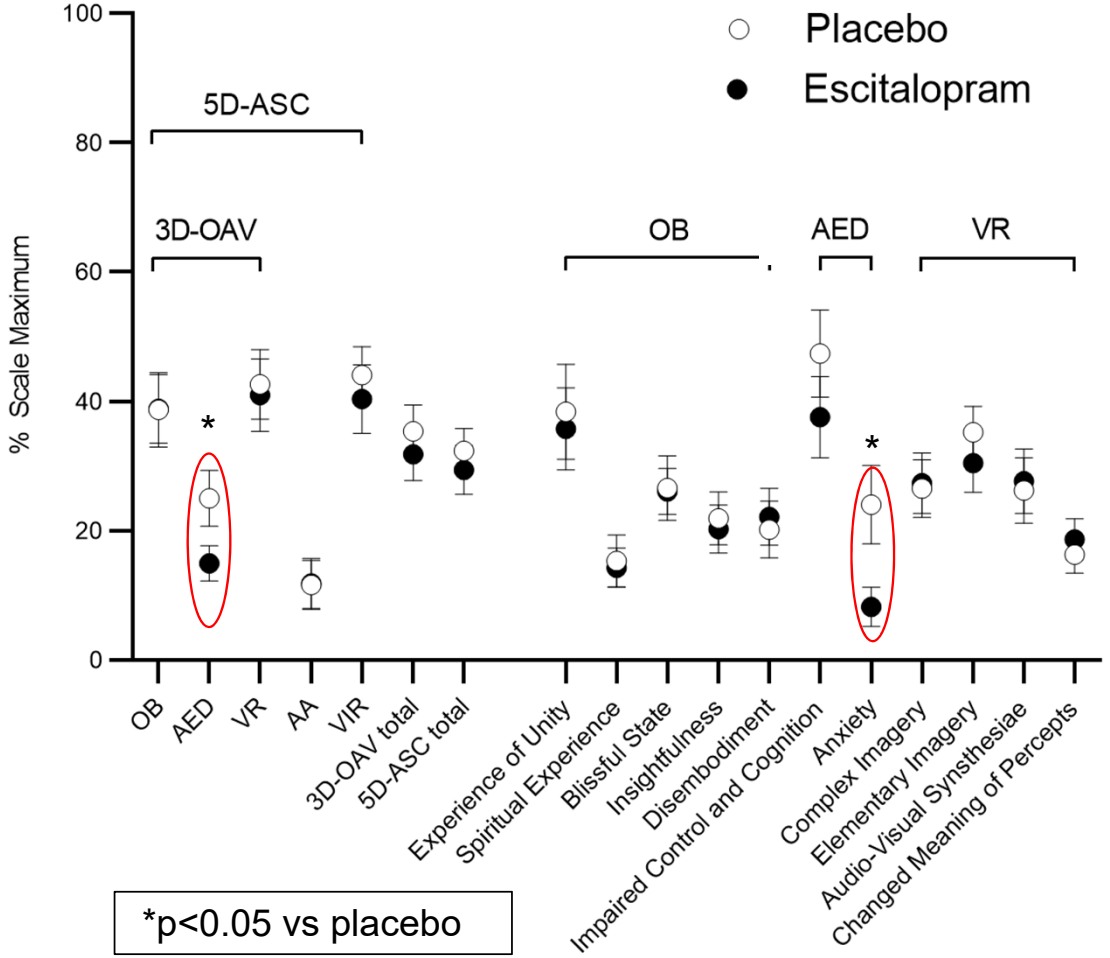
Escitalopram reduced anxiety but not the overall psychedelic response to psilocybin







*p<0.05 vs placebo

Becker et al. 2022 *Clin Pharmacol Ther*, 111:886-895

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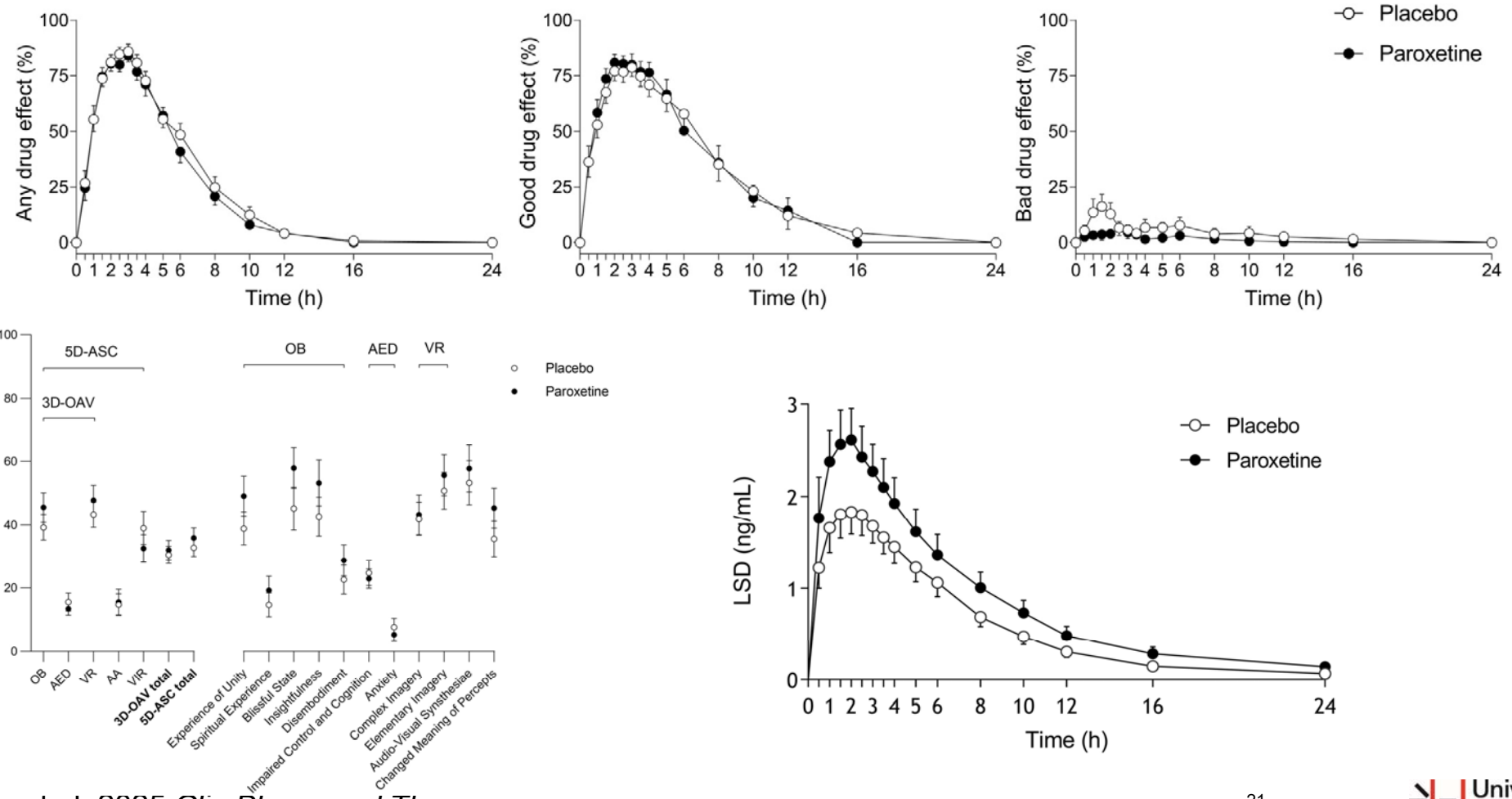
Combined PK and PD interaction
Paroxetine + LSD



Becker et al. 2025 *Clin Pharmacol Ther*

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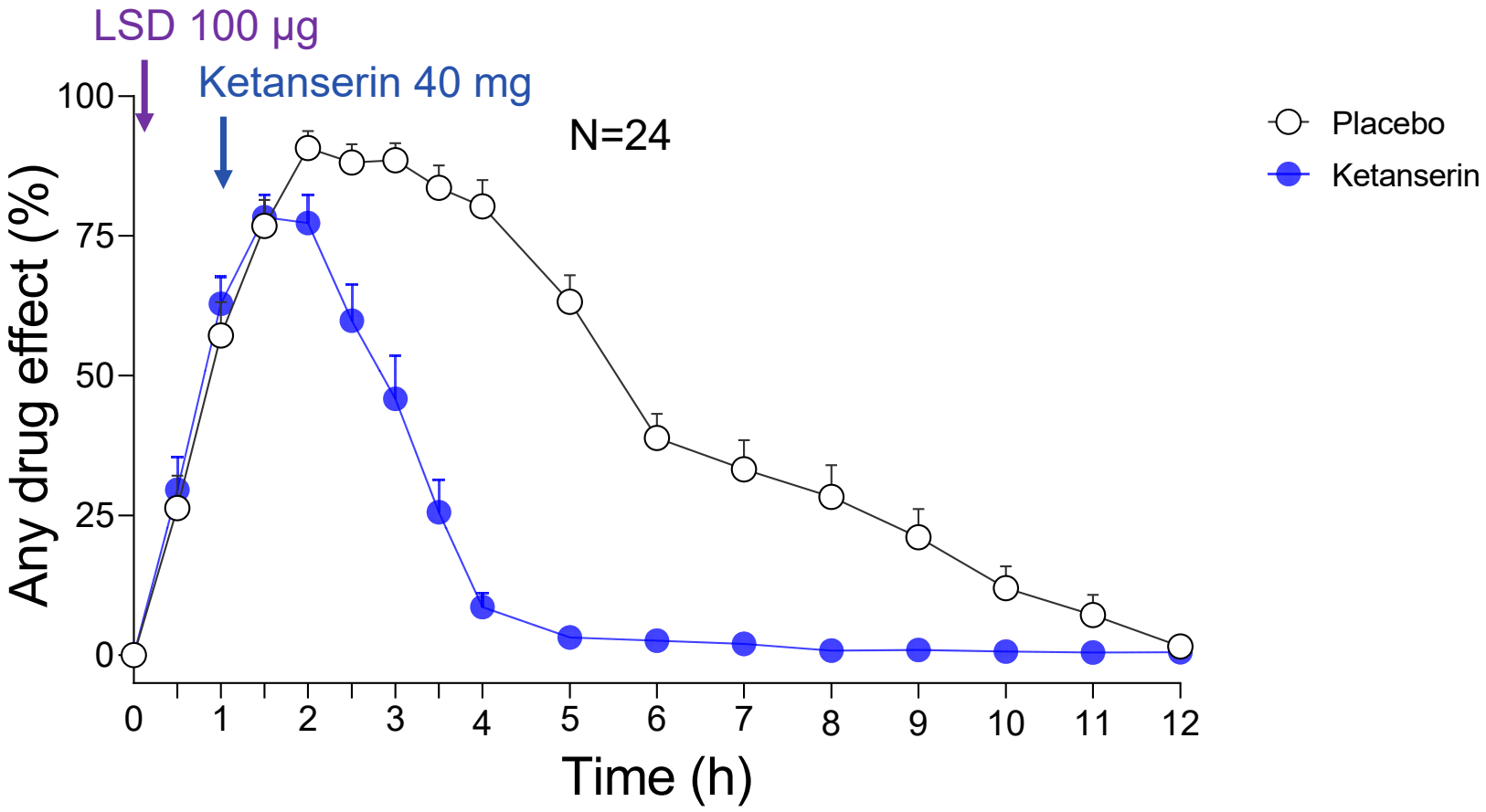
The 5-HT_{2A} receptor antagonist Ketanserin reverses the acute LSD response



Becker et al. 2022 *Int J Neuropsychopharmacol*

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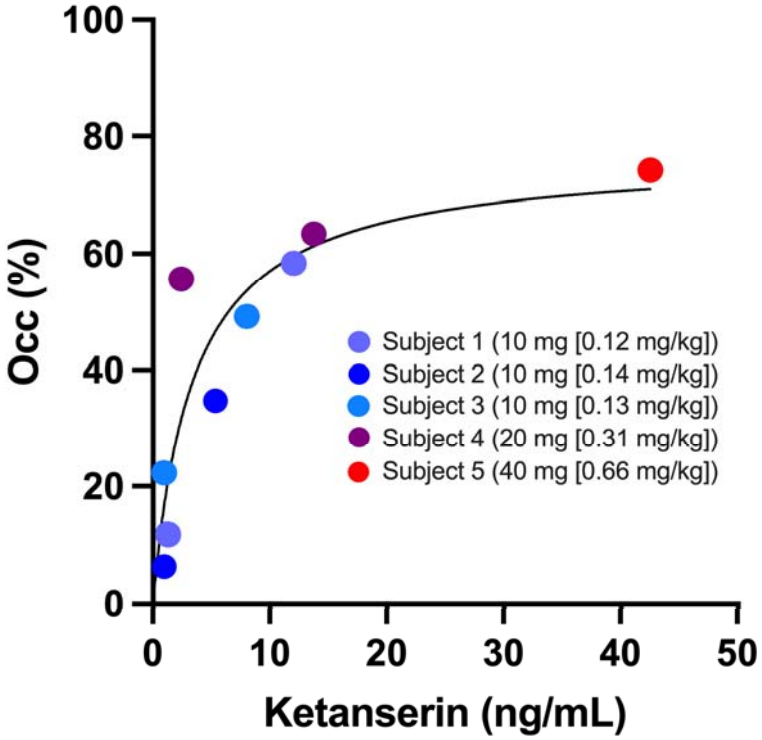
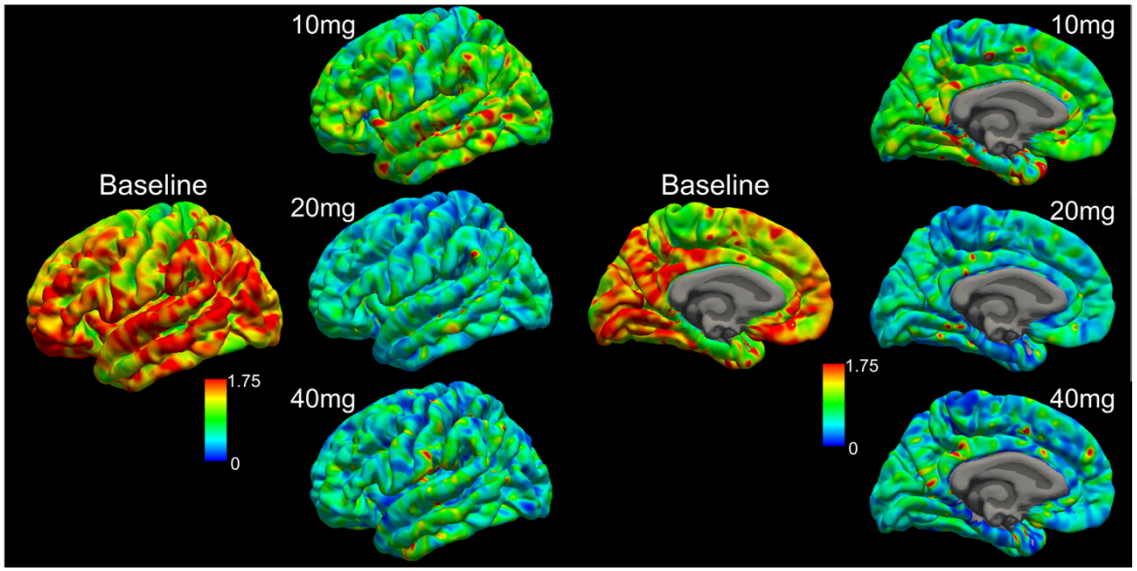
Dose-occupancy relationship of ketanserin





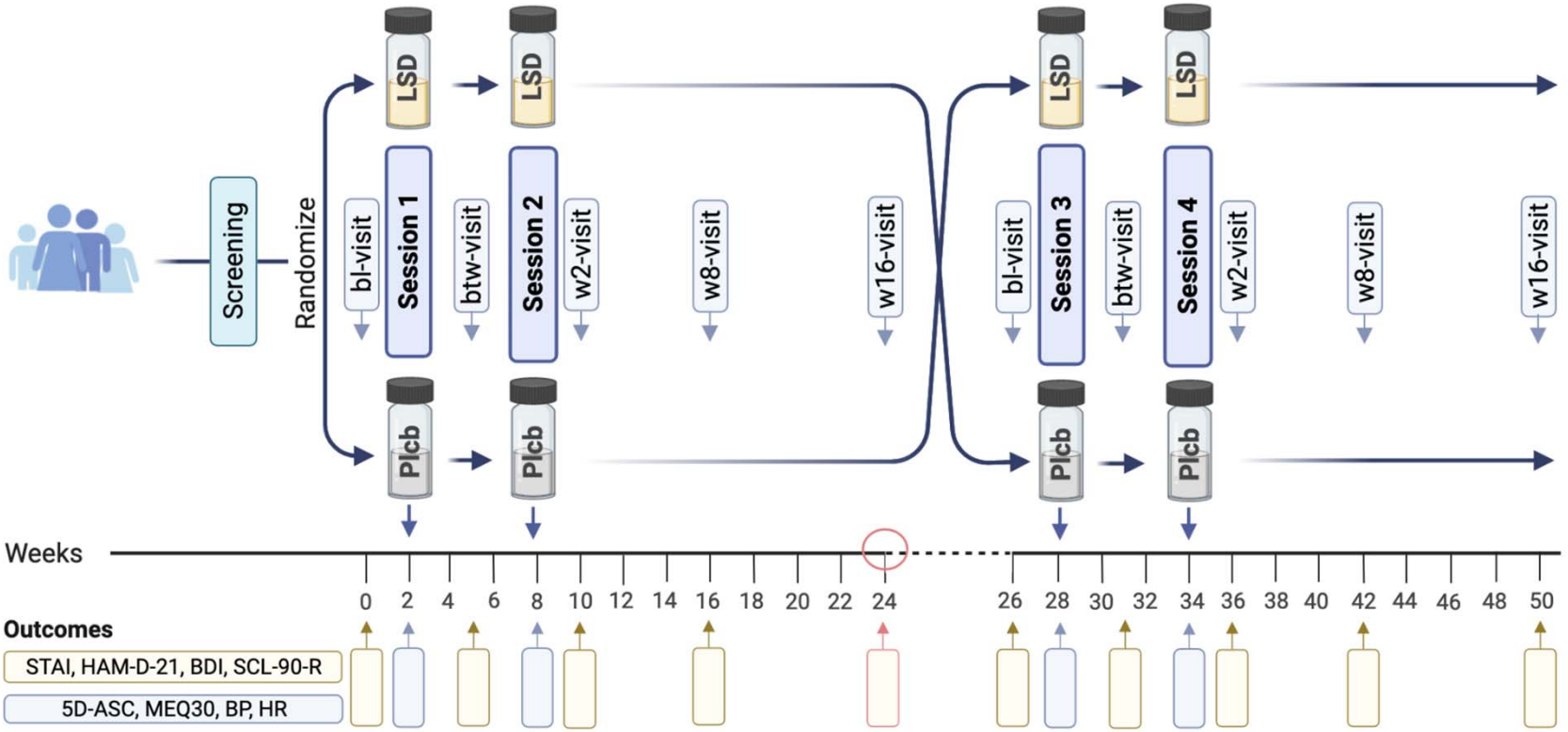
EC_{50} (95% CI): **2.5** (0.8; 8.1) ng/mL

Occ_{max} (95% CI): **77** (54; 114)%.

04
Dose optimization

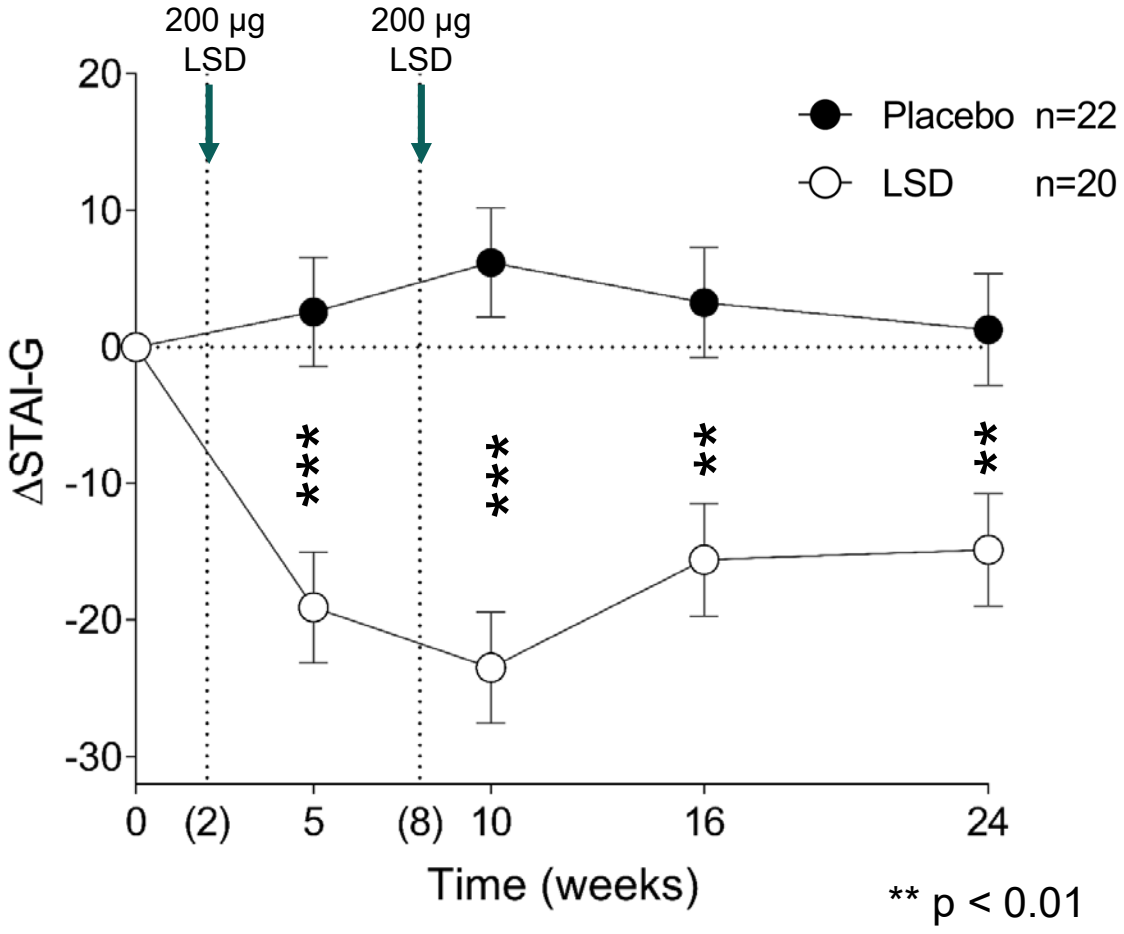
Study Design

- Double-blind, placebo-controlled, 2-period, cross-over design
- 2 x 200 µg LSD vs. 2 x placebo and vice versa
- Primary Endpoint: STAI-G at 16 weeks after last treatment



Holze et al. 2023 *Biological Psychiatry*

LSD Produced a Rapid and Lasting Reduction in Anxiety



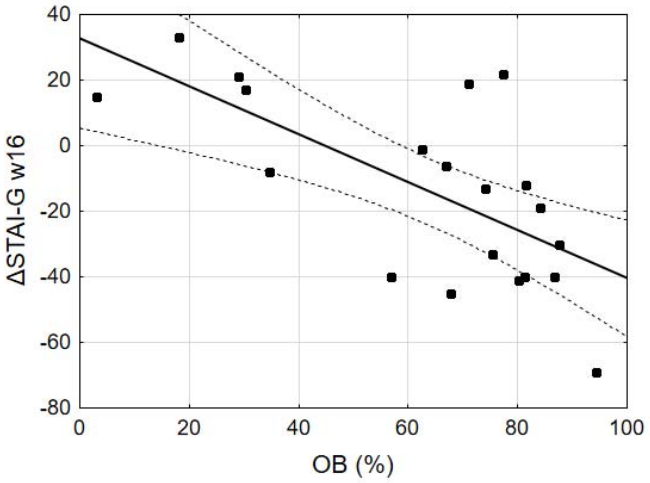
** p < 0.01
*** p < 0.001

- **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** (≥ 30% reduction of STAI-G scores)**:**
  - **65%** in LSD group vs **9%** in placebo group (*p* = 0.003)

Holze et al. 2023 *Biological Psychiatry*

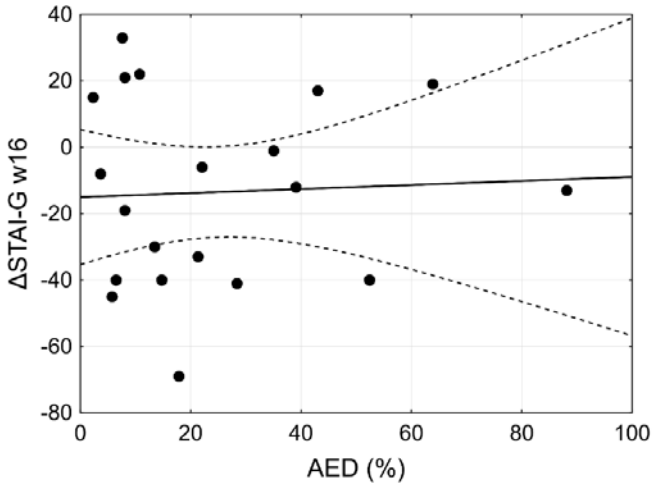
Acute Positive or Mystical Experience in Response to LSD Predicts Therapeutic Outcome

Positive effects (OB)



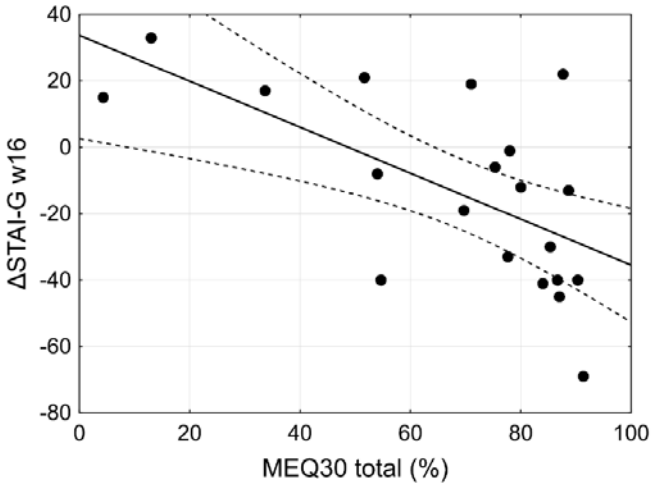
r = -0.67, p = 0.0012**

Negative effects (AED)



r = 0.049, p = 0.83

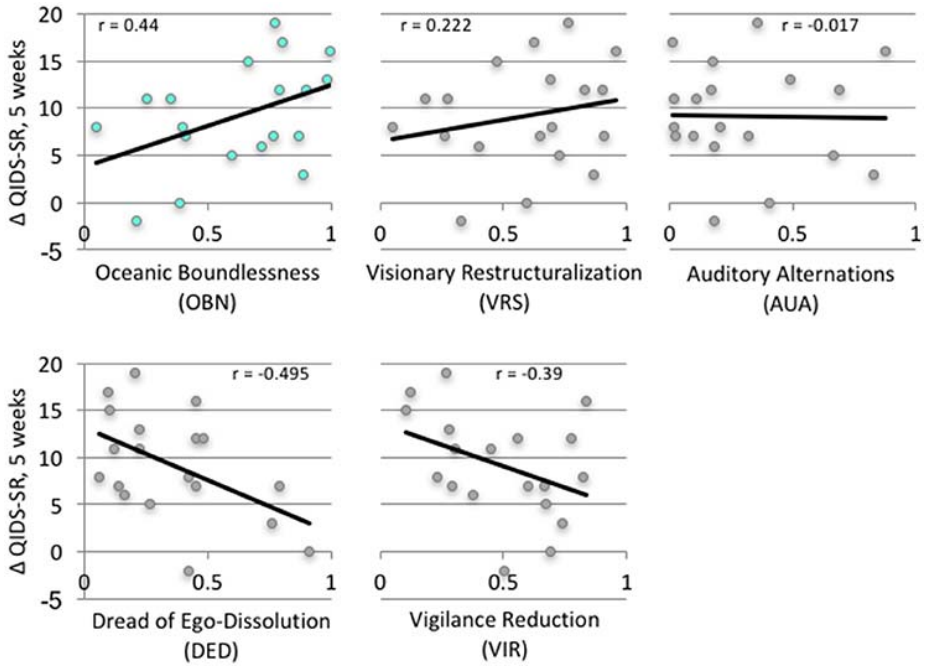
Mystical-type experiences (MEQ30 total)

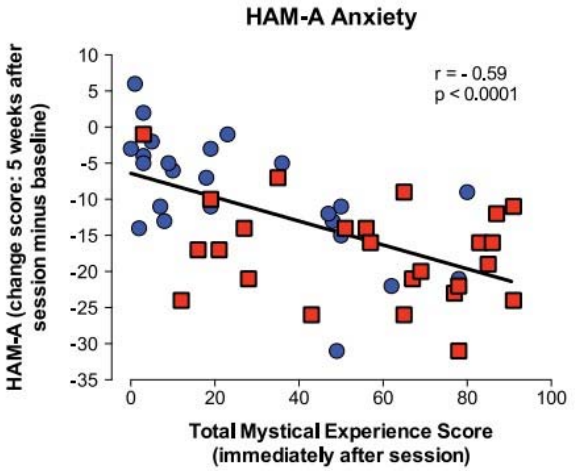


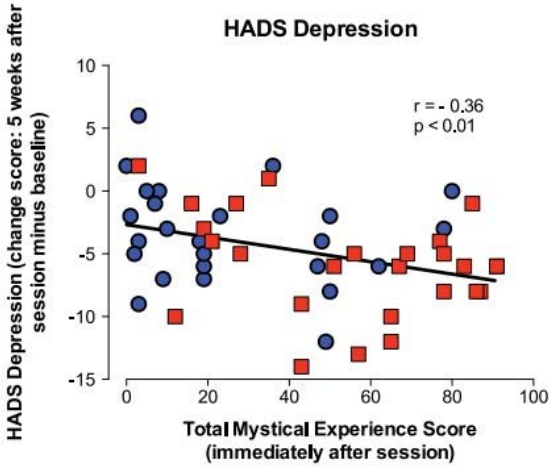
r = -0.62, p = 0.0032**

n=20

Acute Effects as Predictor for Therapeutic Outcome







Roseman et al. 2017 *Frontiers in Pharmacology*
Griffiths et al. 2016 *Journal of Psychopharmacology*

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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

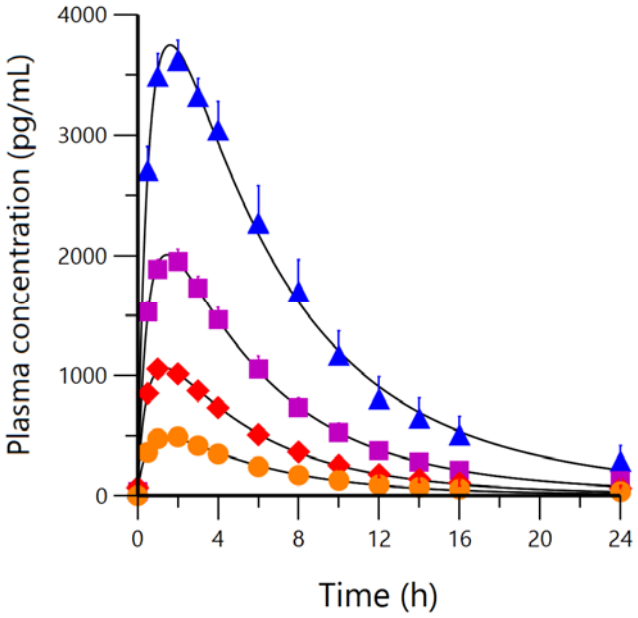
      ➡ second LSD dose reduced to 100 µg

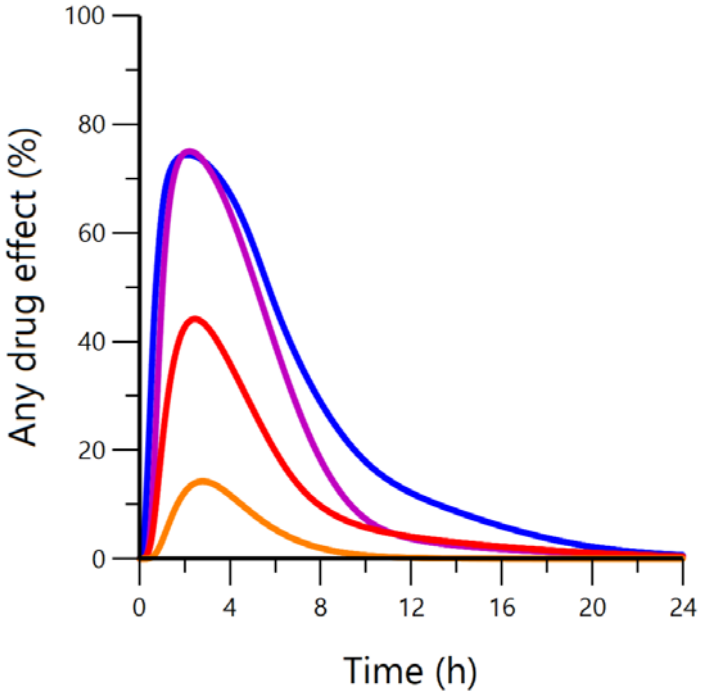
Non-treatment-related events

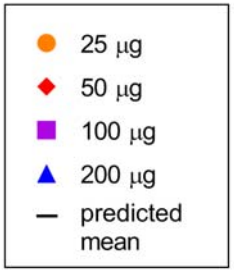
- Adverse events during entire study duration:
  - Total: 229, similar in placebo and LSD condition
  - Most frequently: headache, nausea, dizziness, difficulty concentrating, common cold, insomnia
- Serious adverse events
  - Total: 8
  - Mostly due to underlying illness (cancer patients)

n=44

«Ceiling Effect» of LSD



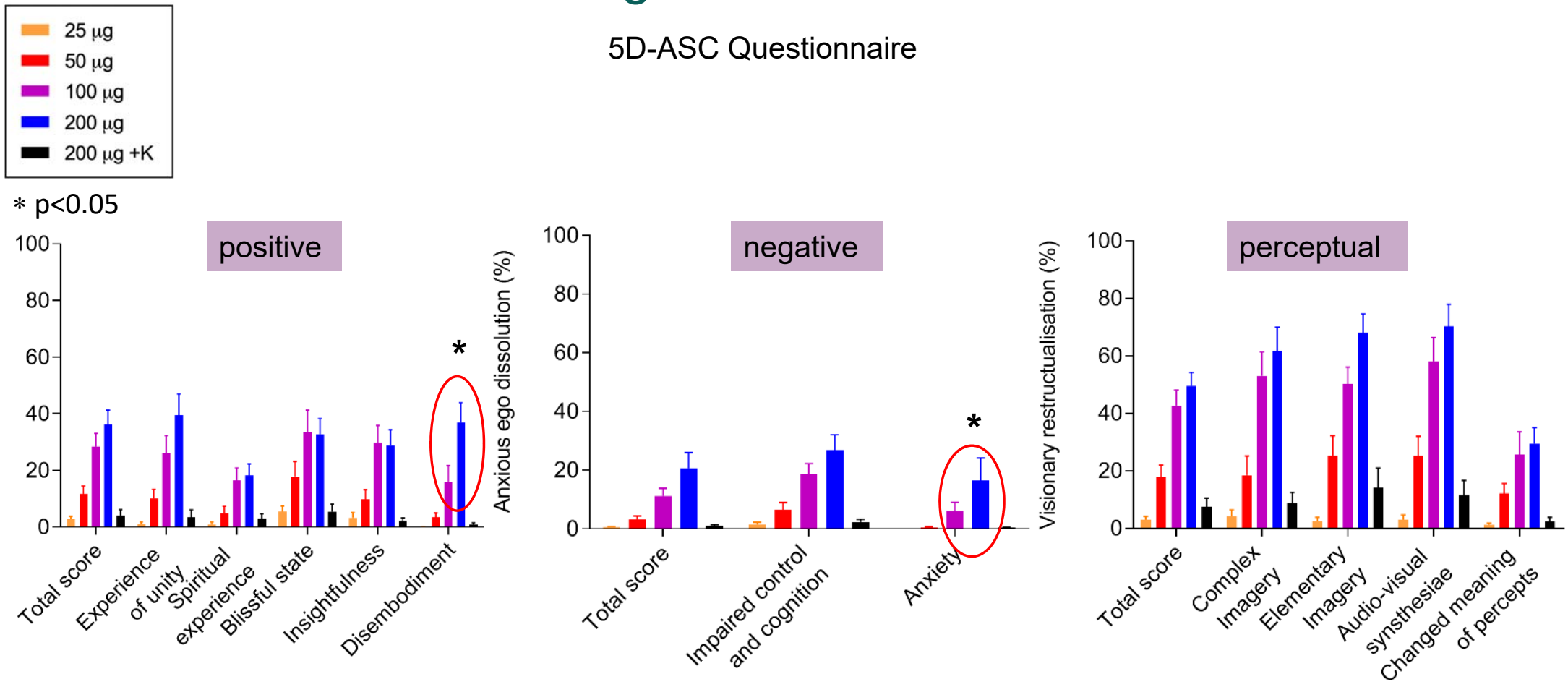




Mean ± SEM
n=16
LLOQ: 5 pg/ml

Holze et al. 2021 *Neuropsychopharmacology*

LSD-induced Changes in State of Consciousness



Holze et al. 2021 *Neuropsychopharmacology*

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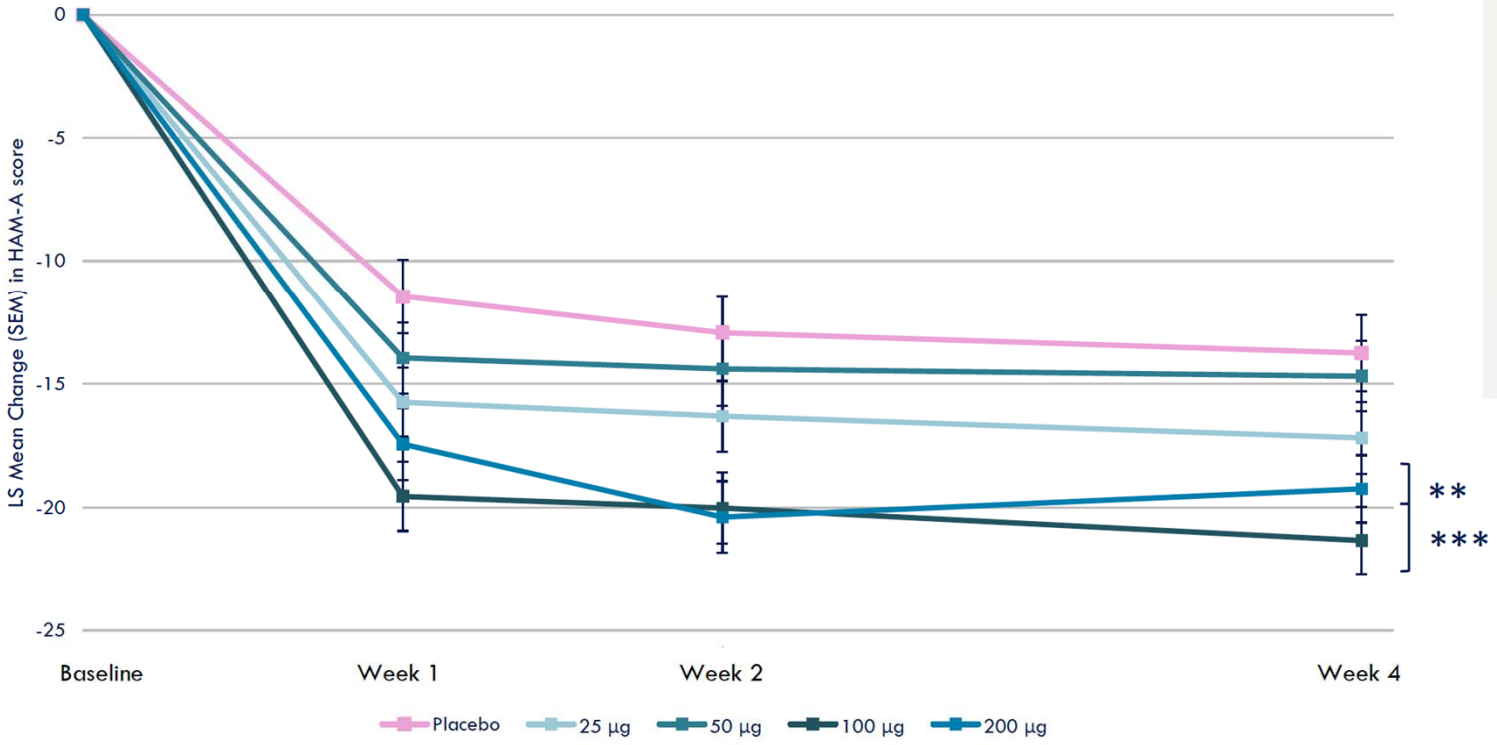
Primary Endpoint | Change in HAM-A Score through Week 4[1]

Statistically and clinically significant reductions in HAM-A score at all timepoints through week 4 in 100 and 200 µg dose groups

HAM-A Change from Baseline



Change to Week 4

- 100 µg: -21.3 points
- 200 µg: -19.3 points

Improvement over Placebo

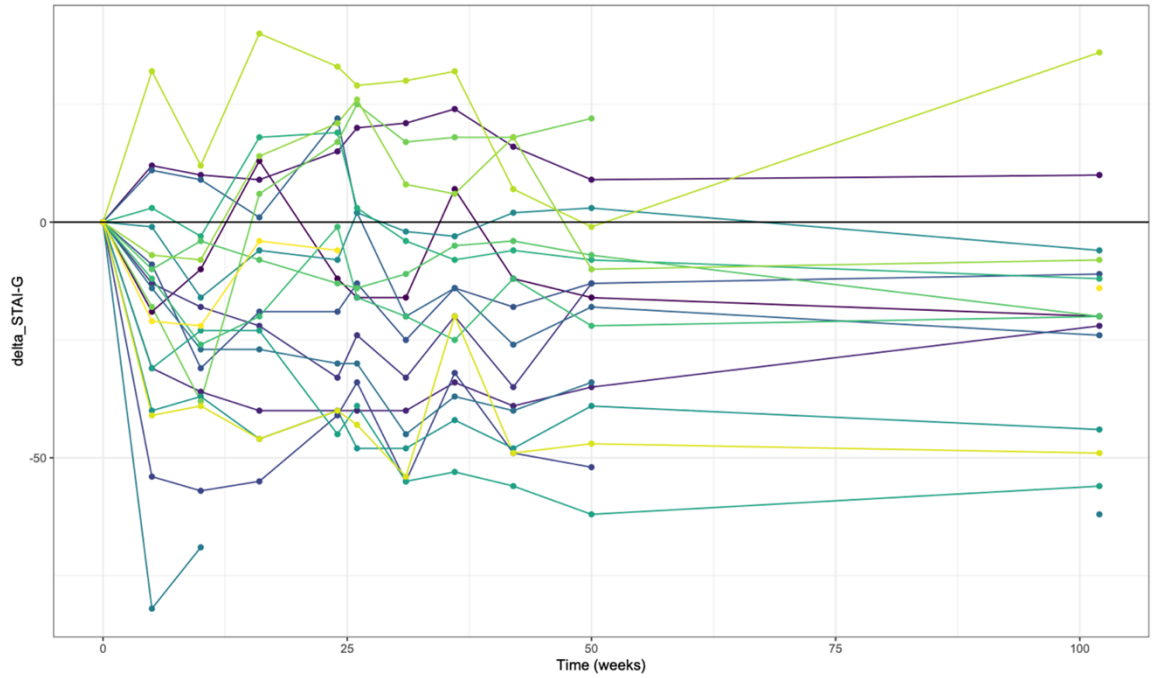
- 100 µg: -7.6 pts, p=0.0004
- 200 µg: -5.5 pts, p=0.01

**p≤0.01
***p≤0.001

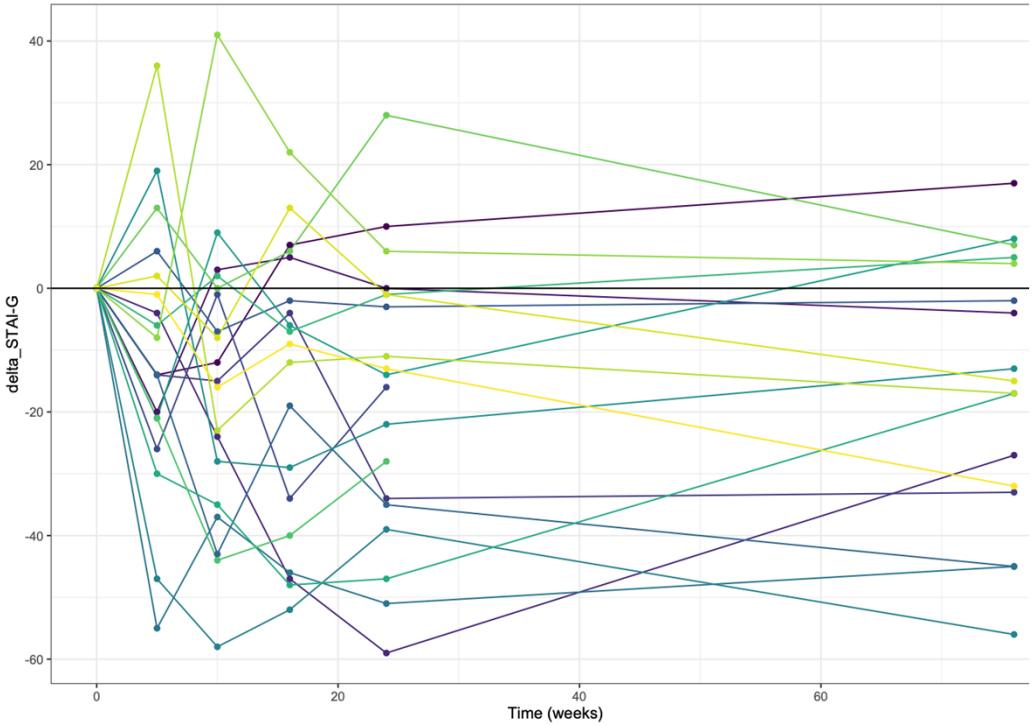
1. Source: Study MMED008 internal study documents and calculations. Full analysis set population.
µg - microgram; HAM-A - Hamilton Anxiety Rating Scale
NOTE: Significance achieved despite study not being powered for these pairwise comparisons.

Individual outcomes

LSD-first group



Placebo-first group



05

The placebo response

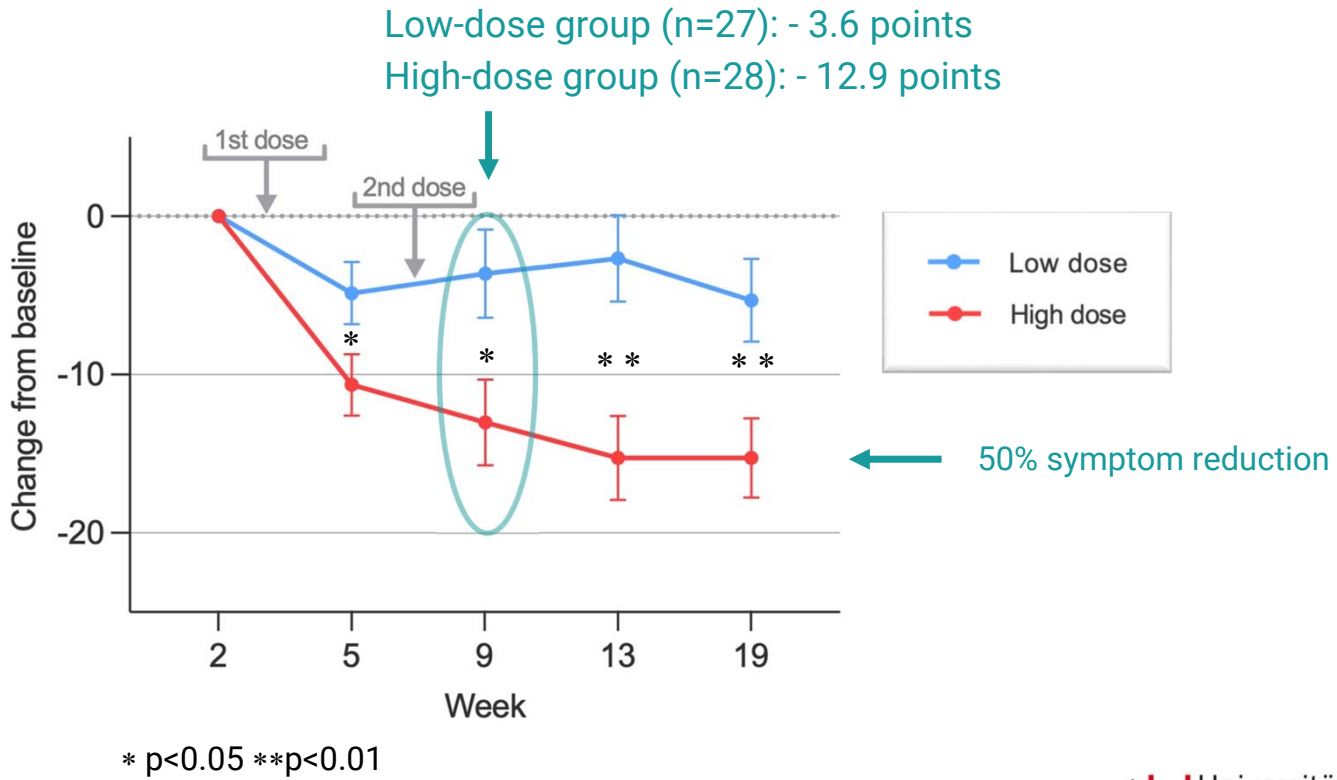
Results

Primary endpoint

IDS-C score over time. Lower score indicates less depressive symptoms

Total possible score: 84 points.
Interpretation:

0 – 11	not depressed
12 – 23	mildly depressed
24 – 36	moderately depressed
37 – 46	severely depressed
> 47	very severely depressed



∗ p<0.05 ∗∗p<0.01

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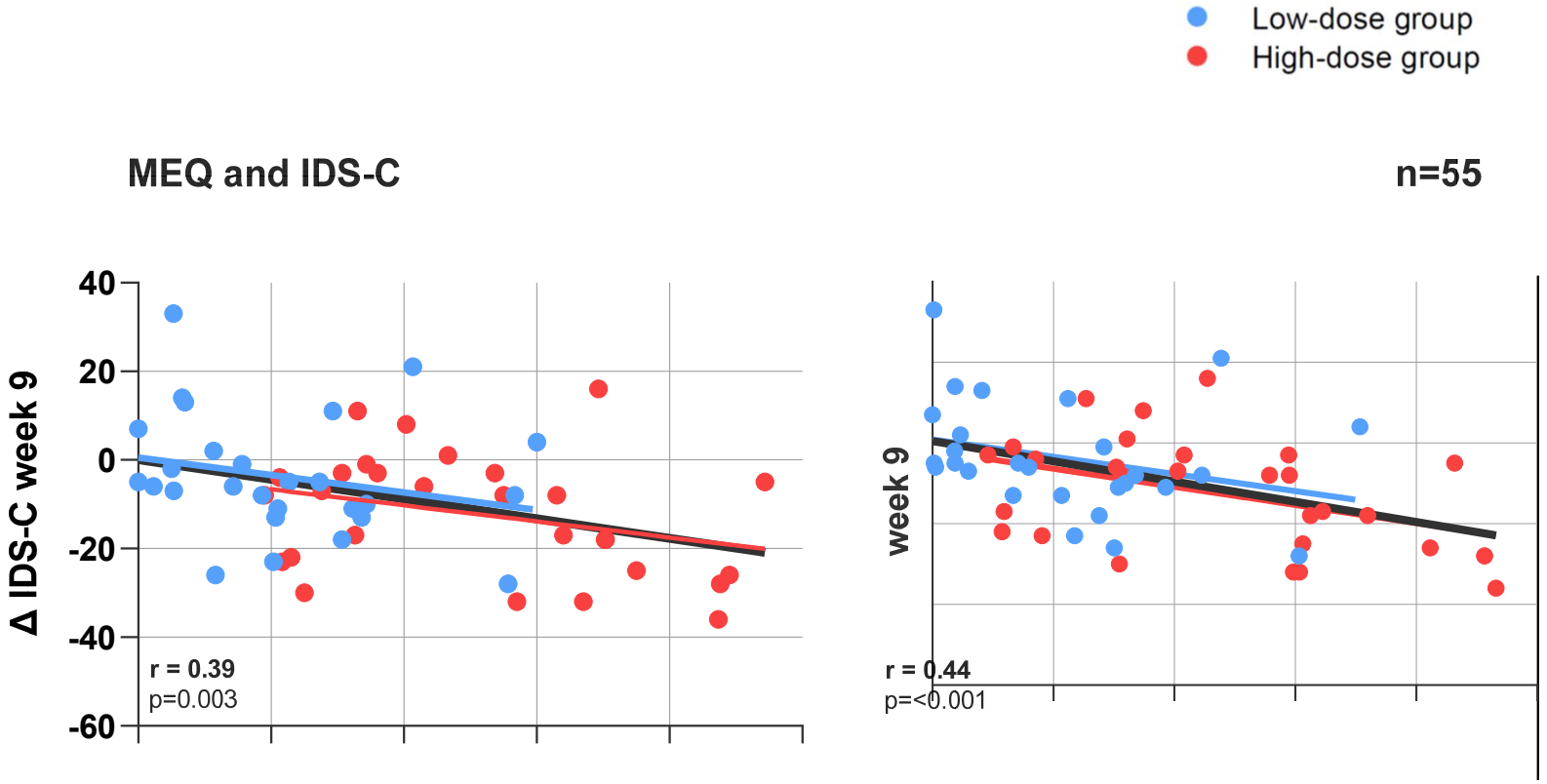
Acute effects correlate with outcome in both dose groups



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Thank you for your attention!
Questions?

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