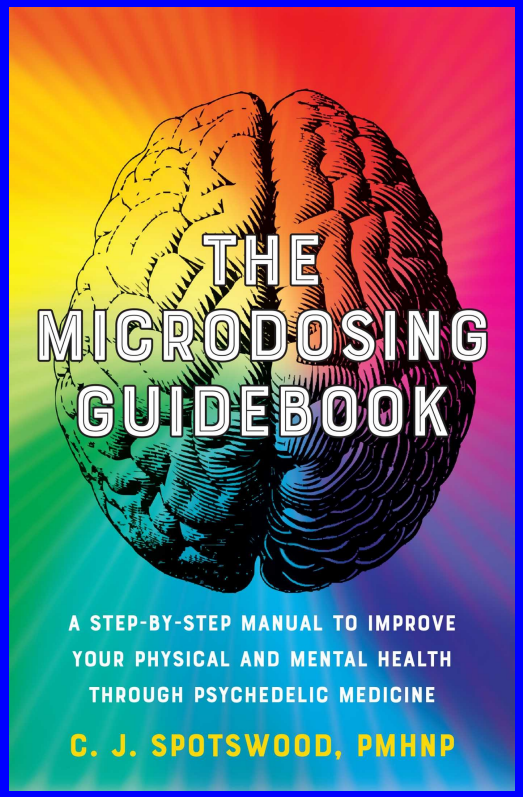
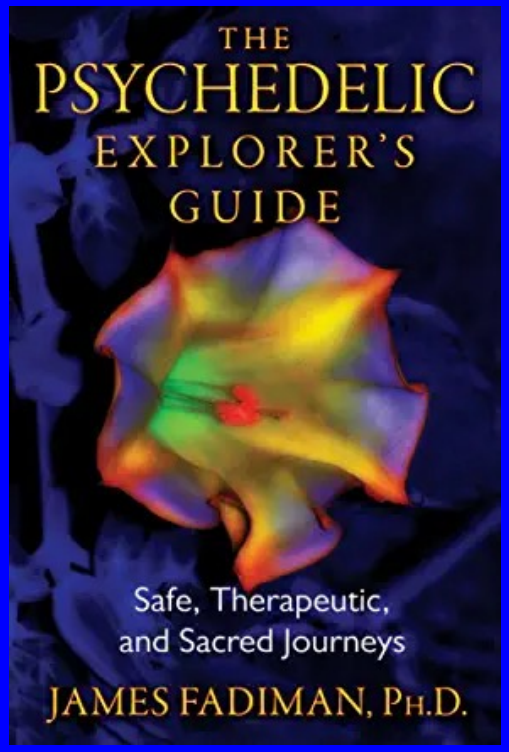
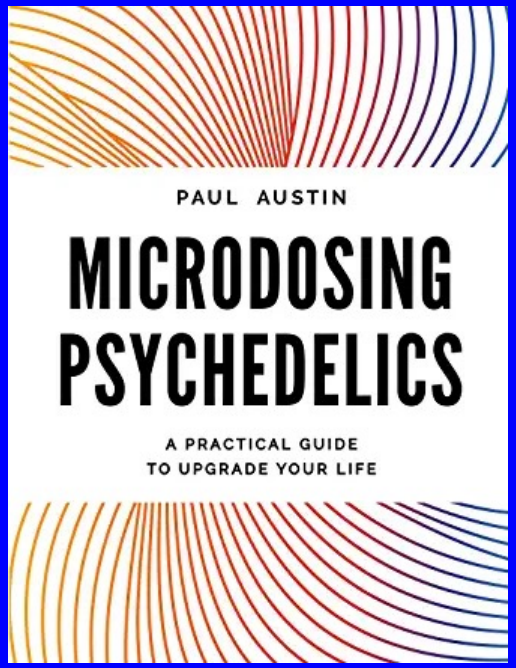
LSD Microdosing: Fact or Fiction?

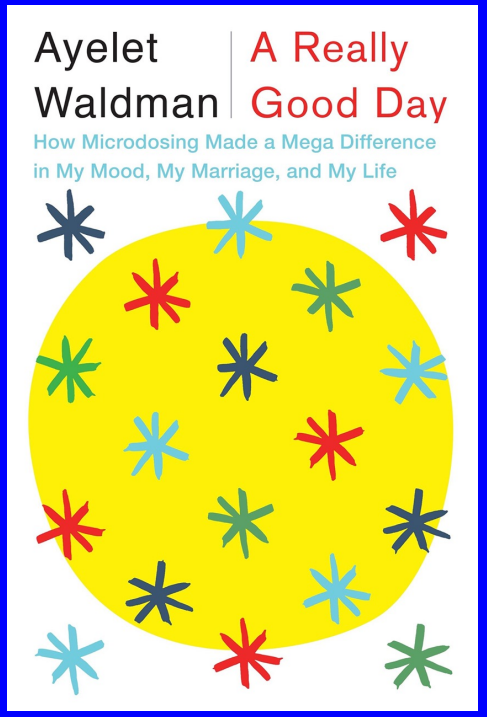
Harriet de Wit
University of Chicago

Microdosing: taking low doses of LSD every 3-4 days to improve mood, cognition, creativity



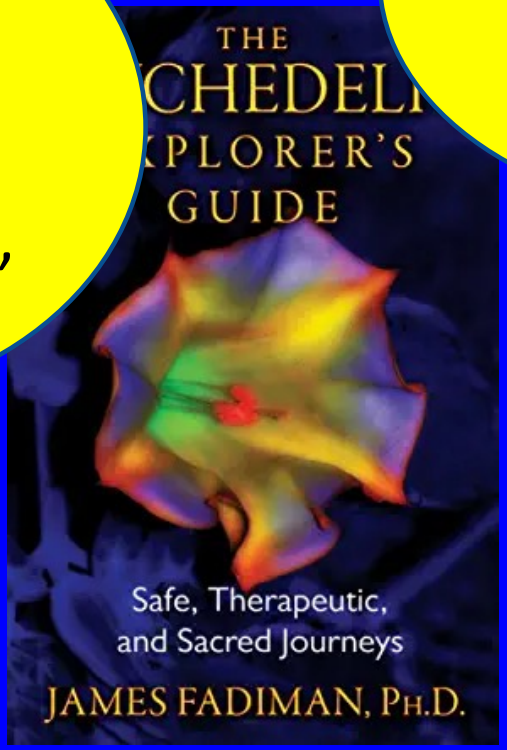




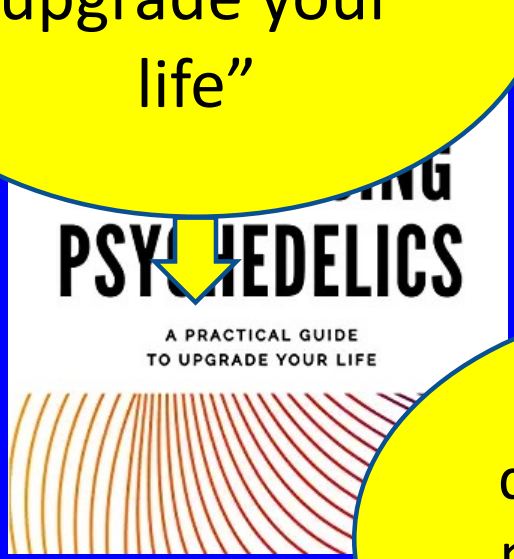


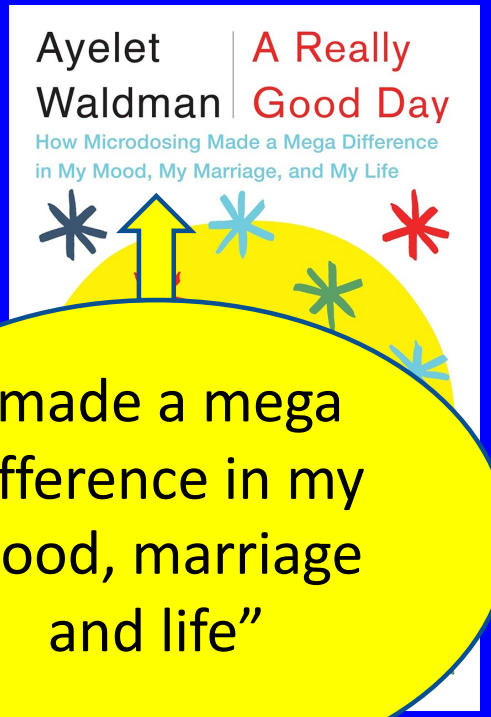
Microdosing

"A step-by-step manual to improve your physical and mental health"



"A practical guide to upgrade your life"





"made a mega difference in my mood, marriage and life"

Microdosing

- What does it do?
- How does it work?
- Few controlled studies
- Reasons for both optimism and skepticism

Reasons for optimism

- Popularity of the practice
- Plausible neural mechanisms
  - LSD acts on serotonin circuits, like anti-depressant drugs
  - Possible anti-inflammatory and neurogenic effects
- Promising clinical reports with high doses of LSD (antidepressant, anxiolytic)
- Some preclinical evidence

Reasons for skepticism

- Popular reports deeply confounded by expectancies
- Pharmacology poorly understood (e.g., optimal doses, interdose intervals, receptor adaptations, tolerance, sensitization)
- Diversity of apparent benefits….

Claimed benefits

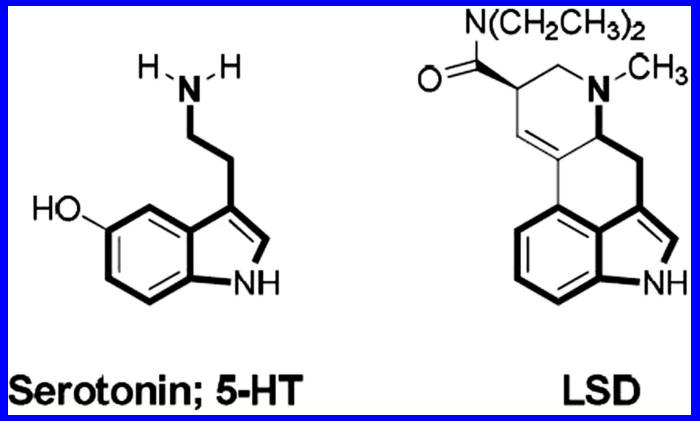
- increased creativity, energy, productivity, focus, flow states
- improved empathy and social relational skills
- heightened spiritual awareness
- enhanced senses
- elevated mood, decreased depression and anxiety
- adoption of better health habits
- better quality of life
- reduced menopausal symptoms
- athletic coordination
- leadership development
- wisdom, open-mindedness

Many Unknowns

- Behavioral effects?
- Acute or chronic? Optimal dose, dose regimen?
- Mechanisms: Metabolites, receptors, circuits, genetics
- Who benefits: age, sex, psychiatric symptoms, prior drug use?
- Expectancies?

LSD Mechanisms of Action

- Serotonin 2A receptor agonist (effects blocked by 2A antagonist ketanserin)
- Also acts at numerous other serotonin, adrenergic and dopamine receptors
- Receptor actions of chronic, low doses?



Questions about repeated doses

Is there accumulation of drug? *Half life 5 h, but drug may be trapped in receptor for 12-18 hours; Wacker et al, Cell, 2017*

Is there tolerance, specific to some effects?

Sensitization?

Are there receptor adaptations after chronic administration?

Studies with animals

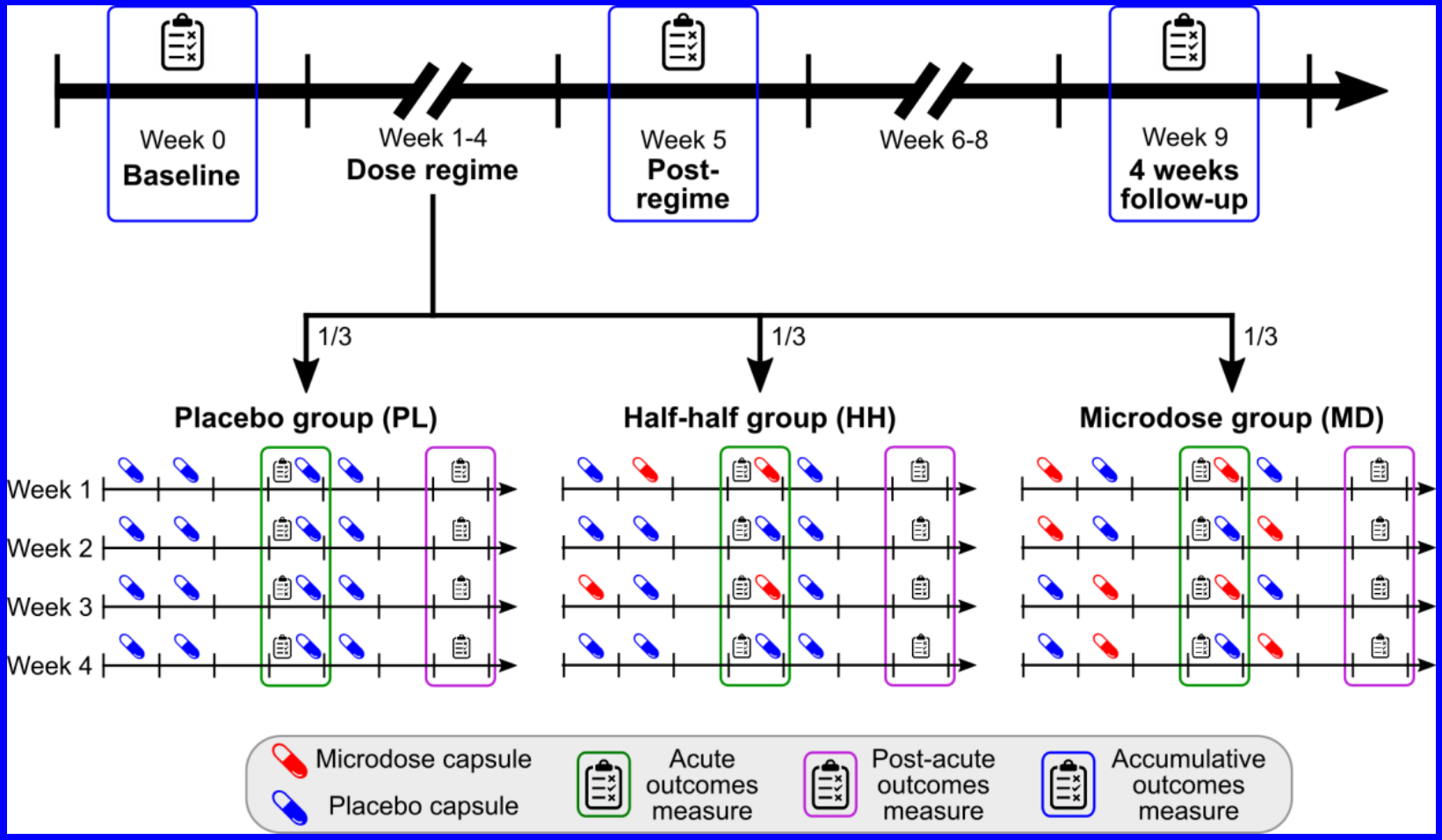
- In an animal model of depression (olfactory bulbectomy), repeated LSD normalized active avoidance learning and reversed anomalies of monoamine receptor signaling in hippocampus (*Buchborn et al, 2014)*

- LSD increased indicators of neuronal growth, including structure and function (neuritogenesis, spinogenesis and synaptogenesis) *(Ly et al, 2018)*

Human studies

- Survey self-report studies
- Repeated doses in older adults *(Yanakieva et al 2019)*
- ”Citizen science” study *(Szigeti et al 2021)*
- Single dose studies (behavioral, EEG, fMRI)
- Double blind repeated dose study

Self-blinding ‘citizen science’ *Szigeti et al 2021*



N=159
Experienced users

Results of Szigeti study

Psychological outcomes (eg mindfulness, well-being, life satisfaction) improved in both ***drug and placebo groups***

Acutely, LSD increased emotional state, drug intensity, mood, energy, creativity, compared to placebo

When data were examined without participants who correctly identified the drug, the beneficial effects disappeared

Benefits attributable to ‘broken blind’?

Our laboratory studies

Study 1: Behavioral dose selection *(0, 6.5, 13, 26 µg)*

Study 2: fMRI functional connectivity *(13 µg)*

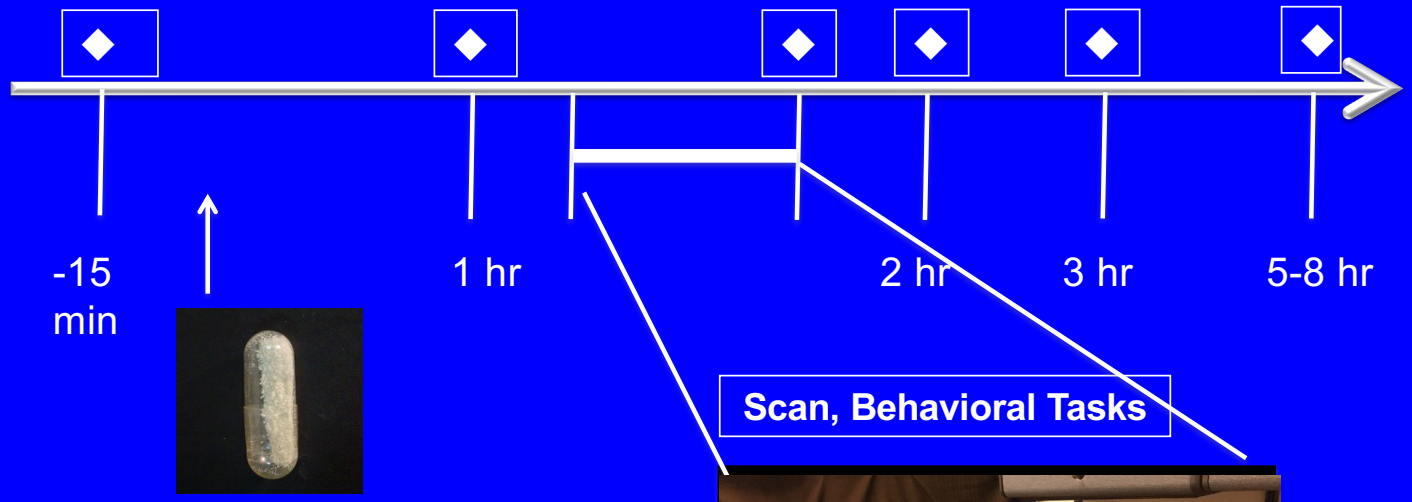
Study 3: EEG *(13 and 26 µg)*

Study 4: Repeated doses *(0, 13, 26 µg)*

Methods

- Double blind, placebo controlled
- LSD doses (6.5,13, 26 µg)
- Healthy men and women aged 18-35
  - No psychiatric diagnoses or substance dependence
  - Minimum high school, BMI 18-26
  - At least one use of a psychedelic drug or MDMA
- Sessions conducted in comfortable living-room like environment

Session Timeline



Scan, Behavioral Tasks

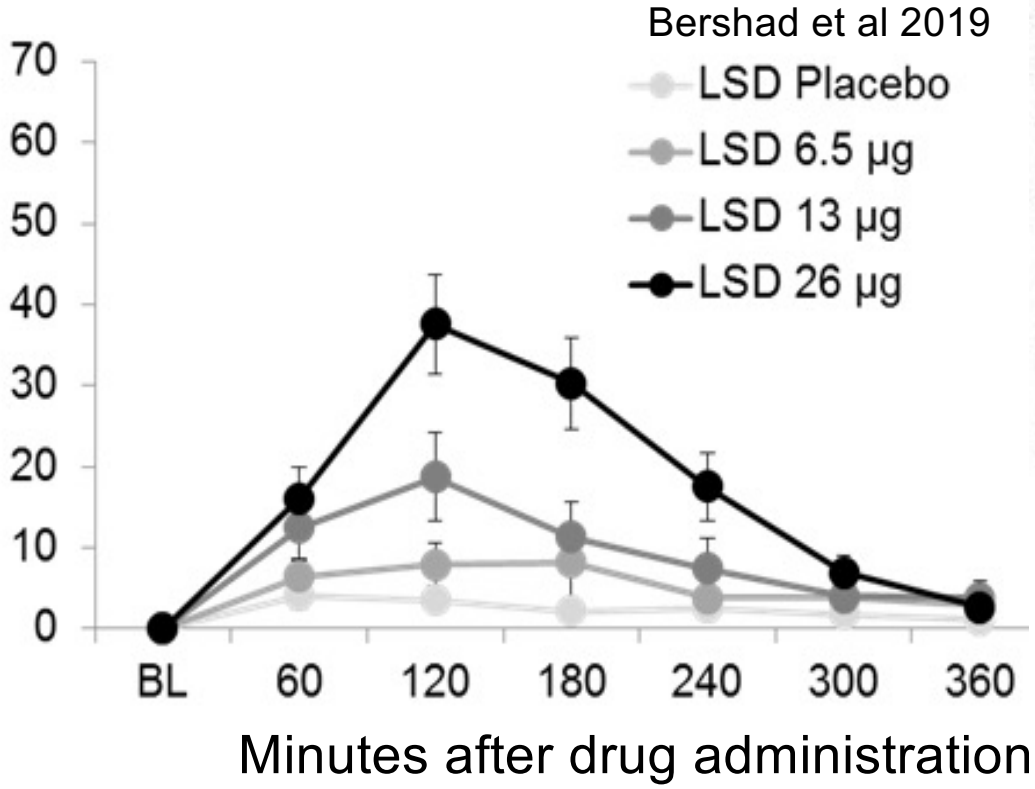
◆= Blood pressure, heart rate, subjective measurements taken

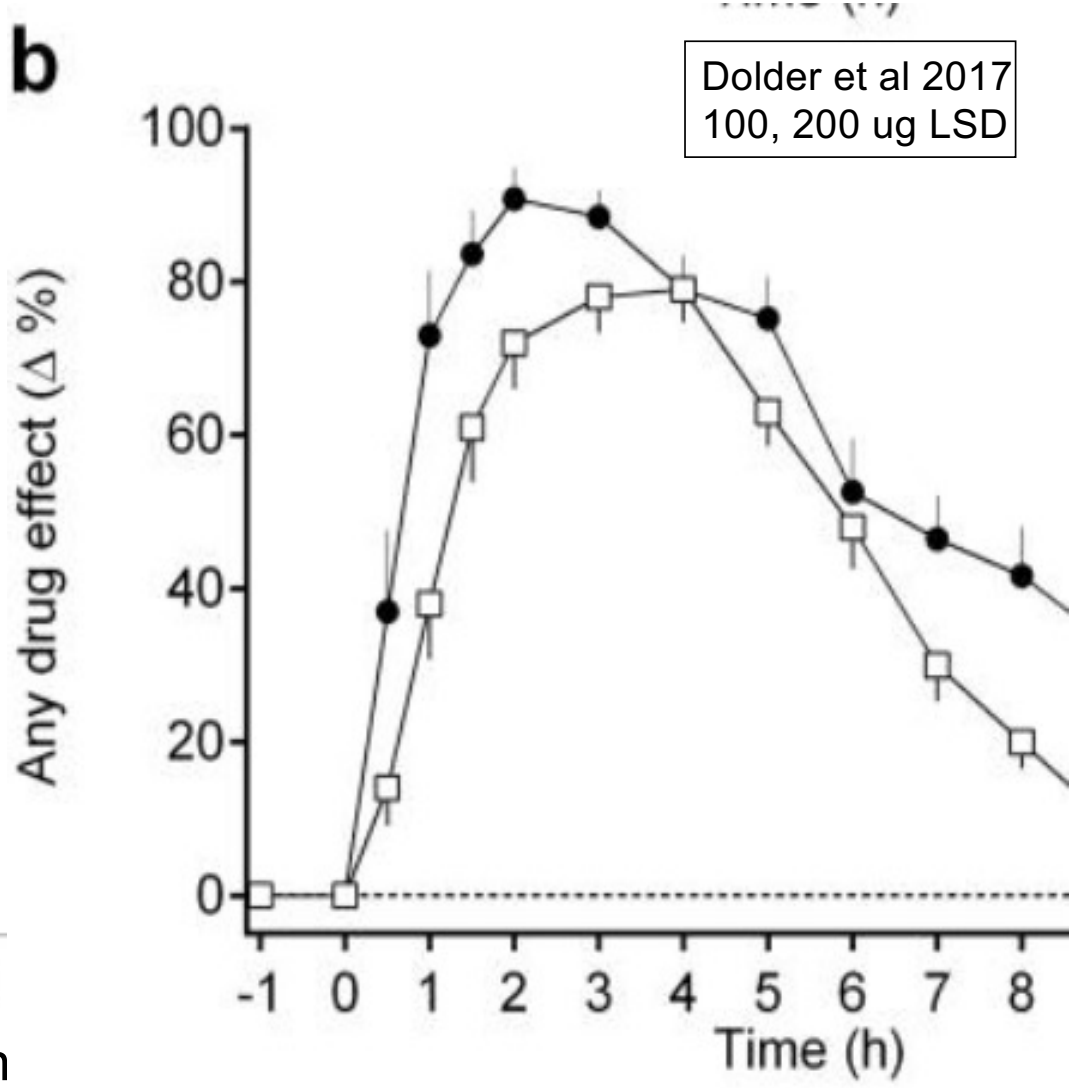
Study 1: Behavioral dose determination

- 20 men and women
- Four 8-hr sessions, 1-week intervals
  - 0, 6.5, 13 and 26 µg
  - Double blind, randomized order
- Subjective ratings, behavioral and cardiovascular measures

Bershad et al, 2019

Ratings of ‘feel drug’ after LSD





Challenge #1: how to measure psychedelic subjective effects?

- Standardized drug questionnaires not designed for psychedelic drugs
  - sensory, perceptual effects, feelings of religiosity, changes in state
- 5-Dimensional Altered States of Consciousness

Unity:

I felt one with my surroundings.

I experienced a touch of eternity.

Spiritual:

I felt connected to a higher power.

I experienced a kind of awe.

Blissful:

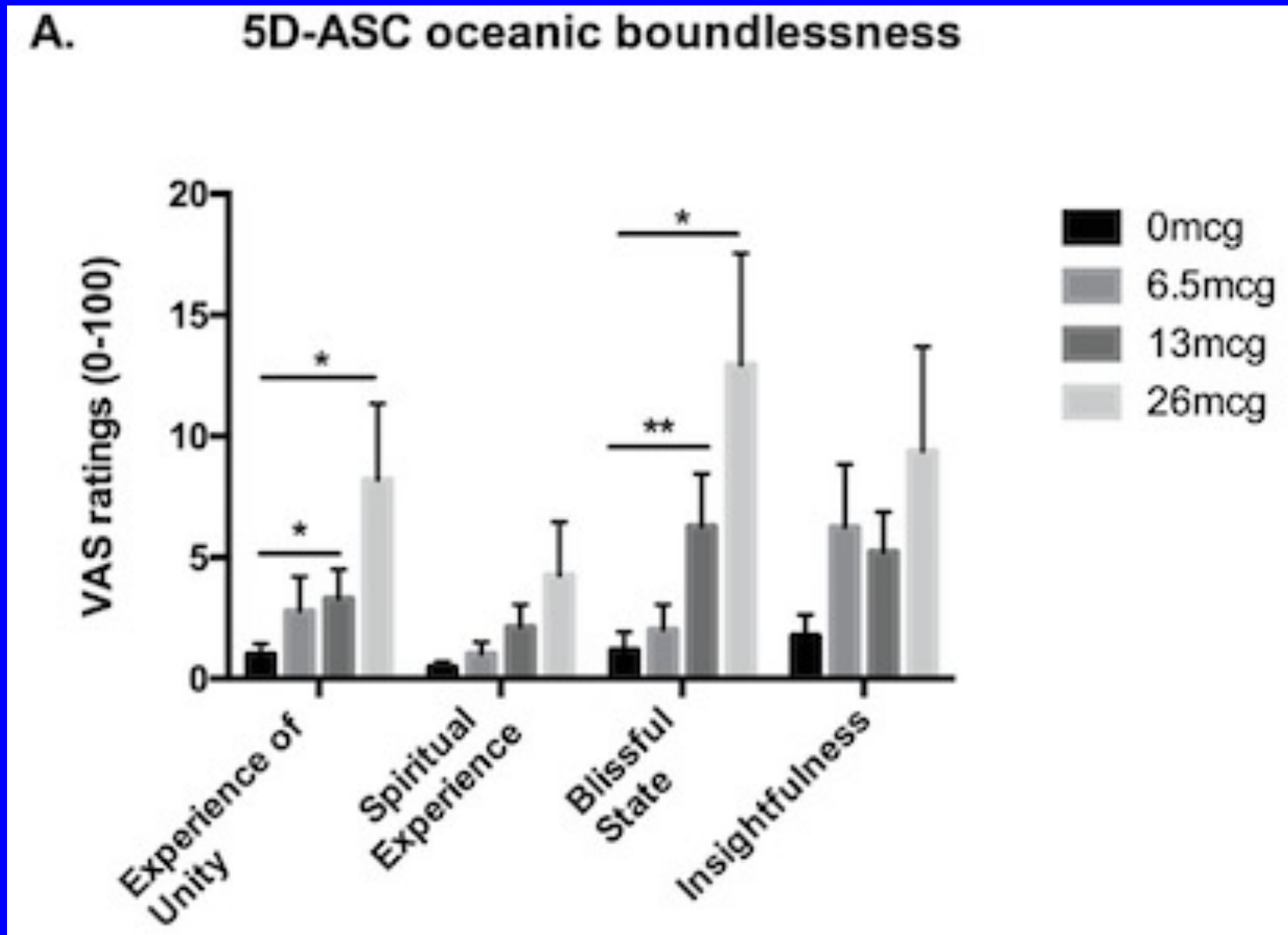
I experienced boundless pleasure; profound inner peace; an all-embracing love.

Insightful:

I felt very profound.

I had insights into connections that previously puzzled me.

I had very original thoughts.



Bershad et al, 2019

Challenge #2: With only minimal subjective effects, how do we know if microdoses produce any effects?

- Can microdoses that are too low to produce acute effects be effective if given repeatedly?

- Can we find any subtle behavioral or neural acute effects that predict benefits after repeated dosing?

Study 2: Effect of LSD on functional connectivity fMRI

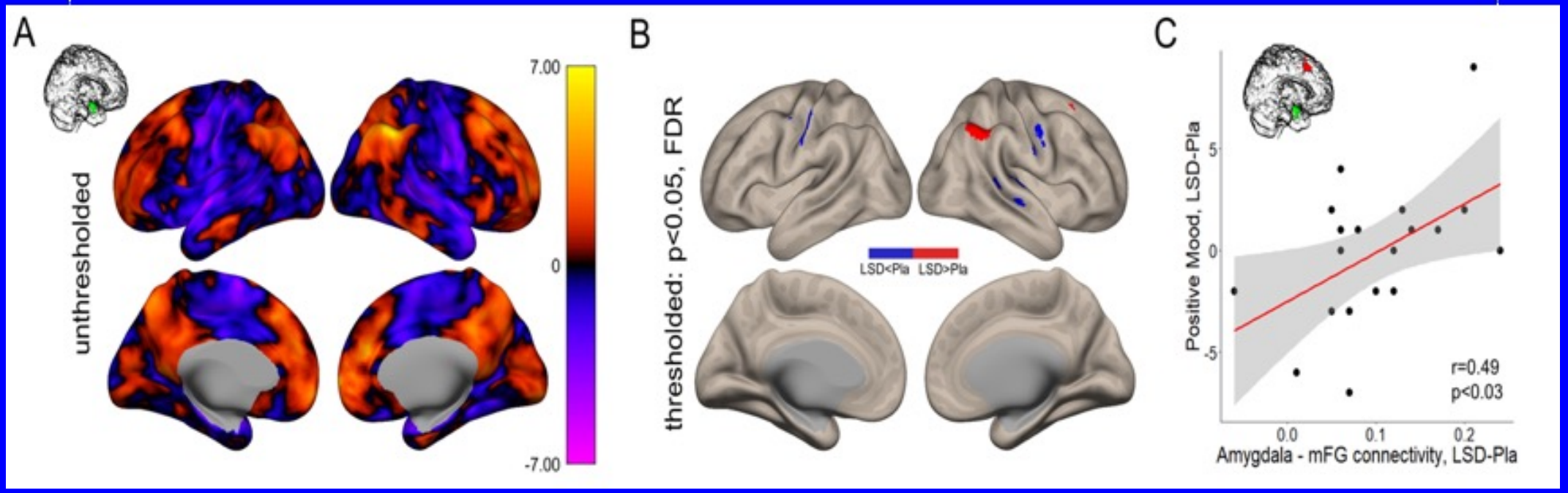
- 20 men and women
- Two 5-hr sessions at 1-week intervals
  - 0 and 13 µg LSD
  - Double blind, mixed order
- Subjective ratings, BOLD resting state functional connectivity, ASL

Bershad, Preller et al, 2019

Results

- Negligible subjective effects

- *Increased* resting state connectivity between amygdala and right angular gyrus, right middle frontal gyrus and cerebellum
- *Decreased* connectivity with amygdala and left and right postcentral gyrus and superior temporal gyrus



Red/orange: LSD increased amygdala based connectivity
Blue/pink: reduced Amygdala based connectivity

Corrected for multiple comparisons

Correlation between positive mood and connectivity

Study 2 conclusion

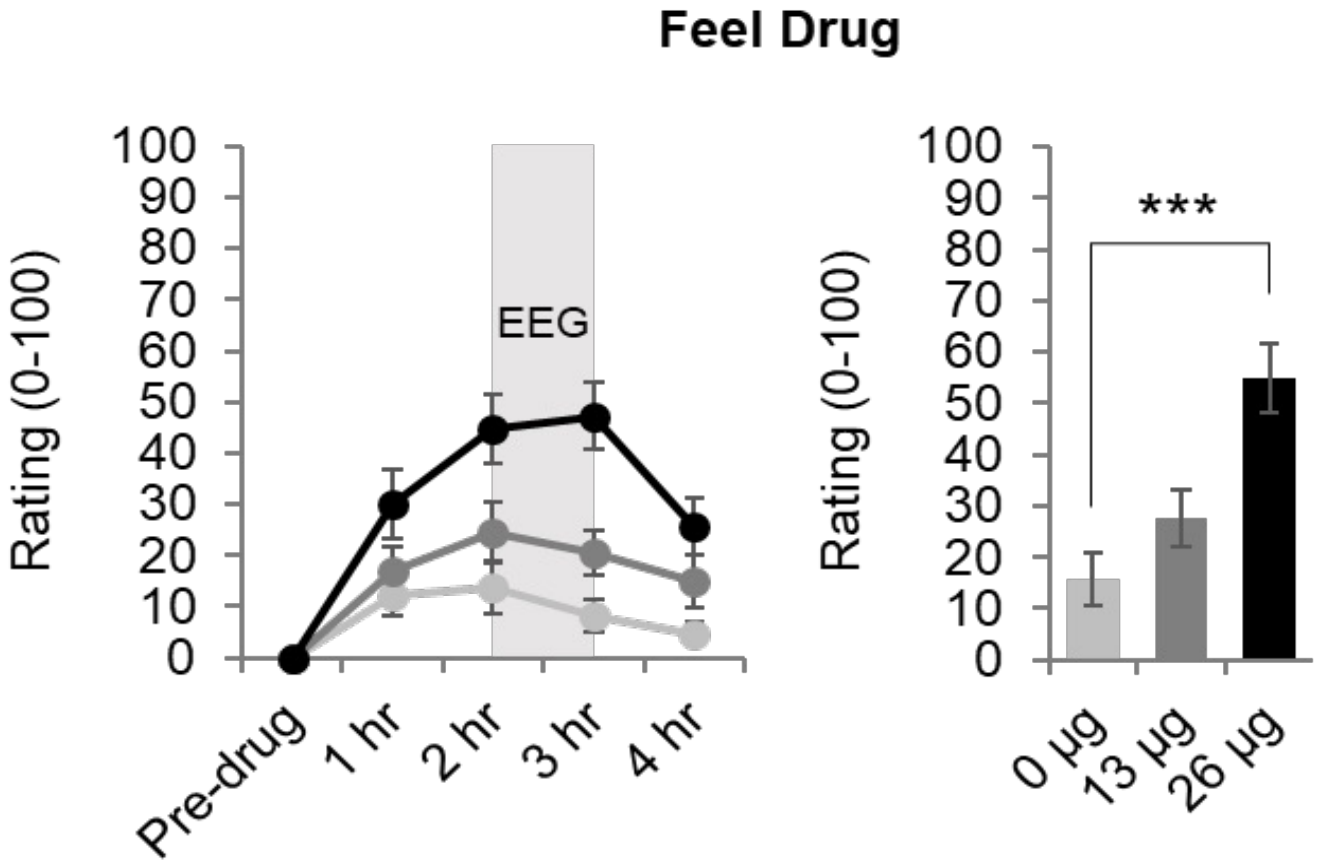
- LSD altered resting state connectivity *without* producing significant subjective effects

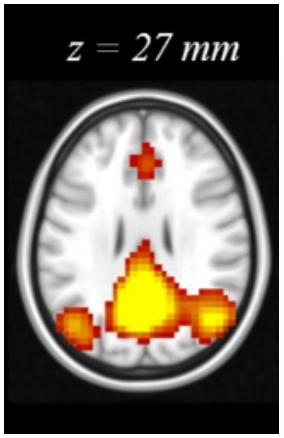
- Connectivity consistent with effects seen at higher doses *(reduced amygdala modulation, dampened amygdala response to negative emotions, decreased amygdala connectivity)*

Study 3: Effects on EEG

- 22 healthy adults
- Three 5-hour sessions (0, 13 and 26 µg)
- 128 lead EEG
- Two measures
  - –Resting state: delta, theta, alpha, beta, gamma
  - –P300 response to novelty
  - –P3 response to reward in eMID

Study 3 EEG


Feel Drug
Rating (0-100)
100
90
80
70
60
50
40
30
20
10
0
EEG
Pre-drug
1 hr
2 hr
3 hr
4 hr
***
0 µg
13 µg
26 µg



128 electrodes

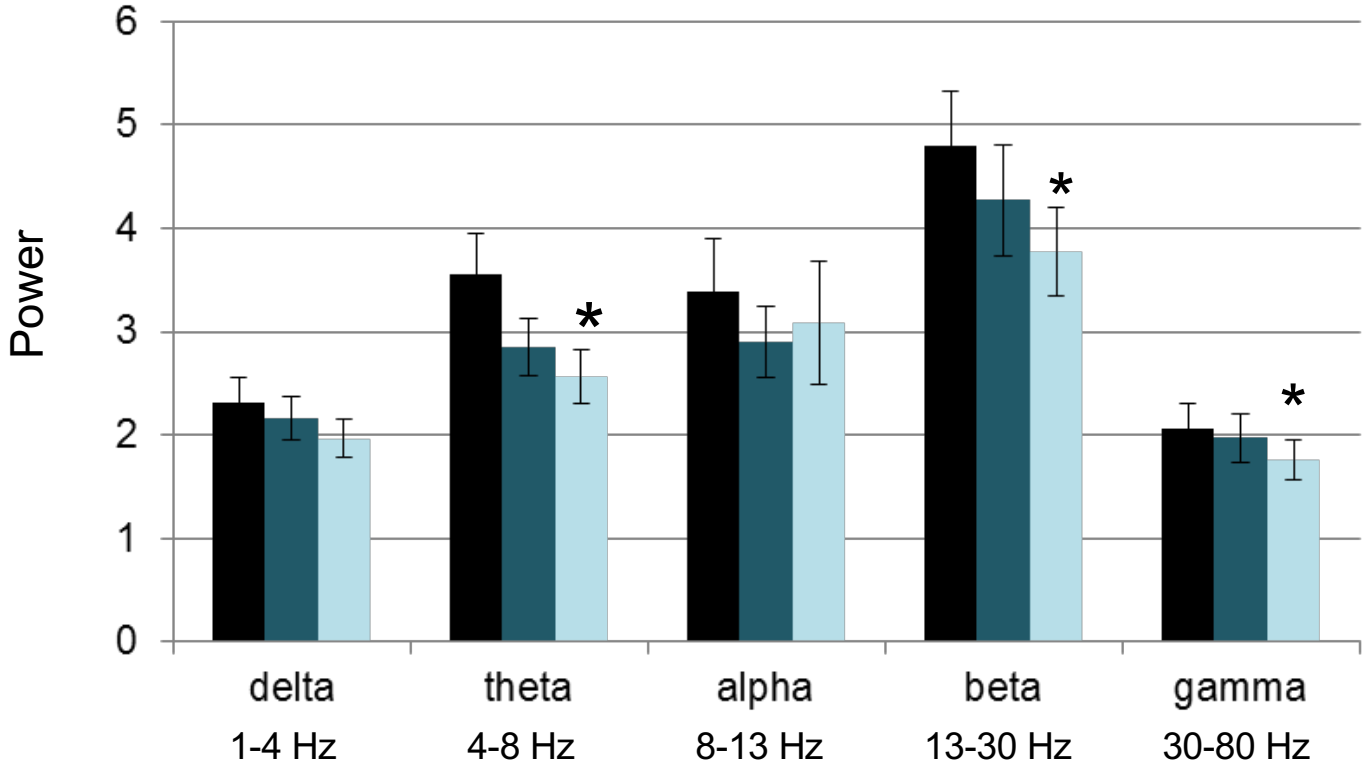
mPFC ROI

Left temporoparietal ROI

Right temporoparietal ROI

PCC ROI

Resting state: LSD Dose-dependently decreased power in default mode network

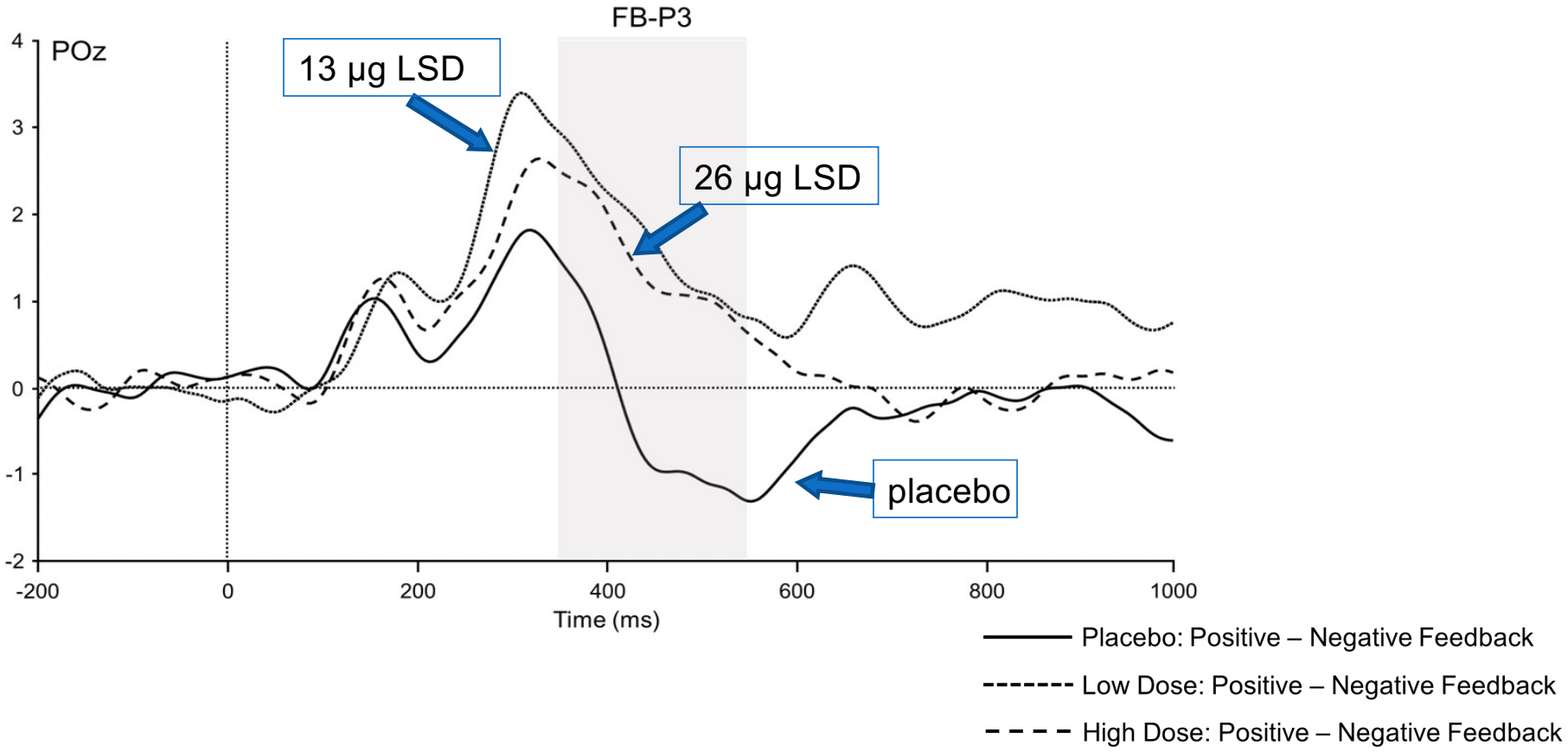


Main effect of dose
($p = 0.001$) ANOVA

0 µg
13 µg
26 µg

LSD increased P3 after reward feedback during eMID task.

(Positive minus negative feedback trials; *in prep)*



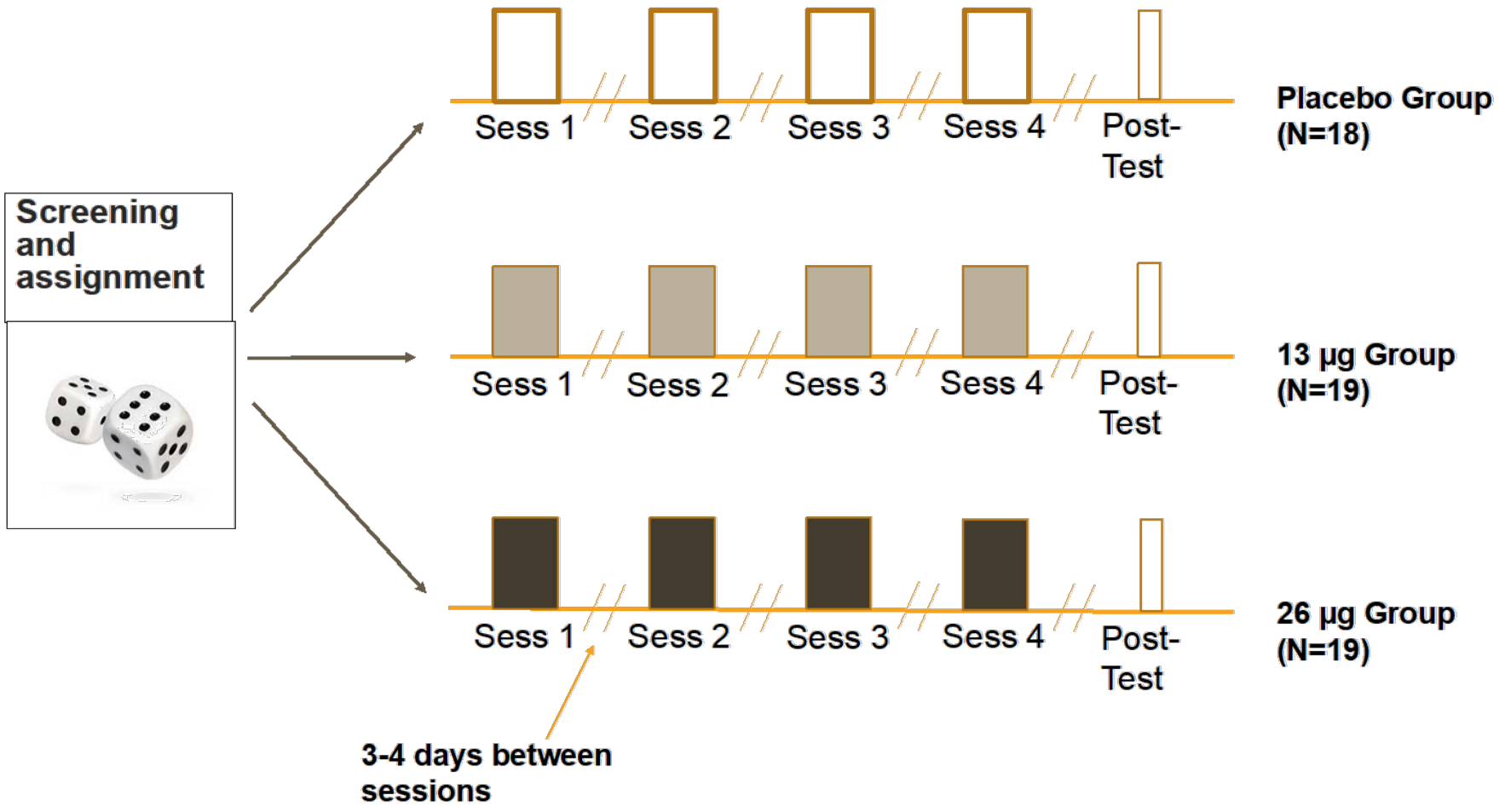
Conclusions from fMRI and EEG studies

- Very low doses of LSD produced some neural changes, even at doses that produced negligible subjective effects
  - Reduced amygdala activity, decreased power in default mode network, increased P300 response to reward feedback
- Future question: Do these neural effects seen with acute doses change with repeated doses?

Study 4: Repeated microdose study

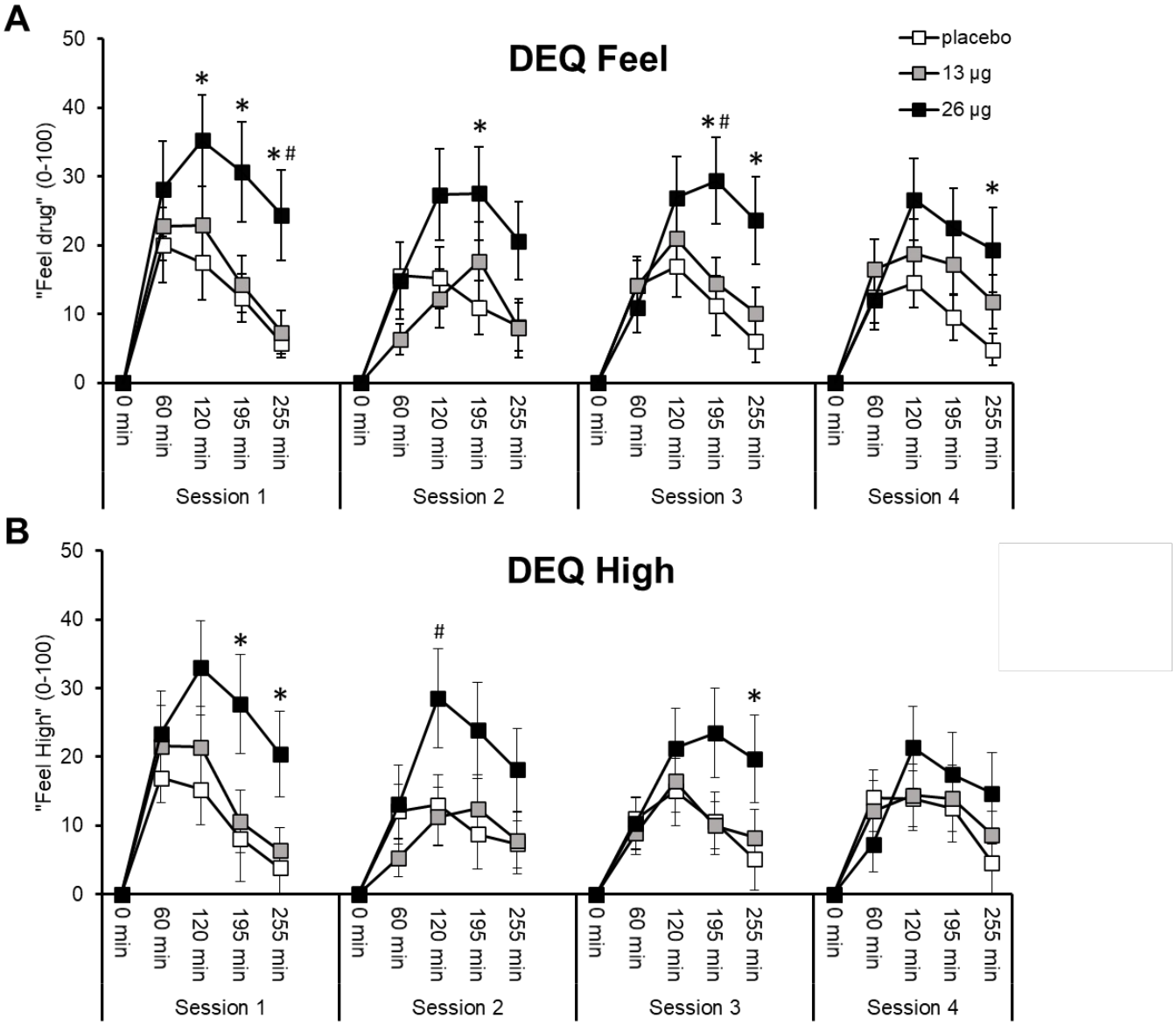
(de Wit et al, 2022)

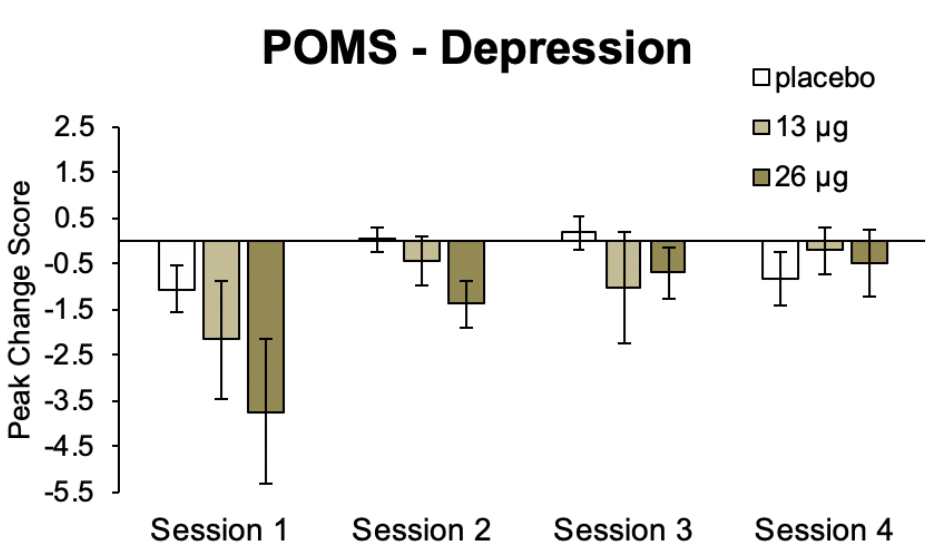
- Participants: young adults who reported some negative mood
- Four laboratory sessions, every 3-4 days for two weeks
- Three groups:
  - Placebo (N=18)
  - LSD 13 microgram (N=19)
  - LSD 26 microgram (N=19)
- Outcome measures: mood, cognition, emotional reactivity

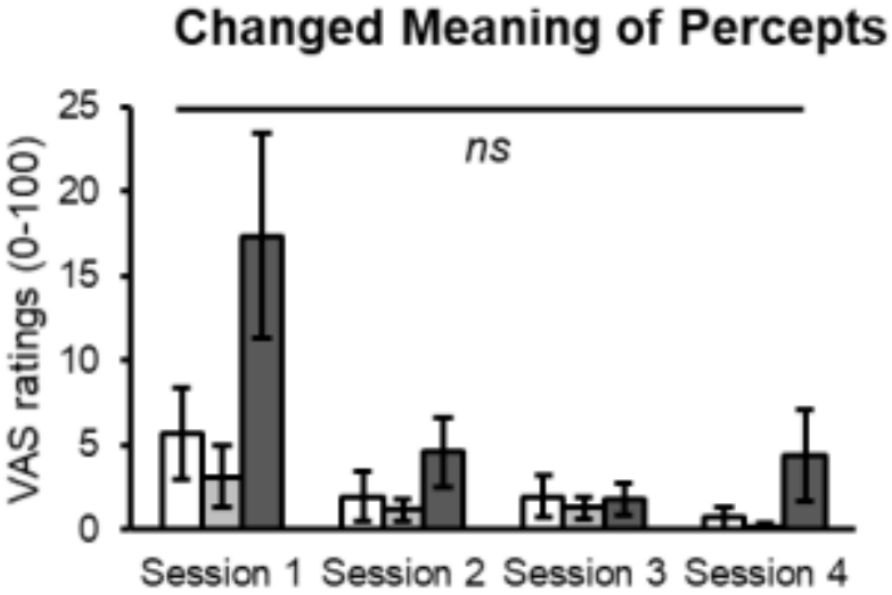

Screening and assignment
Sess 1
Sess 2
Sess 3
Sess 4
Post-Test
Placebo Group (N=18)
13 µg Group (N=19)
26 µg Group (N=19)
3-4 days between sessions

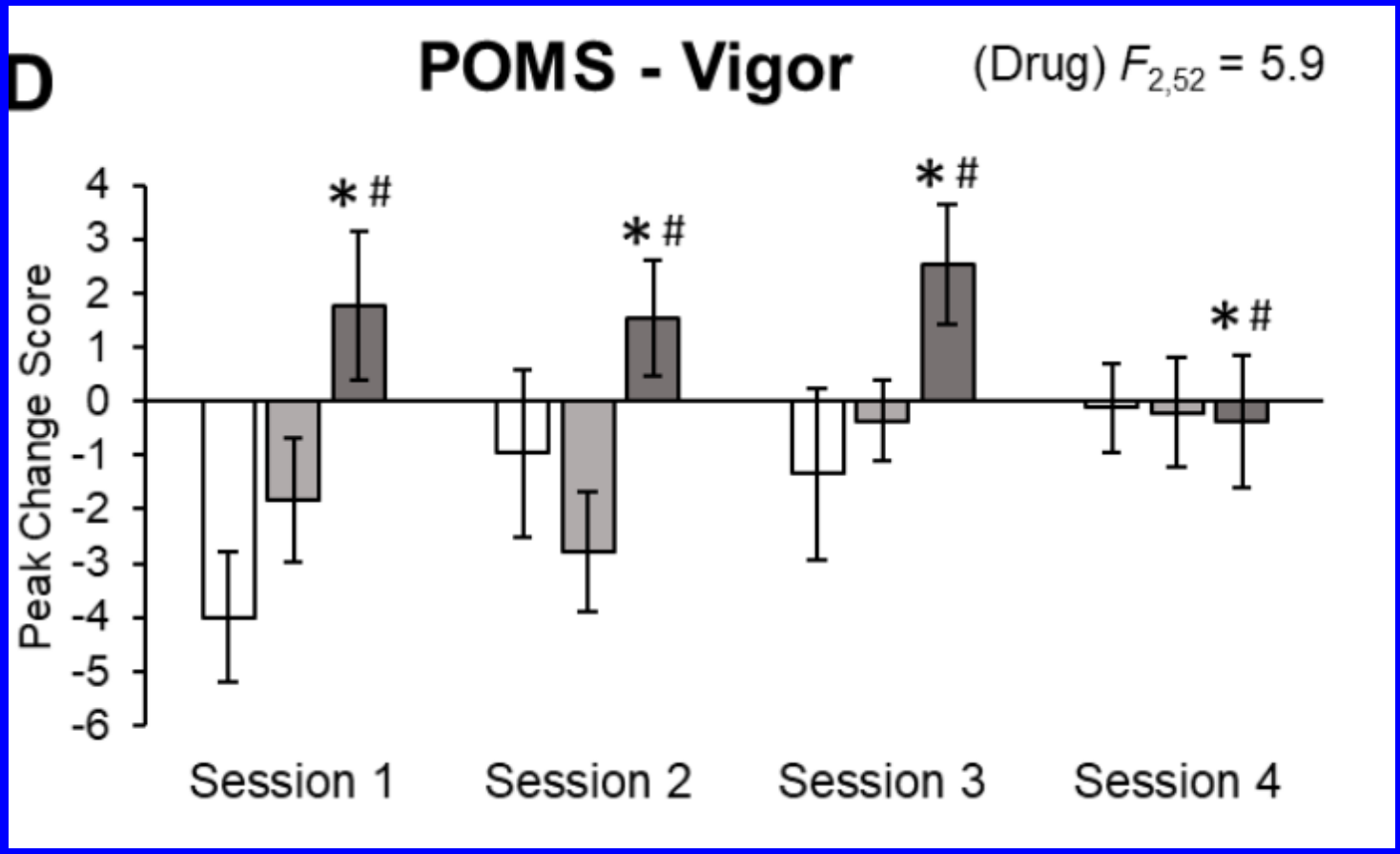
Dependent measures

- Subjective measures: mood states (PANAS, POMS, DASS), drug effects (ARCI, 5D ASC, drug identification)
- Cognitive measures: Digit symbol substitution task, N-back
- Emotional function: social rejection (Cyberball), emotional images task, emotional faces
- Physiological: Heart rate, blood pressure

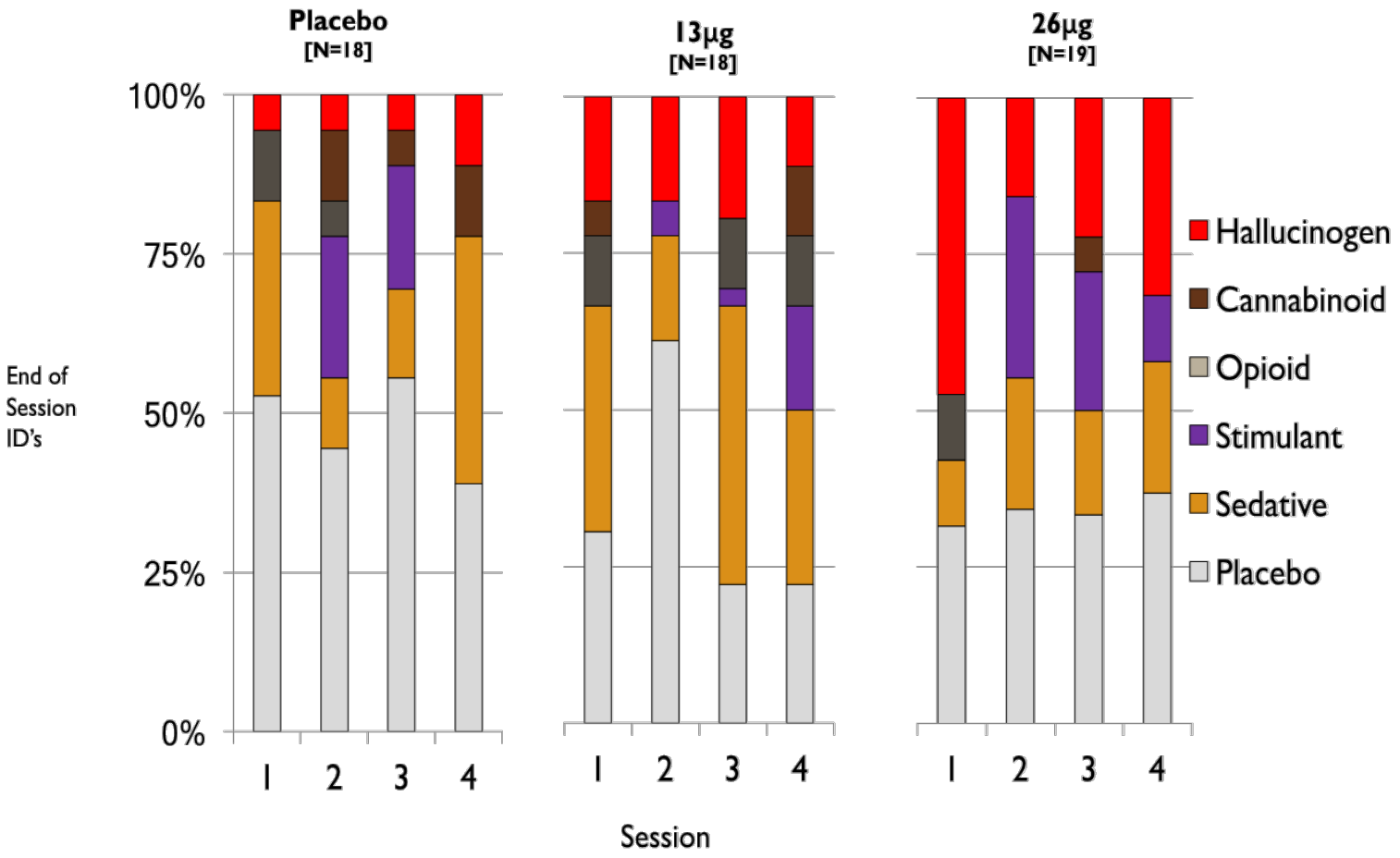

A
DEQ Feel
placebo
13 µg
26 µg
"Feel drug" (0-100)
50
40
30
20
10
0
0 min
60 min
120 min
195 min
255 min
Session 1
Session 2
Session 3
Session 4
B
DEQ High
"Feel High" (0-100)


POMS - Depression
placebo
13 µg
26 µg
Peak Change Score
2.5
1.5
0.5
-0.5
-1.5
-2.5
-3.5
-4.5
-5.5
Session 1
Session 2
Session 3
Session 4


Changed Meaning of Percepts
ns
VAS ratings (0-100)
25
20
15
10
5
0
Session 1
Session 2
Session 3
Session 4


D
POMS - Vigor
(Drug) $F_{2,52}$ = 5.9
Peak Change Score
4
3
2
1
0
-1
-2
-3
-4
-5
-6
* #
* #
* #
* #
Session 1
Session 2
Session 3
Session 4

What do you think you received?



Repeated doses of LSD did NOT affect

- Mood (PANAS; Depression, Anxiety and Stress Scale)
- Drug ‘liking’ or ’wanting more’
- Social function
  - Ratings of positive or negative emotional images
  - Identification of emotions
  - Social rejection (Cyberball)
- Cognitive tasks (N-back, DSST)
- Heart rate, blood pressure

Summary of repeated dose study

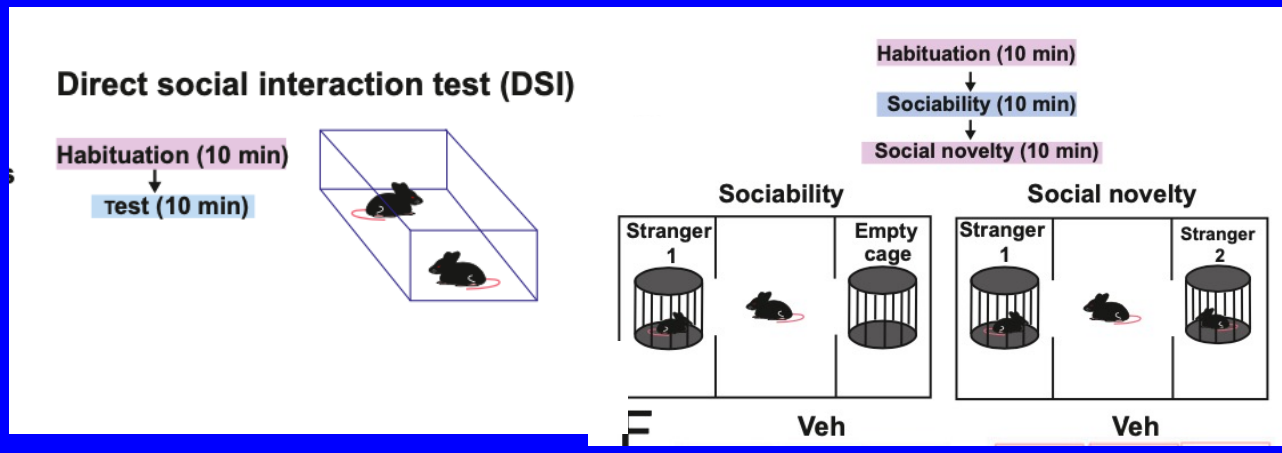
- Doses produced mild stimulant-like subjective effects
- Effects declined slightly across 4 sessions
- Few effects on measures of emotion or cognition

Many remaining questions

- Did we test for long enough?
- Did we test the right people?
- Did we use the most sensitive outcome measures?

Effects of LSD on Social Behavior in Mice

G Gobbi, McGill University PNAS 2020

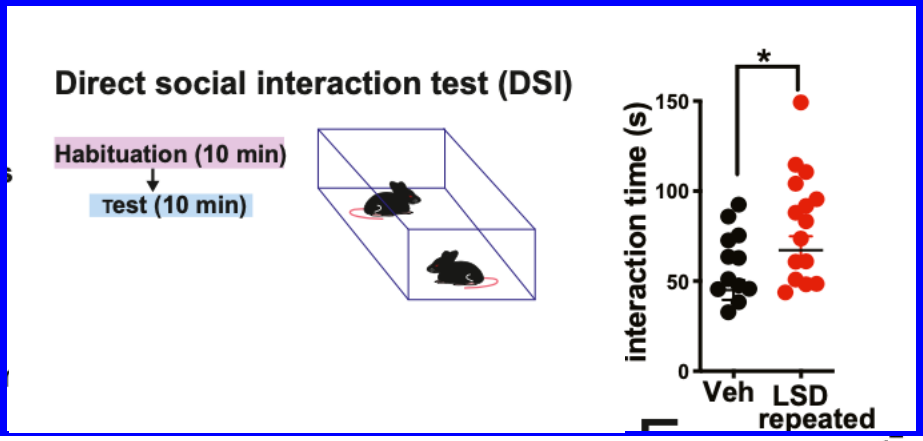


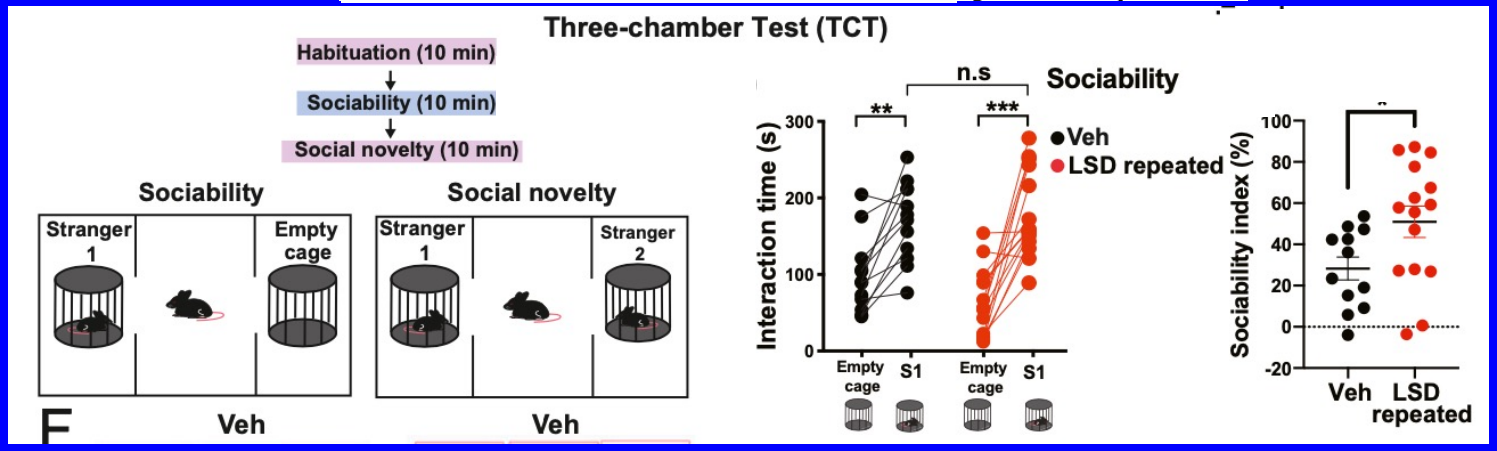
LSD (30 µg/kg)
Acute, or
Daily for 7 days

Repeated doses of LSD promoted social behavior

No antidepressant or anxiolytic-like effects

No effect after acute administration





Repeated LSD after chronic stress in mice *(Gobbi et al, NPP 2022)*

- Chronic stress induced anxiety-like behavior
- LSD (30 µg/kg, 7 days) prevented these effects
- No effect of single doses
- No effect in unstressed mice

Future research

- What are the behavioral effects (esp social effects) of repeated microdoses of psychedelic drugs in humans?
- What brain mechanisms mediate these effects?
- Is there therapeutic potential? For what indication?
- Dose, duration? Side effects? Individual differences?

Huston Smith

(Cleansing the Doors of Perception, 2003)

.. this led Grof to conclude that LSD is not a specific causal agent, but rather a catalyst.. an unspecific amplifier of neural and mental processes. [It raises] to consciousness for the patient material that is otherwise buried, and [enlarges] this material .. so that it appears as if under a magnifying glass.

Acknowledgments

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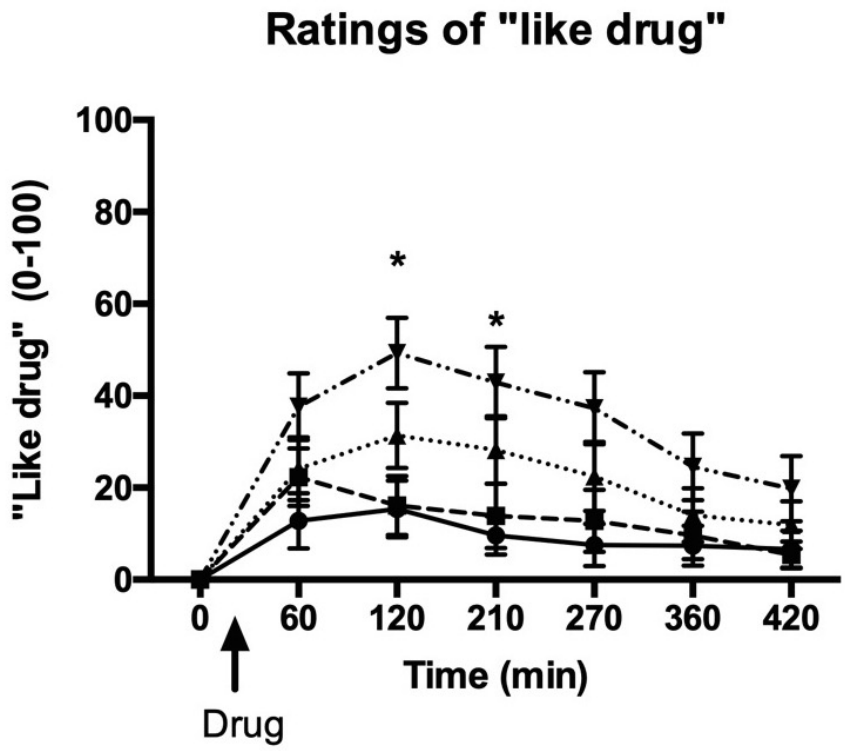
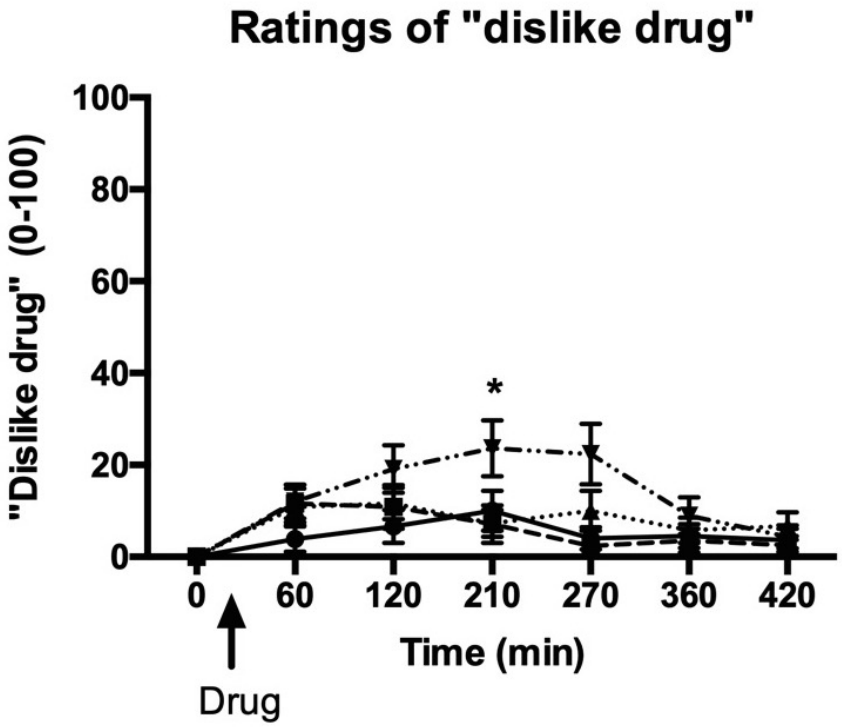
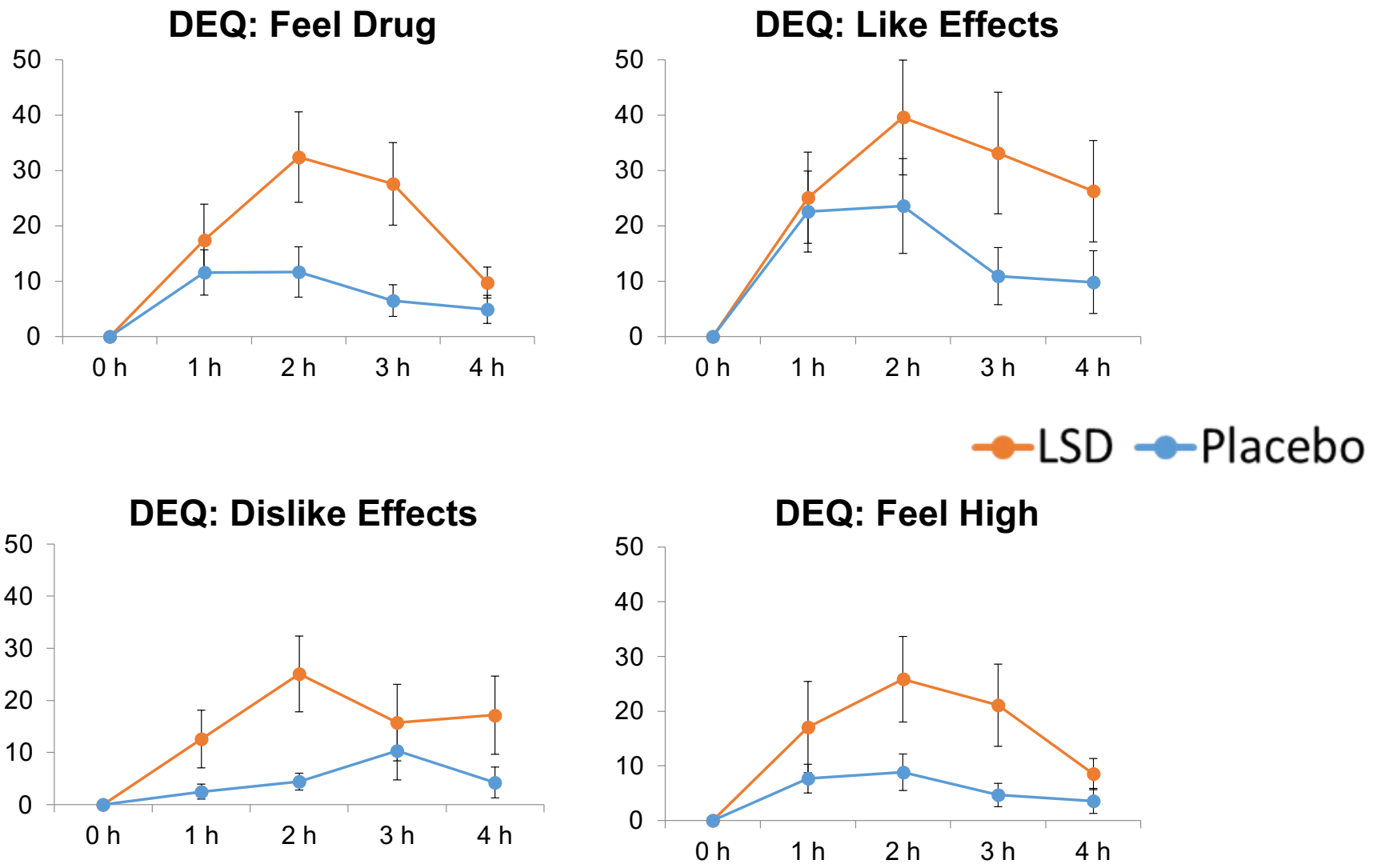
- Robin Nusslock, PhD
- James Glazer, PhD
- Sarah Keedy, PhD
- Hanna Molla, PhD
- MAPS
- NIDA
- Beckley Foundation

c.


Ratings of "like drug"
"Like drug" (0-100)
100
80
60
40
20
0
*
*
0
60
120
210
270
360
420
Time (min)
Drug

d.


Ratings of "dislike drug"
"Dislike drug" (0-100)
100
80
60
40
20
0
*
0
60
120
210
270
360
420
Time (min)
Drug


DEQ: Feel Drug
50
40
30
20
10
0
0 h
1 h
2 h
3 h
4 h
DEQ: Like Effects
50
40
30
20
10
0
0 h
1 h
2 h
3 h
4 h
LSD
Placebo
DEQ: Dislike Effects
50
40
30
20
10
0
0 h
1 h
2 h
3 h
4 h
DEQ: Feel High
50
40
30
20
10
0
0 h
1 h
2 h
3 h
4 h

Wave patterns

- **Delta** (0-4 hz) seen during sleep
- **Theta** (4-7 hz) seen during relaxation, meditation
- **Alpha** (7-13 hz) relaxation, seen with eyes closed
- **Beta** (14-30 hz) active thinking, concentration, anxiety
- **Gamma** (30-100 hz) binding of networks to perform a cognitive or motor function

OTHER DRUG EFFECTS ON WAVE PATTERNS

1.5-4 Hz δ DELTA	4-8 Hz θ THETA	8-13 Hz α ALPHA	13-20 Hz β BETA	30-100 Hz γ GAMMA
ANESTHETICS, SEDATIVES				
↑ cortical power[3]	↑ cortical power[3]	↑ frontal power[2,3]	↑ amplitude[1] ↑ frontal power[2,3]	↑ midline power[4]
STIMULANTS				
↓ frontal power[5]	↓ cortical power[6]	↓ frontal power[5] ↓ cortical power[6]	↓ frontal power[5]	
SEROTONIN 2A RECEPTOR (5-HT_{2A}) AGONISTS				
↓ PCC power[7,10] ↓ cortical power[8,9,11]	↓ PCC power[7,8,10] ↓ cortical power[9,11]	↓ PCC power[7,8,10] ↓ cortical power[9,11]	↓ PCC power[7,8,10] ↓ cortical power[8,9,11]	↓ frontal power[10]

1) Greenblat et al., 1989; diazepam and midazolam
2) Freshchenko et al., 2004; propofol and thiopental Hagihira 2017; isoflurane
3) Murphy et al., 2011; propofol Albrecht et al., 2016; dexamphetamine
4) Dimpfel et al., 1993; caffeine
5) Carhart-Harris et al., 2014; psilocybin
6) Carhart-Harris et al., 2016; LSD
7) Rodin & Ludy 1966; LSD
8) Muthukumaraswamy et al. 2013; psilocybin
9) Riba et al., 2002; DMT

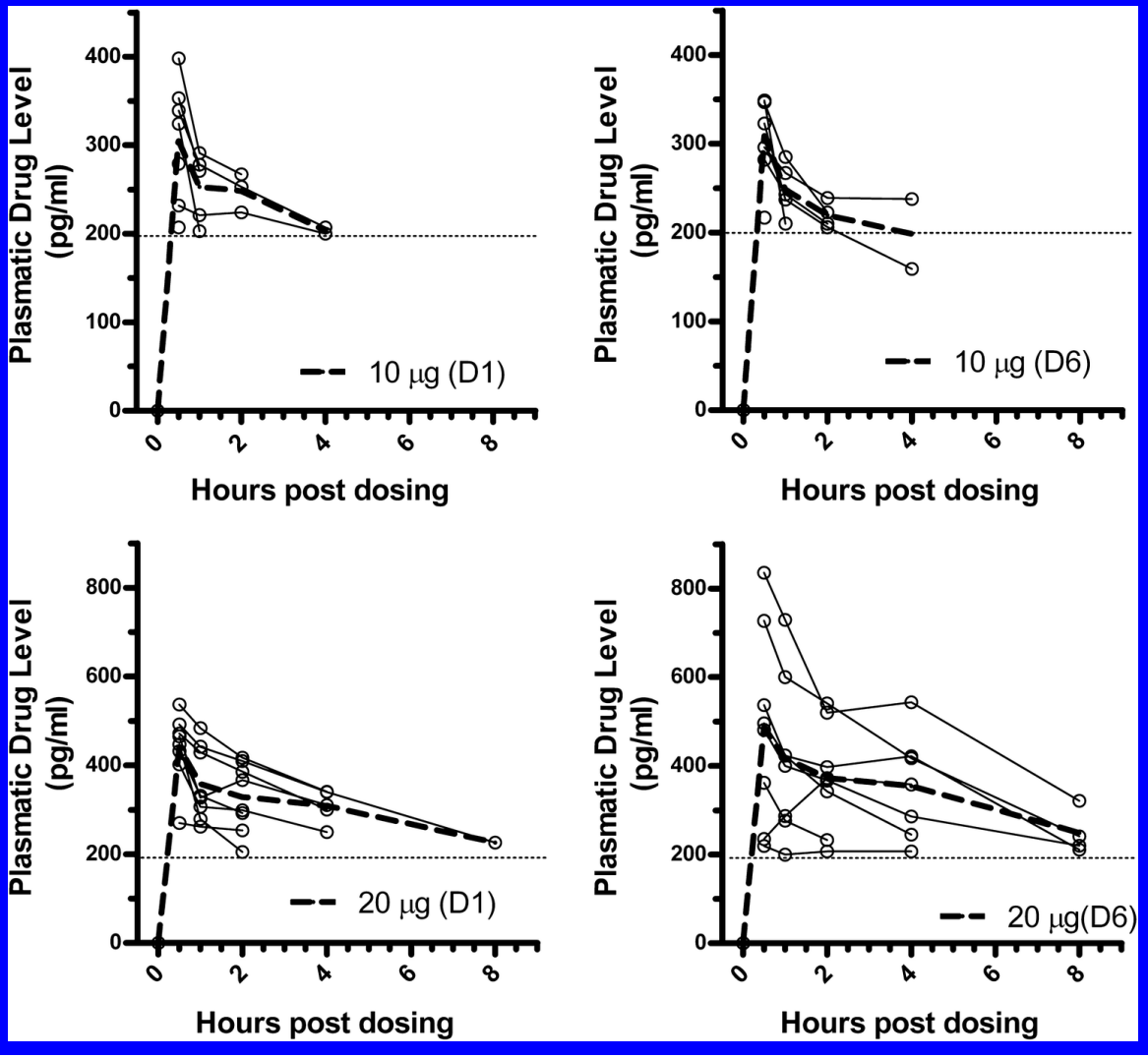
Repeated doses *(Family et al 2020)*

Healthy older volunteers (early 60's)

Received placebo, 5, 10, 20 ug on 6 sessions every 4 days

Few behavioral effects

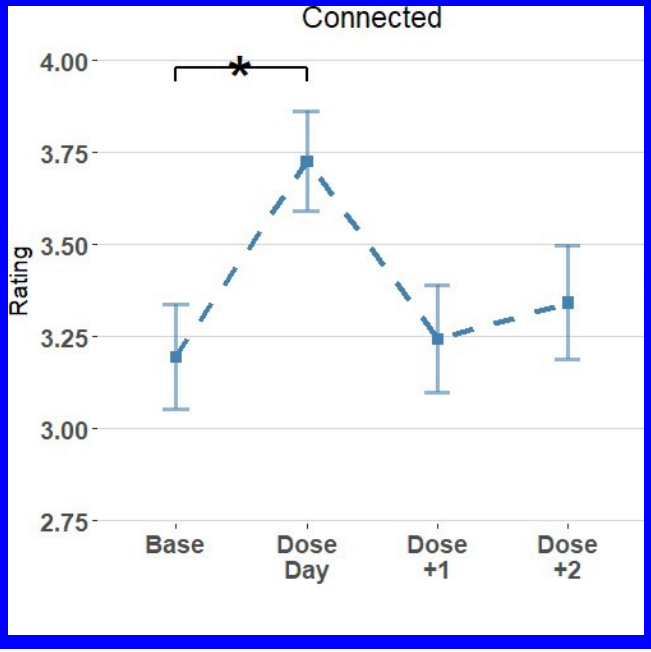
Pharmacokinetic profile

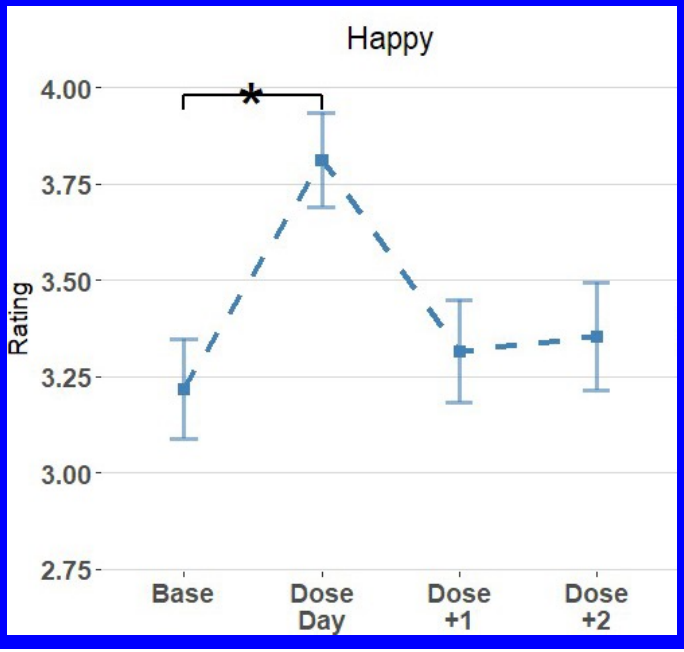


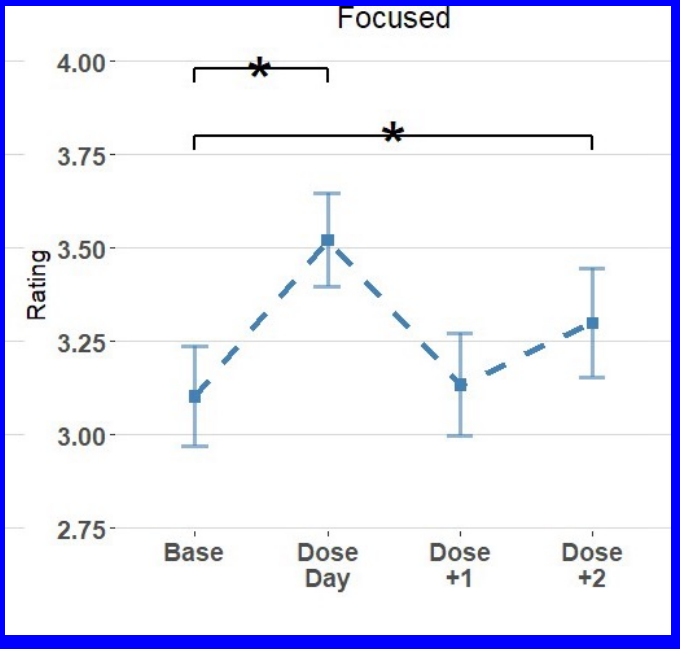
Expectancies

Polito and Stevenson 2019

- Online survey tracked 98 microdose users before, during and two days after single microdose (LSD 13.5 µg, psilocybin 0.3 g)







Compared expected experiences to reported experiences

Expected *and* reported after using microdose

- Decreased depression, stress, mind-wandering
- Increased Absorption (openness to altered states)

Expected *but not* reported after using microdose

- Increased creativity, wellbeing, mindfulness
- Decreased neuroticism

Reported *but not* expected after microdose

- Increased neuroticism