Universität Zürich[UZH]

Psychiatrische Universitätsklinik Zürich

# Psychedelika in der psychiatrischen Therapie:
# Entwicklung und Geschichte


Prof. Dr.med. Franz X. Vollenweider

Psychiatric University Hospital Zürich
Center for Psychiatric Research
Neurophenomenology and Consciousness

Dept. for Adult Psychiatry and Psychotherapy

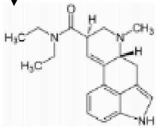

PUK-ZH, 9.11. 2024


Heffter Reseach Institut (USA), Usona Institut(USA),
Swiss Neuromatrix (CH), ZenResearch (CH), MIND Foundation (G)

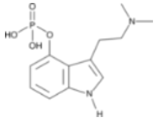
# Brief History of Psychedelic Research (PUK-ZH)

1926 | 1938 | 1943 | 1947 | 1952 | 1953 | 1958 | 1962 | 1963 | 1965 | 1966 | 1970 | 1983 | 1988 | 1990 | 1999 | 2000 | 2006 | 2010 | 2012 | 2016 | 2018 | 2024

Methergin



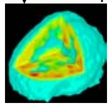
LSD



Psilocybin

US:Schedule1

5-HT **agonists**
(Sander-Bush)



### Clinical Revival of Psilocybin / LSD

**Depression/Anxiety** in terminal ill patients
(Grob et al. 2011, LSD: Gasser et al. 2014)

**Alcohol dependence** (Bogenschütz et al.2015)

**Depression** (TRD) (Carhart-Harris et al. 2016)

**2020ff: Major Depression (MDD)**

PUK-ZH 1947: LSD **as model of psychosis (hallucinations)**(W. Stoll)

1948: LSD **as an ajunct in depression** therapy (Condrau)

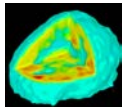
**Psycholytic Therapy** (EU/CH: Gnirss, Leuner, Sandison;
low/moderate doses, repeatedly)

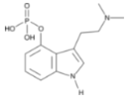
**Psychedelic Therapy** (CAN/US: Osmond, Pahnke, Cohen;
1-2 high doses)

- Depression (64-68%)
- Anxiety in cancer patients (56-70%)
- Alcohol dependence (46%)

PUK-ZH:
1971-1986: **Psychology of Altered States (ASC)**(Dittrich)

1988-1993 and ff : **Compassionate use** (SÄPT)(Styk, Gasser)





**1992-ff: Neuroscience of Psychedelics** (Vollenweider)

**2018-ff: Translational Animal Research** (Pryce)

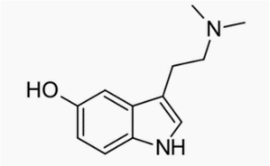
Volllenweider and Kometer Nat.Rev. Neurosci. 2010

# Chemical Classification: Serotonergic Hallucinogens or Psychedelics

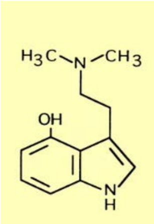
- Tryptamines (Indoleamines)
- Ergoloides
- Phenylethylamines



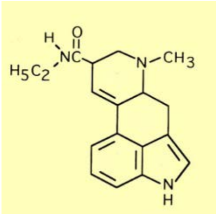




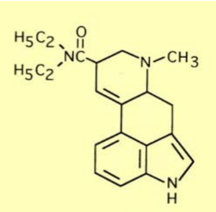

**DMT in Ayahuasca**



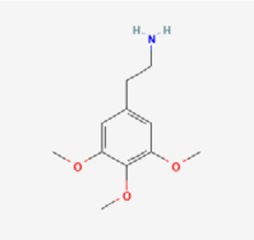

**Psilocybin**



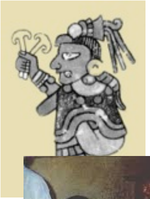

**LSA**

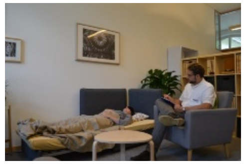



**LSD**




**Mescaline**


# Classic Psychedelics: Phenomenology - first-person perspective

**Altered Waking State of Consciousness (ASC):**

characteristic changes in*:*

- *sensory perception*
- *emotions, mood*
- *cognition, meta-cognition*
- *self & self-other boundaries*

*Such experiential phenomena are otherwise rarely reported except **in dreams**, contemplative states, religious exaltations, and psychotic states*

«vision»

«Satori»

«mysical rapture»

Selflessness
Non-duality

**Sensory Perception**
**space-time, imagery**

**Cognition**
**mode of thinking**

**Self/ego-boundaries**

Self-reference

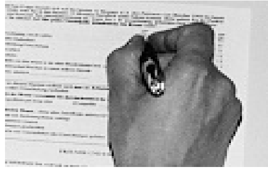
**Self/other boundaries**

**Affects, Emotions**
**arousal**

**Social cognition**
**self-environment**

# Assessment of Psychological Dimensions of Altered States of Consciousness (ASC: 5 main factors)

5D-ASC Rating Scale (96 visual AS)



**„Altered Perception"**
**-Visionary restructuralisation: VR**

Second order Scales:
- elementary /complex imagery
- synesthesia
- changed meaning of percepts
- recollection of memories

**Altered Vigilance**

**Acoustic Alterations**

**„Positive Self-dissolution"**
**-Oceanic self-boundlessness: OBN**

Self /ego
boundaries

**medium doses**
e.g. psi < 25 mg)

**higher** doses
e.g. psi > 25 mg)

**„Negative Self-dissolution**
**-Dread of ego-dissolution: DED**

11D-ASC Rating Scale

Second order Scales:
- loosening of self-boundaries: experience of unity/connectedness
- disembodiment
- positive emotions – bliss
- altered space-time sense
- insightfulness
- spiritual experience

MEQ (30 categ. items)
(Mystical Experience Scale)

- experience of unity
- inner subjectivity
- ego-loss
- altered space-time sense
- ineffability
- positive emotions
- sacredness
- noetic quality

Second order Scales:
- fear of loss of thought control
- fear of loss of autonomy
- thought disturbances
- anxiety, panic, delusions

**OBN-tot Score** ↔ **MEQ-tot Score**
R=0.68-0.8

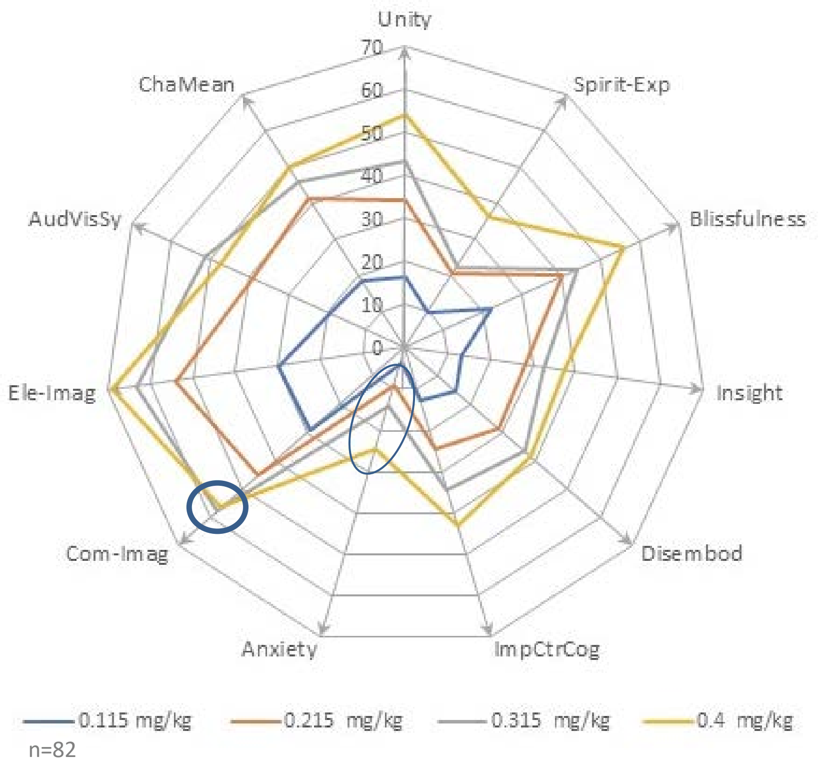
Dittrich 1985, 1998: (n=345)

Hood 2012, 2016

Studerus et al . 2010, 2011 (n=312)

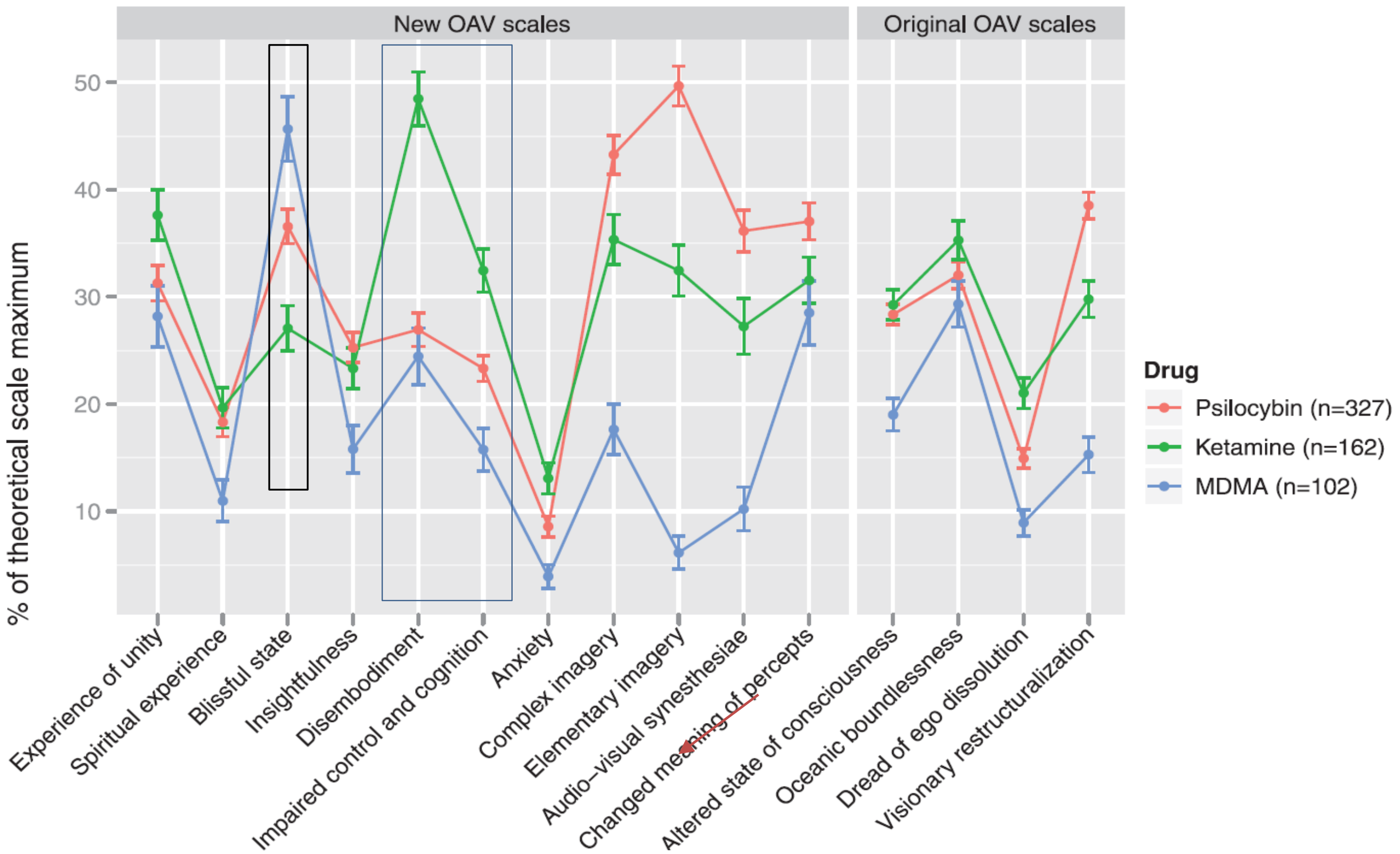
# Dose-response effects of Psychedelics and discrimination from related compounds

## 11-ASC Sub-Scores for Psilocybin




low medium **25mg** high

11D-ASC 5D-ASC

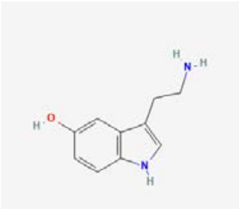



Psi: 20 mg po, S-ketamine: 12 µg/kg*min iv; MDMA: 100 mg po

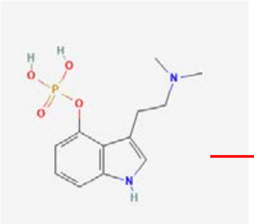
Studerus et al. 2010, 2011, Kometer at al. 2013

Kometer at al. 2013

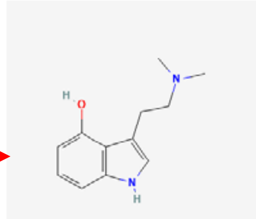
# Psychedelics: Primary and downstream mechanism: 5-HT2A agonists



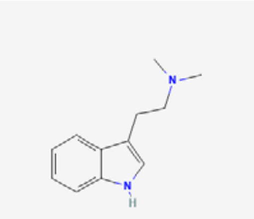
Serotonin im Gehirn



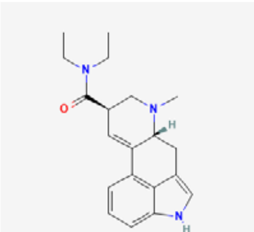
Psilocybin



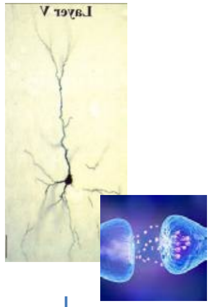
Psilocin



DMT



LSD




- 5-HT 7

5-HT 5,6

+ 5-HT 1

-

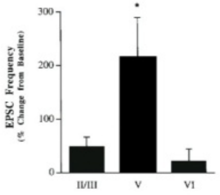
+ **5-HT2A**

D2

D1

α1

α2




EPSC, sensitivity
Layer V pyramidal neurons
(Aghajanian and Marek 1999)

+ GABA

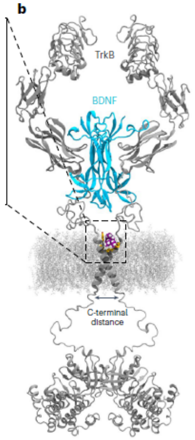
+ Dopamine

Glu release

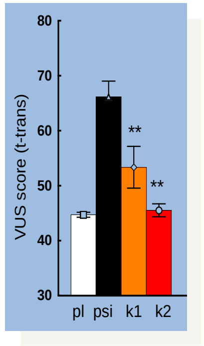
AMPA → *BDNF* > mTOR >**TrkB**> neuroplasticity

NMDA → Learning, memory

direct allosteric modulation of **TrkB**



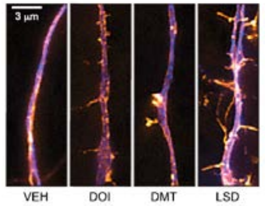

Moliner et al. 2023




5-HT2A antagonist Ketanserin blocks psi mediated psych. effects

Vollenweider et al. 1998

also of LSD
Preller et al. 2016




in animals:
Ly et al. 2018
De Gregorio et al. 2020
Shao et al.2021

**Human studies:**

MRS: mPFC GABA( +)
Mason et al. 2020

PET: DA (+)ventr. Str.
Vollenweider et al 1999

MRS: PFC GLU (-), Hipp Glu (+)
Mason et al. 2020

# Multiple factors influence the Dynamics of the Psychedelic Experience and Outcome

Preparation/Instruction:
- turn inward, surrender
- focus on the present moment,
- encourage self-observation

**Pharmacological Factors:**
- **Dose**

**Quality and Intensity** of acute psychedelic experience

multiple Mediators ?

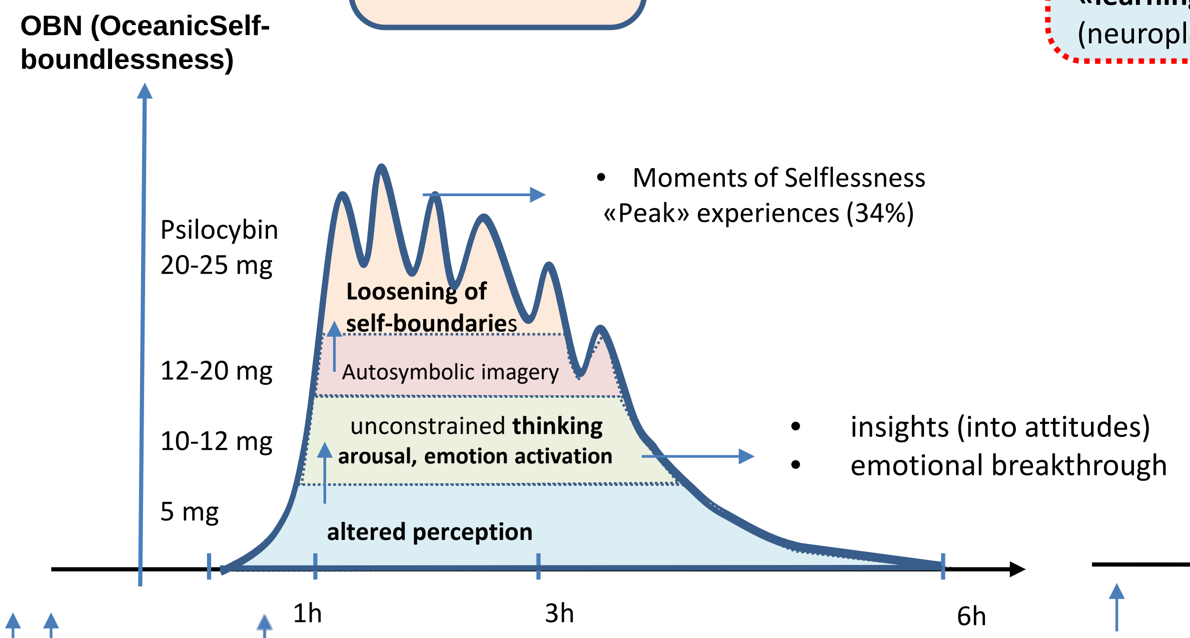
Outcome

**Integration:** postacute **interventions «learning»** (neuroplasticity)

**Sustained symptom reduction and changes in spec. functions/ behavior**

**« Set» and core processes**
- personality traits (openness)
- previous experience, age
- **emotion regulation**
  - -Acceptance (+)
  - -Suppression (-)
- **absorption capacity, attention**
- mood state (past 7 days)

**«Setting»: environment, music**




3-6mth

- **Mindset, expectancies (participant, therapist) ?**
- **Therapist-patient relationship** (alliance, trust, empathy) (+)
- **Therapeutic model ? or Common Factors ?**

Preparation sessions

Dosing session

Integration sessions

Studerus et al. 2012, Vollenweider and Smallridge 2023

# Postulated psychological mechanism of psychedlics (Leuner 1982)

**Therapist: empathic support**
**„working through" emotions and behavioral patterns**

***Process factors***

*Altered self or self-other representation*

++

***«Regression» of the self's synthetic «functions»*** (cohesion)

***Lowering «defence», cogn. control***
\> primary process thinking

\+

++

***activation of basic feelings*** *(embodiment)*
***activation of emotions***
***recall*** *of personel relevant (challenging)* ***memories***
\> ***insight*** *into emotional/cognitive schemas*

\+

*autosymbolic self-relevant imagery*

*Reduced/altered body sense and expression*

Leuner 1982

Self and self-referential cognition

Social cognition

Cognitive control

cognition

Emotion regulation

affects emotions

embodiment feelings

**Cortical:**

Top-down

upper **limbic**

Bottom-up

**Brainstem**
**PAG**, ARAS

## Cognitive-emotional models of MDD

enhanced self-focus
decreased environmental focus

negative cognitive bias
e.g. rumination

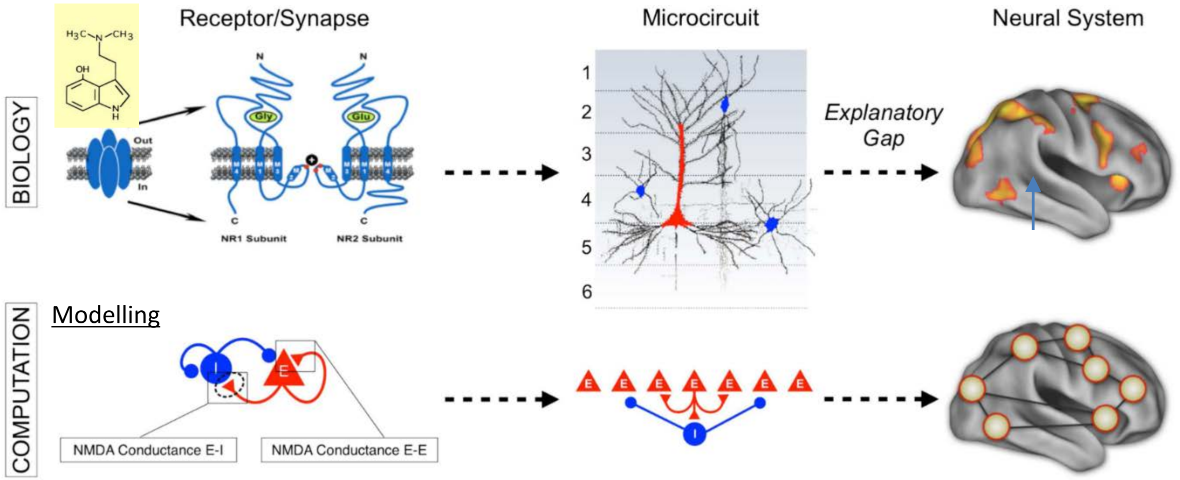
negative emotional bias

increased body-focus

# Methods: Mapping the brain-mind-behavior space relationships along the psychedelic spectrum

Cause -> effect power

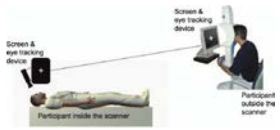
Psychological,
genetic,
social Factors




correlational:

**Psychological Concepts:**

**Subjective** Experience
(1.Person Perspective)



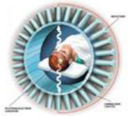
**Neuroscience-based Concepts:**

- **percetual,**
- **Emotional,**
- **cognitive** processing

(3.Person Perspective)

e.g synaptic gain

e.g. acute change in functional connectivity
(hypothesis: neuroplasticity and longterm change?)



PET, MRS (20-60 min)
Resting state:

- activation/deactivation
- receptor occupancy
- transmitter release

fMRI (2 sec): (MRS)
Resting state / task:

- activation/deactivation (ASL)
- functional and directed connectivity
- complexity (e.g., entropy, granularity)

EEG/MEG (msec)
Resting state / task (ERP)

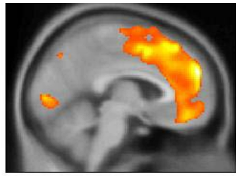
- spectral power
- synchronisation,
- long-range oscillations
- complexity (e.g. entropy)

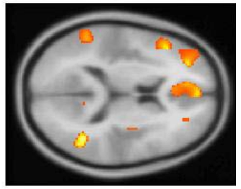

TMS-EEG (msec)
(evoked response)

- Pertubation complexity index (PCI)

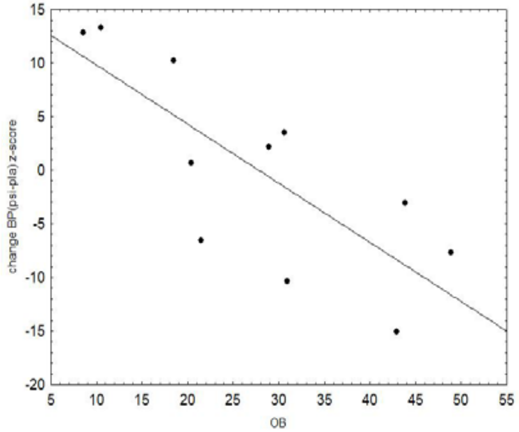
(adapted from Anticevic et al. 2013, Vollenweider and Smallridge 2022)

# Positive self-dissolution correlates with 5-HT2AR occupancy in cortical and subcortical regions



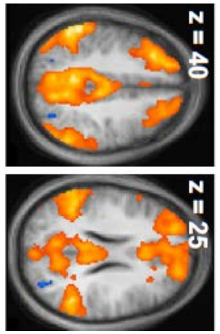


**OBN** correlates with 5-HT2AR binding potential




OBN

- **dorsomed. & dorsolat. prefrontal cortex**
- **dorsal anterior cingulate cortex** (ACC)
- **temporal Cortex**
- **angular Cortex**
- **insula**

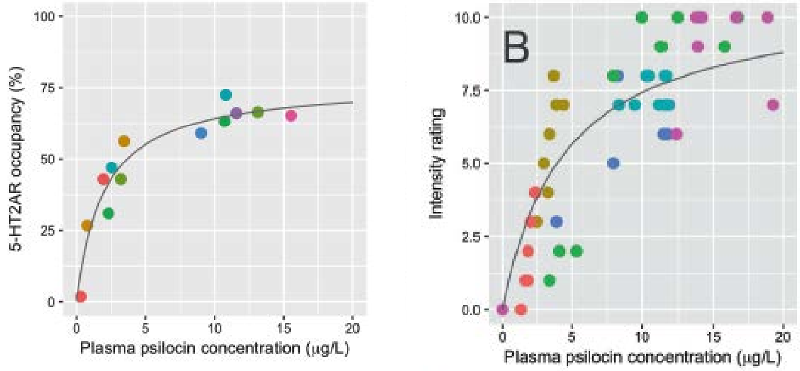


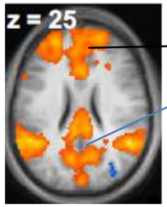

**Default Mode network (DMN) hubs**:

- **d/v medial prefrontal cortex** : self
- **anterior cingulate cortex** (ACC) : self
- posterior cingulate cortex (PCC) : self-other
  and tempoparietal junction (TPJ)
- precuneus, hippocampus
- **insula** : body-self

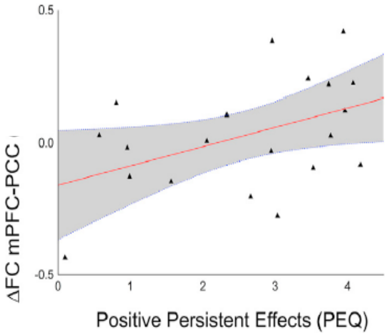
Hasler & Vollenweider 2011, Quednow et al. 2012

Psychedelic effects of psilocybin correlate with serotonin 2A receptor occupancy and plasma psilocin levels and subjective effects (Madsen et al. 2019)



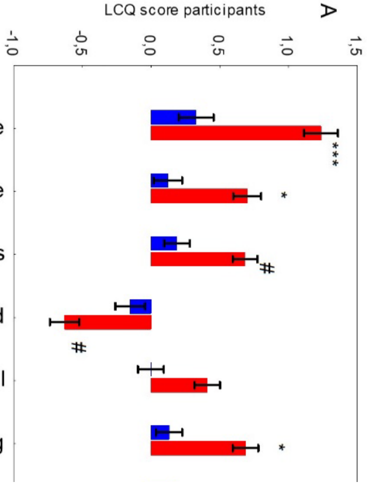




**OBN correlates with reduction of ACC-PCC fCON**



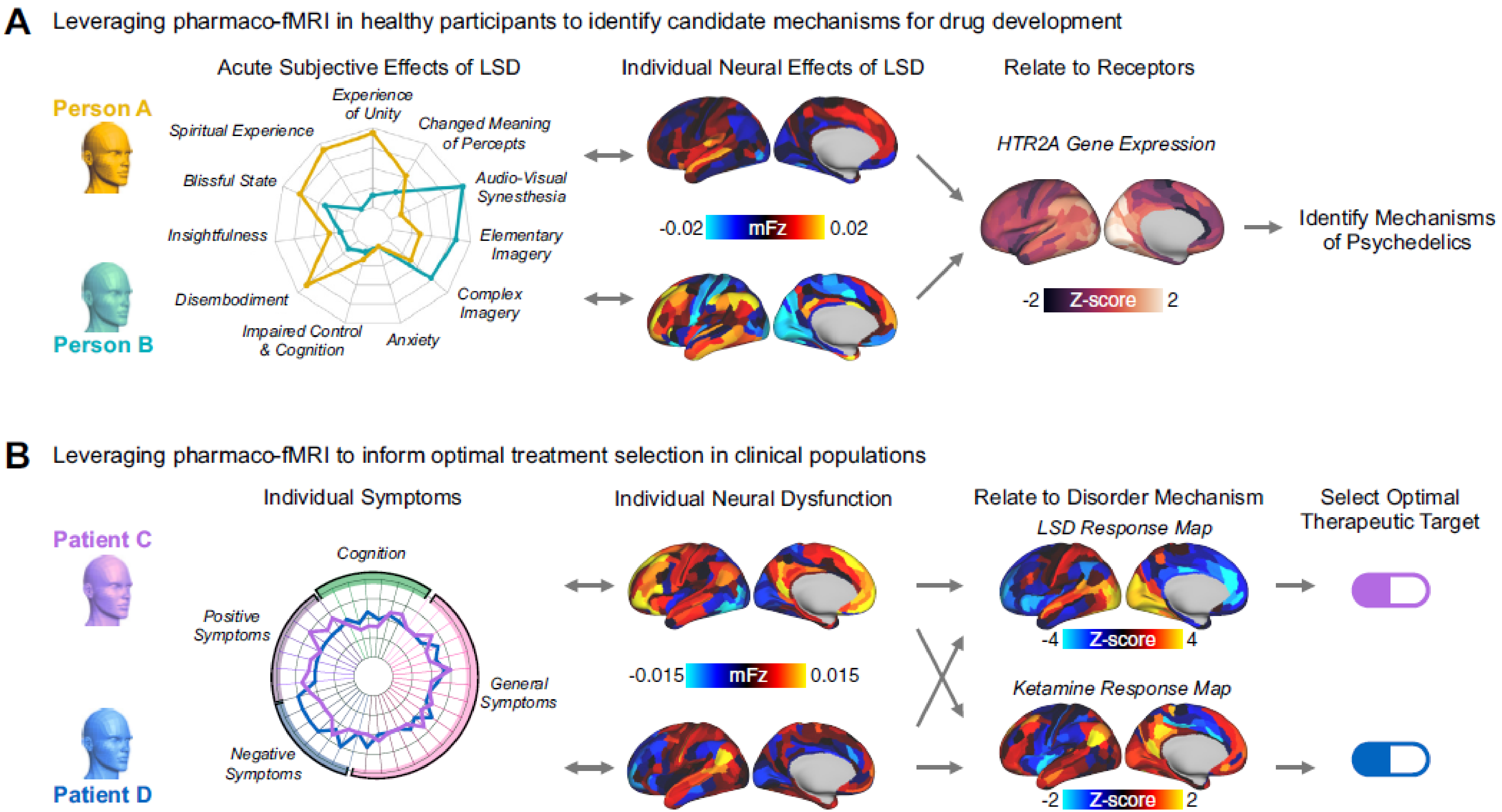

Mediators

| | | |
|---|---|---|
| Pos. emotions | → | Appreciation life |
| Emotions (+/-) | | Self acceptance |
| unity | → | Concern others |
| | | Concern world |
| | | Concern social |
| Pos. emotions | → | Quest meaning |




Smigielski et al 2019

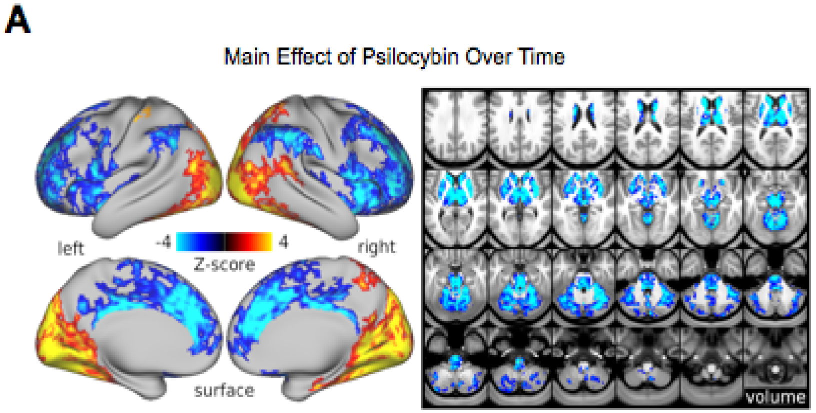
# Resting state (global/functional) brain connectivity, receptor gene expression and psychological response

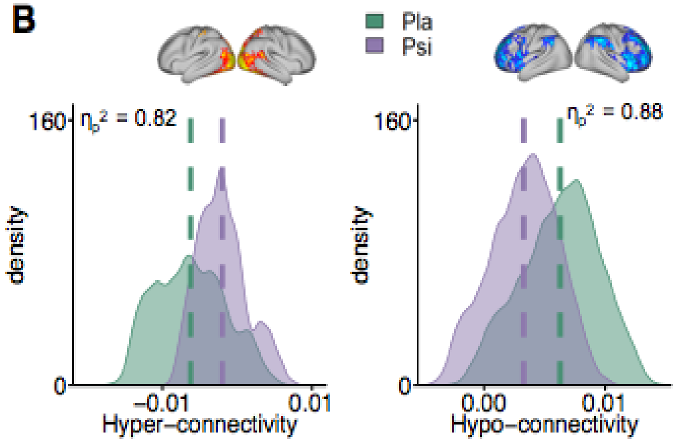



Moujaes et al. Biol.Psych 2023

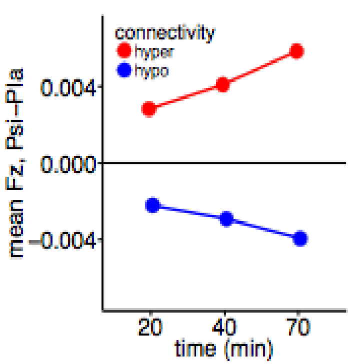
# Psychedlic-induced changes in resting state global brain connectivity (GBC) and disembodiment

## Psilocybin and GBC (n=23)

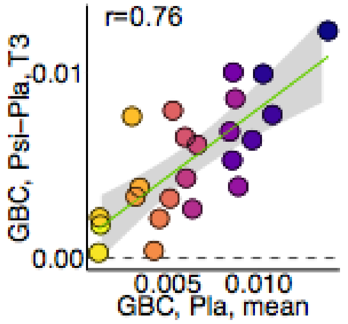


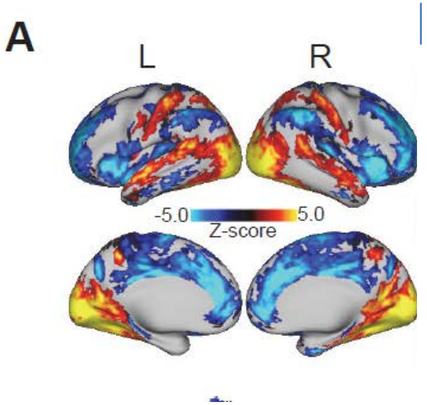

Change over time (dose)



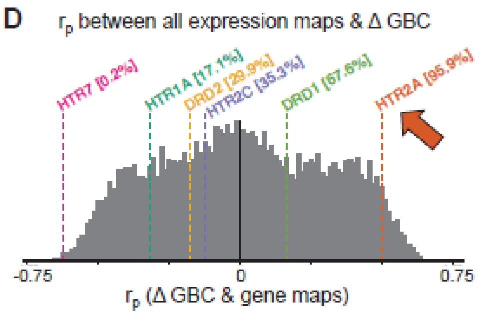

baseline pla FC predicts change of FC under psi

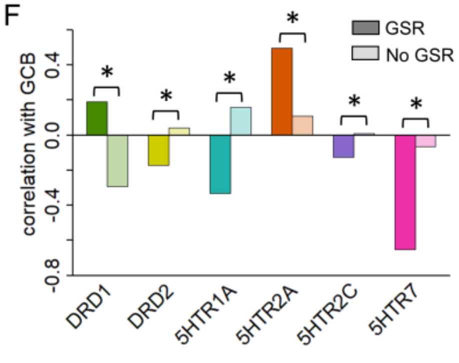



## LSD and GBC (n=24)

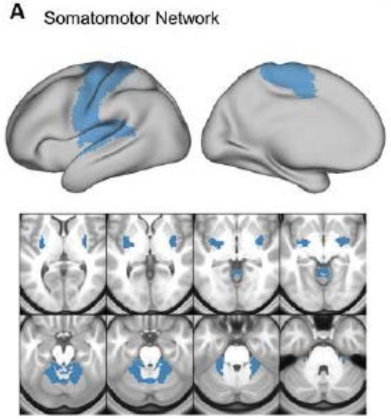


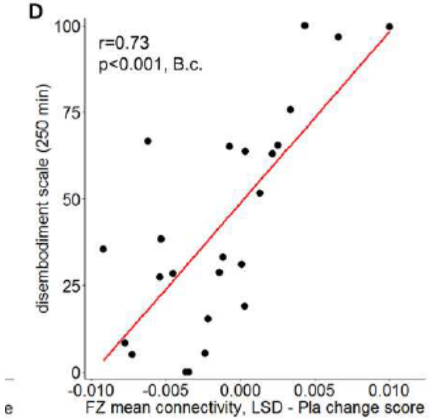

## 2HT2A Cortical gene expression maps correlate LSD-induced changes in GBC



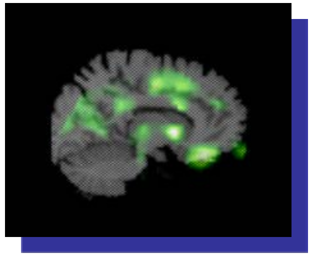

## LSD: Dysconnection of somatomotor Network correlates with *disembodiment (&OB)*



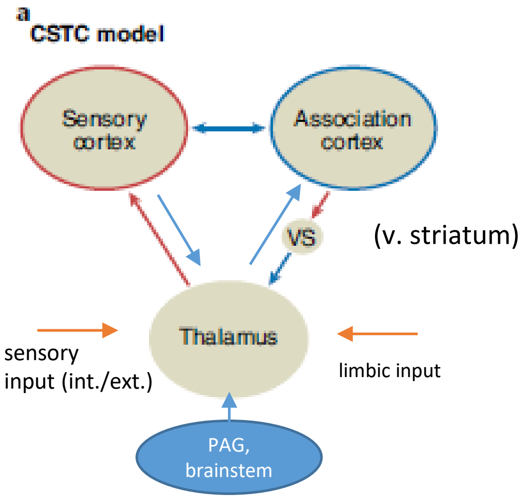

Preller et al. eLIFE 2018, Preller et al. Biol. Psych.2019, Burt et al. elife 2021

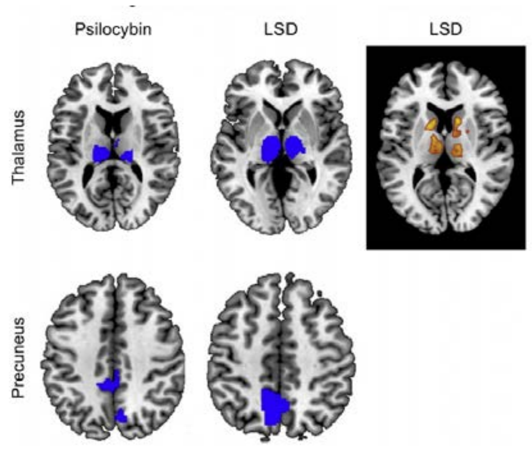
# Proposed system mechanism of Psychedelic–induced changes in global brain connectivity



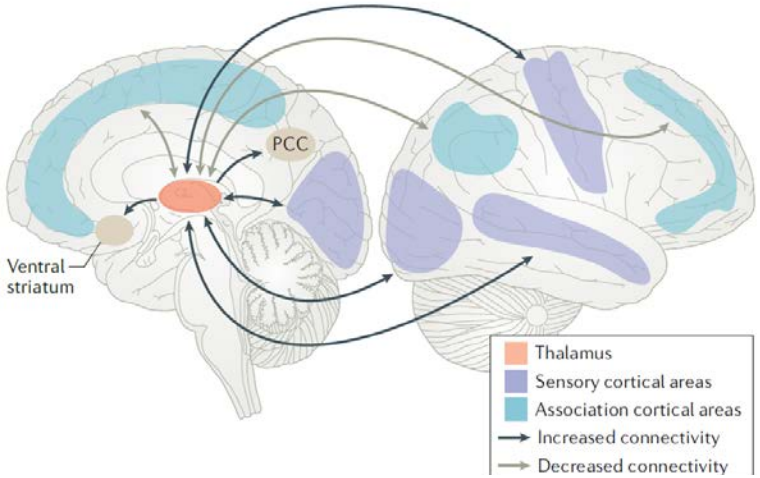
Psilocybin

Reduced CSTC gating



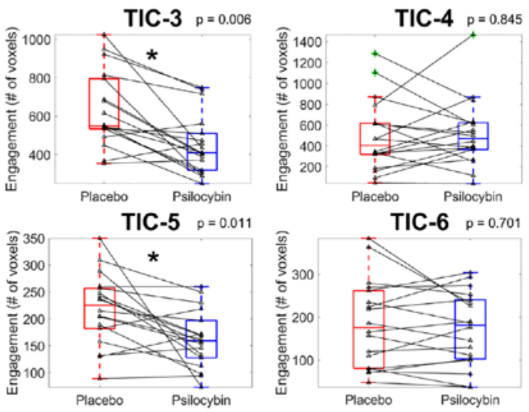

Müller et al. 2018, Liechti et al 2020

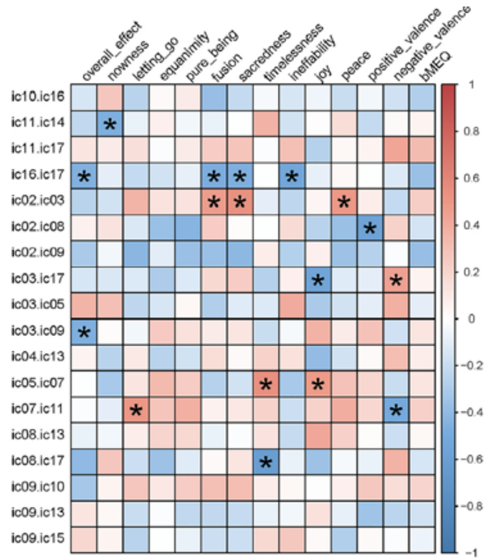



increased thalamo – sensory Cx CON

Reduced thalamo –assoc. Cx Con

Specific thalamic nuclei:

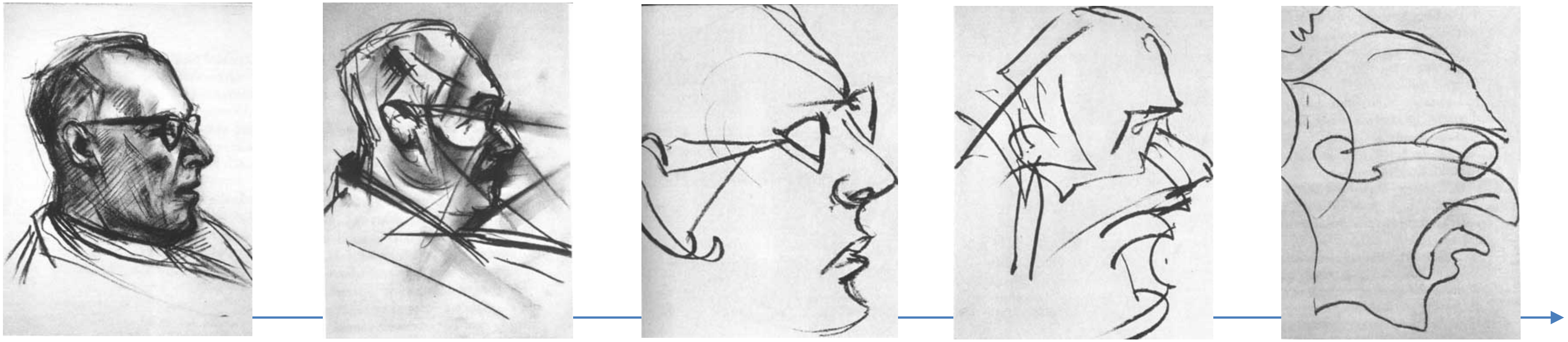


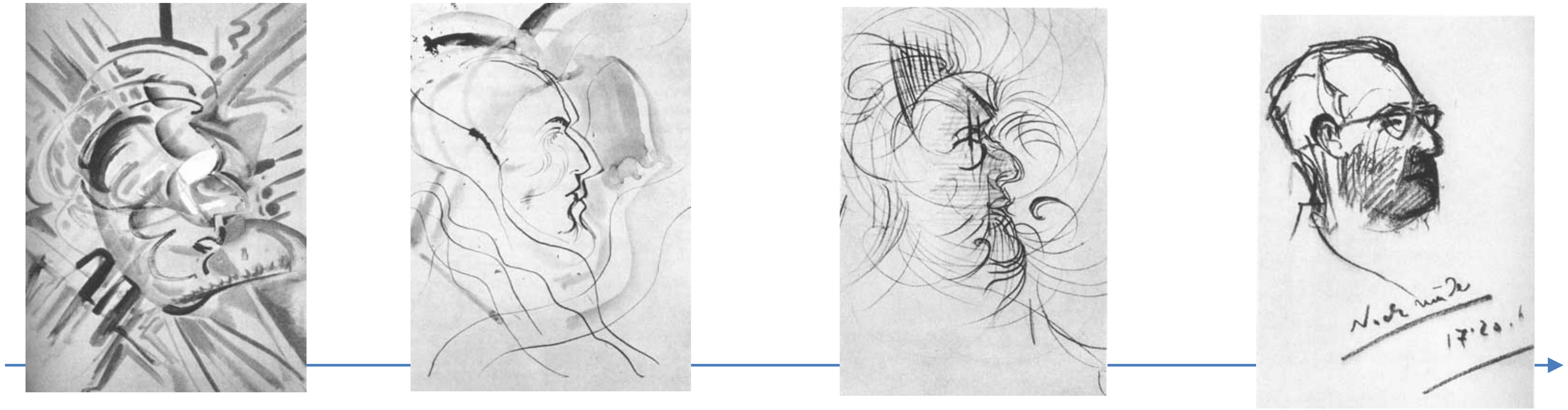

Gaddhis et al. 2022

Vollenweider and Geyer 2001, 2008, Vollenweider and Preller Nat. Rev. Neurosci. 2020

# LSD changes the experience of self and self body image



time



Peak effect (2.5 h)

Künstler (n=30) wie
Mac Zimmermann
Erich Brauer,
Arnulf Rainer,
F. Hundertwasser
Alfred Hirdlicka
F. Scheurer
und weitere

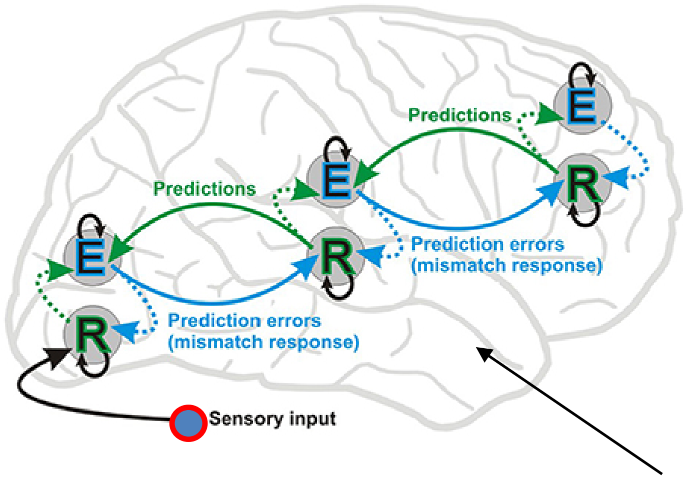
R.P. Hartmann 1976, Malerei aus Bereichen des Unbewussten, Künstler experimentieren mit LSD (n=125) (MPI, Munich)

# Neurocognitive approach to self representation and bodily self experience: predictive coding

- The predictive coding framework posits that the brain continuously **learns to model and update** the **predictions** across multiple levels of **representations** (e.g.body perception) and to minimize surprise

- at each hierarchical level**, top-down predictions** based on current **beliefs** (priors) are subsequently compared and **matched** with
- bottom-up lower-level representations

- a **discrepancy** between the **predicted** and the **actual** incoming bottom-up content produces a **predictions error** (PE) signal




external

e.g. tactile, auditory stimuli

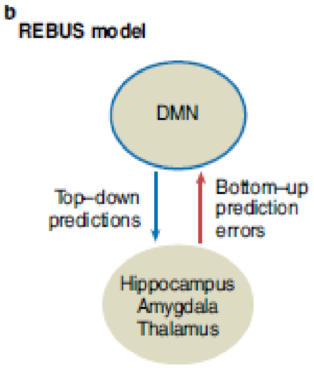
internal stimuli

Ho et al. 2018, Stefanics et al. 2014

> predictive codes integrating bodily states and sensory inputs are thought to give rise to self-awareness (bodily awareness)

**Psychedelics may impair prediction error signaling**

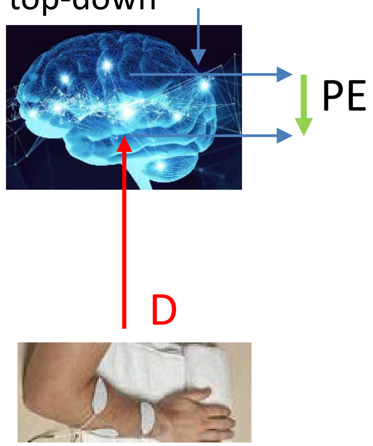
e.g. *reduce high-level priors,* which may be linked to altered bodily self experience



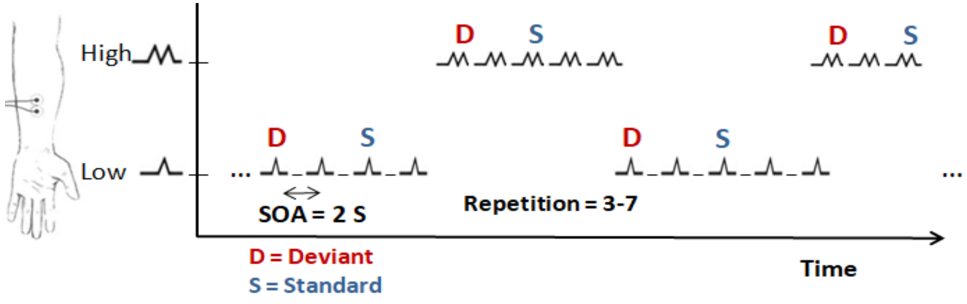

*Psychedelics may reduce the precision of high level priors > relaxed beliefs*

Carhart-Harris et al. 2019

top-down




bottom-up

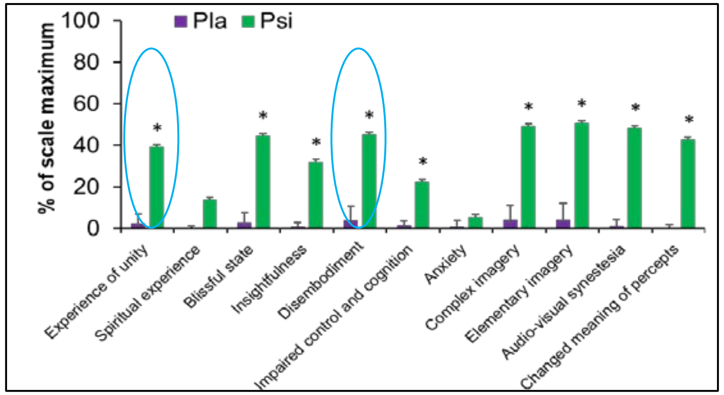



- Unpredicted stimuli: Deviant (D)

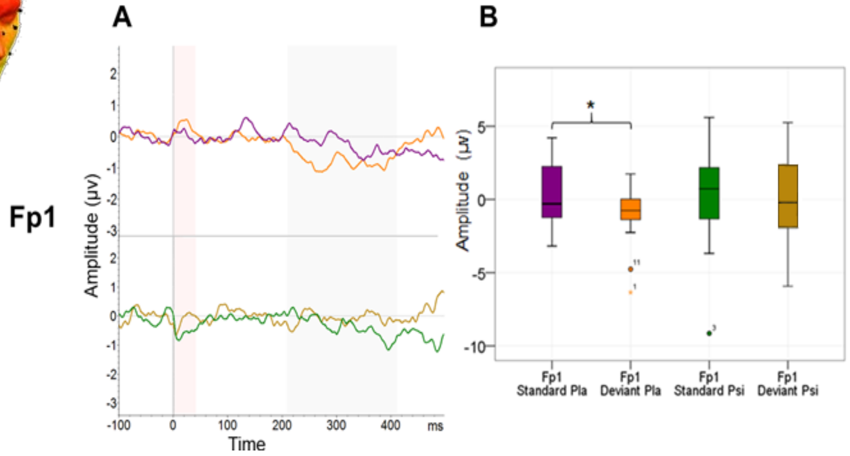
Dürler et al. 2021

# Psilocybin induces aberrant prediction error processing for tactile mismatch responses

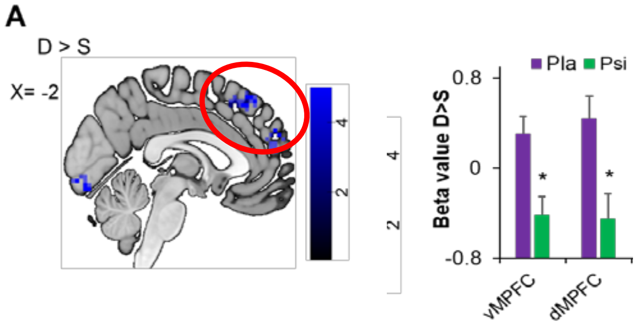
- Psychometrics: Unity, Disembodiment




- ERP: Psilocybin reduced MMN in **frontal Cortex** electrodes

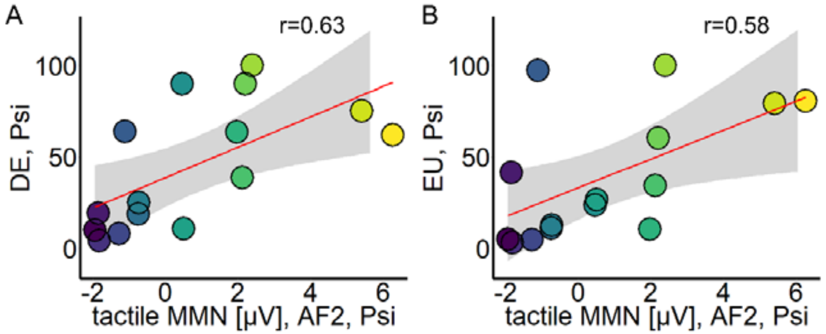


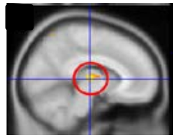

- fMRI: Psilocybin reduced the response to unpredicted stimuli versus standard in brain regions implicated in bodily-awareness




1) **ventral Medial PFC**
2) **dorsal Medial PFC**
3) Thalamus
4) Sensory cortex

- MMN change and Altered Self-Experience



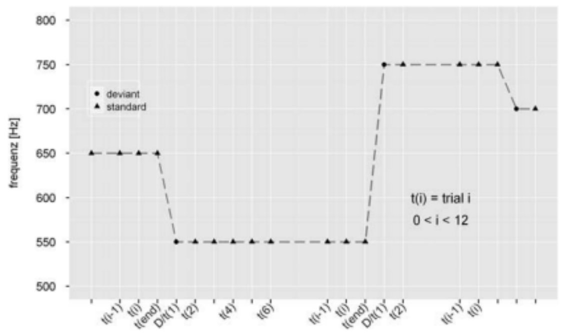
Psilocybin alters integration of tactile stimuli through (top-down) abberant PE signalling

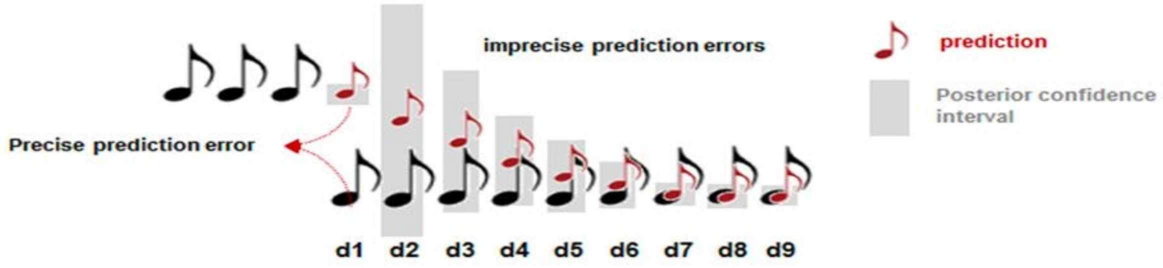
reduced tactile MMN responses at frontal electrodes correlates with altered body- and self-experience: **disembodiment** and feelings of **unity (connectedness)**

Dürler et al. 2021

# Auditory mismatch: Hierarchical Precision-weighted Prediction Error during sensory learning (Single trial approach)

## Model of sensory learning



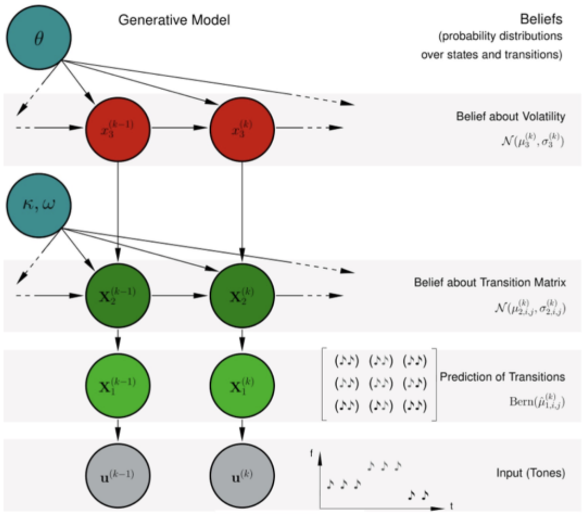



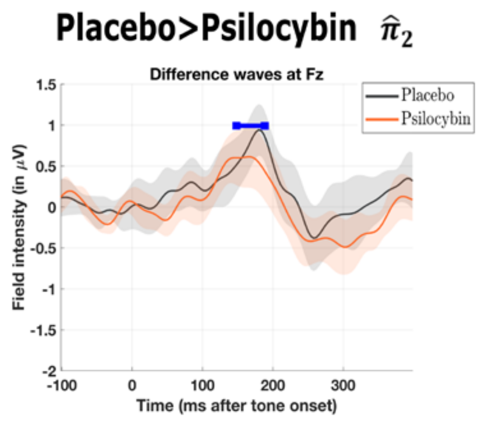

Posterior:
Outcome Precision
(sensory P.)

$$\frac{\hat{\pi}_1^{(k)}}{\pi_2^{(k)}}$$

Belief Precision

## General linear model




Psilocybin (in contras) to ketamine) does not sig, reduce the outcome precision $(\widehat{\boldsymbol{\pi}_1})$

psilocybin **reduces the expression of belief precision** $(\widehat{\boldsymbol{\pi}_2})$ that is informational precision implying that participants' **confidence in their "model of the world" is diminished:**

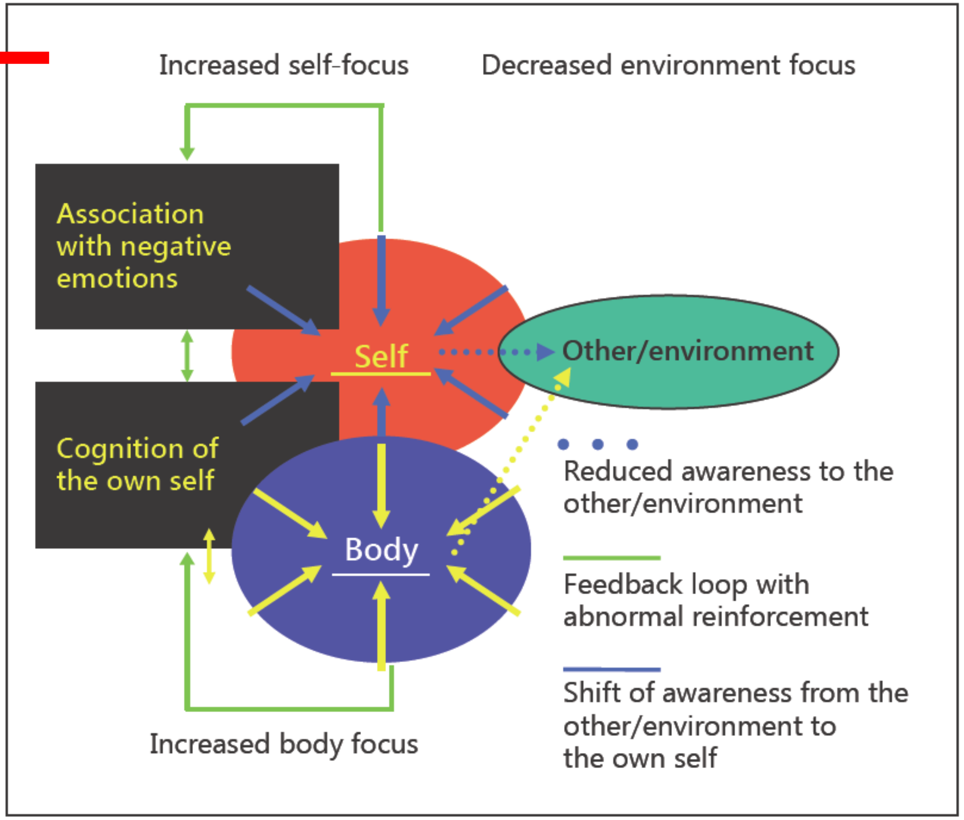
- Both a reduction in belief and sensory precision –
- **potentiates learning and may open cognitive flexibility**

Weber et al., 2024, work in progress

Diaconescu, Allohverdi, Vollenweider 2024, work in progress

# Proposed Neurocognitive model of major depressive disorders (MDD): negative emotional and cognitive processing bias

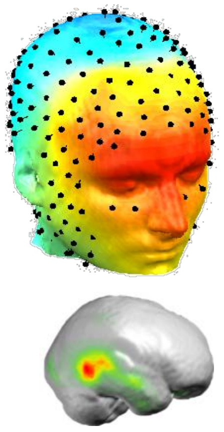
1

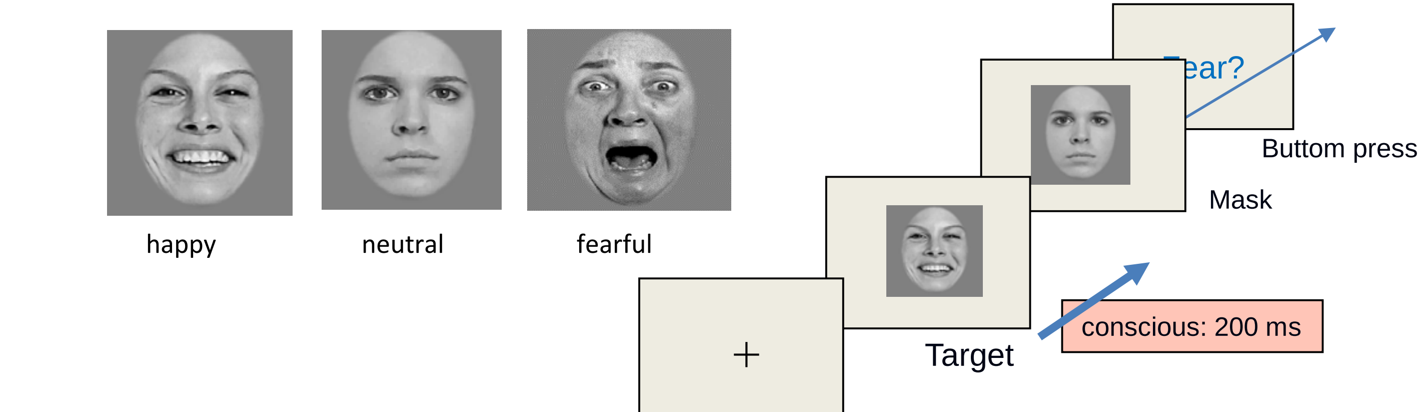


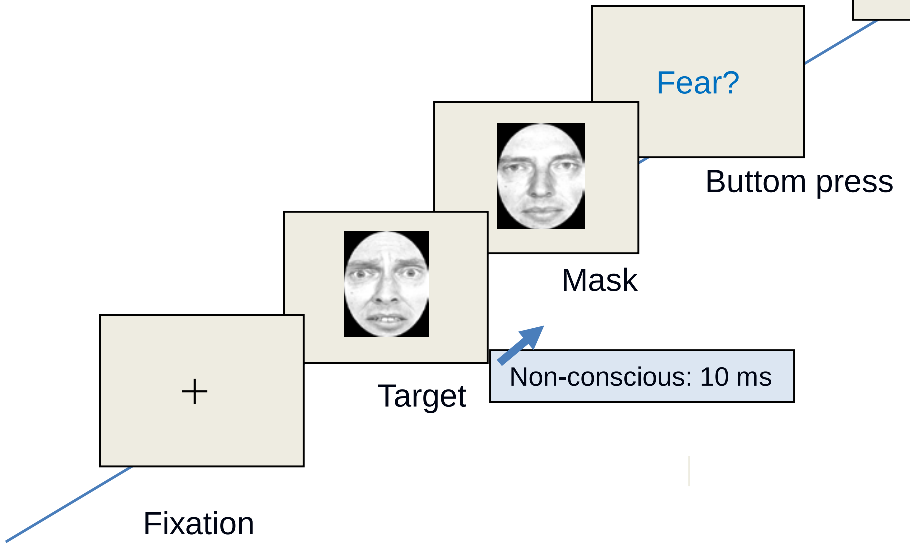

**-negative emotional bias:**
e.g. negative self-attribution
e.g. increased response to negative stimuli (e.g. fearful faces)

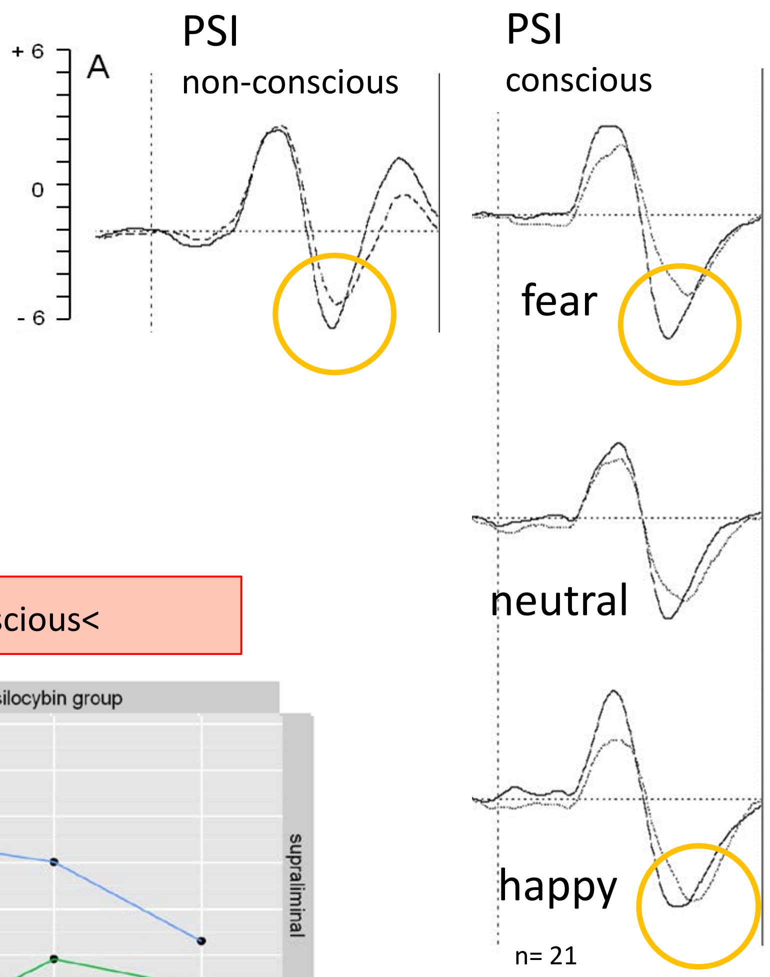
Adapted from Northoff 2014

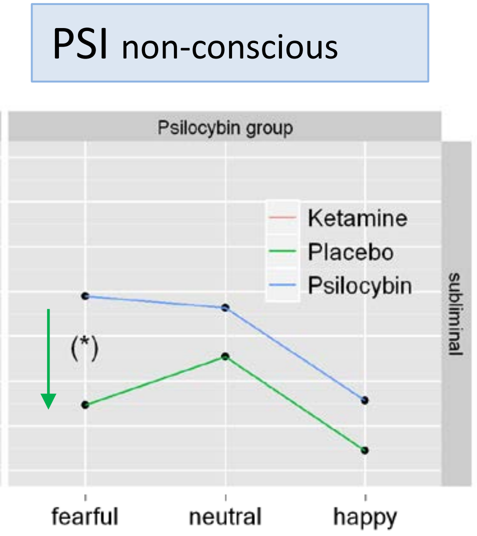
# Effect of psilocybin on non-conscious and conscious emotional face processing (N170 ERP)

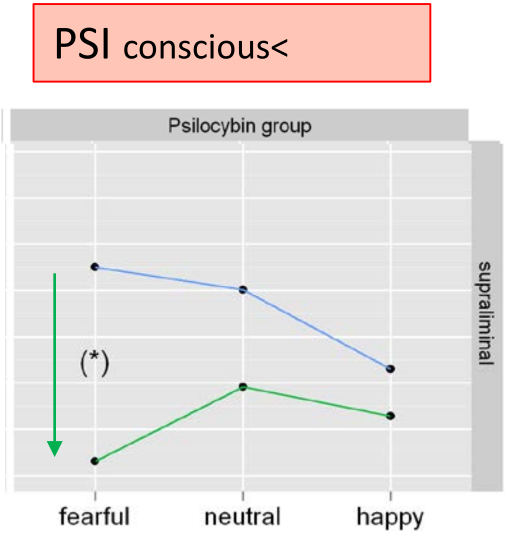




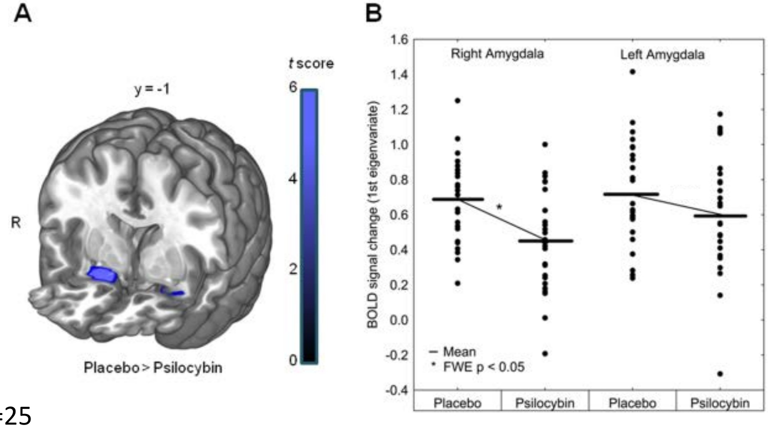



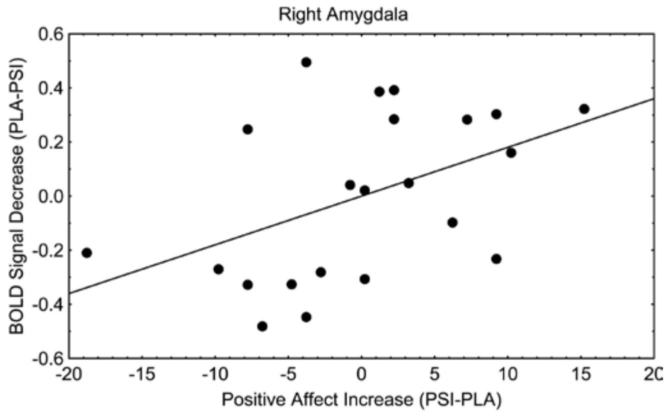

Schmidt et al. 2012, 2013

# Emotion processing: Psilocybin reduces amygdala response to fearful stimuli

versus




n=25




decrease in BOLD response correlates with acute increase in pos. mood

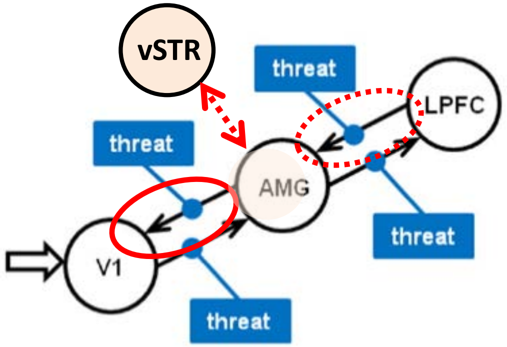
Kraehenmann et al. 2015, 2016, Grimm et al. 2018

## Direct effective connectivity (DCM)

-increased amygdala visual Cx dir. connectivity

-decreased coupling: **amygdala – ventral striatum FC**

(**saliency detection**) during neg. emotional faces perception

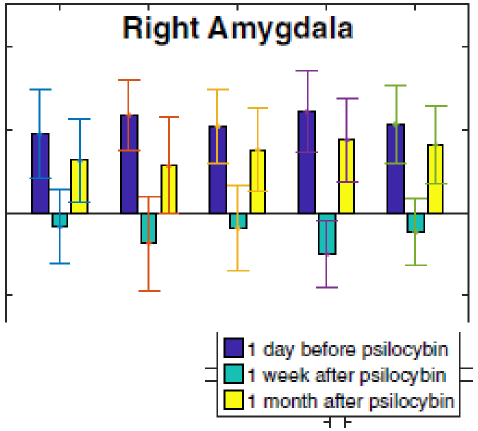



?

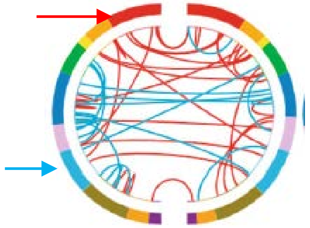
«**decentring**»: a state allowing a broader spectrum of emotions and thought patterns

Grimm et al. 2018

## Decreased amygdala response lasted up to 1 month follow-up



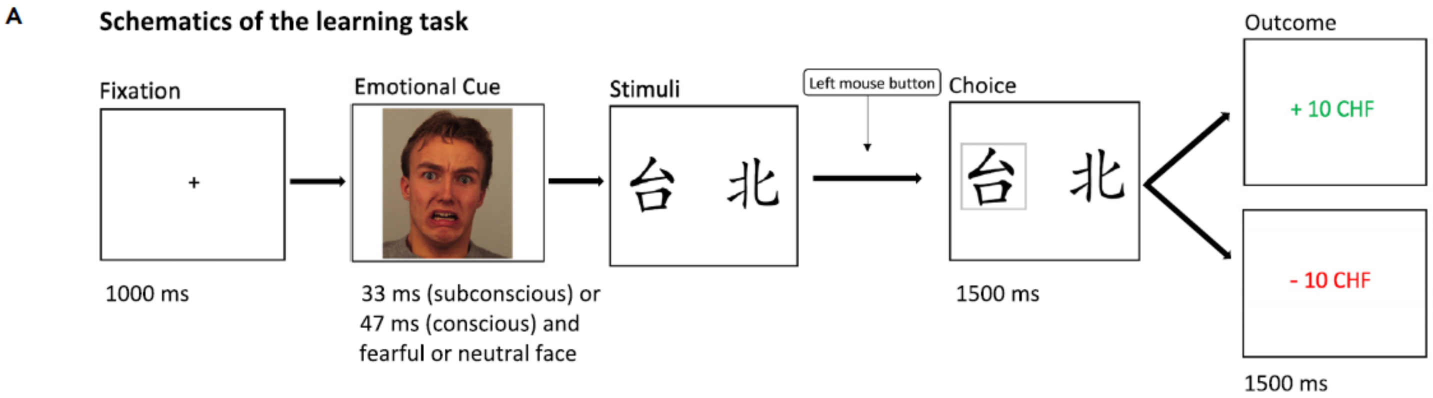

B. 1 Month > BL



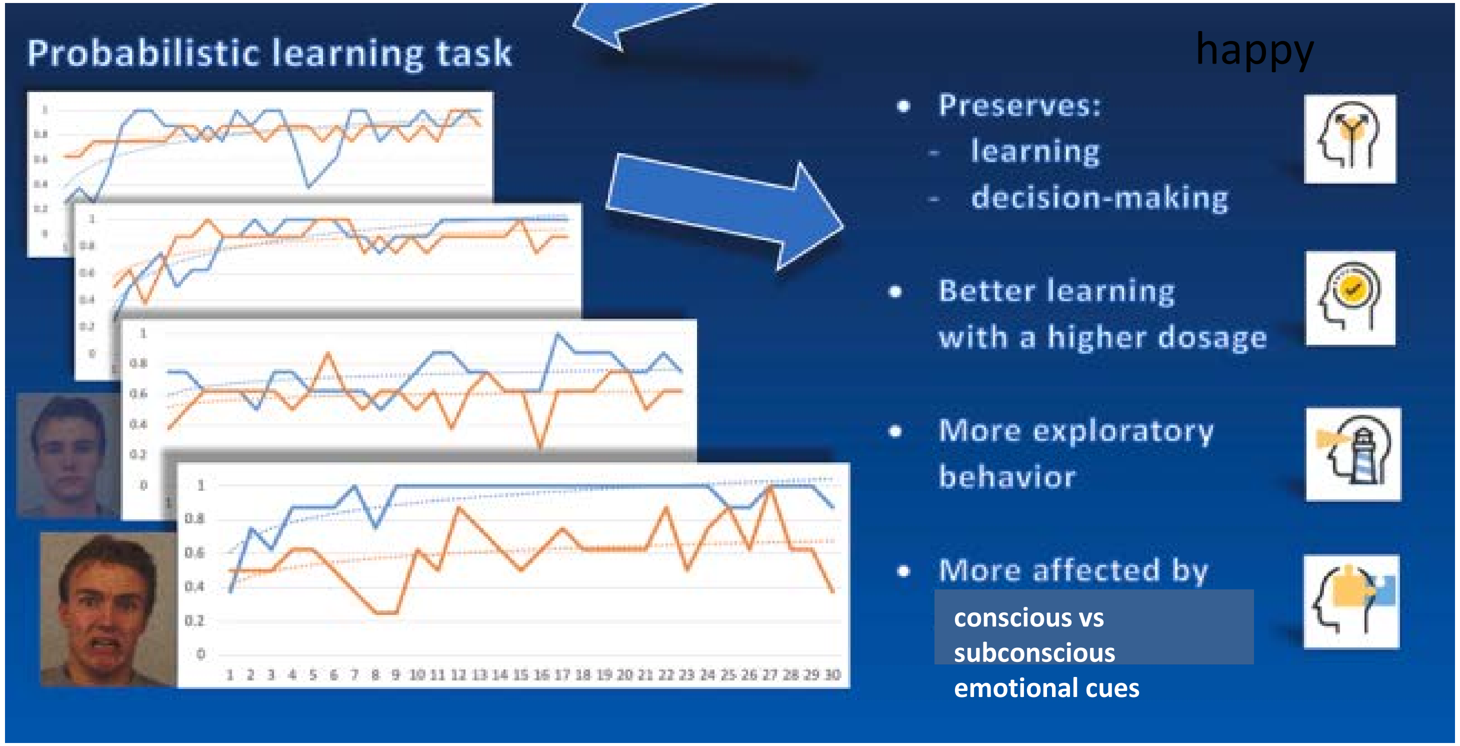
e.g:
increased PFC –limbic lobe FC
increased dlPFC activity

Barett et al. 2020

# The influence of psilocybin on subconscious and conscious emotional reward learning




B Probabilistic learning task (20%, 80%), positive conscious and unconscious emotional cues, neutral and fearful stimuli




Psilocybin beeinträchtigt die notwendigen Entscheidungs-prozesse nicht

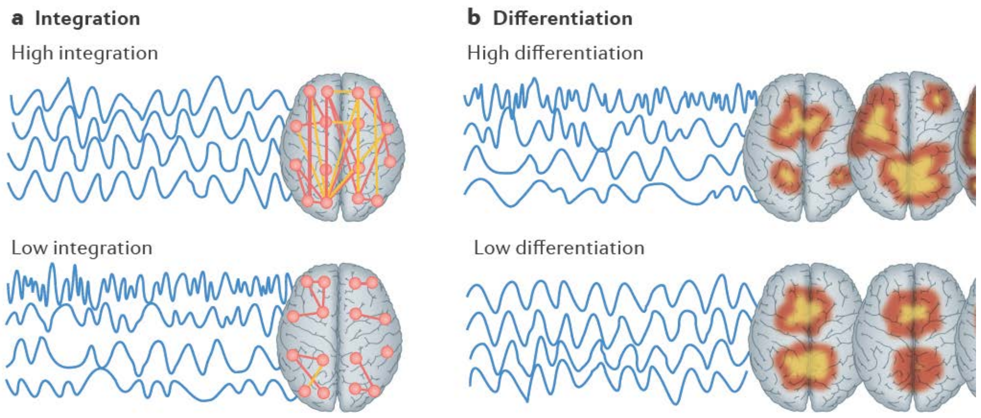
Höhere Dosen an Psilocybin (20 mg vs 12 mg) verstärken Lernprozesse

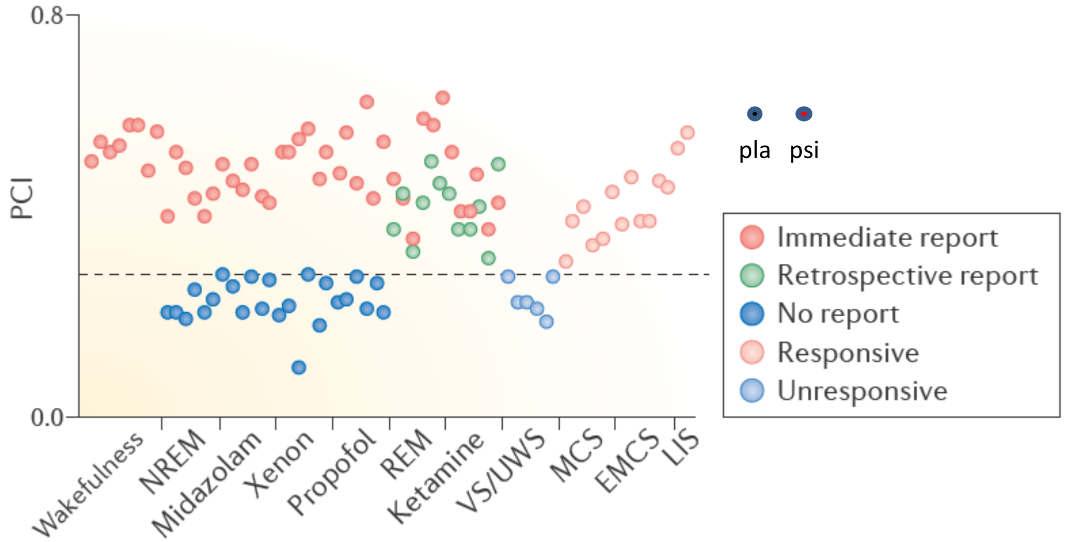
Psilocybin erleichtert exploratives Verhalten

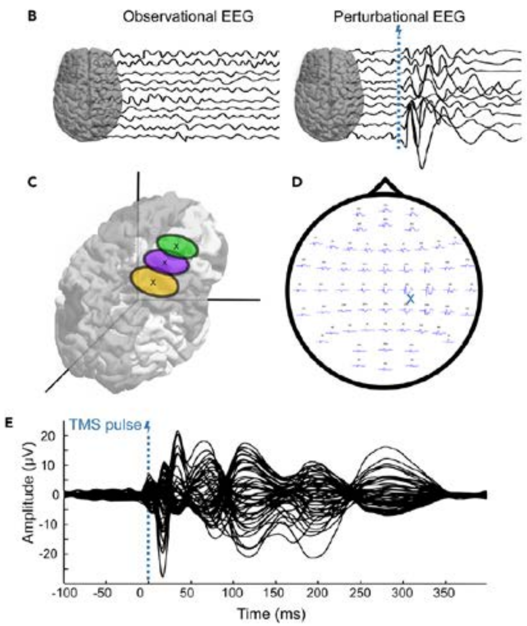
Bewusste emotionale Cues facilitieren gegen über unbewussten Cues Lernprozesse verstärkt

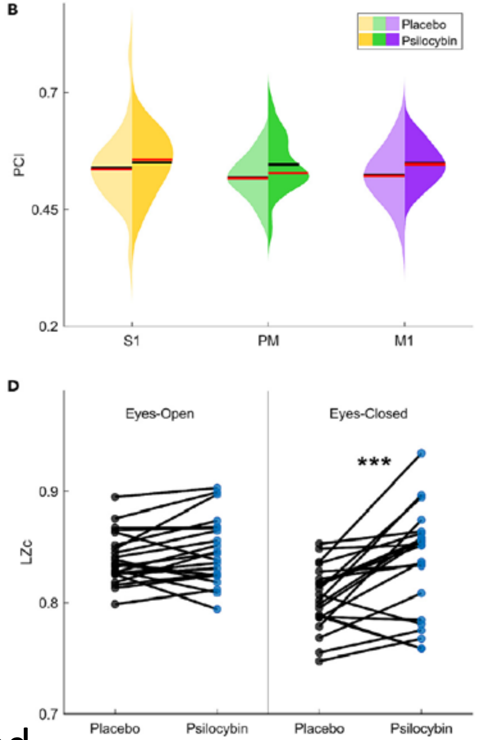
Casanova et al. iScience 2024

# TMS-EEG; Consciousness, Oscillations, and Complexity



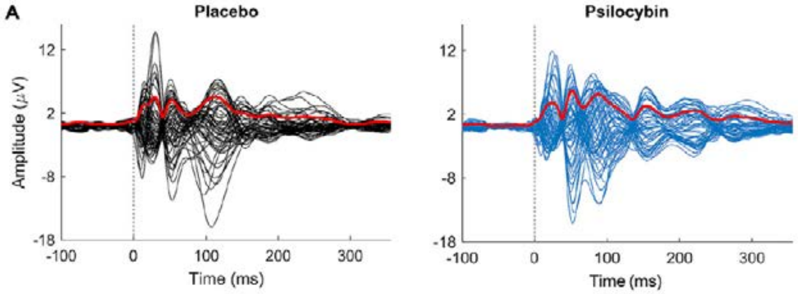




Restin state entropy: increased

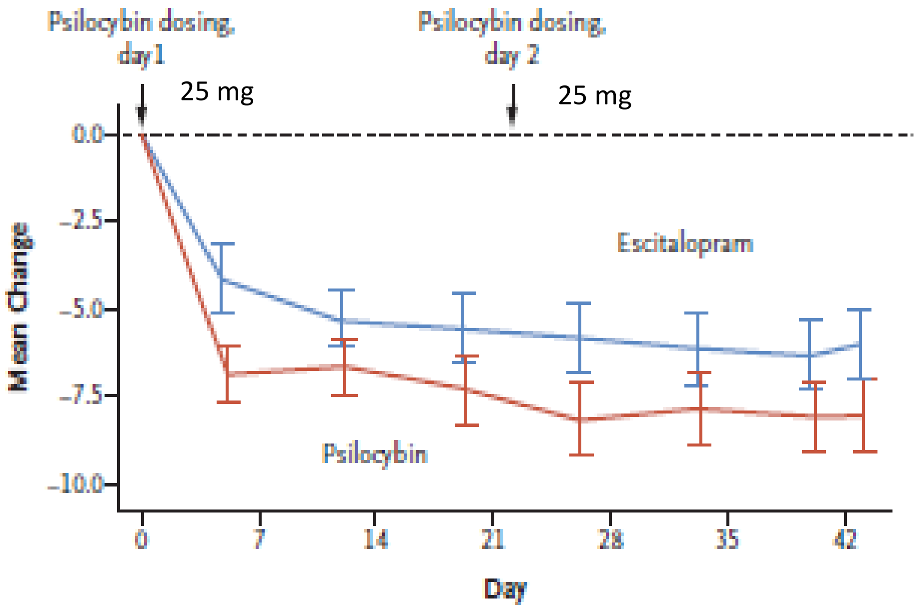
TMS-evoked complexity : normal range




Ort et al, iScience 2023

# Psilocybin: Treatment resistant depression (TRD)

TRD

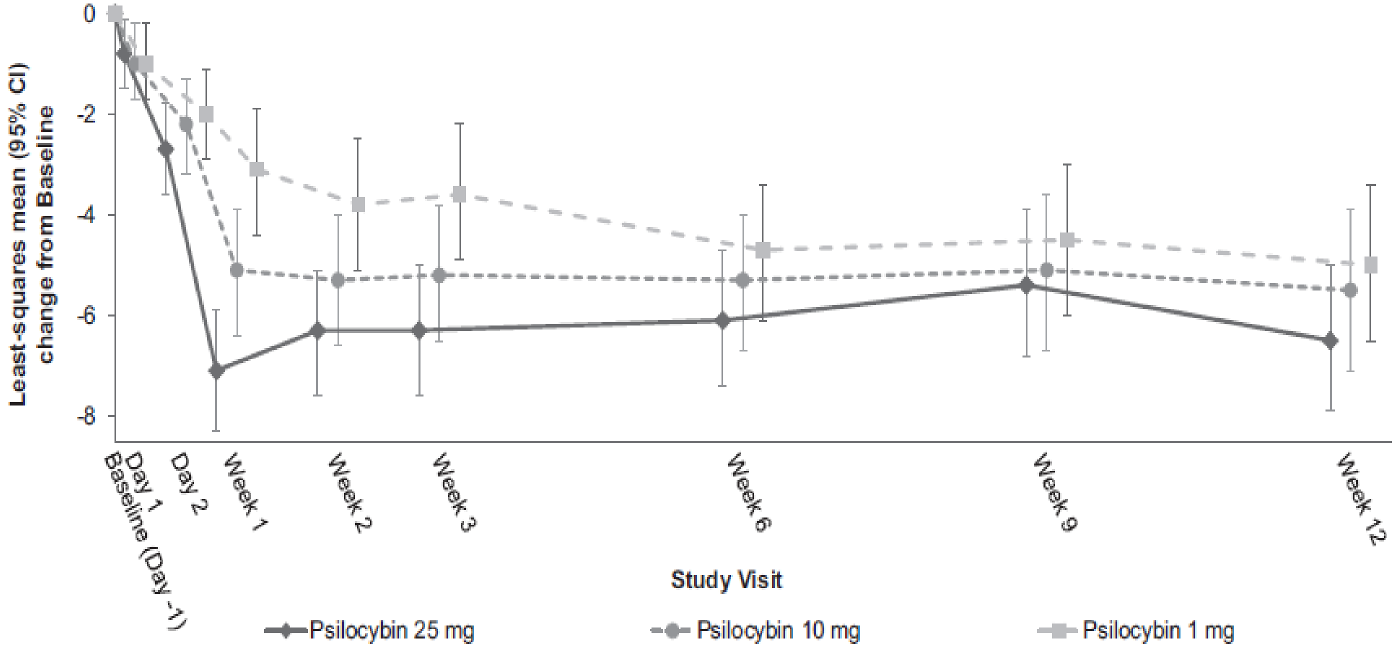



N=59
Randomized double-blind placebo-controlled
Dose: first and second doses 25 mg compared with 6 week dayly citalopram

Model: nondirective psychological support
On accept connect embody model

Carhart-Harris et al. 2021

TRD

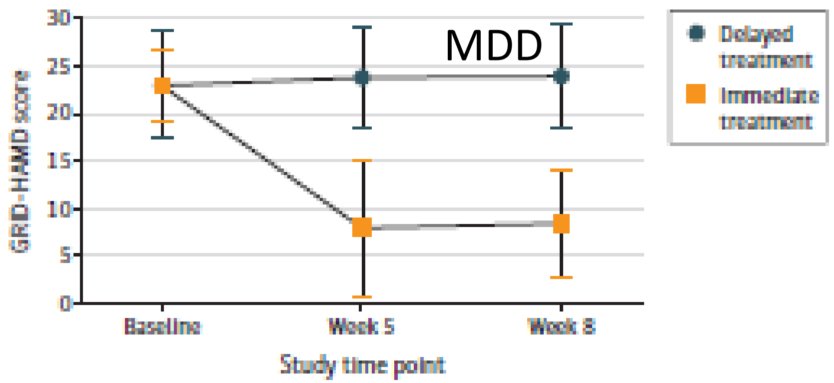



N=232
Randomized double-blind placebo-controlled
Dose: 10 vs 25 mg
Placebo: 1mg

Model: nondirective psychological support manualized

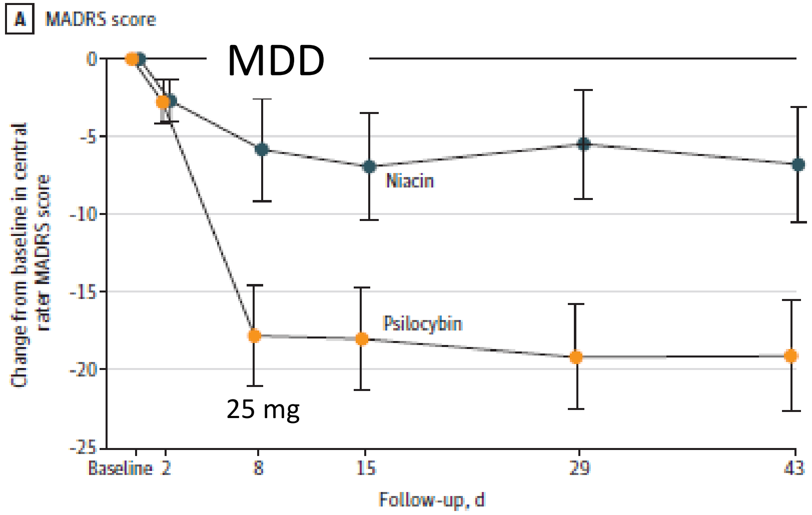
Goodwin et al. 2023

# Psilocybin in major depression (MDD)



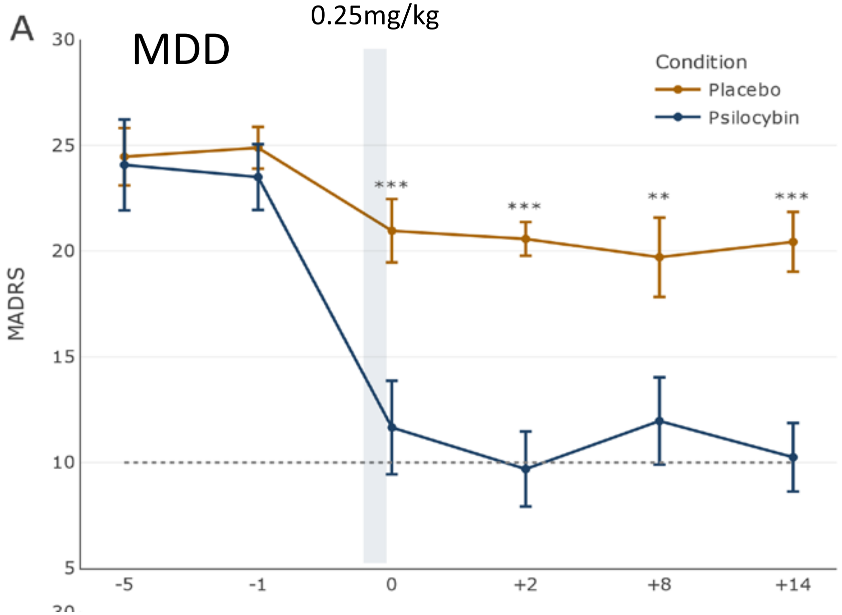

Davis et al. 2020

Randomized , N=24, first dose 20 mg/70kg; sec.30mg/70kg
Model: nondirective psychological support, manualized




Raison et al. 2023

Randomized , N=104,
dose 25 mg
Model: nondirective psychological support, manualized




Remission: 54%
> enduring up to 3 month

R: 58%

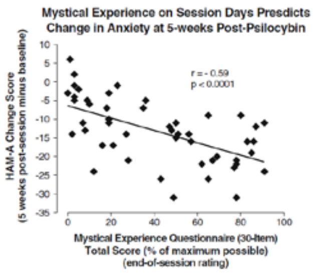
von Rotz et al. 2023

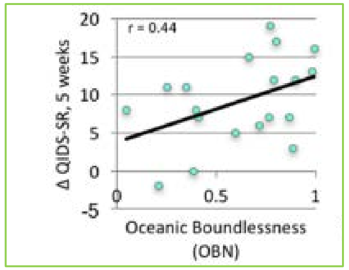
Randomized , double-blind placebo-controlled , N=52,
Model: nondirective psychological support

## Current Depression studies:

- 42% of psilocybin subjects did clinically not significantly respond
- Role of expectancy
- Role of unblinding
- Role of dose
- Role of common therapy factors

# Potential Mediators of acute experience and long-lasting outcome




Griffiths et al. 2018
Ross et al. 2016

Roseman et al. 2018

Mystical-type experience
Oceanic self-boundlessness

- altered self-boundaries
- emotion activation
- challenging emotion

X

- Expectation
- Thr. Alliance

baseline

improvement

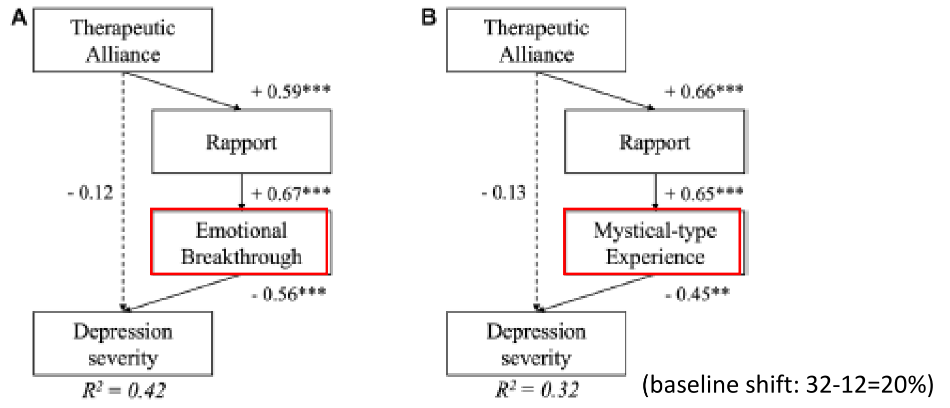
- no relationship between the intensity of MEQtot/OBN and symptom reduction in MDD:
  Rotz et al. 2023, Raison et al. 2023, Sloshower et al. 2023
- 

Impact of challenging emotions
Palhano-Fontes et al. 2018

## Therapeutic Alliance and Rapport Modulate Responses to Psilocybin Assisted Therapy for Depression

Roberta Murphy[1,2]*, Hannes Kettner[1], Rick Zeifman[1,3], Bruna Giribaldi[1], Laura Kartner[1], Jonny Martell[1,4], Tim Read[1], Ashleigh Murphy-Beiner[1,5], Michelle Baker-Jones[1], David Nutt[1], David Erritzoe[1], Rosalind Watts[1†] and Robin Carhart-Harris[1,6†]

reduction



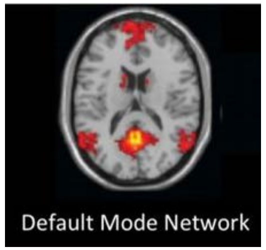

(baseline shift: 32-12=20%)

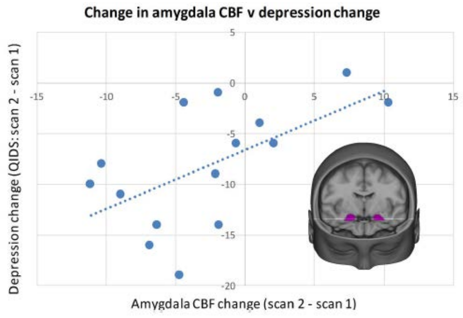
**FIGURE 3** | Path models testing the primary hypothesis that therapeutic alliance would lead to better depression scores 6 weeks following psychedelic-assisted psychotherapy. Serial mediation of therapeutic alliance via pre-session rapport and A) Emotional Breakthrough and B) Mystical-type experiences were supported by the models. Depression severity at the 6-weeks Endpoint was adjusted for baseline depression scores ($p > 0.1$, not displayed in the figure), which by itself accounts for $R^2 = 0.12$, i.e., 12% of variance in the final outcome. Numbers represent standardised regression coefficients for significant (solid) and non-significant (dashed) paths. **indicates $p < 0.01$, *** $p < 0.001$.

- N=30; psi: 2 x 25 mg, interval 3 w (vs escitalopram)
- Ther. Relationship: STAR-P
- MEQtot, EBI, QUIDS
- non-directive support
- Integration: ACE (accept, connect, embody) 35-40 h

Murphy et al. 2022

# BOLD activity and Functional Connectivity after Psilocybin in TRD



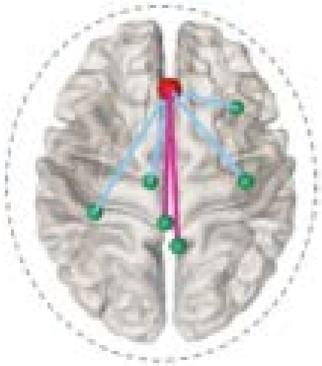




Carhart-Harris et al 2017:
**Reduced BOLD activity in DMN and amygdala**

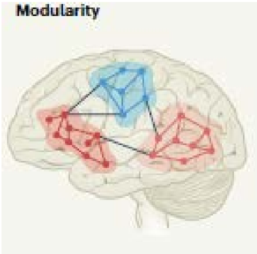
decreased parahippocampal-prefrontal Cx rs-FC
increase bw. vmPFC – inf-lat parietal Cx rs-FC

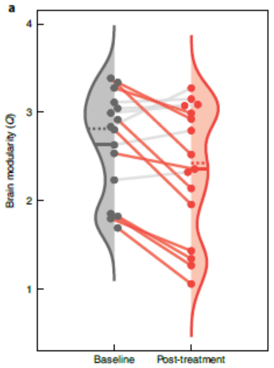
Predicted antidepressant response
at 5 weeks

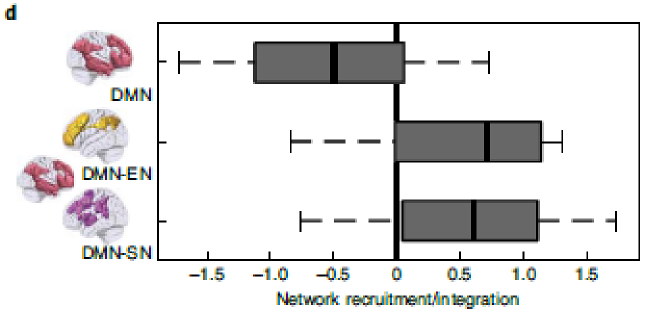
Doss et al 2021:
increased cognitive flexibility and neural flexibility
Change in **dynamic FC bw. ACC –PCC** up to 1-week



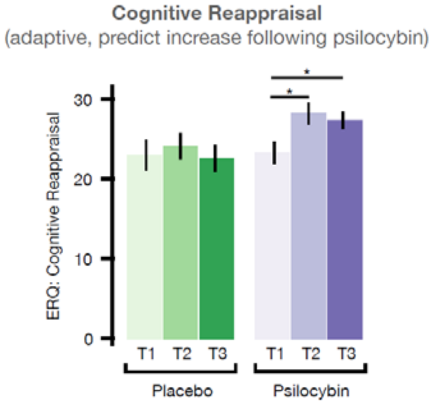
Daws et al. 2022:
**increase global network integration**
(reduced granularity)



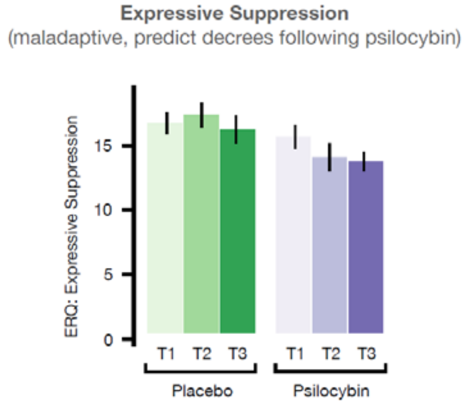



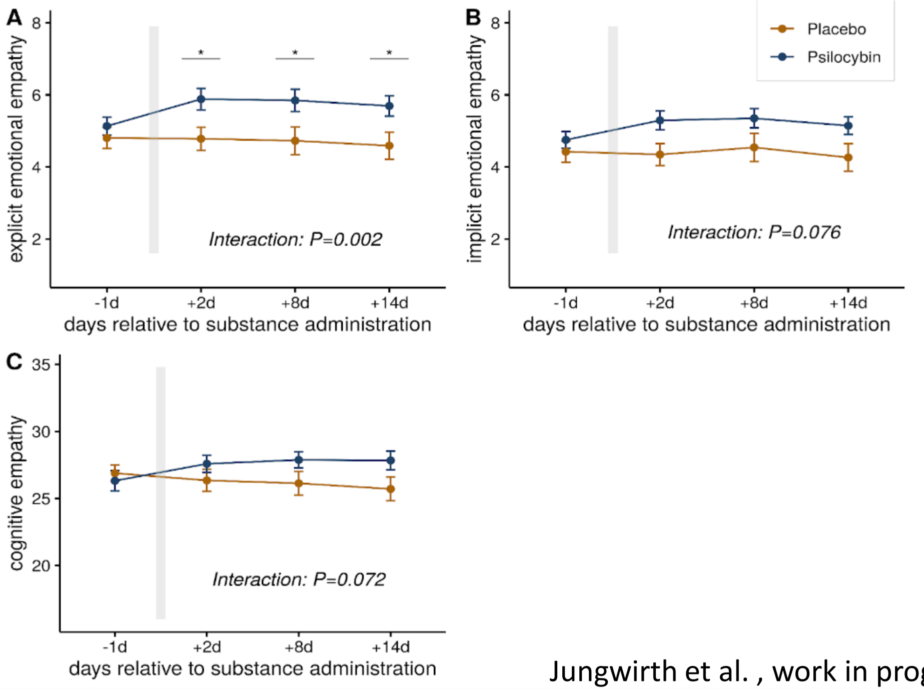



# Emotion Regulation and Empathy after psilocybin treatment in MDD (2 w follow-up)



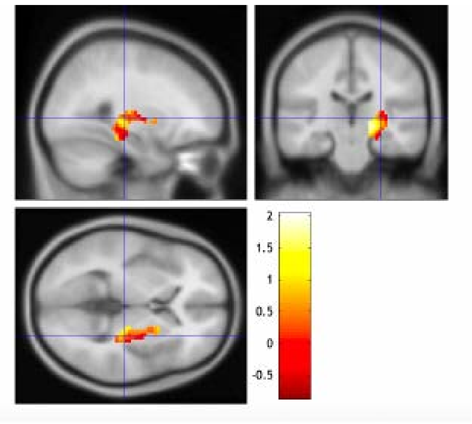

Psilocybin facilitate cognitive reappraisal

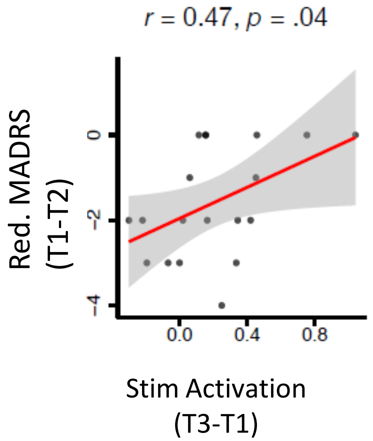


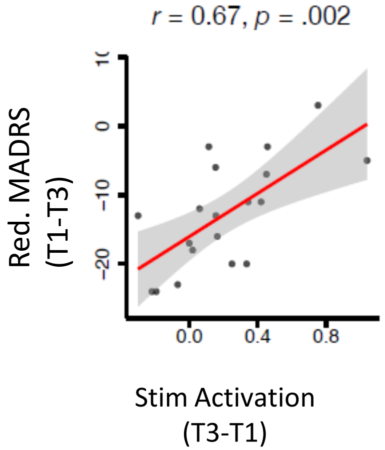




Jungwirth et al. , work in progress

## Emotional fMRT Task






- Psilocybin increase emotional empaty,
- modulates cortical responses to emotional cues correlating with reduced MADRS scores at 1 / 2 weeks follow-up

Moujaes et al., work in progress

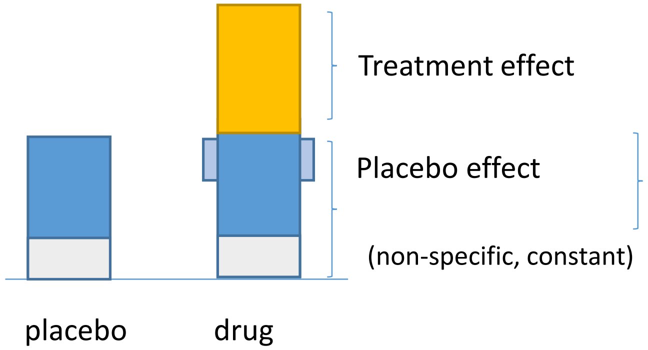
# Challenges in psychedelic treatment: assessment of „placebo“ and interaction effects

## Current designs:

- randomized two-arm
- double-blind
- placebo-controlled

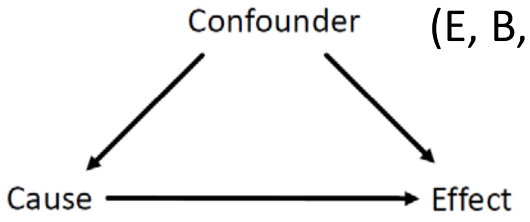
- with psychological support

Additive or interactive




**1) the placebo response refers to the** average symptom response of a group of patients receiving a placebo in a CRT,

2) the **placebo (or nocebo) effect** refers to the **individual** therapeutic effect of receiving a treatment.




(E, B, CTh etc.)

Placebo **response:**

- regression to the mean
- spontaneous remission
- response bias

**no-treatment control condition**
**(**ethical problem)

Placebo **effect**: (mES=0.48)

- P/T: **expectancies** (of success)
- mindset of patient & therapist (beliefs, myth etc.)
- therapy model & rationale
- (rituals)
- **therapeutic alliance** (trust, emotional support etc.)

Contextual effects

**Common factors**
(Allgemeine Wirkfaktoren)
not therapy-specific

The **placebo effect is strongly influenced** by patient‘s **expectancies (E)**

and by the **efficacy of the condition blinding (B)**

as well as by other **non-pharmacological factors** related to the „set“ and „setting“ including the (non-specific) effects from the **concomitant therapy** (CTh)

Lambert 2013, Enck et al, 2008, 2017, Pecina et al. 2014, Enck and Klosterhalfen 2019

# Must Psilocybin Always "Assist Psychotherapy"?

Guy M. Goodwin, F.Med.Sci., Ekaterina Malievskaia, M.D., Gregory A. Fonzo, Ph.D., Charles B. Nemeroff, M.D., Ph.D.

**Drug as catalyst**

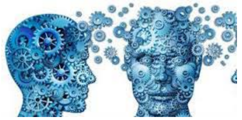
alters

**Psychotherapy**
(evidence-based,
manual-based,
according Guidelines)

modulates

specific techniques

cognition



social cognition

emotions

Self-awareness

translation

Depression

(-Psychopathology
-Cognitive-emotional
models of Depression
-RDoC-guided measures)

Therapeutic support:

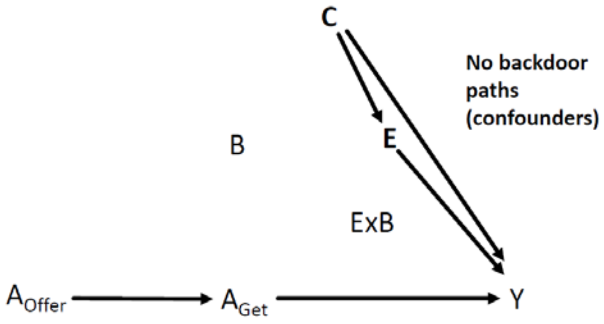
**nondirective counseling**: is applied in most of current studies for psychological safety
it remains unclear to what extend this effort enhances efficacy

Regulatory agencies (FDA, EMA Swissmedic): approve drugs based on efficacy and safety, but not psychotherapies

Am J Psychiatry 2024,181, 20-25

# Casual Model in a Blind RCT

**C** = confounders (vector)
**E** = Expectancies (vector)
Y = Outcome
$A_{Offer}$ = Treatment offered
$A_{Get}$ = Treatment received
B = Blinding
ExB = Expectancy/Blinding Interaction




Intention-to-treat effect is:

$A_{Offer} \longrightarrow A_{Get} \longrightarrow Y$

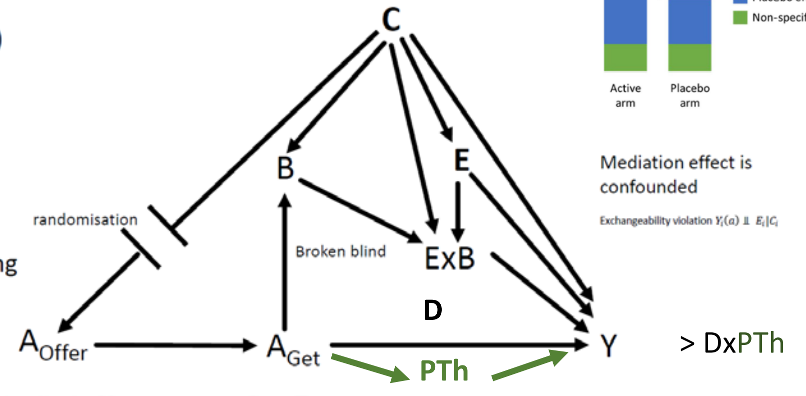
Placebo Treatment with Blind: $Y_{(a=0,b=0)} = C + E$
Active Treatment with Blind: $Y_{(a=1,b=0)} = C + E + A$

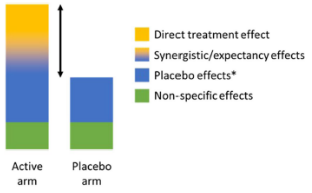
Treatment effect (A) is identified

Muthukumaraswamy et al. 2021, FDA Workshop Jan. 2024

# RCT – with Blind Broken

C = confounders (vector)
E = Expectancies (vector)
Y = Outcome
$A_{Offer}$ = Treatment offered
$A_{Get}$ = Treatment received
B = Blinding
ExB = Expectancy/Blinding Interaction




Mediation effect is confounded

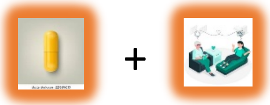
Exchangeability violation $Y_i(a) \not\perp E_i|C_i$

Placebo Treatment with Blind: $Y_{(a=0,b=0)} = C + E$
Active Treatment with Blind: $Y_{(a=1,b=0)} = C + E + A$
Active Treatment no blind: $Y_{(a=1,b=1)} = C + E + A + ExB$

Treatment effect is not identified (in a two-arm trial with broken blind)

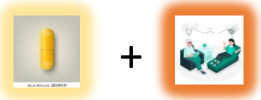
We cannot distinguish treatment effect (A) from placebo effect (ExB)

## Solution: 4-arm randomized db pla-contr. D (2X2)

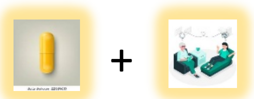


(1) Drug + psychotherapy (e.g. CBT)

(2) Drug + "non-directive counseling"



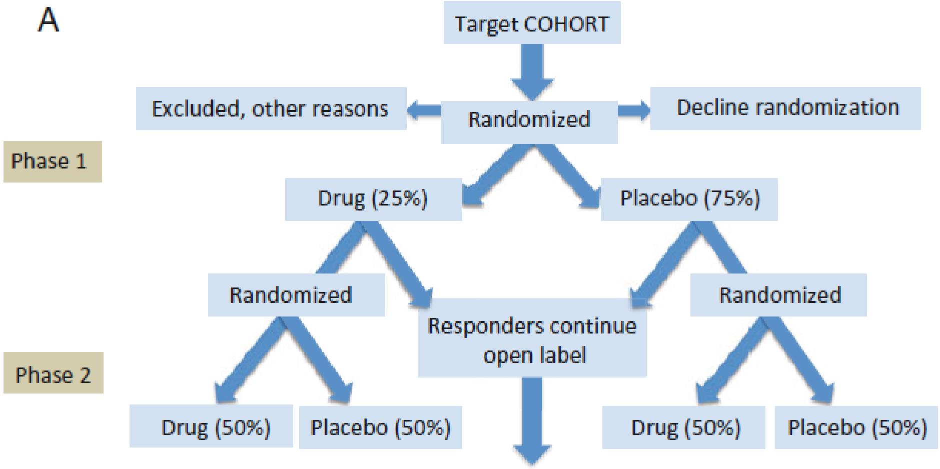
(3) Placebo + psychotherapy (e.g. CBT)



(4) Placebo + "non-directive counseling"

## Sequential 2 x 2 db plac-contr. D (e.g. S-ketamine phase III)

A

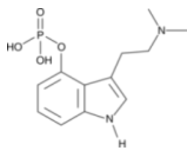



Enck and Klosterhalfen 2019, Butler et al. 2020

# Neuroplasticity and learning: timing of combination treatment – maintenace dosage

5-HT5, 5-HT-7

Psilocybin



5-HT1A

**5-HT2A**

Psychedelic effects

-

+

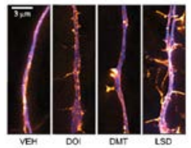
Glutamate

MRS: PFC GLU (-), Hipp Glu (+)
Mason et al. 2020

NMDA → Learning, memory

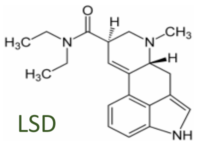
AMPA → *BDNF* > neuroplasticity

trkB
mTOR

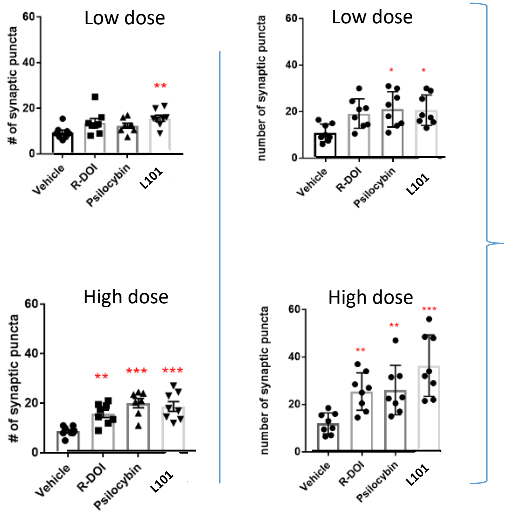



Ly et al. 2018
De Gregorio et al. 2020
Shao et al.2021

(allosteric modulation)



LSD

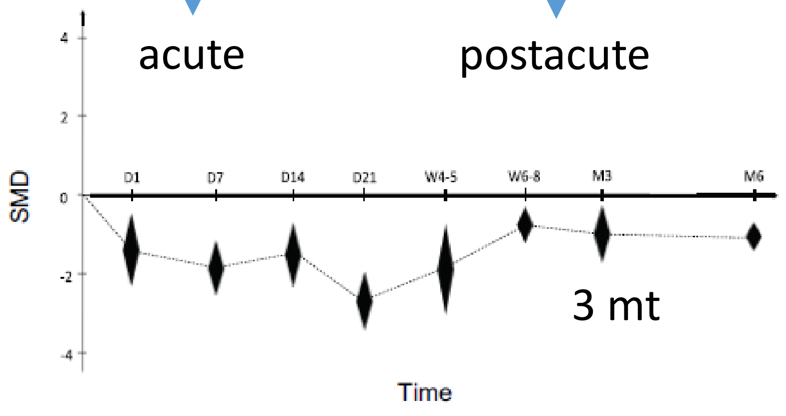



Single dose: after 5 days

repeated doses: after 1 day

increase/decrease of fear memory conditioning depending on timing and context

CBT, MBST, E-R, M




long-term

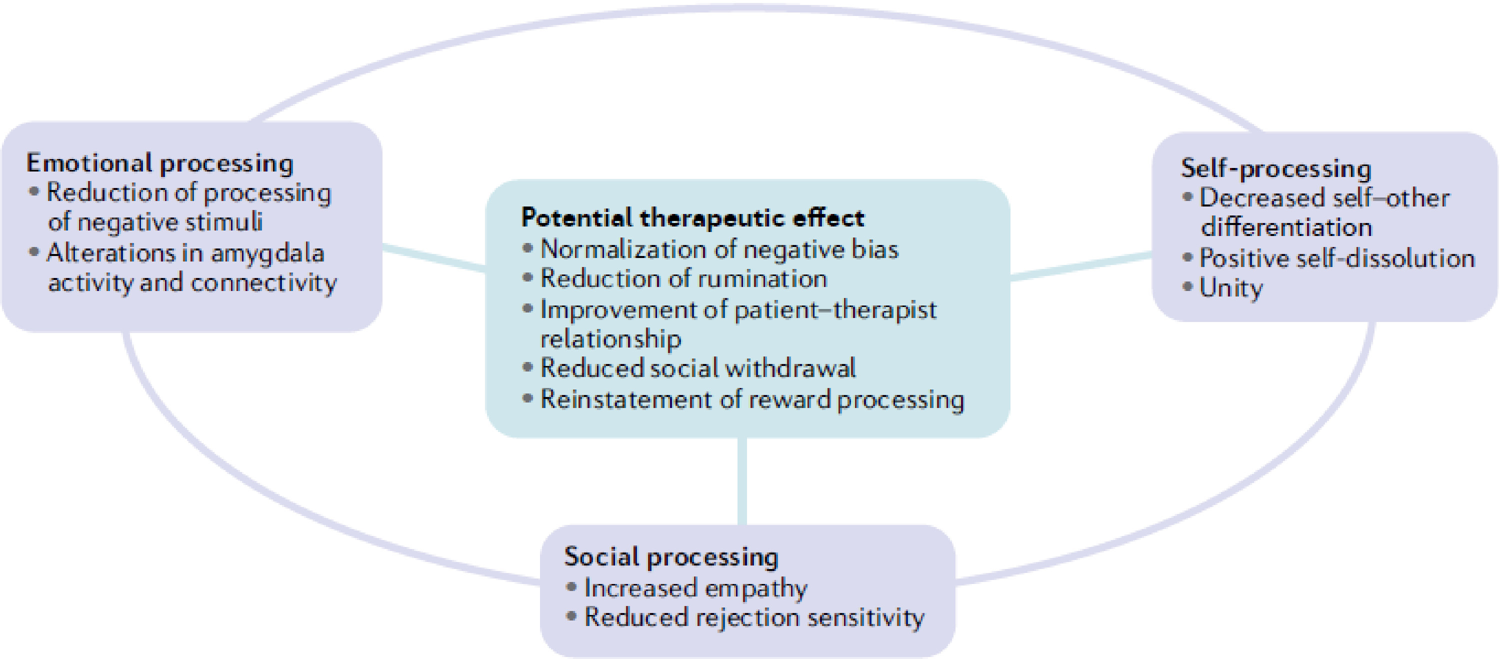
Psychotherapy:
Fast onset > better long-term outcome

ANX/MDD: Duration of symptom reduction

Pryce and Vollenweider, work in progress

Psi(5), DMT (1), LSD (1) Romeo et al. 2020

# Conclusion: Proposed mechanisms that may underlie therapeutic effects




## Outlook and needs:

better understanding of the mechanisms of psychedelic dug action > predictors of outcome

of the dose-response relationship

of the placebo effect which **is strongly influenced** by patient‘s **expectancies** and by the **efficacy of the condition blinding**

of the impact of psychedelic experience, therapy model, and the contribution of the 5-HT2AR for neuroplasticity and learning

# Thanks to

Psychiatrische Universitätsklinik Zürich

Vollenweider Lab

Katrin Preller
Social Cognition
EEG/fMRI

Michael Kometer
Imagery, Cognition
EEG/ERP

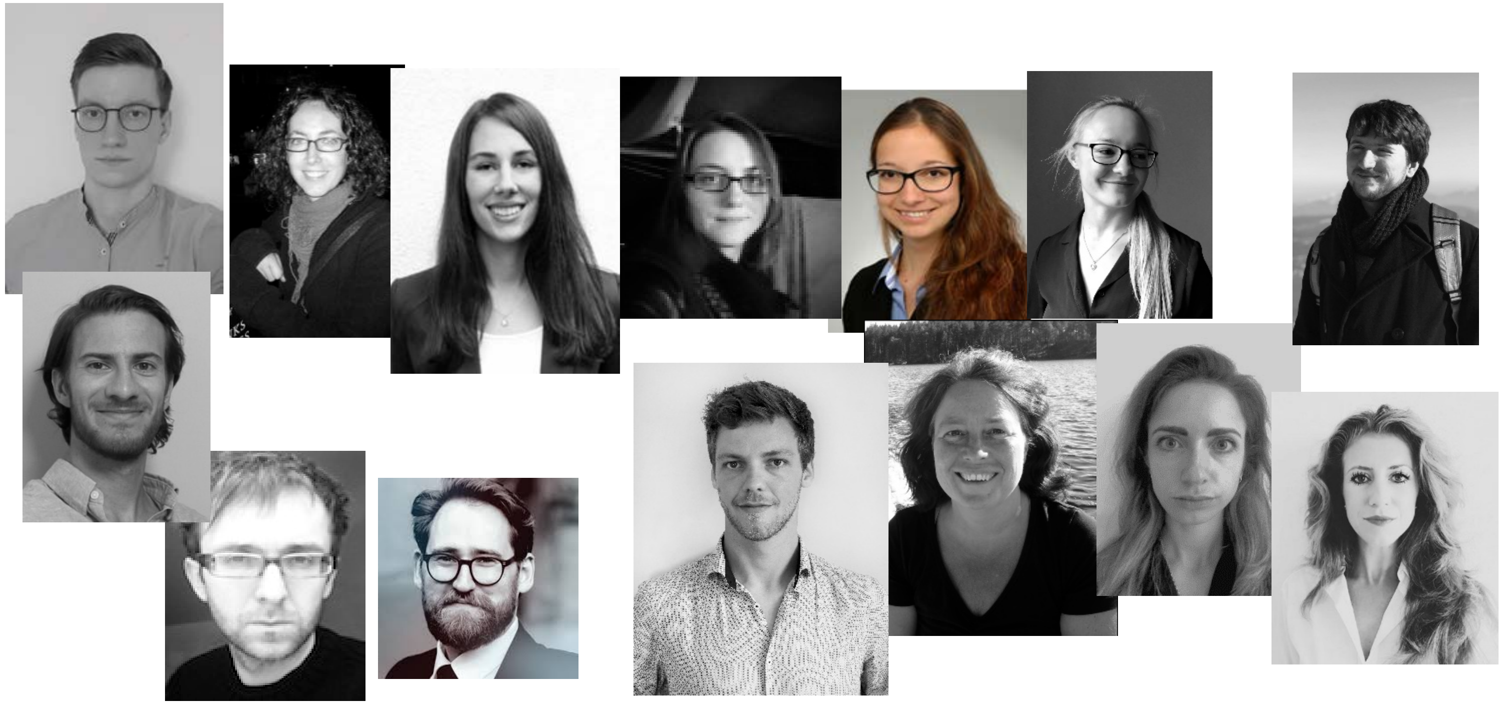
Andres Ort
TMS-EEG, fMRI

Eva Schindowski
Clinical Research
Depression

Markus Herdener
Clinical Research,
Head, Addiction

Chris Pryce
Translational Res.
Head Preclinical Lab.

Philipp Stämpli,
Head MTI Centre



Robin von Rotz
John Smallridge
Andrea Casanova
Fabian Schäfli
Sascha Fink
Raphaela Schöpfer
Lukasz Smigielski
Patricia Dürler
Nathali Rieser
Flora Moujaes
Katharina Zahoranszky
Anja Seidl
Sara Romer

# Acknowledgments


## Collaborators

**Institute for Biomedical Engineering ETH-ZH:**
Klaas E. Stefan
Anke Henning
Andrea Diaconescu

**MPI of Psychiatry Munich:**
Leonhard Schilbach

**University of Ulm:**
Dan Pokorny

**FU Berlin:** Isabel Dziobek

**UCSD:** Mark Geyer

**UCSD:** Martin Paulus

**University of Milano:**
Marcello Massimimi, Simone Sarasso

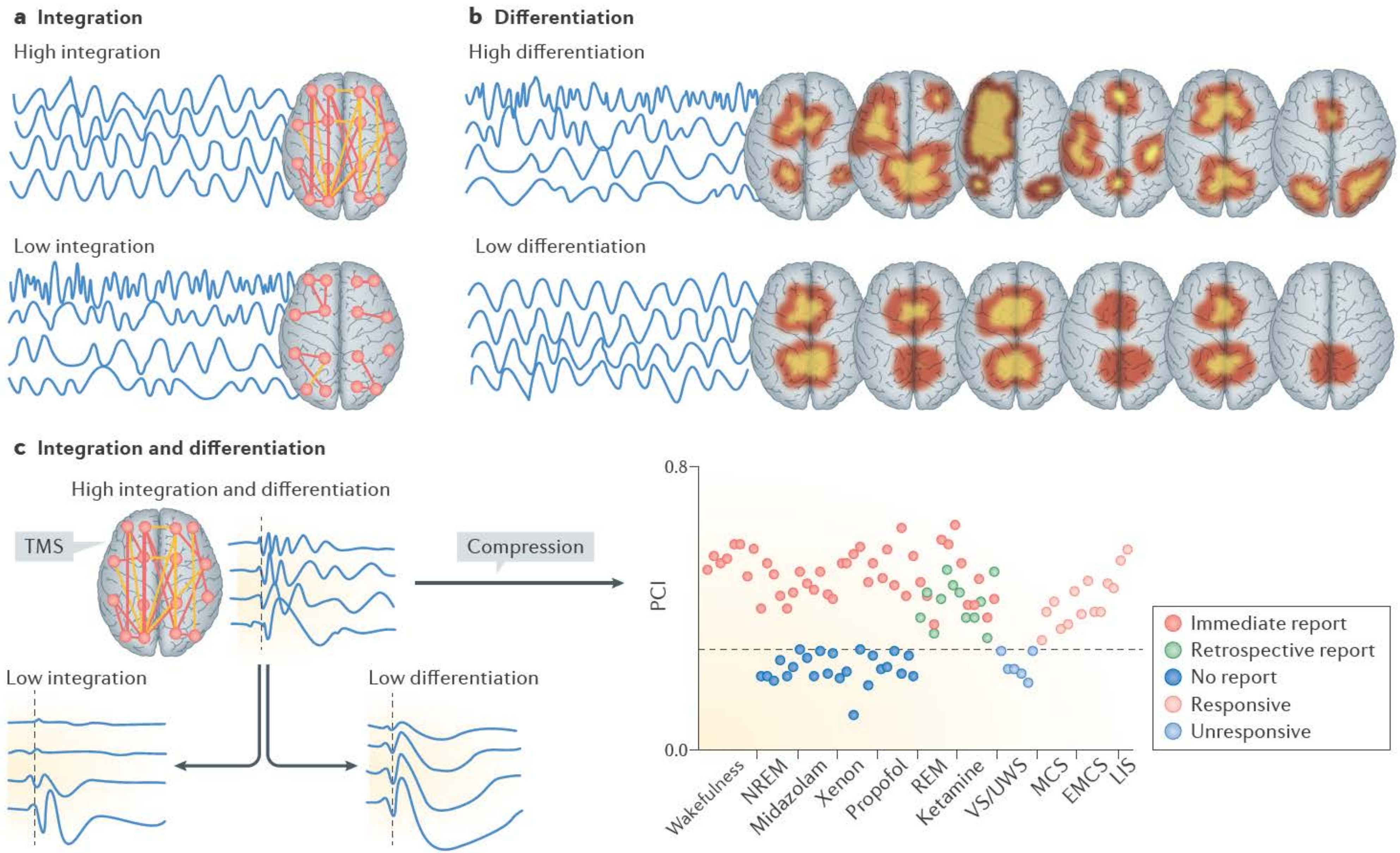
**Wellcome Trust Centre for Neuroimaging**
Karl Friston
Peter Zeidman
Adeel Razi

**University of Madison:**
Giulio Tononi

**Paul Alan Institute Seattle**
Christof Koch

**Yale University:**
Alan Anticevic
John Krystal

**Monash University, Australia**
Devon Stoliker
Adeel Razi



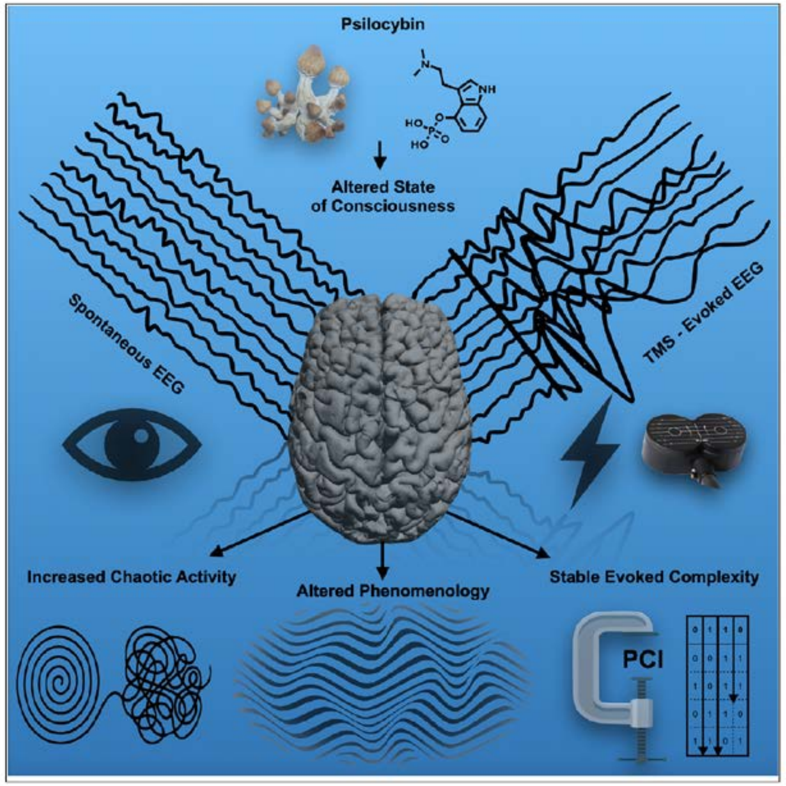
a Integration
High integration
Low integration
b Differentiation
High differentiation
Low differentiation
c Integration and differentiation
High integration and differentiation
TMS
Compression
Low integration
Low differentiation
0.8
0.0
PCI
Wakefulness
NREM
Midazolam
Xenon
Propofol
REM
Ketamine
VS/UWS
MCS
EMCS
LIS
Immediate report
Retrospective report
No report
Responsive
Unresponsive

iScience

CellPress
OPEN ACCESS

Article

# TMS-EEG and resting-state EEG applied to altered states of consciousness: oscillations, complexity, and phenomenology




Andres Ort, John W. Smallridge, Simone Sarasso, ..., Katrin H. Preller, Giulio Tononi, Franz X. Vollenweider

ort@bli.uzh.ch (A.O.)
john.smallridge@uzh.ch (J.W.S.)

## Highlights

Psilocybin induces a state of increased sensory-emotional awareness and arousal

Psilocybin induces both spontaneous and TMS-evoked EEG spectral changes

Perturbational complexity is unaltered unlike that of spontaneous EEG activity

These results help characterizing drug-induced altered states of consciousness

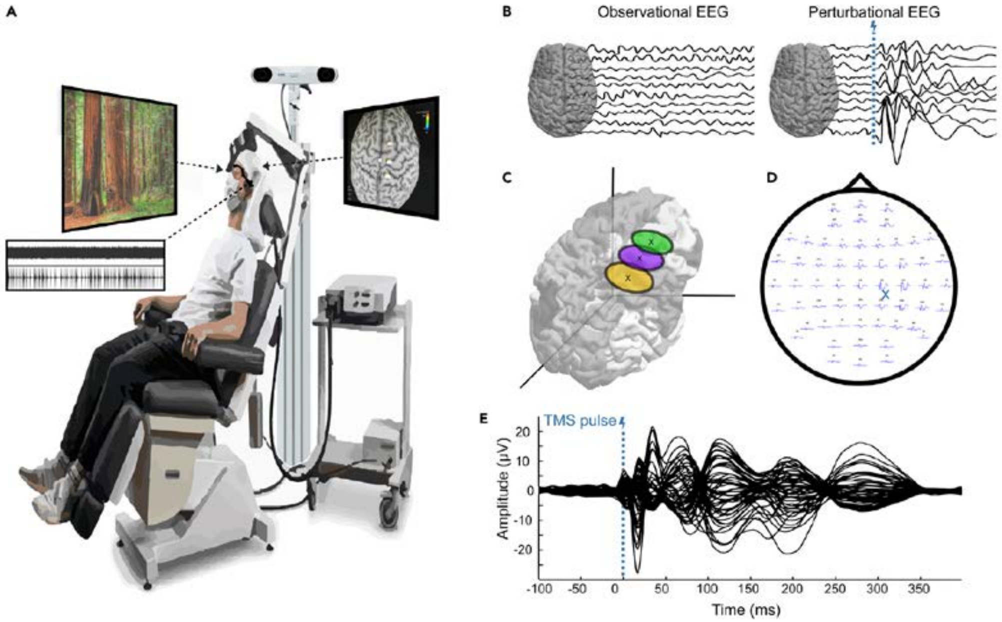
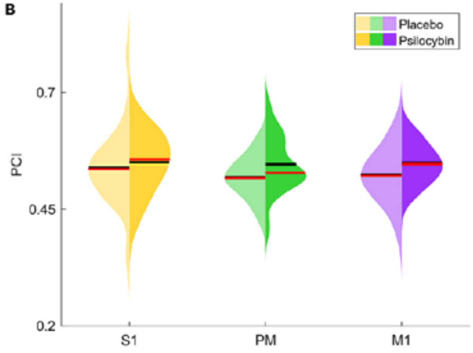
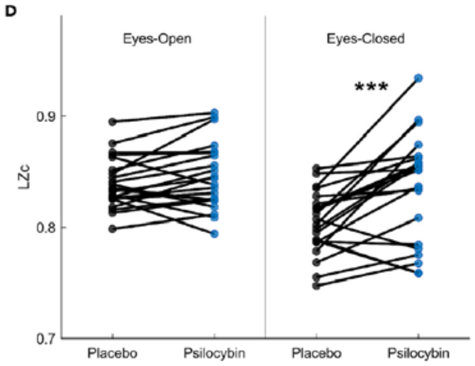



**Figure 1. The TMS-EEG setup for real-time monitoring**

TMS Network activation during psilocybin states:
e.g. somatosensory cx: S1




Resting state
LZ complexity

(index for entropy)

**Placebo**

**Psilocybin**