Psilocybin: Wirkmechanismen und Anwendung in der Depression

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Themen

1. Kurze Geschichte der Pschedelika-Forschung (Schweiz)

2. Was sind Psychedelika?

    -Neuropharmakologie
    -Psychologische Perspektive - Phänomenologie

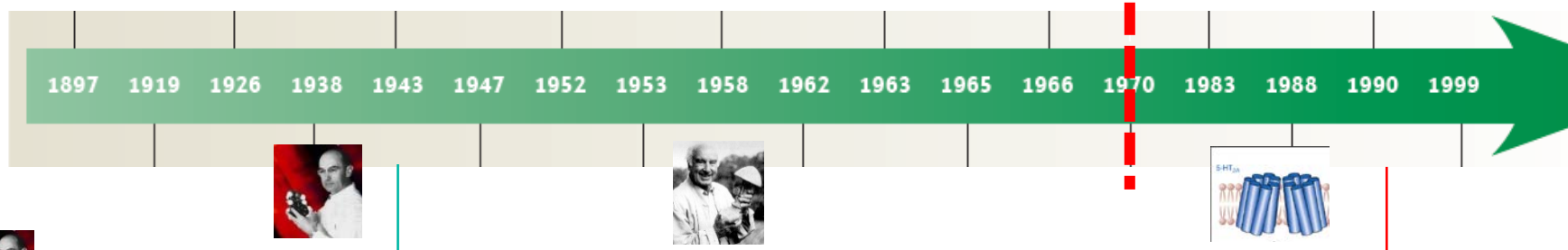
3. Ergebnisse früher klinischer Studien und postulierte psychologische Wirkmechanismen

4. Neurokognitive Modelle der Depression und postulierte Wirkmechanismen von Psilocybin

    - Emotionsregulation
    - Selbst und selbst-referenzielle Prozesse (Body self)
    - Soziale Kognition

5. Ergebnisse aktueller klinischer Studien mit Psilocybin: Depression und Angst

Brief History of Psychedelic Research (PUK/CH)

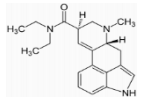


1988. Sander-Bush

«revival of clinical use»

CH: 2010 (Gasser)

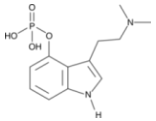
USA/GB: 2016 (Grob)



1947: LSD **as model of psychosis** (Stoll)

1948: LSD **as ajunct in depression** (Condrau and others)

1959-ff: **Psilocybin** as ajunct in **psychotherapy** (Gnisss, Heimann and others)



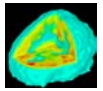
1950-1970:

Psycholytic Therapy (Europe)(e.g., Sandison, Leuner, Bastiaans)

Psychedelic Therapy (US)(e.g., Richards, Pahnke, Cohen)

1975-1986: Psychology of psychedelics, 5D-ASC (Dittrich, Angst, Scharfetter and others)

1988-1993ff: SAePT: **Psychedelic-assisted psychotherapy** (Styk, Gasser, Oehen and others),



1992-ff: Neurobiology of Psychedelics (Vollenweider)

- Phenomenology
- Neuropharmacology, Safety

- Neurophysiology (e.g. perception, emotion, self)

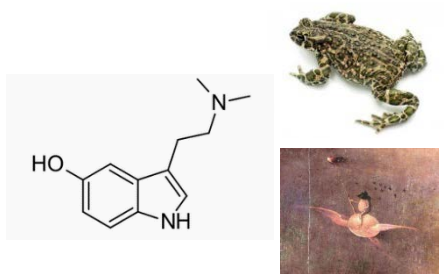
- Molecular basis and behavior (neuroplasticity) (Pryce)

2018-ff: Proof-of concept Clinical Trials with Psilocybin (depression, alcohol use disorder)

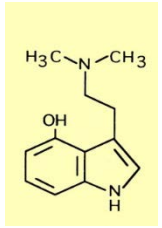
Volllenweider and Kometer Nat .Rev. Neurosci. 2010

Chemical Classification: Psychedelics (or classic Hallucinogens)

- Tryptamines (Indoleamines)

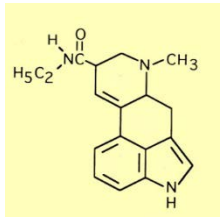


DMT in Ayahuasca

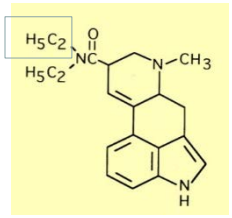


Psilocybin

- Ergoloides

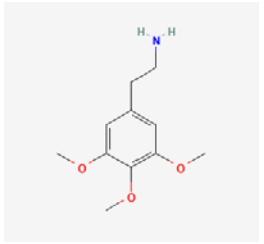


LSA



LSD

- Phenylethylamines

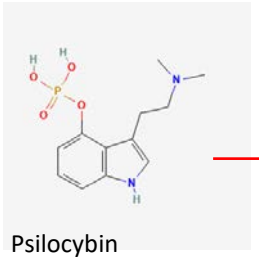


Mescaline

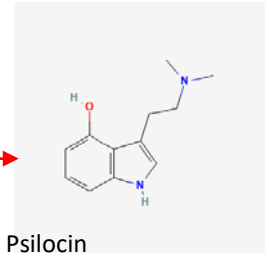
Eleusis, Plotin

Neuropharmacology: Serotonergic mechanisms and downstream effects

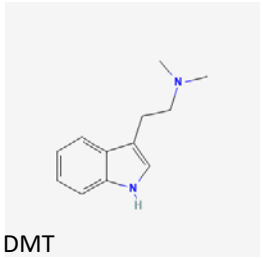
Serotonin im Gehirn



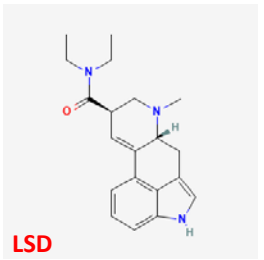
Psilocybin



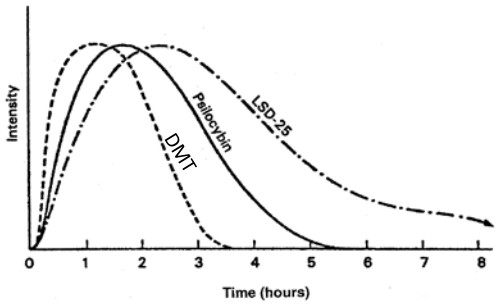
Psilocin

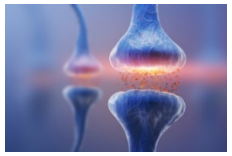


DMT



LSD





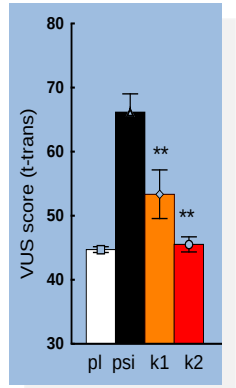
Agonists

5-HT 7 5-HT 6 5-HT 1 **5-HT2A** D2 D1

\- + (+)

GABA Dopamine

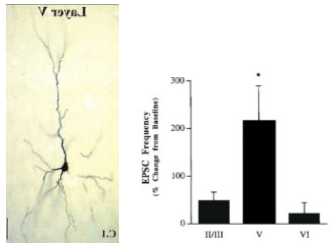
Glu release



Psilocybin
LSD

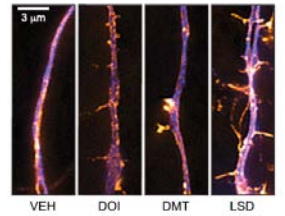
5-HT2A Antagonist Ketanserin

Vollenweider et al. 1998
Preller et al. 2016



Aghajanian & Marek 1999

AMPA → *BDNF* > neuroplasticity
trkB
mTOR



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

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

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

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

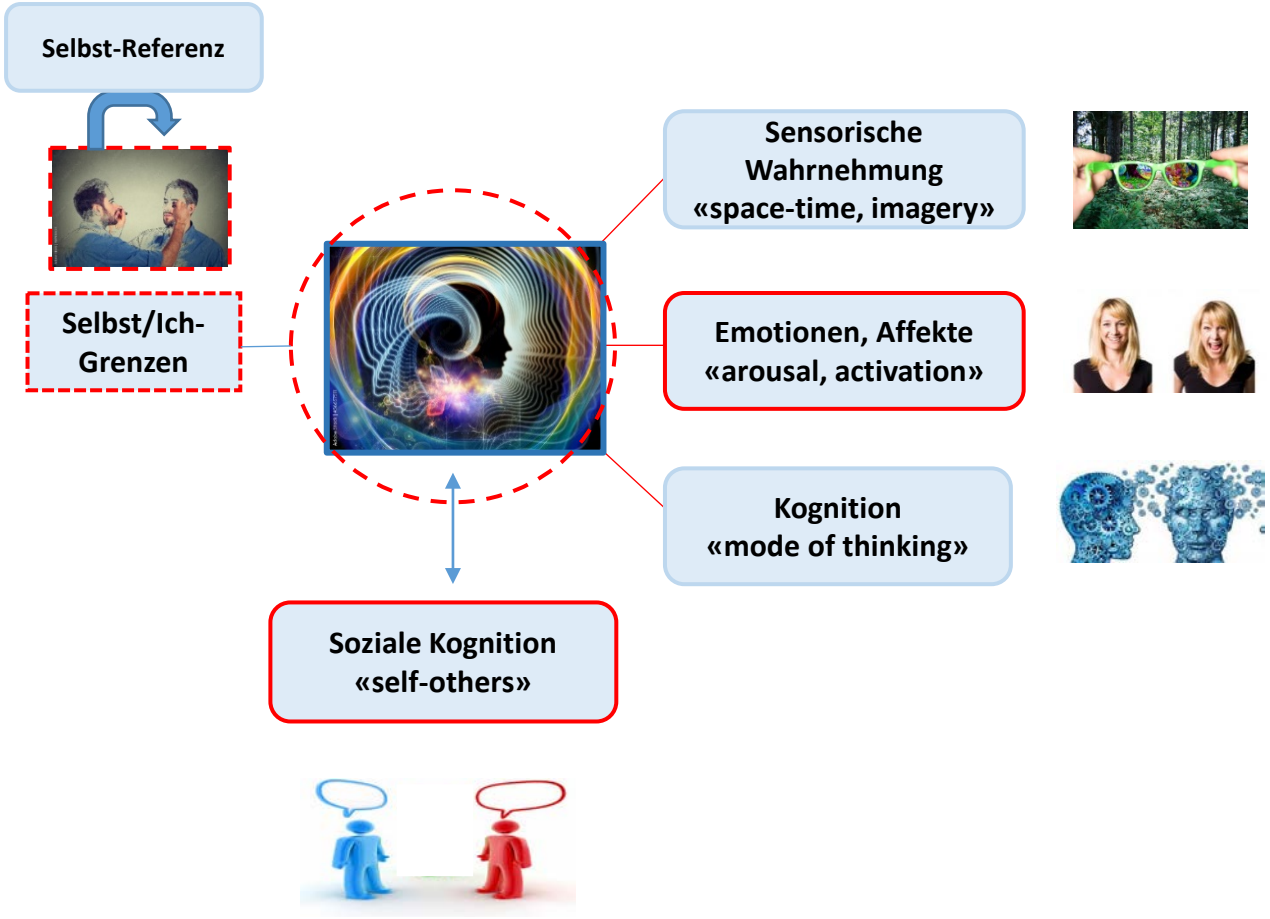
NMDA → Learning, memory

Phänomenologie der Psychedelika-Erfahrung (1. Pers.-Perspektive)

Veränderter Wach-Bewusstseinszustand (ASC)

charakteristische Veränderungen*:*

- *Sensorischen Wahrnehmung*
- *Affekte, Emotionen*
- *Cognition und Meta-Cognition*
- *Selbstwahrnehmung, Selbst-Umweltabgrenzung*



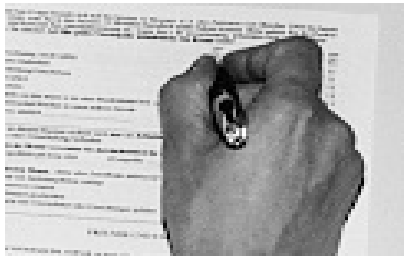
Ähnliche Erfahrungen:

z.B. im Traum, in meditativen Zuständen oder visionären Ekstasen



Assessment of Psychological basic Dimensions of Psychedelics States (5 main factors)

5D-ASC Scale (96 vis. AS)



„Altered Perception“
-Visionary restructuralisation: VR

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

Altered Vigilance

Acoustic Alterations

„Positive Self/ego-dissolution“
-Oceanic self-boundlessness: OBN

Self /ego
boundaries

medium doses

high doses

„Negative Self/ego-dissolution“
-Dread of ego-dissolution: DED

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

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

11D-ASC Scale

OBN-tot Score ⟷ **MEQ-tot Score**

R=0.68-0.8

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

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

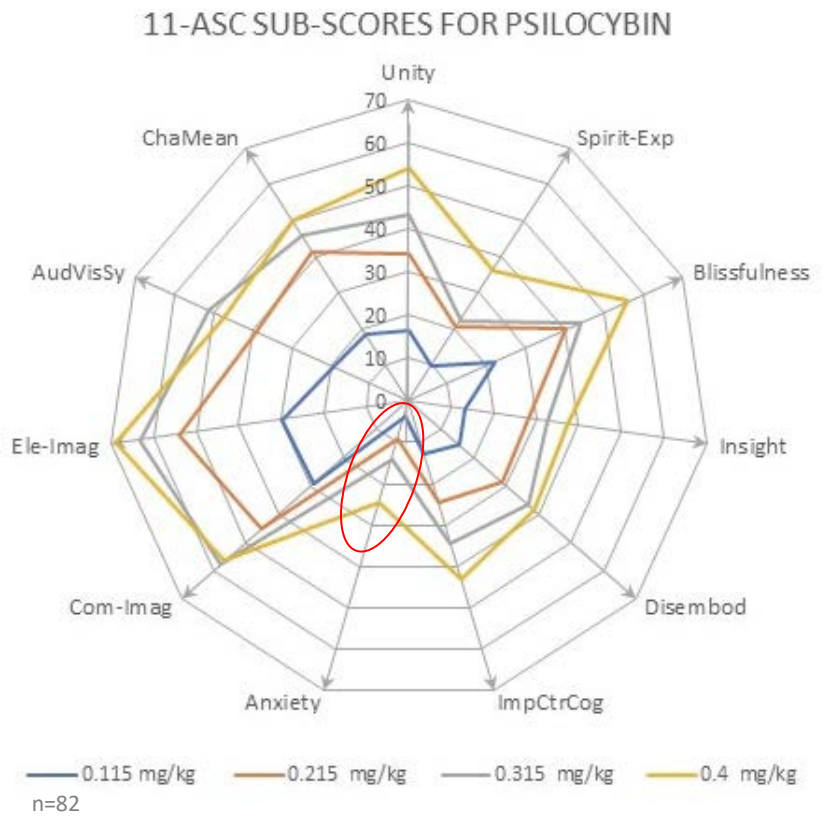
EDI Inventory (16 items)

R=0.73

Dittrich 1985, 1998: (n=345), Studerus et al . 2010, 2011 (n=312)

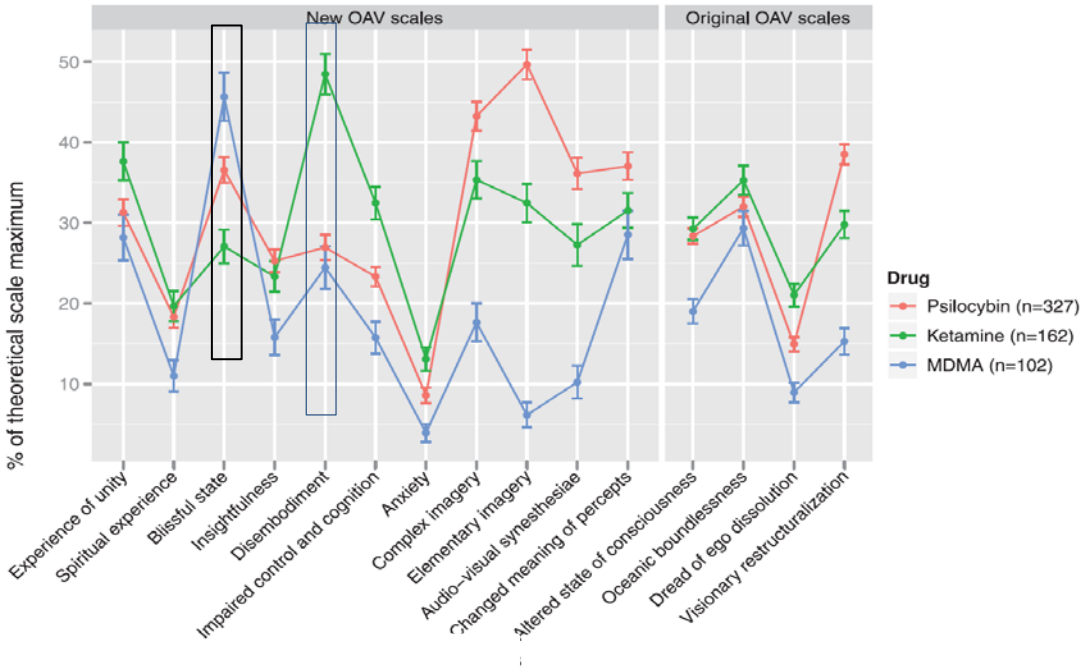
Hood 2006, 2016, Hood et al. 2009, Barrett et al 2015, Nour et al. 2015

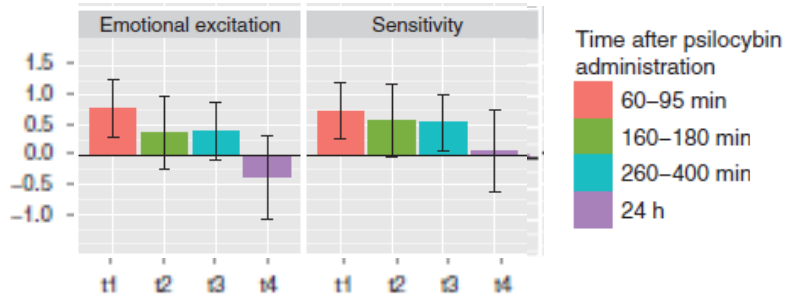
Dose-response relationship and discrimination of Psychedelics and related compounds



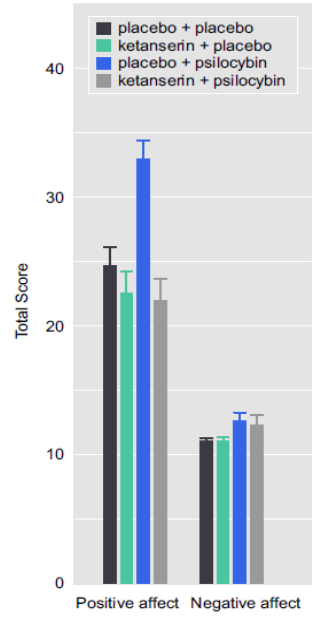
11D-ASC and 5D-ASC

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

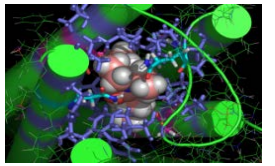




PANAS (pos./neg. emot.)



The 5-HT2AR antagonist Ketanserin: blocks the increase in pos. emotions

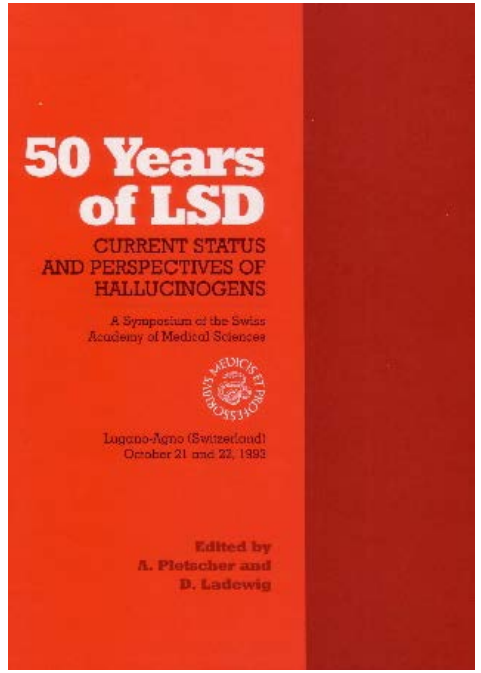


Kometer et al. 2013

Studerus et al. 2010, 2011,Vollenweider und Kometer 2010

Frühe klinische Ergebnisse zur Psychedelika Therapie

1956 - 1972: > 150 Publikationen zu psychodynamisch-orientierten (vorwiegend „*psycholytischen*“) Psychotherapien mit LSD und Psilocybin:



- Leuner 1994 (n=422): Verbesserung der Symptomatik bei Patienten mit **therapie-resistenten Depressionen (64%),** **Angsterkrankungen (56%),** **Alkoholabhängigkeit** (46%)

- Mascher 1967: Metaanalyse von 42 Studien (n=1603): Verbesserung der Symptomatik bei Patienten mit „**neurotischen“** **Depressionen (68%) und Angsterkrankungen (70%)**

- Panke 1968 (Maryland Psychiatric Research Center, Spring Grove) *„Psychedelische“ Therapie*, Existentiell-humanistischer Therapieansatz: sign. **Angstreduktion** bei **terminalen Krebspatienten** (n=132)

Kritische Re-Analyse

- Rucker et al. 2016: Metaanalyse von 19 Studien (n= 423): 79.2% klin. sign. Verbesserung bei Patienten mit **unipolarer** Depression

(Kontrollbedingungen oft mangehaft, unterschiedliche Anzahl an drug sessions)

Therapie-Design und postulierte Psychologische Wirkmechanismen von Psychedelika (n. Leuner 1982)

Formale Elemente des Therapieprozesses:

Vorbereitung (3-4 Sitzungen)

- *Vertrauensbildung (ther. Allianz und Rapport)*
- *Themenfokussierung, Intension*
- *Bedeutung & Haltung des Therapeuten*
- *Erwartungen des Patienten*
- *Aufklärung des. Pat. über mögliche Erlebnisformen*

Substanz-Sitzung(en) (1-2 S. im Abstand 2-4 Wo).)

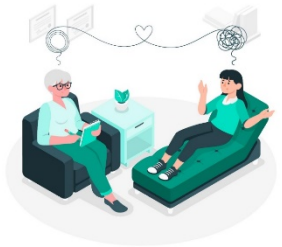
- *Therapeut: empathisch supportive Haltung*
- korrigierende Neuerfahrung
- (Musik bis über Peak-Erfahrung)
- erste Integration der Erfahrung nach akuten Wirkung

Integration: Nachsitzungen (7-12 S.)

- Verstehen und »Durcharbeiten» der Erfahrungen und Einsichten und deren Übernahme in den Alltag
- korrigierende Neuerfahrung

6-12 Wochen

Neue Studien: Kombination mit CBT,
Emotion-focused Therapy
Mindfulness Übungen als Vorbereitung



Inhaltliche Elemente des Therapieprozesses

Regression des Selbst & Ich-Funktionen

Lockerung der kognitiven Kontrolle («Abwehr»)

\+ indirekt

+ dir

emot. Arousal, Aktivierung schwer-zugänglicher persönlich relevanter Emotionen und Schemata, Auflösen von Ambivalenzen: Einsicht, Verstehen, Akzeptanz, Trauer

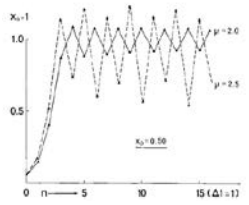
Visualisierung / Symbolisierung von Emotionen, Erinnerungen und Verhaltensmustern, Einsicht, Verstehen

Leuner 1982: Halluzinogene in Forschung und Therapie

Grundformen und Dynamik des akuten Psychedelischen Erlebens

Fluktuierend-szenische,
(«oneiroide») Verlaufsform

Psycholytisch bis psychedelisch:

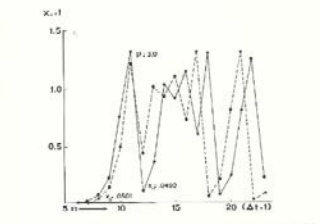


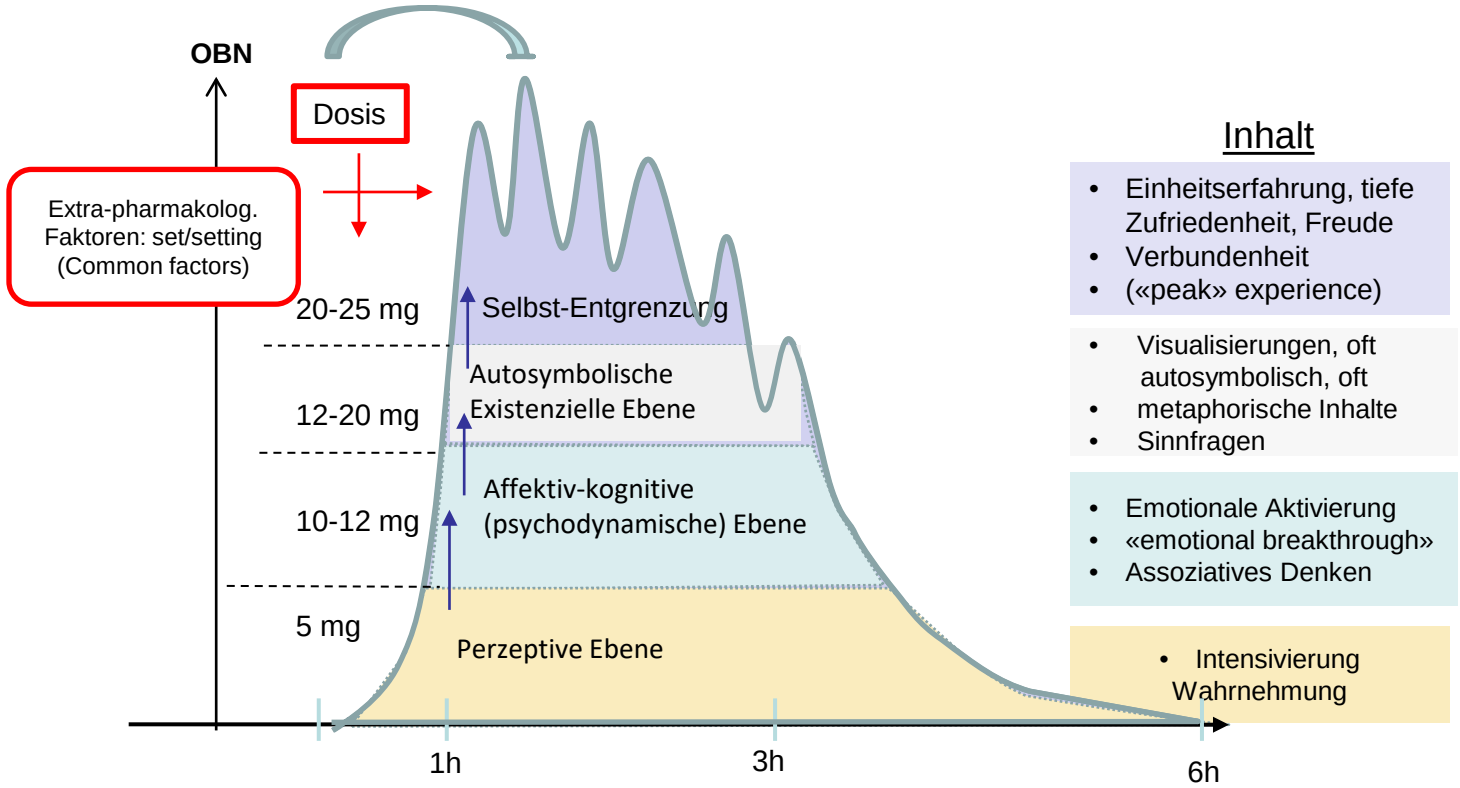
Dosierung

Ziel:
Aufrechterhaltung der kognitiven Einsicht

Stagnierend-fragmentarische,
(«psychotische») Verlaufsform

mit höheren Dosis steigt die Inzidenz für angstvolle Erfahrungen





Inhalt

- Einheitserfahrung, tiefe Zufriedenheit, Freude
- Verbundenheit
- («peak» experience)

- Visualisierungen, oft autosymbolisch, oft
- metaphorische Inhalte
- Sinnfragen

- Emotionale Aktivierung
- «emotional breakthrough»
- Assoziatives Denken

- Intensivierung Wahrnehmung

Prozesse:

- Selbstrepräsentanz
- Selbstreferenz
- soziale Kognition

- Imagination
- Körperwahrnehmung

- Emotions-Regulation
- Kognition
- kognitiv-emotionale Interaktion

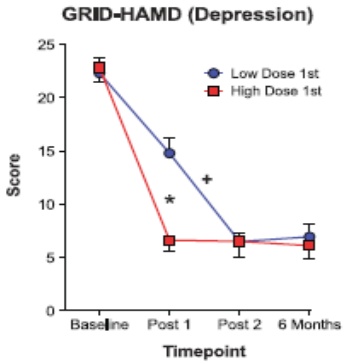
Modulation durch Psychedelica?

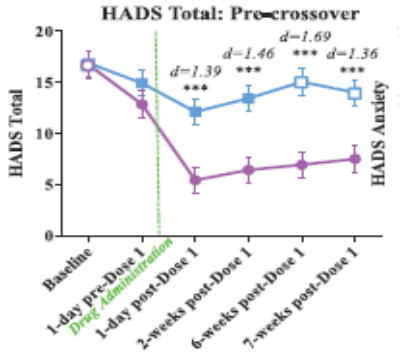
Relevanz für den therapeutischen outcome?

Leuner 1981, Masters and Houstons 1969, Preller und Vollenweider 2018

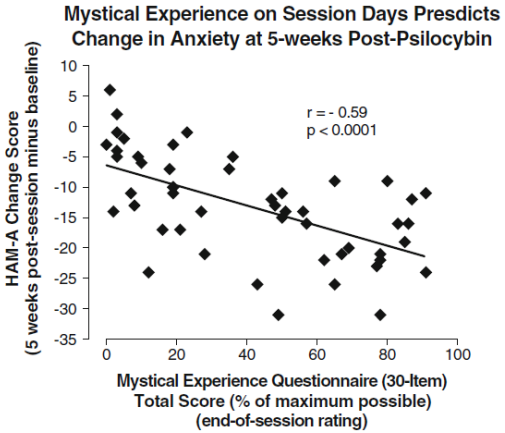
«Rivival»: Neue Studien: Psilocybin – Pos. Selbstentgrenzung und Symptomreduktion

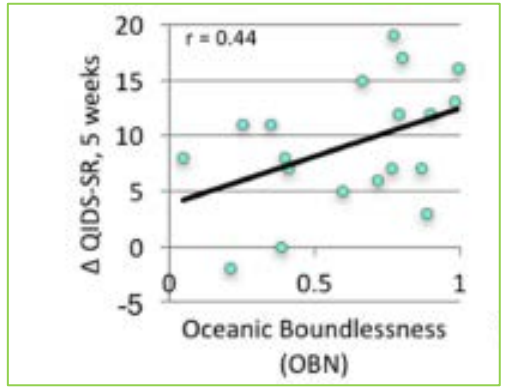
- **Summenscore** für “mystical-type experience” (MEQ) sowie “positive Selbst-Entgrenzung (OBN) mediiert /korreliert mit der Reduktion von Angst und Depression bei Patienten mit MDD und TRD



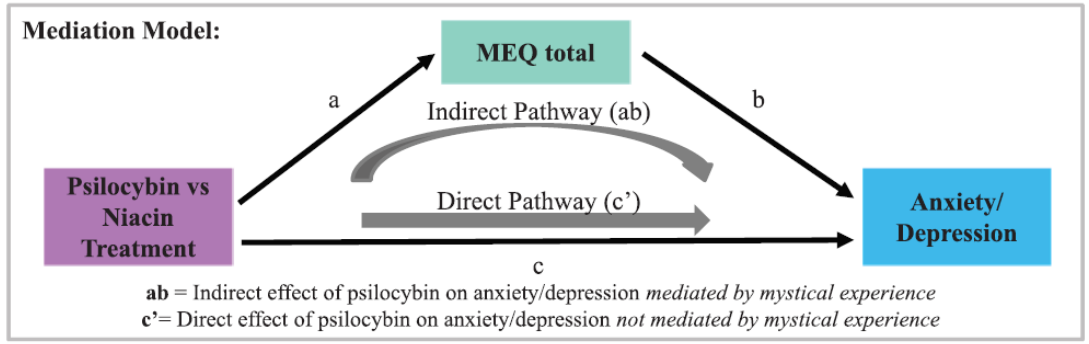


Griffith et al., JP 2016, 2022 Ross et al., JP 2016, 2018

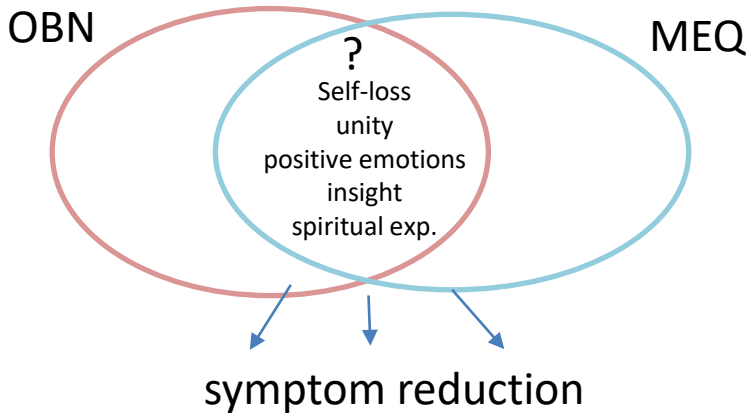




Roseman et al. 2018



Offene Frage:



Griffiths et al. 2016, 2011, Ross et al. 2016, MacLean et al. 2001, Smigielski et al. 2019, Carhart-Harris et al. 2016

Neurokognitive Modelle der Majoren Depression

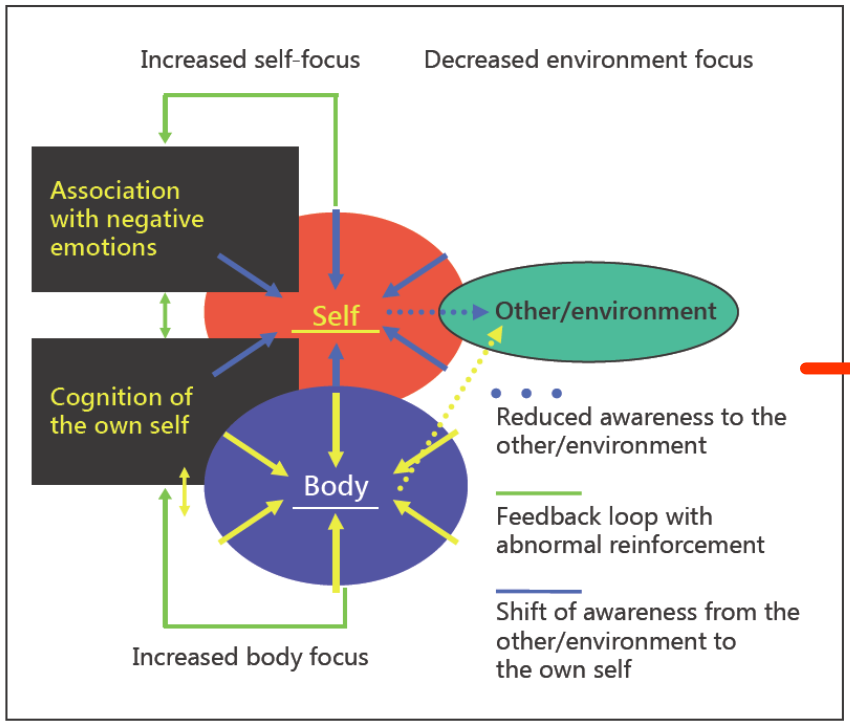
Neurocognitive Perspektive:

negativer Bias bezüglich **Emotionsverarbeitung** und Denkmuster

Selbst-Selbstreferenz: erhöhter **Selbst-Fokus und Body-Fokus**

Sozial Kognition: erniedrigte Umweltwahrnehmung, z.B. Empathiefähigkeit

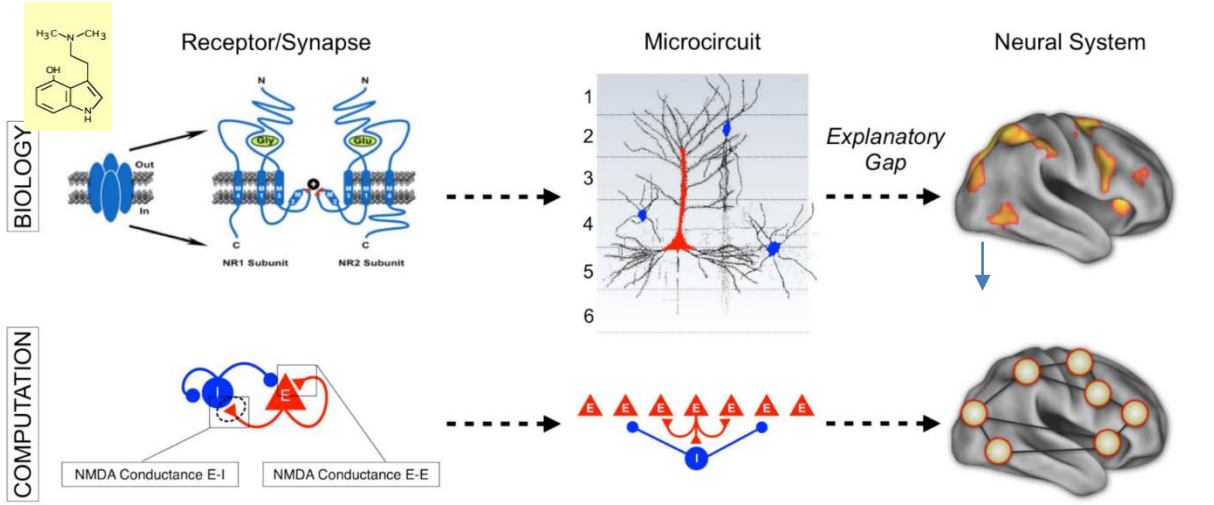
- z.B. negative emotionale Selbstattribuierung
- Rumination
- Somatisierung



- z.B. verarmte soziale Interaktion

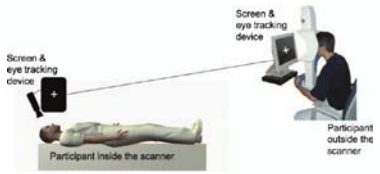
Adapted from Northoff 2014

Hin zu Neurobiologischen Mechanismen der Psychedelika-Wirkung



(e.g. RS connectivity)

Subjektive Erfahrung
(1.Personperspektive)
- Psychometrie



Verhalten
(3.Personperspektive)
Funtionelle Tests:
- Kognition
- Emotionsregulation
- Selbstreferenz

PET, MRS (20-60 Minuten)

- Rezeptor-Besetzung
- Neurotransmitter Release

Translationale molekulare Ansätze und Verhalten

EEG/ERP, TMS-EEG, MEG (1 msec)
fMRT (2 sec)

- neuronale Aktivierung/Deaktivierung (CBF, ASL)
- **Netzwerk-Konnektivität** (funktionelle, effektive)

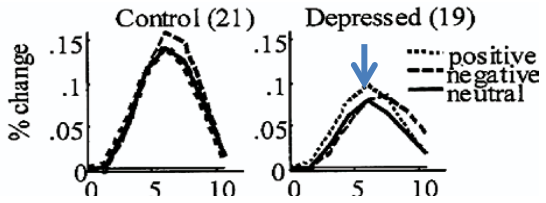
Receptor occupancy, Geneexpression maps

Computational models > prediction of individual responses

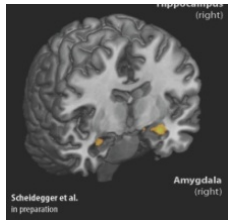
Anticevic et al. 2013, Moujaes et al. 2023

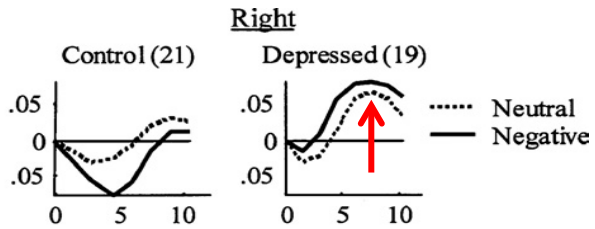
Emotional Bias und neurale Korrelate der Emotionsverarbeitung in der Depression

Depression: <u>erhöhte neuronale Reaktion auf negative Stimuli, z.B. emotionaler Gesichtsausdruck</u>

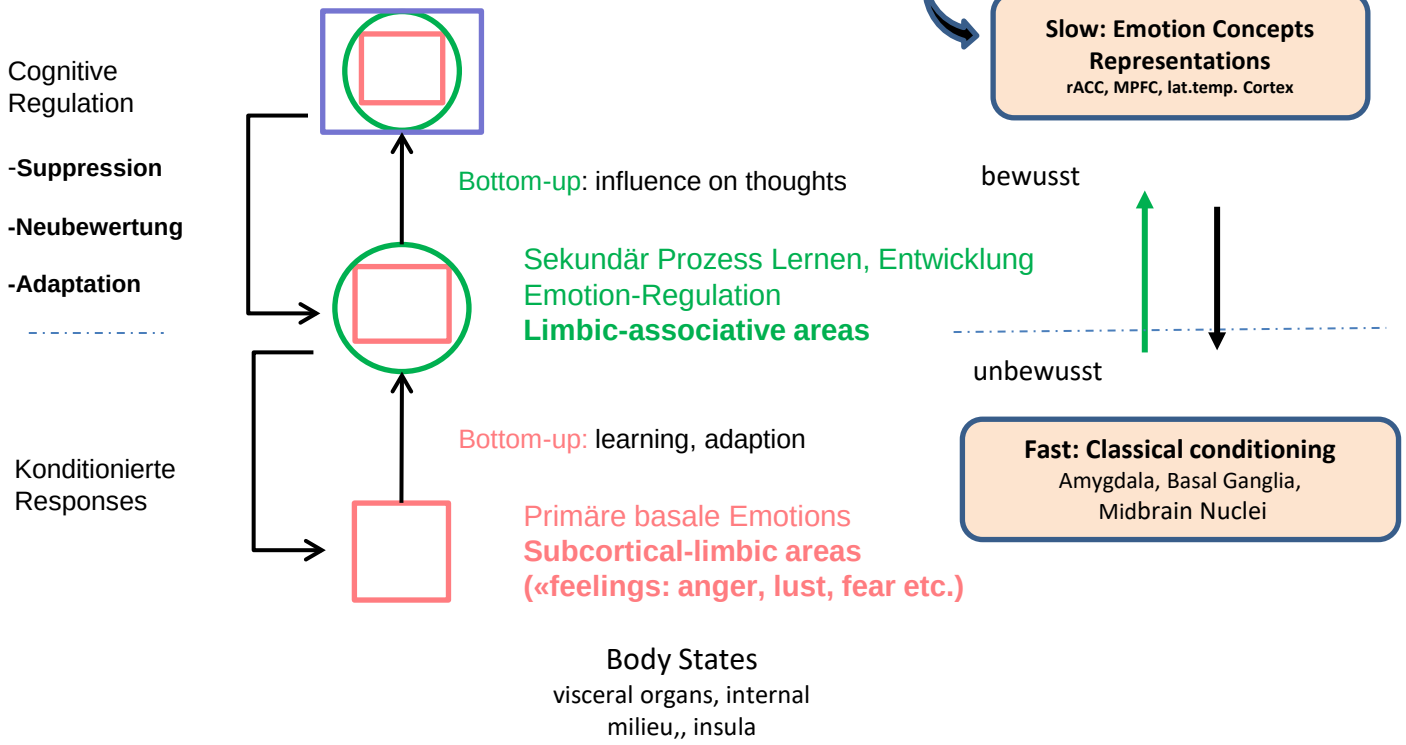


DLPFC/VLPFC:
reduzierte Aktivierung



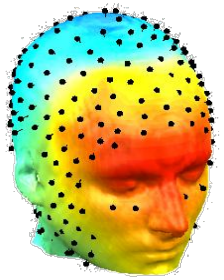


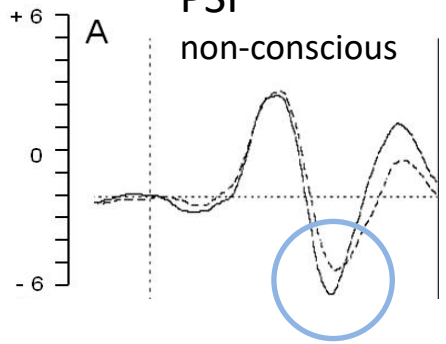
Amygdala (v.a. rechts)
erhöhte Aktivierung

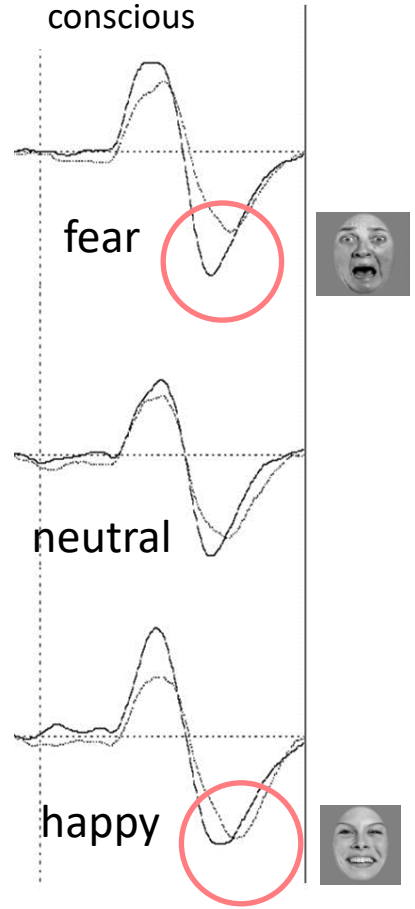


Davidson et al . 2006, Disner er al. 2011 NNR, Dima et al. 2011, Panksepp et al. 2018

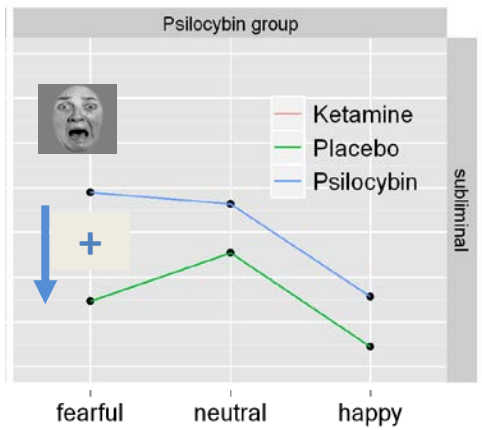
Wirkung von Psilocybin auf die unbewusste und bewusste Emotionsverarbeitung (N170, ERP-EEG)



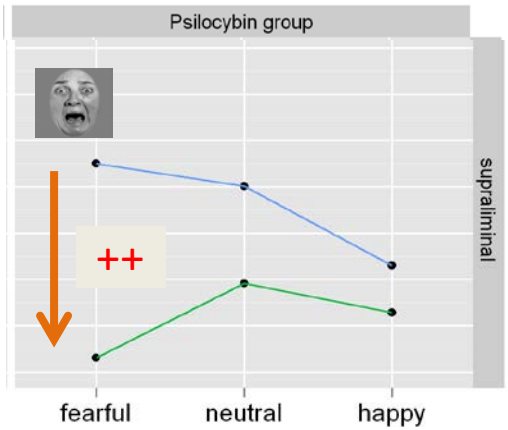


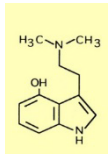


PSI nicht-bewusst



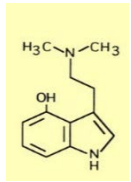
PSI bewusst





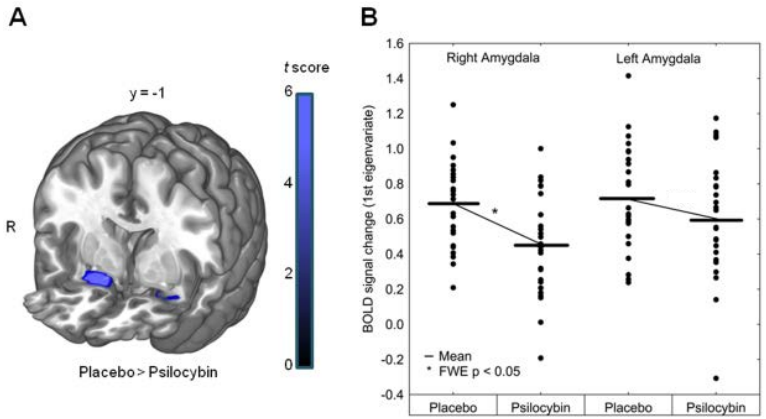
Schmidt et al. 2012
Diaconescu, work in progress

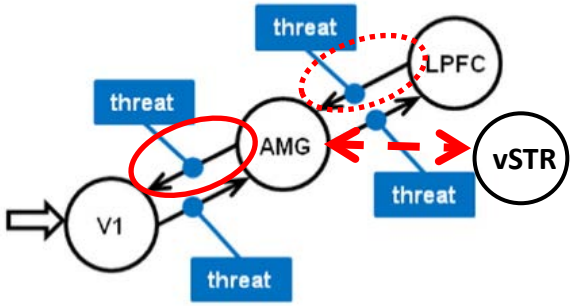
Neuronale Korrelate der Wirkung von Psilocybin auf Stimmung und Emotionsverarbeitung



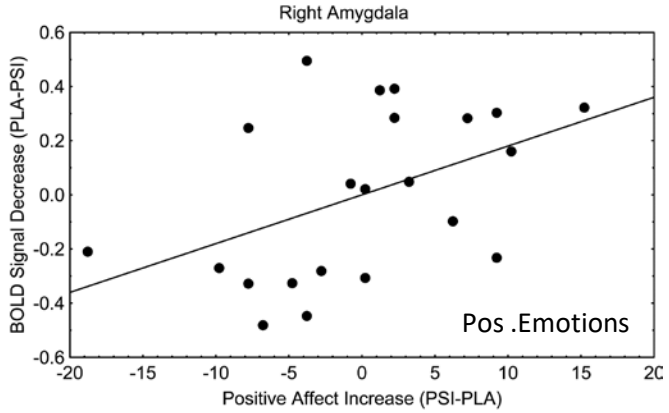
versus

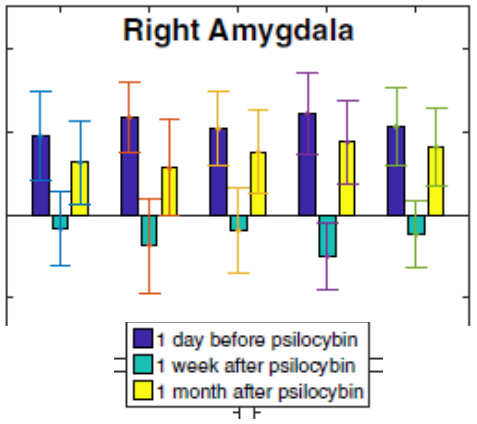
Veränderte **cortico-limbische Regulation:**
gerichtete CON: Amygdala – V1
fCON: ventral Striatum – Amygdala (saliency detection)



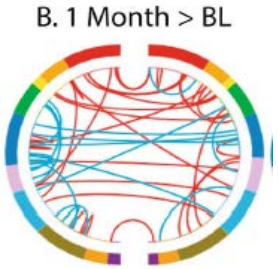


Abschwächung der Salienz (limbisch, dopaminerg)
> «**decentring**»: a state allowing a broader spectrum of emotions and thought patterns





Reduzierte Amygdala-Reaktion
dauert bei Gesunden bis zu einem Monat an nach 1 Dosis Psilocybin

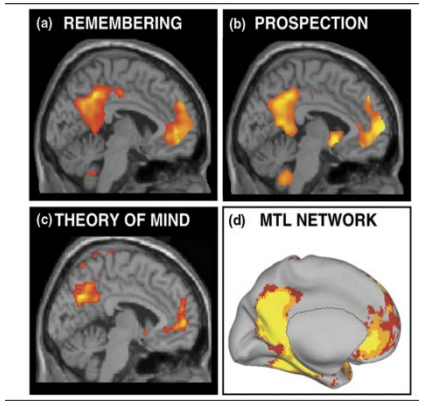


Veränderte fCON:
frontal cortex - amygdala

Barett et al. Sci.Rep.2020

Kraehenmann et al. 2015 Biol.Psych., 2016 Neuroimage, Grimm et al. 2018

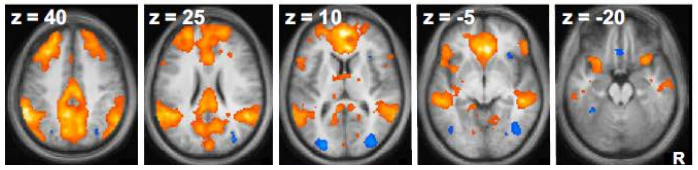
Wirkung von Psilocybin auf die Selbstwahrnehmung - Korrelate von OBN (RS DMN - 5-HT2AR occupancy)



Cortical-subcortical midline structures (MS) overlapping with the **Default Mode network (DMN)** are involved in differentiating *self- versus non-self-referential* stimuli

MS and 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

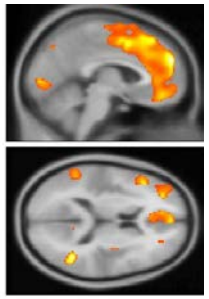


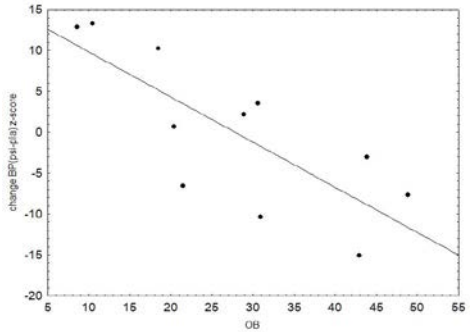
Andrews-Hanna et al. 2010, Quin and Northoff 2011, Bruckner et al .2011

Self-referential processing is proposed to be a pre-requisite for the development a «concept» of one's own self (self perspective, ego):

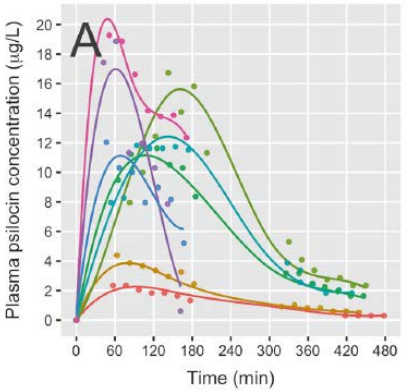
In addition to one's own **cognitions**, also **emotions** and internal and external stimuli of **body perception** are examinded in regard to self-reference

Psilocybin-induced **positive self-dissolution (OBN)** correlated with decreased 5-HT2AR Binding Potential (PET) in cortical regions





OBN



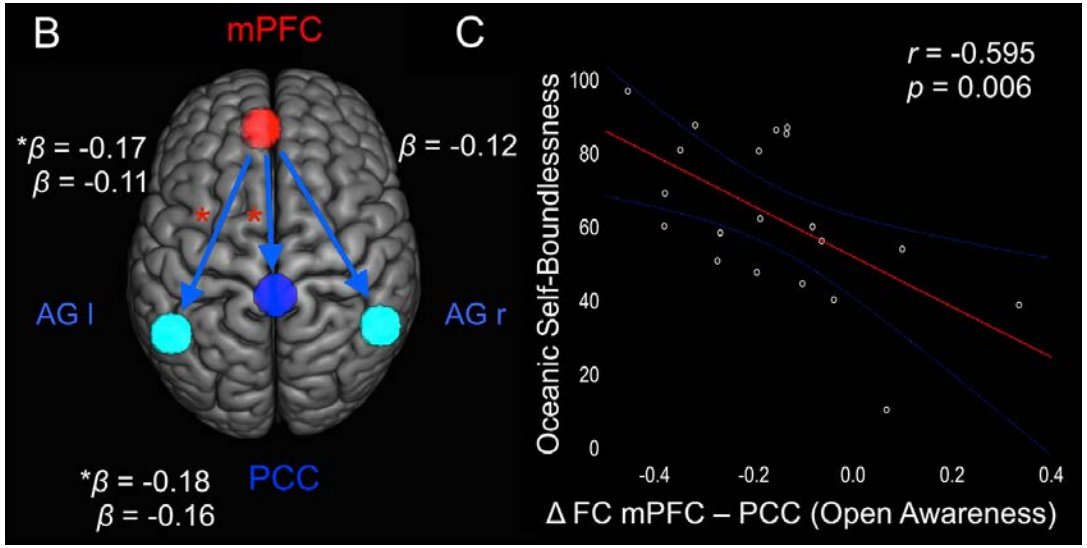
OBN: dm/dl PFC, dACC, tem. Cx, angular Cx, insula

Hasler & Vollenweider 2011, Quednow et al. 2012

3-30 mg psilocybin ~72% Rec. Occup.
Approx. linear dose-response effect

Madsen et al. 2019

Selbstentgrenzung (OBN) korreliert mit veränderter default mode network (DMN) mPFC-PCC-Konnektivität

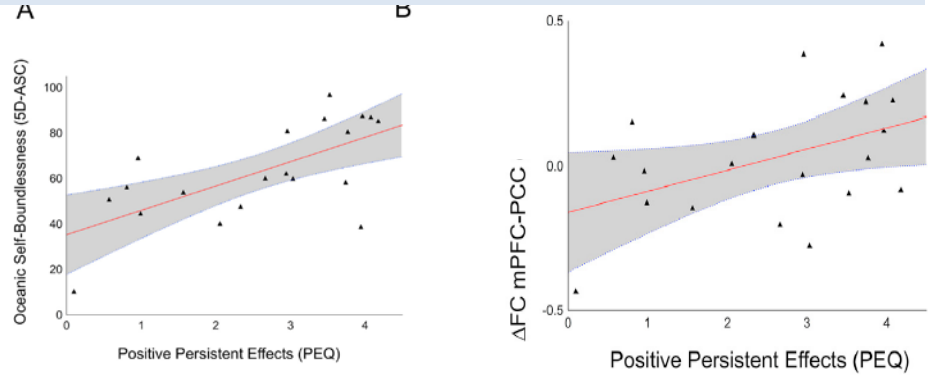


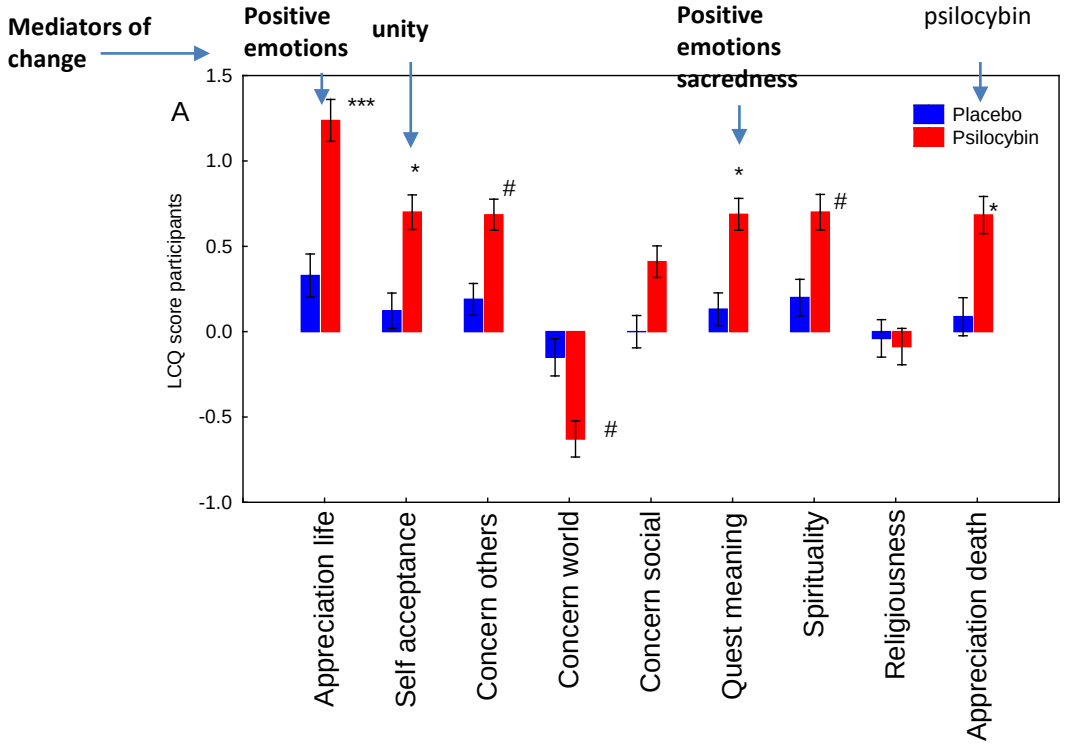
- medial prefrontal cortex (mPFC/ACC) : self
- right angular gyrus; left angular gyrus: body
- posterior cingulate cortex: self-other

- Psilocybin reduziert die **funktionelle Konnektivität zwischen mPFC und PCC (2 Tage nach Einnahme** (n=39 , trained meditators: mindfulness/ZEN Buddhists)

Smigielski et al. Neuroimage 2019

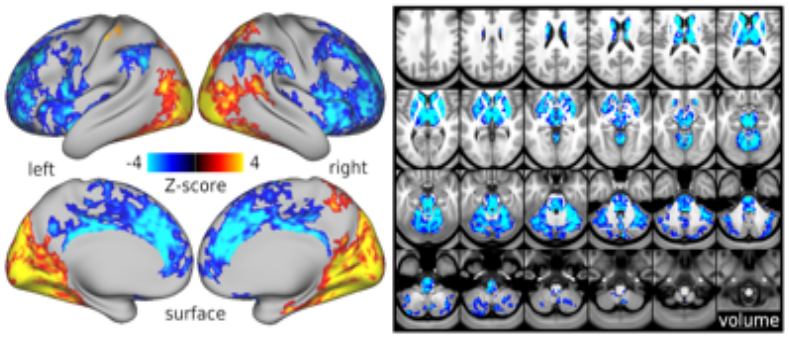
Reduzierte fCON korreliert mit anhaltenden positive psychosozialen Veränderungenn (4 month follow-up)

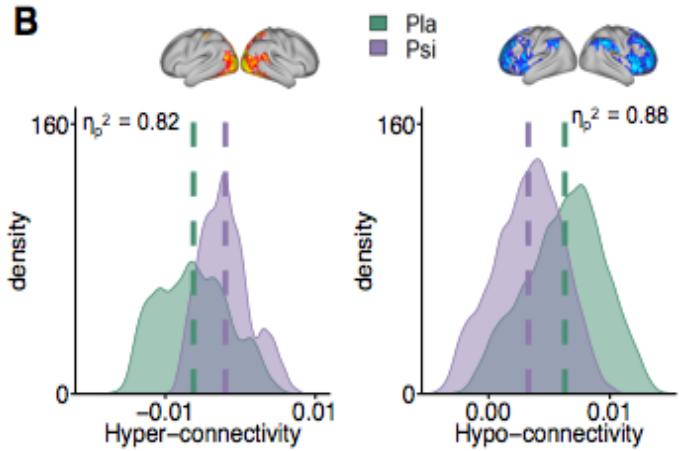


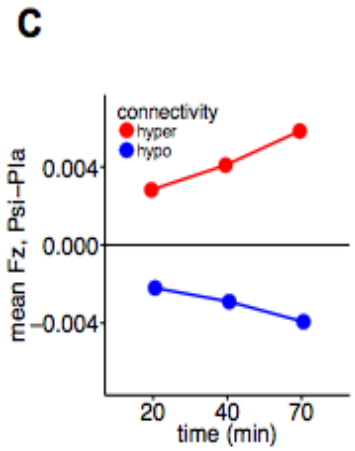


Wirkung von Psilocybin/LSD auf die global func. resting state connectivity und Selbstentgrenzung

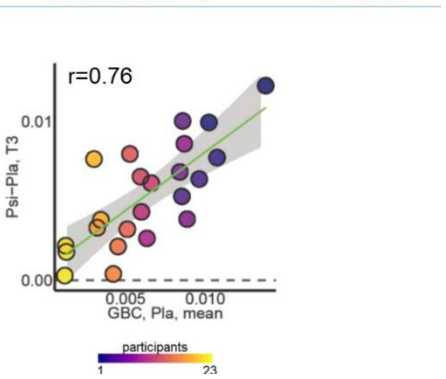
Psilocybin and GBC over time





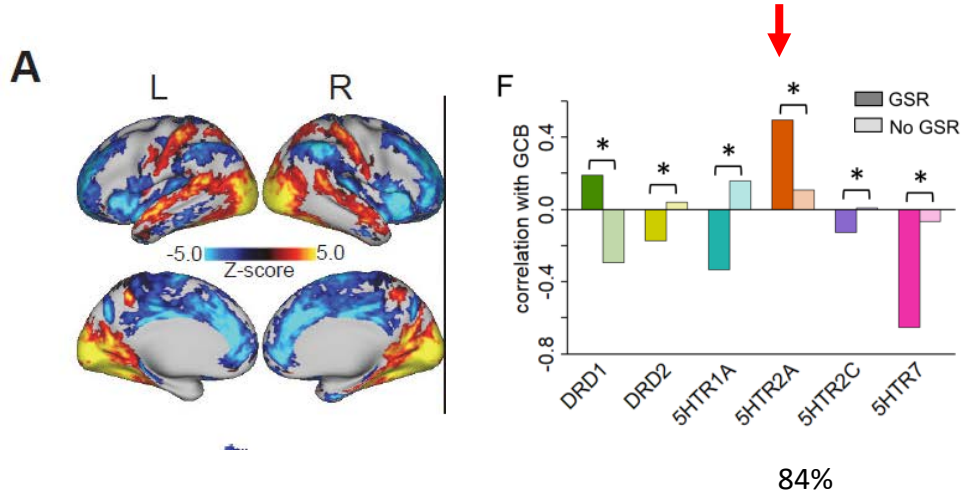


Baseline RS CON als Response predictior



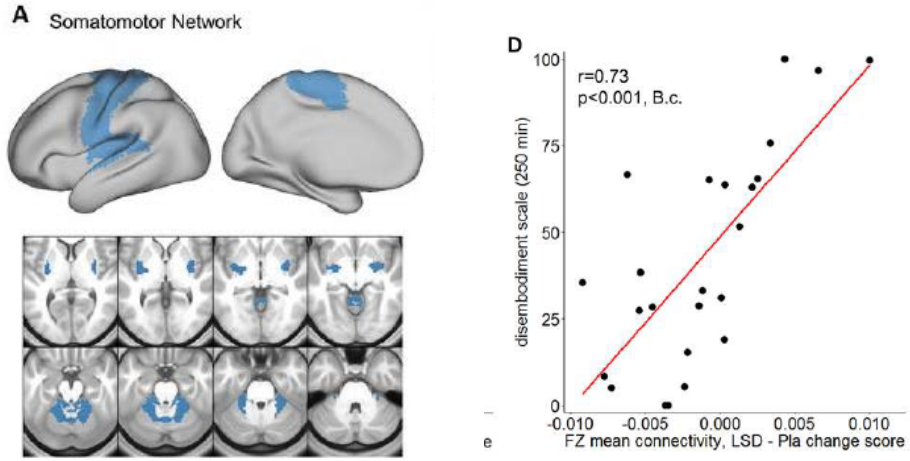
Preller et al. Biol.Psych.2020

LSD and GBC and Cortical 5-HT2A gene expresion maps



84%

Dysconnection of somatosensory network and disembodyment (OBN)

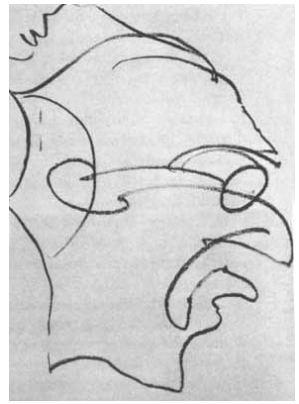


Preller al. eLIFE 2018

Körperselbst-Wahrnehmung unter Psychedelica (LSD) - embodies self







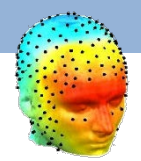



(at peak 2-3h)

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

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

Körperselbst-Wahrnehmung: taktilen mismatch Response – prediction error processing (EEG-fMRT co-Registrierung)

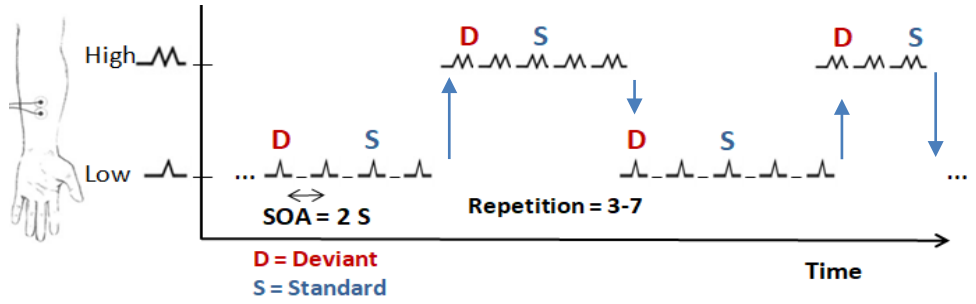



- Das Gehirn lernt aus eintretenden sensorischen Reizen ein **Modell** der Körper-wahrnehmung zu konstruieren und minimiert dabei unerwarteter Abweichungen (surprises) über die Vorhersage der möglichen Körperrepräsentationen

- Die **Diskrepanz** zwischen dem **verhergesagten** Modell (predicted) und dem bottom-up **aktuell generierten** Inhalt (Bild, Reiz) produziert ein Vorhersagefehler Signal (**prediction error signal, PE**)

Roving Somatosensory Oddball Task during EEG-fMRT Co-registration (psi/pla, n=21)

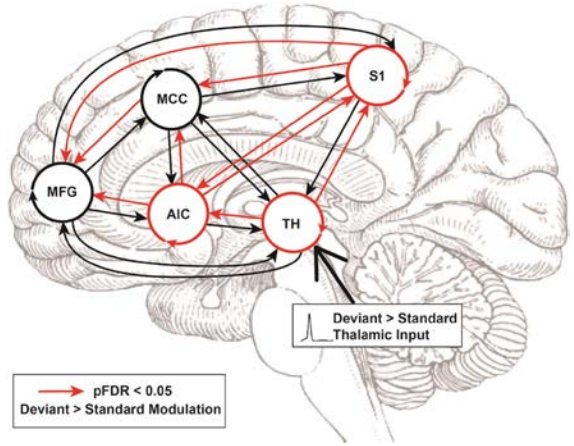
- Induktion von tactile mismatch **responses**: Applikation einer Serie an taktilen Stimuli randomisiert mit hoher (Doppelpulse) und nierdiger (Siglepulse) Intensität, Wiederholungen 3-7

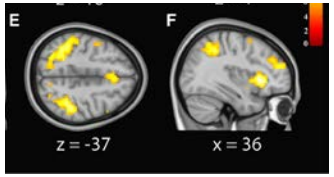


- Unpredicted stimuli: Deviant (D)

Top-down: Vorhersage

Bottom-up sensorischer Reiz





Result: Placebo; Deviant > Standard

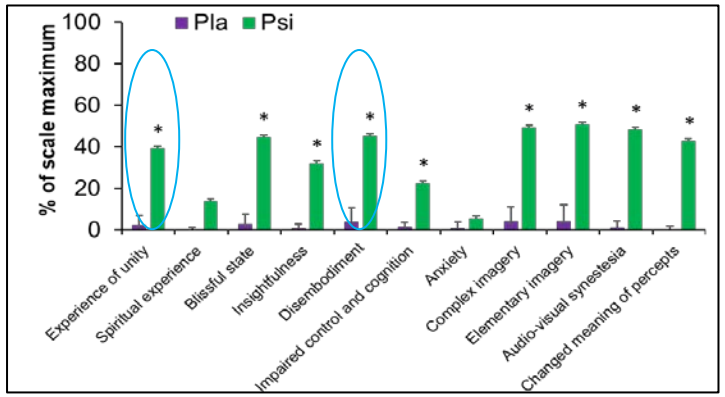
Medial cingulate Cortex, medial frontal Cortex, dorsal medial PFC, Thalamus, Primary Somatosensory Cortex, Insula

Dürler et al. 2021, Neoroimaging

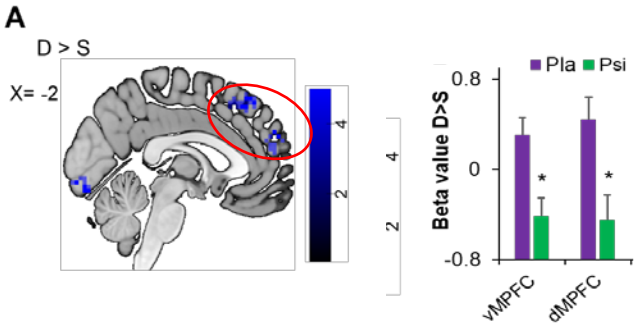
Adabted from Allen et al. 2016, Nagai & Asada 2015

Psilocybin induces aberrant prediction error processing for tactile mismatch responses

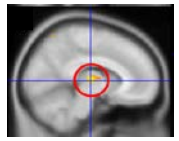
- Psychometrics: Unity, Disembodiment



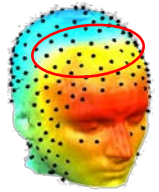
- fMRI: Psilocybin reduced the response to Unpredicted stimuli versus Standard in brain regions implicated in bodily-awareness



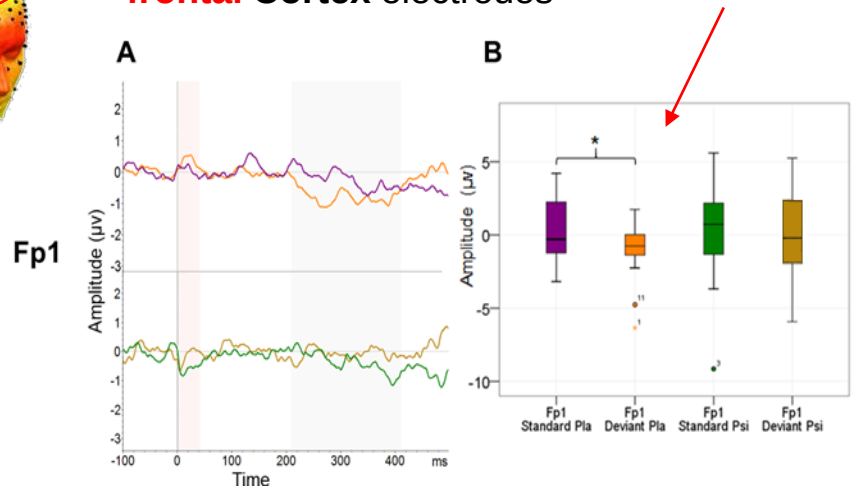
1) ventral Medial PFC
2) dorsal Medial PFC
3) Thalamus
4) Sensory cortex



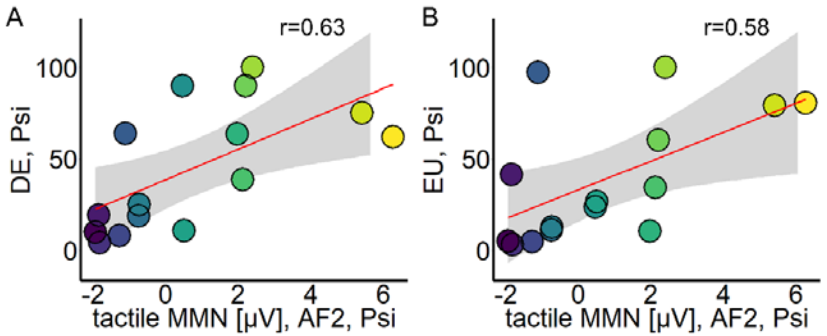
Psilocybin alters integration of tactile stimuli through (top-down) aberrant PE signalling



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



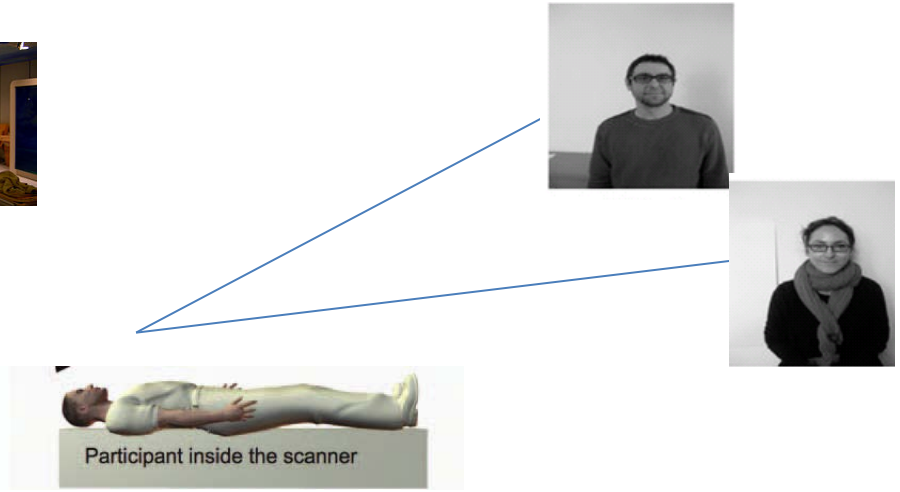
- MMN change and Altered Self-Experience

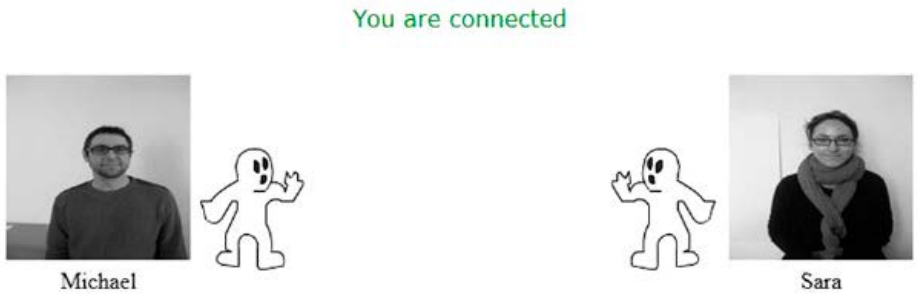


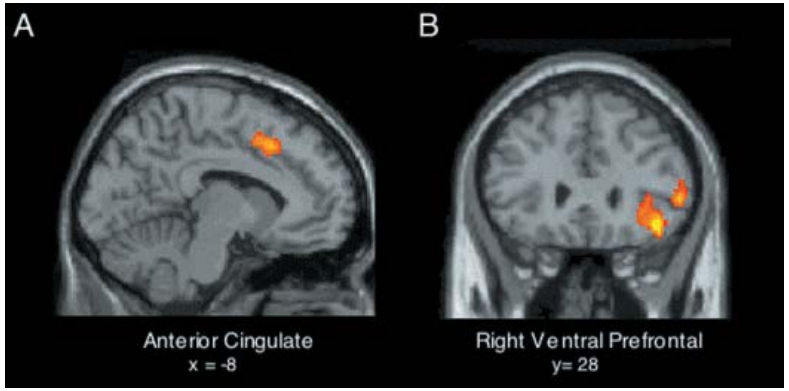
reduced tactile MMN (EEG) responses at frontal electrodes correlates with altered body- and self-experience: **disembodiment** and **unity**

Dürler et al. 2021

Soziale Kognition: Sozialer Ausschluss (Cyberball) Test; fMRT-MRS







- „Social Pain“, *Eisenberger, Science, 2003*
- ***Ausschluss vom Ballspiel führt zu einem social pain Signal in ACC*** *(Preller et al. PNAS 2016)*

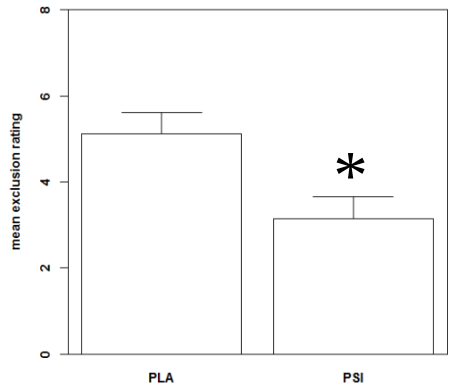
Study:
N=32 (17 men; 15 women, age 26.72 ±5.34)

Psilocybin (0.21 mg/kg) vs placebo

Preller et al. PNAS 2016

Results: Psilocybin reduziert «social pain signal» und erhöht emotionale Empathie

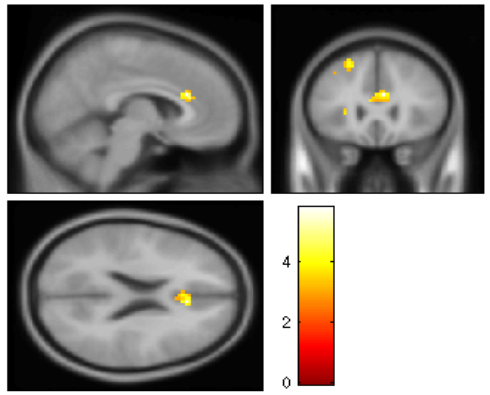
Behavioral Results



- Mean exclusion rating

Psilocybin subjects felt less excluded
No other behavioral parameters were affected
-> attention, aware of the exclusion

fMRT: reduced BOLD Signal in ACC



Placebo > Psilocybin

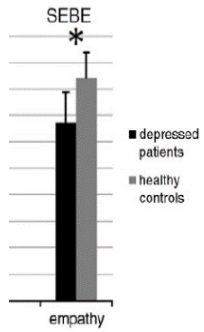
Exclusion > Inclusion

Wilbertz et al., 2010

Empathy-related processes are thought to motivate prosocial behavior,

caring for others, and to **inhibit aggression**

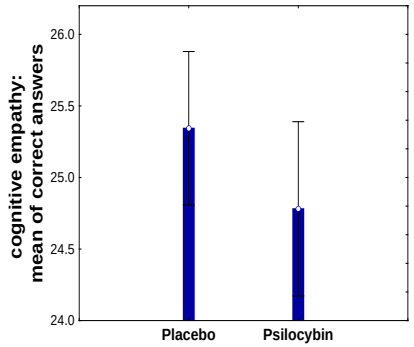
MDD



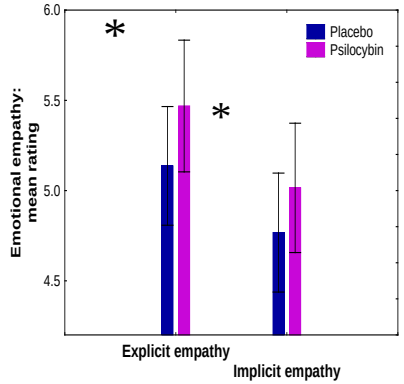
What is this person feeling?

How concerned are you for this person?

Cognitive Empathy

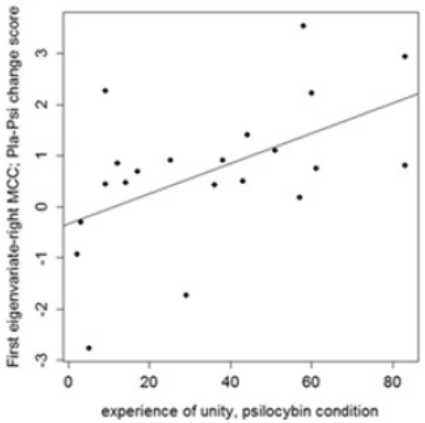


Emotional Empathy (concern)



- Psilocybin increased **emotional empathy correlated with altered meaning of percepts**

Change in BOLD response and altered Self experience



- **the reduced BOLD signal in ACC correlated with feelings of „unity“ (connectedness)**

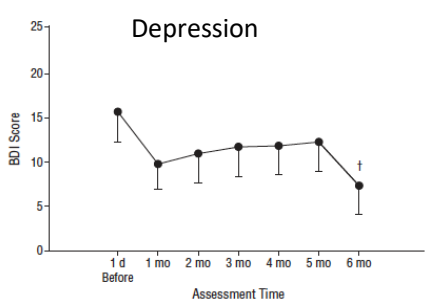
➢ **Self-processing and social cognition are intertwined**

Preller et al. PNAS 2016

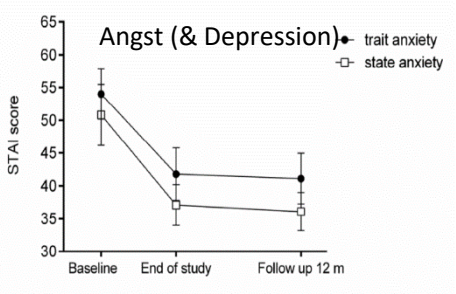
Revival der klinischen Forschung mit Psilocybin & LSD

2011-ff: Erste neue state-of the-art kontrollierte Studien:

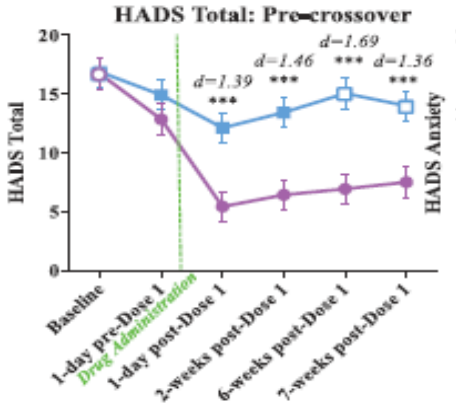
- Grob et al. 2011: UCLA Studie, **Reduktion von Depression und Angst** bei terminalen Krebspatienten (n=2x12) nach 15 mg Psilocybin, bis zu 6 Monaten follow-up
- Gasser et al. 2012, CH Studie: **Reduktion von Angst und Zunahme des Wohlbefindens** bei Krebspatienten (n=12) nach 2 x 200 µg LSD (vs 20 µg), anhaltend bis 12 Monaten follow-up
- Ross et al. 2016, NY University: **Reduktion von Depression** bei Krebspatienten (n=29) nach 22 mg (vs 0.3 mg/kg, cross-over) Psilocybin, anhaltend bis 7 week follow-up, **kombiniert mit CBT**
- Griffith et al. 2016, John Hopkins University, sign. Reduktion **von Depression und Angst** bei Krebspatienten (n=59) nach 22 mg (vs 1/3 mg, cross-over) Psilocybin, anhaltend bis 6 Mt. follow-up, kombiniert mit „Spiritual Awareness Practice“



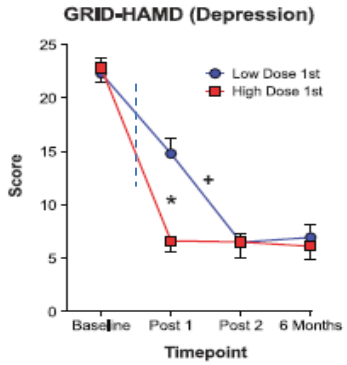
Grob et al. AJP 2011

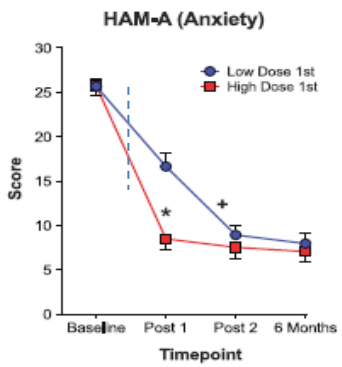


Gasser et al. JP 2012

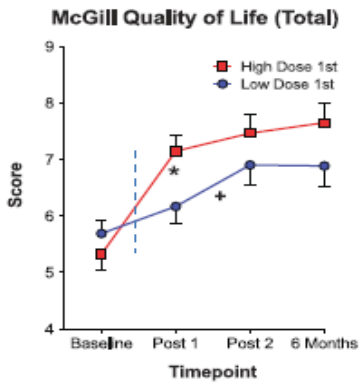


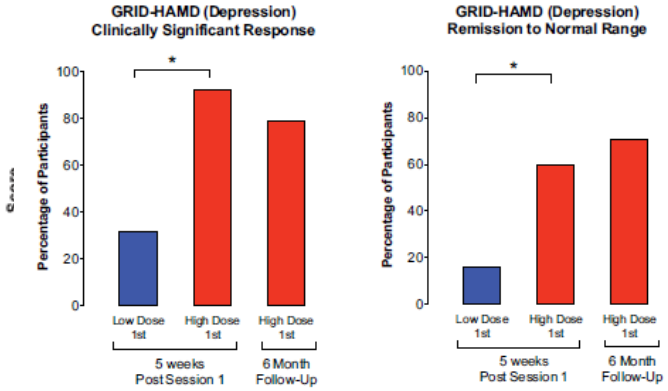
Ross et al., JP 2016





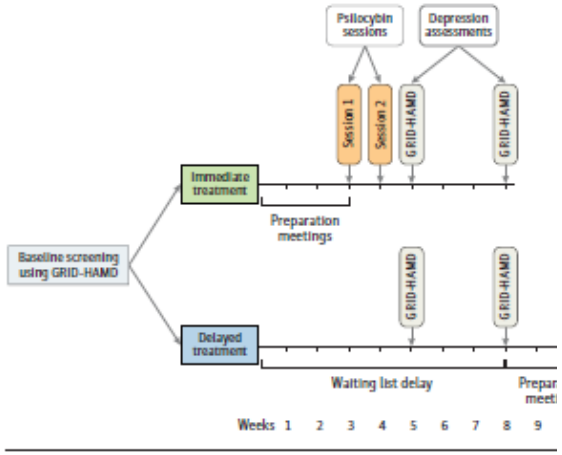
Griffith et al., JP 2016

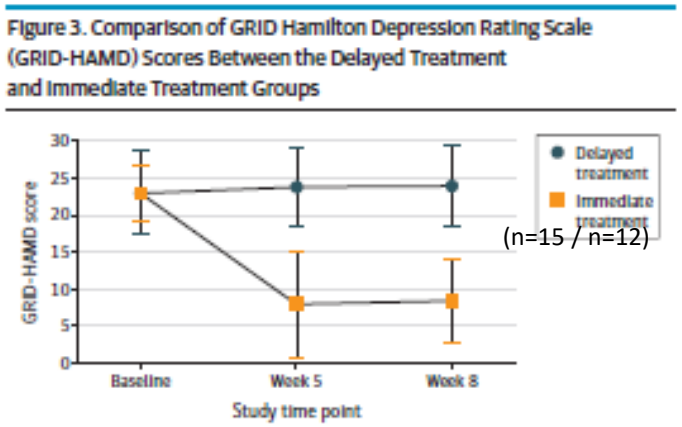




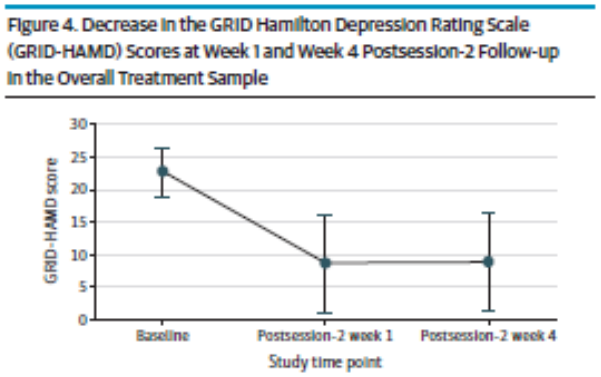
Griffith et al.2018

Effects of Psilocybin-Assisted Therapy on Major Depressive Disorder



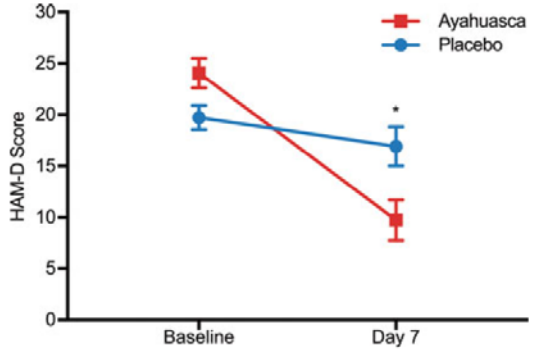


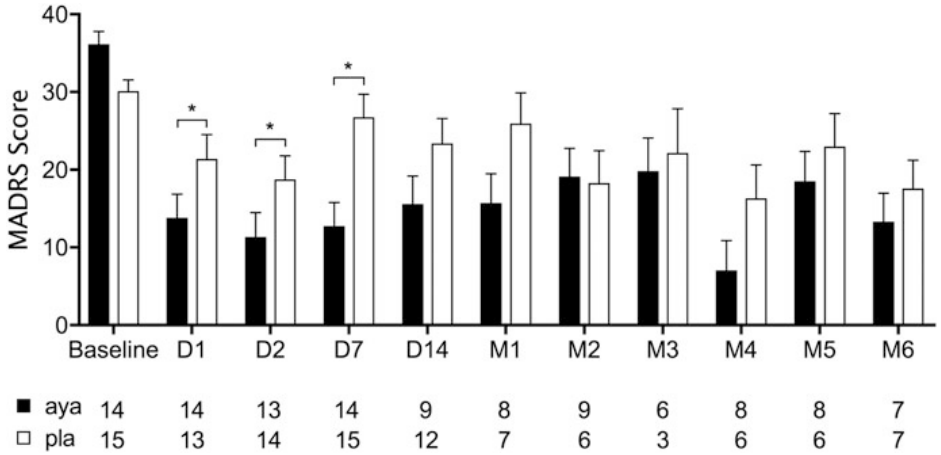
(n=15 / n=12)



Davis et al. 2020, JAMA

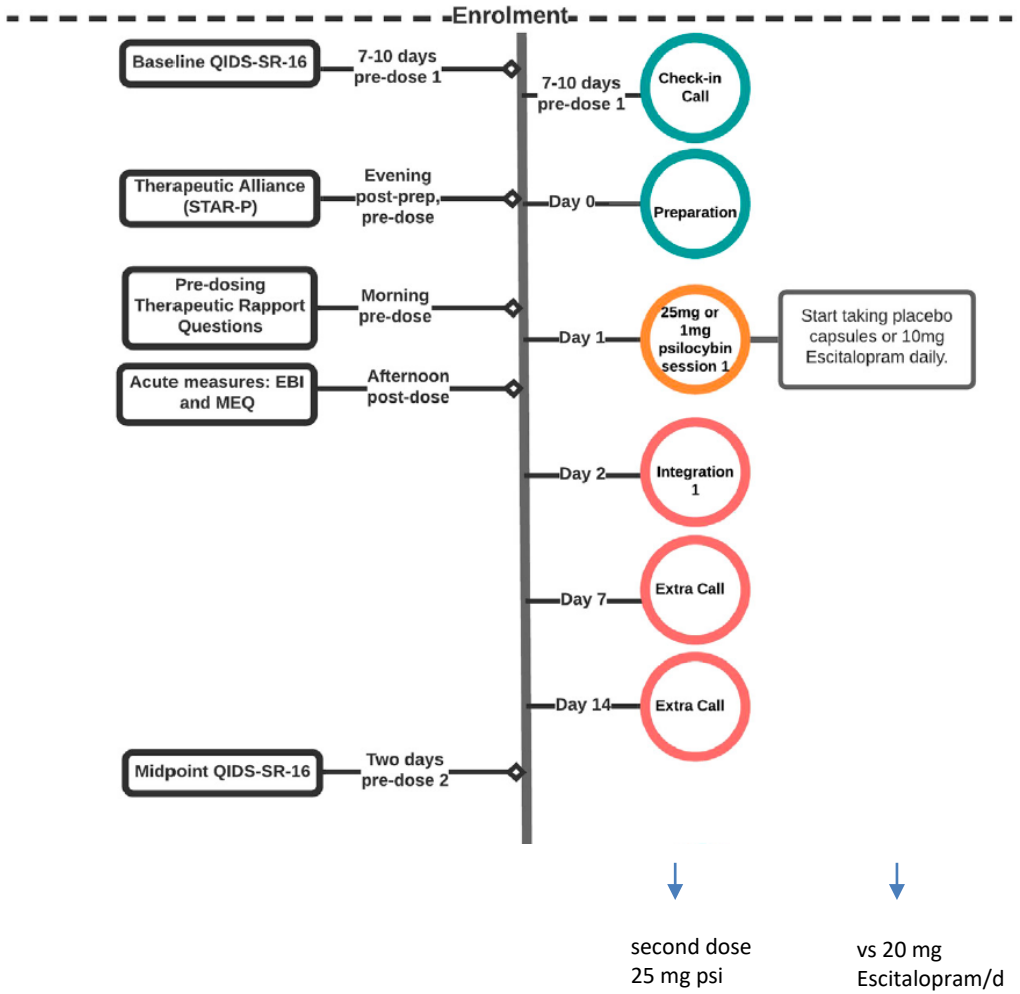
Effects of the psychedelic ayahuasca in treatment-resistant depression: a randomized placebo-controlled trial (n=19)



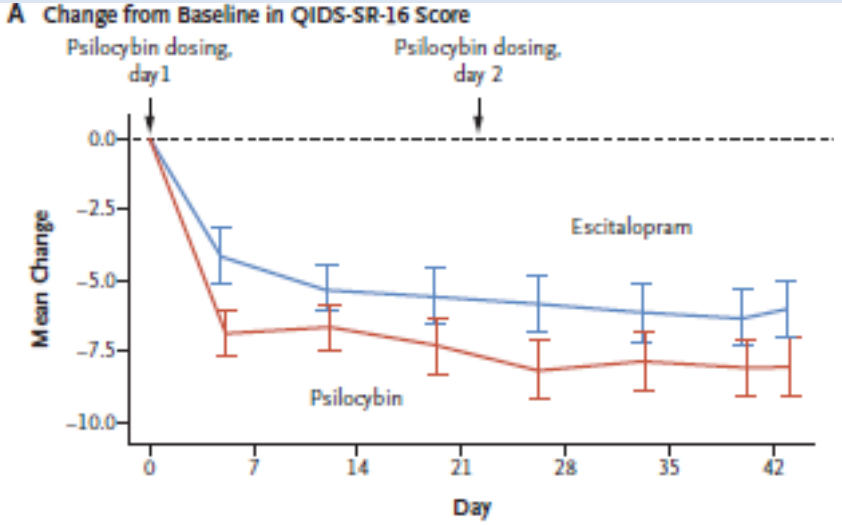


Palhano-Fontes et al. 2019, 2022

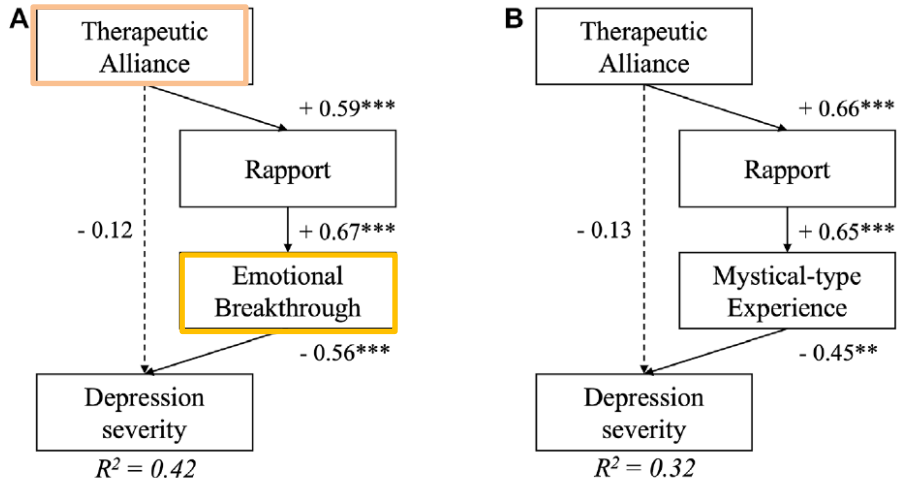
Effects of psilocybin vs escitalopram in treatment resistant depression (TRD), a double-blind randomized trial (n=30/29)



total 35-40h
davon 2x 6h für drug session



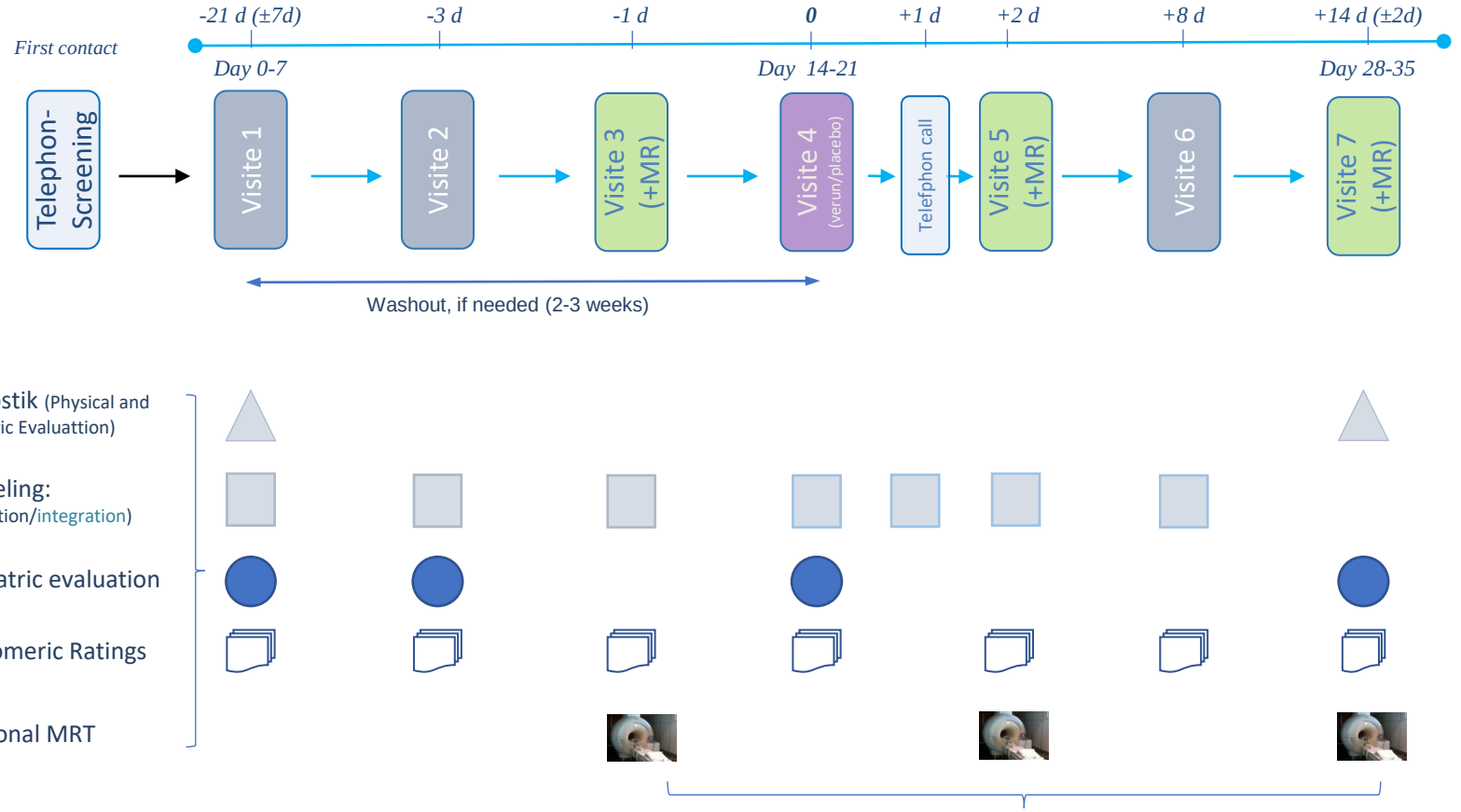
Carhart-Harris et al 2021

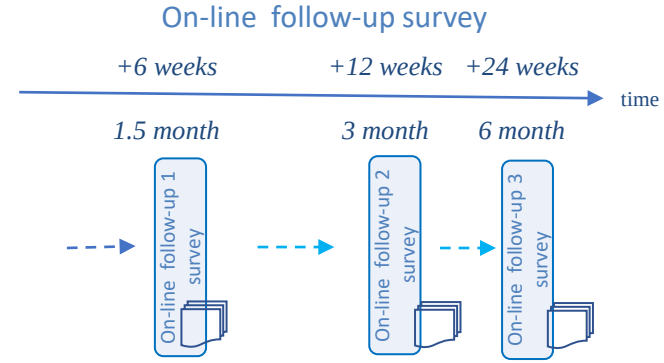


<u>Emotional Breakthrough Scale:</u>
Emotional release, overcoming difficult emotions or memories or previously inaccessible emotions, gainig personal or interpersonal insight

Murphy et al. 2022

Proof-of concept Phase II randomized, double-blind, placebo-controlled parallel group study of psilocybin in major depression (MDD, n=2 x 30)





→ Resuming therapy by referring psychiatrist

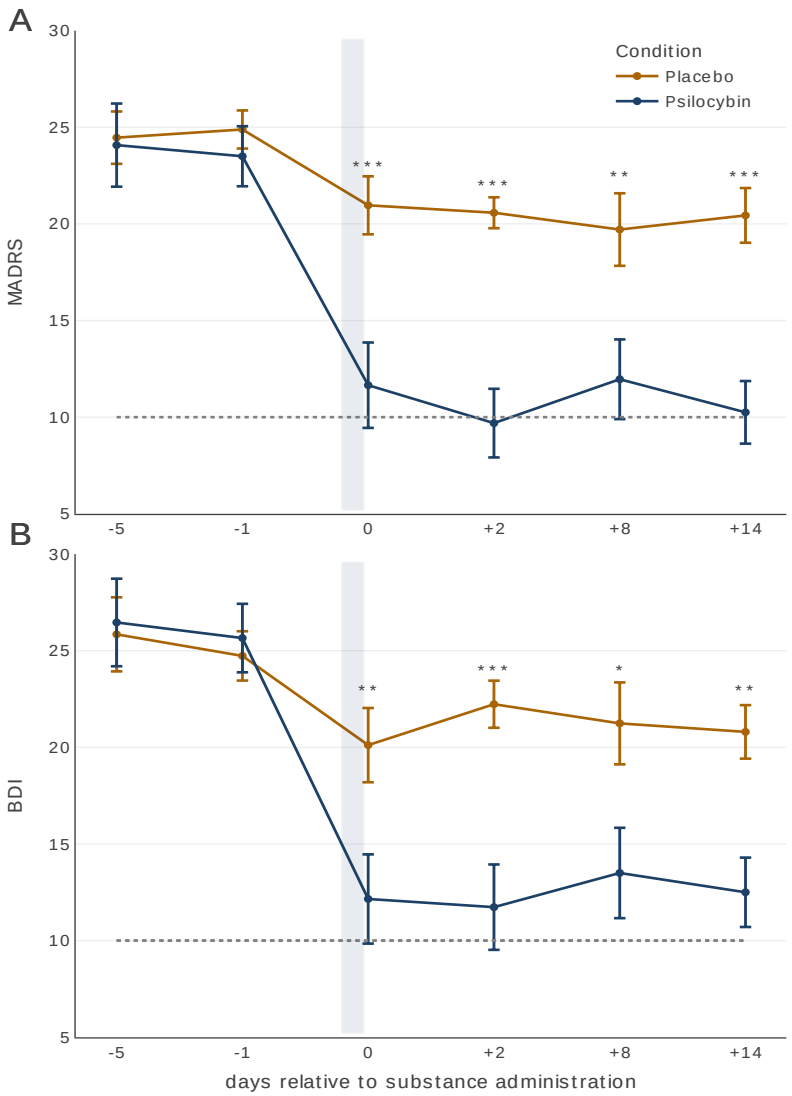
Primary outomes: depression severity on **MADRAS, BDI**

Secondary outcomes: RS fMRT, **emotion- and self-regulation task, Multifaceted Empathy Task**, & BDNF at -1 ,+2,+14d

Psychiatrische Universitätsklinik Zürich

von Rotz et al. 2023, The Lancet eClinical Medicine

Results: Effect of a single dose of psilocybin vs placebo on depressive symptoms (MADRS,BDI)(follow-up:14days)



Pla: Response rate 16%

PSI: Response rate 58%
Remission rate: 54% (at 14d)

Dose: single moderate dose of 0.215 mg/kg Psilocybin vs placebo

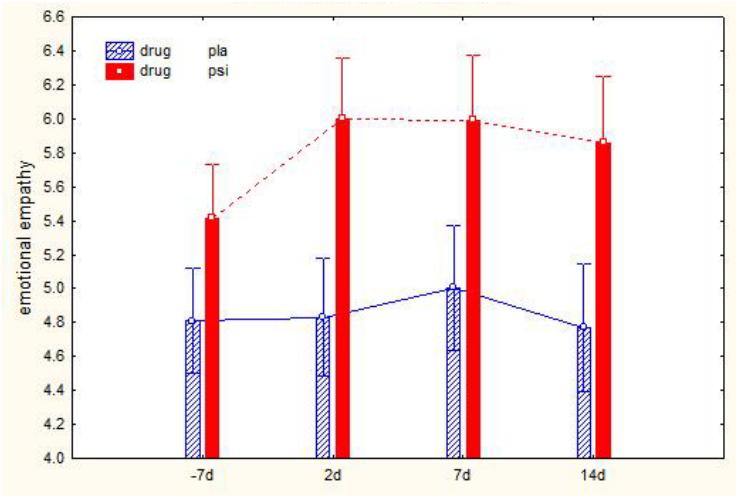
Response rate: 50% symptom reduction

Remission: MADRS <=10

Psi: Suicidal ideation: 14 day post-drug: none (no change from baseline)

Psi: Main AES: Mild headache in psi group the next day (11%)

Multifaceted Empathy Task



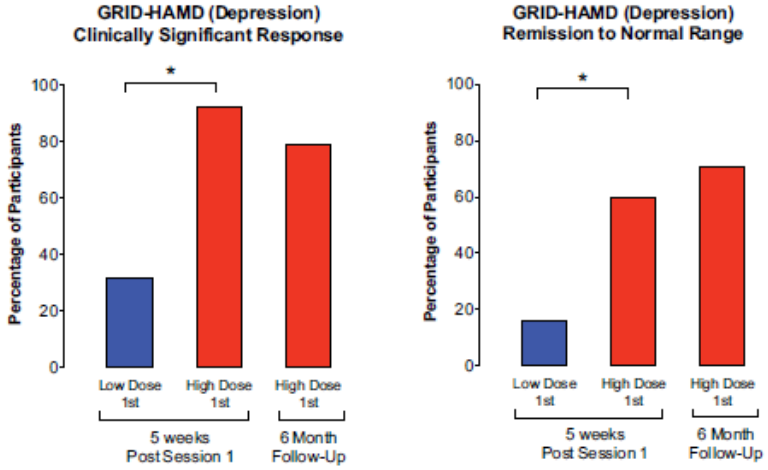
von Rotz et al. 2023, The Lancet eClinical Medicine

Meta-Analysis: Persisting effects of 1 or 2 doses of psilocybin on depressive Symptoms (MADRS, HAM-D, BDI)

Table 1. Included studies.

Study	Population	Treatment	Sex (% female)	Age (years)	Depression scale	Score baseline	Main findings
Grob et al., 2011	Depressive symptoms in patients with advanced-stage cancer	Psilocybin 0,2 mg/kg	91.7	36 to 58	BDI	16.1	No difference between 1 day prior to 2 weeks after administration. Difference became significant at the 6 months follow up
Griffiths et al., 2016	Depressive symptoms in patients with life-threatening cancer	Psilocybin 20 to 30 mg/70kg	49	56.3	HAM-D	22.58	Significant decrease of depressive score after psilocybin at 5 weeks and 6 months
Ross et al., 2016	Depressive symptoms in patients with life-threatening cancer	Psilocybin 0,3 mg/kg	62	56.3	BDI	15	Significant decrease of depressive symptoms compared with control group
Carhart-Harris et al., 2016	Resistant MDD	Psilocybin 10 mg then 25 mg 7 days after	50	42.7	MADRS	31	Significant decrease of depressive symptoms at week 1; 2; 3; 5 and 3 months compared with baseline score
Carhart-Harris et al., 2018	Resistant MDD	Psilocybin 10 mg then 25 mg 7 days after	30	44.1	HAM-D	24.1	Significant decrease of depressive symptoms at week 1; 2; 3; 5 and 3 and 6 months compared with baseline score
Sanches et al., 2016	Recurrent MDD	Ayahuasca 1,76 mg/kg	82.4	42.7	MADRS	25.65	Significant decrease of depressive symptoms at 40; 80; 140; 180 minutes day 1; 7; 14; and 21 compared with baseline score
Palhano-Fontes et al., 2019	Resistant MDD	Ayahuasca 0,36 mg/kg	78.6	39.7	MADRS	36.14	Significant decrease of depressive symptoms compared with control group at day 1; 2 and 7.
Gasser et al., 2014	Depressive symptoms in patients with Life-threatening Diseases	LSD 200 µg twice at 1 week	36.4	51.7	HADS	13.3	No statistical analysis

(8 studies)



Dose: 10 und 25 mg

Griffith et al. 2016,2021

(remisssion: 3-6 m)

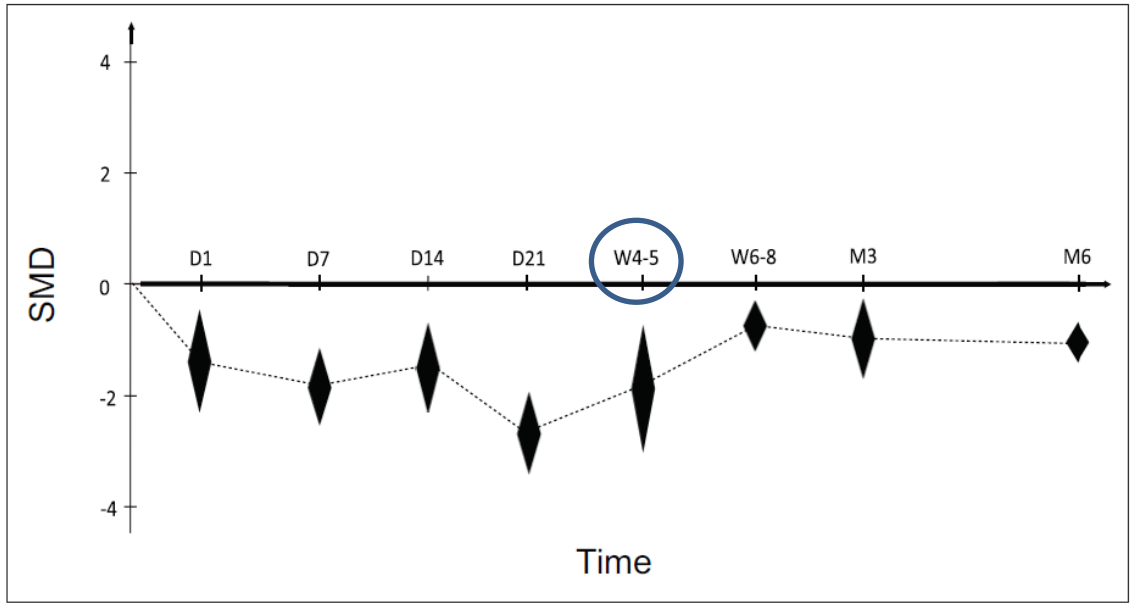


Figure 1. Time-course of overall standardized mean differences (SMD) between baseline and each time point of depressive score.

Romeo et al. 2022

Zusammenfassung möglicher therapeutischer Mechanismen

Selbst-Prozessierung
- Positive Selbst-Auflösung
- Unity, oneness
- Lockerung vorbestehender «beliefs»
- Systems (cognition) und Perspektivenwechsel
- Veränderung in der DMN Aktivierung & ACC-PCC Konnektivität

Cognition
- Verminderte top-down Kontrolle
- erleichterte Kognitive Flexibilität
- Divergentes Denken
- «insight»

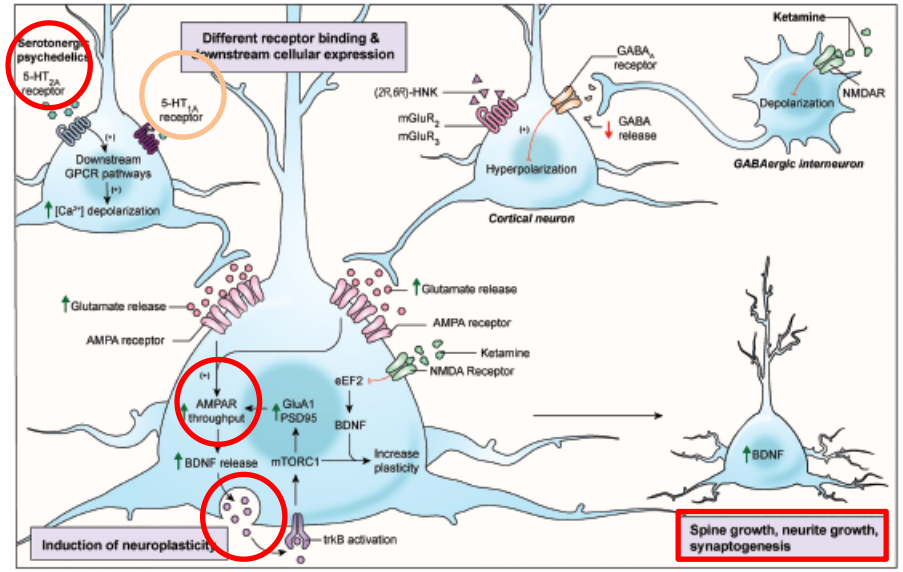
Potentielle therapeutische Wirkung:
- Normalisierung des negative Bias
- Wiedereinstellung des Belohnungssystems
- Verminderte Rumination
- Verminderter sozialer Rückzug
- Verbesserte Patient-Therapeuten Beziehung
- **Emotional breakthrough and insight**

Emotionsverarbeitung
- Angehobene Affektivität
- Reduzierte Verarbeitung negativer Stimuli (decentring)
- Emotional breakthrough,and insight
- Veränderungen in der Amygdala Aktivierung und Konnektivität

Sociale Cognition
- Verbundenheit (connectedness)
- Gesteigerte Empathie
- Reduzierte Kränkbarkeit (rejection sensitivity)
- «Pro-Spiritualität»

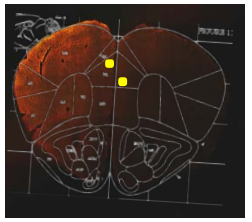
Vollenweider and Preller Nat.Rev.Neurosci. 2020

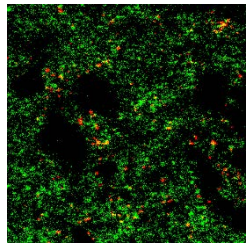
Outlook: Neuroplastizität (Psilocybin) und Verhaltensveränderungen (z.B. fear mem. extinction)



Kadriu et al. 2021

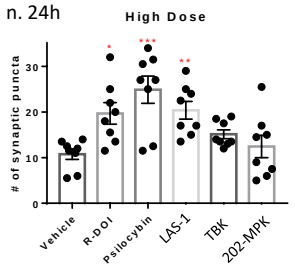
fmc

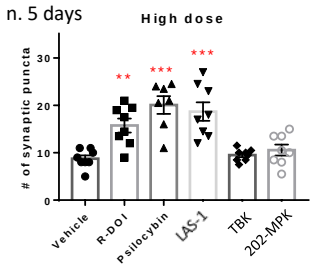


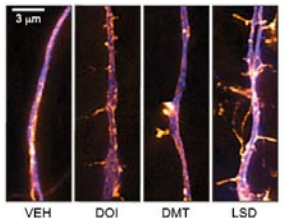


pre- & postsynaptic markers

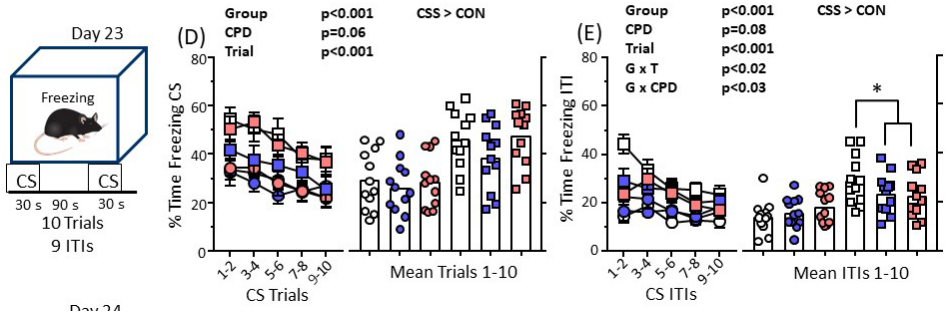
Synaptogenesis







Pavlovian aversion (contextual) learning, social defeat



Pryce, Romanos, and Vollenweider 2022, work in progress

Psychedelika aktivieren die Synaptogenese im Cortex und Hippocampus, und erleichtern «fear memory extiction» im Mausmodell.

<u>Offene Fragen</u>

Einfluss der Erwartungshaltung von Patient und Therapeut

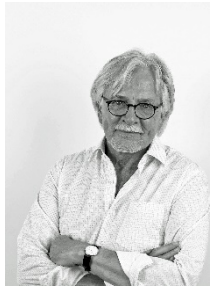
Qualität der therapeutischen Allianz und outcome

Welche therapeutischen Interventionen optimieren den outcome? Wieviele Substanzsitzungen sind notwendig?

Verblindung als Problem (kleine gegen hohe Dosis? Niacin und andere Vergleichssubstanzen)

Thanks to

Psychiatrische Universitätsklinik Zürich



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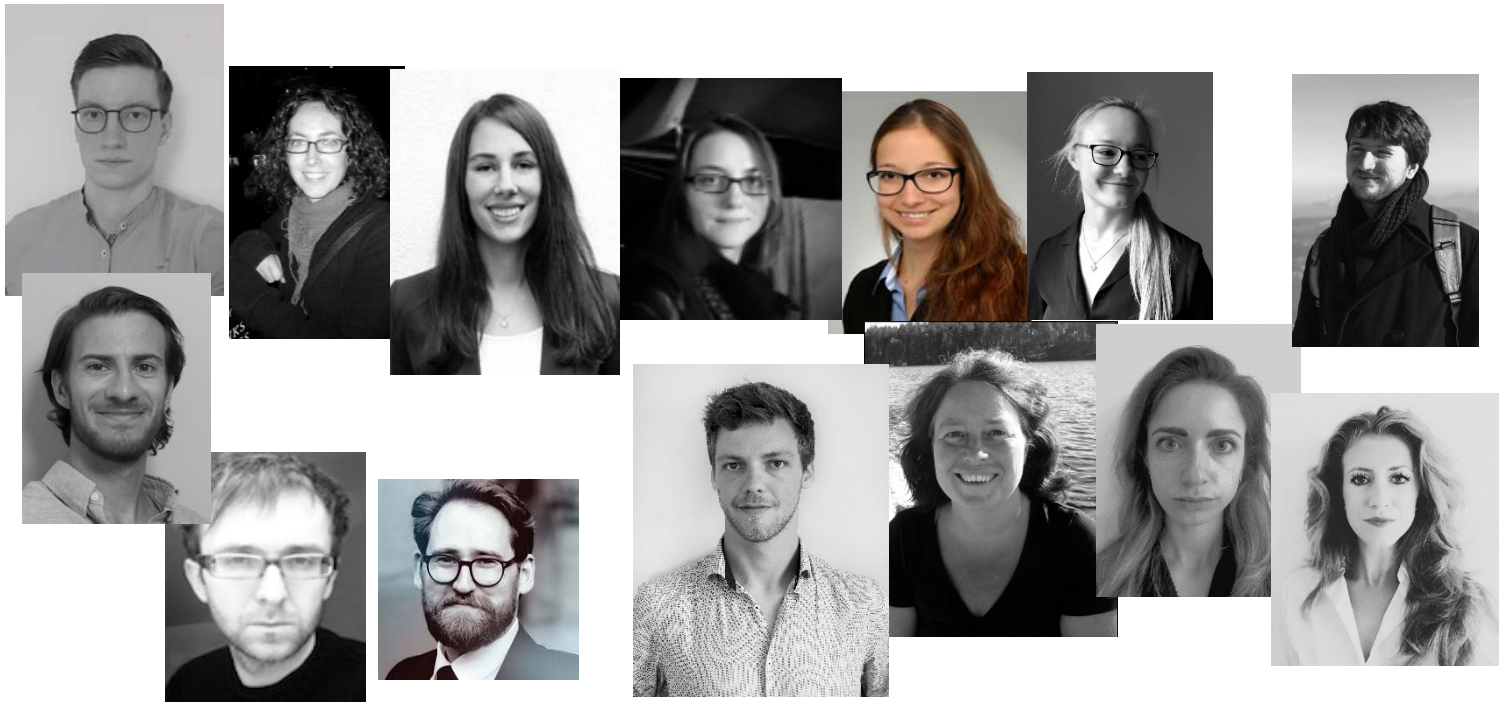

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Flora Moujaes
Katharina Zahoranszky
Anja Seidl
Sara Romer

Acknowledgments

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Anke Henning
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Wellcome Trust Centre for Neuroimaging
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FNSNF
Schweizerische Eidgenossenschaft
Confédération suisse
Confederazione Svizzera
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Swiss Neuromatrix Foundation
HEFFTER RESEARCH INSTITUTE
RESEARCH AT THE FRONTIERS OF THE MIND
Usona Institute

For more literature on the topic explore renect work

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Franz X. Vollenweider - Google Scholar