



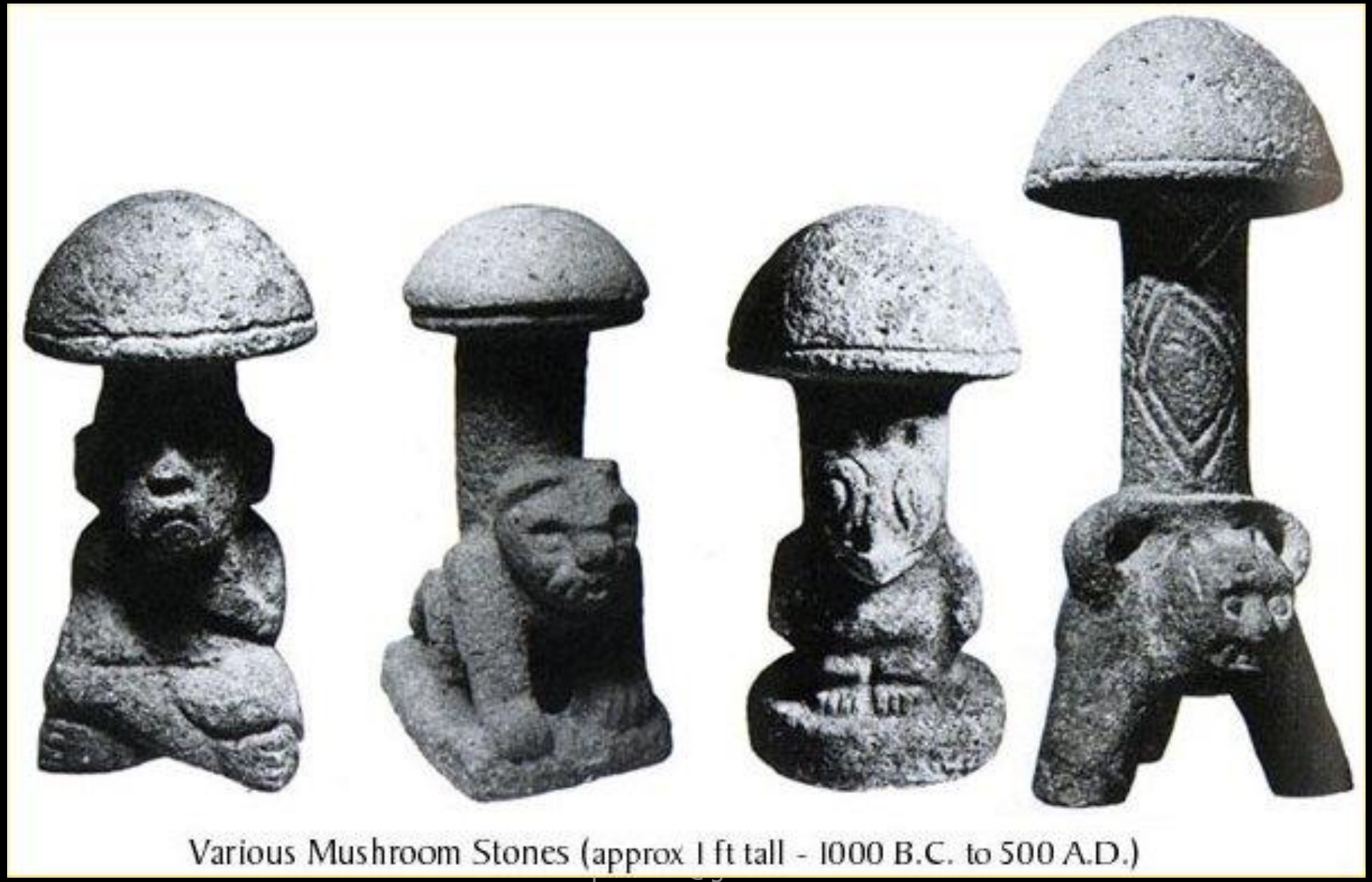
Psilocybin: Psychedelic or Psychotherapeutic?

قارچ جادویی روانگردان یا روان درمانگر؟

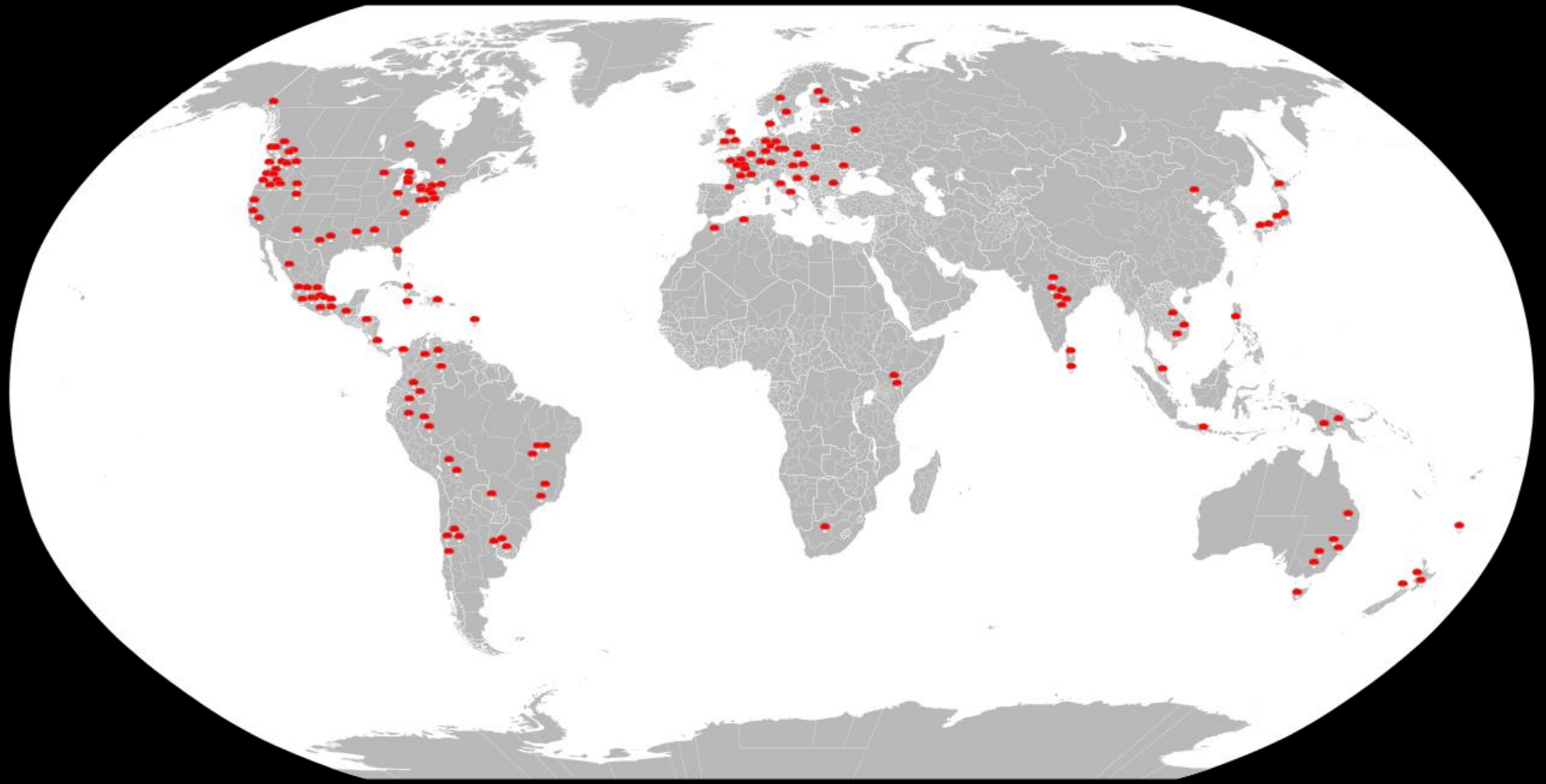
Dr.AA Pourshanazari

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@dr.pourshanazari YouTube



Various Mushroom Stones (approx 1 ft tall - 1000 B.C. to 500 A.D.)



aapoursha@gmail.com

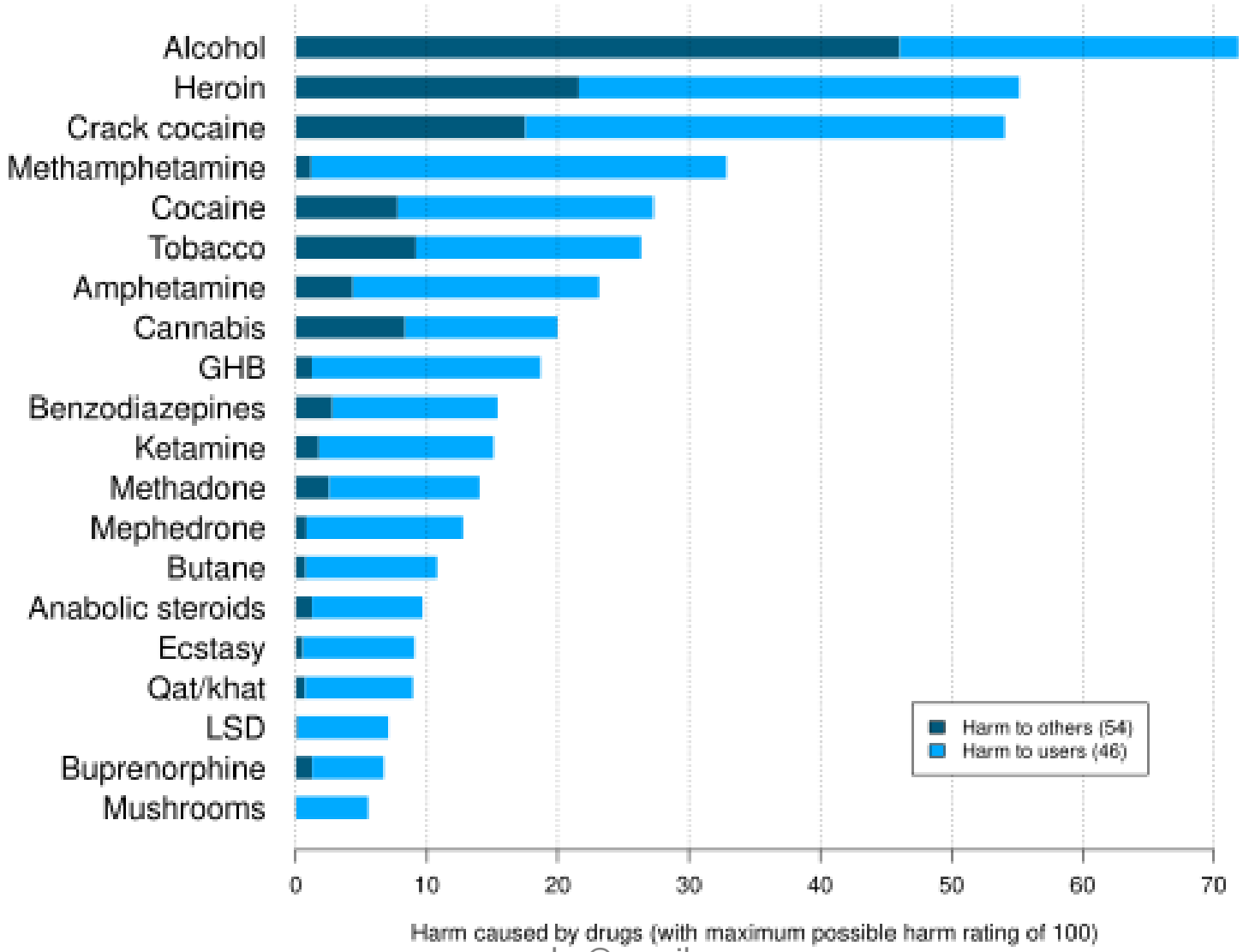




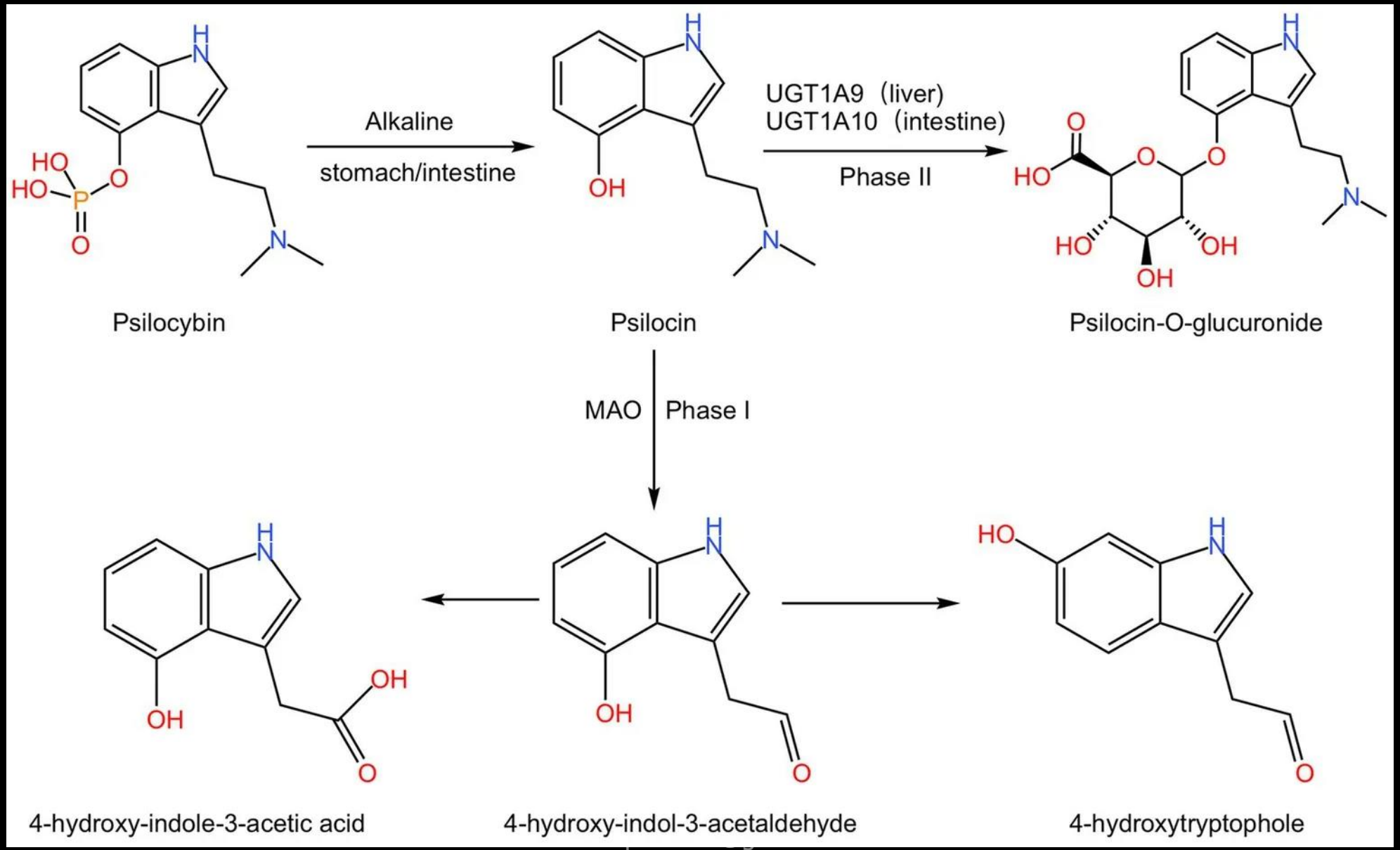


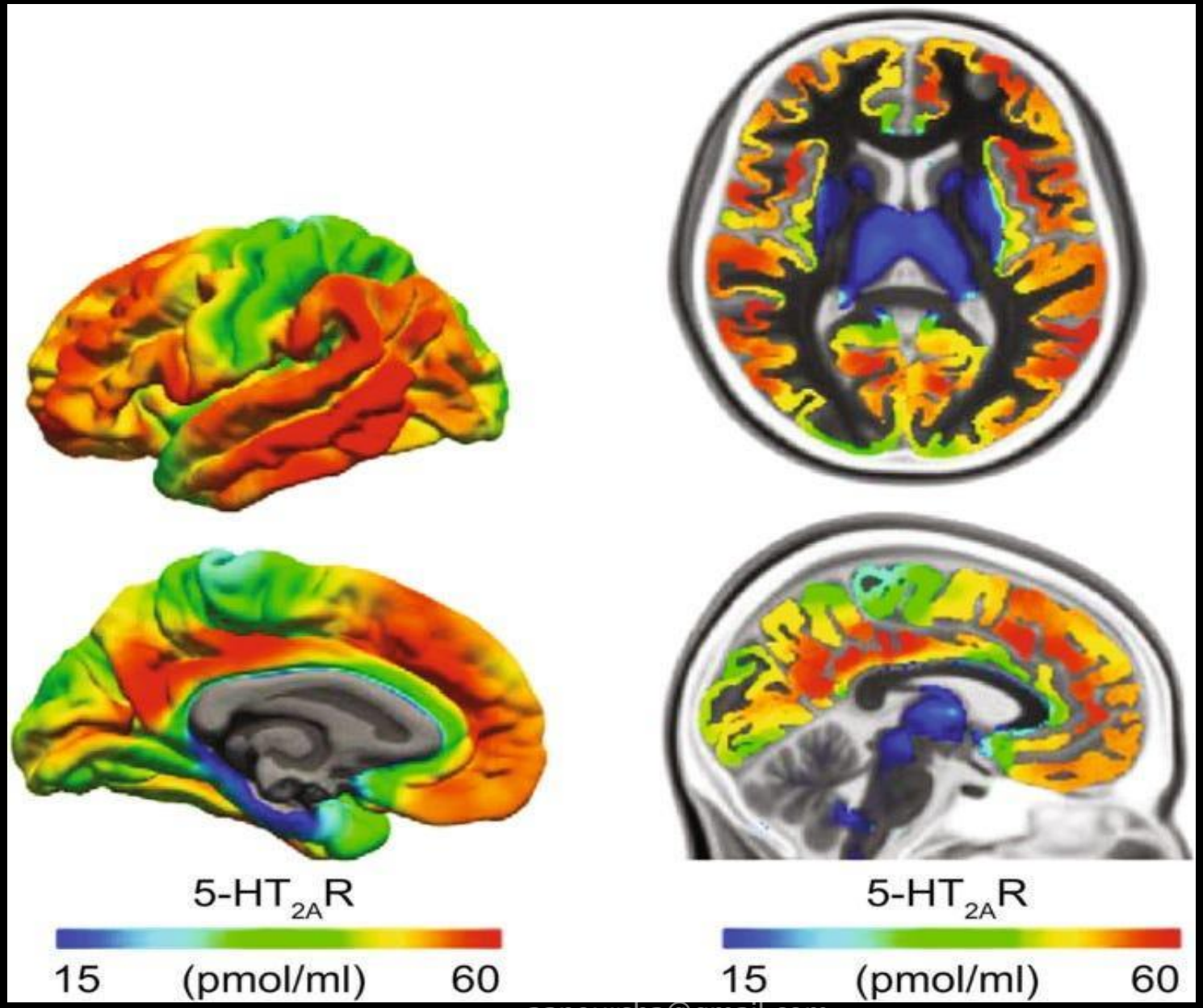
aapoursha@gmail.com

Nutt DJ, King LA, Phillips LD (November 2010). "Drug harms in the UK: a multicriteria decision analysis". Lancet.



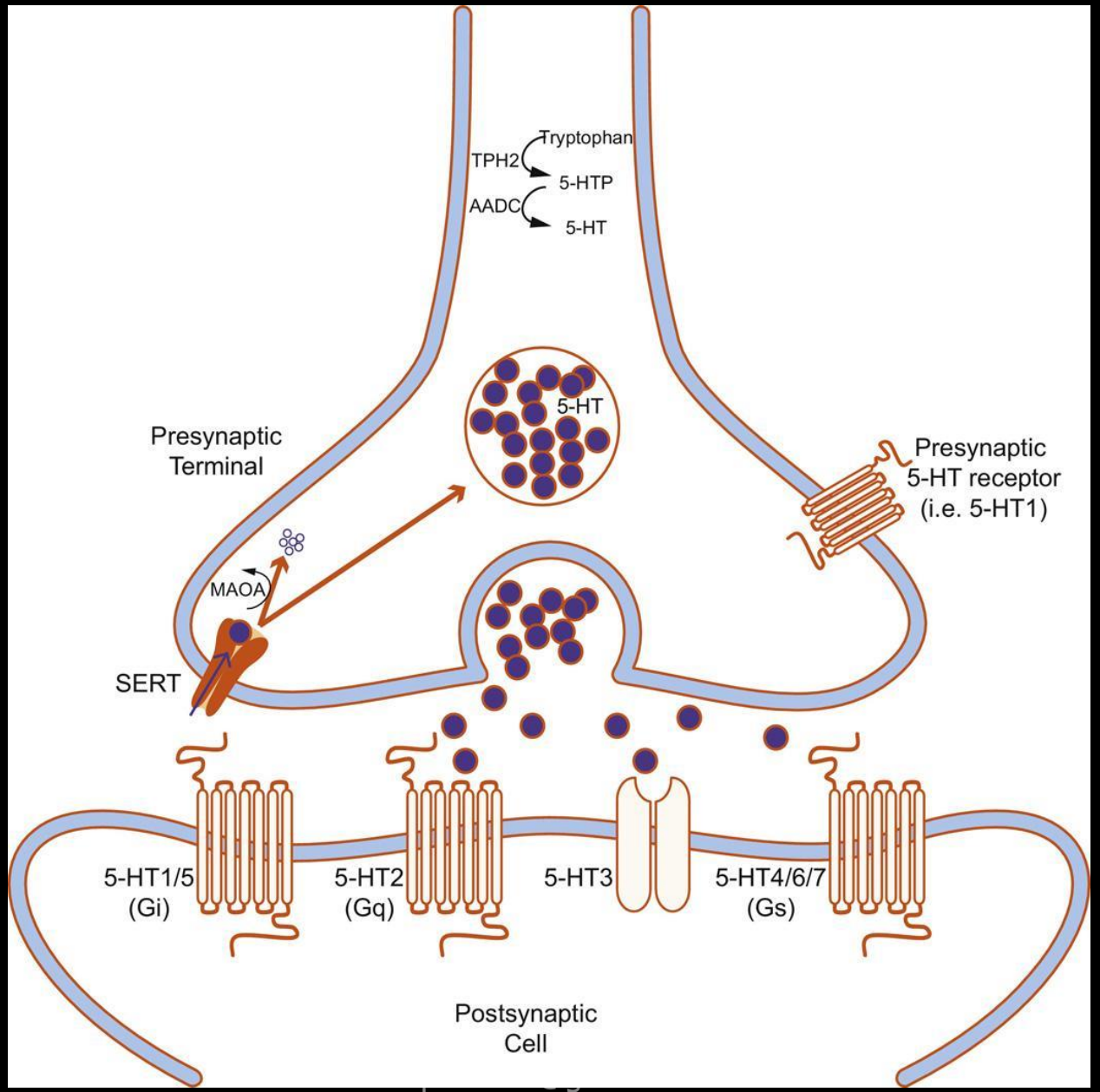
aapoursha@gmail.com

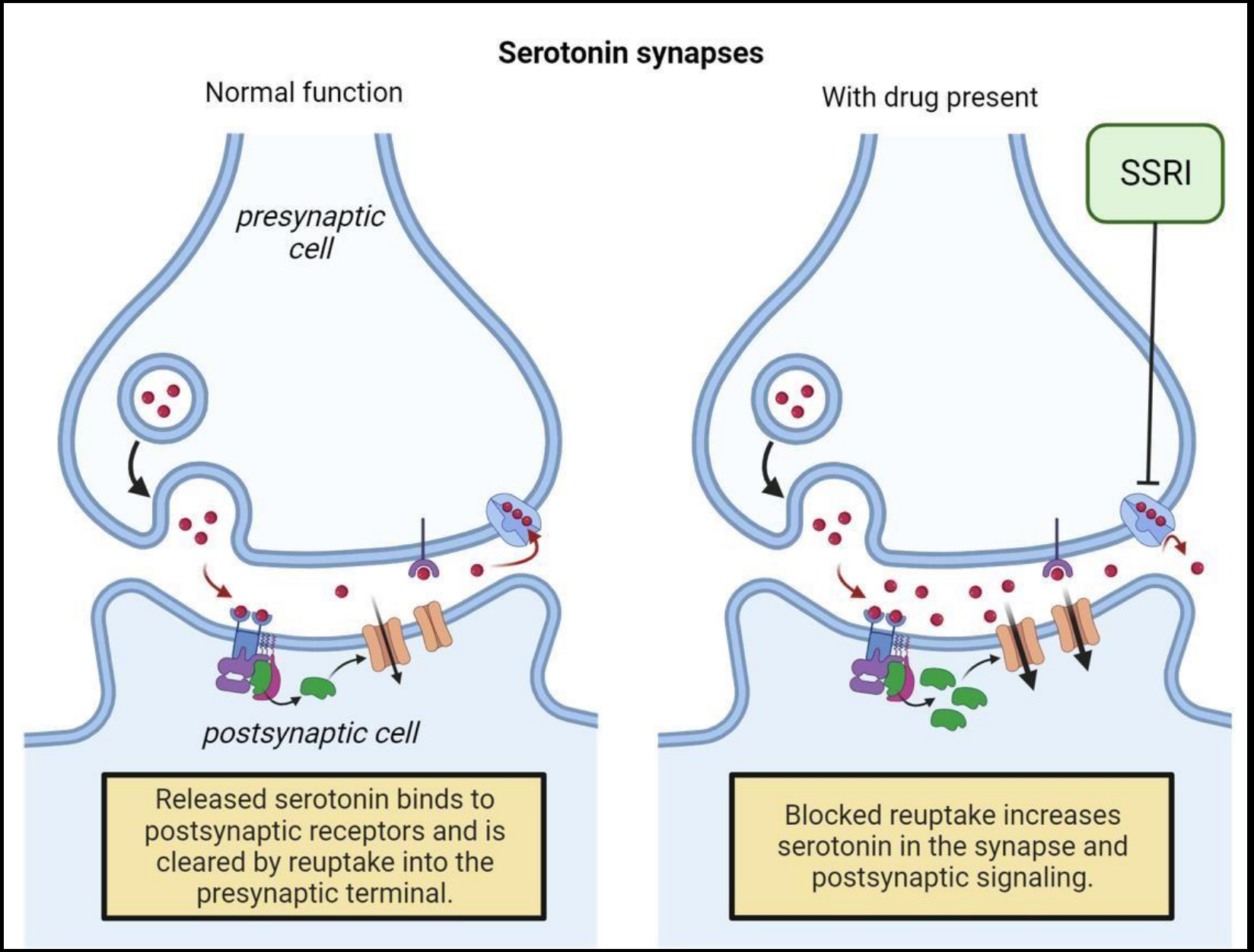

Alkaline
stomach/intestine
UGT1A9 (liver)
UGT1A10 (intestine)
Phase II
MAO
Phase I
Psilocybin
Psilocin
Psilocin-O-glucuronide
4-hydroxy-indole-3-acetic acid
4-hydroxy-indol-3-acetaldehyde
4-hydroxytryptophole

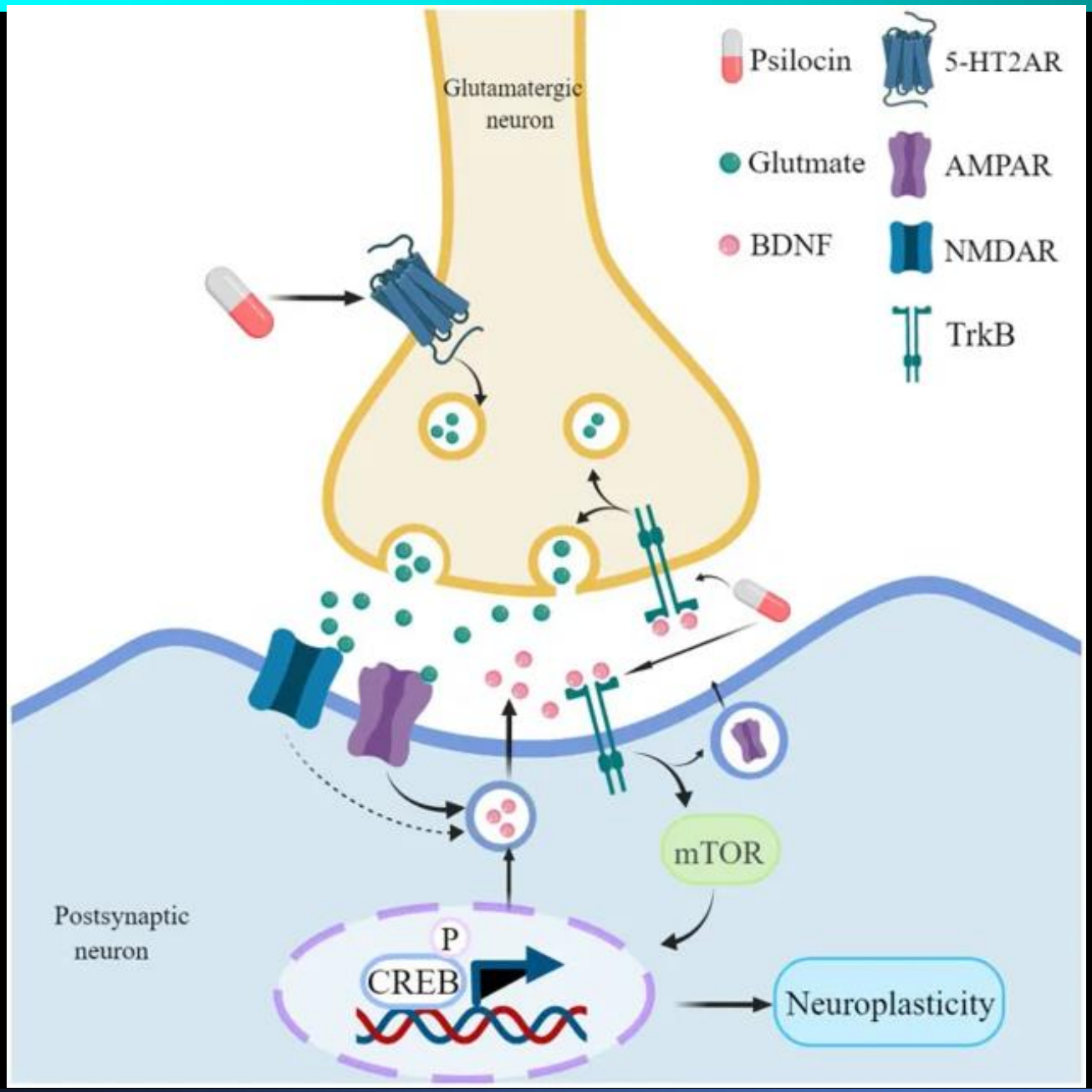

5-HT2AR
15 (pmol/ml) 60
5-HT2AR
15 (pmol/ml) 60

Role of psilocybin in the treatment of depression and other diseases

- anti-apoptotic پیشگیری از مرگ سلولی
- anti-inflammatory ضد التهاب
- improving neuroplasticity بهبود انعطاف‌پذیری عصبی
- improving functional connectivity of brain networks
- بهبود اتصال عملکردی شبکه‌های مغزی


Tryptophan
TPH2
5-HTP
AADC
5-HT
5-HT
Presynaptic
Terminal
Presynaptic
5-HT receptor
(i.e. 5-HT1)
MAOA
SERT
5-HT1/5
(Gi)
5-HT2
(Gq)
5-HT3
5-HT4/6/7
(Gs)
Postsynaptic
Cell


Serotonin synapses
Normal function
With drug present
presynaptic cell
SSRI
postsynaptic cell
Released serotonin binds to postsynaptic receptors and is cleared by reuptake into the presynaptic terminal.
Blocked reuptake increases serotonin in the synapse and postsynaptic signaling.



TrkB= Tropomyosin receptor kinase B

BDNF= Brain-derived neurotrophic factor

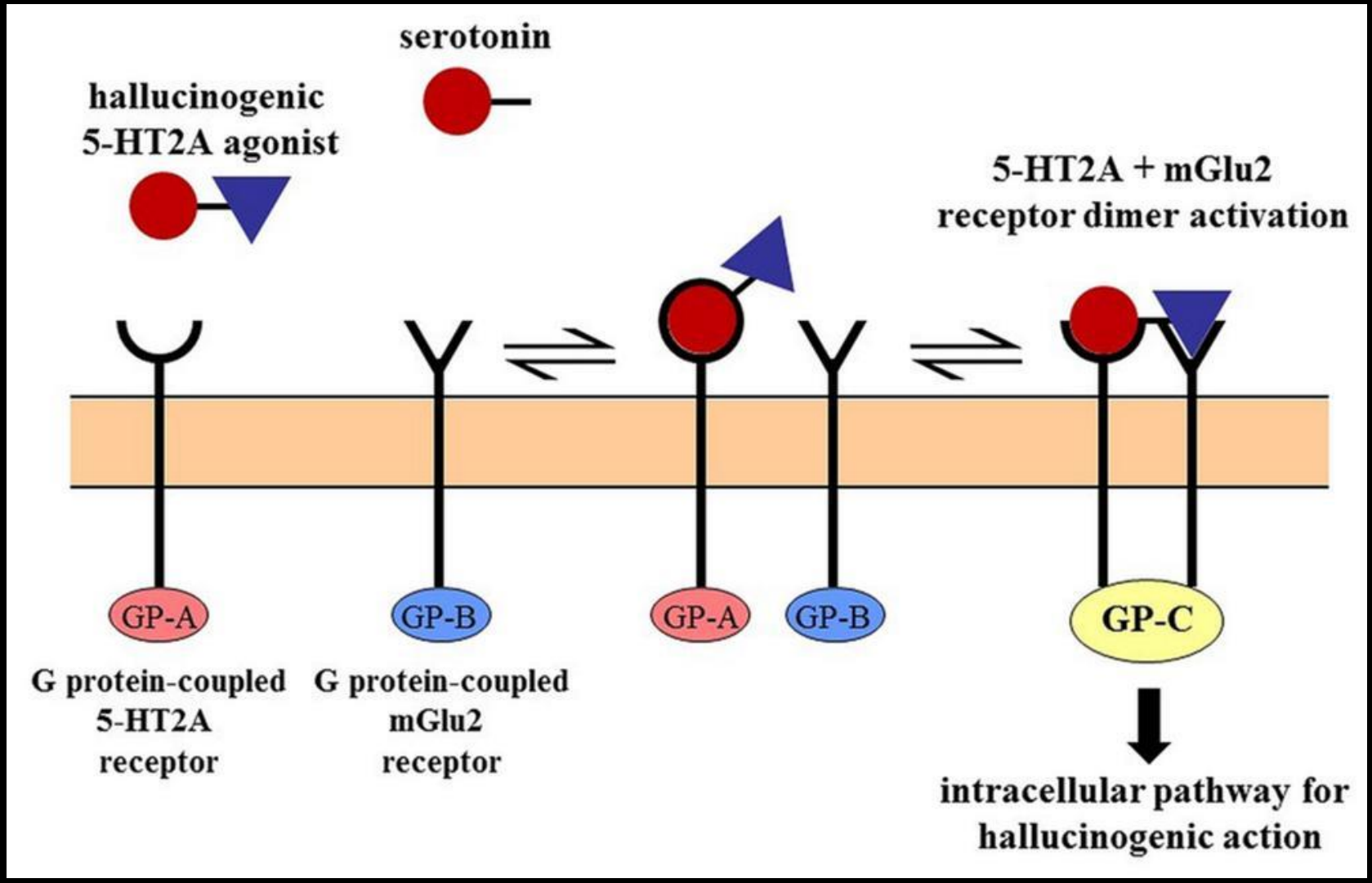
mTOR= Mammalian target of rapamycin

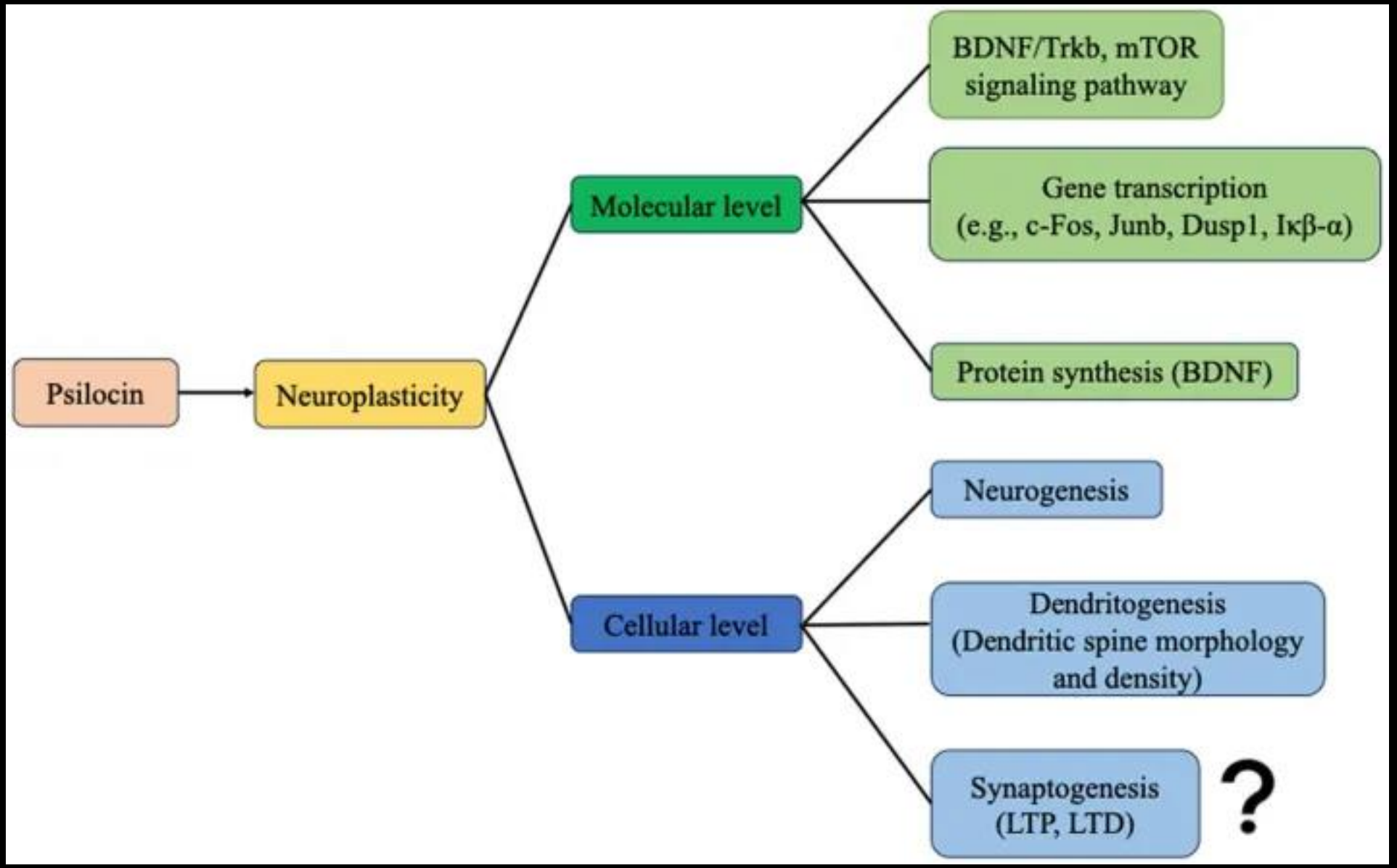
(protein kinase)

CREB = Cyclic AMP-responsive element-binding protein

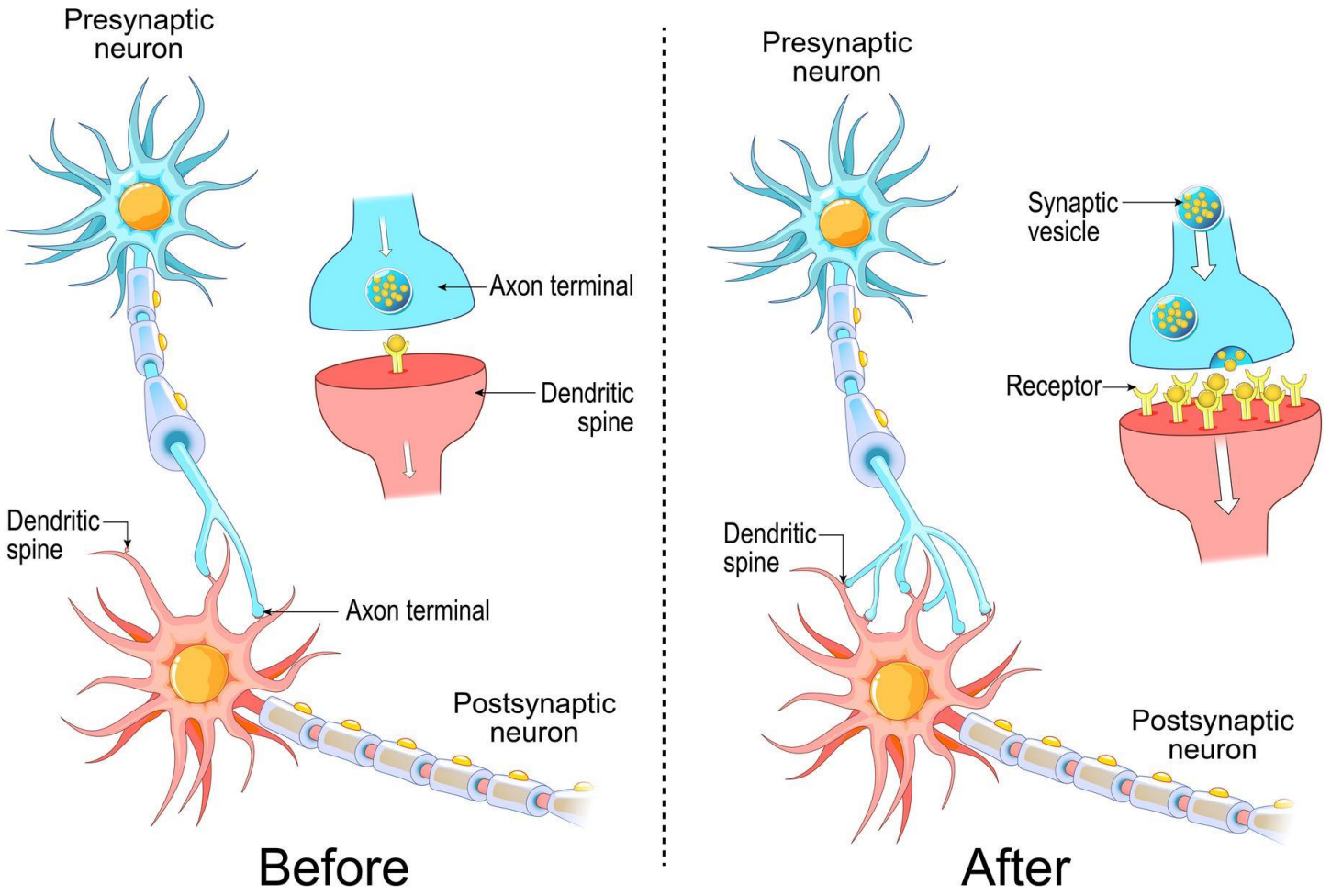
Juan F López-Giménez [1], Javier González-Maeso [2,✉] **Hallucinogens and Serotonin 5-HT_{2A} Receptor-Mediated Signaling Pathways .** Behav Neurosci. 2018;36:45–73. doi

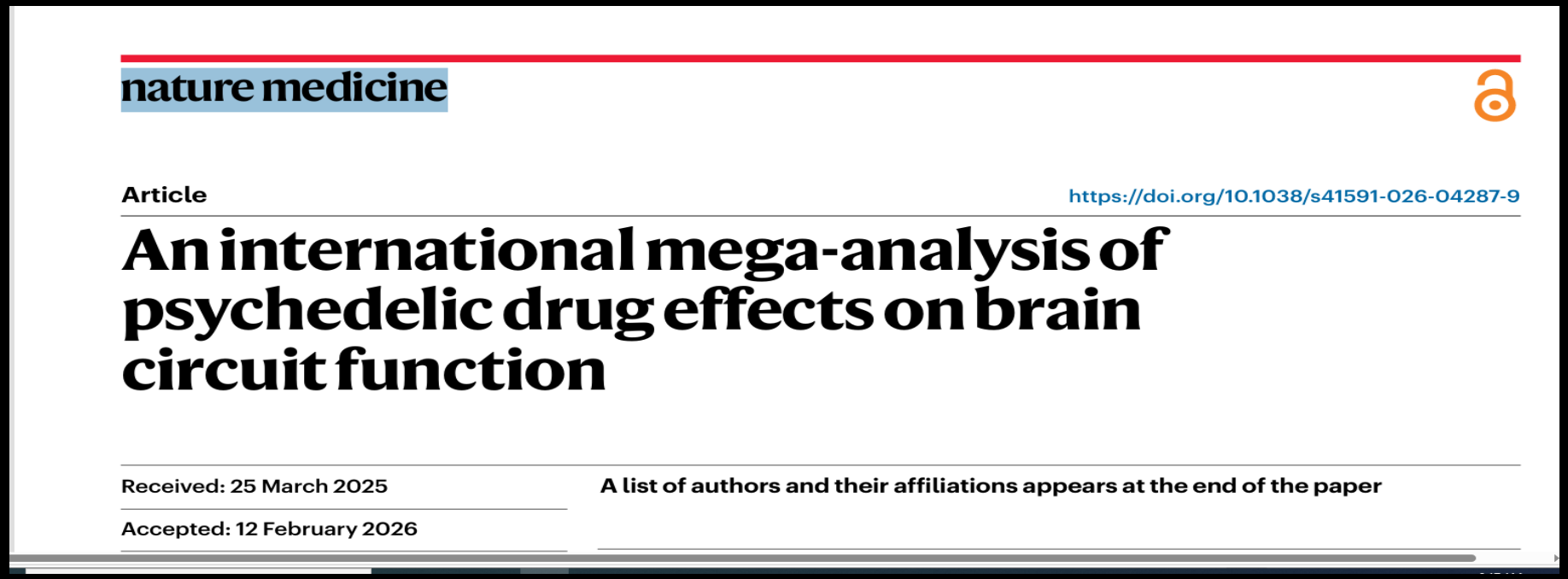
these findings suggest that the 5-HT_{2A}-mGlu2 receptor complex is critical for the hallucinogen-like behaviors induced by 5-HT_{2A} receptor agonists




Psilocin
Neuroplasticity
Molecular level
Cellular level
BDNF/Trkb, mTOR signaling pathway
Gene transcription (e.g., c-Fos, Junb, Dusp1, Iκβ-α)
Protein synthesis (BDNF)
Neurogenesis
Dendritogenesis (Dendritic spine morphology and density)
Synaptogenesis (LTP, LTD)
?

LEARNING


Presynaptic neuron
Axon terminal
Dendritic spine
Dendritic spine
Axon terminal
Postsynaptic neuron
Before
Presynaptic neuron
Synaptic vesicle
Receptor
Dendritic spine
Postsynaptic neuron
After



nature medicine

Article

https://doi.org/10.1038/s41591-026-04287-9

An international mega-analysis of psychedelic drug effects on brain circuit function

Received: 25 March 2025

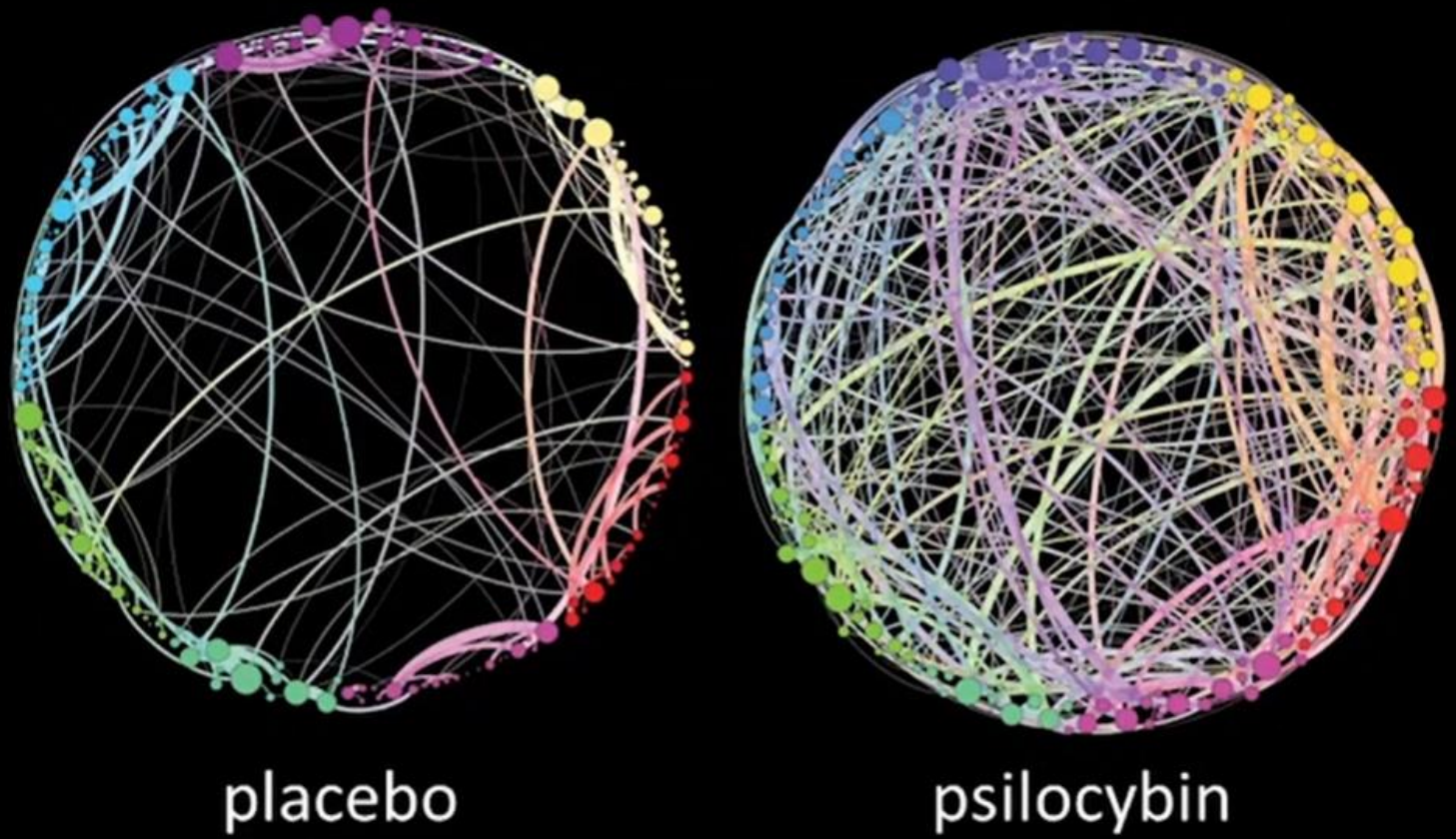
Accepted: 12 February 2026

A list of authors and their affiliations appears at the end of the paper

Method: ‘mega-analysis’ integrating 11 independent resting-state functional magnetic resonance imaging datasets across five psychedelic drugs (psilocybin, lysergic acid diethylamide, mescaline, N,N-dimethyltryptamine and ayahuasca)

Results: we discovered several common features in the induced alterations to brain function across drugs and sites. Most prominently, we identified a core signature of increased functional connectivity between transmodal (default, frontoparietal and limbic) and unimodal networks (visual and somatomotor), with subnetwork specificity.

Freer communication pathways

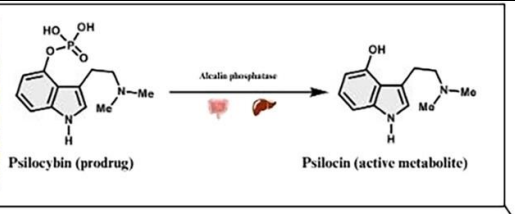


placebo

psilocybin









	Rodents	Humans
Molecular	5-HT2AR + 5-HT1AR + 5-HT2BR + 5-HT2CR + Others 5-HTR subtypes (4,5,7) and non serotonergic receptors ↓ Ala242 ↓ Mainly expressed in pyramidal cells → Psychedelics effects → Antidepressant-like effects ?	5-HT2AR + 5-HT1AR + 5-HT2BR + 5-HT2CR + Others 5-HTR subtypes (4,5,7) and non serotonergic receptors ↓ Ser242 ↓ Mainly expressed in mPFC and cortical areas → Psychedelics effects → Antidepressant-like effects ?
Pharmacokinetic	1. Half-life t1/2 = 117 min 2. Routes of administration : intraperitoneal, subcutaneous 3. Doses : 0.3 - 10 mg/kg	1. Half-life t1/2 = 2.5 hours 2. Routes of administration : oral, intravenous 3. Doses : 10 - 30 mg
 **Systems**	1. Rapid reorganization of the brain network architecture by increased gene expression related to neuroplasticity in various brain regions such as mPFC, neocortex, striatum, amygdala 2. Promotion of neuroplasticity in cortical pyramidals neurons 3. Increase cortical Glutamate release	1. Modification of connectivity between lateral and medial frontoparietal cortex, mPFC and posterior cingulate cortex, visual brain networks - Decreased connectivity within the Default mode network (DMN) and increased sensory and thalamocortical connectivity 2. Promotion of neuroplasticity in cortical pyramidals neurons 3. Increase cortical Glutamate release
Behavior	1. Head Twitch Response (HTR)  2. Fast-acting antidepressants like effect like ketamine : improvement of behavioral despair, anhedonia - anxiolytic like effects	1. Hallucinations - perturbations of perception, cognition, and mood  2. Fast-acting antidepressants effect like ketamine and over several weeks : efficacy in deacreasing depression and anxiety symptoms - low toxicity and low addictive purpose

Effects of Psilocybin

- Onset: ~20–60 minutes after ingestion
- Peak: 2–4 hours
- Total duration: 4–6 hours (sometimes longer)

Effects of Psilocybin
(what people may experience)(Trip)

1- Physical effects

.Nausea

.Increased heart rate

.Dilated pupils

1- اثرات جسمانی

حالت تهوع

افزایش ضربان قلب

گشاد شدن مردمک‌ها

2. Perceptual changes

2- تغییرات ادراکی

- Colors appear brighter — رنگ‌ها درخشان‌تر به نظر میرسند
- Sound quality improves. — کیفیت صدا ها بالاتر میرود
- Time perception may distort — درک زمان ممکن است دچار اختلال شود
- Possible mild hallucinations — احتمال بروز توهمات خفیف
- Patterns may move or “breathe” — الگوها ممکن است حرکت کنند یا گویی «نفس می‌کشند»





3. Emotional and psychological effects

اثرات عاطفی و روانی

.Euphoria or deep calm سرخوشی یا آرامش عمیق

.Increased openness and empathy افزایش گشودگی و همدلی

.Heightened emotions احساسات تشدیدشده مثبت یا منفی

.Possible anxiety or fear احتمال اضطراب یا ترس

4. Changes in thinking and self-perception

۴. تغییرات در تفکر و خودپنداره

.Altered sense of identity (“ego dissolution”)

.تغییر در حس هویت («انحلال نفس و تعالی»)

.New perspectives on personal problems

.دیدگاه های جدید در مورد مشکلات شخصی

.Feeling of connection to nature or others

. احساس پیوند با طبیعت یا دیگران

- **Outcomes strongly depend on:**
  - Mindset ذهنیت
  - Environment محیط
  - Guidance راهنمایی

Risks and negative effects

. **“Bad trip”**

. Intense anxiety or panic اضطراب شدید یا وحشت‌زدگی

. Confusion or paranoia سردرگمی یا بدگمانی(پارانویا)

. Feeling of losing control احساس از دست دادن کنترل



“good” or “bad” is determined by multiple factors:

1- Set **(internal state)**

“Set” refers to everything inside the person before and during the experience:

Mood (calm, anxious, depressed, excited)
Expectations (fear, curiosity, or control)
Personality traits (emotional sensitivity)
Previous experiences and psychological background

مقاومت = جنگ با تجربه

وقتی فرد مقاومت می‌کند: «این موضوع نباید اتفاق بیفتد» «این خطرناک است من باید شرایط را برگردانم»

در مغز چه می‌شود؟

+مغز خطاهای پیش‌بینی را تهدید تفسیر می‌کند.

سیستم ترس (مثل آمیگدالا) فعال‌تر می‌شود.

بدن وارد حالت استرس می‌شود.

نتیجه:

اضطراب بیشتر- افکار آشفته و تکراری.

چرخه‌ی ترس: **ترس** ← **تلاش برای کنترل** ← **آشفتگی بیشتر** ← **ترس بیشتر**.

+

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“good” or “bad” is determined by multiple factors:

2- Setting (external environment)

.Physical location (safe vs. unfamiliar)

.Social context (alone, trusted friends, strangers)

.Sensory environment (lighting, noise, music)

3- Dose differences: low vs high

◆ Low dose

- Subtle perceptual changes
- Enhanced sensory awareness
- Experience usually remains manageable

◆ Moderate to high dose

- Strong alterations in perception of time and space
- Reduced cognitive control
- Emotional amplification
- Increased immersion in the experience

◆ Very high dose

- Ego dissolution (loss of sense of self boundaries)
- Intense hallucinations or dream-like states
- Rapid emotional shifts (peace ↔ fear)
- Higher risk bad trip

اثرات درمانی سیلوسایبین

- ضد افسردگی
- درمان اختلال وسواس فکری
- درمان وابستگی دارویی(سیگار و الکل)
- درمان الزایمر
- کنترل درد(میگرن و سردرد های کلاستر)
- کنترل درماندگی در بیماری های صعب العلاج

Table total

Efficacy and safety of psilocybin for the treatment of substance use disorders: A systematic review

Shakila Meshkat [1], Gunjan Malik [1], Richard J Zeifman [2], Jennifer Swainson [3], Krishna Balachandra [3], Amy C Reichelt [4], Yanbo Zhang [3], Lisa Burback [3], Olga Winkler [5], Andrew Greenshaw [3], Eric Vermetten [6], Leah M Mayo [7], Robert Tanguay [7], Rakesh Jetly [8], Venkat Bhat [9]

Neurosci Biobehav Rev
. 2025 Jun:173:106163.
doi: 10.1016/j.neubiorev.2025.106163. Epub 2025 Apr 15.

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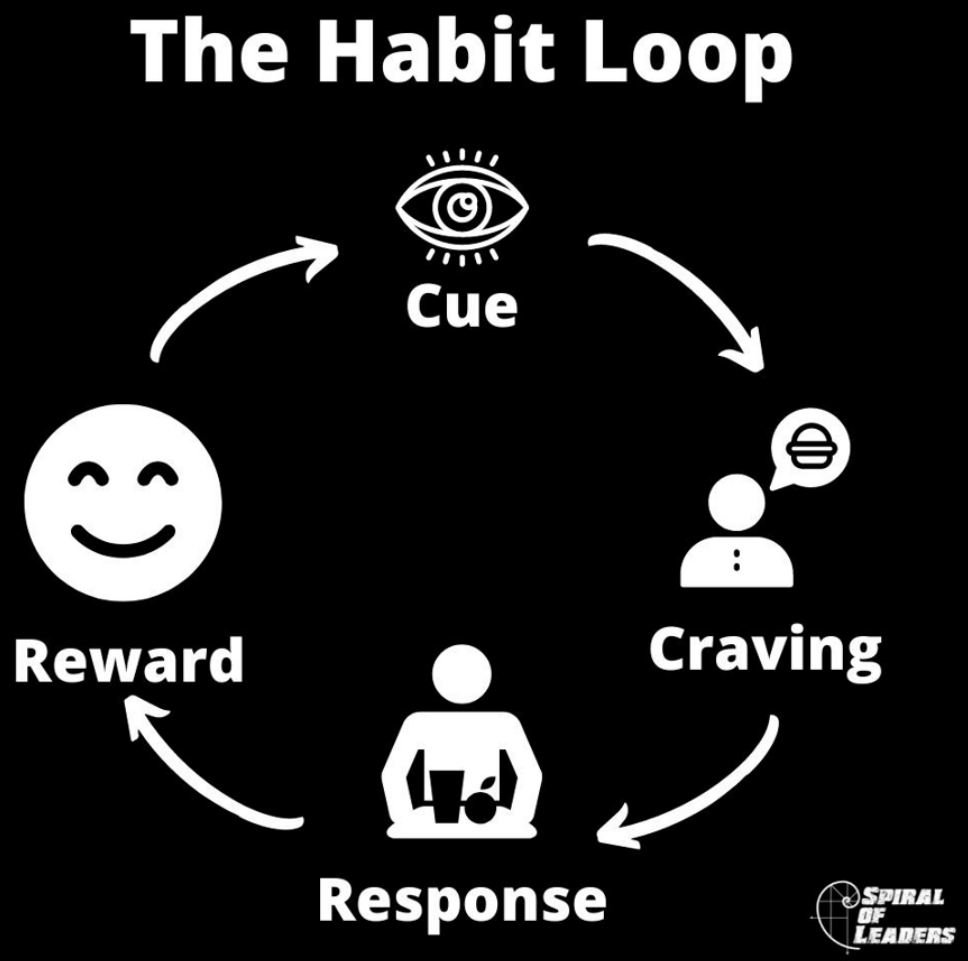
- Psilocybin mushrooms have not been known to cause physical or psychological dependence (addiction).[1]

Refrence:

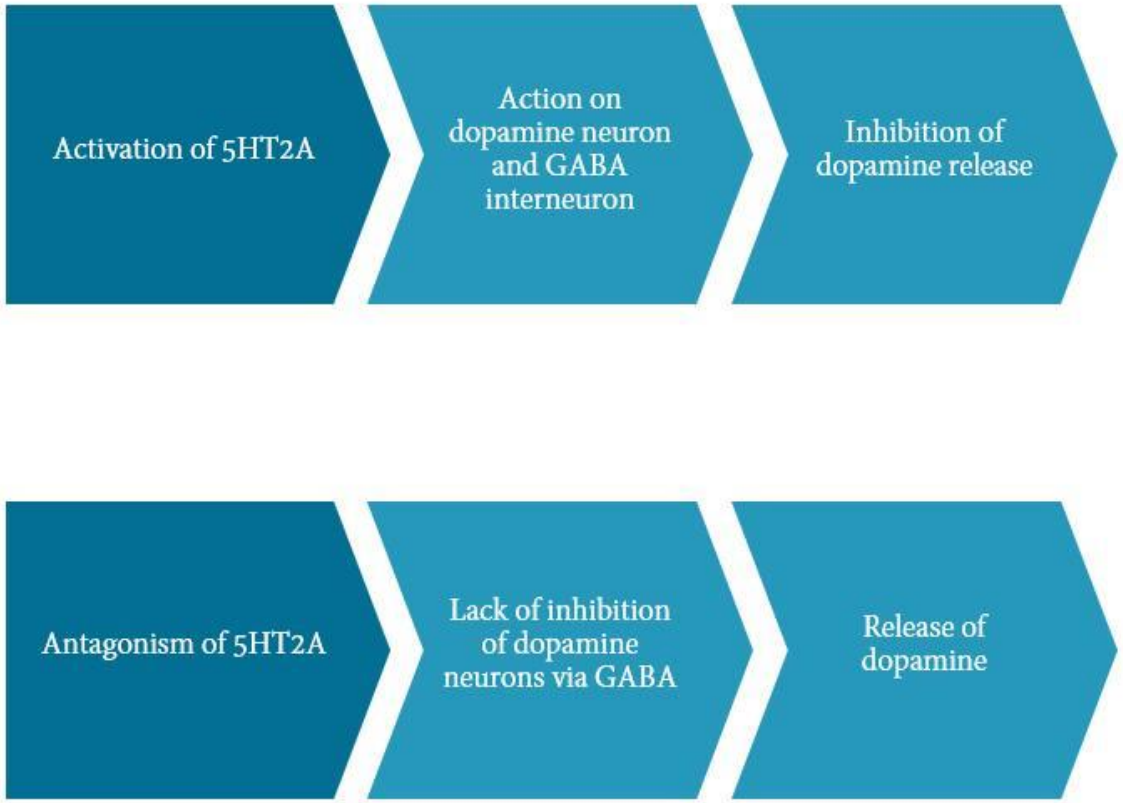
van Amsterdam, J.; Opperhuizen, A.; van den Brink, W. (2011). "Harm potential of magic mushroom use: A review". Regulatory Toxicology and Pharmacology. ***59*** *(3): 423–429.*

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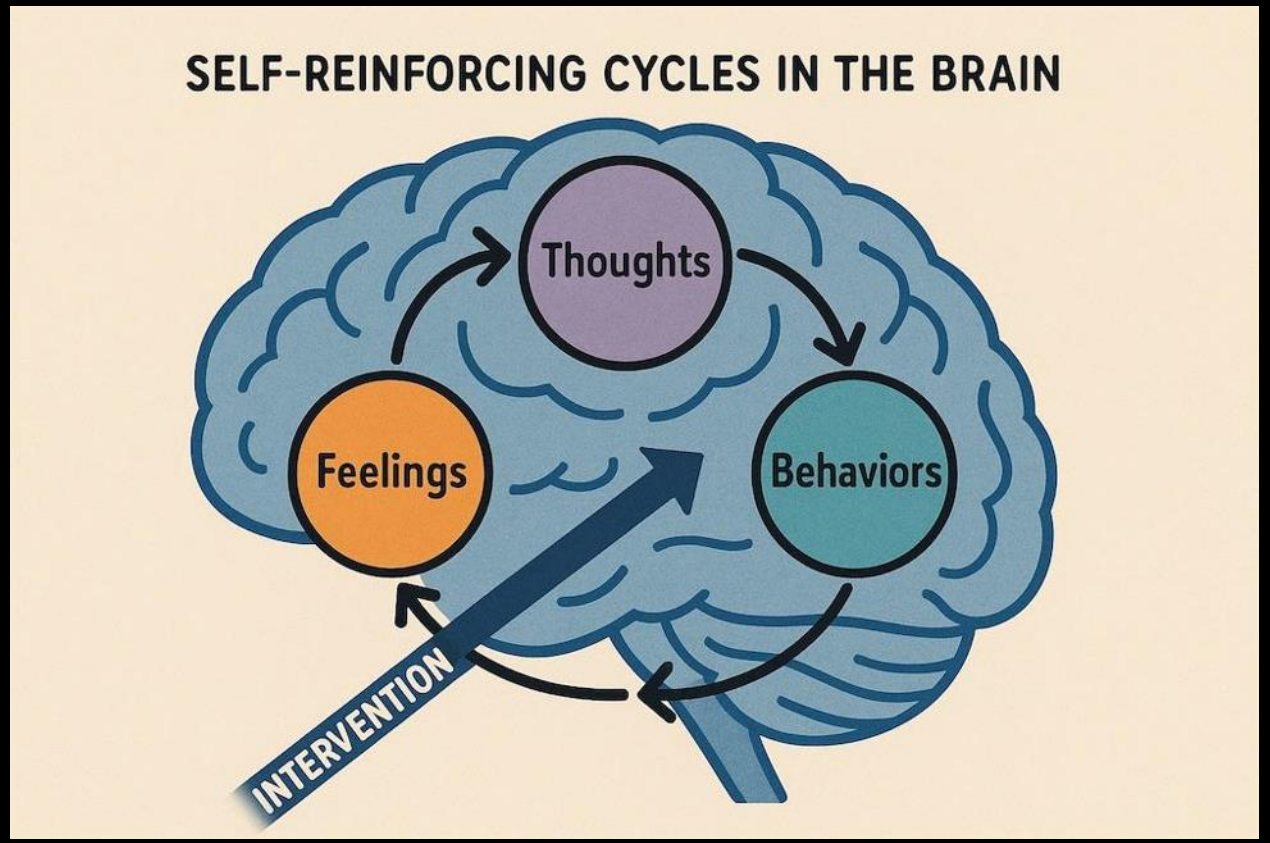
Addiction = strengthening repetitive loops



ROLE OF THE 5HT2A RECEPTOR



- Psilocybin :
  - temporarily **destabilize** these loops
  - increase **neural flexibility and connectivity**



داروهای اعتیاد آور

.Addictive drugs:

- reinforce behavior — رفتار را تقویت می‌کنند
- narrow brain activity — فعالیت مغز را محدود می‌کنند
- increase repeated use — استفاده مکرر را افزایش می‌دهند

سیلوسایبین

.Psychedelics like Psilocybin:

- don’t strongly reinforce use — استفاده را به شدت تقویت نمی‌کنند
- disrupt rigid patterns — الگوهای خشک را مختل می‌کنند
- may create conditions for behavioral change
  - ممکن است شرایطی را برای تغییر رفتار ایجاد کنند

This does **not** mean:

- psychedelics are risk-free
- or that they are guaranteed treatments

It simply means their **mechanism points in the opposite direction of addiction**, not that they are a universal solution.

نقش سیلوسایبین در درمان افسردگی

nature medicine

Article

https://doi.org/10.1038/s41591-026-04541-0

Psilocybin-assisted therapy for treatment-resistant major depressive disorder in a public healthcare setting: a randomized controlled trial

Received: 21 January 2026

Accepted: 24 June 2026

A list of authors and their affiliations appears at the end of the paper

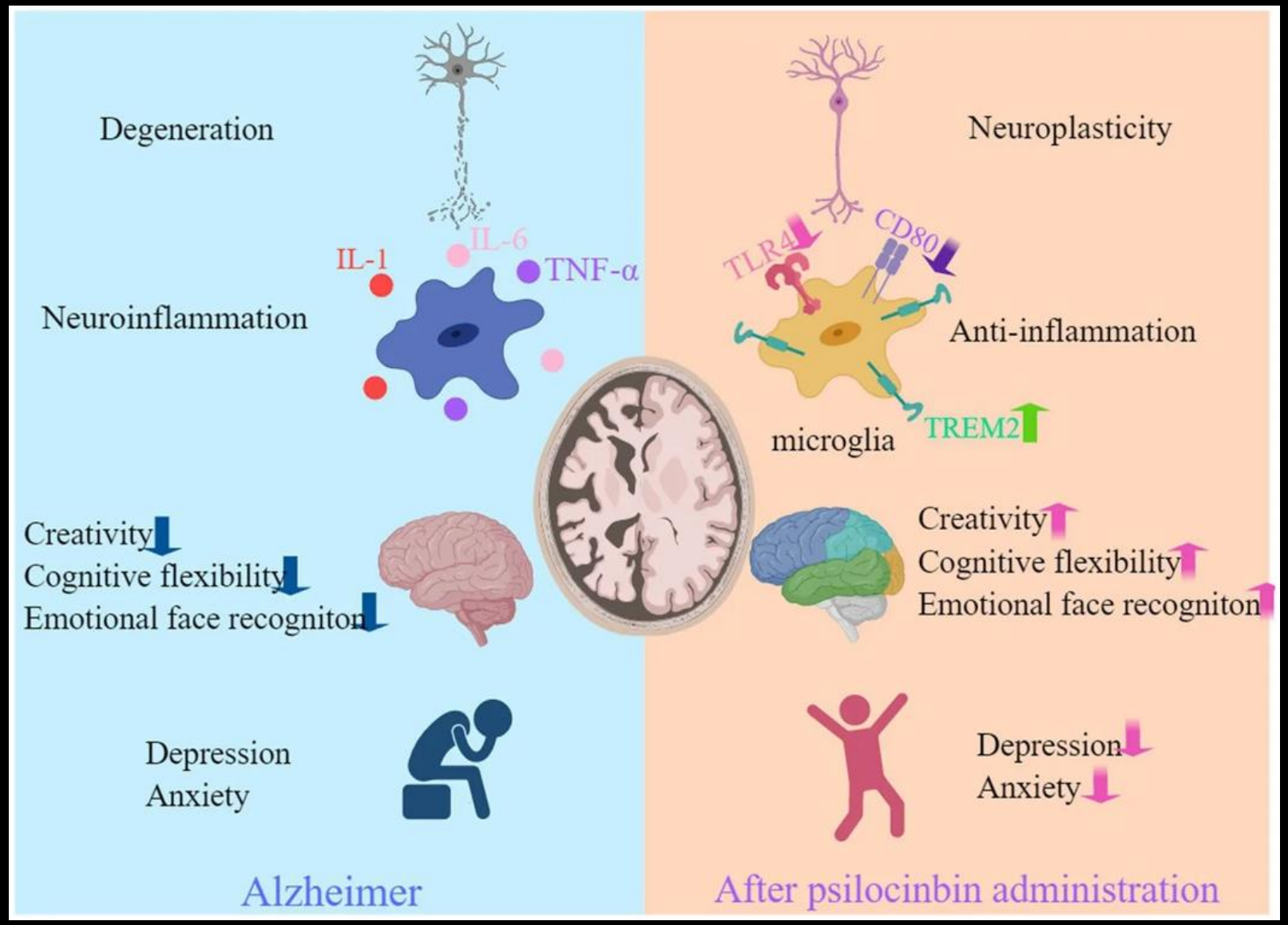
Methods: single 25-mg dose of psilocybin or placebo with 6 weeks of follow-up.

نقش سیلوسایبین در درمان آلزایمر

Psilocybin for the treatment of Alzheimer's disease

This modulation causes heightened neural plasticity, diminished inflammation, and improvements in cognitive functions such as creativity, cognitive flexibility, and emotional facial recognition. Noteworthy is psilocybin's promising role in mitigating anxiety and depression symptoms in AD patients.

REVIEW article
Front. Neurosci., 10 July 2024
Sec. Neurodegeneration
Volume 18 - 2024 |
https://doi.org/10.3389/fnins.2024.1420601



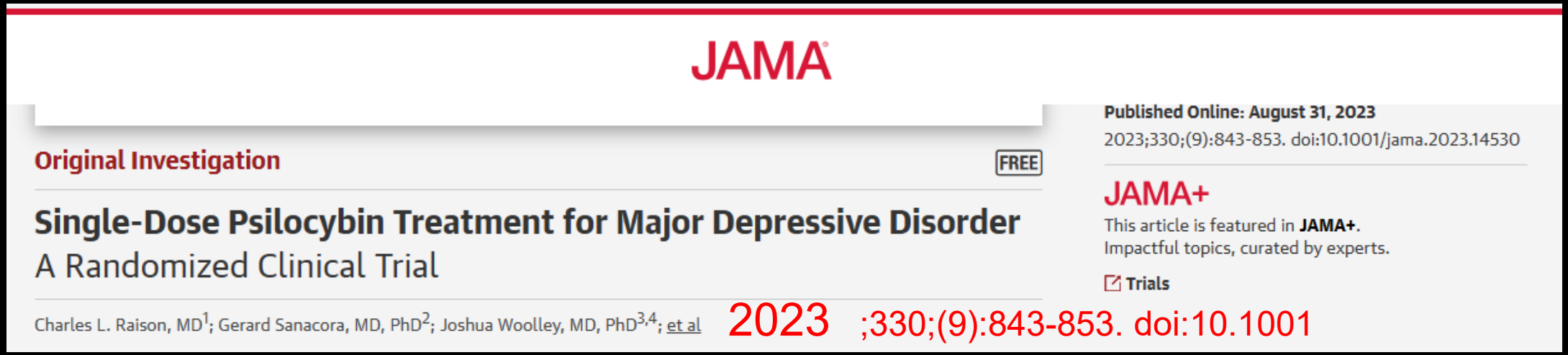
TNF-α = Tumor necrosis factor alpha

TLR4= Toll-like receptor 4

CD80= Cluster of differentiation 80

Trem2= Triggering receptor expressed on myeloid cells 2

IL =Interleukin



JAMA

Original Investigation FREE

Single-Dose Psilocybin Treatment for Major Depressive Disorder
A Randomized Clinical Trial

Charles L. Raison, MD[1]; Gerard Sanacora, MD, PhD[2]; Joshua Woolley, MD, PhD[3,4]; et al

Published Online: August 31, 2023
2023;330;(9):843-853. doi:10.1001/jama.2023.14530

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Trials

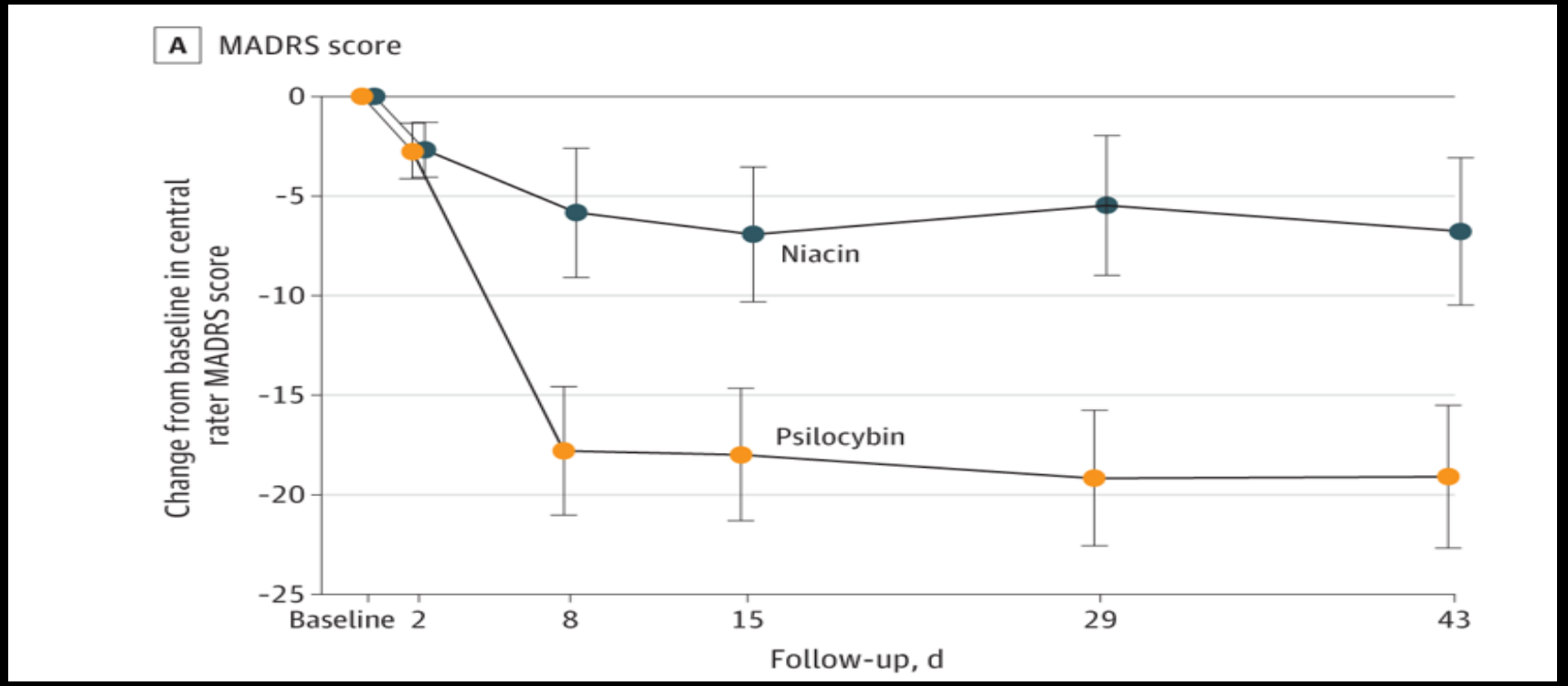
2023 ;330;(9):843-853. doi:10.1001

Method:

Among 1529 potential participants who completed prescreening, 347 signed informed consent, 240 were excluded at screening, 3 were excluded prior to randomization, and 104 were randomized, received the study drug, and comprised the ITT population (51 in the psilocybin group and 53 in the niacin group)

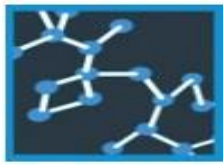
Interventions were a 25-mg dose of synthetic psilocybin or a 100-mg dose of niacin in identical-appearing capsules, each administered with psychological support.

The primary outcome was change in central rater–assessed Montgomery-Asberg Depression Rating Scale (MADRS) score (range, 0-60; higher scores indicate more severe depression) from baseline to day 43.



Results A total of 104 participants (mean [SD] age, 41.1 years; [50%] women)
Psilocybin treatment was associated with significantly reduced MADRS scores compared with niacin from baseline to day 43 .
Psilocybin treatment was also associated with significantly reduced Sheehan Disability Scale scores compared with niacin (mean difference, −2.31 [95% CI, −3.50 to −1.11]; $P < .001$) from baseline to day 43.

More participants receiving psilocybin had sustained response than those receiving niacin. There were no serious treatment-emergent AEs; however, psilocybin treatment was associated with a higher rate of overall AEs and a higher rate of severe AEs.



Fundamental & Clinical Pharmacology

SFPT

REVIEW ARTICLE | Open Access

Psilocybin as Transformative Fast-Acting Antidepressant: Pharmacological Properties and Molecular Mechanisms

Makiath Adebo, Mathilda Bonnet, Ons Laouej, Celine Defaix, Josephine C. McGowan, Florence Butlen-Ducuing, Denis J. David, Erwan Poupon, Laurent Tritschler, Alain M. Gardier

First published: 16 July 2025 | https://doi.org/10.1111/fcp.70038 | VIEW METRICS

World Health Organization (WHO), depression will be the main cause of disability in 2030. Understanding the mechanisms through which psilocybin/psilocin would be an effective antidepressant is crucial to ultimately validate its therapeutic potential when combined with SSRIs/SNRIs in mood disorders.

psilocybin positive effects and mechanism

1)Reduced rigidity of thought patterns(DMN)

2) Increased cross-network brain connectivity

3) Relaxation of rigid Predictive coding models

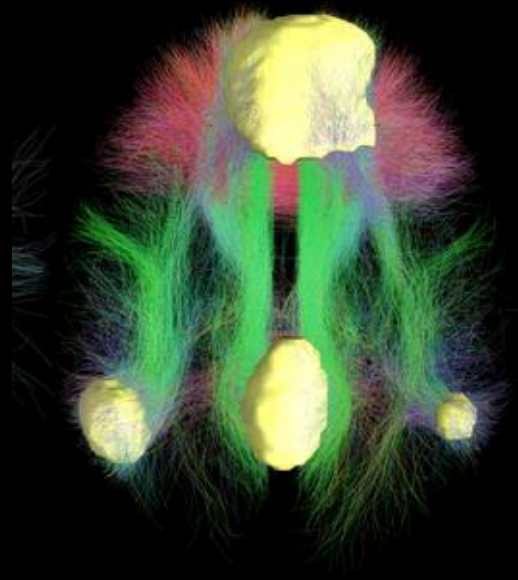
4) Emotional processing and psychological “resetting”

5) Role of “meaningful experience” in lasting change

1)Reduced rigidity of thought patterns(DMN)

- **Default Mode Network (DMN)** is involved in:

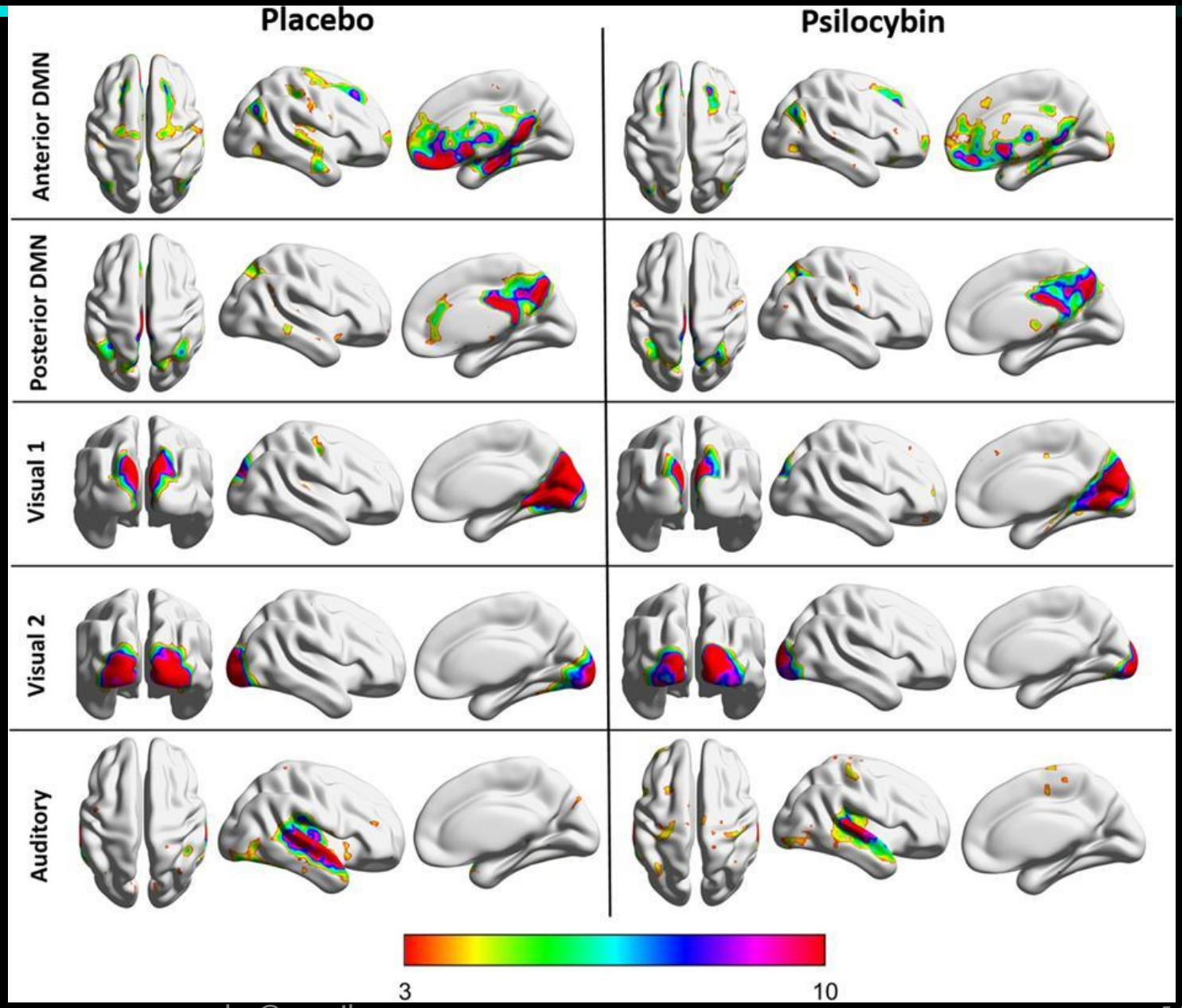
- Self-referential thinking (“اختلال وسواس فکری)
- Rumination and repetitive thoughts(نشخوارفکری)
- self-concept (خود پنداره)



- psilocybin Reduce DMN activity
- Make its connectivity less rigid and more flexible
- Less rumination
- Reduced repetitive negative thinking (often linked to anxiety and depression)
- **Reductions in anxiety**



Acute Changes in functional connectivity (FC) induced by psychedelic drugs,



2) Increased cross-network brain connectivity(Salience network)

normal conditions:

brain networks are relatively compartmentalized.

Under psilocybin:

.Previously separated networks communicate more freely

📌 Result:

.Novel associations between ideas and memories

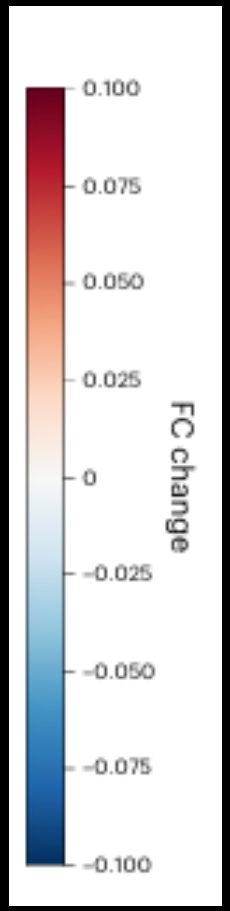
.New perspectives on personal problems

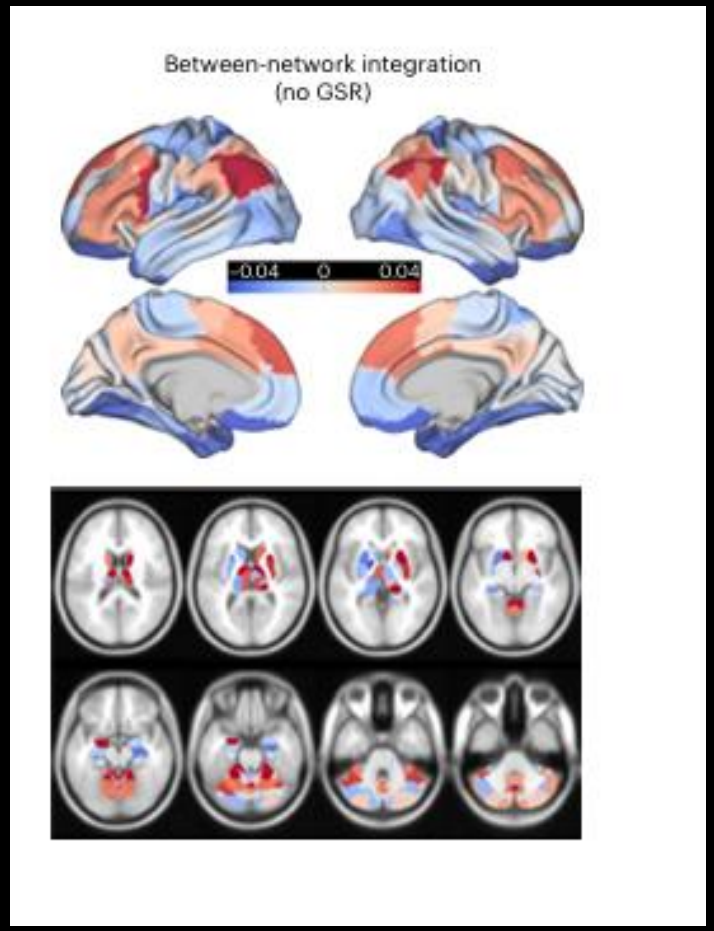
.Increased cognitive flexibility (“insight” experiences)

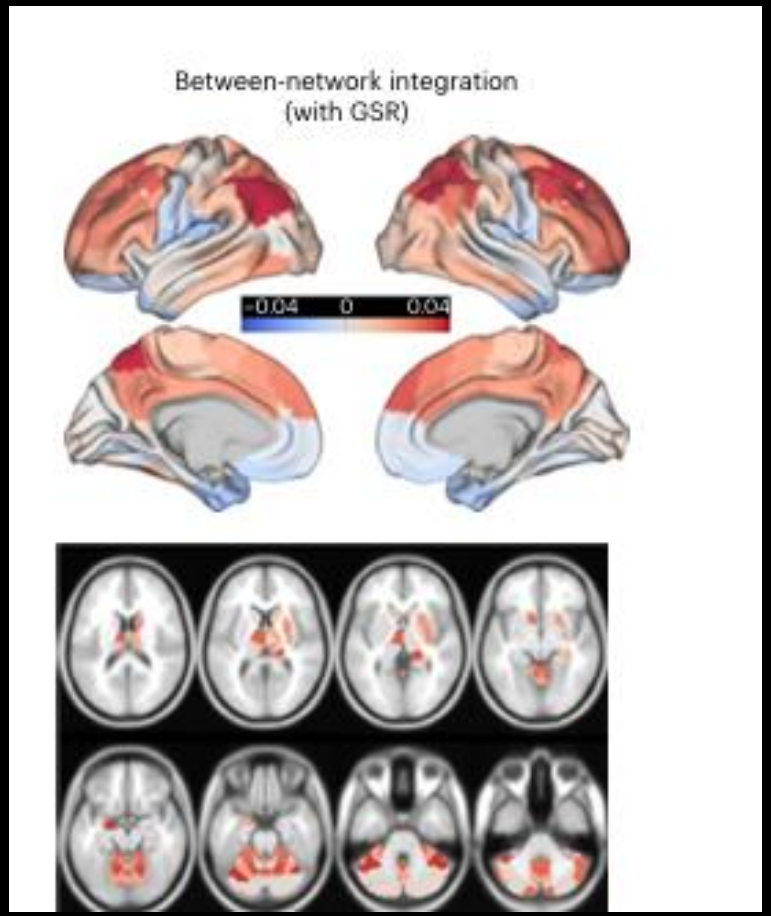
Chronic Changes in functional connectivity (FC) induced by psychedelic drugs,

placebo

psilocybin







3) Relaxation of rigid Predictive coding models (تفکر قالبی)

Predictive coding:

The brain normally maintains stable predictions about reality.

مغز یک دوربین نیست؛ بلکه یک **ماشین پیش‌بینی‌کننده** است.

مغز همیشه در حال "ساختن واقعیت" بر اساس مدل Predictive coding است

در این مدل:

.مغز یک "فرضیه" از واقعیت می‌سازد

.ورودی حسی را با آن مقایسه می‌کند

.چیزی را که «بیشترین انسجام» را دارد به عنوان واقعیت تجربه می‌کنیم

پس "واقعی بودن" یعنی: مدلی که مغز بیشترین اعتماد را به آن دارد

4) Emotional processing and psychological “resetting”

During the experience:

- Suppressed emotions
- Avoiding new experiences

psilocybin can allow:

- Reprocessing of emotional content
- Integration of difficult memories or feelings
- therapeutic effects in clinical studies.

نقش سیلوسایبین در تجربه "اوج‌های احساسی(emotional peaks) "

حافظه انسان بیشتر بر اساس شدت احساسی ساخته می‌شود، نه دقت.

وقتی تجربه شامل:

.هیجان شدید

.آرامش عمیق

.احساس وحدت و گشودگی

.یا insight ناگهانی باشد:

. مغز آن را به صورت "علامت مهم" ذخیره می‌کند، نه به صورت روایت دقیق

نتیجه:

مغز به جای اینکه بگوید: دقیقاً چه دیدم؟"

می‌گوید: این تجربه خیلی مهم بود".

.

5) Role of “meaningful experience” in lasting change

- “I understood something fundamental about myself”

Even if details fade, this can leave a strong imprint on:

- beliefs
- attitudes
- behavior patterns

جمع‌بندی ساده

اثرات مثبت گزارش‌شده معمولاً از این ترکیب می‌آیند:

- کاهش نشخوار فکری(DMN)
- افزایش ارتباط بین شبکه‌های مغزSalience network
- نرم شدن باورهای سخت‌گیرانه(predictive coding)
- پردازش دوباره هیجانات
- شکل‌گیری تجربه‌های معنادار و بازتفسیر خود

Realistic Conclusion

What we know with more confidence:

- Psilocybin does not produce classic addiction
- it has measurable effects on brain networks
- it shows therapeutic potential in controlled settings

What remains uncertain:

- how general and long-lasting the effects are
- the exact mechanism of benefit
- who it helps vs. who it may harm

THANKS FOR YOUR ATTENTION



@dr.pourshanazari YouTube