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We also treat the human spirit.®

Advances in Psychedelic Medicine

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2024

Disclosure

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- I have no actual or potential conflict of interest in relation to this presentation.

Goals

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1. Gain an appreciation and/or curiosity surrounding psychedelics and their medicinal potential
2. Identify situations in which your patients (or yourself or loved ones) may benefit from psychedelic assisted psychotherapy
3. Gain the ability to dispel myths and stereotypes surrounding psychedelic medicine

Objectives

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1. Identify the predominant mechanism of action and pharmacology of the most commonly used psychedelics (including LSD, psilocybin, MDMA, and ketamine)
2. Explain the importance of set, setting, and psychotherapy as it pertains to psychedelic therapy
3. List the therapeutic indications for various psychedelic medicines
4. Identify potential adverse effects of the various psychedelic medicines

Background

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CIIS
Center for Psychedelic Therapies and Research

MAPS
MULTIDISCIPLINARY ASSOCIATION FOR PSYCHEDELIC STUDIES

Bill Richards, PhD
Johns Hopkins

Janis Phelps, PhD
CIIS

Anthony Bossis, PhD
NYU

Michael Pollan
Author

MAPS Team

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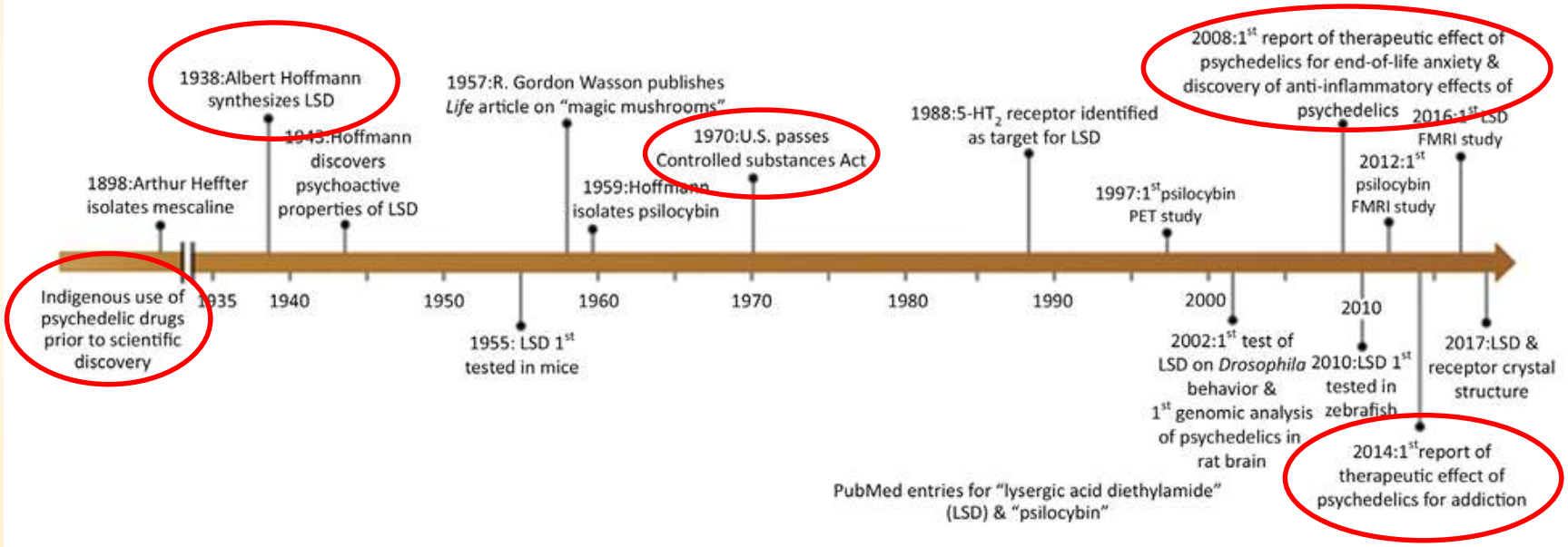
Michael Mithhoefer, MD and
Annie Mithoefer, RN

Rick Doblin, PhD

History of Psychedelic Research



Kyzar EJ, Nichols CD, Gainetdinov RR, Nichols DE, Kalueff AV. Psychedelic Drugs in Biomedicine. Trends Pharmacol Sci. 2017 Nov;38(11):992-1005. doi: 10.1016/j.tips.2017.08.003. Epub 2017 Sep 22. Review. PubMed PMID: 28947075.


Just
say no


THIS IS A
BRAIN ON
DRUGS.


SUPPORT
KEEP K
F DRUG
Just
say no


D.A.R.E.
TO RESIST DRUGS
AND VIOLENCE.
DRUG ABUSE RESISTANCE EDUCATION

Terminology

- Ego dissolution – complete loss of subjective self-identity ("ego death")
- Empathogen - psychoactive drug that produces a heightened sense of connectedness, emotional openness, and compassion
- Entactogen – psychoactive drug that enhances self-awareness
- Entheogen - psychoactive substance that produces or facilitates a spiritual experience

Terminology

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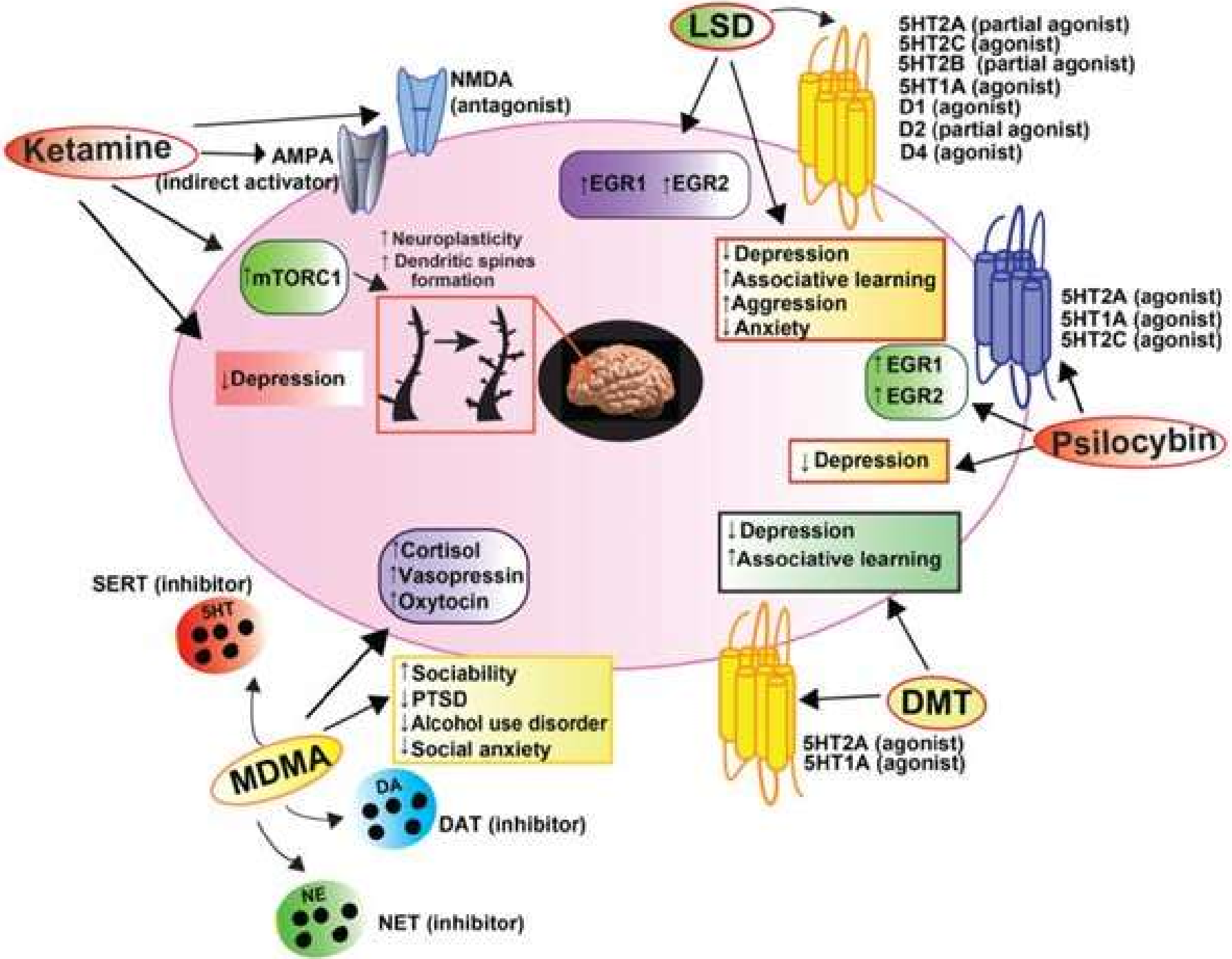
- Psychedelic – altering mood, perception, and cognition. Can distort reality and cause mystical experiences (e.g. LSD, psilocybin, MDMA, etc.)
  - Mystical experience – state of consciousness in which one finds themselves in a continuous state with God, the universe, or ground of being
- Psychotropic – altering mood, emotional state, and behavior. Targeting limbic system (e.g. anti-depressants, mood stabilizers, etc.)
- Psycholytic - dose of a drug, that loosens constraints on the mind, allowing subconscious material to enter one's awareness (used in some forms of psychotherapy)
- Set – "inner environment"
- Setting - "outer environment"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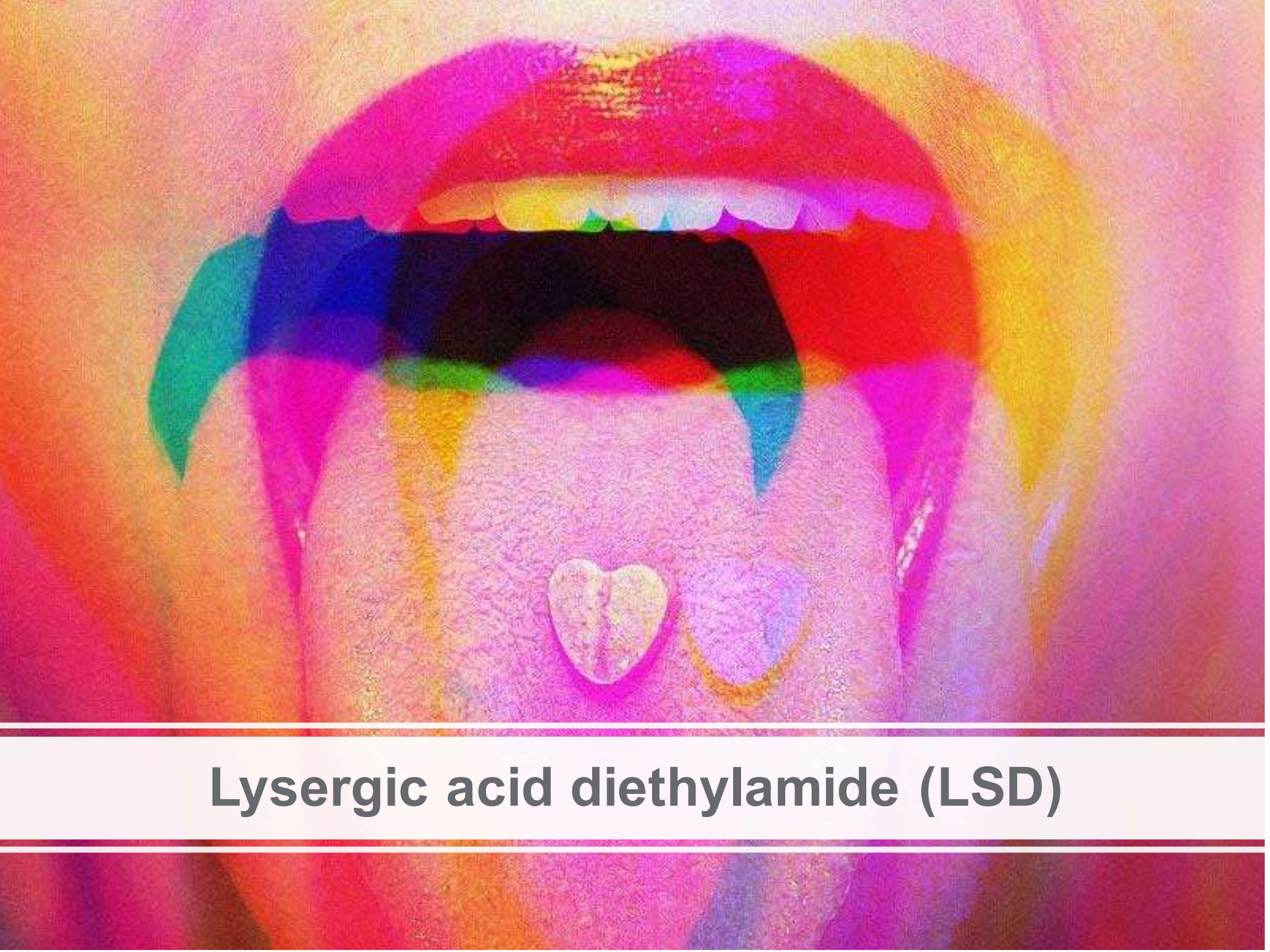

Lysergic acid diethylamide (LSD)

LSD

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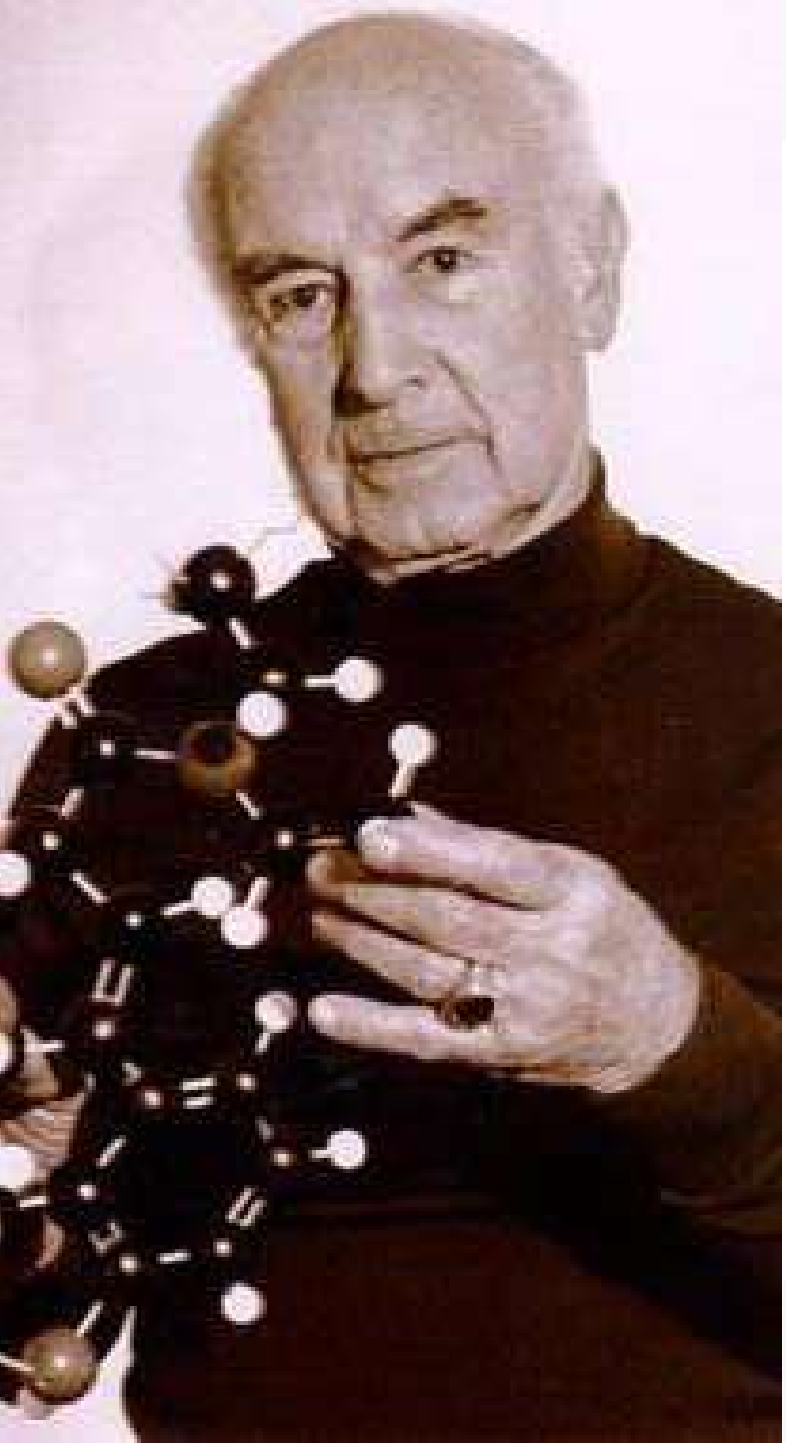
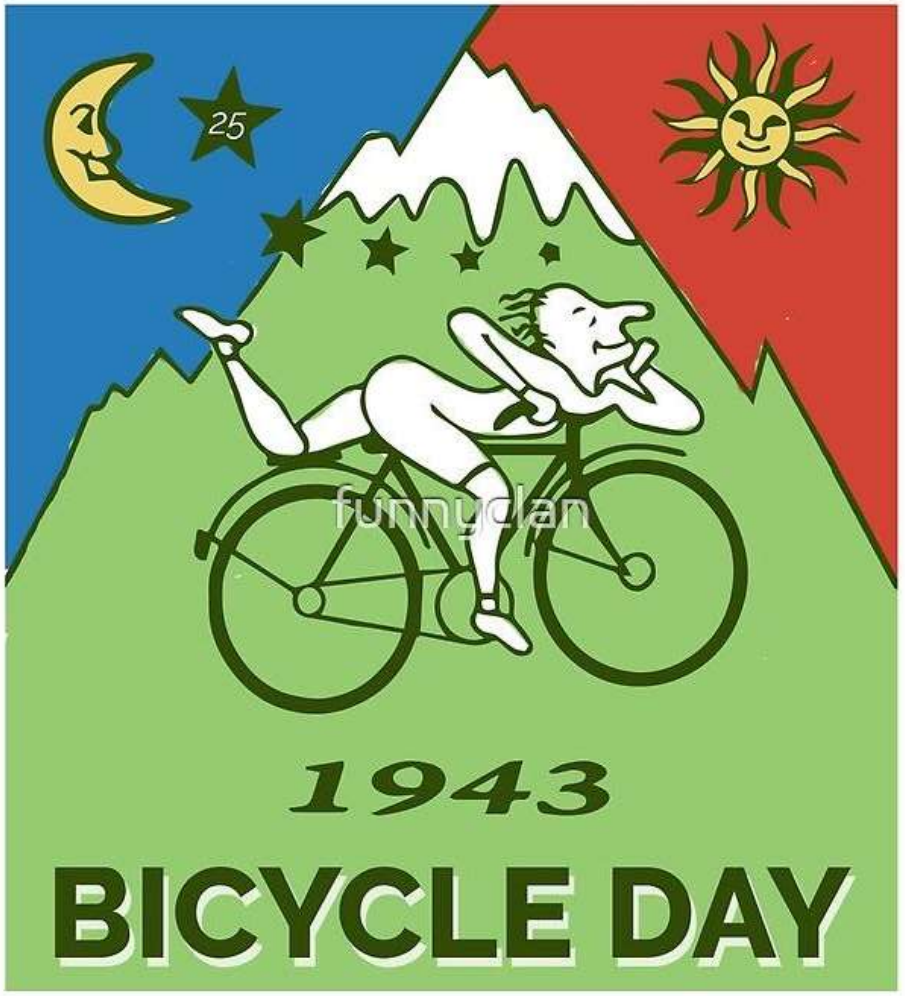
- Discovered on April 19th, 1943 (Albert Hoffmann, Swiss chemist)
  - Commercialized by Sandoz
    - Adjunct to psychotherapy
    - Self-administration by psychiatrists to gain insight
- 1950's-60's
  - >1000 reports published on treatment for mental health disorders
  - Mostly encouraging




25
funnyclan
1943
BICYCLE DAY

LSD

- Half-synthetic of lysergic acid derived from the parasitic rye fungus *Claviceps purpurea*
- Primarily p.o.
- Peak effects: 1-3 hrs
- Duration: 6-12 hrs (dose-dependent)
- Elimination: hepatic

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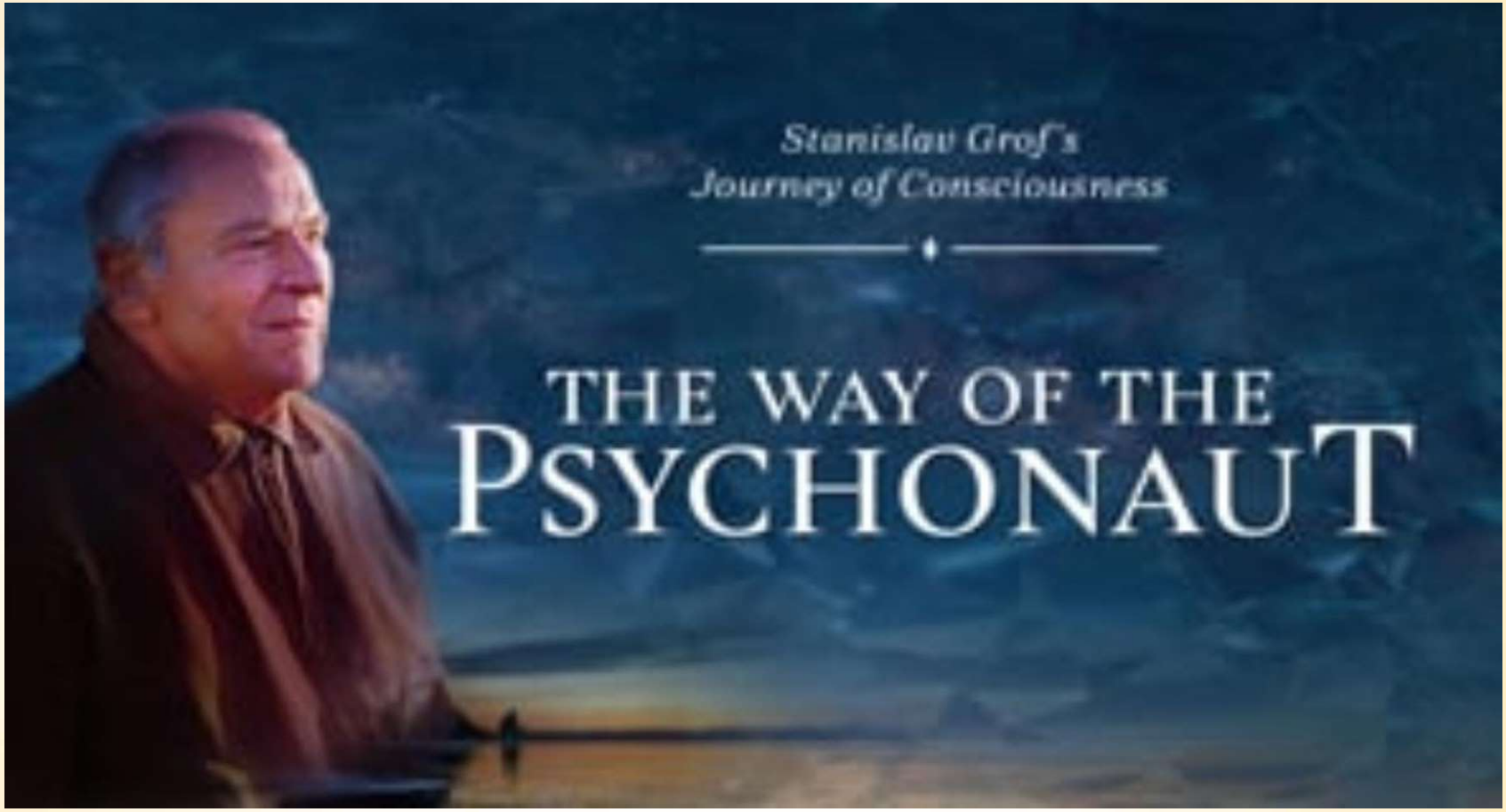
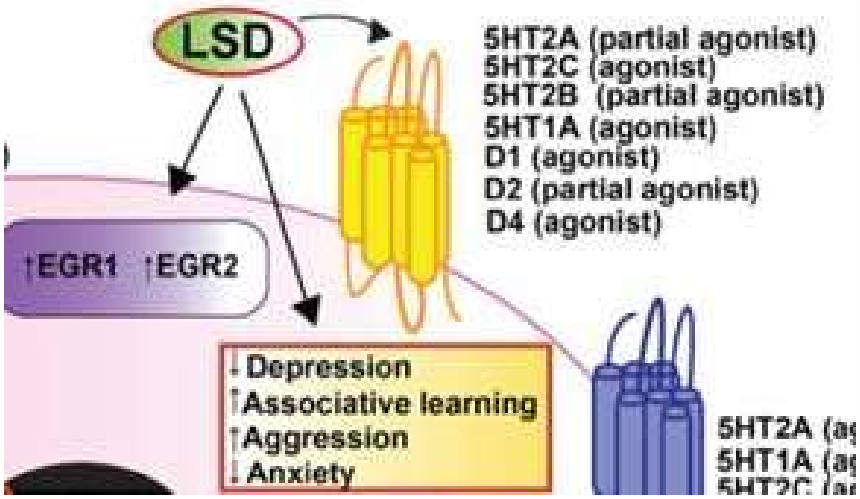


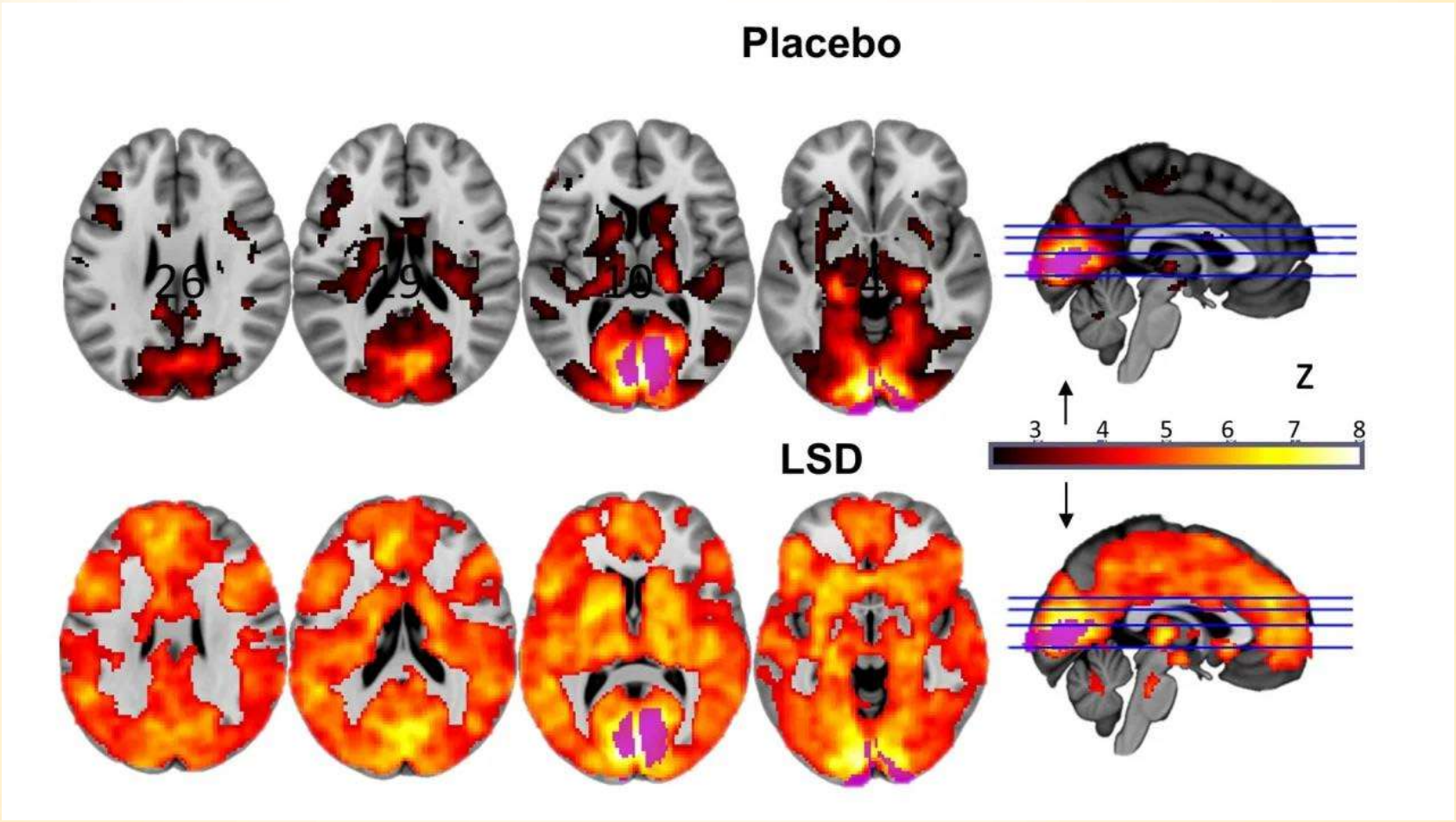
LSD Pharmacology



LSD Pharmacology

- Sympathomimetic effects – moderate increases
  - Blood pressure
  - Heart rate
  - Body temperature
  - Pupil size
- Endocrine effects- increased:
  - Cortisol
  - Prolactin
  - Oytocin
  - Epinephrine

Carhart-Harris – Imperial College of London - 2016



fMRI studies

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- "Integration and Segregation" (Müller, et. al 2019)
  - Compartmentalization between brain networks blurred
  - Integrity of individual networks is "breaking down"
- "Ego dissolution"
  - Significant correlation with decreased connectivity within the default mode network
- Whole brain connectivity
  - Widespread increases in global connectivity in the frontal, parietal, and temporal cortical regions (Tagliazucchi et. al)

"Pathological connectivity patterns associated with diverse mental diseases are acutely modified through destabilization of hub functions with subsequent changes in functional connectivity between various brain regions . . . .

New connectivity patterns are stabilized after the acute effects have subsided, possibly through anti-inflammatory effects" – Felix Müller, David Nichols

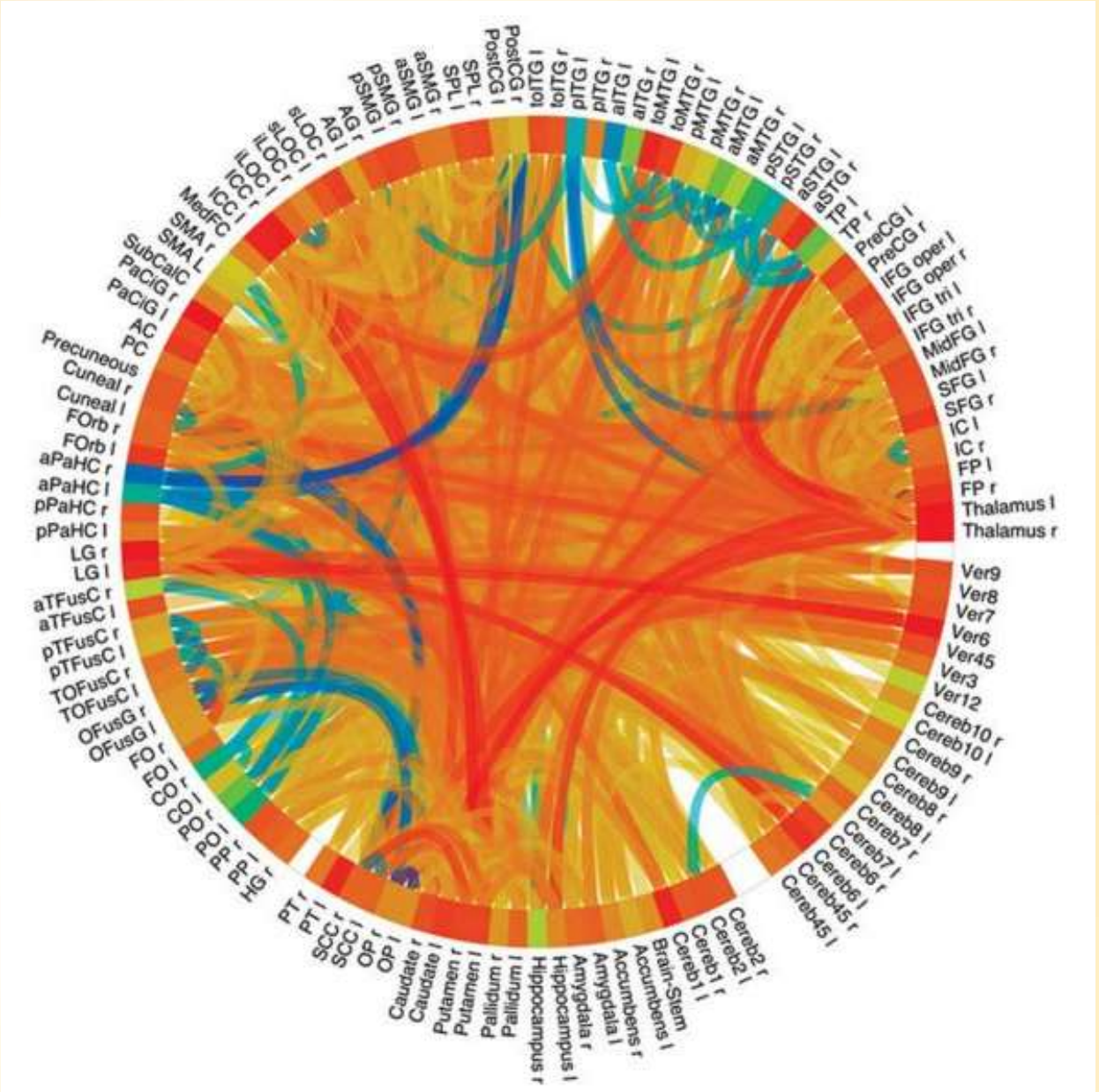
LSD

- Thalamocortical pathways
  - Integrate/transfer information between cortical regions
  - "Conductor" of the brain
- LSD – profoundly alters this functional connectivity
  - Increased awareness
  - Increased perception of the internal and external world normally suppressed
- Grof – "amplifier of brain function"

LSD

- Neurologic disease state --> deviation from optimal connectivity (Stam)
  - LSD->disintegration of local networks + increase global interconnectivity --> emergence of strong, functional connections
  - More likely in therapeutic setting
  - Restoring network connectivity to pre-disease state

- Red and Yellow = increased connectivity
- Blue and Green = decreased



Mueller, et al. 2017

LSD

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- Psychosocial distress with death/dying
  - 1960's-70's → 2/3rds improved mood, reduced anxiety and fear of death (Kast and Pahnke)
  - 2011 (Grob, et al) – 12 patients
    - Speilberg State-Trait Anxiety Inventory (STAI) – reduced at 1 and 3 months
    - Beck Depression Inventory (BDI) – significant improvement at 6 months
  - 2014 (Gasser, et al) – 12 patients
    - STAI scores remained improved after 12 months in 9 patients
      - 7/9 reported a sustained reduction in anxiety

LSD

- Addiction - alcohol
  - Osmond and Hoffer – 1950's
    - LSD and mescaline to treat alcoholism
    - Insightful "mind manifesting" effects that prompted sobriety
  - Johansen – 2012 meta-analysis
    - 6 studies, 325 participants
    - Significant decrease in alcohol misuse compared to placebo

LSD

- Addiction – heroin
  - Savabe and McCabe
    - 12 month study LSD vs. placebo
    - 12-month continuous abstinence 25% vs. 5%
- Broadly applicable?
  - Versus medication like methadone, nicotine, etc.

LSD

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- Depression/Anxiety/OCD
  - Denson et al. - significant differences seen at 6 and 12 months
  - Savage et al. - significant differences at 6 and 8 weeks

LSD – Adverse Effects

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- Anxiety and panic - "bad trips"
  - Importance of therapist
- Several recent studies – no relationship between lifetime use and negative mental health outcomes
- Physiologically safe

LSD – Adverse Effects

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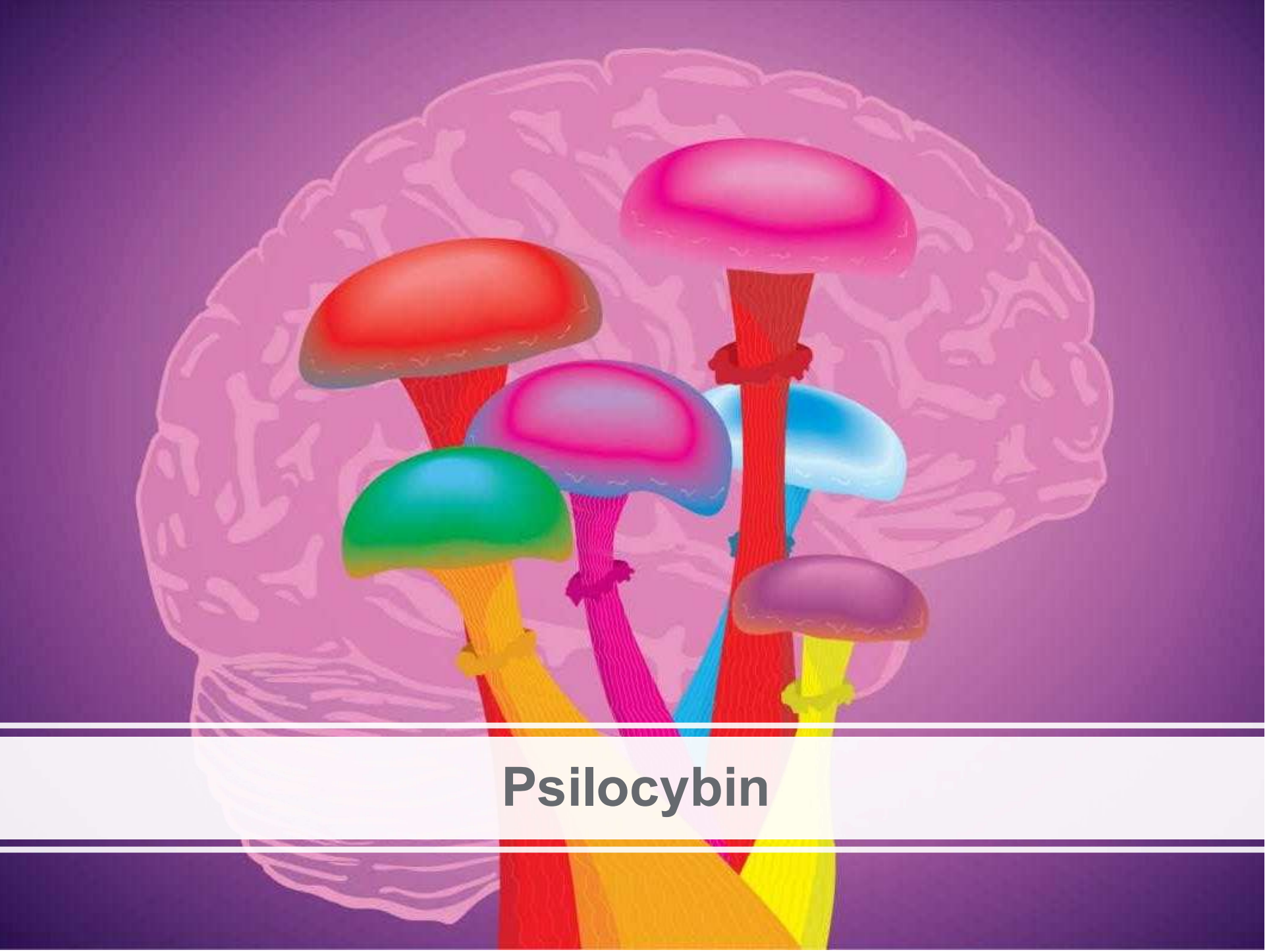
- Flashbacks
  - Hallucinogen persisting perception disorder (HPPD)
    - Rare and difficult to quantify
- Negligible addictive potential



Psilocybin

Psilocybin - History

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- More than 200 species of fungi
  - Found on all continents
- Evidence of human use dates back 9,000 years
- First account in medical literature – 1799 in London
- 1930's – Richard Schultes in northern Oaxaca
- 1950's – R. Gordon Wasson
  - Maria Sabina – Mazatec Shaman in Mexico

THIRD IN A LIFE SERIES: 'GREAT ADVENTURES'

SEEKING THE MAGIC MUSHROOM

A New York banker goes to Mexico's mountains to participate in the age-old rituals of Indians who chew strange growths that produce visions

By R. GORDON WASSON

The author of this article, a vice president of J. P. Morgan & Co. Incorporated, together with his wife, Valentina P. Wasson, M.D., a New York pediatrician, has spent the last four summers in remote mountains of Mexico. The Wassons have been on the trail of strange and hitherto unstudied mushrooms with vision-giving powers.

They have been pursuing the cultural role of wild mushrooms for 30 years. Their travels and inquiries throughout the world have led them to some surprising discoveries in this field in which they are pioneers. They are now publishing their findings in Mushrooms Russia and History, *a large, richly illustrated two-volume book, which is limited to 500 copies and is now on sale at $125 (Pantheon Books, New York).*

ON the night of June 29-30, 1955, in a Mexican Indian village so remote from the world that most of the people still speak no Spanish, my friend Allan Richardson and I shared with a family of Indian friends a celebration of "holy communion" where "divine" mushrooms were first adored and then consumed. The Indians mingled Christian and pre-Christian elements in their religious practices in a way disconcerting for Christians but natural for them. The rite was led by two women, mother and daughter, both of them *curanderas*, or shamans. The proceedings went on in the Mixteco language. The mushrooms were of a species with hallucinogenic powers; that is, they cause the eater to see visions. We chewed and swallowed these acrid mushrooms, saw visions, and emerged from the experience awestruck. We had come from afar to attend a mushroom rite but had expected nothing so staggering as the virtuosity of the performing *curanderas* and the astonishing effects of the mushrooms. Richardson and I were the first white men in recorded history to eat the divine mushrooms, which for centuries have been a secret of certain Indian peoples living far from the great world in southern Mexico. No anthropologists had ever described the scene that we witnessed.

I am a banker by occupation and Richardson is a New York society photographer and is in charge of visual education at The Brearley School.

It was, however, no accident that we found ourselves in the lower chamber of that thatch-roofed, adobe-walled Indian home. For both of us this was simply the latest trip to Mexico in quest of the mushroom rite. For me and my wife, who was to join us with our daughter a day later, it was a climax to nearly 30 years of

CONTINUED

AUTHOR WASSON sits in New York home with recorder, mushroom pictures and "mushroom stone." A onetime newspaperman, he took up banking in 1928.

PREPARING FOR CEREMONY at which author chewed hallucinogenic mushrooms and had visions, *Curandera* Eva Mendez ceremonially turns fungus in the smoke of burning aromatic leaves.

Copyrighted material

Psilocybin - History

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- Heim (who accompanied Wasson) - sent 100g of dried mushrooms to Alber Hoffman (of LSD fame)
  - Extracted two crystals – discovered active ingredient through self-experimentation
  - Psilocybin and psilocin
- Sandoz pharmaceuticals – manufactured purely synthetic psilocybin pills
  - Equally effective

Psilocybin - Pharmacokinetics

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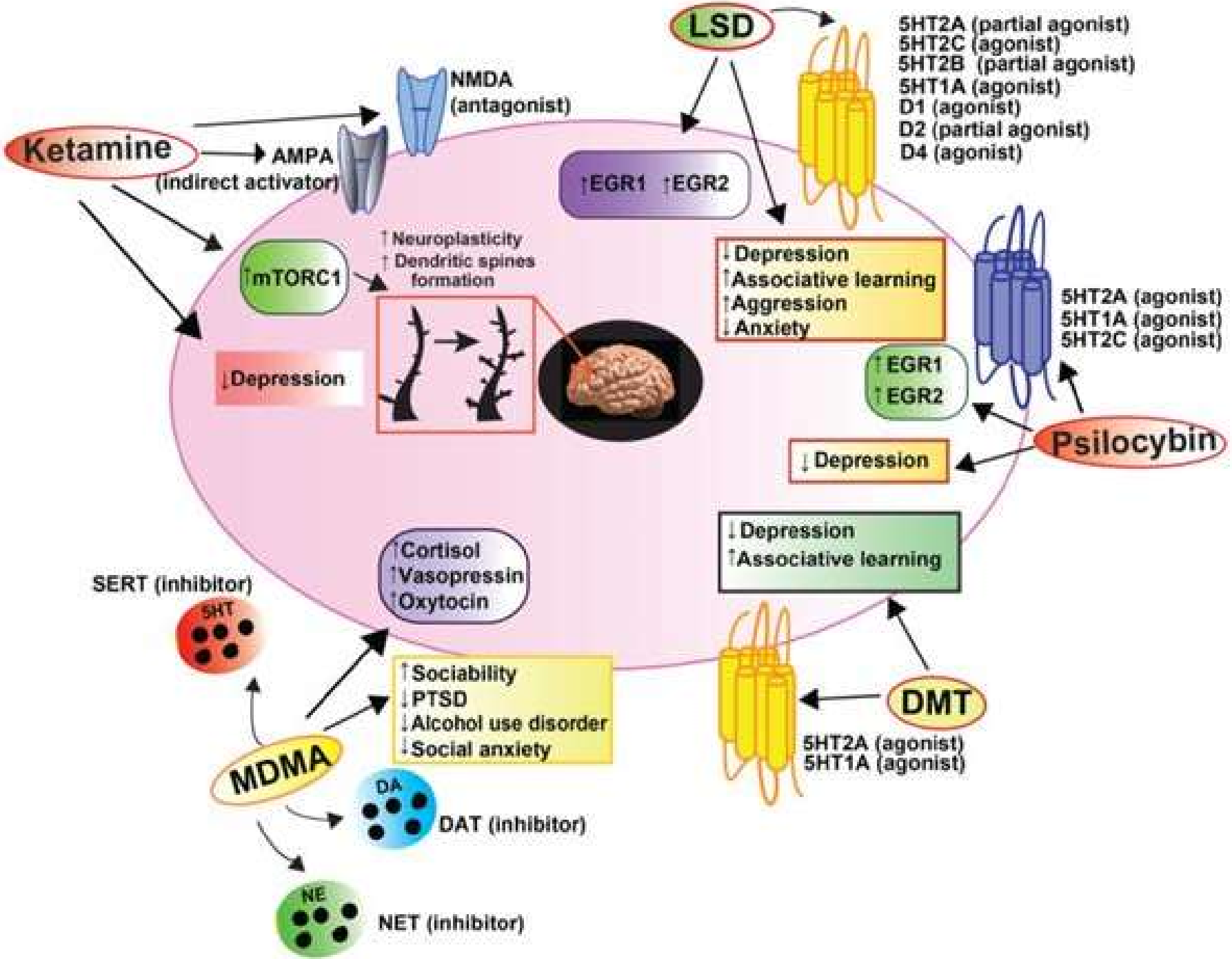
- Typically administered orally
- Tryptamine group
- Half-life 2.5 hrs
- Psychoactive/psychedelic effects within 20-40 minutes
- Peak 60-90 minutes
- 60-minute plateau
- 6-8 hr total duration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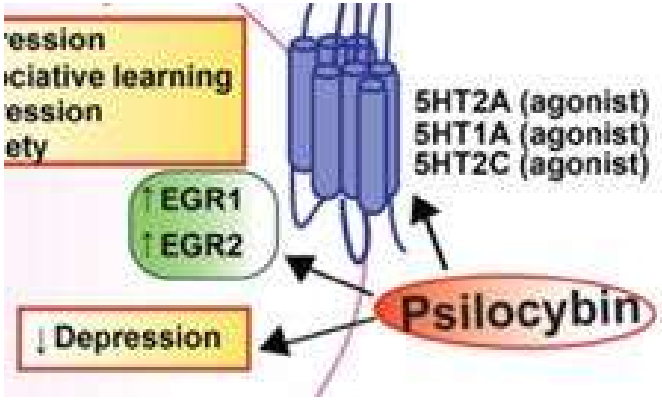
Psilocybin Pharmacology



Psilocybin - Pharmacology

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- Seretonin
  - High affinity (5-HT2A, 5-HT2C, 5-HT1A)
- Dopamine
  - Indirectly increased in striatum
    - Correlate with increased depersonalization and euphoria (Vollen-weider, et al. 1999)
  - Psilocybin – no affinity for dopamine D2 receptor itself

Psilocybin - fMRI

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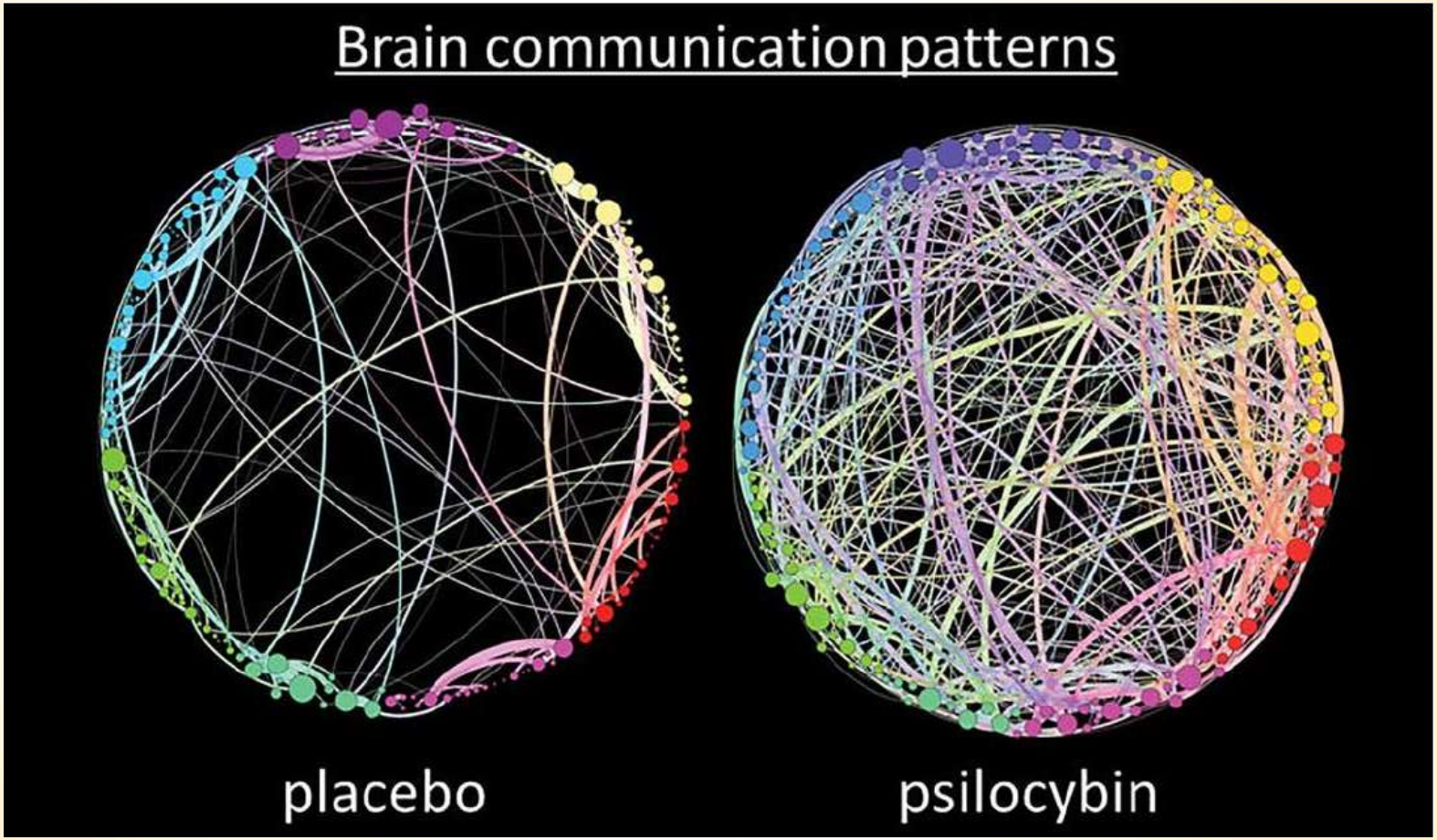
- Carhart-Harris et al.
  - Decreased connectivity within DMN
  - Increased global activity
  - Placebo – connectivity primarily between local regions
- Decreased integrity of DMN = higher ratings of ego dissolution


Brain communication patterns
placebo
psilocybin

Psilocybin - effects

- Visual and auditory illusions
- Alteration in cognition
- Mood changes (euphoria to anxiety)
- Mystical experiences
- Set and Setting!

Psilocybin – Adverse Effects

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- Low levels of medical toxicity
- Minimal addictive potential
  - Least harmful and addictive among 20 psychoactive substances (Gable 2004)
  - Similar to the other sertonergic psychedelics
- Occasional transient increases in BP
- Psychological distress
- HPPD (flashbacks)
  - Reported cases, though extremely rare

Psilocybin – Cancer

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- Cancer-related psychiatric and existential distress (anxiety, depression, etc.)
  - RCT's at UCLA, NYU, Hopkins (2011-2016)
  - Controls – niacin at NYU and UCLA, low dose psilocybin at Hopkins
  - N=92
  - Psychotherapy for all – including preparatory phase
  - Comfortable settings
  - Validated measures like BDI, STAI, etc.

Psilocybin - Cancer

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- Statistically significant improvement in depressive and anxiety sx's
  - Rapid -1 day prior to 1 day postdosing
  - Substantial – large effect size
  - Sustained – up to 7 weeks post single dose
- 83% of psiolcybin subjects --> greater than 50% decrease in BDI
  - 14% in niacin group
- 58% --> greater than 50% decrease in anxiety score
  - 14% in niacin group

Psilocybin - Cancer

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- 60-80% anxiolytic and anti-depressant response rates at 6.5 month follow-up
- Statistically significant improvement in:
  - Demoralization
  - Hopelessness
  - Quality of life
  - Spritual well-being
  - Existential distress
  - Attitudes toward death and dying

Bill Richards, PhD
Johns Hopkins University

Psilocybin - Addiction

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- Tobacco
  - Johnson et al. 2007
    - Open label
    - Moderate-high dose psilocybin with over 2-3 sessions
    - 15-week process also included preparatory phase, mindfulness training, guided imagery
    - 6-month f/u - 80% abstinence (12/15)
    - 12-month f/u - 67% abstinence (10/15)
    - 2.5-year f/u - 75% abstienence (9/12)
  - Far exceeds rate seen in clinical trials of any other available medication

Psilocybin - Addiction

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- Alcohol
  - Bogenschutz et al. (University of New Mexico)
    - Open label study
    - 14 sessions
      - 7 motivational enhancement therapy
      - 2 psilocybin
      - 3 preparatory
      - 2 debriefing
    - Pre-post significant improvements in abstinence after 1st dose of psilocybin ($p<.05$)
    - Intensity of psilocybin session correlated with decrease cravings, increased abstinence self-efficacy and decreased drinking between weeks 5-8

Psilocybin - Addiction

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- Cocaine and opioid addiction
  - Active RCT's ongoing at University of Alabama and UW Madison (respectively)
- No adverse outcomes noted in any aforementioned studies

Psilocybin - Depression

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- Carhart-Harris – 2016, Imperial College of London
  - Open-label pilot study for treatment-resistant depression (TRD)
  - 2 doses of psilocybin
  - fMRI, quick inventory for depressive sx's (QIDS) performed (baseline, 1 week, and 3 months)
  - Significant improvement for all pre-post measures
    - Maintained at 6 months (Carhart-Harris 2018)
- RCT for MDD being conducted at JHU

Psilocybin - OCD

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- Francisco Moreno 2001-2004
  - Safety, efficacy, tolerability study
  - 9 participants
  - 3 doses of psilocybin (100, 200, and 300 mcg/kg)
  - OCD scale measured at 0, 4, 8, and 24 hrs
  - Decreases ranging from 23-100%
- Ongoing RCT's (Yale and U of AZ)

Psilocybin

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- Back, et al. - University of Washington - ongoing
  - "A study of psilocybin-assisted psychotherapy for clinicians with symptoms of depression and burnout related to frontline work in the COVID pandemic"

MDMA

MDMA - History

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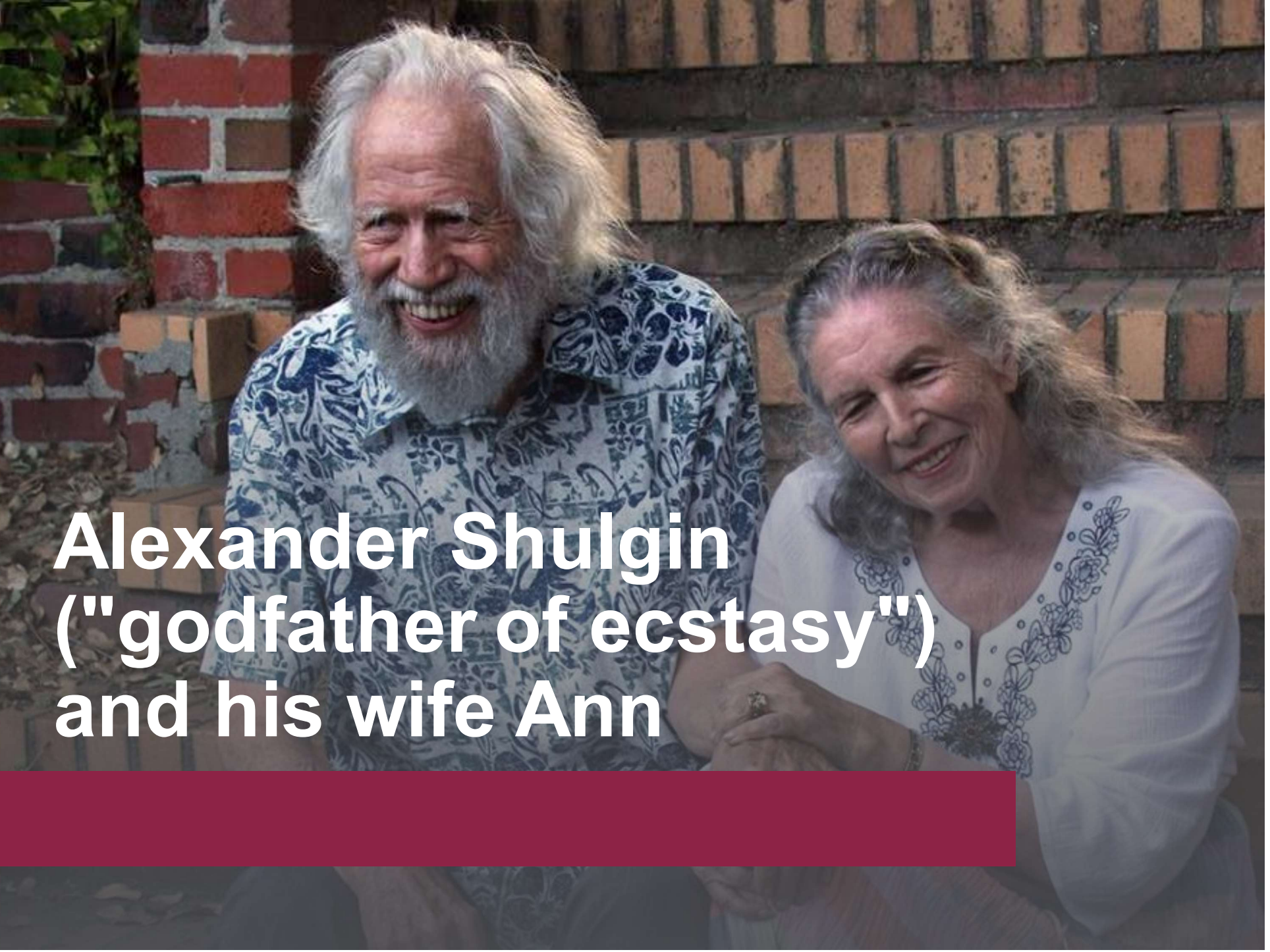
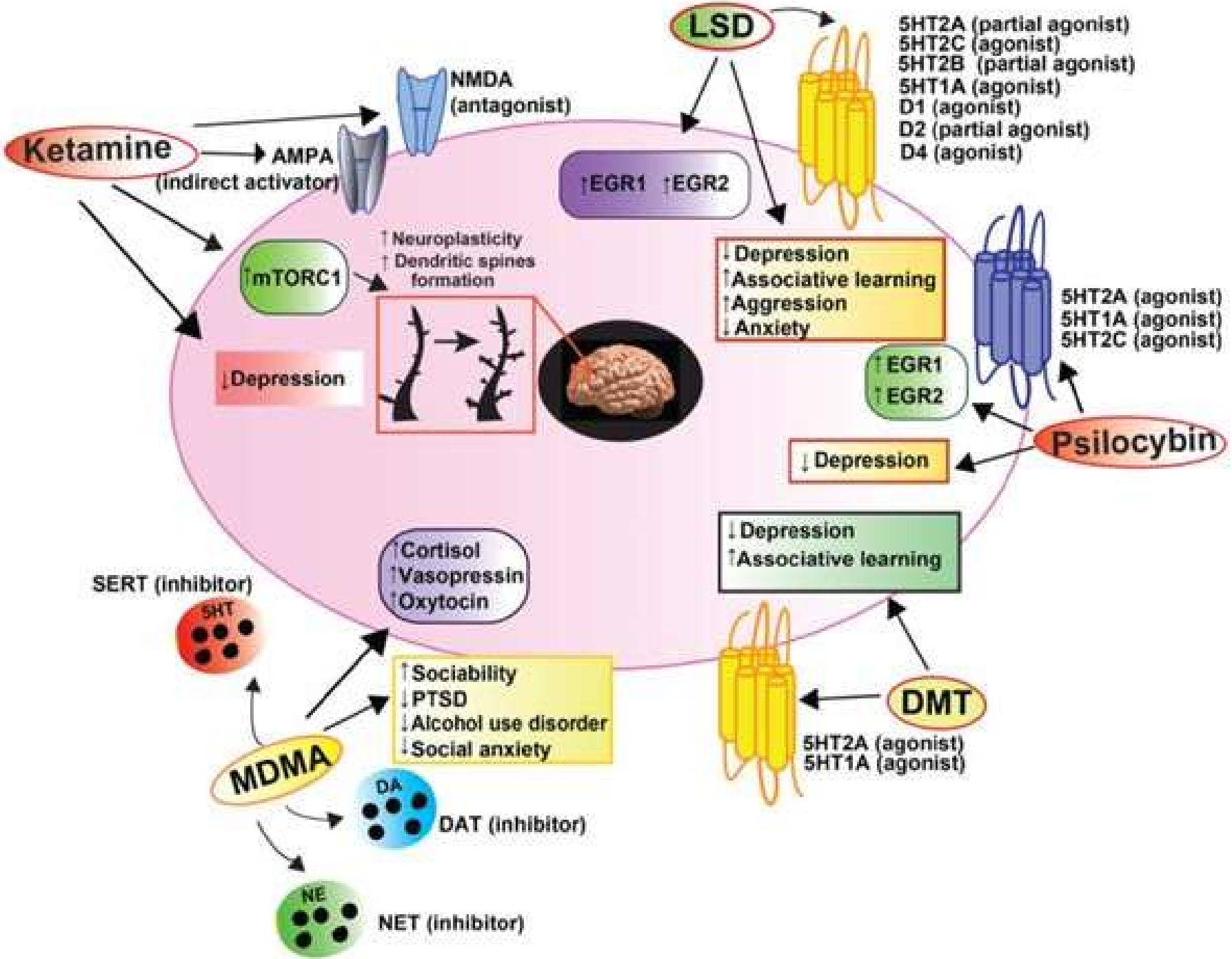
- Synthesized in 1912 by Merk as a possible hemostatic drug
  - Animal studies done – use of drug not pursued
- First human studies – 1970's
  - Alexander Shulgin – instrumental in bringing it therapeutic track 1977
  - Used to catalyze therapy
- Recreational use – made schedule I by DEA 1984



Alexander Shulgin ("godfather of ecstasy") and his wife Ann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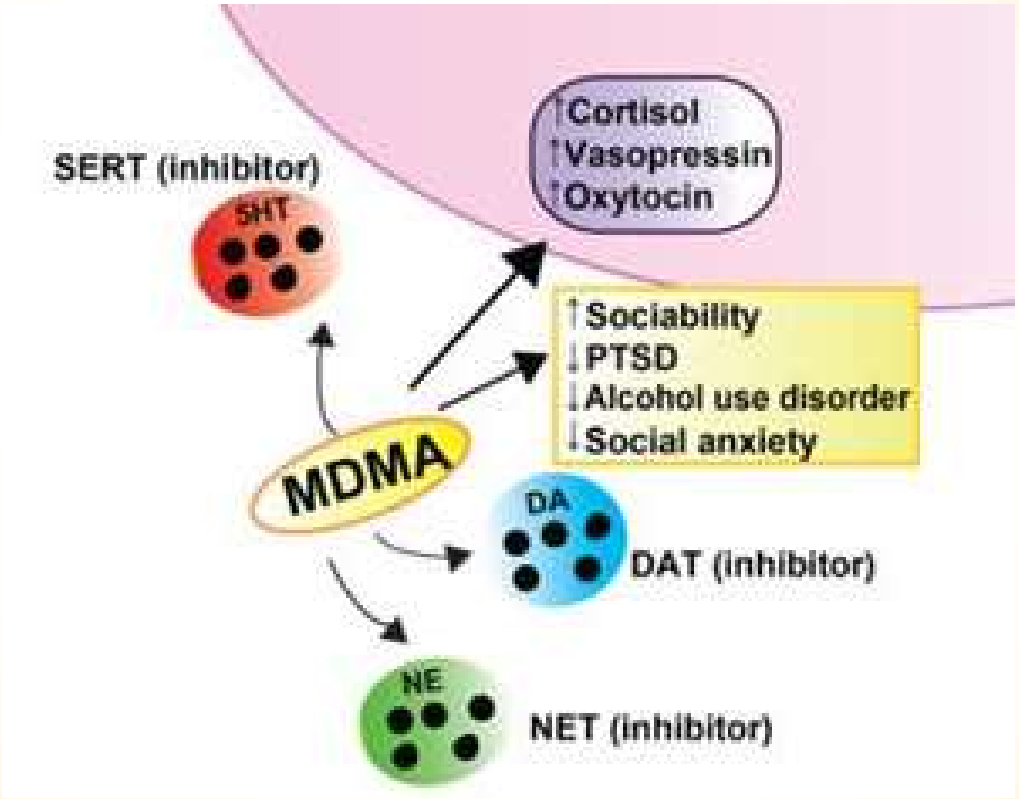
MDMA

- Amphetamine derivative
- MOA – releases supraphysiological levels of serotonin, dopamine, and norepinephrine via reuptake transporters
- Also stimulates release of oxytocin, vasopressin, cortisol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MDMA - Pharmacokinetics

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- Administered orally
- Subjective effects noticed 30-60 minutes later
- Peak effect – 90-120 minutes
- Duration 3-6 hrs
- Elimination half-life 8-9 hrs
- Toxicity studies in animals – no liver damage after 28 days
- Study of 166 MDMA-naïve volunteers failed to detect any changes in liver function

MDMA - Subjective Effects

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- Rarely causes hallucination
- Less likely to be disorienting compared to psiolocybin or LSD
- "Empathogen"/"Etactogen"
  - Increased empathy and increased self-awareness
- Reduces defensiveness and fear
- Allows one to revisit traumatic experiences without being overwhelmed or anxious

MDMA - fMRI

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- Carhart-Harris 2015
  - Decreased CBF in amygdala and hippocampus
  - Increased CBF in prefrontal cortex
    - Correlates with ability to approach traumatic memories without overwhelm or anxiety
  - Changes in resting-state functional connectivity (RSFC)
    - Sledding analogy and negative thought patterns

MDMA – Physiologic Effects

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- Sympathomimetic
  - Elevated HR and BP (NE release)
  - Caution in those with CAD or CVD
- Thermoregulatory
  - Mean temp elevation of 0.6 degrees C
  - Distinct from serotonin syndrome, MH, etc.
- Other possible side effects:
  - Dizziness, fatigue, headache, jaw clenching, loss of appetite, nausea

MDMA - PTSD

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- Sessa – 2011
  - MDMA useful in assisting emotional processing
- Mithoefer et al. 2011
  - First RCT pilot study
  - Signficant and long-lasting reductions in PTSD sx's
    - Lasting 1-year after tx

MDMA - PTSD

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- Phase II trials
  - MAPS-sponsored
  - 7 sites, 4 countries
  - Pooled analyses from 6 phase-2 clinical trials (Mithoefer, 2019) --> Breathrough Therapy status --> Phase 3 trials

MDMA - PTSD

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- Study design
  - 3, 90-minute preparatory sessions
  - 2-person (1 male, 1 female) therapy teams
  - Randomized to active dose MDMA or inactive placebo vs. low dose MDMA (depending on site)
  - MDMA or comparator given in two 8-hour therapy sessions (1 month apart)
  - Each session followed by overnight stay in clinic with 90-minute integration session the next day
  - 2 or 3 integration sessions over next few weeks before next experimental session

Psychopharmacology (2019) 236:2735–2745

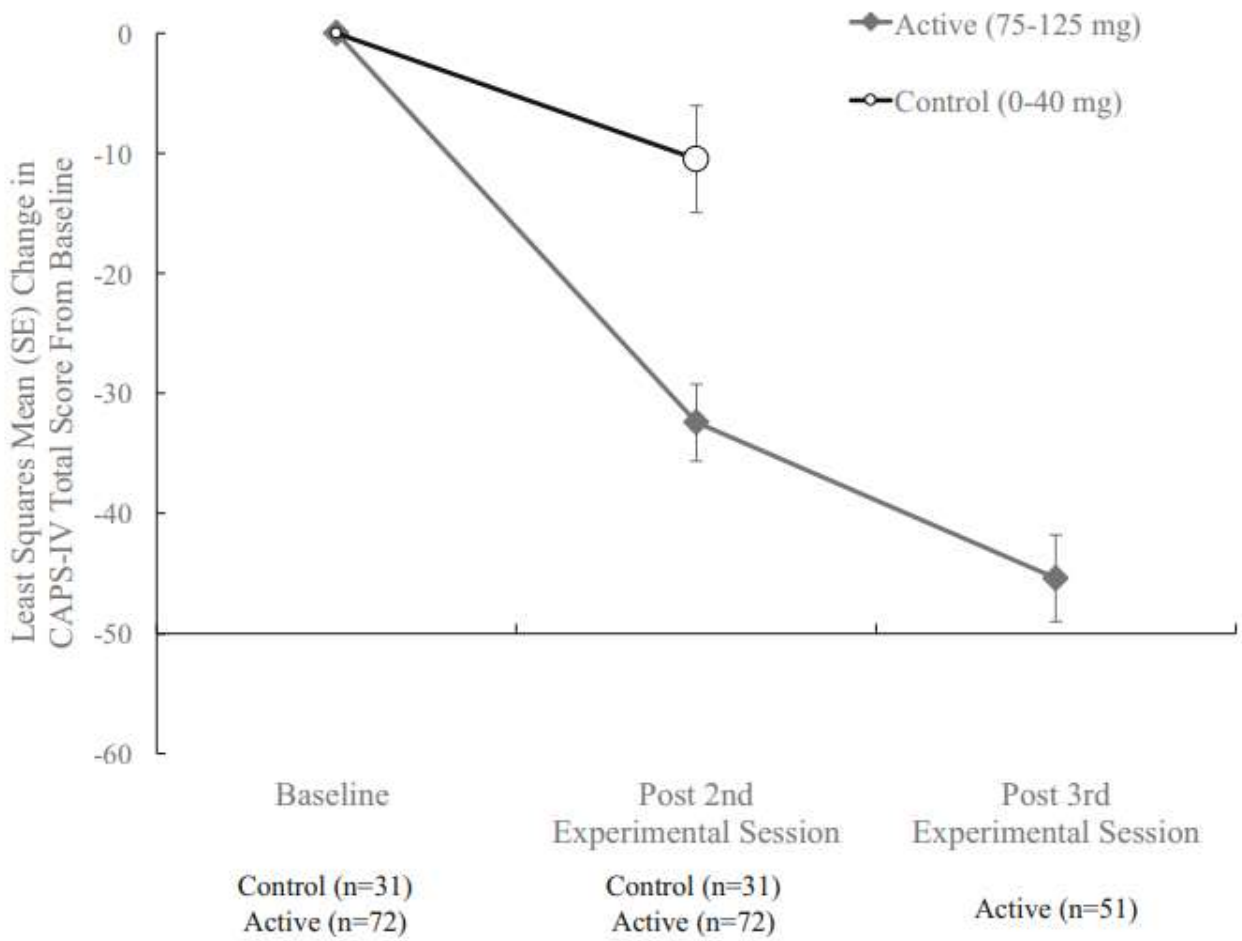
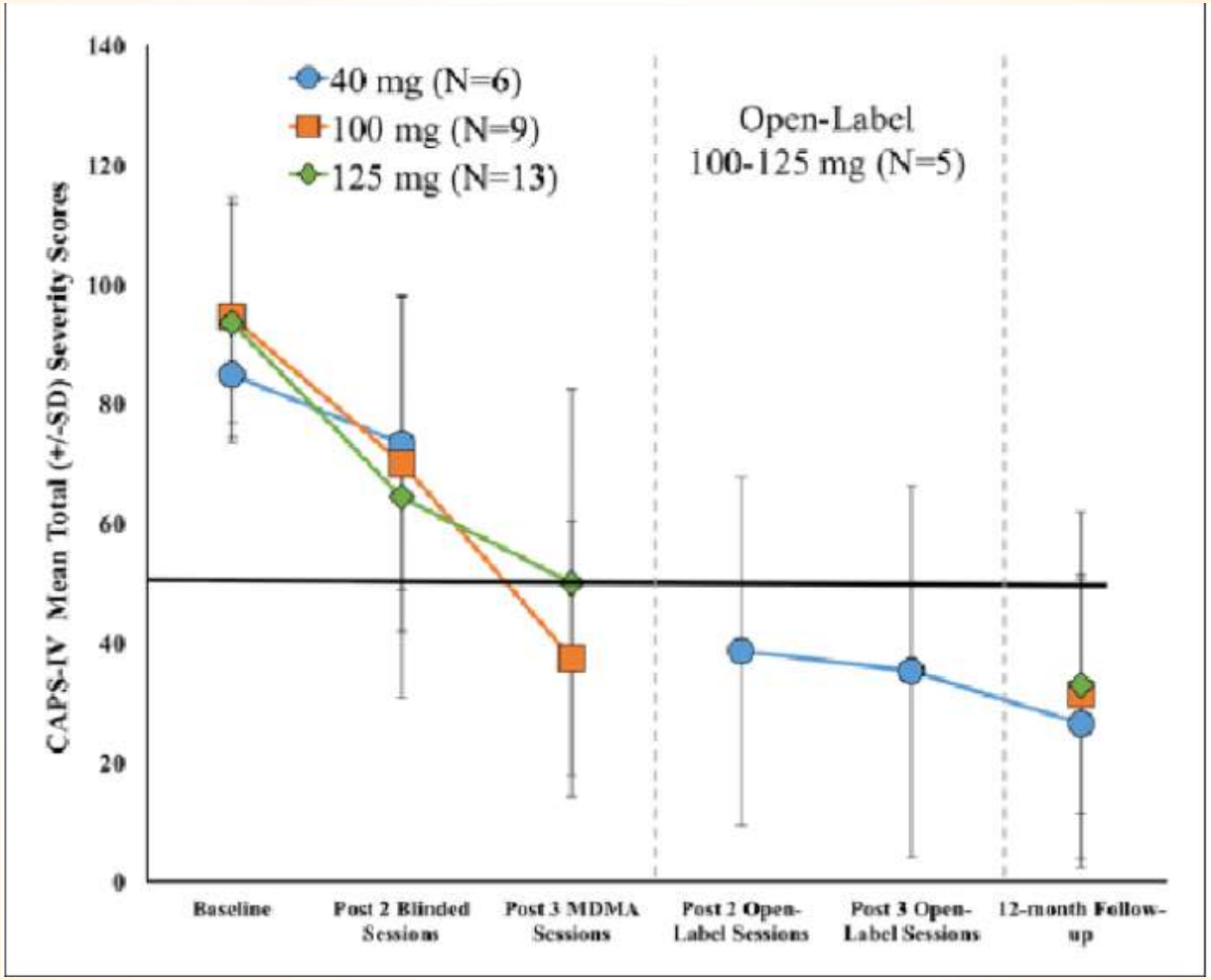


Figure 1 CAPS-IV total score least squared mean estimates at endpoints. The change in scores from baseline to post two experimental sessions were significantly different between MDMA and control groups (***$P < 0.0001$). After the third MDMA session, the active dose group showed further improvement compared to post two MDMA sessions (***$P < 0.0001$)


140
120
100
80
60
40
20
0
CAPS-IV Mean Total (+/-SD) Severity Scores
40 mg (N=6)
100 mg (N=9)
125 mg (N=13)
Open-Label
100-125 mg (N=5)
Baseline
Post 2 Blinded Sessions
Post 3 MDMA Sessions
Post 2 Open-Label Sessions
Post 3 Open-Label Sessions
12-month Follow-up

MDMA – Other Studies

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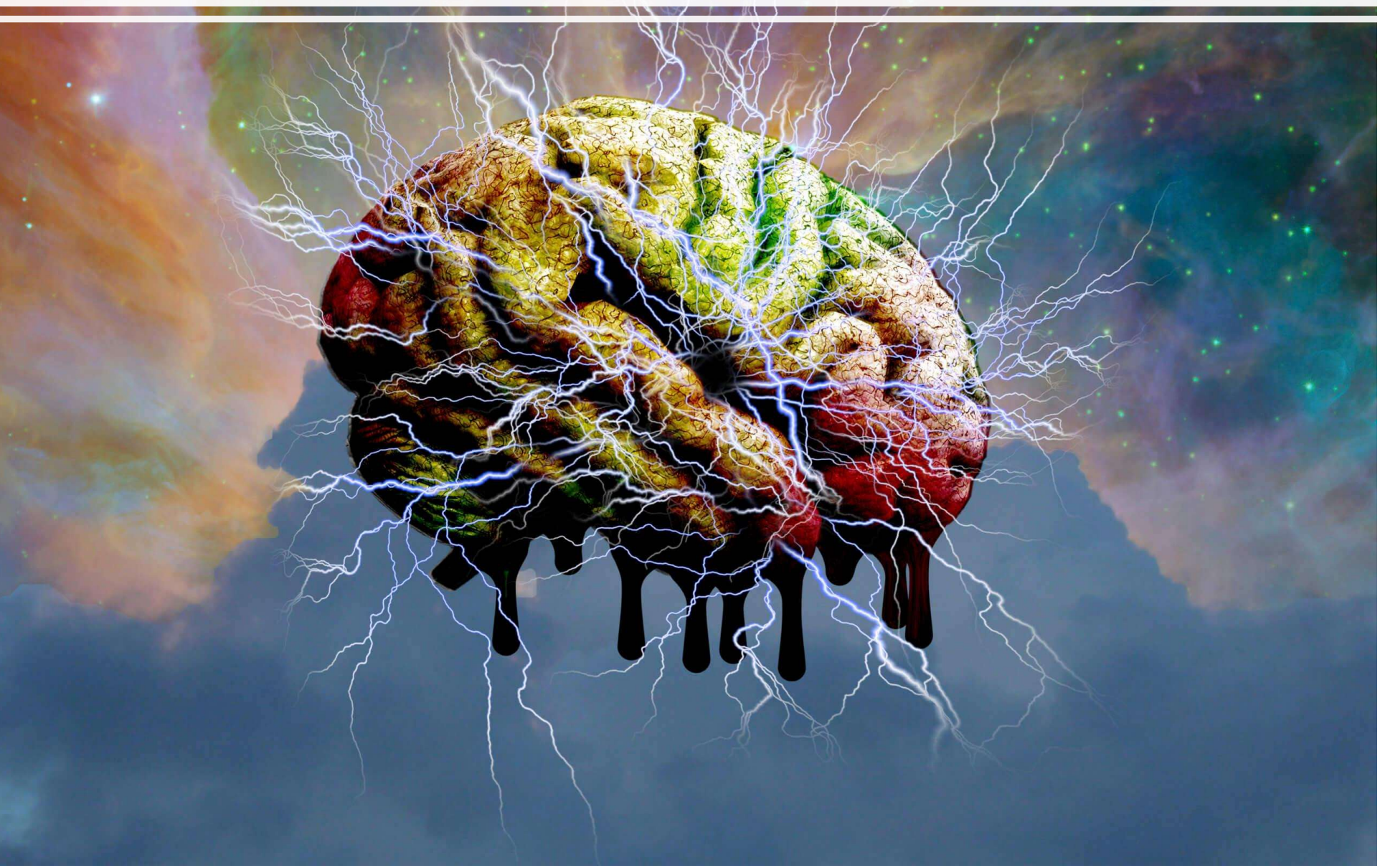
- MAPS has funded studies for the following indications
  - Social anxiety and adults with autism
  - Anxiety associated with life-threatening illness
  - Cognitive-behavioral conjoint therapy
    - Couples or family therapy
    - Most commonly involving PTSD

Ketamine



Ketamine - History

- Arylcyclohexylamine
  - Same class as PCP
  - Safer, more predictable than PCP
- Developed by Parke-Davis as an anesthetic
  - 1962
- First used in the Vietnam War
  - Could affect consciousness without depression of cardiopulmonary systems
- Introduced to the psychiatric community in 1970's by Salvador Roquet (Mexican psychiatrist)

Ketamine - History

- FDA approved as an anesthetic currently
- Subanesthetic doses
  - Analgesia and sedation
- Johnson and Johnson – Esketamine
  - S enantiomer
  - Nasal spray (Spravato)
  - Approved by FDA in 2019 for TRD

Ketamine - Pharmacology

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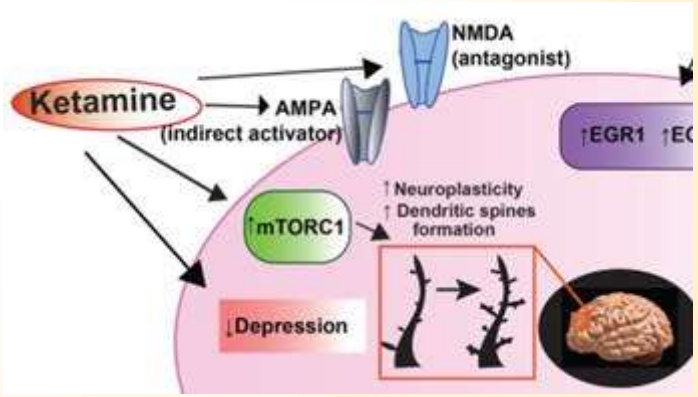
- Most common routes – IV and IM
  - Nasal, sublingual, and suppository also utilized
- NMDA glutamate receptor antagonist
  - Effect on synaptogenesis and neuroplasticity – basis of antidepressant effect? (Galvez, 2017)
  - Also active at opioid, dopamine, muscarinic, and nicotinic ACH receptors



Ketamine

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- Anti-inflammatory mechanism?
  - Transient decrease in IL-6 and IL-1 alpha
  - Decrease in TNF-alpha

Ketamine - Pharmakokinetics

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- Nitrogen demethylation – norketamine
  - Cytochrome P450 liver enzymes
- Norketamine – further demethylation
- Rapid distribution due to lipid solubility
- 2-4 hr half-life

Ketamine – effects/side effects

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- Consciousness – dose dependent
  - Mild sedation -> dreamy, out of body -> vivid imagery and hallucination, ego dissolution -> lose awareness of outside environment (anesthetic dose)
    - Anxiety and fear response attenuated/absent
- Sympathomimetic
  - Elevated HR and BP
- Addiction potential
- Urinary sx's/interstitial cystitis
- Nausea/vomiting

Ketamine - TRD

LOYOLA UNIVERSITY HEALTH SYSTEM

- Treatment-resistant depression (TRD)
  - 9 RCT's from 2000-2015
  - Robust evidence for ketamine's antidepressant response (Ryan et al. 2016)
  - Remission of depression – 60-70%
    - Short-lived (only 10% in remission after 10 days)
    - Noted utility in acute suicidality (Murrough 2015, Zhang 2019)
      - 55% free of suicidal ideation after 1 infusion (60% of those after 1 week)

Ketamine - KAP

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- Ketamine-assisted psychotherapy (KAP) (Bennett)
  - Psycholytic (ego loosening)
    - Ketamine as a "lubricant"
    - Emphasis on verbal expression during session
    - 3 to 6 weeks apart with talk therapy in between
  - Psychedelic (ego dissolving)
    - Intentionally induce a profound altered state of consciousness
    - Involves preparation, integration, and maintenance sessions

Ketamine – Healthcare Providers

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- Dames et al. 2022 (post-pandemic)
- KAP in a community of practice for HCP with PTSD and depression
  - 12 weeks (2 hrs per week)
  - Three 4-hr ketamine sessions (weeks 4, 5, and 7)

Aggregate Mean Scores

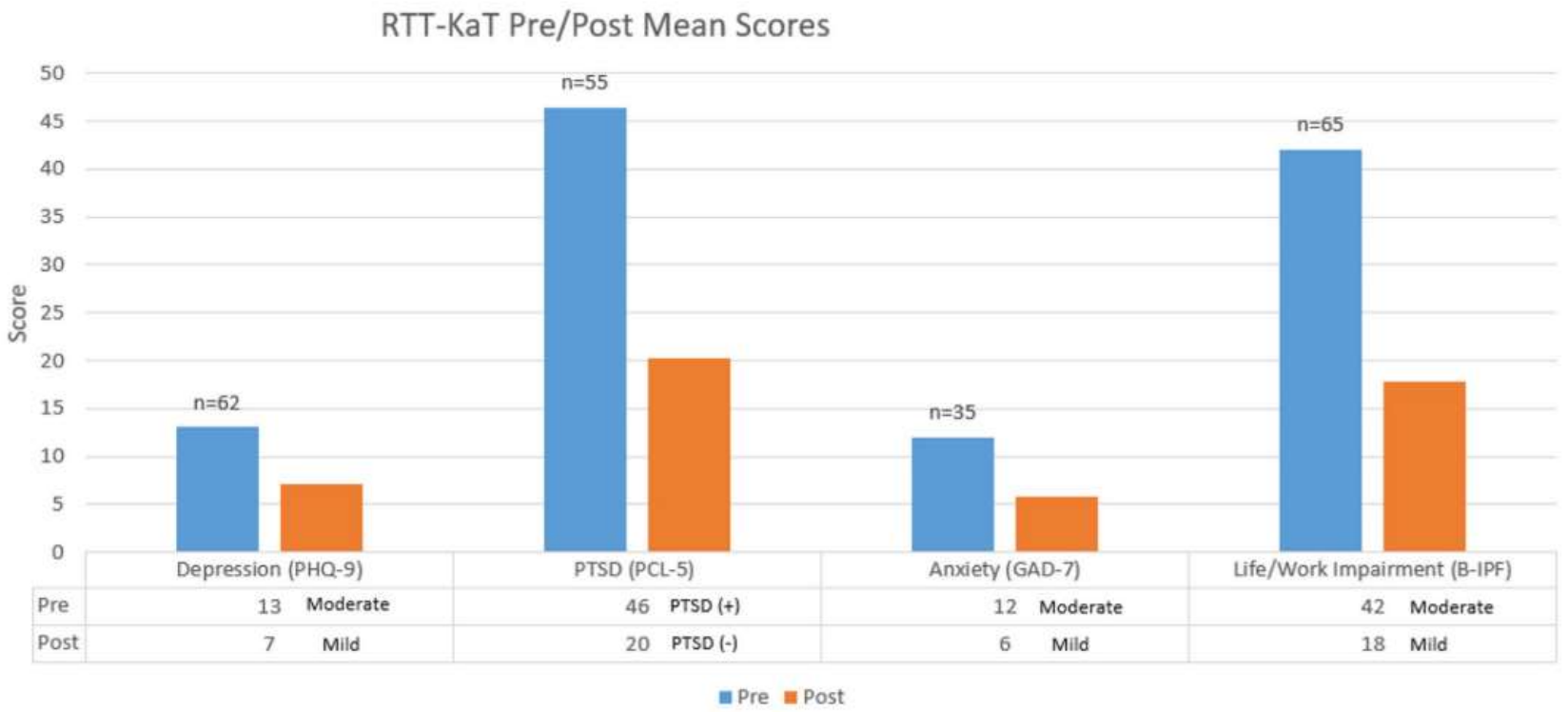

FIGURE 2 | Cohort 1, 2, and 3 aggregate: mean scores. The "*n*" represents the number of participants who screened positive for PTSD, depression, or generalized anxiety disorder upon entry into the RTT-KaT program. The pre-results were taken within 1 month of the program beginning and post results were taken directly after the 12-week program was completed. If data was missing, it was not included.

Ketamine – Other

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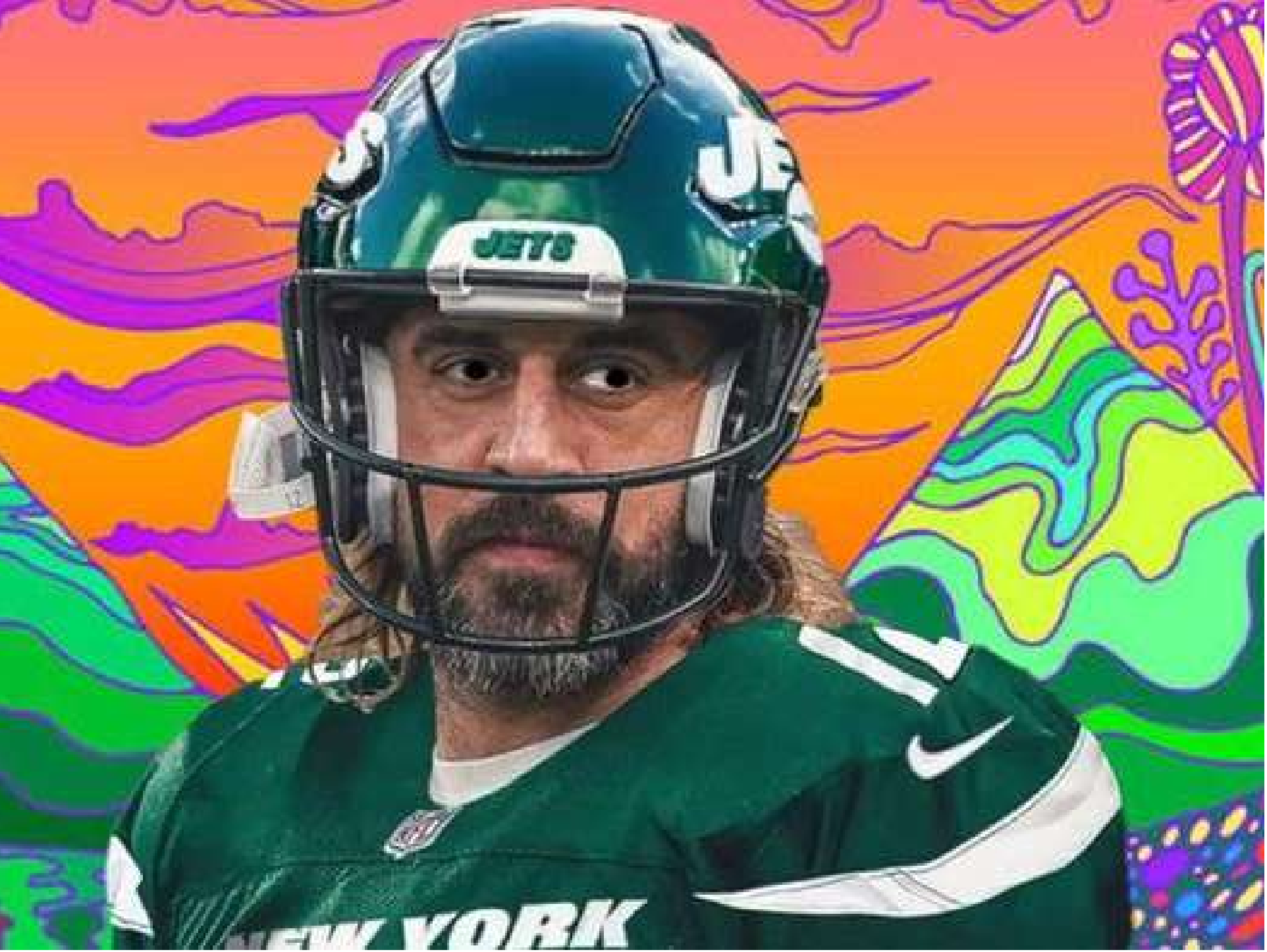
- OCD
- PTSD
- Biploar I and II
- Addiction
- Eating disorders


JETS
NEW YORK

Ayahuasca

Ayahuasca

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- "Vine of spirits" in Quechua
  - A brew of *Banisteriopsis caapi* and
  - Detected in Andean mummies between 500-1000 C.E.
  - Records of use among dozens of Amerindian ethnic groups
- Contain N,N-DMT and B-carboline alkaloids
  - High affinity for 5-HT receptors
  - Also act on glutamate, ACH, and dopamine

Ayahuasca

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- Onset 20-40 minutes
- Peak 1-2 hrs
  - Subside for 4 hrs after peak
- Visual phenomena are common
  - Often of ancestors or spirits
- Increased introspection, transient dissociation, depersonalization, distortions of space and time

Ayahuasca

LOYOLA UNIVERSITY HEALTH SYSTEM

- Therapeutic applications being studied
  - Parkinson's
  - Addiction
  - Depression
  - PTSD
  - Autoimmune dz
  - Cancer
  - Alzheimer's
  - Eating disorders
  - OCD

Peyote

Peyote/Mescaline

- Ceremonial use among Native Americans and other indigenous groups for thousands of years
- Mescaline
  - Primary ingredient
  - Also found in the San Pedro cactus
  - Phenethylamine
  - 5-HT2A receptor activity
  - Oral dose 300-500 mg
  - Lasts 6-8 hrs

Peyote/Mescaline

LOYOLA UNIVERSITY HEALTH SYSTEM

- Studies – very little new research since 1950's
  - Alcoholism
    - Natrualistic observational studies – Native American Church
  - Cognitive effects and quality of life study in Native Americans
- Peyote "crisis"
  - Threat of decriminalization
  - Sustainability and scarcity of peyote

Summary

References

- Back, A. L. (2019). What Psilocybin Taught Me About Dying. In *Journal of Palliative Medicine* (Vol. 22, Issue 7, pp. 861–862). Mary Ann Liebert Inc. https://doi.org/10.1089/jpm.2018.0561
- Bershad, A. K., Preller, K. H., Lee, R., Keedy, S., Wren-Jarvis, J., Bremmer, M. P., & de Wit, H. (2020). Preliminary Report on the Effects of a Low Dose of LSD on Resting-State Amygdala Functional Connectivity. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, *5*(4), 461–467. https://doi.org/10.1016/j.bpsc.2019.12.007
- Bogenschutz, M. P., & Forcehimes, A. A. (2017). Development of a Psychotherapeutic Model for Psilocybin-Assisted Treatment of Alcoholism. *Journal of Humanistic Psychology*, *57*(4), 389–414. https://doi.org/10.1177/0022167816673493
- Bossis, A. P. (n.d.). *Psychedelic Research: Implications for Palliative Care & End-of-Life Existential Distress*.
- Carhart-Harris, R. L., Wall, M. B., Erritzoe, D., Kaelen, M., Ferguson, B., De Meer, I., Tanner, M., Bloomfield, M., Williams, T. M., Bolstridge, M., Stewart, L., Morgan, C. J., Newbould, R. D., Feilding, A., Curran, H. V, & Nutt, D. J. (2013). *The effect of acutely administered MDMA on subjective and BOLD-fMRI responses to favourite and worst autobiographical memories*. https://doi.org/10.1017/S1461145713001405
- Davis, A. K., Averill, L. A., Sepeda, N. D., Barsuglia, J. P., & Amoroso, T. (2020). Psychedelic Treatment for Trauma-Related Psychological and Cognitive Impairment Among US Special Operations Forces Veterans. *Chronic Stress*, *4*. https://doi.org/10.1177/2470547020939564
- de Gregorio, D., Aguilar-Valles, A., Preller, K. H., Heifets, B. D., Hibicke, M., Mitchell, J., & Gobbi, G. (2021). Hallucinogens in mental health: Preclinical and clinical studies on LSD, psilocybin, MDMA, and ketamine. *Journal of Neuroscience*, *41*(5), 891–900. https://doi.org/10.1523/JNEUROSCI.1659-20.2020
- Dick, S. (n.d.). *Destigmatizing Psychedelic Therapy*.
- Felix, M., & Stefan, B. (2019). Acute effects of lysergic acid diethylamide (LSD) on resting brain function. *Swiss Medical Weekly*, *149*(39–40). https://doi.org/10.4414/smw.2019.20124
- Fuentes, J. J., Fonseca, F., Elices, M., Farré, M., Torrens, M., Borgwardt, S., Prospéro-García, O., & Wallach, J. (1950). *Therapeutic Use of LSD in Psychiatry: A Systematic Review of Randomized-Controlled Clinical Trials*. https://doi.org/10.3389/fpsyt.2019.00943

References

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- Grob, C. S., Bossis, A. P., & Griffiths, R. R. (2022). Use of the Classic Hallucinogen Psilocybin for Treatment of Existential Distress Associated with Cancer. In *Psychological Aspects of Cancer: a Guide to Emotional and Psychological Consequences of Cancer, their Causes, and their Management, Second Edition* (pp. 69–89). Springer International Publishing. https://doi.org/10.1007/978-3-030-85702-8_5
- Holze, F., Caluori, T. V., Vizeli, P., & Liechti, M. E. (2022). Safety pharmacology of acute LSD administration in healthy subjects. *Psychopharmacology*, *239*(6), 1893–1905. https://doi.org/10.1007/s00213-021-05978-6
- Johnson, M. W., & Griffiths, R. R. (2017). Potential Therapeutic Effects of Psilocybin. In *Neurotherapeutics* (Vol. 14, Issue 3, pp. 734–740). Springer New York LLC. https://doi.org/10.1007/s13311-017-0542-y
- Liechti, M. E. (2017). Modern Clinical Research on LSD. *Neuropsychopharmacology*, *42*, 2114–2127. https://doi.org/10.1038/npp.2017.86
- *MDMA (Ecstasy) Abuse Research Report*. (2017).
- Nichols, D. E., Johnson, M. W., & Nichols, C. D. (2017). Psychedelics as Medicines: An Emerging New Paradigm. *Clinical Pharmacology and Therapeutics*, *101*(2), 209–219. https://doi.org/10.1002/cpt.557
- Pahnke, W. N., & Richards, W. A. (1966). Implications of LSD and Experimental Mysticism. In *Source: Journal of Religion and Health* (Vol. 5, Issue 3). https://about.jstor.org/terms
- Passie, T., Halpern, J. H., Stichtenoth, D. O., Emrich, H. M., & Hintzen, A. (2008). The pharmacology of lysergic acid diethylamide: A review. In *CNS Neuroscience and Therapeutics* (Vol. 14, Issue 4, pp. 295–314). https://doi.org/10.1111/j.1755-5949.2008.00059.x
- Presti, D. E., & Boston, O. (2022). *Special Topics in the Neurobiology of Psychedelics CIIS CPTR*.

References

- Richards, W. A. (2017). Psychedelic Psychotherapy: Insights From 25 Years of Research. *Journal of Humanistic Psychology*, *57*(4), 323–337. https://doi.org/10.1177/0022167816670996
- Ross, S. (2018). *International Review of Psychiatry Therapeutic use of classic psychedelics to treat cancer-related psychiatric distress Therapeutic use of classic psychedelics to treat cancer-related psychiatric distress*. https://doi.org/10.1080/09540261.2018.1482261
- Ross, S., Bossis, A., Guss, J., Agin-Liebes, G., Malone, T., Cohen, B., Mennenga, S. E., Belser, A., Kalliontzi, K., Babb, J., Su, Z., Corby, P., & Schmidt, B. L. (2016). Rapid and sustained symptom reduction following psilocybin treatment for anxiety and depression in patients with life-threatening cancer: A randomized controlled trial. *Journal of Psychopharmacology*, *30*(12), 1165–1180. https://doi.org/10.1177/0269881116675512
- Sessa, B. (2017). Why Psychiatry Needs 3,4-Methylenedioxymethamphetamine: A Child Psychiatrist's Perspective. In *Neurotherapeutics* (Vol. 14, Issue 3, pp. 741–749). Springer New York LLC. https://doi.org/10.1007/s13311-017-0531-1
- Sessa, B. (2018). Why MDMA therapy for alcohol use disorder? And why now? In *Neuropharmacology* (Vol. 142, pp. 83–88). Elsevier Ltd. https://doi.org/10.1016/j.neuropharm.2017.11.004
- Sessa, B. (2020). How Well Are Patients Doing Post-Alcohol Detox In Bristol? Results From The Outcomes Study. *Journal of Alcoholism, Drug Abuse and Substance Dependence*, *6*(1), 1–7. https://doi.org/10.24966/ADSD-9594/100021
- Sessa, B., Sakal, C., O'Brien, S., & Nutt, D. (2019). First study of safety and tolerability of 3,4-methylenedioxymethamphetamine (MDMA)-assisted psychotherapy in patients with alcohol use disorder: Preliminary data on the first four participants. *BMJ Case Reports*, *12*(7). https://doi.org/10.1136/bcr-2019-230109
- Trope, A., Anderson, B. T., Hooker, A. R., Glick, G., Stauffer, C., & Woolley, J. D. (2019). Psychedelic-Assisted Group Therapy: A Systematic Review. In *Journal of Psychoactive Drugs* (Vol. 51, Issue 2, pp. 174–188). Routledge. https://doi.org/10.1080/02791072.2019.1593559
- Tylš, F., Páleníček, T., & Horáček, Ř. (n.d.). *Psilocybin-Summary of knowledge and new perspectives*. https://doi.org/10.1016/j.euroneuro.2013.12.006