PSYCHEDELICS IN ADDICTION TREATMENT: PROMISE, PITFALLS, AND PRACTICAL REALITIES

Presenter: Jennifer Trihoulis MD, MPH, DFASAM

CLEAR BOUNDARY STATEMENT

- This is not an endorsement of illegal activities
- This talk is respectful of AA, MAT, and established care models
- This is not a promotion of a specific ideology
- This is not a talk about one treatment philosophy over another
- This does not replace clinical judgment or individualized care decisions

WHAT IS A PSYCHEDELIC?

The term originates from the Greek words psyche ("mind" or "soul") and deloun ("to manifest"), literally meaning "mind-manifesting".

Psychedelic drugs can significantly alter perception, cognition, mood, affect, social relatedness, and sense of self or meaning.

CORE CHARACTERISTICS OF PSYCHEDELICS

Mechanism: "Classic" psychedelics primarily work by activating serotonin **5-HT2A** receptors in the brain, particularly in the prefrontal cortex.

Effects: They can induce vivid visual and auditory hallucinations, a distorted sense of time, and ego dissolution (the loss of one's sense of self).

Subjectivity: Experiences are heavily influenced by "set" (the user's mindset) and "setting" (the physical and social environment).

CLASSIC PSYCHEDELICS

- Psilocybin: From “magic mushrooms”—most studied for addiction
- LSD (Acid): Lysergic acid diethylamide—used in1950s-1960s addiction research
- DMT: An indole alkaloid found in various species of plants
- Mescaline: Found in the Peyote and San Pedro cacti

ATYPICAL PSYCHEDELICS AND RELATED DRUGS:

- MDMA (Ecstasy): Often called an entactogen because it primarily increases feelings of social connection rather than causing hallucinations.
- Ketamine: Technically a dissociative but used in similar clinical contexts for its mind-altering properties.
- Ibogaine: From the Iboga plant-studied for opioid use disorder
- MDMA and ketamine are often categorized with psychedelics because they induce profound, non-ordinary, or "expanded" states of consciousness that share subjective, therapeutic, or experiential qualities with classic psychedelics like LSD, despite different pharmacological mechanisms.

ENTACTOGEN OR EMPATHOGEN?

- Entactogen = "touching within"
- Empathogen = "empathy producing"
- MDMA assisted psychotherapy sessions are theorized to help diminish barriers to self-compassion

LANDMARK STUDIES: GENERAL CONSIDERATIONS

- Mechanisms are still under investigation: Psilocybin, MDMA, and ketamine likely exert effects by enhancing neuroplasticity, altering neural network activity, and facilitating psychological insights, which may help disrupt addictive patterns.
- Context matters: All meaningful clinical effects observed to date have been within structured psychotherapy settings, not casual use.
- Evidence gaps: Most MDMA addiction research is preliminary, and ketamine RCTs remain limited. Psilocybin has the strongest controlled trial evidence to date, particularly for AUD.

LANDMARK STUDIES: PSILOCYBIN

- Does psilocybin improve the percentage of heavy drinking days in patients with AUD undergoing psychotherapy?
- Bogenschutz & Ross (JAMA Psychiatry October 2022)

LANDMARK STUDIES: PSILOCYBIN

- In this double-blind randomized clinical trial, participants were offered 12 weeks of manualized psychotherapy and were randomly assigned to receive psilocybin vs diphenhydramine during 2 day-long medication sessions at weeks 4 and 8.
- Outcomes were assessed over the 32-week double-blind period following the first dose of study medication.
- The study was conducted at 2 academic centers in the US. Participants were recruited from the community between March 12, 2014, and March 19, 2020.

LANDMARK STUDIES: PSILOCYBIN

- Inclusion criteria: Adults aged 25 to 65 years with a DSM-IV diagnosis of alcohol dependence and at least 4 heavy drinking days during the 30 days prior to screening were included.
- Exclusion criteria: Exclusion criteria included major psychiatric and drug use disorders, hallucinogen use, medical conditions that contraindicated the study medications, use of exclusionary medications, and current treatment for AUD.

LANDMARK STUDIES: PSILOCYBIN

- Interventions: Study medications were psilocybin, 25 mg/70 kg, vs diphenhydramine, 50 mg (first session), and psilocybin, 25-40 mg/70 kg, vs diphenhydramine, 50-100 mg (second session). Psychotherapy included motivational enhancement therapy and cognitive behavioral therapy.
- Main outcomes and measures: The primary outcome was percentage of heavy drinking days, assessed using a timeline followback interview, contrasted between groups over the 32-week period following the first administration of study medication using multivariate repeated-measures analysis of variance.

LANDMARK STUDIES: PSILOCYBIN

- Key finding: Psilocybin group had a significantly lower percentage of heavy drinking days over 32 weeks than placebo.
- Heavy drinking days were ~9.7% vs ~23.6%, favoring psilocybin
- P=.01
- Demonstrated that psychedelic-assisted therapy can produce substantial sustained behavioral change in a SUD context.

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Clinical Trial

The effects of MDMA–assisted therapy on alcohol and substance use in a phase 3 trial for treatment of severe PTSD

Christopher R Nicholas et al. Drug Alcohol Depend. 2022.

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Abstract

Background: Post-traumatic stress disorder (PTSD) is commonly associated with alcohol and substance use disorders (ASUD). A randomized, placebo-controlled, phase 3 trial demonstrated the safety and efficacy of MDMA-assisted therapy (MDMA-AT) for the treatment of severe PTSD. This analysis explores patterns of alcohol and substance use in patients receiving MDMA-AT compared to placebo plus therapy

LANDMARK STUDIES: MDMA

Does MDMA-assisted therapy decrease AUDIT and DUDIT scores in a study population with severe PTSD?

Post-traumatic stress disorder (PTSD) is commonly associated withalcohol and substance use disorders (ASUD).

Christopher Nichols (Drug and Alcohol Dependence April 2022)

LANDMARK STUDIES: MDMA

- A total of 90 adults with severe PTSD were randomized to receive three sessions of trauma-focused psychotherapy with either MDMA-AT or placebo plus therapy.
- Participants could have current mild or moderate alcohol or cannabis use disorder (ASUD), but more severe substance use disorders were excluded.

LANDMARK STUDIES: MDMA

- MDMA-AT was associated with a **significantly greater reduction in hazardous alcohol use scores** (measured by the Alcohol Use Disorders Identification Test) compared with placebo plus therapy.
- This effect was small-to-moderate (Hedges' g ~ 0.45), suggesting subclinical improvements in alcohol consumption or risk.
- No significant differences were found between the MDMA-AT and placebo groups on drug use measures (Drug Use Disorders Identification Test).

LANDMARK STUDIES ON KETAMINE

- A Single Ketamine Infusion Combined With Motivational Enhancement Therapy for Alcohol Use Disorder: A Randomized Midazolam-Controlled Pilot Trial
- American Journal of Psychiatry ("green journal")
- Dakwar et al., 2020

LANDMARK STUDIES: KETAMINE

- In this pilot study, the authors tested whether a single subanesthetic infusion of ketamine administered to adults with alcohol dependence and engaged in motivational enhancement therapy affects drinking outcomes.
- Subanesthetic dose use = 0.71mg.kg
- Study applicants were considered eligible if they were <70 years old, had no medical illness or psychiatric comorbidity, and met DSM-IV criteria for alcohol dependence and minimum daily (at least four heavy drinking days over the past 7 days) or weekly (35 drinks per week for men and 28 drinks per week for women).

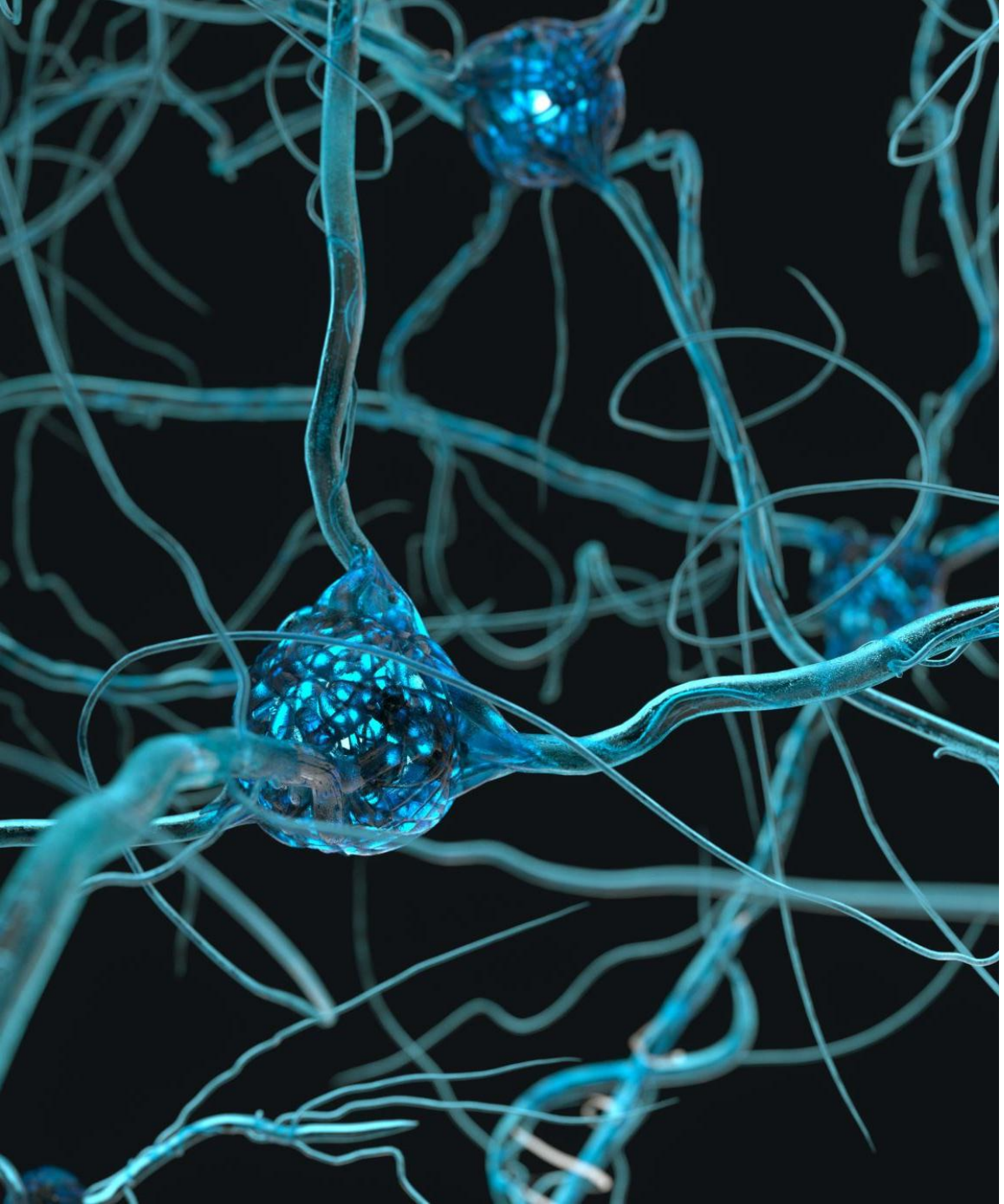
LANDMARK STUDIES: KETAMINE

- Exclusion criteria:
- History of severe withdrawal symptoms (e.g., seizures, cardiac instability, and delirium) were excluded, as were those
- History of psychotic or dissociative symptoms and with current depressive symptoms indicative of a DSM-IV disorder.
- Use of other substances

LANDMARK STUDIES: KETAMINE

- Participants were randomly assigned to a 52-minute intravenous administration of ketamine (0.71 mg/kg, N=17) or the active control midazolam (0.025 mg/kg, N=23), provided during the second week of a 5-week outpatient regimen of motivational enhancement therapy.
- Ketamine significantly increased the likelihood of abstinence, delayed the time to relapse, and reduced the likelihood of heavy drinking days compared with midazolam.
- A single ketamine infusion was found to improve measures of drinking in persons with alcohol dependence engaged in motivational enhancement therapy.

NEUROBIOLOGICAL AND PSYCHOTHERAPEUTIC MECHANISMS



5-HT2A RECEPTOR REVIEW

- Classic psychedelics like psilocybin, LSD, and DMT are partial agonists at the 5-HT2A receptor.

- This leads to:
- Increased cortical excitation
- Increased entropy in brain networks
- Destabilization of rigid network patterns

SHARED TARGET — THE 5-HT2A RECEPTOR

- Classic psychedelics like: Psilocybin, LSD, and DMT are 5-HT2A receptor **agonists**.
- Most atypical antipsychotics like Risperidone, Olanzapine, Quetiapine, and Clozapine are 5-HT2A antagonists.
- Same receptor. **Opposite actions**
- **Think of the 5-HT2A receptor as the brain's "meaning amplifier."**
- **Psychedelics amplify meaning-sometimes therapeutically**
- **Antipsychotics reduce excessive meaning-making (think ideas of reference for example).**

THE 5-HT2A RECEPTOR

- What Happens When You Turn It UP?
- 🧠 Increased cortical excitation
  - 🧠 Increased brain network flexibility
  - 🧠 Loosening of rigid thought patterns
  - 🧠 Increased emotional access
  - 🧠 Decreased default mode network integrity

THE 5-HT2A RECEPTOR

- Clinically, this can look like:
- Enhanced psychological flexibility
- Disruption of depressive rumination
- Breakup of addictive habit loops
- Altered sense of self

THE 5-HT2A RECEPTOR

- What Happens When You Turn It DOWN?
- When atypical antipsychotics block (antagonize) 5-HT2A receptors:
- 🧠 Reduced cortical excitation
  - 🧠 Stabilization of perception
  - 🧠 Dampening of aberrant salience
  - 🧠 Reduced hallucinations

THE 5-HT2A RECEPTOR

- Clinically, this can look like:
- Decreased psychosis
- Reduced agitation
- Emotional blunting (sometimes)
- Cognitive slowing (in some patients)

5-HT2A Receptor: Opposite Actions

Feature	Agonist	Antagonist
Cortical Effect	↑ Excitation / glutamate	↓ Excitation / stabilizes networks
Network	↑ Flexibility / entropy	↑ Stability / coherence
Salience	Amplifies meaning	Dampens pathological salience
Dopamine	↑ Cortical → subcortical drive	↓ Mesolimbic drive + D2 blockade
Clinical Use	Addiction therapy, depression	Psychosis, mania, agitation

Key Point: **Same receptor, opposite direction:** *psychedelics increase cortical flexibility; atypicals restore stability.*

5-HT2A RECEPTOR REVIEW

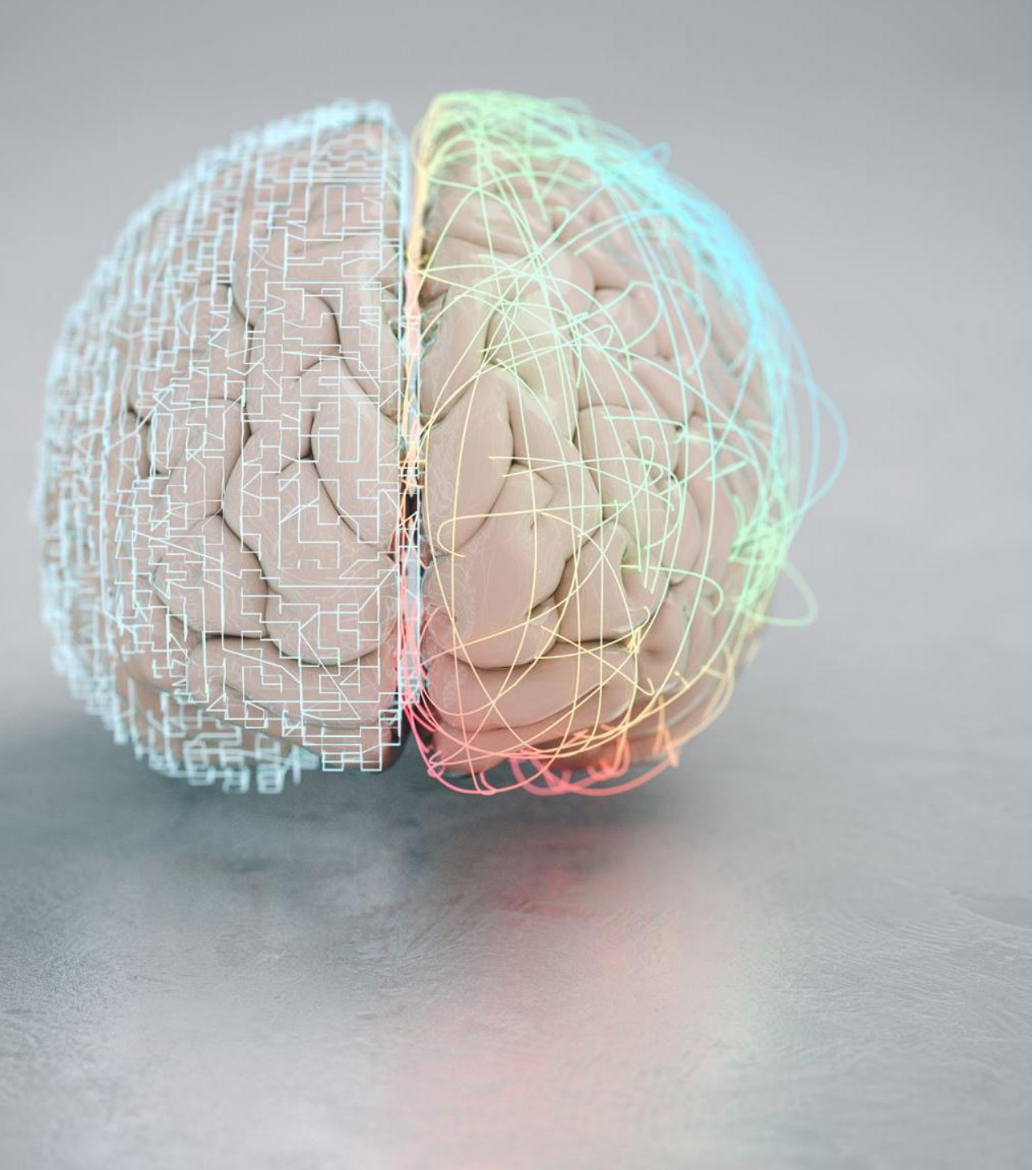
THE ENTROPIC BRAIN THEORY

- The Entropic Brain Theory (EBT), proposed by Dr. Robin Carhart-Harris and colleagues in 2014, is a neuroscientific framework that explains the quality of conscious states based on the level of entropy (disorder or randomness) in brain activity.

- The core premise is that the brain operates within a "critical" zone between complete order and complete chaos, with entropy serving as a measure of the richness, variety, and uncertainty of mental states.

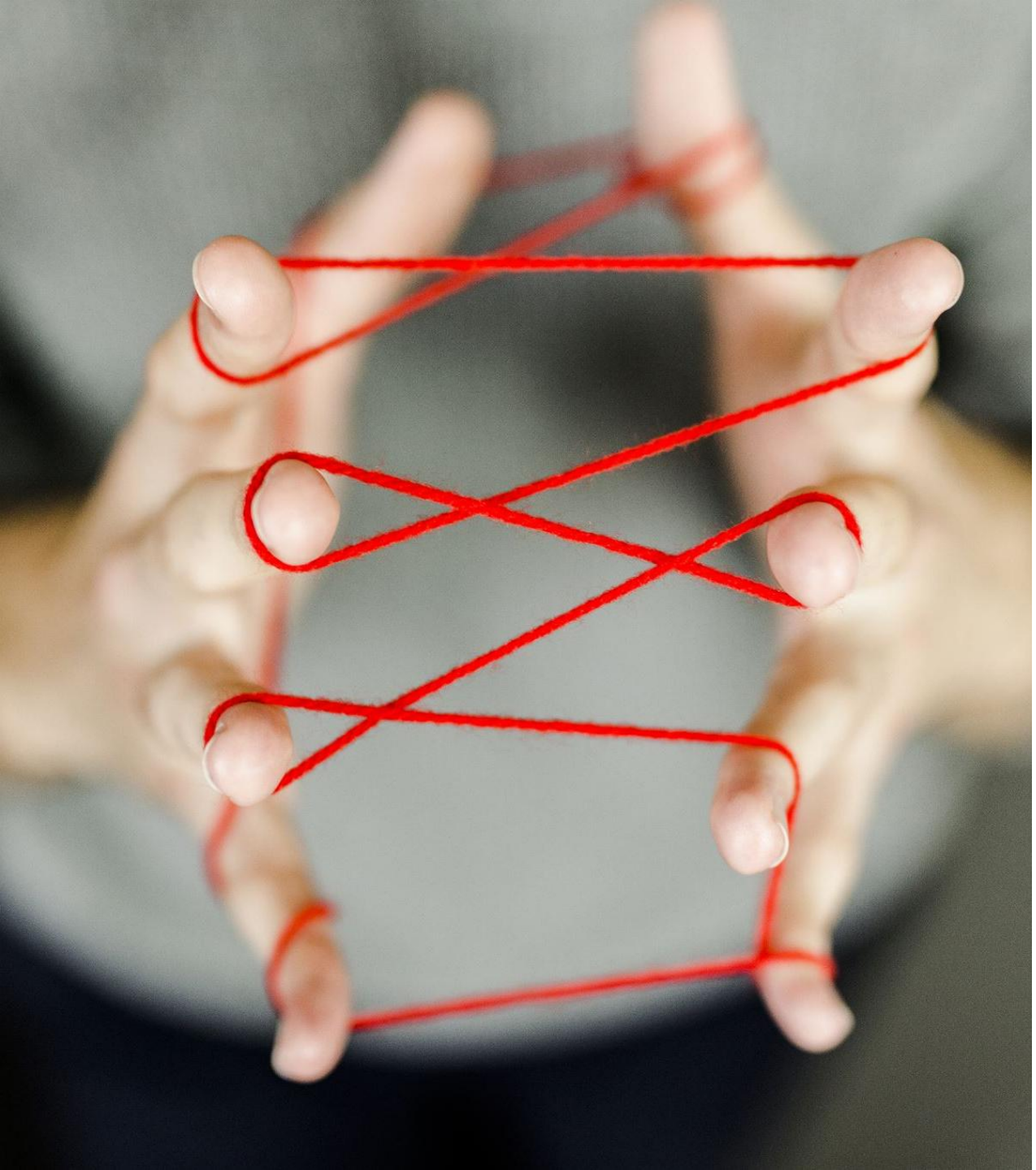
THE ENTROPIC BRAIN THEORY

- **Low-entropy states**: Highly organized, predictable brain activity. Associated with rigid patterns of thought and behavior—seen in depression, PTSD, and addiction.
- **High-entropy states**: More flexible, unpredictable, and diverse neural activity. Associated with creativity, insight, and novel ways of thinking.
- **Key idea:** Psychedelics temporarily increase entropy, disrupting entrenched pathological patterns of brain activity and allowing the brain to reorganize in healthier ways.



THE DEFAULT MODE NETWORK (DMN)

- The default mode network is a group of brain regions active during self-referential thought, rumination, and autobiographical memory.
- Major nodes include the medial prefrontal cortex and posterior cingulate cortex.

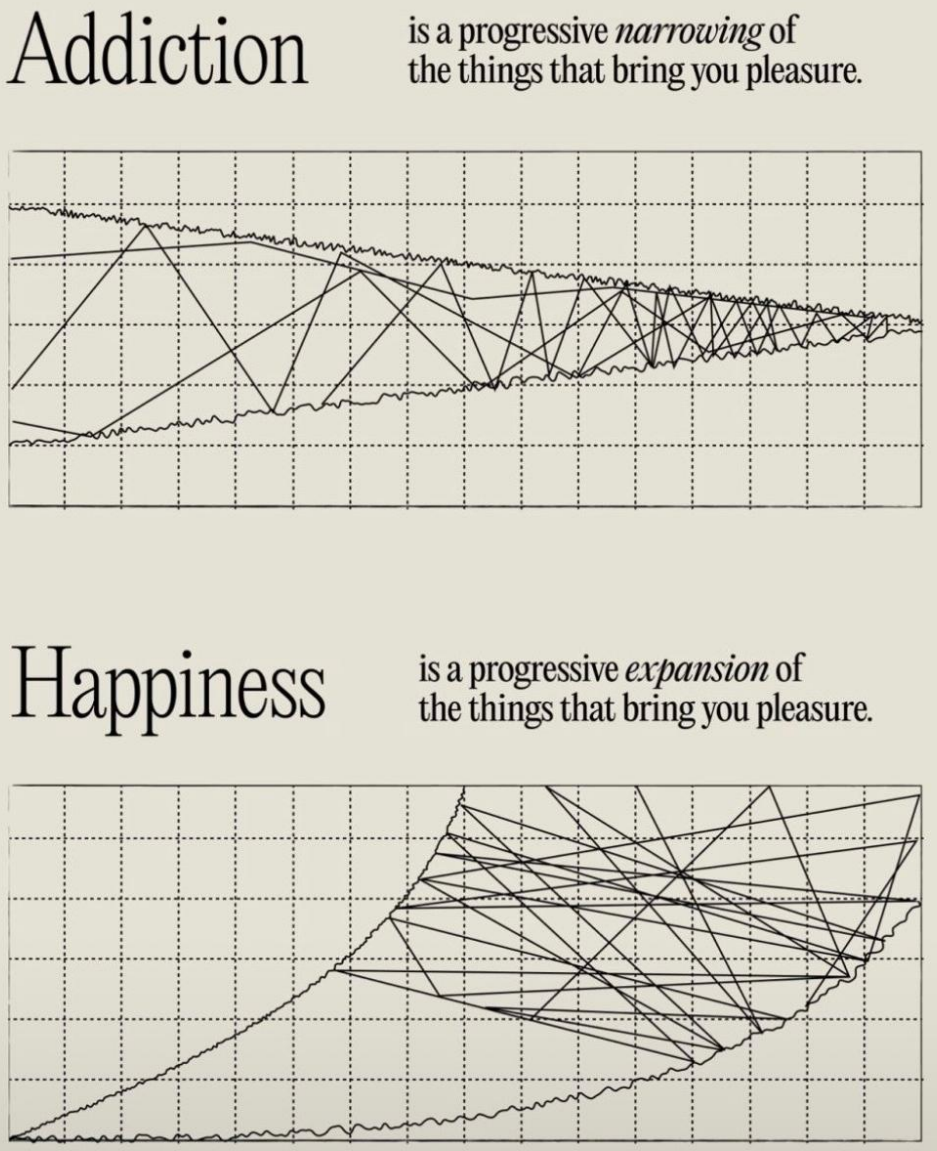


THE DEFAULT MODE NETWORK (DMN)

- In depression, PTSD, and addiction, the DMN tends to be hyperactive or overly rigid, reinforcing negative self-concepts, cravings, and compulsive behaviors.

ADDICTION: HYPERACTIVE DEFAULT MODE NETWORK

- “I am broken” (depression)
- “I am unsafe” (PTSD)
- “I cannot tolerate craving” (addiction)



DEFAULT MODE NETWORK IN ADDICTION

- Addiction involves **rigid reward-related and habitual circuits**, often reinforced by DMN interactions with limbic regions.
- Psychedelics disrupt these circuits → increase flexibility and **"reset" maladaptive patterns**, supporting abstinence.
- Studies show improved psychological flexibility correlates with reductions in substance use (Johnson et al., 2014; Carhart-Harris et al., 2017).

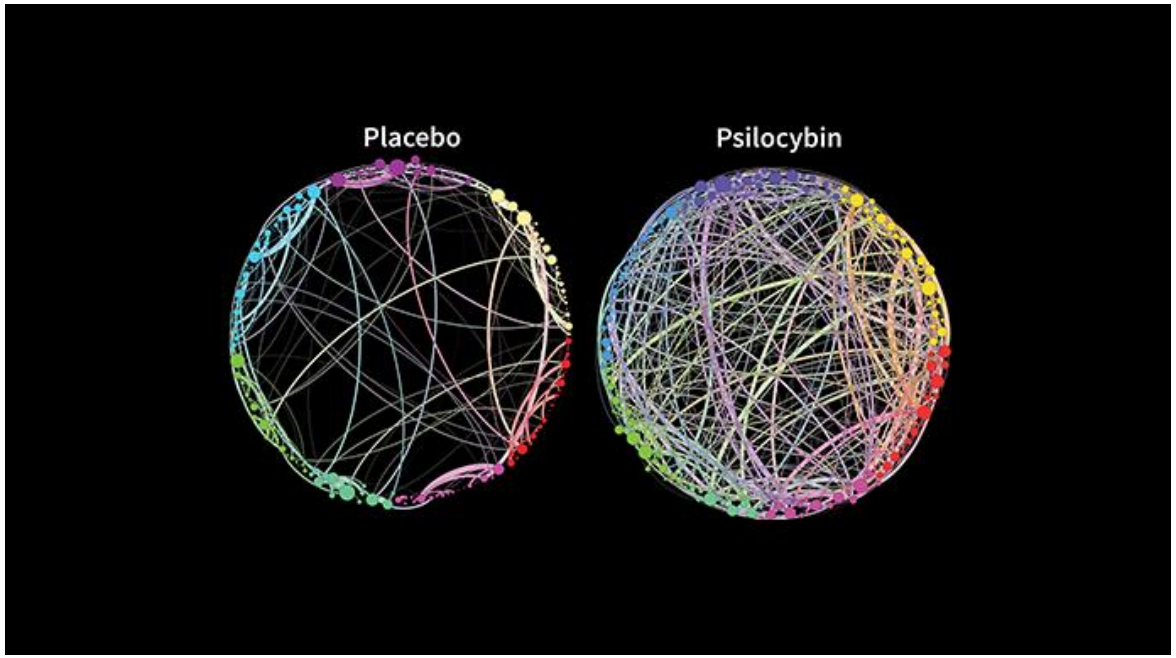
DEFAULT MODE NETWORK IN PTSD

- Traumatic memories are rigidly encoded, often supported by DMN-dominated patterns.
- Psychedelics increase entropy → allow **emotional reconsolidation** and new perspectives on trauma.
- Facilitates guided exposure therapy by reducing avoidance and defensive rumination.

DEFAULT MODE NETWORK IN DEPRESSION

- Hyperactive DMN → persistent negative thoughts and rumination.
- Psychedelics reduce DMN integrity → temporarily break negative thought loops.
- Increased entropy allows patients to reinterpret experiences, fostering psychological flexibility.
- Clinical outcome: Rapid and sometimes sustained reduction in depressive symptoms (Carhart-Harris et al., 2016, 2021).

THE DEFAULT MODE NETWORK (DMN)



- Under psychedelics (like psilocybin or LSD), DMN activity decreases, leading to:
- Reduced rumination and negative self-focus
- Dissolution of rigid self-concepts (“ego dissolution”)
- Increased connectivity between previously segregated brain networks

PUTTING IT ALL TOGETHER

- Psychedelics disrupt the DMN->>>>increasing global brain entropy->>>>enabling more flexible thinking and novel associations

AN ANALOGY FOR HOW IT WORKS

- The Brain is a Snow-Covered Hill: Your brain's habitual thoughts and behaviors are like sleds moving down a hill, creating deep, established ruts or grooves in the snow.
- The DMN is the Well-Worn Path: The Default Mode Network acts like those primary, deepest ruts—representing repetitive, often automatic, ways of thinking (such as rumination, self-criticism, or rigid, unhelpful habits).

AN ANALOGY FOR HOW IT WORKS

- Psychedelics are Fresh Snow: A psychedelic experience is like a fresh, heavy snowfall covering those old ruts, or like a snowplow clearing the slope.
- Seeing Things Differently (Entropy): With the old paths covered, the brain is no longer forced into the same, rigid, "low-entropy" patterns. The mind becomes more flexible ("high-entropy"), allowing the "skier" to choose new, different, and more creative paths down the mountain.
- Changing: As the snow settles, the brain has the opportunity to form new, healthier pathways rather than falling back into the old, deeply ingrained ones.

PSYCHOTHERAPUETIC MECHANISMS

SUMMARY OF PROPOSED CORE PSYCHOTHERAPEUTIC MECHANISMS

- Increased psychological flexibility
- Emotional breakthrough and reconsolidation
- Reduced experiential avoidance
- Identity and meaning reconstruction
- Enhanced motivation and behavioral commitment

PSYCHOLOGICAL FLEXIBILITY & NARRATIVE DISRUPTION

- **Core Therapeutic Mechanism:**
  Temporary loosening of rigid self-narratives

- **What Happens in Session:**
- **Reduced dominance of self-referential processing (Default Mode Network softening)**
- **Decentering from thoughts and beliefs**
- **Increased openness and cognitive flexibility**

CLINICAL TRANSLATION

- Depression → disengagement from rumination
- PTSD → reduced avoidance and rigid trauma schemas
- Addiction → separation of craving from identity

- Takeaway:
  Psychedelics may accelerate processes targeted in ACT, CBT, and motivational therapies.

EMOTIONAL BREAKTHROUGH & MEMORY RECONSOLIDATION

- Core Therapeutic Mechanism:
  Revisiting emotionally charged material in a safe, supported state

- Observed Effects:
- Heightened emotional access
- Reduced defensive avoidance
- Increased self-compassion

PSYCHOTHERAPEUTIC IMPACT

- Trauma memories reprocessed with reduced fear response
- Substance-related cues recontextualized
- Shame-based beliefs softened

MEANING-MAKING, IDENTITY SHIFT & BEHAVIOR CHANGE

- Core Therapeutic Mechanism:
  Reorganization of personal narrative and values

- Common Psychological Outcomes:
- Increased connectedness
- Renewed purpose
- Reprioritization of health and relationships

WHY THIS MATTERS?

- Motivation shifts from external pressure → internal commitment
- “I have to stop using” becomes “I want to live differently”
- Insight + integration = sustained behavioral change

- Clinical Framing:
  The medicine may open a window.
  Psychotherapy consolidates the change.

WHAT DO WE MEAN BY A "MYSTICAL EXPERIENCE"?

- Core components:
- Unity / Non-duality
- Sacredness
- Deep positive mood
- Transcendence of time/space
- Ineffability
- Noetic quality ("felt truth")

THE "MYSTICAL EXPERIENCE = MECHANISM" HYPOTHESIS

- Early and influential work by Roland Griffiths and colleagues at Johns Hopkins showed:
- The **intensity of mystical experience predicted long-term positive outcomes**
- Correlated with:
  - Smoking cessation
  - Decreased alcohol use
  - Decreased depression
  - Increased well-being

THE "MYSTICAL EXPERIENCE = MECHANISM" HYPOTHESIS

- Similarly, research at Imperial College London under Robin Carhart-Harris found:
- Mystical-type experience scores correlated with reductions in depression
- "Ego dissolution" predicted therapeutic response

- The key statistical finding:
- Mystical intensity often mediates clinical outcome.
- This led to the early view:
  - Mystical experience may be a primary therapeutic mechanism.

MYSTICAL EXPERIENCE MAY BE HELPFUL BUT IS IT NECESSARY?

- Recent work suggests:
- - Some patients improve without full mystical experiences
  - Emotional breakthrough may predict outcomes as strongly or more strongly
  - Psychological flexibility is often a stronger predictor than mystical score

MYSTICAL EXPERIENCE MAY BE HELPFUL BUT IS IT NECESSARY?

- Ketamine produces antidepressant effects without reliably producing mystical experiences
- MDMA-assisted therapy for PTSD often works through emotional processing, not mystical transcendence

- For example, in phase 3 trials led by MAPS using MDMA:
- Treatment response correlated more with trauma processing than mystical intensity.

THE EMERGING VIEW: MYSTICAL EXPERIENCE AS ONE PATH, NOT THE ONLY PATH

- There are at least three candidate therapeutic mechanisms:
- Mystical-type experience
- Emotional breakthrough
- Enhanced psychological flexibility
- Some researchers now argue:
- Mystical experience may be a marker of deep neural plasticity and cognitive flexibility rather than the mechanism itself.
- Others argue:
- It is the meaning-making integration afterward that determines outcome.

PRACTICAL, ETHICAL, AND REGULATORY CONSIDERATIONS

- Federal Status (U.S.)
- Most classic psychedelics (e.g., psilocybin, LSD, DMT) remain Schedule I under the Controlled Substances Act
- Defined as:
- “No currently accepted medical use”
- “High potential for abuse”
- Lack of accepted safety under medical supervision
- MDMA remains Schedule I despite advanced clinical trials
- Ketamine is Schedule III (FDA-approved anesthetic; used off-label for depression)

STATE-LEVEL EXCEPTIONS

- Oregon: Licensed psilocybin service program
- Colorado: Regulated natural medicine framework underway
- Key Point:
  Clinical use outside approved research protocols remains federally illegal (with narrow state-specific exceptions).

EVIDENCE: PROMISING, BUT STILL DEVELOPING

- What We Know
- Strong Phase 2 data for:
  - Psilocybin in depression and addiction
  - MDMA-assisted therapy for PTSD
- Rapid antidepressant effects with ketamine

WHAT WE DON'T YET FULLY KNOW

- Long-term safety data (5–10+ years)
- Optimal dosing models
- Standardized psychotherapy protocols
- Comparative effectiveness vs. existing treatments
- Real-world implementation outcomes
- Bottom Line:
  The field is transitioning from proof-of-concept → scalability and systems-level implementation.

RESPONSIBLE PATH FORWARD

- Continued randomized controlled trials
- Development of standardized therapist training pathways
- Clear ethical guidelines
- Thoughtful regulatory reform based on evidence
- Integration with existing addiction and mental health systems

- Psychedelic-assisted therapy is not a panacea —
  but it may become a powerful tool if implemented carefully, ethically, and scientifically.