NIH Psychedelics Workshop—Where are the Research Gaps and Opportunities?

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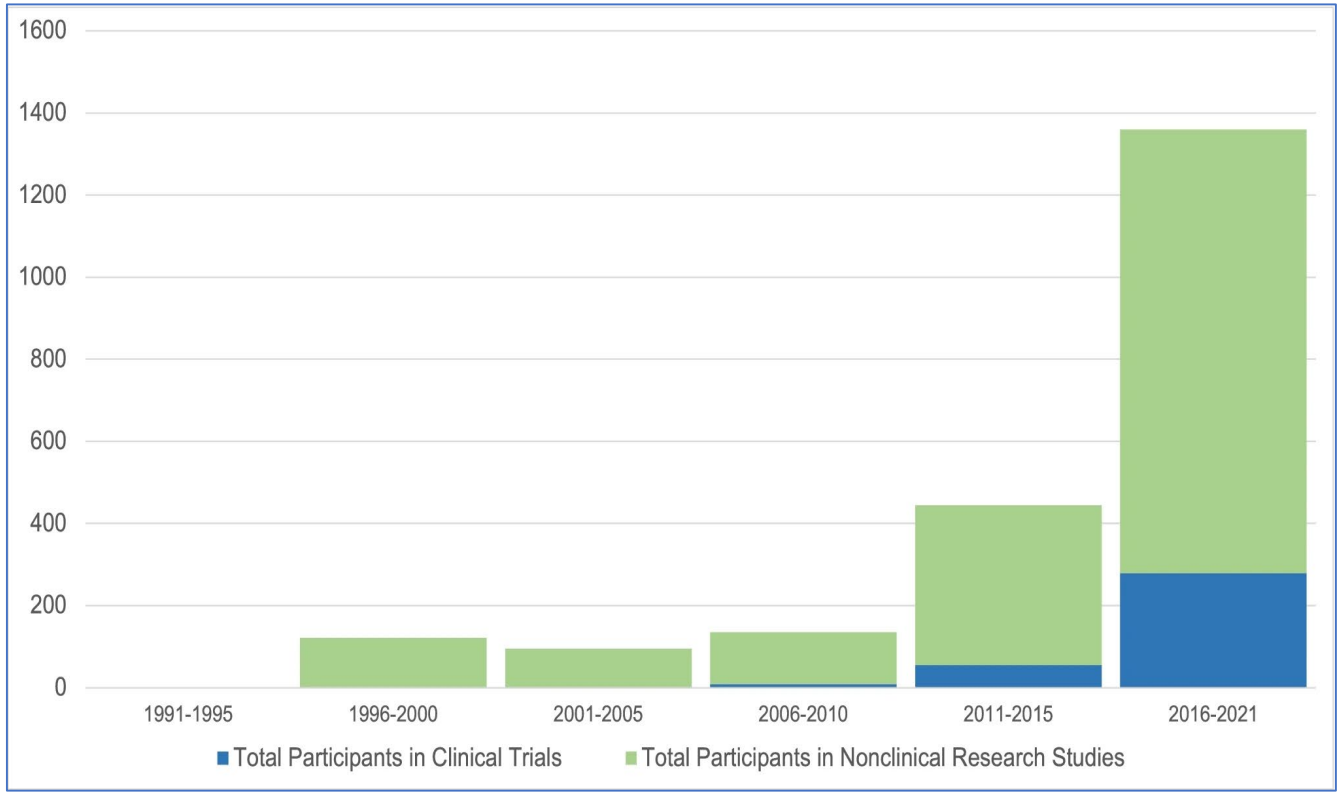
Surge of scientific and public interest

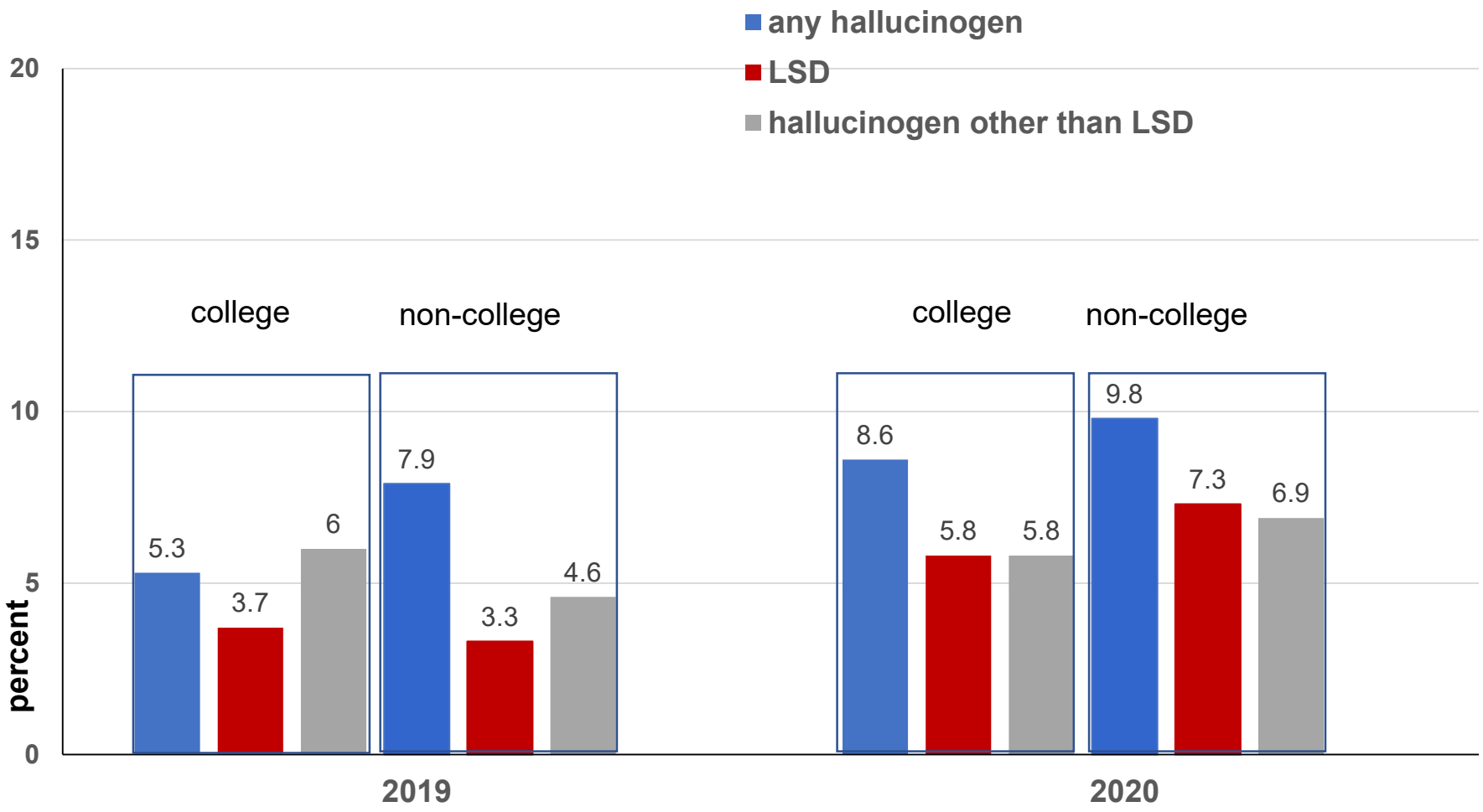


- Increased non-medical and off-label use
- Lack of patient diversity
- Research “going off the rails”

(Yaden, *et al*. 2020)

Need to move forward with robust, reliable research.

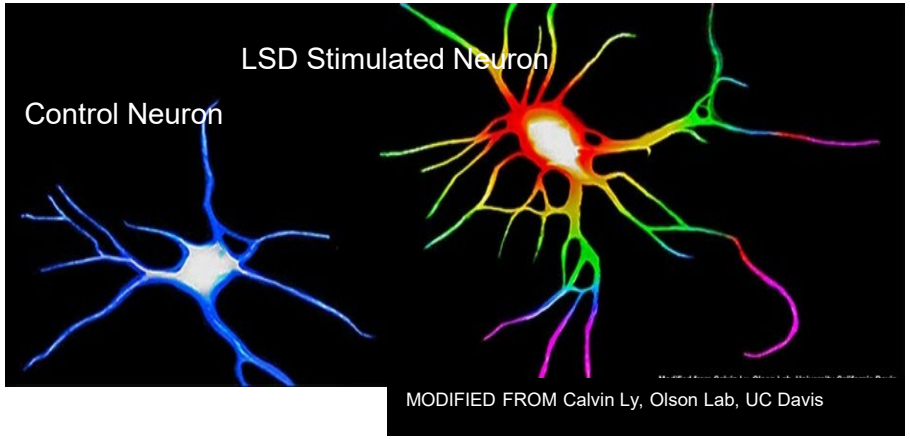
Hallucinogen Use in College Age Adults in 2020 MTF



NIH Workshop: Psychedelics as Therapeutics

January 12-13, 2022, Sponsored by NIMH, NIDA, and NIAAA

Examined gaps, challenges, and opportunities in research exploring psychedelics to treat psychiatric and substance use disorders.



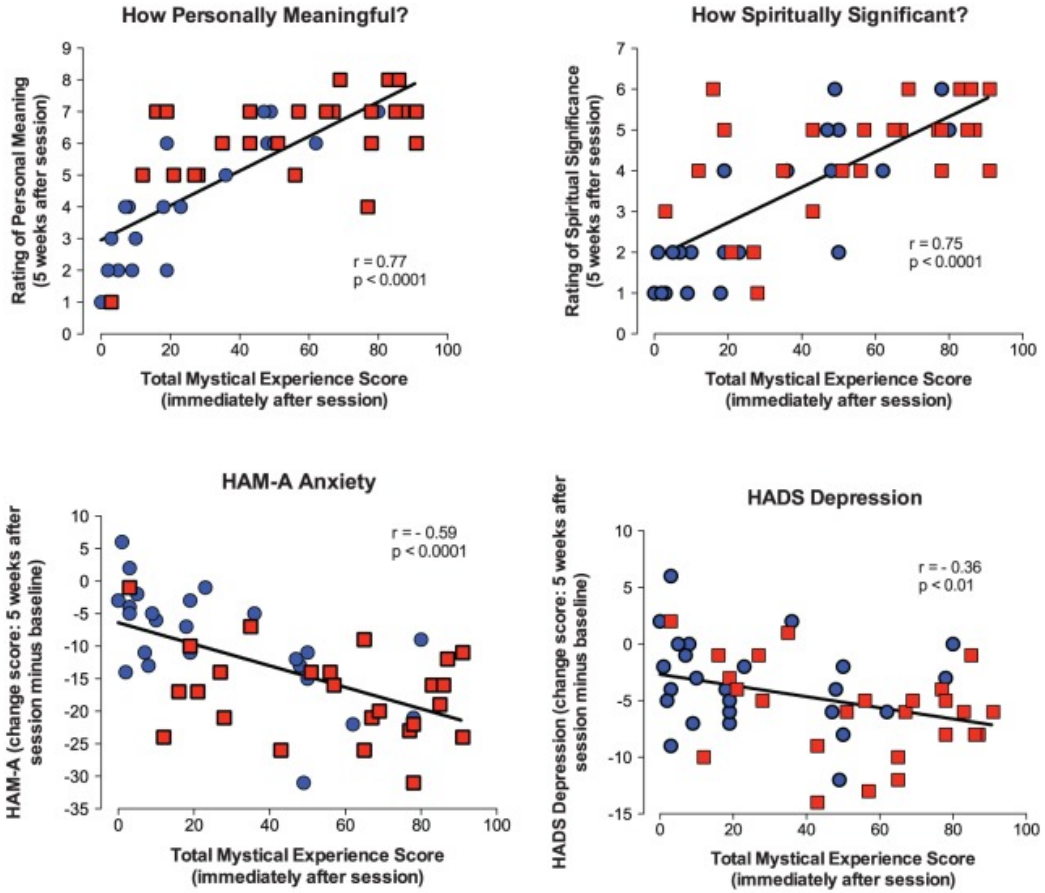
- Classic Hallucinogenic Drugs
  - Psilocybin
  - Mescaline
  - LSD
  - Dimethyltryptamine (DMT)
  - Ayahuasca
- Dissociative drugs
  - Ketamine
  - Phenilcyclidine (PCP, angel drust)
- Others
  - MDMA (ecstasy, classified as hallucinogenic + stimulant)
  - Ibogaine (classified as dissociative by some)

Psychedelics: What do we know?

- **Subjective effects?**
  - Variable across substances, individuals, context (set and setting).
  - Some positive (e.g., spiritual, reflective, empathic).
  - Some negative (e.g., anxiety, invincibility, hallucinations).
- **Mechanisms of action?**
  - Most target the serotonergic system, + distinct molecular targets and downstream effectors, some unknown.
  - Many induce neuroplasticity but long-term effects are unclear.
- **Low toxicity?**
  - Not all.
    - Ibogaine blocks cardiac K^+ channels, has cardiotoxic effects.
    - Recreational MDMA use assoc. with subclinical heart valve disease.
- **Low addiction liability?**
  - Not all, e.g., recreational ketamine is assoc. with dependence.
  - Epi data are supportive for most others, but clinical data are lacking.
- **Therapeutic potential?**
  - Promising
    - Psych disorders
    - SUD
  - Many knowledge gaps on safety and efficacy.

Mechanisms of action of classic psychedelics

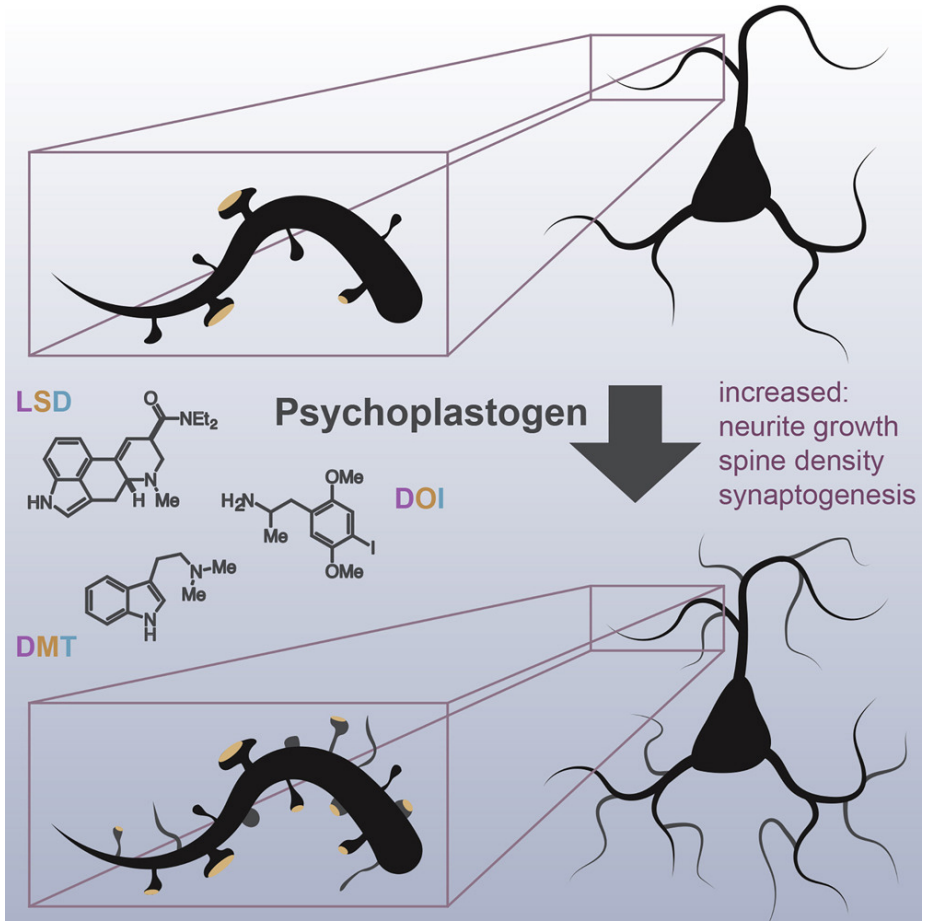
- **Subjective effects** of psychedelics correlate with therapeutic efficacy, but are they required?
  - Important for understanding cellular and molecular targets for therapy.
    - 5-HT_{2A} receptor is critical for subjective effects of classic psychedelics.
    - But is it critical for therapeutic effects?
  - Potential to design psychedelic therapies that do not produce negative subjective effects (e.g., anxiety).



Mystical experience from psilocybin correlates with reduced anxiety and depression in patients with cancer. Griffiths, *et al*. 2016.

Mechanisms of action of classic psychedelics

- What is the **role of plasticity** in psychedelic therapy?
  - Is it required for efficacy?
  - What cells, synapses, and circuits are the most important to change?
  - Are there ideal or critical time periods for these changes to occur?
  - What is the potential for maladaptive plasticity?



Ly C, *et al*. 2018

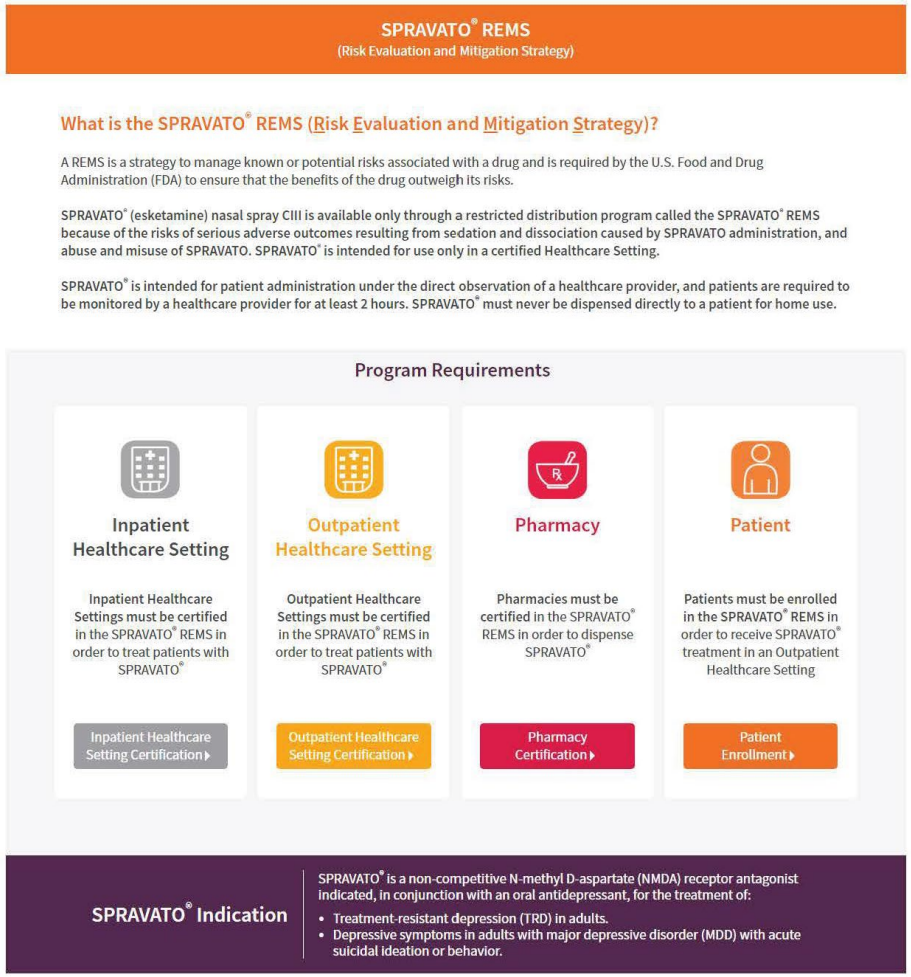
Gaps, Challenges, and Opportunities: Clinical trials

- How to conduct rigorous trials given that the psychedelic experience prevents **blinding** of participants (and researchers)?
  - Assess blinding *after* drug administration and *before* outcomes.
  - Instead of placebo, use an active comparator (e.g., different drug or lower dose).
  - Use placebo with physio effects like those of test drug (e.g., mild GI upset, facial flush).
  - Include objective surrogate outcome measures (e.g., brain imaging, task performance).
  - Conduct longer follow-up to assess durability of therapeutic outcomes. Goldberg, *et al*. 2020

- How to translate controlled conditions of psychedelic trials into **real-world practice**?
  - Psychedelic trials emphasize **Set** (mindset/intention) and **Setting** (supportive environment) to optimize outcomes.
    - Important for building rapport with therapist and reducing negative subject experience.
    - But what are the optimal Set and Setting for a given psychedelic?
    - And how will limited resources affect implementation?
      - Barriers to access and affordability?
      - Payors and providers may cut corners, e.g., cutting therapist involvement, not screening for risks, stretching off-label use.

Gaps, Challenges, and Opportunities: Clinical trials

- How to translate controlled conditions of psychedelic trials into **real-world practice**? *(continued)*
  - Common exclusion criteria—e.g., history of psychosis, suicide attempts—limit knowledge about outcomes in diverse patients.
  - Translation likely to require **Risk Evaluation and Mitigation Strategies** (REMS) that account for Set, Setting, and exclusions.
    - Ex: Spravato/esketamine REMS (www.accessdata.fda.gov/scripts/cder/rems)



THANK YOU!

RESEARCH GAPS AND OPPORTUNITIES

BASIC AND TRANSATIONAL RESEARCH

Is 5HTa the only critical receptor?

- 5HT2a agonist /antagonist and KO studies show the key involvement of 5HT2a, but psilocybin (PSY) and other psychedelics have activity at several 5-HT receptors: 5HT2b, which is a cardiovascular risk, and 5HT-2c antagonists modulate animal responses to PSY.
- PSY relieves depressive responses in mice but the relief is NOT blocked by 5HT 2a antagonist, suggesting other receptors are involved.
- Clinical PET 5HT2a occupancy correlates with dose and intensity of mystical experience the degree of mystical experience varies with individual, indicating 5HT2a ***IS*** responsible.

Dendritic spine formation

- Lower presynaptic vesicle density is associated with depression, but brief exposure to LSD or PSY increases dendritic spine (synapse) formation over long term (PET imaging)

Can perceptual and therapeutic effects be separated?

RESEARCH GAPS AND OPPORTUNITIES

CLINICAL TRIALS

Set and Settings

The Set: (patient mental state), Intent, expectation, personality, mood

The Setting (External, physical environment, social interaction with therapists and other people present. Cultural.

Set/Settings alter research results and because psychedelics intensify experiences and *in current trials S/S are tightly controlled. but how translatable are these conditions?*

- Conditions are also variable between trials, so it is ***unclear what aspects of set and setting are most important.*** We need to work out the optimal conditions before FDA registration trials begin.
- Different cultures may have different requirements. Eliminating cultural controls risks loss of safeguards.
- Psychedelics may not be either a “Commodity” treatment like many drugs or a “sacrament” like ancient rituals, but Psychedelics ***need specific use parameters for implementation in practice and in State/Fed law***
- For modern western environments, perhaps ***communal therapy setting*** may reduce costs while maintaining support and reducing risk

KEY QUESTIONS

1) How do we conduct valid clinical trials with drugs that can be experienced (includes psychedelics, cannabis, kratom, etc.)?

- We *need to develop alternative clinical trial "technologies" including designs and appropriate measures that are validated and acceptable to FDA*

2) How do we decide what are the most important of the psychotherapeutic "Set and Settings"?

- This is essential to both standardize clinical trials AND to ensure the essentials are included as FDA "Risk Evaluation and Mitigation Strategies (REMS) when the drug is approved.

- "Essential" set/settings are needed to ensure efficacy AND need to be minimal to be affordable if the treatments are to become paid for by Medicaid and Insurers.

RESEARCH GAPS AND OPPORTUNITIES

THE FUTURE: Overcoming Trial Confounds, and Considering Consequences of Real-World Use

BIAS AND EXPECTANCY:.Over the course of any drug trial, the ***better the intervention, the more unblinding (Phillips paradox)*** so expectancy is shaped throughout trials as the subjects gain information.

To account for this ***need large and long trials***

- if blinded trials don't work, we can use the ***Bradford-Hill criteria*** ***(****"strength of the association, consistency, specificity, temporal sequence, biological gradient, biologic rationale, coherence, experimental evidence")*

Example: MDMA for PTSD-> There are good animal data to support MDMA efficacy in (re)opening "adolescent" social plasticity windows in adult animals→The clinical data looks good and resilient over time, but blinding is poor.

- Sustained results over long time (1y), suggest it is not a placebo result →the strong subjective effect may make blinding impossible but ***the long lasting effects give a high probability that the therapeutic effects are real (and durable)***
- We also ***need to consider ways of doing trials that don't depend on blinding.***

ETHICAL CONSIDERATIONS

- Currently studies are done in highly selected populations without ***vulnerable populations***. (Depression trials don't include suicidal or psychotic subjects- but they WILL be exposed after approval. → need to include now.

Informed Consent

Potential participants expectations: allure and media coverage, potential unreasonable expectations- particularly problem with placebo controlled trials

Suggestibility and vulnerability- Potential sexual and other exploitation.

- After approval rigorous Set/Settings ***are unlikely to be adhered to*** as psychedelics become profit centered, off-label use occurs and research setting precautions are eroded. Currently seen in i.v. ketamine clinics

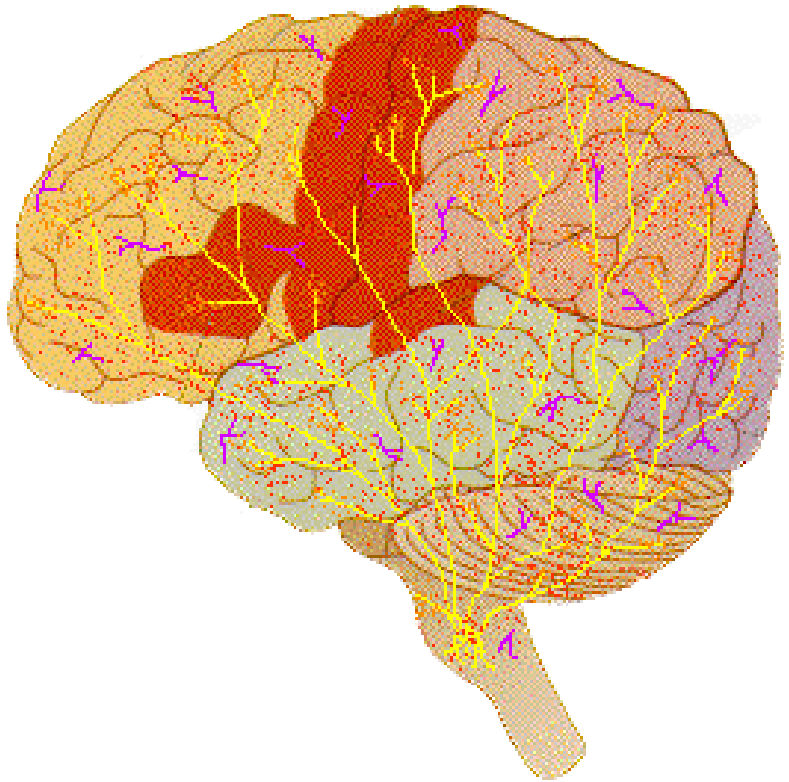
- Psilocybin has been studied for the treatment of depression (Carhart-Harris et al., 2016, 2017)
- Tobacco and alcohol addiction (Johnson et al., 2014, 2017; Bogenschutz et al., 2015, 2018)
- Obsessive-compulsive disorder (Moreno et al., 2006)
- Depression and anxiety in patients with life-threatening diagnoses (Grob et al., 2011; Griffiths 2016; Ross et al., 2016).
- Currently, several trials with psilocybin- and LSD-assisted psychotherapy are being conducted in Europe and the United States. Although no formal clinical trials have yet investigated these substances for the treatment of PTSD, the available evidence (e.g., Leuner, 1981; Bastiaans, 1983) does warrant such an investigation.

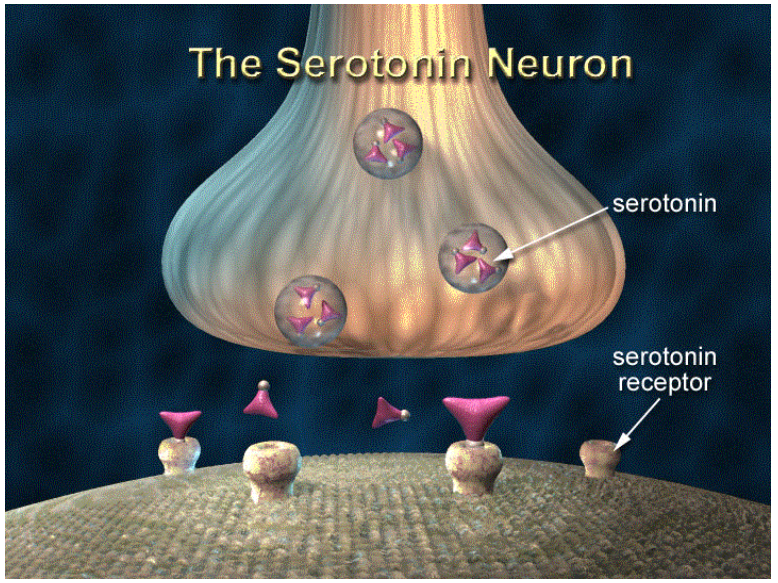
FDA's Breakthrough Therapy designation **is one of the ways the FDA seeks to encourage and expedite the development and review of drugs that are intended to treat a serious condition**

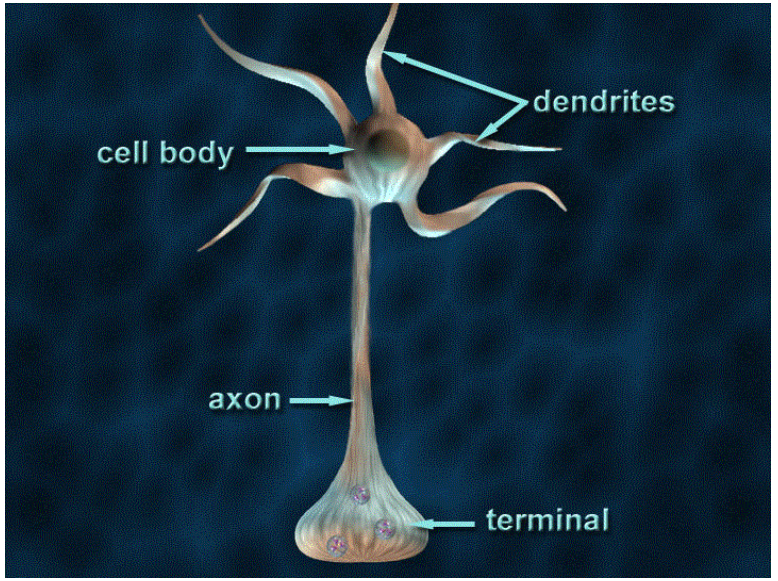
- **confers a number of benefits, including eligibility for all Fast Track designation features,** ***MDMA*** **received the Breakthrough Therapy designation from the FDA in August 2017.**
- **The FDA also granted** ***psilocybin*** **Breakthrough Therapy status for research in October 2018 and again in 2019.**
- **Johnson & Johnson obtained the designation for** ***ketamine*** **(a Schedule 3 substance) in 2018, which paved the way for its patented drug,** ***Esketamine,*** **to obtain the designation in 2020.**
- **Other psychedelics that are currently undergoing research that have not yet been granted Breakthrough Therapy status include** ***LSD, Ibogaine, and DMT*****.**

Psychedelics Act on Serotonin Receptors

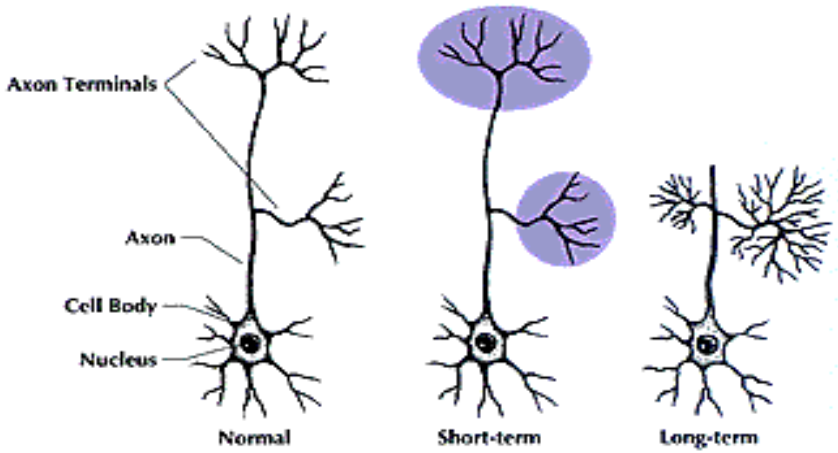
Normal Serotonin-containing Neurons (Yellow) in Human Brain

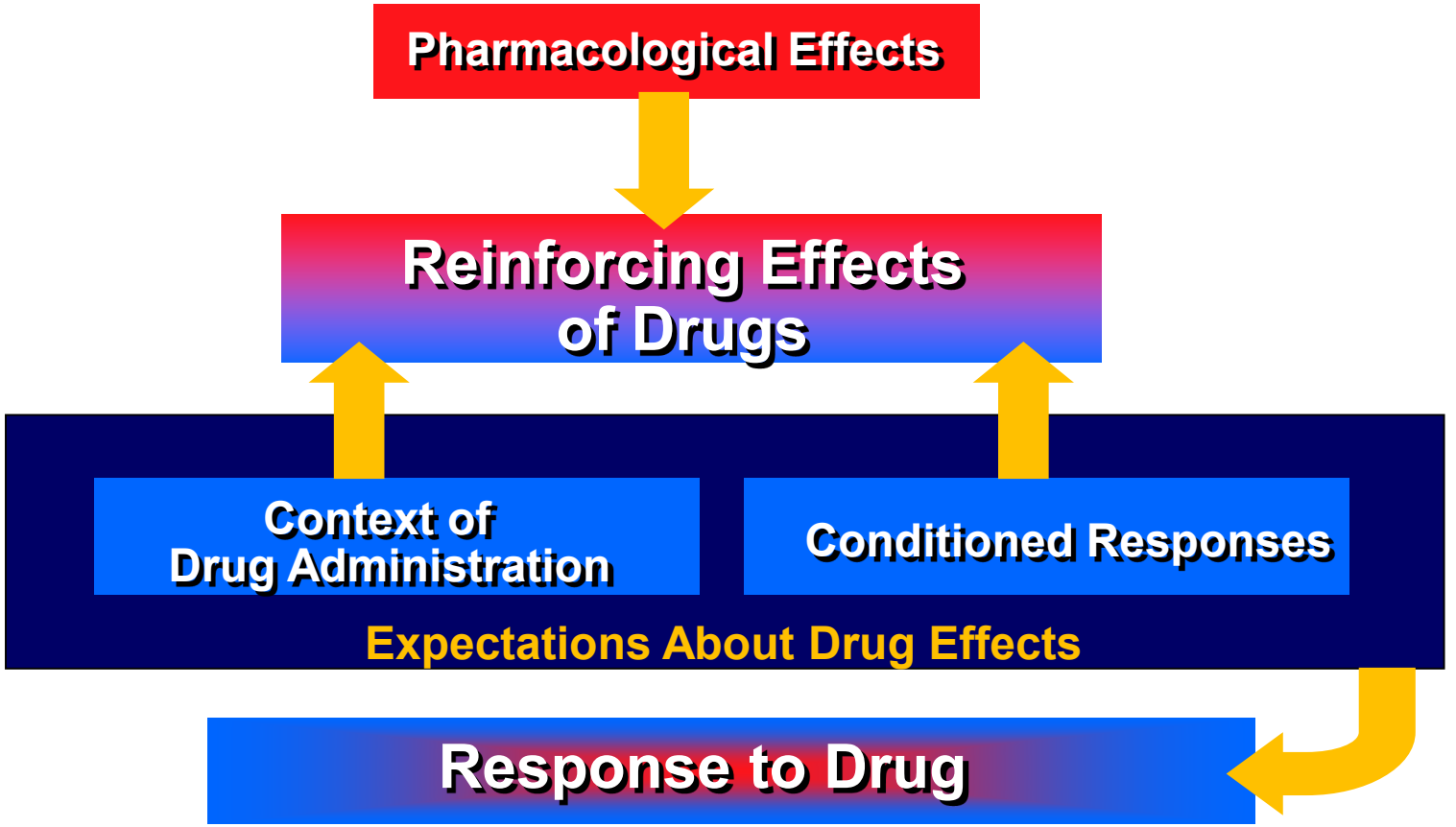






"Pruning" of Serotonergic Axons and Terminals





The reinforcing effects of drugs of abuse are not just a function of their pharmacological effects… but also of the expectation of what the drug will do

99 Ecstasy (MDMA) Tablets