



The Past, Present & Future of Psychedelics & Psychosis

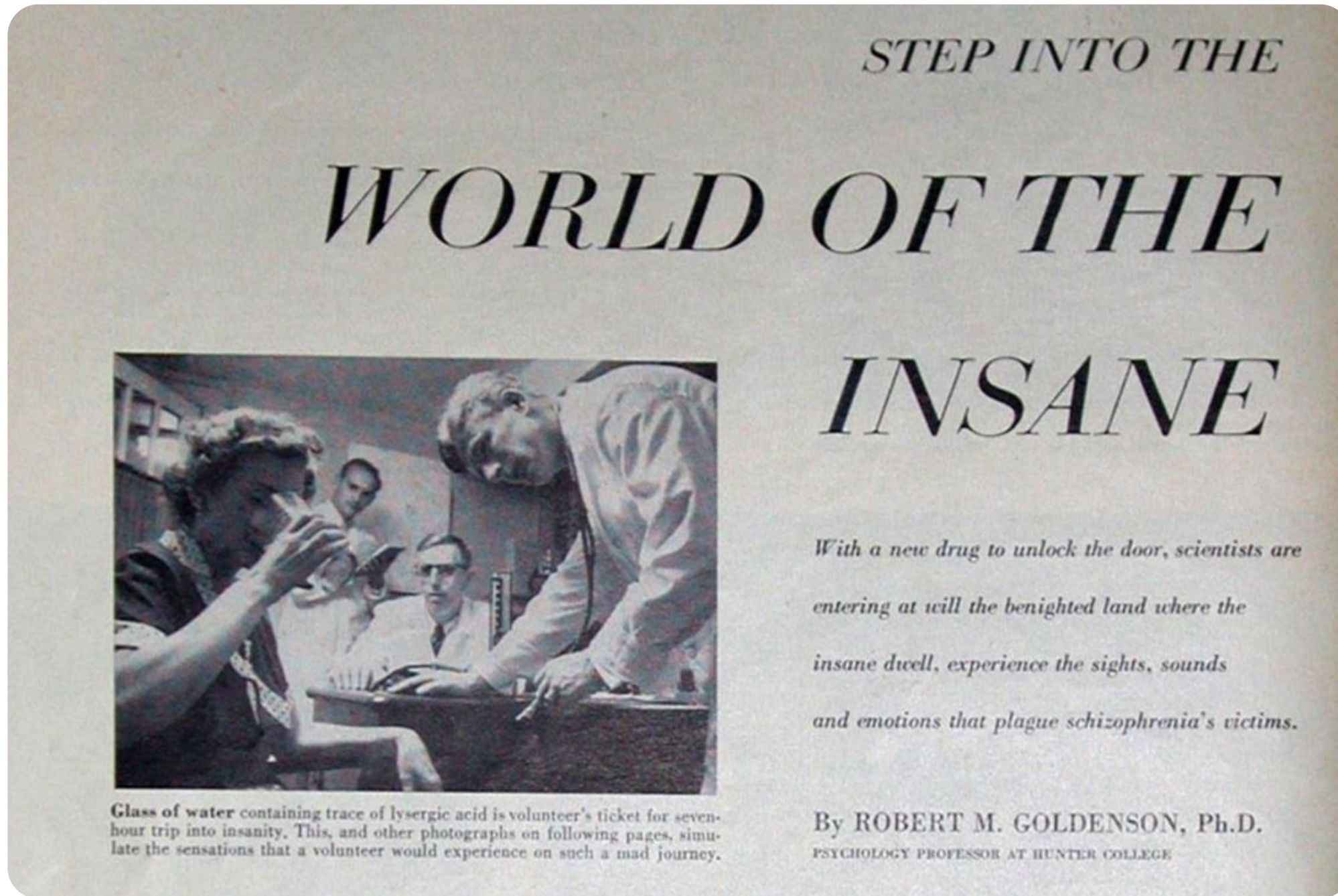
Haley Maria Dourron, PhD candidate

Disclosure: Neither I nor my spouse/partner has a relevant financial relationship with a commercial interest to disclose.

**What do you think of when you
think of psychedelics and
psychosis?**



Psychedelics may cause psychosis



Drug effects somewhat like psychosis



Syd Barrett



Skip Spence



What you don't think about....



Many of the first studies of
psychedelics
were in people with
psychotic disorders

100s of people with
psychotic disorders were
administered psychedelics
in the 1950s - 1960s

1947

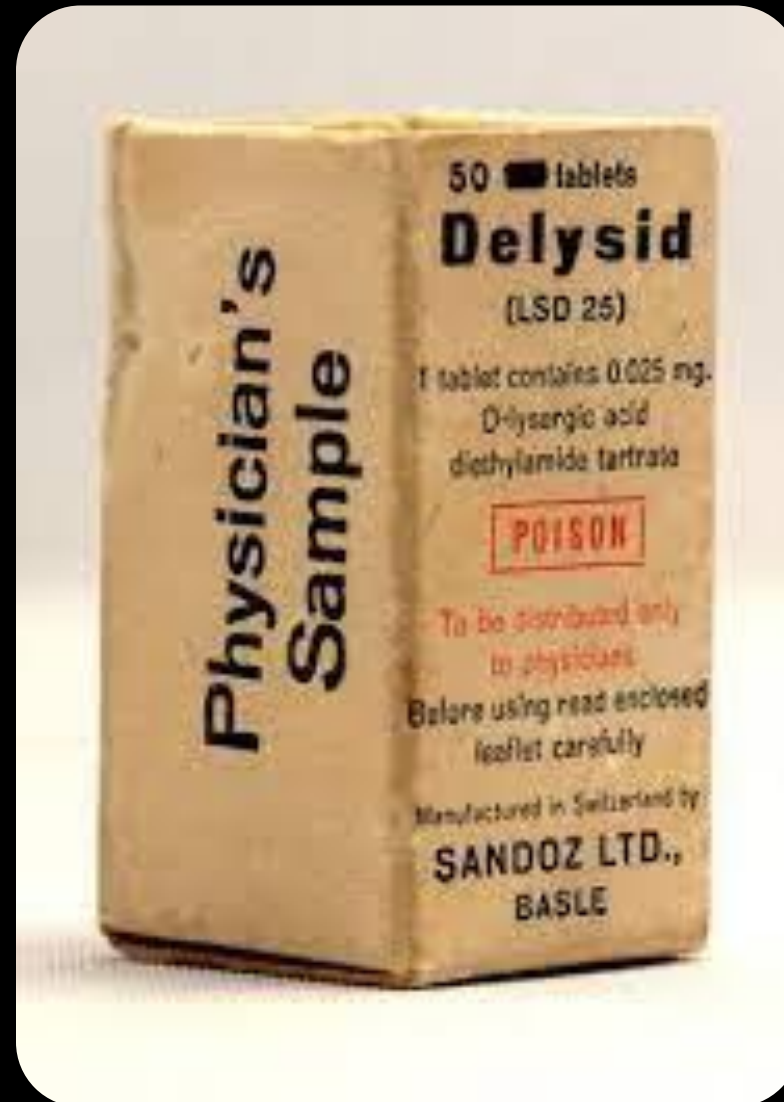
First study of LSD

11. Lysergsäure-diäthylamid,
ein Phantastikum aus der Mutterkorngruppe.

Von W. A. STOLL.

“LSD was administered a total of twenty times to 3 female and 3 male schizophrenics (1 hebephrenic, 5 paranoid). Patients were chosen where the usual active therapy showed no improvement or could not be continued for some reason.”

some improved, some stay the same.



1950

First study of LSD as an aid in Psychotherapy

L. S. D. 25 As an Aid in Psychotherapy

(Preliminary Report of a New Drug)

ANTHONY K. BUSCH, M.D.

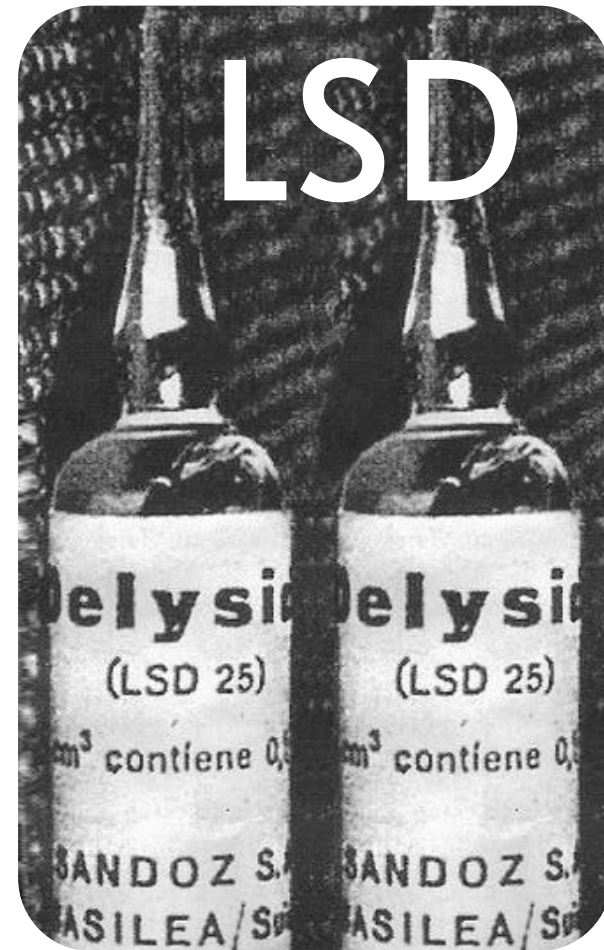
WARREN C. JOHNSON, M.D.

St. Louis, Missouri

20 patients out of 29 had
schizophrenia

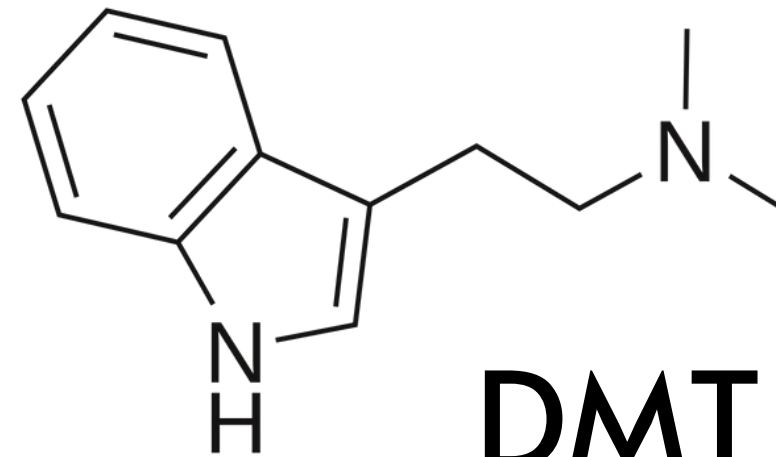
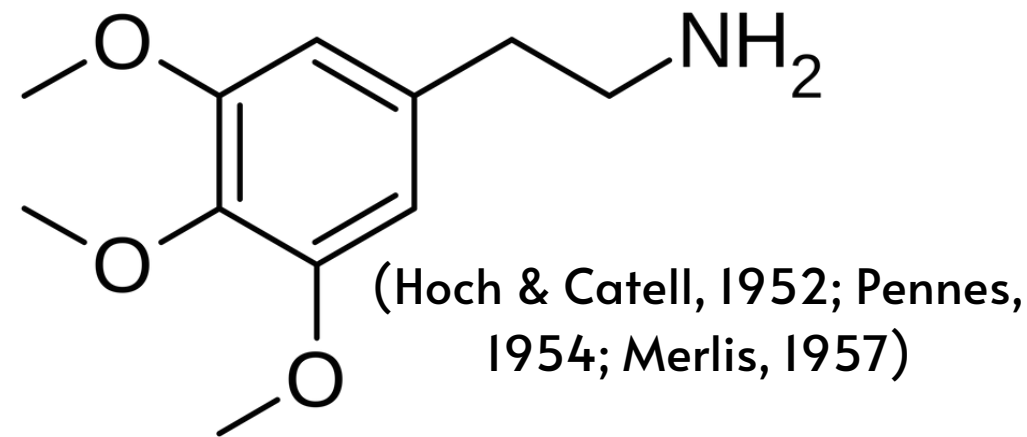
Other diagnoses include
“psychoneurosis” and
“manic-depressive”

Hundreds of people with psychotic disorders were given psychedelics



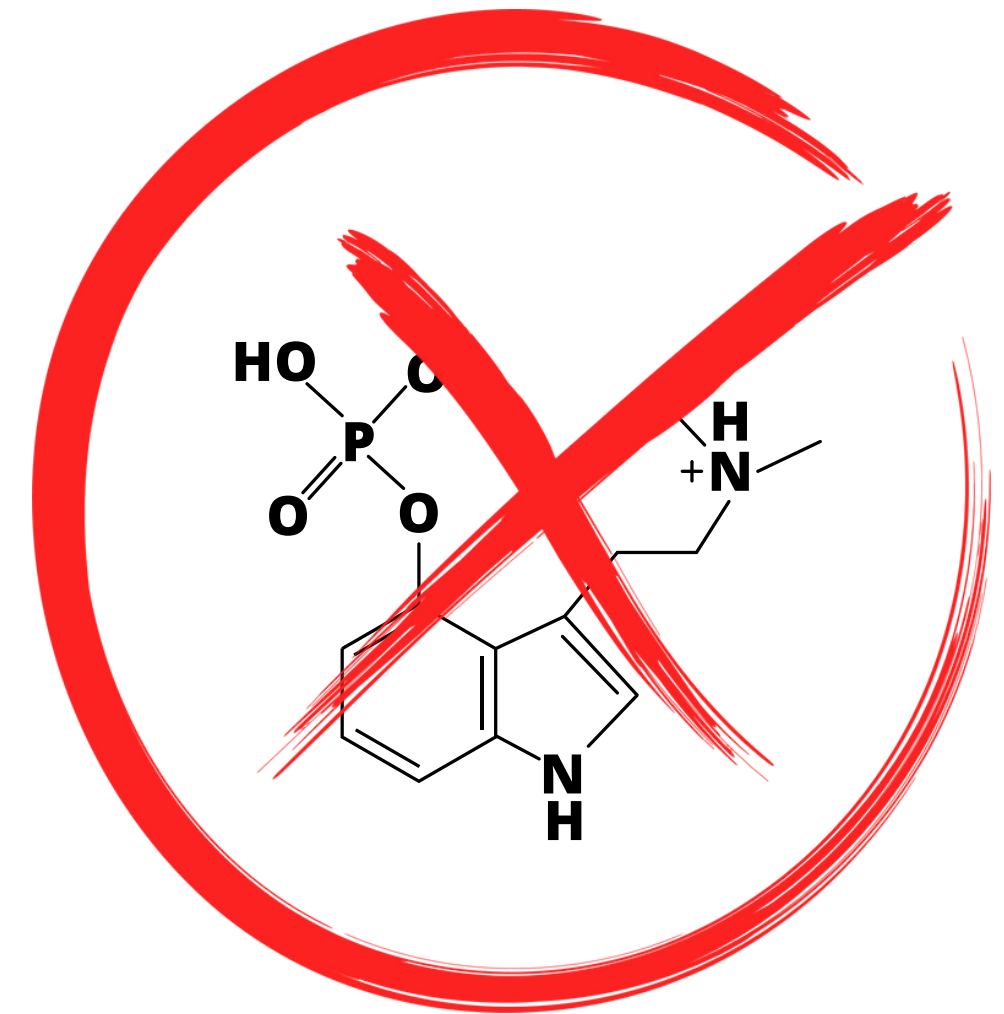
(Forrer & Goldner, 1951; Pennes, 1954; Cholden et al., 1955; Liebert et al., 1956; Clark & Clark, 1956; Sokoloff et al., 1957; Machover, 1960; Jørgensen et al., 1964)

Mescaline



DMT

(Böszörményi & Szára, 1958)



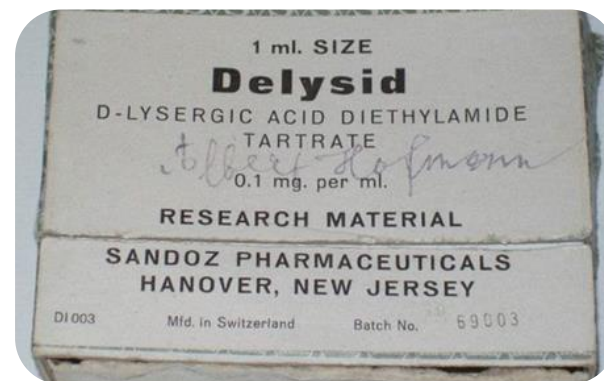
No study of psilocybin in Schizophrenia

What were these early studies like? Some examples

Many drugs, in a short amount of time

2 to 3 days between administration

LSD



Methamphetamine Injected



Injected mescaline



Pennes, 1954



Very high doses

Hoch & Catell, 1952

6 micrograms per kilogram

Average male:
~ 420 micrograms

repeated dosing

day 1 ~ 100 µg

day 2 ~ 200 µg

day 3 ~ 300 µg

day 4 ~ 400 µg

day 5 ~ 500 µg

Cholden et al., 1955

Some were in more supportive context

Group therapy



Abramson et al., 1958

“Top Quality” Science ~ an example

Manchover & Liebert, 1960

Different Dosages

“Thus, in attempting to achieve equivalence of LSD stimulation our schizophrenics received much higher doses than our normals. Fourteen patients received 100 μ g, 1 received 150 μ g, and 3 received 200 μ g. Of our normals, fifteen subjects received 40 μ g, and 3 received 25 μ g.”

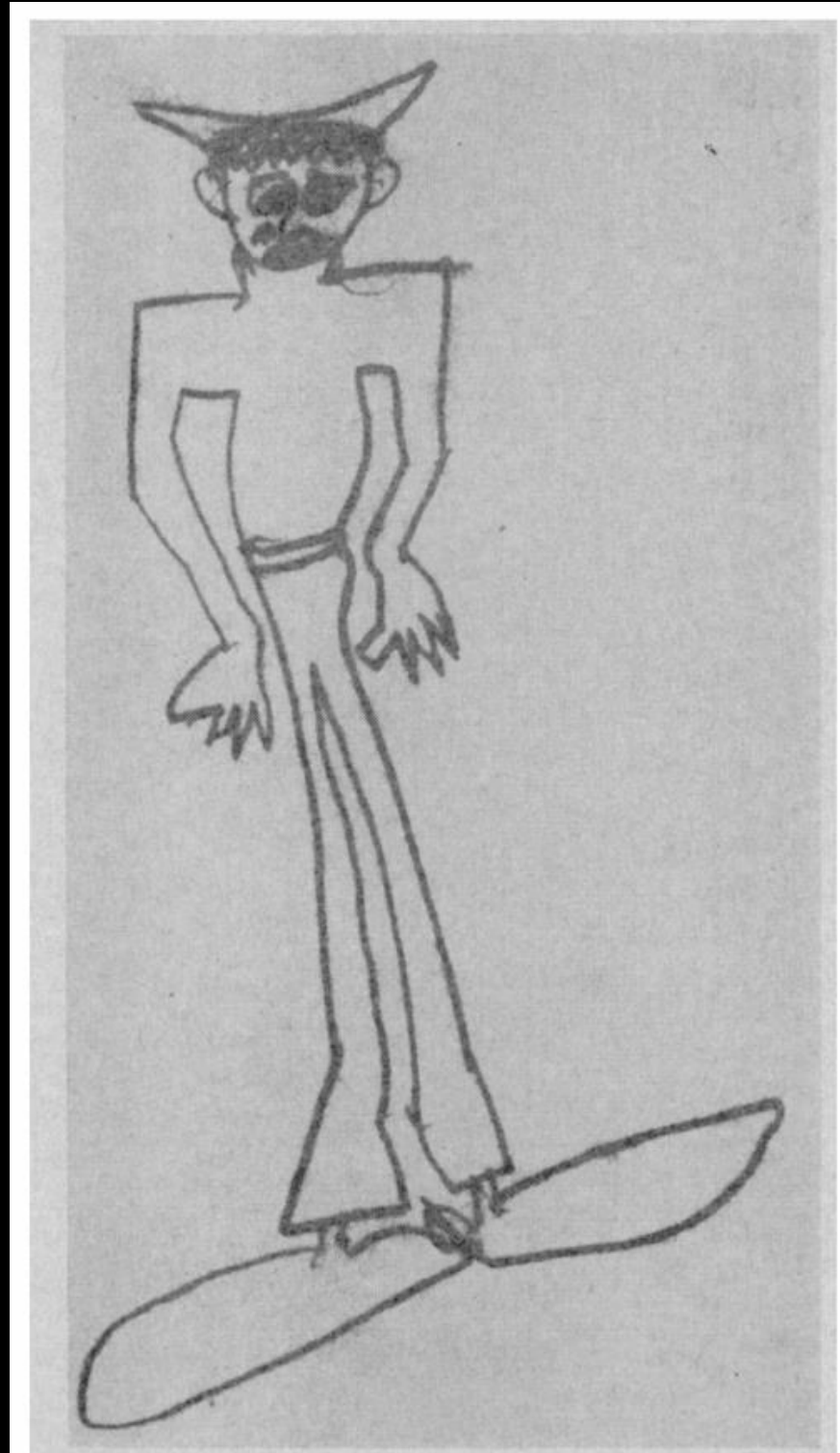


Fig. 5.—Male figure drawn by a schizophrenic man after being given a placebo.

placebo

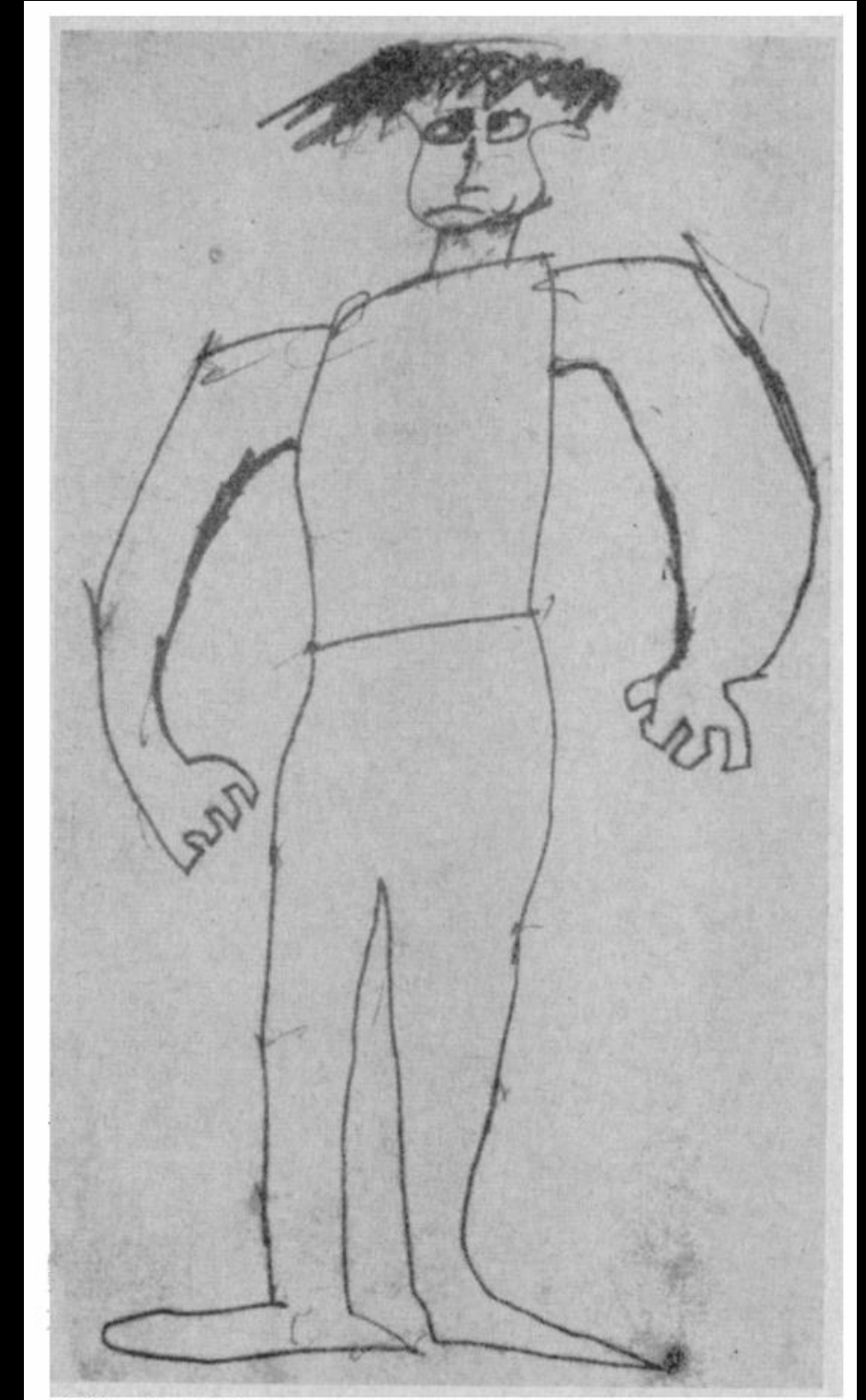


Fig. 8.—Male figure drawn by a schizophrenic man after receiving LSD.

LSD

Differences in Diagnostic Criteria

Pseudoneurotic Schizophrenia

(Hoch & Polatin, 1949)

Personality disorder? OCD? A mix?

These conditions have different risk profiles
(Marrocu et al., 2024)

Example of “pseudoneurotic schizophrenia”

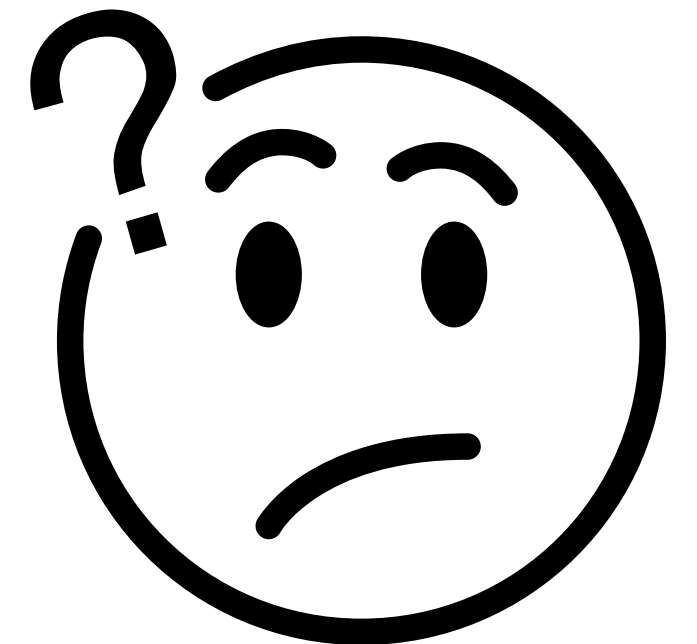
“I have fears of food; I have fears of something happening to my family; I cannot sleep; I get depressed; I become tense, anxious, and agitated.”

She was co-operative and pleasant during the interview and her conversation was relevant and coherent. Her affect showed tension with considerable anxiety and moderate depression. **She denied hallucinations or delusions, and she was well oriented in all spheres.**”

“Schizophrenic” was often used as broader adjective

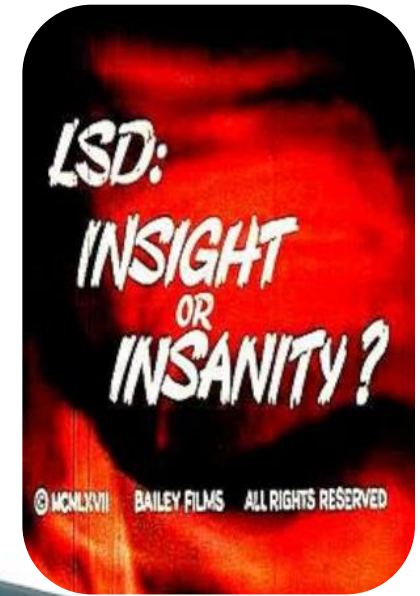
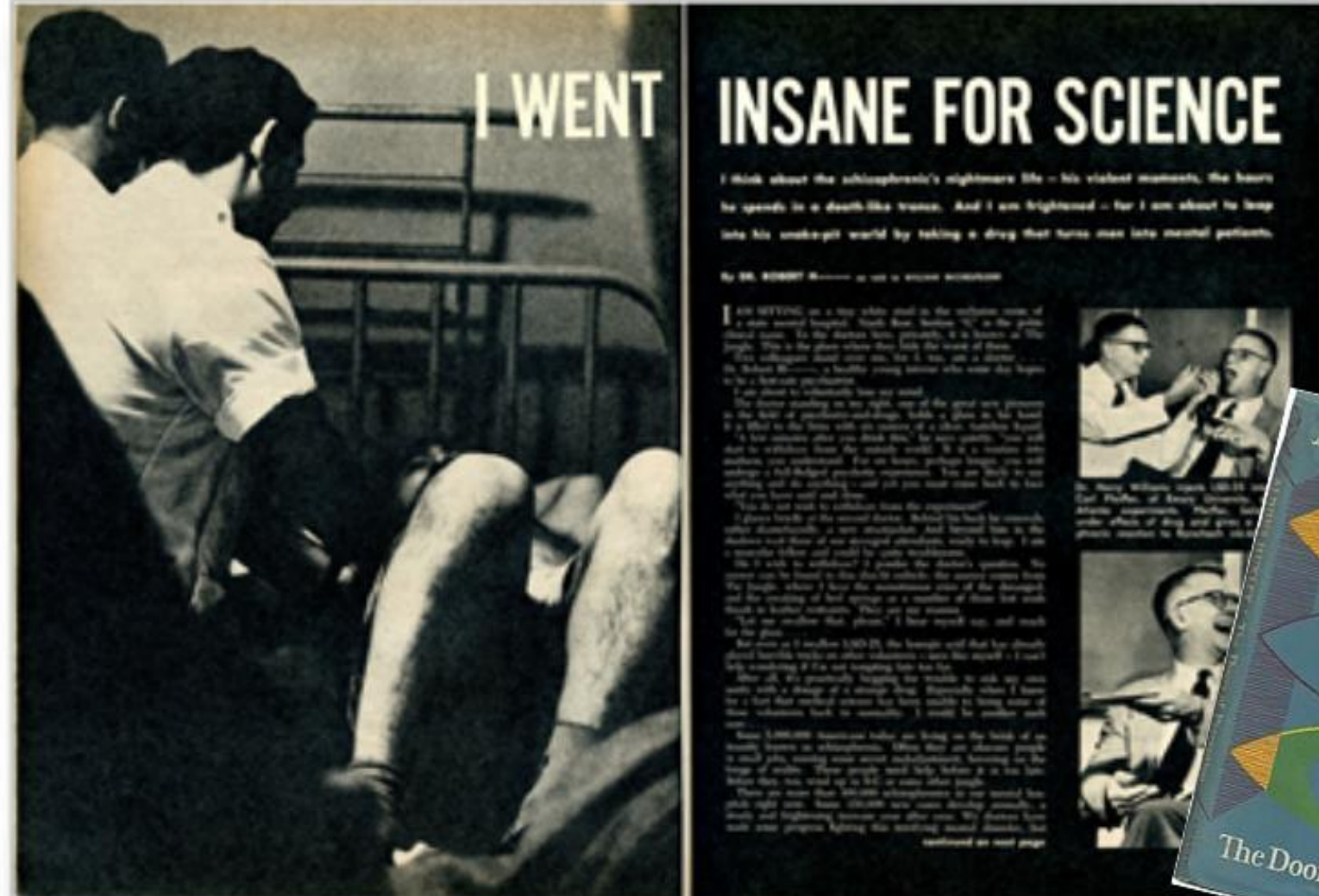
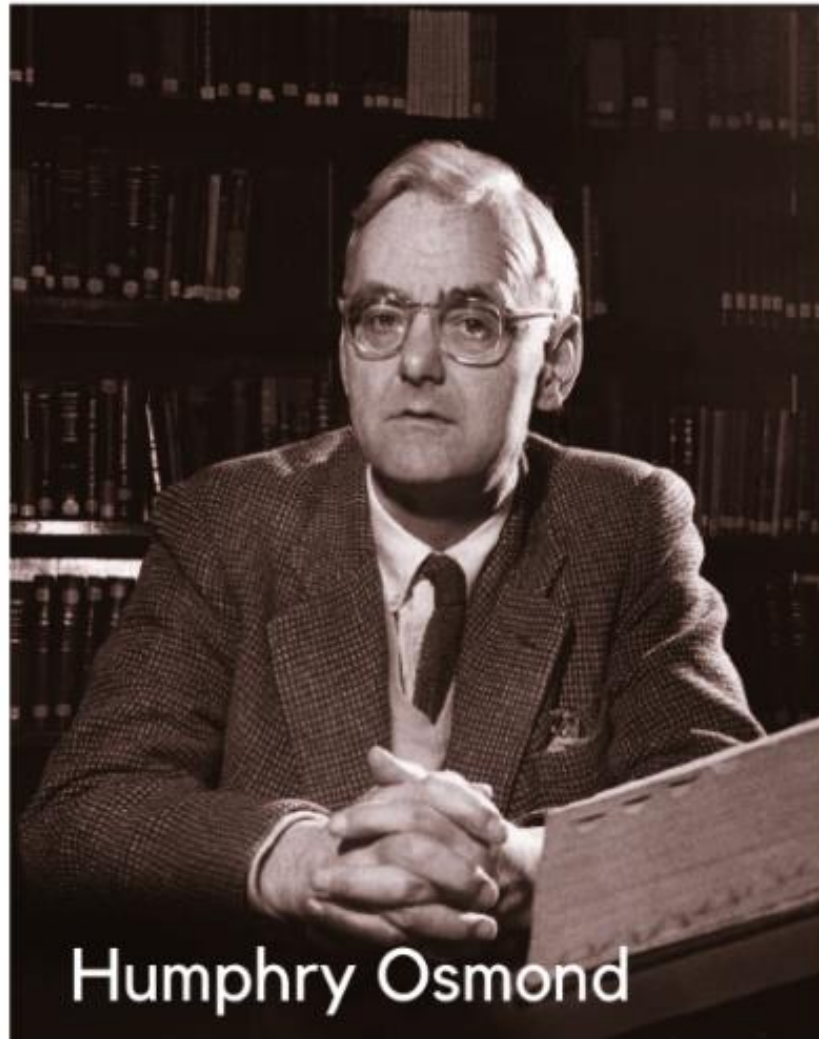
“It is undeniable that the drug precipitates an overt schizophrenic psychosis in some individuals in whom pseudoneurotic schizophrenia is diagnosed. However, these overt psychotic responses produced in pseudoneurotic schizophrenics will have to be qualitatively and quantitatively differentiated from schizophrenic-like clinical pictures in so-called normals under the drug. We feel that in a number of instances we are able to differentiate between schizophrenic-like responses in normals and overt psychotic reactions in pseudoneurotics, but not invariably .”

Can we really tell what is going on in these early studies?



"Try-it-yourself" Schizophrenia

"All models are wrong, but some are useful" - George Box



"LSD-25, used as a psychotomimetic, allows us to study these problems of communication from the inside and learn how to devise better methods of helping the sick" - Osmond (Tanne et al., 2024)

Dourron et al., 2022; Siff, 2015 for an overview of history

A 1950s Guide to How Psychedelics Explain

Psychosis

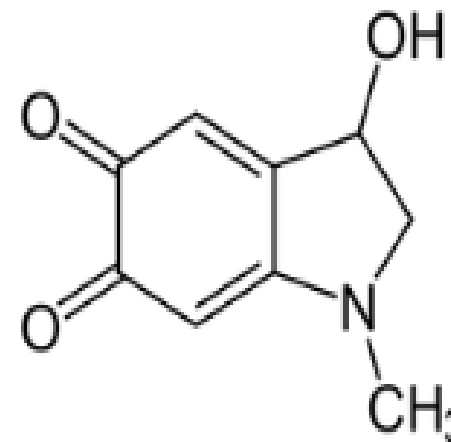
SCHIZOPHRENIA: A NEW APPROACH.

By HUMPHRY OSMOND, M.R.C.S., D.P.M.,

and

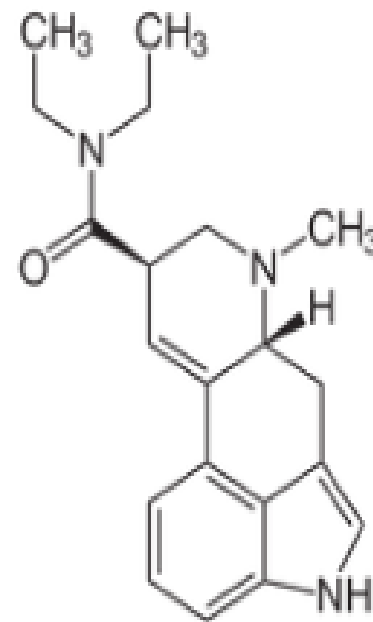
JOHN SMYTHIES, M.B., B.Ch.

From the National Hospital, Queen Square, W.C.1.



Adrenochrome

+



+

Both Chronic & Acute

=

↓ response to LSD

Cholden et al., 1955; Cline & Freeman,
1956; Krus, 1963

↓ response to DMT

Böszörményi & Szára, 1958

Active in
low doses

↓ Response in

Schizophrenia
Due to "tolerance?"

A Biological
Basis of
Schizophrenia?*

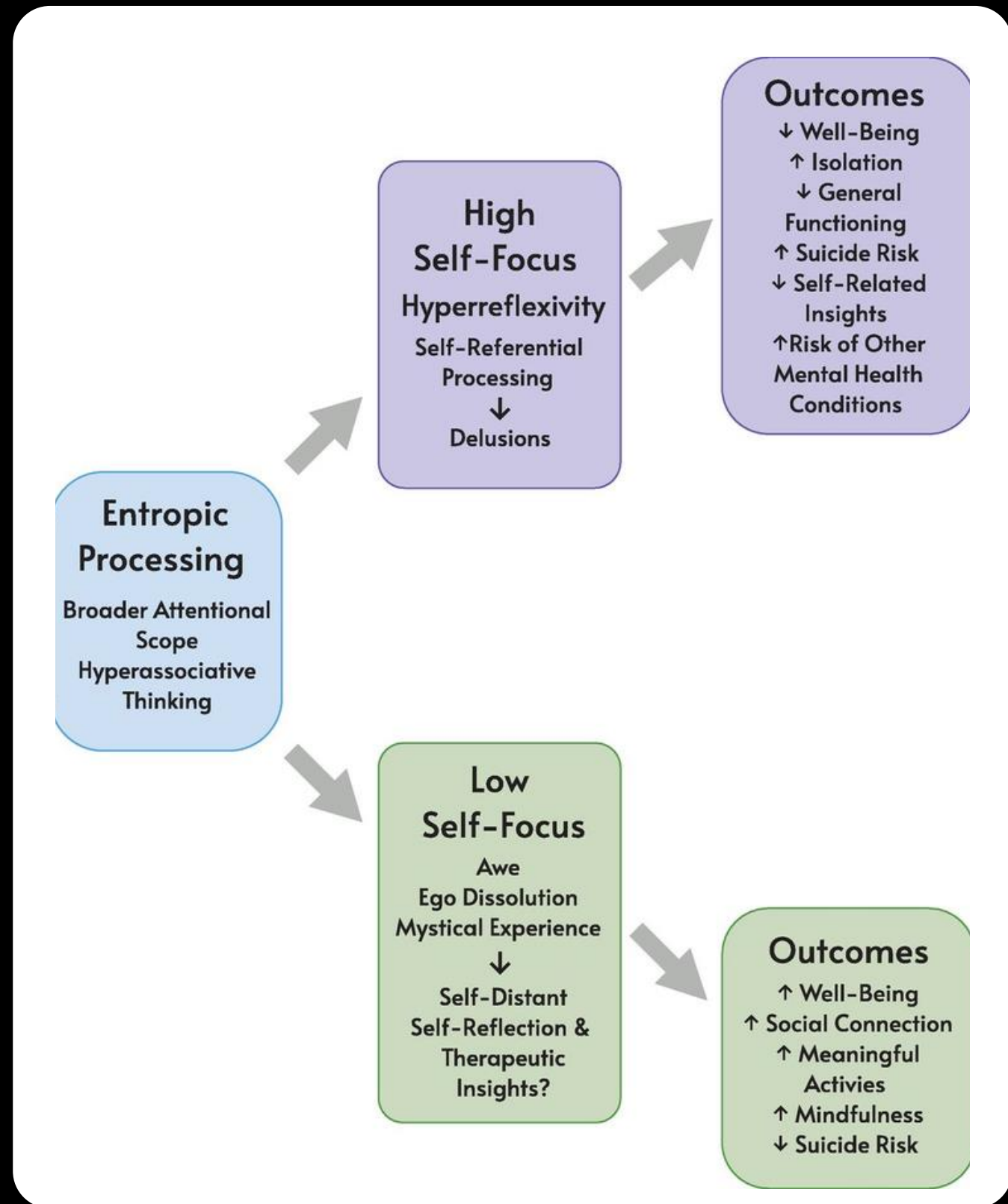
"a metabolic
redefinition of
schizophrenia as
something like
diabetes"

(Tanne, 2004)

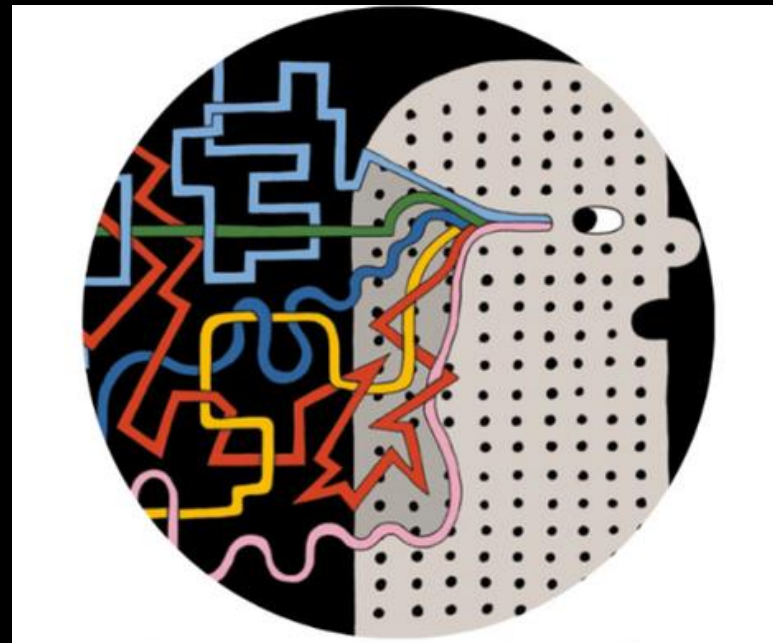
Like Endogenous
Neurotransmitters

Theories of Psychedelics Mechanism of Action have long relied on Comparison to Psychotic Disorders

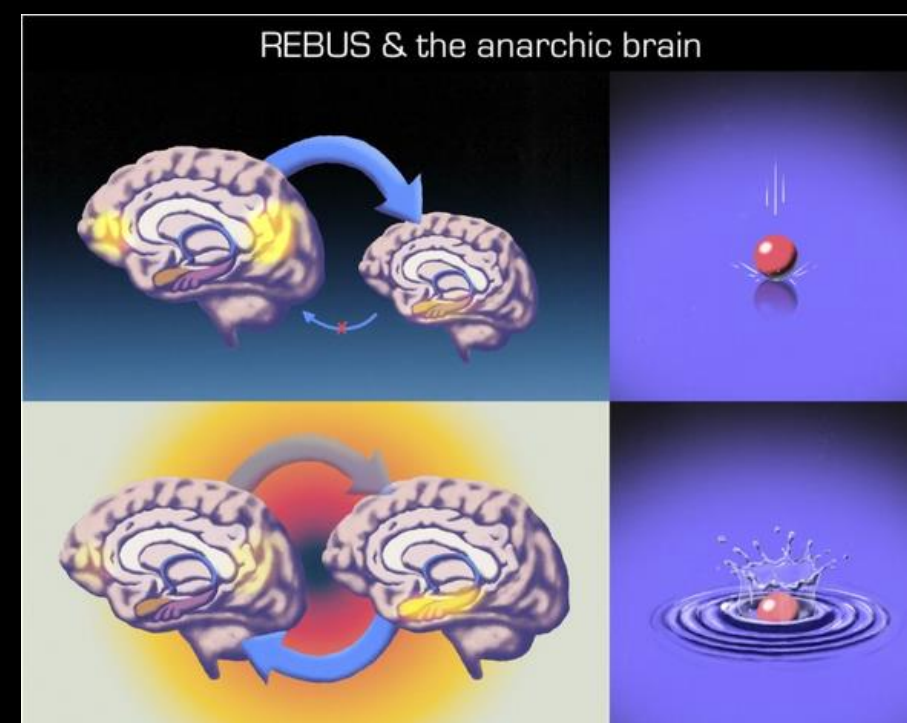
Self-Entropic Broadening Theory



Dourron et al., 2022

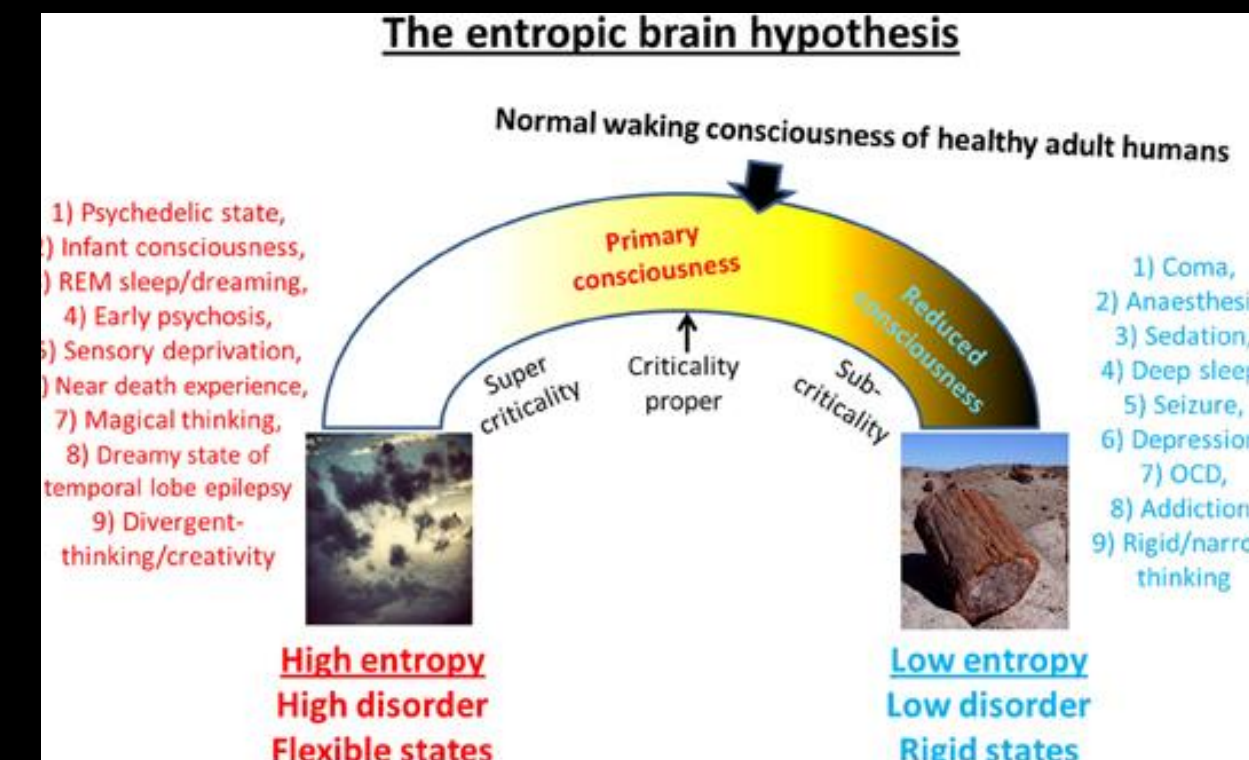


Thalamic Gating Theory
(Vollenweider et al., 2008;
Vollenweider & Smallridge, 2022)



Pivotal Mental States

Brouwer & Carhart-Harris, 2020



What we learn...

Psychedelics have been
given to people with
psychotic disorders

It's not clear how psychedelic became
associated with severely worsening psychotic
symptoms

How do people with
psychotic disorders
respond to psychedelics?



Qualitative Study

Experiences with Classic
Psychedelics after a
Non-Affective Psychotic Disorder

2 Interviews

Focused on Impact

Describing Impactful Experiences with

Psychosis & Psychedelics

Both **Negative** & **Positive**

Long-Term Impact

Comparison

Similarities? Differences?



Drug	Lifetime Use	Frequencies Among users median, [range]
Psilocybin	18 (94.7%)	12, [1 – 132]
LSD	17 (89.5%)	12, [1 - 50]
DMT	11 (57.9%)	3, [1 - 200]
Analogue (e.g., 1P-LSD)	8 (42.1%)	5.5, [1- 100]
Ayahuasca	2 (10.5%)	1.00 [1]
Peyote/San Pedro	3 (15.8%)	2.50 [2 - 3]
5-MeO-DMT	3 (15.8%)	3.00 [1- 50]

Clearly, a bunch of psychonauts



Drug	Lifetime	Year	Month
ECigarette/Tobacco	17 (89.5%)	12 (63.2%)	11 (57.9%)
Cannabis	19 (100.0%)	11 (57.9%)	6 (31.6%)
MDMA	14 (73.7%)	6 (31.6%)	1 (5.3%)
Benzodiazepines	14 (73.7%)	5 (26.3%)	2 (10.5%)
Ketamine	12 (63.2%)	5 (26.3%)	0
Opiates/Opioids	10 (52.6%)	3 (15.8%)	2 (10.5%)
2C-x series	9 (47.4%)	0	0
DXM	9 (47.4%)	2 (10.5%)	0
Cocaine	9 (47.4%)	2 (10.5%)	1 (5.3%)
Diphenhydramine	6 (31.6%)	0	0
Methamphetamine	7 (36.8%)	2 (10.5%)	1 (5.3%)
Salvia	5 (26.3%)	0	0

Demographic & Mental Health History

n = 19 mostly white (79%), males (79%),
average age 31

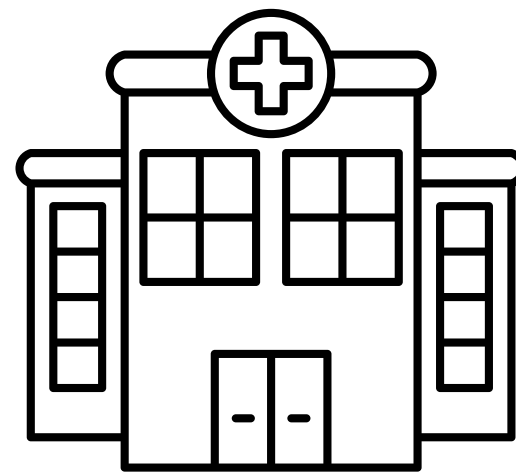
International sample: American, Canadian, German, British,
Swedish, Danish, Bulgarian, Czech

history of
antipsychotic use



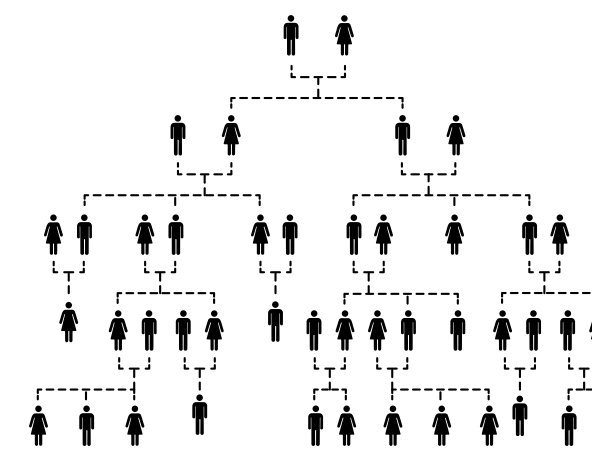
17 (89.5%)

history of mental
health hospitalization

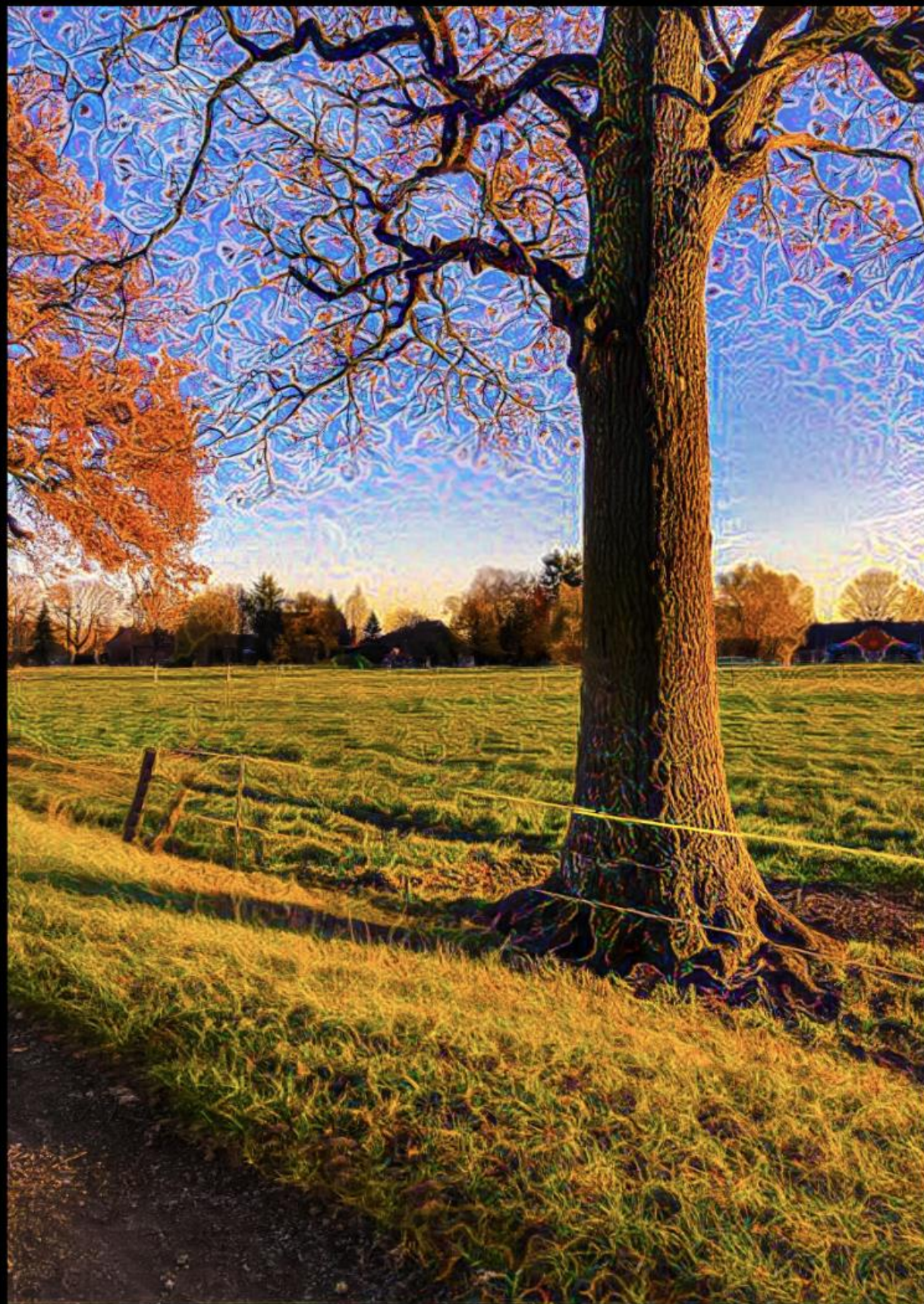


13 (68.4%)

Family history of
psychosis



8 (42.1%)

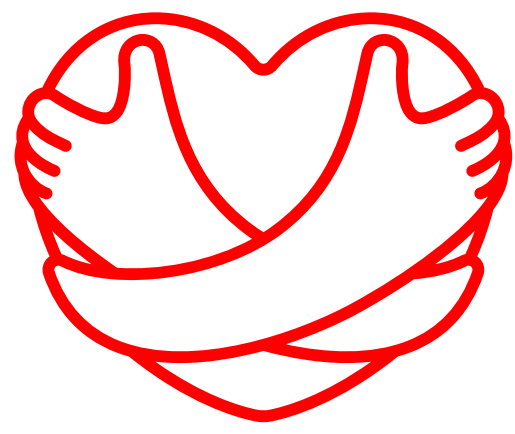


During

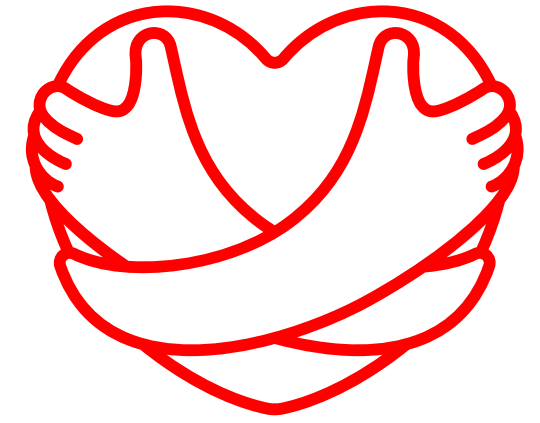
Both positive & negative acute experiences but within the scope of "normal"

Logistic Notes

- **Participants did mention briefly stopping their medication prior to having an experience**
- **Some did report use during the acute episodes**
- **Most impactful experiences were not in the acute effects of psychosis**



Self-Compassion & Reduced Shame

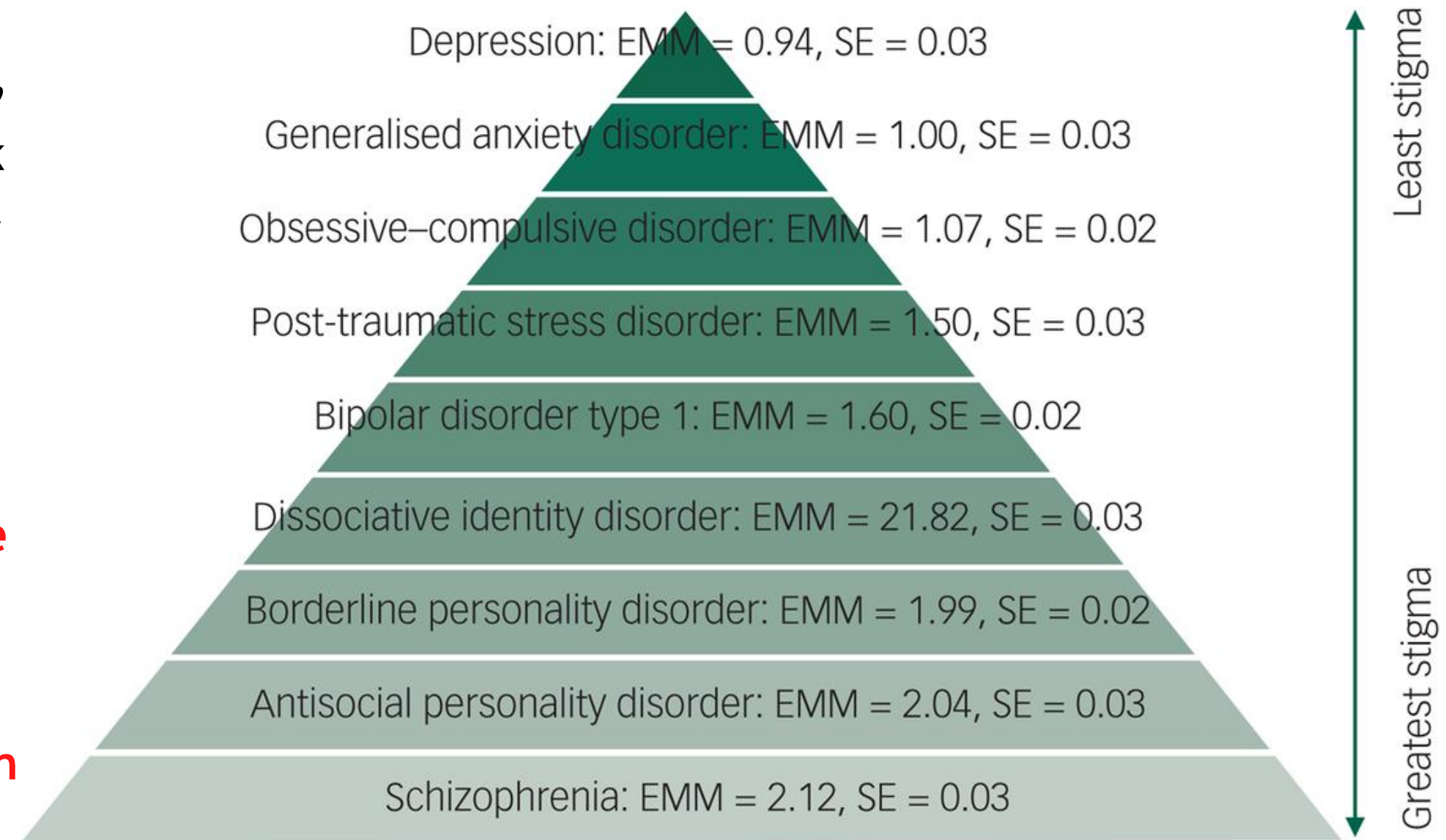


“And a big thing it helped me with, I guess, is one **not feeling ashamed about what I've gone through.**

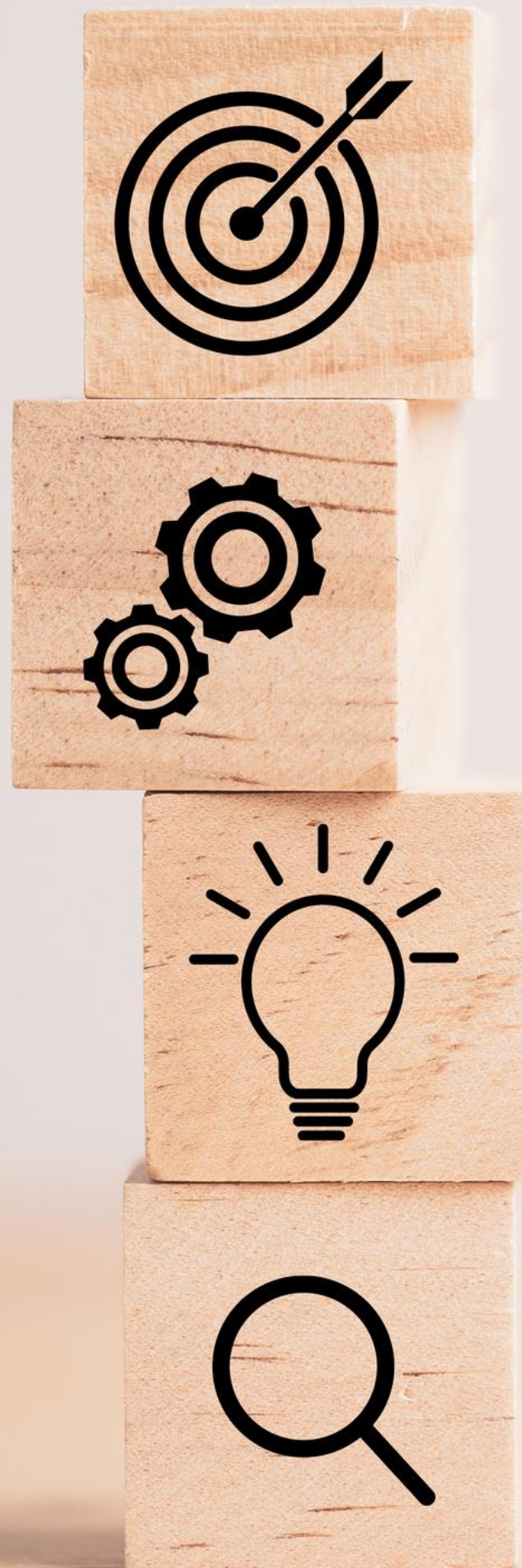
Because typically, you know, if you meet somebody tell ya, “Oh, I've had psychosis, I've been, you know, crazy.” You know, many people they're going to look at you and sort of think, oh, this person's been crazy before... I have this idea of, “Oh, am I tainted person?”

And I guess DMT helped me sort of, you know, come to the conclusion that, no, I'm not, you know, I just went through something negative, it doesn't mean I'm ruined as a person, it doesn't mean that I'm worth less now or anything, I shouldn't see myself like that. And so that's the biggest thing it helped with.” - Ian

Important for the most stigmatized condition



Hazell et al.,
2022



Increased Motivation Lifestyle Changes

“When I think back to a certain period of my life, where I was, I was able to keep a consistently stable schedule. I was going to work every day. I went out on the weekends, created art, meditated, exercised, and breathed. That period of my life was marked by pretty consistent use of LSD and magic mushrooms intermittently.” - Harry

ACUTE PSYCHOSIS ~ PSYCHEDELIC USE

"When I did DMT during the psychosis, I had a trip that told me I need to go to the doctor because I'm trusting my mind. And, you know, my mind being the source of information that I'm getting stuff from isn't reliable, it doesn't make sense... and that's why I went to the doctor, and that's when I got help, and I started taking antipsychotics and, I'm fine now."

"I did actually have an LSD trip when I was still early on in the psychosis buildup period. And not only myself, but my partner and others around me, said that I was very lucid, and almost like disengaged temporarily from the amount of psychosis I was going through. And after I exited the psychedelic state, I went right back to it."



Insight

“When whenever I hallucinate now, I'm very aware of reality and it just doesn't seem to bother me. Before, I'd look for reassurance and someone else to see if they heard the same thing as me.

But now, I don't bother because I know what I just experienced wasn't real. I'm aware of what's a hallucination now. So, yeah, it's definitely having a positive impact on my life, definitely. [W]hen you're able to have insight, it definitely reduces the distress.”

- Ben



“I actually didn't really feel attached to the whole delusional narrative. And I decided, like, even if it's possible that that's a true narrative, I think I should just act confident around them and act like normal. And then I started doing that and it just kind of like shifted everything. Like, everyone was like treating me more normal, the more that I acted normal...And I basically escaped the loop of that situation” – Greg

More about Hallucinations & Psychedelics

Table 5. Interaction Effects Between Lifetime Psychedelic Use and Psychotic/Bipolar Disorder History on Psychotic Symptoms

Scale	Lifetime Psychedelic Uses x Psychotic Disorders (Personal History)		Lifetime Psychedelic Uses x Psychotic Disorders (Family History)		Lifetime Psychedelic Uses x Bipolar Disorder (Personal History)		Lifetime Psychedelic Uses x Bipolar Disorder (Family History)	
	Unadj β (p -value)	Adj β (p -value)	Unadj β (p -value)	Adj β (p -value)	Unadj β (p -value)	Adj β (p -value)	Unadj β (p -value)	Adj β (p -value)
MIS	0.018 (0.677)	-0.075 (0.739)	-0.002 (0.963)	-0.159 (0.260)	0.011 (0.801)	-0.052 (0.552)	0.050 (0.242)	-0.011 (0.889)
RTS	-0.078 (0.069)	-0.312 (0.165)	0.006 (0.889)	0.048 (0.731)	-0.075 (0.079)	-0.076 (0.386)	-0.008 (0.855)	0.051 (0.525)
SNS	-0.024 (0.583)	-0.305 (0.158)	0.008 (0.843)	0.017 (0.898)	-0.064 (0.132)	-0.017 (0.842)	-0.024 (0.583)	-0.006 (0.934)
CAHSA	0.001 (0.980)	-0.545 (0.017)	-0.032 (0.460)	-0.188 (0.190)	-0.011 (0.796)	-0.037 (0.678)	0.003 (0.949)	0.028 (0.732)

Abbreviations: Unadj, unadjusted; adj, adjusted; MIS, Magical Ideation Scale; RTS, Referential Thinking Scale; SNS, Self-evaluation of Negative Symptoms; CAHSA, Continuum of Auditory Hallucinations-State Assessment. Significant β coefficients are bolded ($p < 0.05$).

Psychedelics Associated with Fewer Hallucinations

Estimated lifetime psychedelic use occasions was associated with lower CAHSA scores in those with psychotic disorders
($n = 62$, $\beta = -0.539$, $p = 0.009$)

How?

Improved Sensory Integration?

Changes in connectivity with SN-thalamic regions? Avram et al., 2022

Also suggest HPPD and psychotic-related hallucinations are distinct



Context Matters

like people without a history of psychosis, setting matters

“So I make a beautiful atmosphere in my room, I put some candles, some oils, I put in the floor like a very warm and cozy things.

And I put the playlist of this guy and then he was amazing because it was quite quick when it, when that started to kick. And when it's time to peak, I was still like finishing putting everything together and I felt like I was preparing my spaceship in the moment. Like it started to hit and then I wasn't just seeing me putting everything perfectly for my spaceship”

- Victor



All Drugs can be used Recklessly Including psychedelics

"I had a good one [trip] this Christmas, because me and my best friend, we didn't have no family around. So he came over here with this big toolbox full of drugs. And we went on a four-day acid trip just non-stop for four days. It impacted my mental health very temporarily, but I don't think it had some kind of long-term effects, like making things more messed up or anything like that. So it was just like a really magical Christmas."

Chris



Also included:
meth, cannabis,
opioids



Cases of Seeking Hospitalization During Acute Effects

5 grams of mushrooms

“So I took five, five grams of magic mushrooms and powdered them down and put them in water and just gulped it all down. It was the stupidest thing I ever did. It was really, really dumb. I didn't have a particularly bad trip, but I was just very felt, very much uneasy, just, and then I saw, I got a taxi, and then I went to the mental hospital and asked if I could sleep there for the night, you know, just in case.”

- Dan



Psychedelics are not perfect, including for people with psychotic disorders



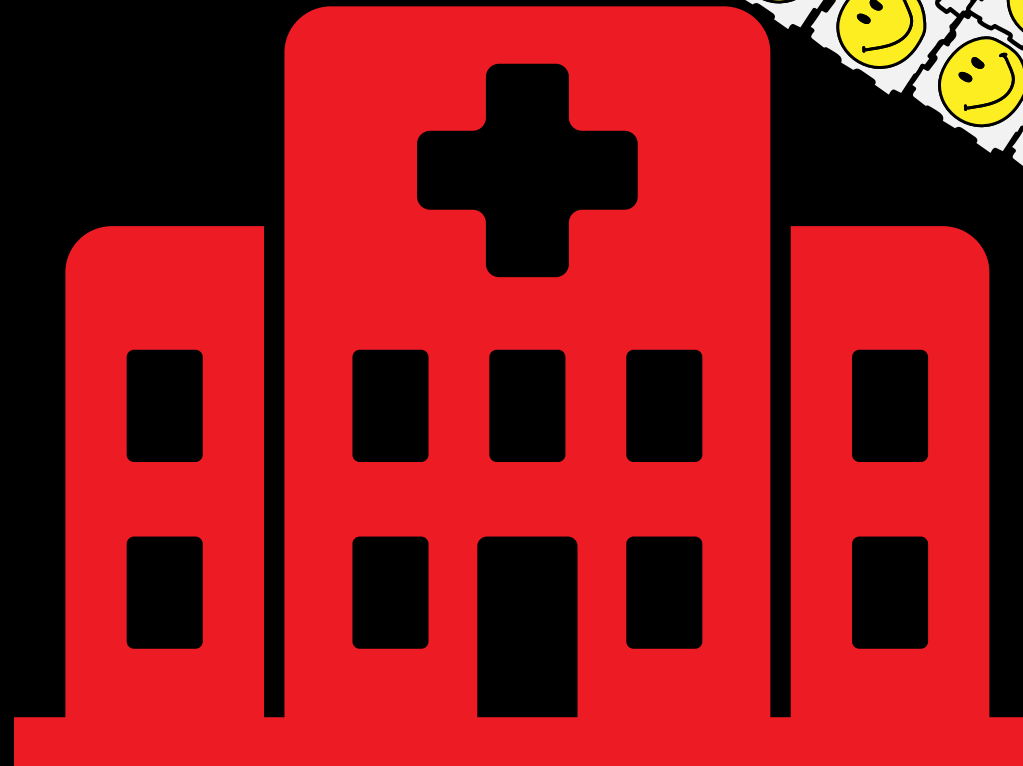
8 tabs AL-LAD

“[T]he one time I got temporarily admitted to hospital on a psychedelic where I because I ended up asking my mom for help. And then she drove me to the hospital and I was temporarily certified. But I was, I was been agitated and wanting to leave. So the.. essentially, the weird thing was, is that he gave me a dose of IM ketamine for a drug agitated state. And I, I pretty much just passed out after a short while after...And then, when I woke up, I was doing so much better than I was able to be discharged, actually was quite strange.” –

Justin

3 Hits & 2C-P

“I learned that I shouldn't take three hits of acid and 2C-P together, and I should just stick to like, lower doses. Um, but yeah, I had, I had some, like, you like pain, like, internal pain that I like, had just seemed like an emergency at the time, which probably wouldn't have happened if I was sober. So yeah, I guess, I guess that counts as a negative effect? I mean, it wasn't really caused, like the physical issue wasn't caused directly by the psychedelics, but I was just so.. tripping so hard that I just like, focused on it.” – George



Take Aways

- high doses
- temporary ~ hours or a day or so

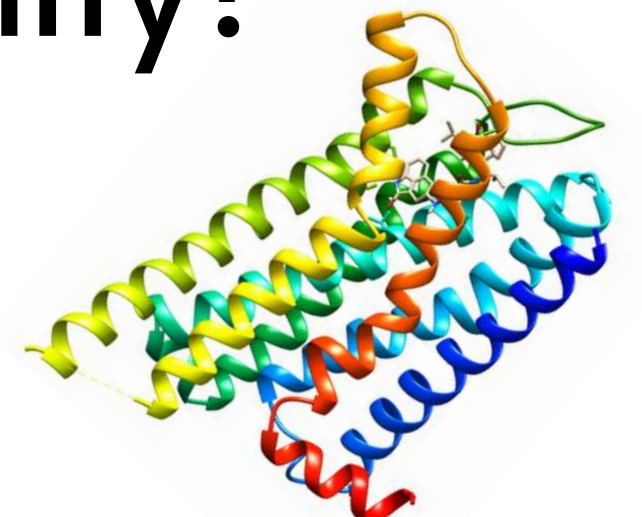


more problematic for
people with manic tendencies?



“I have done LSD during my acute psychosis. And that, it just, it heightened and intensified the feeling of being the son of God, of being Jesus. And it just made me stronger in my delusion, or it made the delusion stronger in a sense, but then when it wears off, then you're sort of back to the psychosis, or you're back to the recovery phase that you were in before, and then you sort of leave the psychedelic behind.” - Danish Dan

**Might LSD be
more
problematic
do to D2
affinity?**



Differences Between Psychosis & Psychedelics

Psychosis

Paradoxical Uneasy Certainty

- Sense of uncertainty that provokes confusion
 - "Anything can happen at any moment"
- Delusions feel "absolutely certain and urgent"
- Lack of ability to control affect

Psychedelics

- Sense of novelty, but also clarity
- Sense of malleability of experience
- "experiences are more predictable and consistent."
- Ability to "choose" affect

Psychotomimetics?

Similarities of Psychosis & Psychedelics

- Both experiences “push the mind to new limits.”
- Experiencing coincidences & synchronicities
- More awareness than typical



Cannabis was described as the drug most similar to psychosis. Worsening of symptoms was frequently noted.

“I guess being more observant or noticing more things, noticing everything that's the same...That there's too much stimulus and you can't filter anything out.”

Laura

Worst than everyday

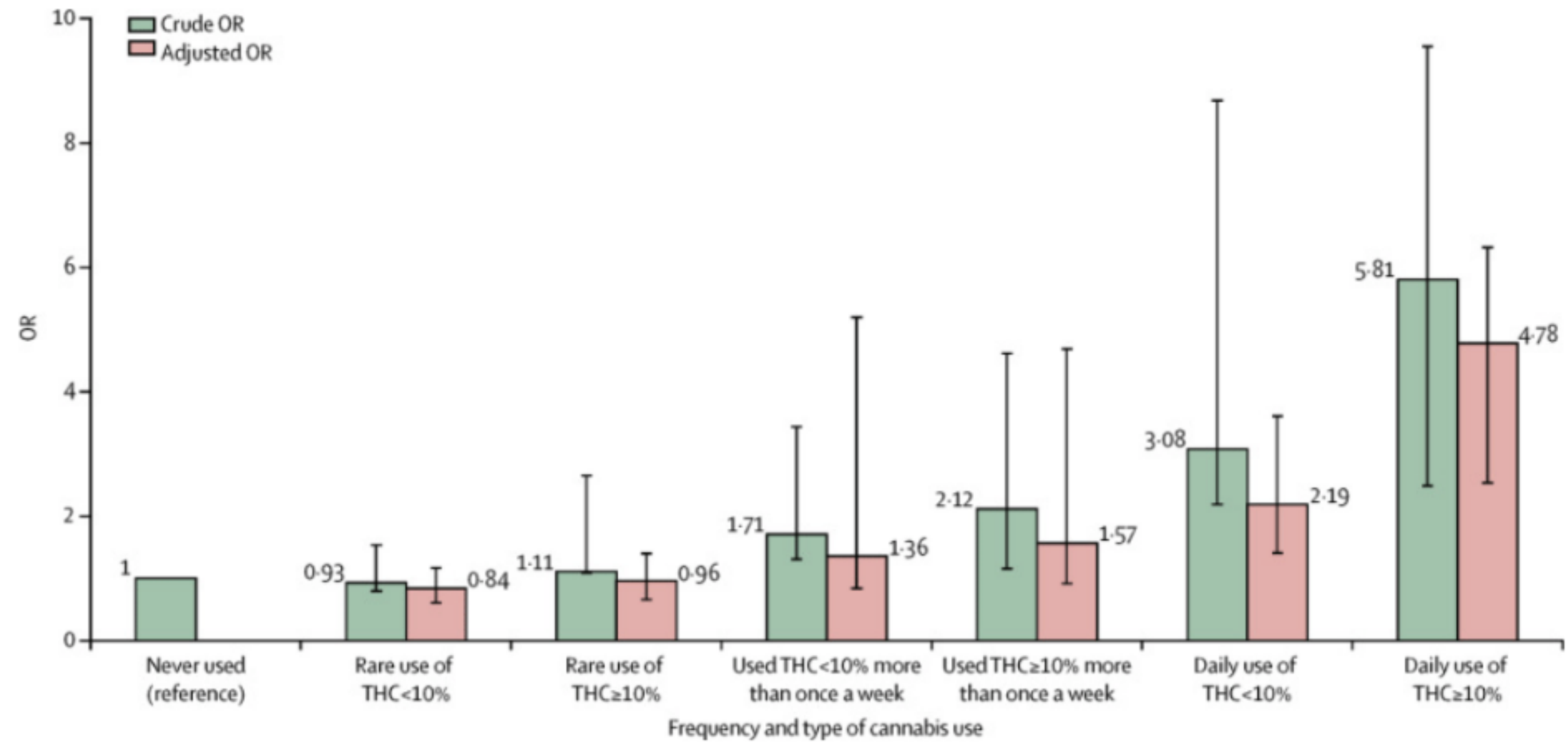
“Just pure THC will be like, way beyond what I experienced every day.” - Maggie

psychosis?

“[I]t's like almost like marijuana brings on psychosis. And I know I'm not supposed to say that because of all those pipe fanatics but I honestly think that might be the case.” - Chris

“It would be even worse than like sober psychosis. It feels like sober psychosis, but like really strong auditory hallucinations and almost like feeling stuff that's not there.” - Robert

Cannabis & Psychosis



Di Forti et al., 2019

People who use high-potency THC daily are at ~ 5X the risk of developing a psychotic disorder

**97.7% of
Psychedelic users
have used cannabis**
Hendricks et al., 2015

**How much might
this explain
psychedelics
"causing"
psychosis?**

Psychedelic Scape Goating

Avoiding Discussing Other Documented Risk

Watch out for a
psychotic break!

Suicidal
Ideation?
Existential Anxieties?
Depression?
Other?



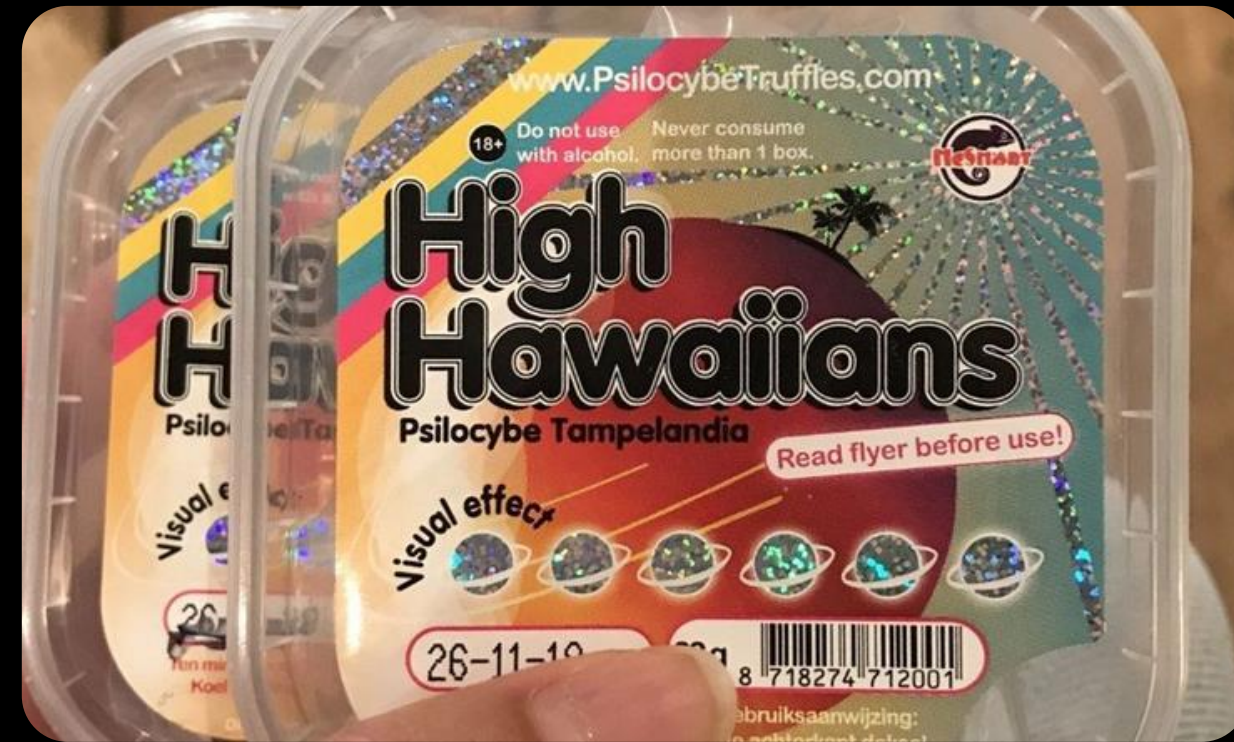
Hallucinogen
Persisting
Perceptual Disorder?
Seizures?
Mania ?

Derealization?

Why care now? Changing Drug Policy

“So, my first classic psychedelic would have been psilocybin. So obviously, being from Europe, it's quite accessible to go to Amsterdam, where it's legal. So I went with my friends, and we were taking truffles and just eating them in a hotel room.” -
British Student

Is legal/decriminalized
access coming to the
US?



“But then I thought I needed something or another. And then I thought, maybe magic mushrooms would be nice. So I bought a magic mushroom grow yourself kit, from Holland. And then I grew some magic mushrooms.” - Danish Dan

The Need for Controlled Experimental Psychedelic Studies in People with Psychotic Disorder

Other drug studies...



Studies should be conducted in highly supportive environments in people with prior use



Lahti et al., 2001:
Malhotra et al.,
1997



THC and vaporized cannabis while
in an MRI
(Whitfield-Gabrieli et al., 2018)

Thank you!

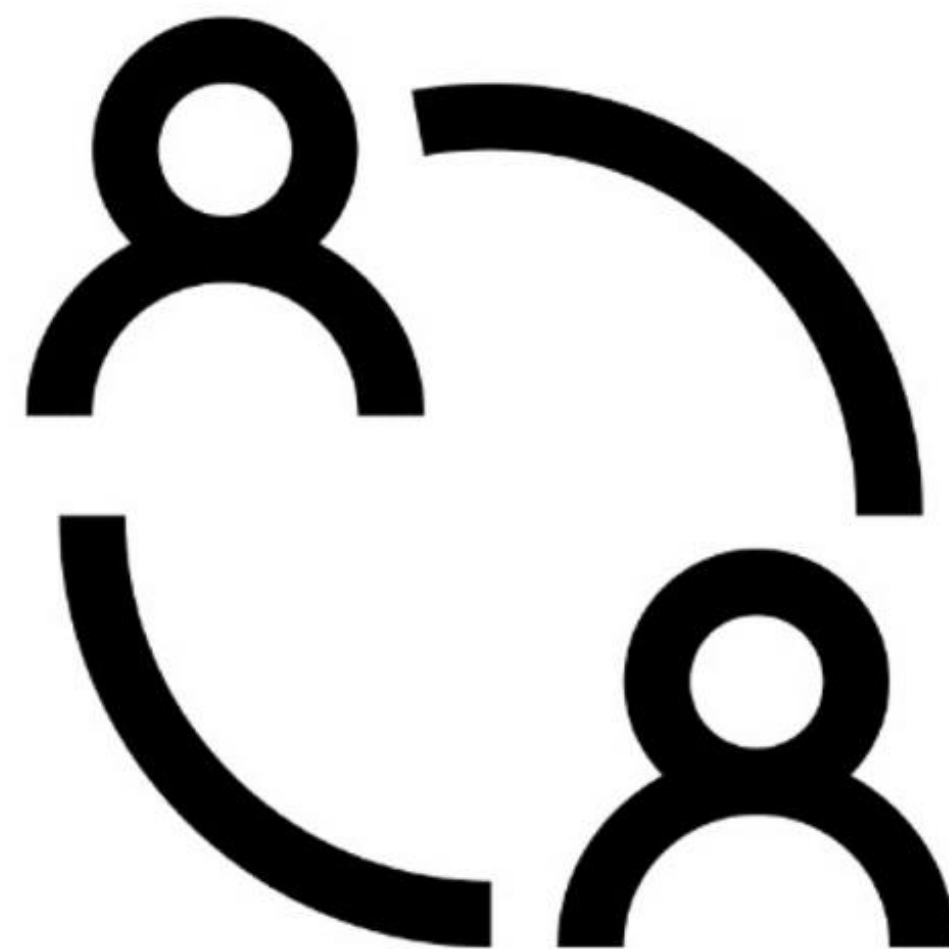
Participants



UAB

**University of Alabama
at Birmingham**

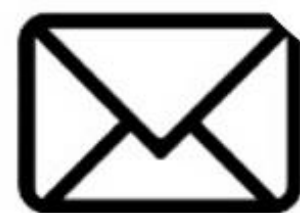
Connect



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ndourron@uab.edu