

GETTING INTO THE WEEDS: NEUROSCIENCE, PSYCHOSIS + CANNABIS

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Conflicts of Interest/Disclosure

I have no biomedical or financial conflicts of interest to disclose.

If one type of treatment or perspective worked for everyone, we would (or should) all be doing that thing or thinking that way.



PHILOSOPHY

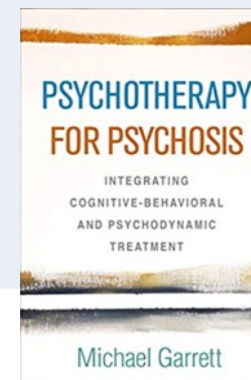
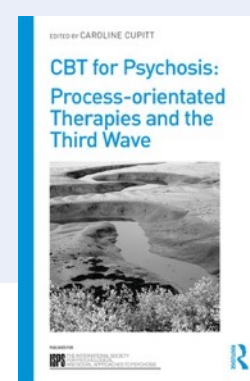
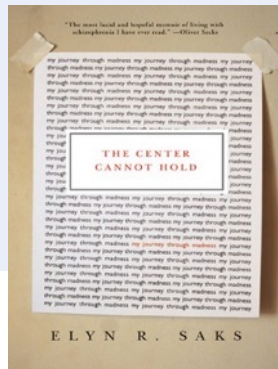
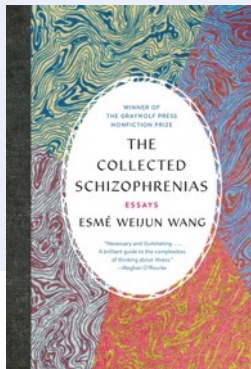
There isn't. We aren't.

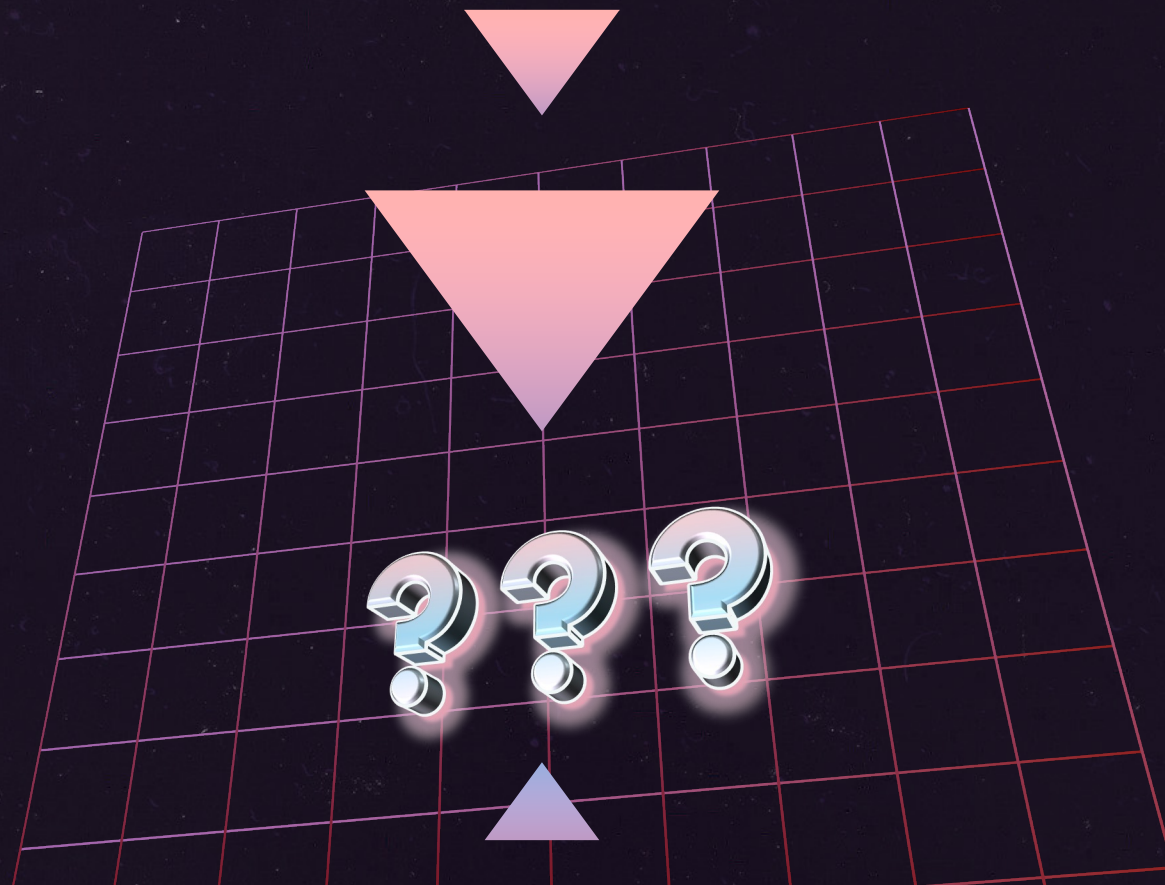
Every person deserves to have access to a form of treatment they find welcoming and interesting offered by people they can trust.

Who am I? Stories. Science. Strategy.

Craigian Usher

- Program Director, Child & Adolescent Psychiatry Training at OHSU
- Kienle Scholar for Medical Humanities through Penn State College of Medicine
- Assistant Editor—Book Forum, *Journal of the American Academy of Child & Adolescent Psychiatry*
- Medical Education Consultant, Oregon Early Assessment & Support Alliance
- Grateful to my colleagues at EASA, specifically Halley Knowles & Megan Sage for inviting me to present today
- 5 Favorite books...about story and choice





When you think about cannabis and psychosis, what
comes to mind?

What questions are you wrestling with right now?

How might our time together help?

CENTRAL OBJECTIVES:

By the end of this session, participants should be able to:

1. Identify three neuroscientific theories which explain the underlying pathophysiology (NOT CAUSE) of psychosis
2. List two major components of cannabis and talk about the general impact of these.
3. Discuss the findings of at least three studies which have explored the link between psychosis and cannabis
4. Describe the findings of studies involving treatment with cannabidiol (CBD) for people with schizophrenia-spectrum disorders
5. Offer to friends, family members, clients, and young people two resources that can help them consider the link between cannabis and psychosis and to guide their decision-making.

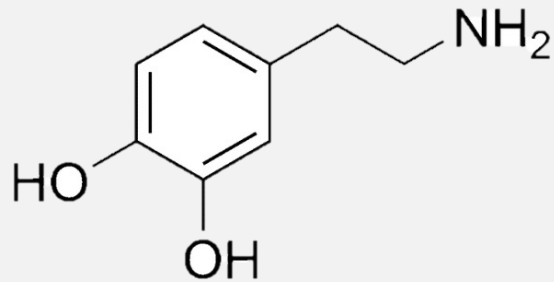


Vocabulary

Three neurotransmitters

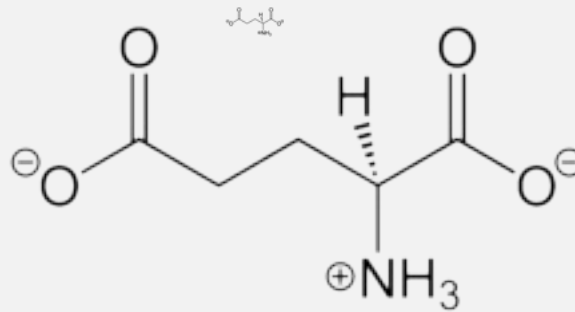
Dopamine

- Dopamine Receptors
- Emotional Salience
- Movement
- Pleasure



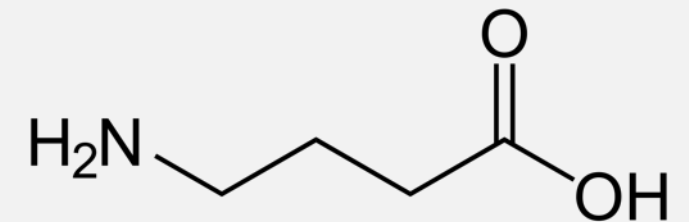
Glutamate

- Excitatory Neurotransmitter
- Synapsis on NMDA, AMPA, kainite, mGluR receptors
- Learning, memory



γ amino-butyric acid (GABA)

- Inhibitory Neurotransmitter
- GABA receptors are modulated by benzodiazepines, barbiturates, alcohol

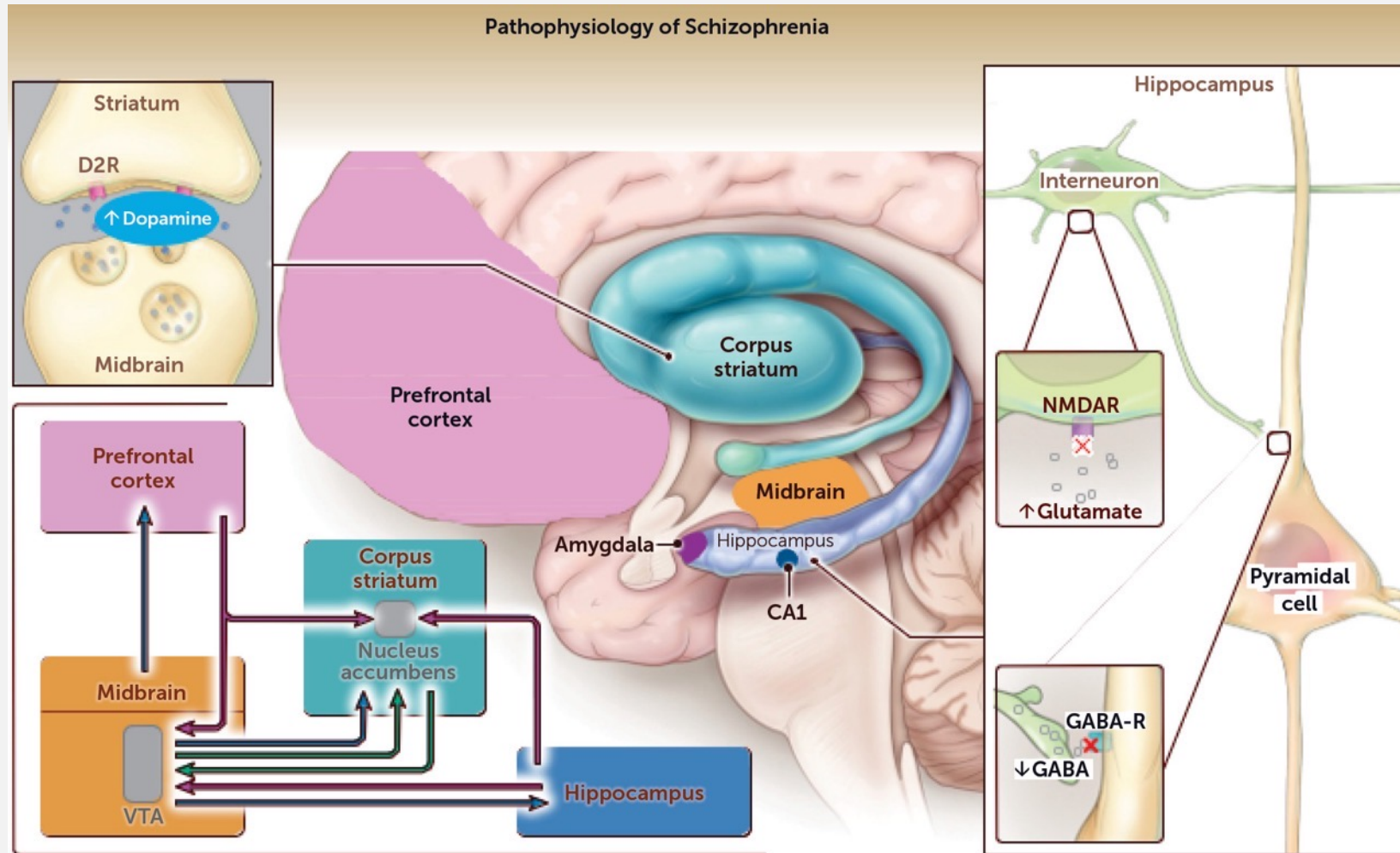


There are
presently three
theories about the
underlying
pathophysiology of
psychosis /
schizophrenia



1. Dopamine Theory
2. Synaptic Pruning / Immune Theory
3. Glutamate & GABA Theory

3 Viable Theories

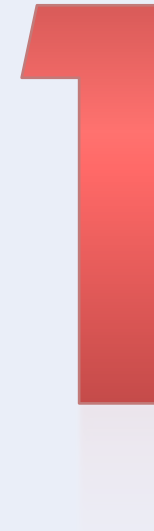


Lieberman JA, Small SA, Girgis RR. Early detection and preventive intervention in schizophrenia: from fantasy to reality. Am J Psychiatry. 2019 Sep 26;176(10):794-810.

DOPAMINE theory

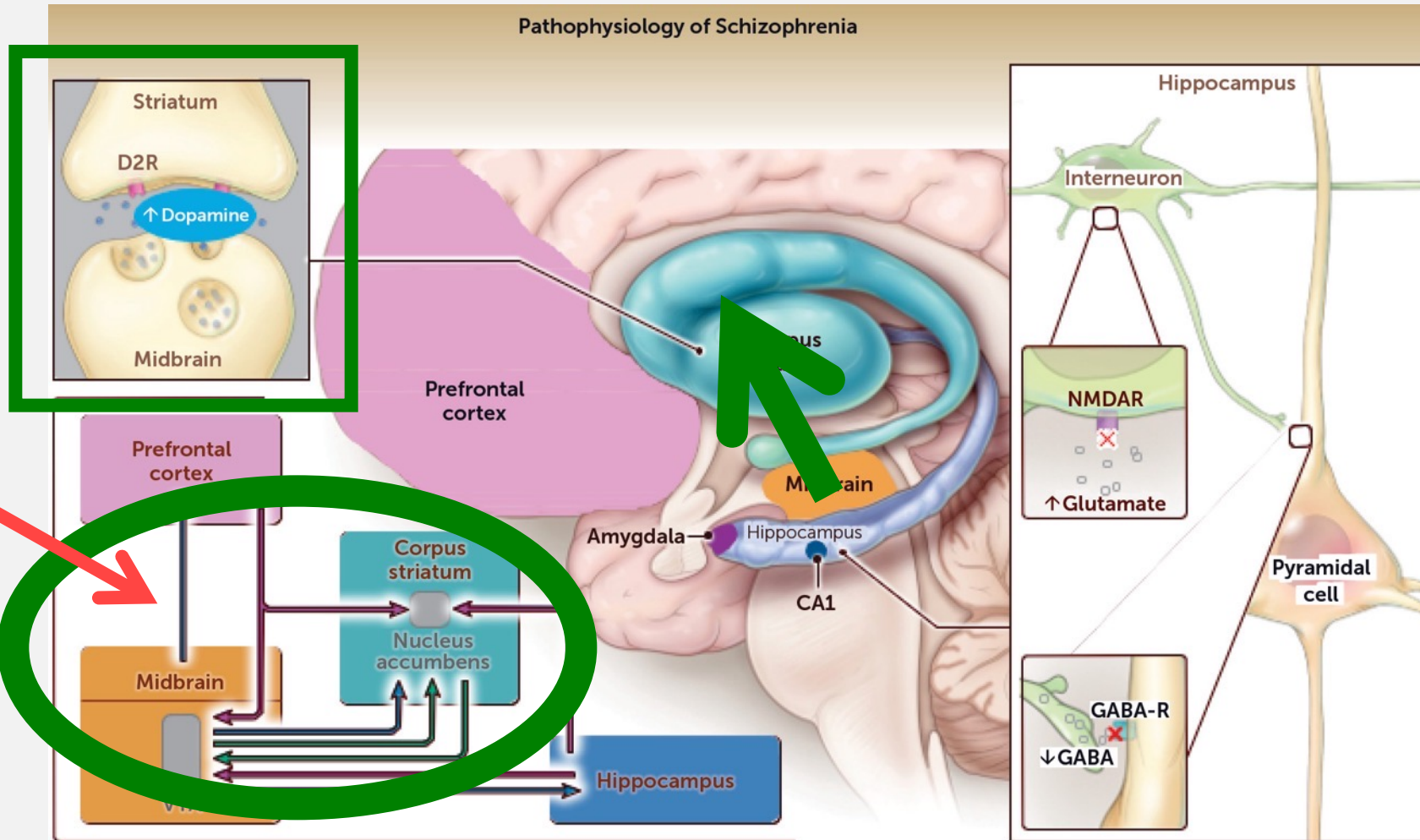
Originally postulated in 1974

- Central idea: abnormal transmission of dopamine including
 - HYPER activity in the mesolimbic pathway (connection between midbrain and nucleus accumbens)
 - HYPOactivity in the mesocortical pathway (connection between ventral tegmentum/midbrain to prefrontal cortex)
- Emotional Salience impacted wherein whispers and glances, internet pop-ups and ambient stimuli progress...
 - Ideas of reference → Delusions
 - Illusions (Auditory, Visual) → Hallucinations



“Positive” Symptoms = too much dopamine in the mesolimbic pathway

“Negative”
Symptoms =
too little
dopamine in
the
mesocortical
pathway



Lieberman JA, Small SA, Girgis RR. Early detection and preventive intervention in schizophrenia: from fantasy to reality. Am J Psychiatry. 2019 Sep 26;176(10):794-810.

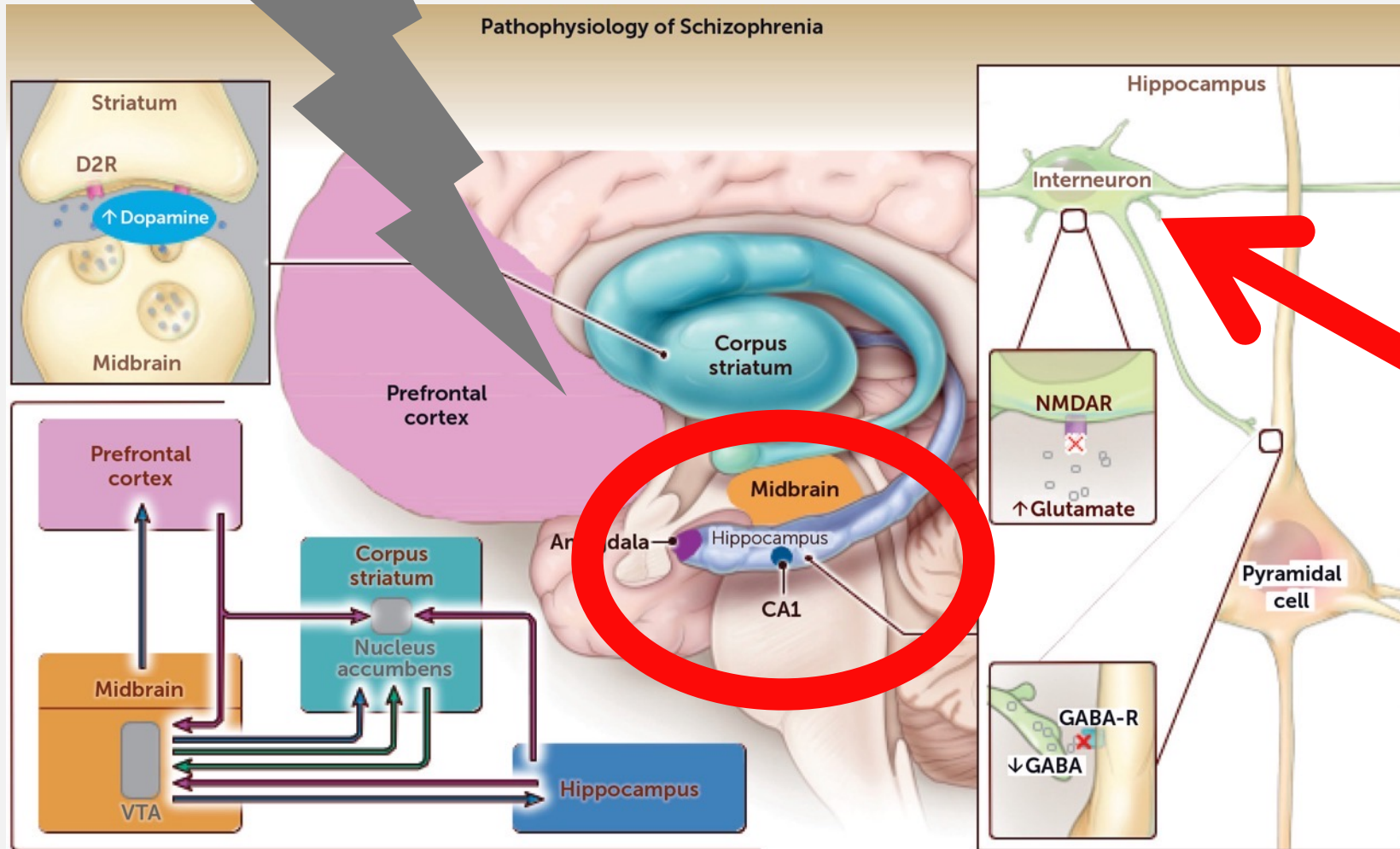
ABNORMAL SYNAPTIC PRUNING / IMMUNE theory

Originally postulated in 1982 and updated in 2016

- Central idea: in young people's teens and twenties, there is a normal reduction in pruning of synapses; in schizophrenia-spectrum disorders, this is hyperactive.
- Complement genes are transcribed and create proteins (called complement) that help recruit the immune system to fight infection; they are also used to help clear out synapses that are not useful
- Complement C4 may activate microglia to attack key areas of the brain, including the hippocampus



ABNORMAL SYNAPTIC PRUNING theory



LOSING
THESE
IMPORTANT
INHIBITORY
NEURONS

Lieberman JA, Small SA, Girgis RR. Early detection and preventive intervention in schizophrenia: from fantasy to reality. Am J Psychiatry. 2019 Sep 26;176(10):794-810.

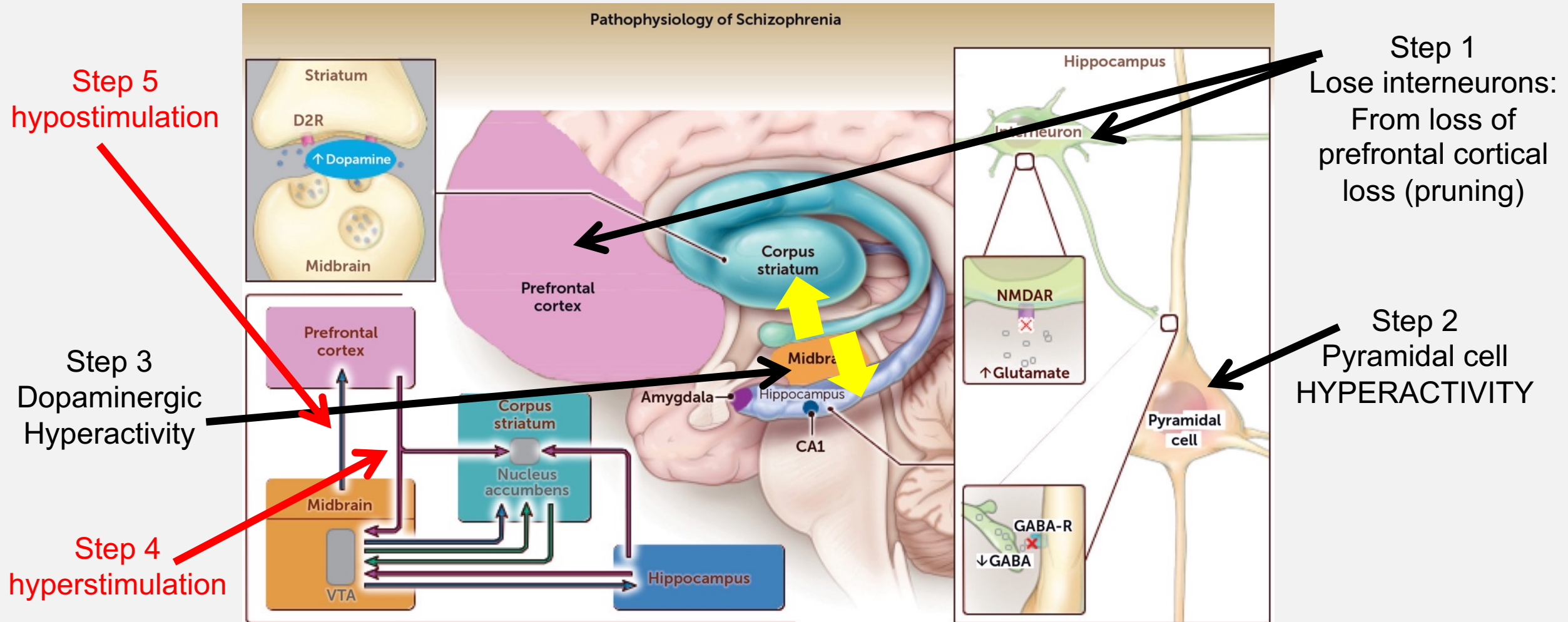
GLUTAMATE (excitatory) & GABA (inhibitory) theory

Originally postulated in early 1990s

- Losing inhibition of Pyramidal Cells by Interneurons (GABA release onto Pyramidal cells) →
- Excessive activity of pyramidal cells which connect the hippocampus to the ventral tegmental area using GLUTAMATE (Hippocampus → VTA)
- This causes VTA to release more DOPAMINE to the nucleus accumbens (VTA → NA)

3

THE 3 THEORIES FIT TOGETHER a viable possibility



Lieberman JA, Small SA, Girgis RR. Early detection and preventive intervention in schizophrenia: from fantasy to reality. Am J Psychiatry. 2019 Sep 26;176(10):794-810.

IDEAS for biological treatments...

Dopamine Hypothesis

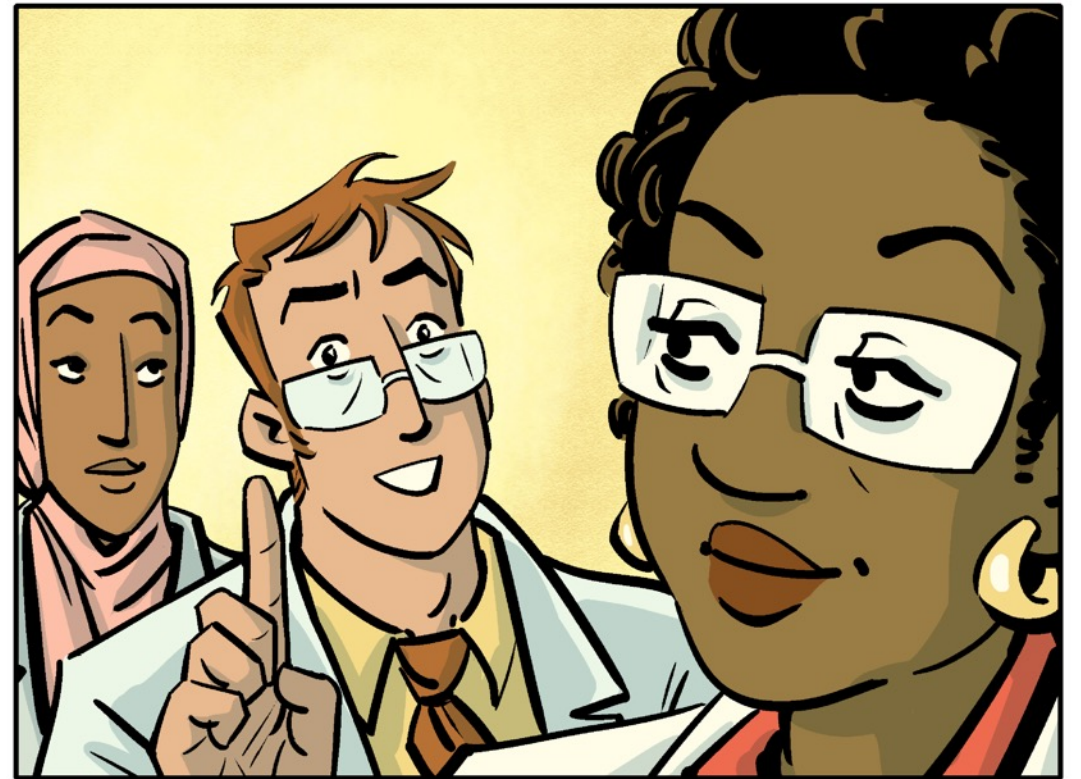
- Better early prediction models
- Better, more targeted medications

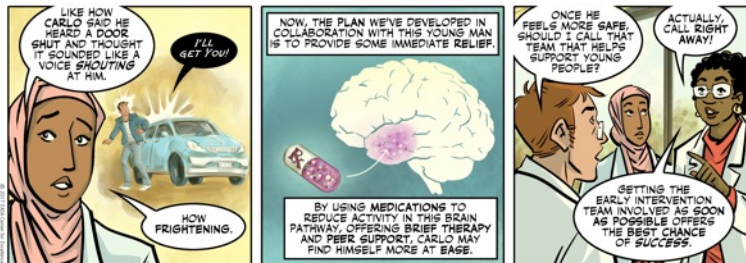
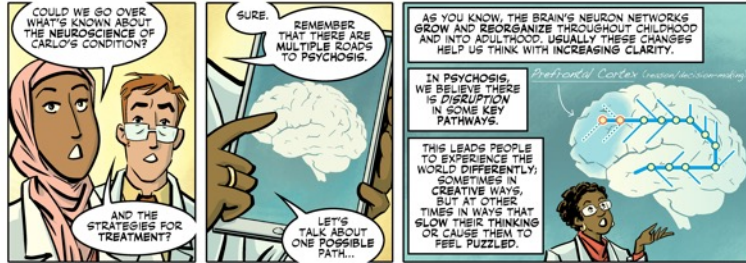
Glutamate Hypothesis

- NMDA receptor modulators to improve functioning

Synaptic Pruning Hypothesis

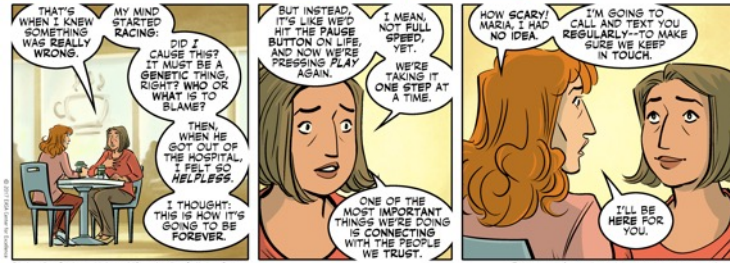
- Anti-inflammatory medications
- Immunomodulators
- Antioxidant Neuroprotective Agents





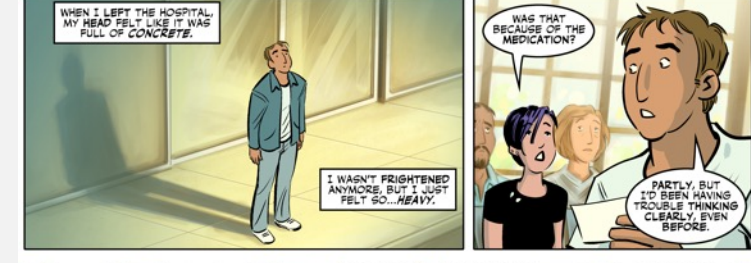
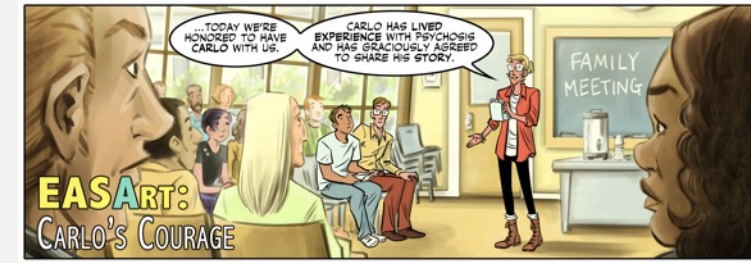
Dialog by Craigan Usher, MD • Art by Colleen Coover

For more information, visit www.easacommunity.org



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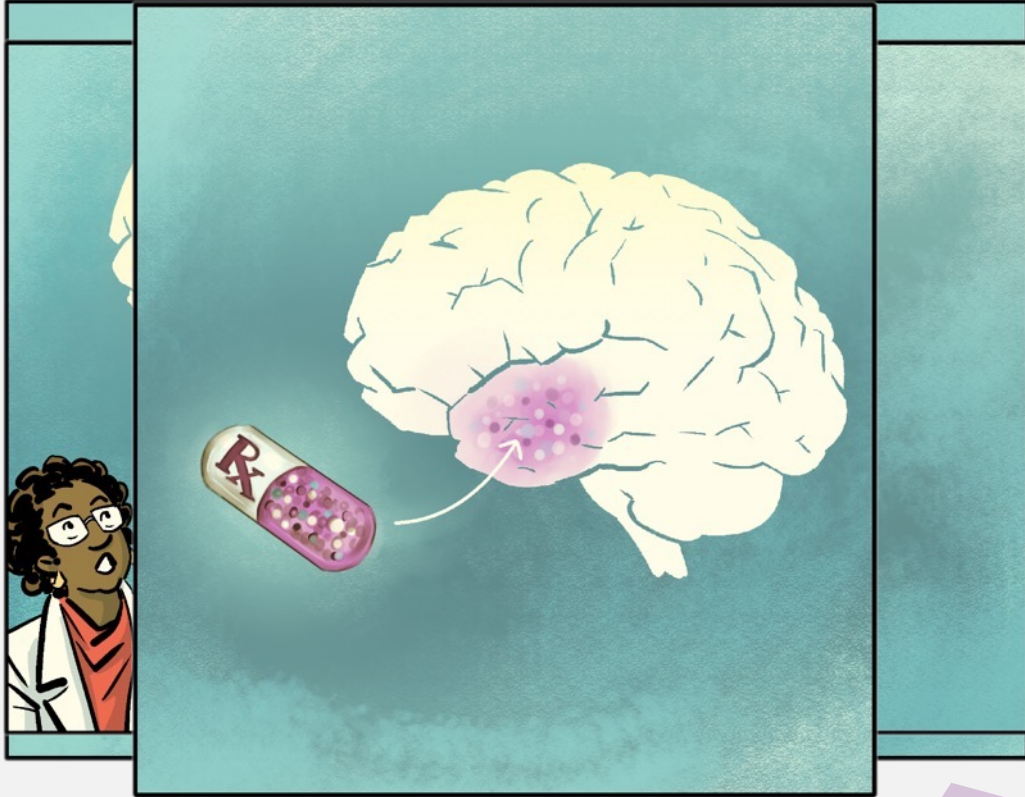
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Education About Psychosis: using the comics



We do not know precisely why people develop psychosis, but one reason that it might occur goes like this.

During puberty there is a reshaping of connections in the brain. Like someone might trim the limbs of a tree to shape it, the body uses our own immune system to cut some of the extra branches between nerves and whole networks in our brain in order to make the brain more efficient.

Sometimes that process can become hyperactive—particularly in this region called the dorsolateral prefrontal cortex (the side and back of the frontal lobes). It trims too much of the brain's gray matter. This leads to people's thoughts becoming less efficient; they become more confused, less able to make plans and carry them out.

The emotional part of the brain then starts to take over. This region, called the ventral tegmental area starts to mark everything we see, hear, feel as vitally important, often frightening...We use therapy, the family guidelines, and medications to try and turn the volume down on this part of the brain which tells us to be frightened.

Education About Psychosis: the “filter” discussion

- Please take notice of everything that you are sensing right now. *EVERYTHING*.
- Imagine for a moment if your brain's filter, that ventral tegmental area, tagged each of one of these sights, sounds, smells as vitally important.
- It would be pretty overwhelming, right?



ACKNOWLEDGING TRAUMA

Trauma / Violence

Adverse Childhood Events

Displacement

Confusion About Language / Worry About Missing Communication

Poverty

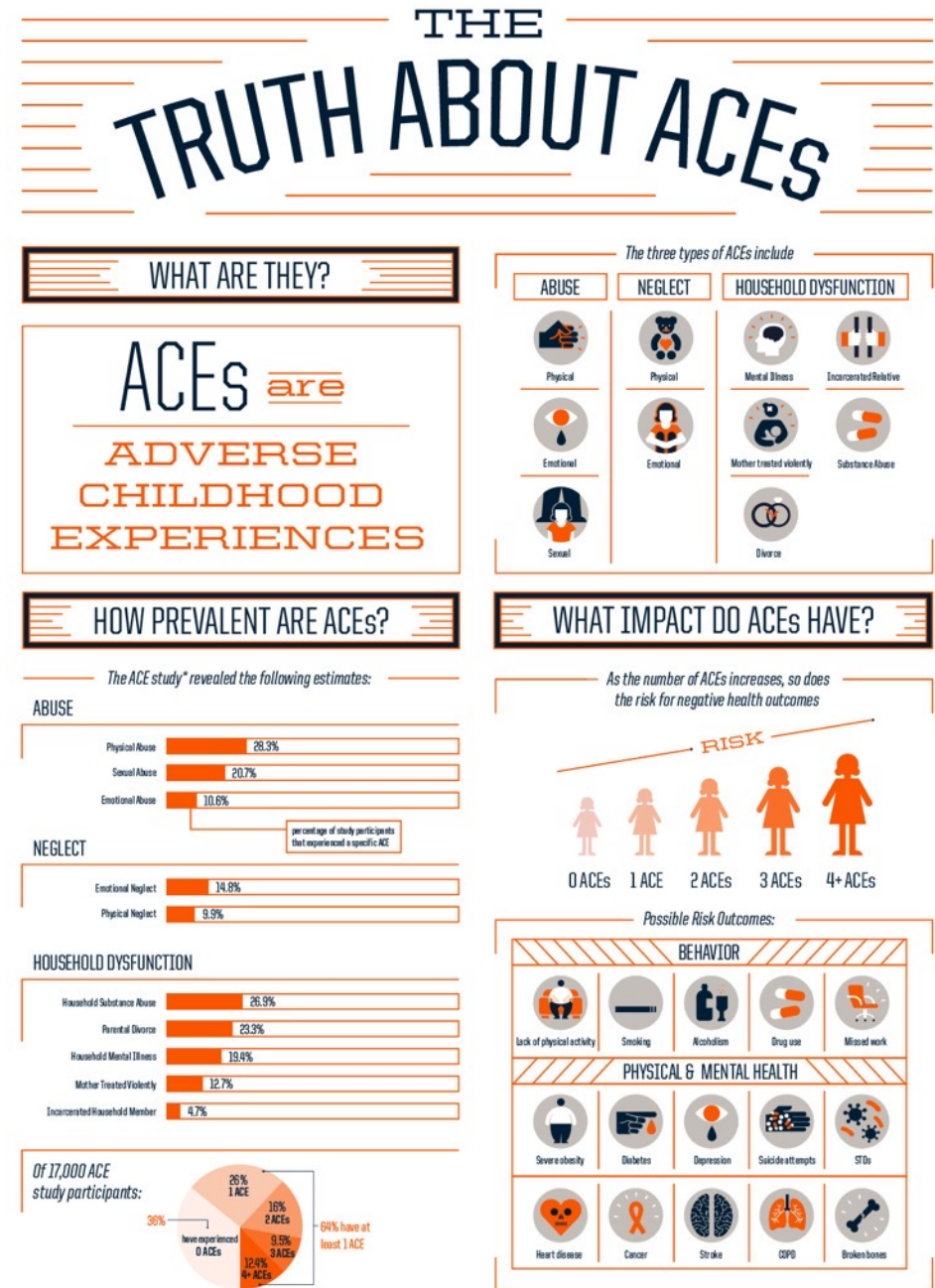
Bullying

Racism

Poor Nutrition

Disrupted Early Attachments...

ALL stressors childhood and adolescents—particularly in the absence of secure attachments and relationships—disrupt biology, specifically development of inhibitory centers, they impair learning and activate threat mechanisms that disrupt emotion regulation; they may predispose an individual to the kinds of disruptions outlined thus far, to self-medicate or attempt to connect with others via cannabis use...



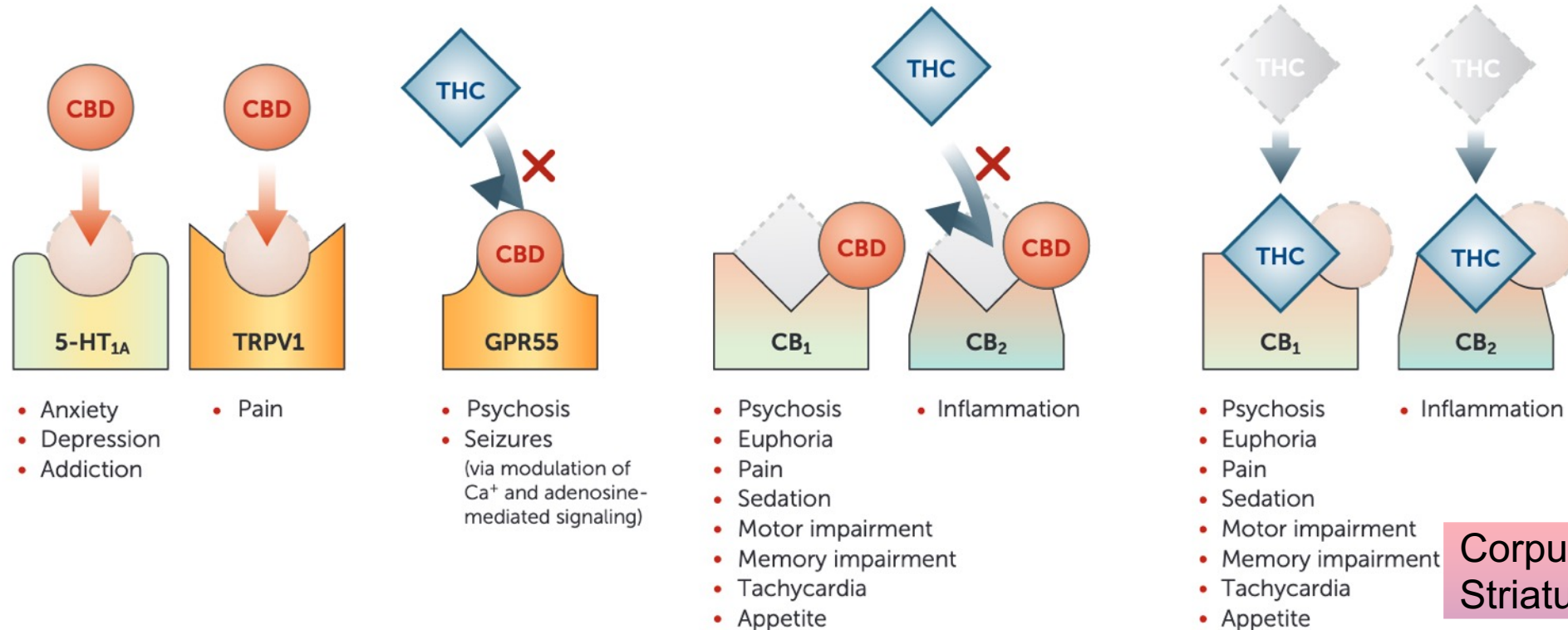
Shifting our focus to CANNABIS & PSYCHOSIS



- **Cannabis** is a plant which contains over 600 chemical components. The two major components are cannabidiol (**CBD**) and tetrahydrocannabinol (**THC**).
- **THC** works on CB1 and CB2 receptors in the brain; it is chiefly responsible for the feeling of being “high” and giddy. It is also believed to be responsible for sparking feelings of anxiety, causing problems with memory, contributing to a sense of time-lapse, stimulating appetite, and even psychotic symptoms. **It is linked to NMDA receptor activity**
- **CBD**, meanwhile, may exert some medicinal and calming properties. It does not directly interact with the endocannabinoid system.
- The two major subspecies of cannabis are ***Cannabis Sativa***—which tends to have a higher THC:CBD ratio and ***Cannabis Indica***—which tends to have a lower THC:CBD ratio.

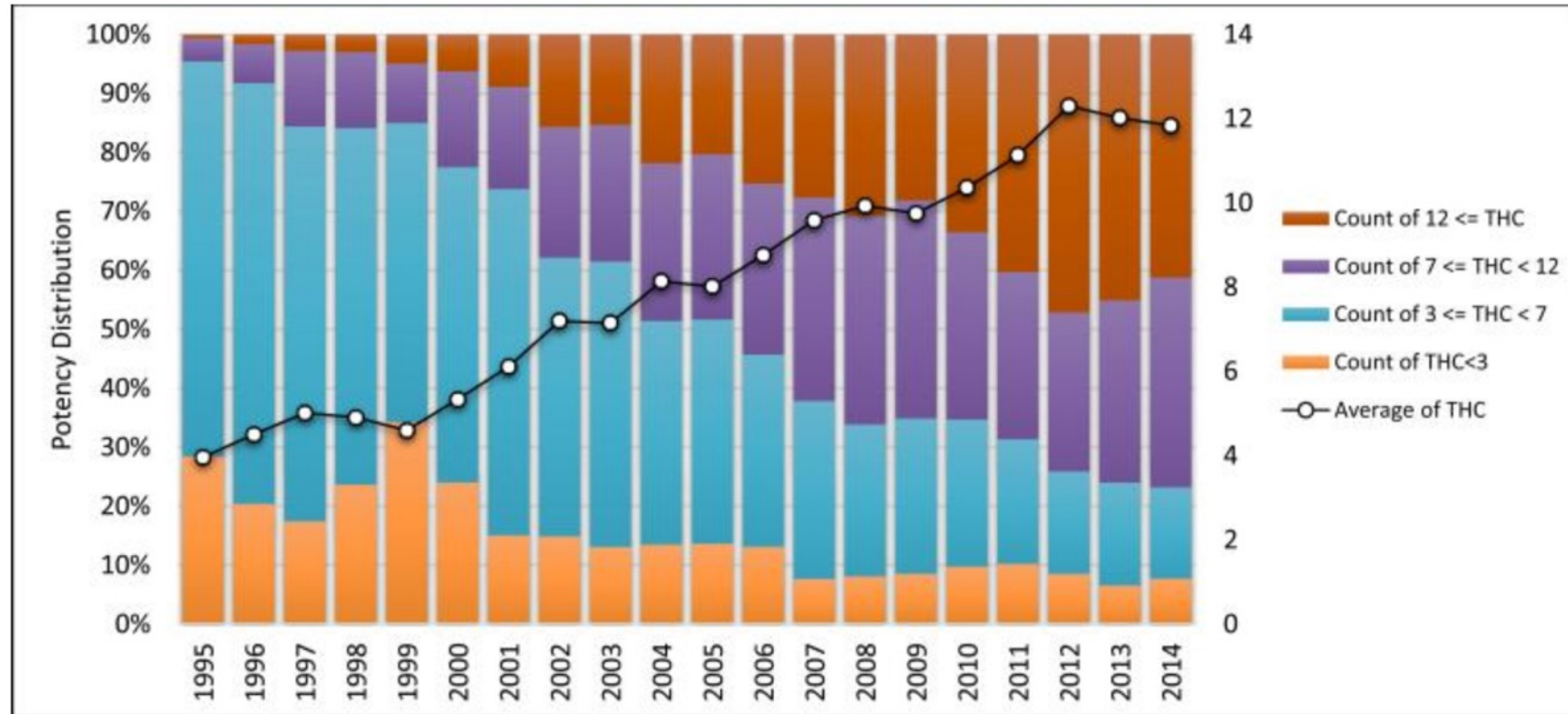
Impact: THC & CBD

FIGURE 1. Cannabinoid interactions with receptors and neurotransmitter systems in human brain and proposed target symptoms and conditions^a



^a CBD=cannabidiol; THC=delta-9-tetrahydrocannabinol.

Higher Highs: THC Concentration



THC potency distribution of cannabis samples from DEA specimens and average THC by year, 1995 – 2014.

MORE BACKGROUND

- “**Weed**” growers and the people who market cannabis products use a lot of creative names for the strains that they grow. In general, high content THC is referred to as *Sinsemella*, or “skunk,” but companies use creative names for their different high potency THC strains—like “Girl Scout Cookies,” “Irish Cream,” “Godfather OG,” or “White Tahoe Cookies.”



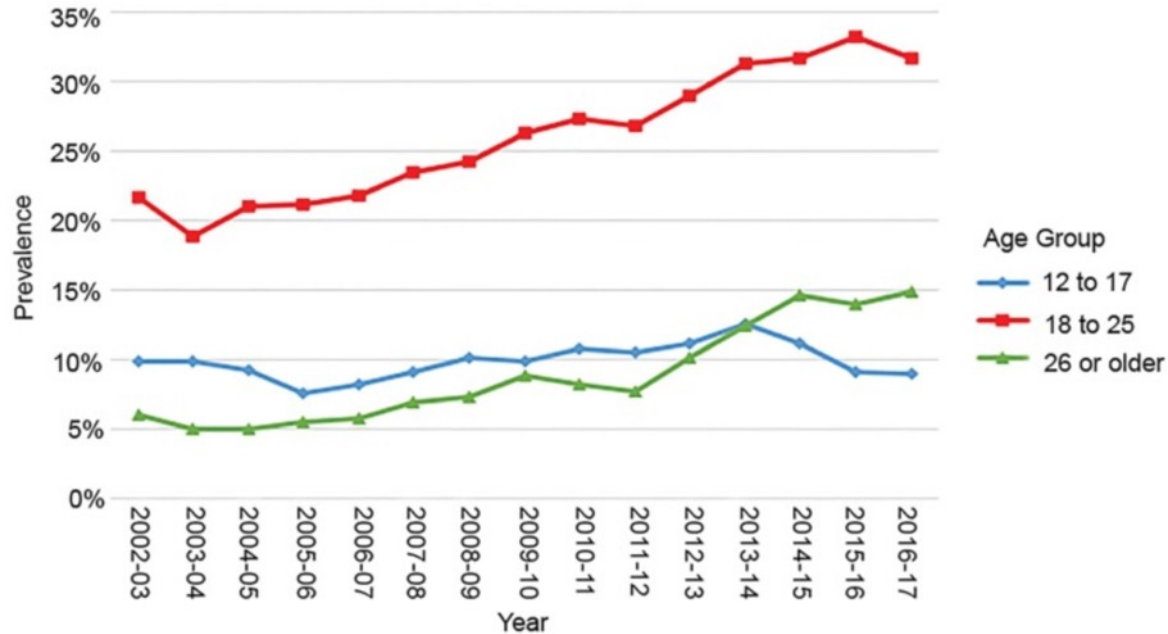
Oregon legalized marijuana for medical use in 1998 and presently an individual can obtain a “Medical Marijuana Card” if it is recommended by a physician for treating cancer, glaucoma, a degenerative or pervasive neurological condition, HIV/AIDS, post-traumatic stress disorder (PTSD), or some specific medical problems.

Oregon legalized recreational marijuana use in 2015, such that marijuana containing products can be purchased by individuals 21 and over.

Rates of Oregon young people who report current use of marijuana:

- 2012: 24% of 11th graders / 9% of 8th graders
- 2018, 20% of 11th graders / 8% of 8th graders

MORE BACKGROUND



Roberts BA. Legalized Cannabis in Colorado Emergency Departments: A Cautionary Review of Negative Health and Safety Effects. *West J Emerg Med.* 2019;20(4):557-572.

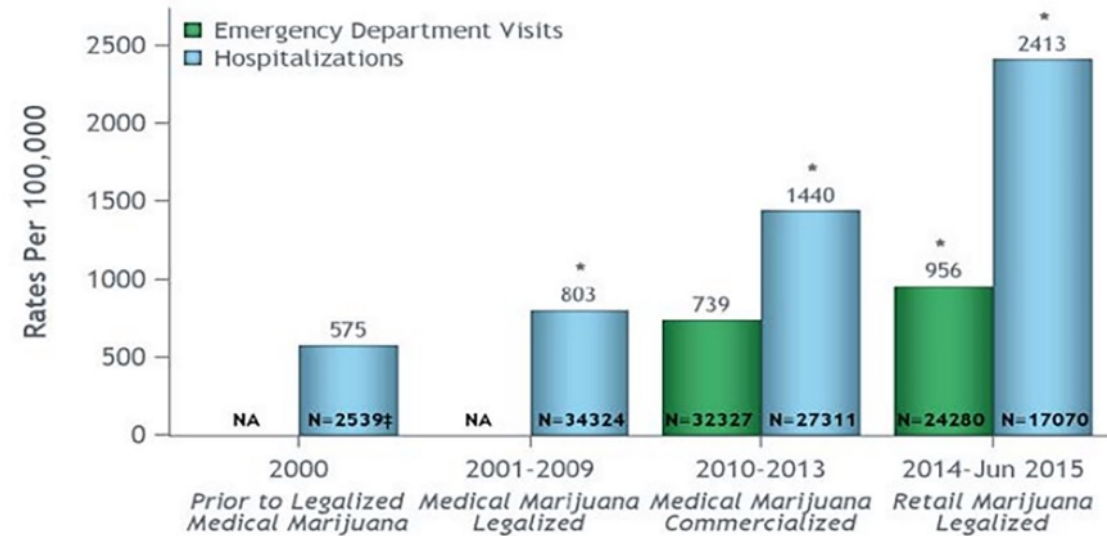
Colorado

- 2000-2009: Medical cards issued, but no commercial availability
- 2010-2012: Medical marijuana commercialized
- In 2014 recreational cannabis is legal and commercially available

Rates of Colorado middle school/high school youth who report use of marijuana in past 30 days:

- 2013 (19.7%) and 2019 (20.6%).

More Colorado Data



*Rate significantly increased from previous time period with a p-value <0.001.

†ICD-9-CM codes 305.2, 304.3, 969.6, and E854.1 were used to determine HD and ED visits with possible marijuana exposure, diagnoses, or billing codes.

‡The Ns are the total number of HD or ED visits with possible marijuana exposures, diagnoses, or billing codes in the specified time period.

Figure 3. Rates of hospitalizations (HD) and emergency department (ED) visits per year with possible marijuana exposures, diagnoses, or billing codes per 100,000 HD and ED visits, by legalization eras in Colorado.

NA, Data not available.

Data provided by Colorado Hospital Association with analysis provided by Colorado Department of Public Health and Environment.

Note: Data for 2015 covers January 1, 2015 – June 30, 2015. An individual can be represented more than once in the data; therefore, the rate is HD or ED visits with marijuana codes per 100,000 total HD or ED visits.

Reproduced from Marijuana Legalization in Colorado: Early Findings. A Report Pursuant to Senate Bill 13-283. Colorado Department of Public Safety. 2016. Available at: <http://cdpsdocs.state.co.us/ors/docs/reports/2016-SB13-283-Rpt.pdf>. Accessed March 2018.

Does “weed” cause psychosis?

It's complicated

- There **is** a relationship: people with FEP are more likely to report current and/or past use
- Cannabis alone, though, has not been shown to cause psychosis
- Cannabis use is associated with/one of a group of “risk” behaviors (early sexual activity, poor school performance, general problems)
- These “risk” behaviors are associated with life adversity—poverty, bullying, family history of mental illness
- Smoking weed may actually be a reaction to *and* a further cause of the stress of low academic achievement, dis-engagement from friends, family, potential support
- It may be easy to “blame weed” but smoking cannabis is usually part of a larger life story

Silva TB, Balbino CQ, Weiber AF. The relationship between cannabidiol and psychosis: a review. *Annals of Clinical Psychiatry*. 2015 May 1;27(2):134-41

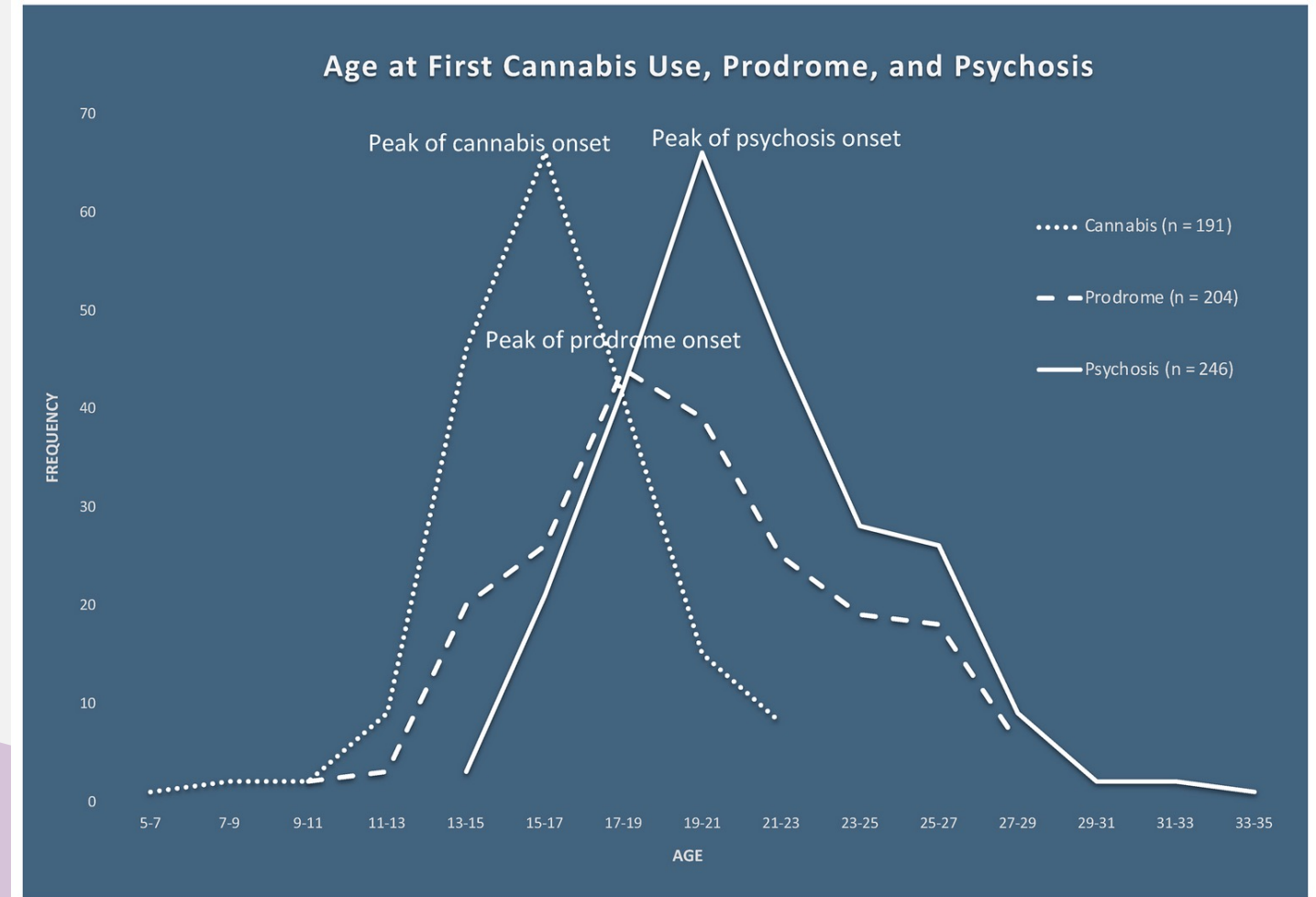
Hamilton I. Cannabis, psychosis and schizophrenia: unravelling a complex interaction. *Addiction*. 2017 Sep;112(9):1653-7.



Recent Study Challenges Findings

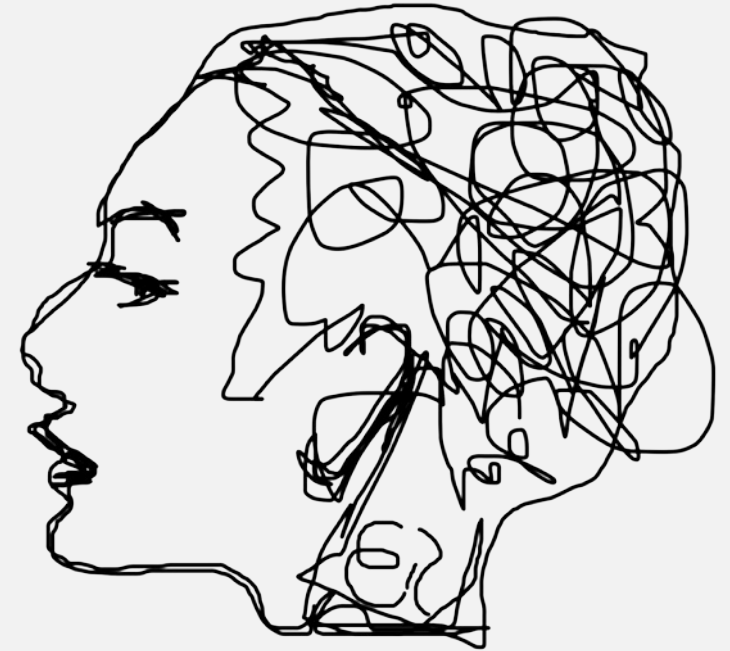
One study comparing FEP program participants:

- 54 not exposed
- 192 exposed to cannabis
- 47% met criteria for CUD
- “Earlier age of first cannabis use was significantly associated with worse premorbid functioning, more problematic use at time of admission, and earlier age at both prodrome and psychosis onset.”



CHR & Conversion:

- Young people with CHR have reported feeling that it enhance their mood, helped them relax, and was a means of socially connected with others.
- A meta-analysis showed that use of cannabis has not been associated with conversion
- One study revealed, though, that **Cannabis Abuse/Dependence** is associated with conversion to psychosis
- The conclusion of a recent meta-analysis suggested that the relationship between cannabis and psychosis appears dose dependent.

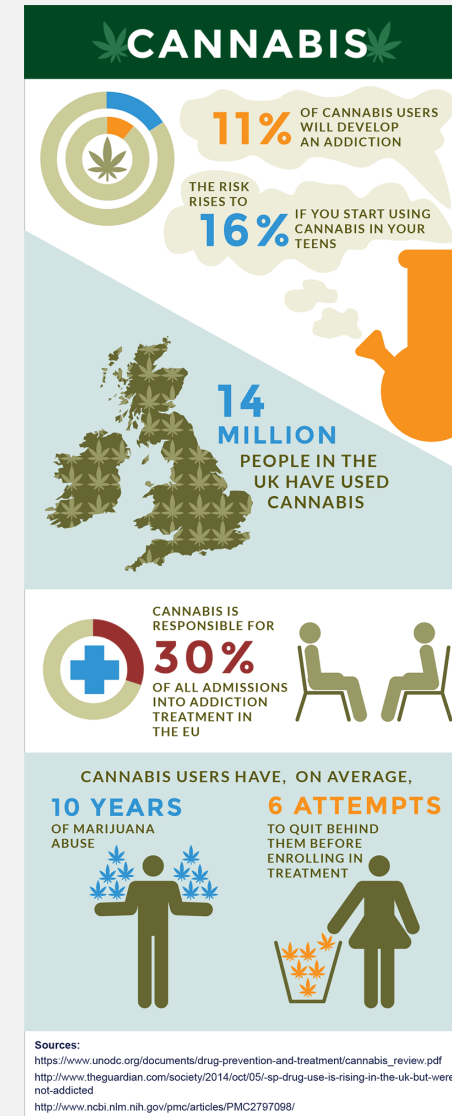


Kraan T, Velthorst E, Koenders L, Zwaart K, Ising HK, van den Berg D, de Haan L, van der Gaag M. Cannabis use and transition to psychosis in individuals at ultra-high risk: review and meta-analysis. *Psychological medicine*. 2016 Mar;46(4):673-81.

Murray RM, Quigley H, Quattrone D, Englund A, Di Forti M. Traditional marijuana, high-potency cannabis and synthetic cannabinoids: increasing risk for psychosis. *World Psychiatry*. 2016 Oct;15(3):195-204.

Sparked by Cannabis?

- If one has a psychotic episode that is sparked by cannabis use, then family history opposed to cannabis use is MOST predictive of progression to schizophrenia.
- However, there may be a gene x cannabis relationship, such that reduction and cessation of cannabis use in those with a + family hx of schizophrenia is particularly important (particularly in those with risk COMT Val/Val and AKT1 C/C gene variants)
- If one has schizophrenia, there is ample evidence that those who stop using cannabis may be:
 - less likely to be hospitalized
 - have less psychotic symptoms
 - show improvement in their cognition over time

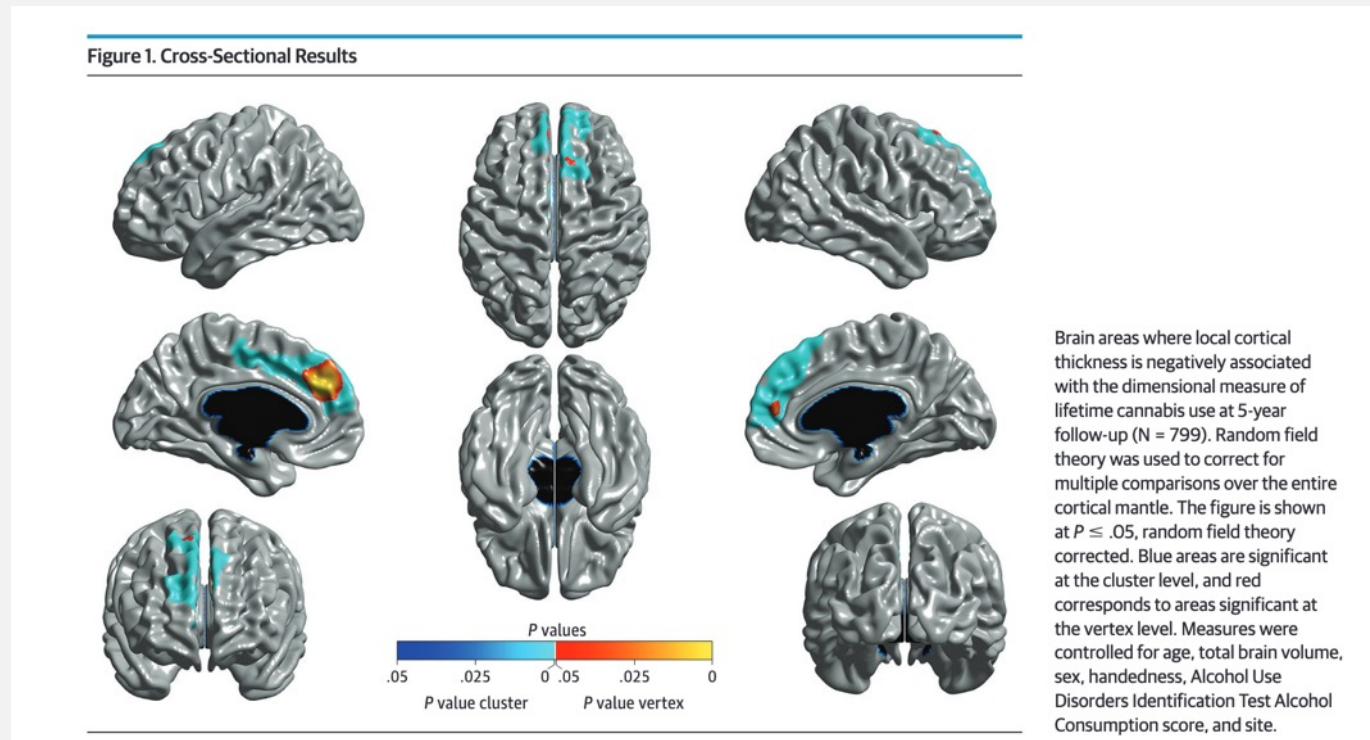


Murray RM, Quigley H, Quattrone D, Englund A, Di Forti M. Traditional marijuana, high-potency cannabis and synthetic cannabinoids: increasing risk for psychosis. *World Psychiatry*. 2016 Oct;15(3):195-204.

10 Colizzi M, Burnett N, Costa R, De Agostini M, Griffin J, Bhattacharyya S. Longitudinal assessment of the effect of cannabis use on hospital readmission rates in early psychosis: A 6-year follow-up in an inpatient cohort. *Psychiatry research*. 2018 Oct 1;268:381-7.

It's Pretty Clear: THC is bad for young people & Quitting Isn't Easy

- One study of 799 youth age 14 – 19 at 5 year follow, there was cortical thinning (particularly in the L prefrontal cortex) in the cannabis group compared to non-users



- Tolerance/dependence with withdrawal effects occur in 10 – 30% of people with cannabis use disorder

Current Individual Approaches Lack Evidence...

The authors of a high quality, large study completed through the British National Health Service examining a specific manualized intervention that drew 551 participants from their Early Intervention in Psychosis (EIP) Clinics humbly put it this way:

*overall, this is another trial that demonstrates how challenging it is to address the problem of cannabis use in psychosis. **It may be that a substantially different approach is required to address this significant clinical problem.** It has been noted that young people who have psychosis and problematic cannabis use are often multiply disadvantaged. Despite this, trials of interventions in this area are often narrowly focused on changing cannabis use. A more inclusive management that takes in patients' social contexts, including engagement in work or education, might prove more fruitful.*



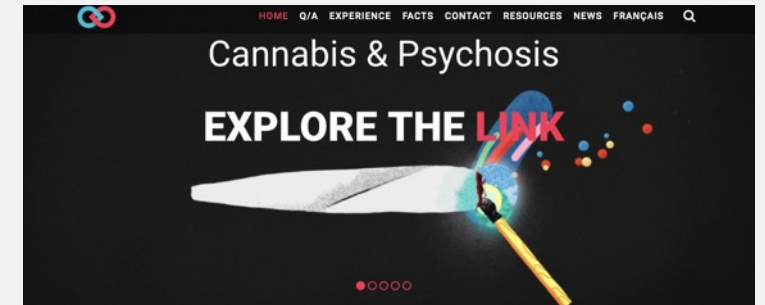
Should we give up on trying to help people stop?

Absolutely not. The EASA Program aims to provide coordinated specialty care (CSC) tailored to the specific needs of each individual and family/circle of supports for whom we're honored to provide support/care.

Creativity, improvisation, breaking down silos is what we do best.

We can honor the unique life circumstance of each individual, the role that cannabis is playing in their life and use principles from Motivational Interviewing:

- Having/expressing empathy
- Rolling with resistance to change
- Helping people identify some discrepancies in their way of thinking/operating
- Supporting young people's self-efficacy—what might lead you to feel this is problematic and what might you then do to act on what you've discovered?



Please see:
<https://cannabisandpsychosis.ca/>

4:20.00

SHARING EXCELLENT RESOURCES

A related organization, the Early Psychosis Intervention Ontario Network provides these recommendations for empowering youth:

- ① remind youth that driving “high” is DUI and can be quite dangerous
- ② educate young people about neuroscience—the brain develops until 25 and those under 25 are at more risk for problems related to brain development than older people;
- ③ note that people with a family history of psychosis/schizophrenia are at greater risk for psychotic symptoms with cannabis use;
- ④ be aware of THC:CBD ratios, with higher levels of THC possibly placing them at greater risk.
- ⑤ utilize harm reduction strategies: “Abstaining from cannabis use is the least risky choice. Otherwise: -start low and go slow; -know your source and strain; -wait until age 25.”



Please see:

<https://cannabisandpsychosis.ca/>

&

<http://mycannabisiq.ca/portfolio/cannabisiq-youth/>

Finally, a word on CBD treatment for psychosis/schizophrenia

McGuire et al. Cannabidiol (CBD) as an adjunctive therapy in schizophrenia: a multicenter randomized controlled trial. AJP 2017 Dec 15;175(3):225-31.

Multi-center, Outpatient RCT

- 6wk RCT, w 1000mg CBD qd
- Placebo (n = 45)
- Active Tx (n = 45)
- CBD group showed lower “positive” symptoms on PANSS
- More likely to be rated as improved
- Less likely to be rated as severely unwell

Leweke et al. Cannabidiol enhances anandamide signaling and alleviates psychotic symptoms of schizophrenia. Translational psychiatry. 2012 Mar;2(3):e94.

Inpatients (Germany) ages 18-50, 28 days

- Amisulpride (N=21)
 - 1 d/c'd, 1 withdrew consent
- CBD (N=21)
 - 2 d/c'd, 1 PNES, 1 wd consent, 1 chronic suicidality
- No significant difference in PANSS/BPRS, CGI
- Wt gain, EPS, PRL > in Amis group

Boggs et al. The effects of cannabidiol (CBD) on cognition and symptoms in outpatients with chronic schizophrenia a randomized placebo controlled trial. Psychopharmacology 2018 Jul;235(7):1923-1932.

Outpatient, 6wk, RCT

- N = 36 on antipsychotics, ages 18-65
- 18 Placebo, 18 CBD (600mg qd)
- No difference in MATRICS
- Consensus Cognitive Battery
- No difference in PANSS

QUESTIONS & THOUGHTS?

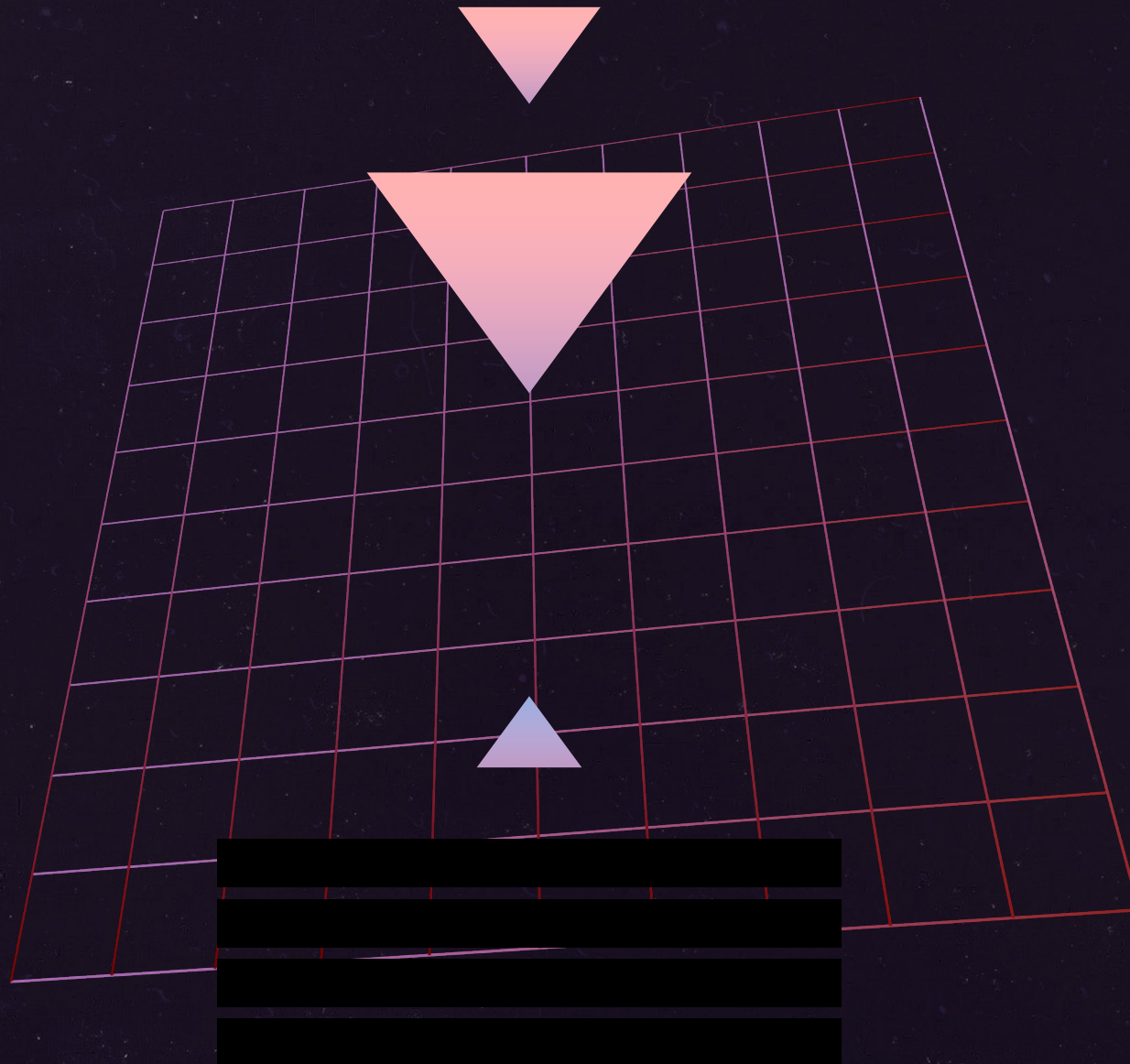


LEARNING OBJECTIVES: REVISITED

So, today you learned that:

- 1) That three main neurobiological theories of psychosis/schizophrenia are:
 - Dopamine Theory
 - Synaptic Pruning / Immune Theory
 - Glutamate & GABA Theory
- 2) These do not compete with life-experience/trauma-related understandings—they simply offer a model of what may occur in the brain during conditions of extreme stress or neurodevelopmental compromise
- 3) Cannabis is part of a number of risk behaviors that increase risk of psychosis
- 4) Cannabis can alter DOPAMINE transmission in the corpus striatum (part of the models we discussed above)
- 5) It can be hard to quit, but the science is clear: quitting is worth it! Use MI strategies, empathize, find out what role weed is playing in someone's life and what might fill the void. Harm reduction strategies such as low dose THC higher dose CBD may be useful.





How long does cannabis exert an impact on the brain?