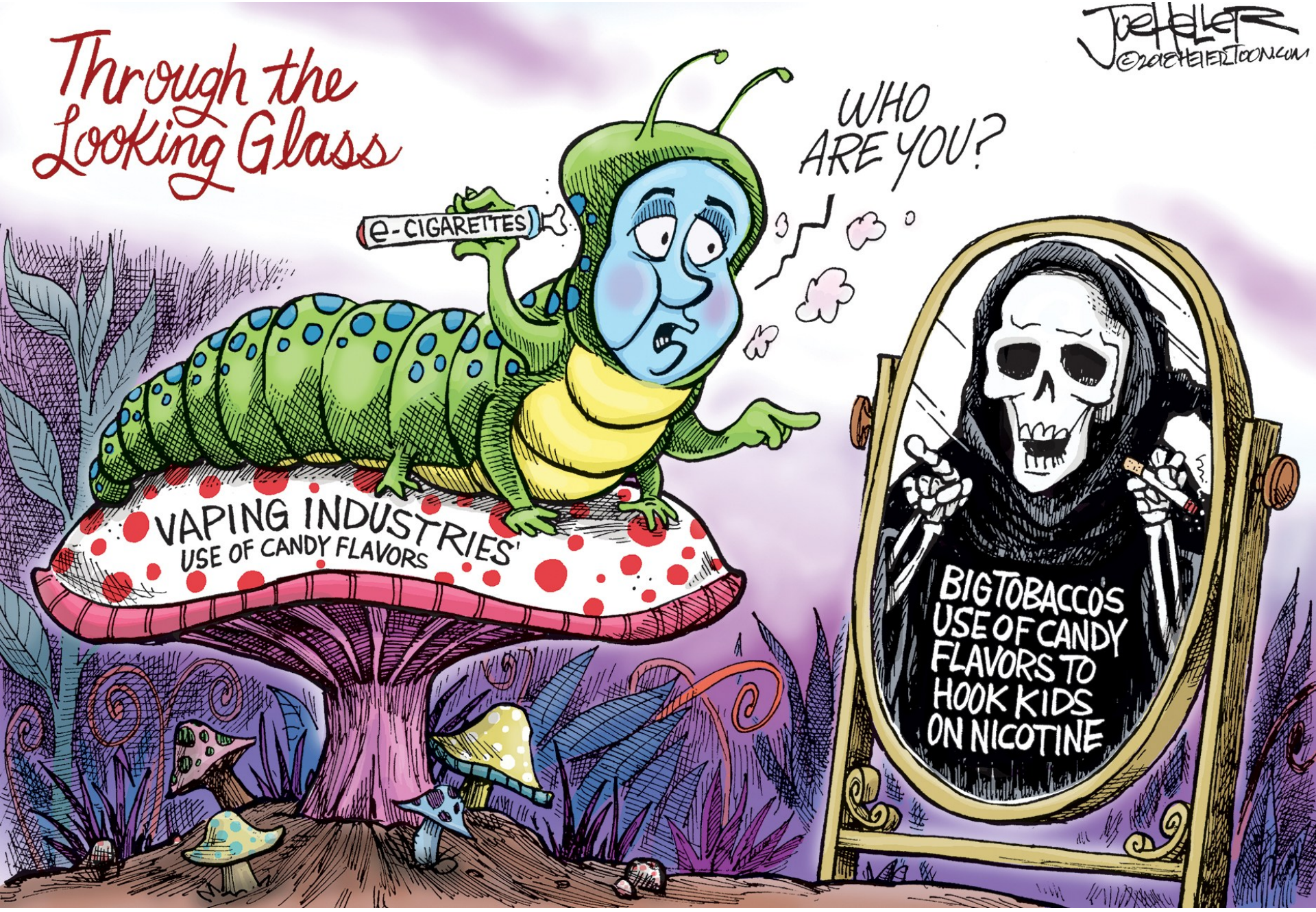
Vaping and Cannabis Apocalypse of the Prefrontal Cortex

James W. Nachbar M.D.


Alice said,
"Would you tell me,
please, which way I
ought to go from
here?"
"That depends a good
deal on where you
want to get to,"
said the Cat.


Through the Looking Glass
JoeHeller
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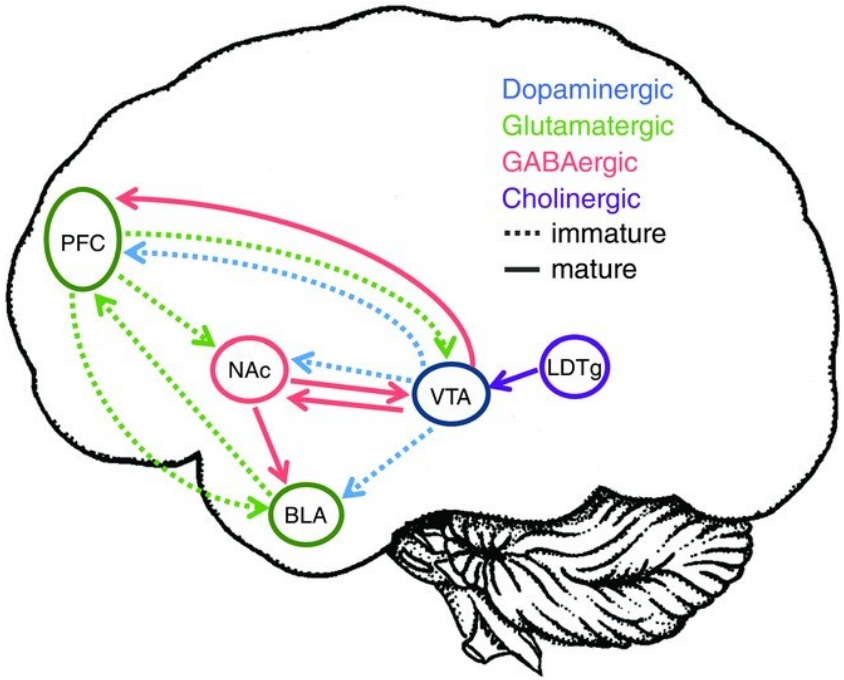
WHO ARE YOU?
e-CIGARETTES
VAPING INDUSTRIES' USE OF CANDY FLAVORS
BIG TOBACCO'S USE OF CANDY FLAVORS TO HOOK KIDS ON NICOTINE



Immature Adolescent Brain Undergoes Substantial Growth, Reorganization and Pruning

"Have you guessed the riddle yet?" the Hatter said, turning to Alice again.

"No, I give up," Alice replied.

"What's the answer?"

"I haven't the slightest idea," said the Hatter.

"Nor I," said the March Hare.

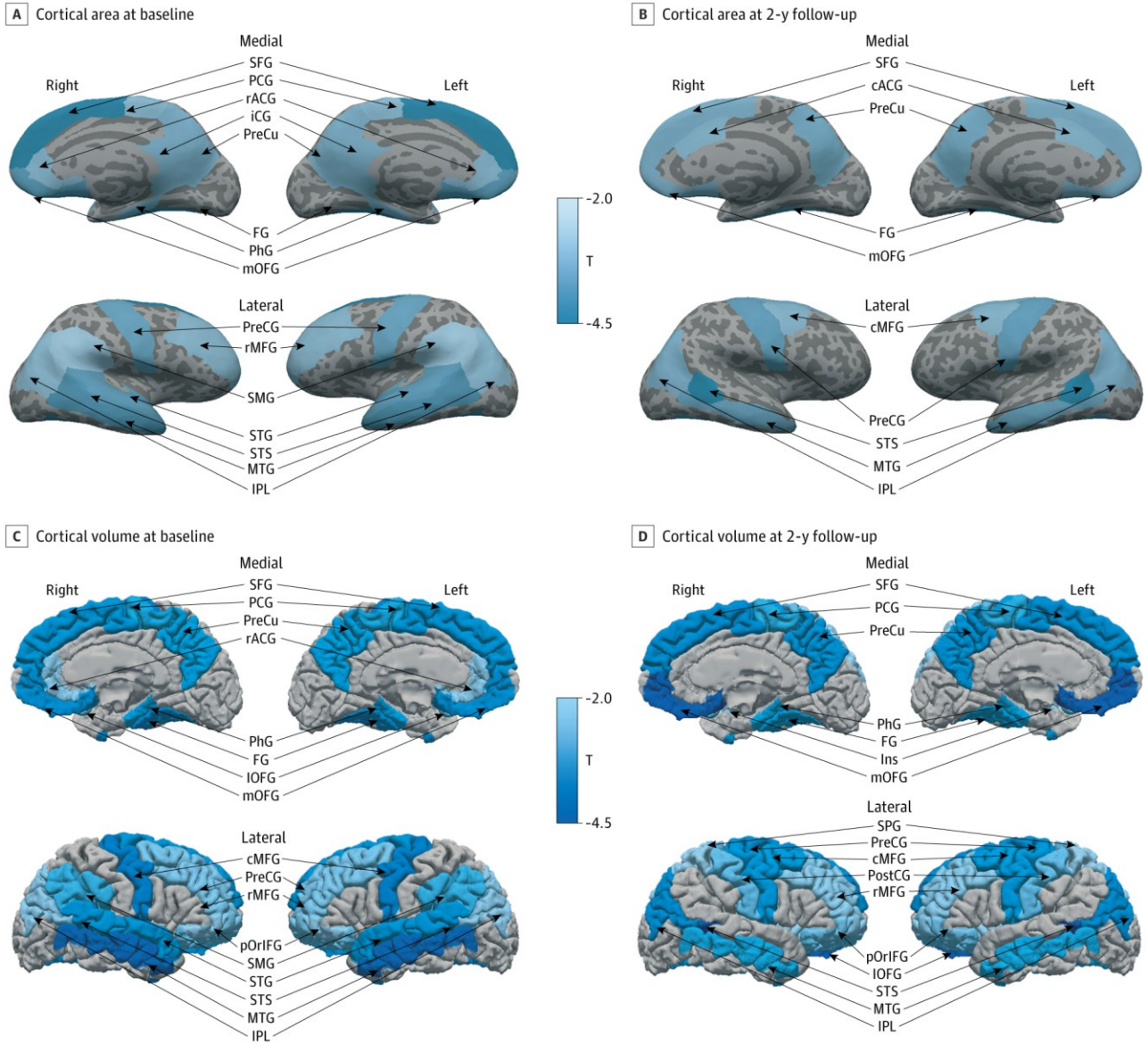
Prefrontal Cortex

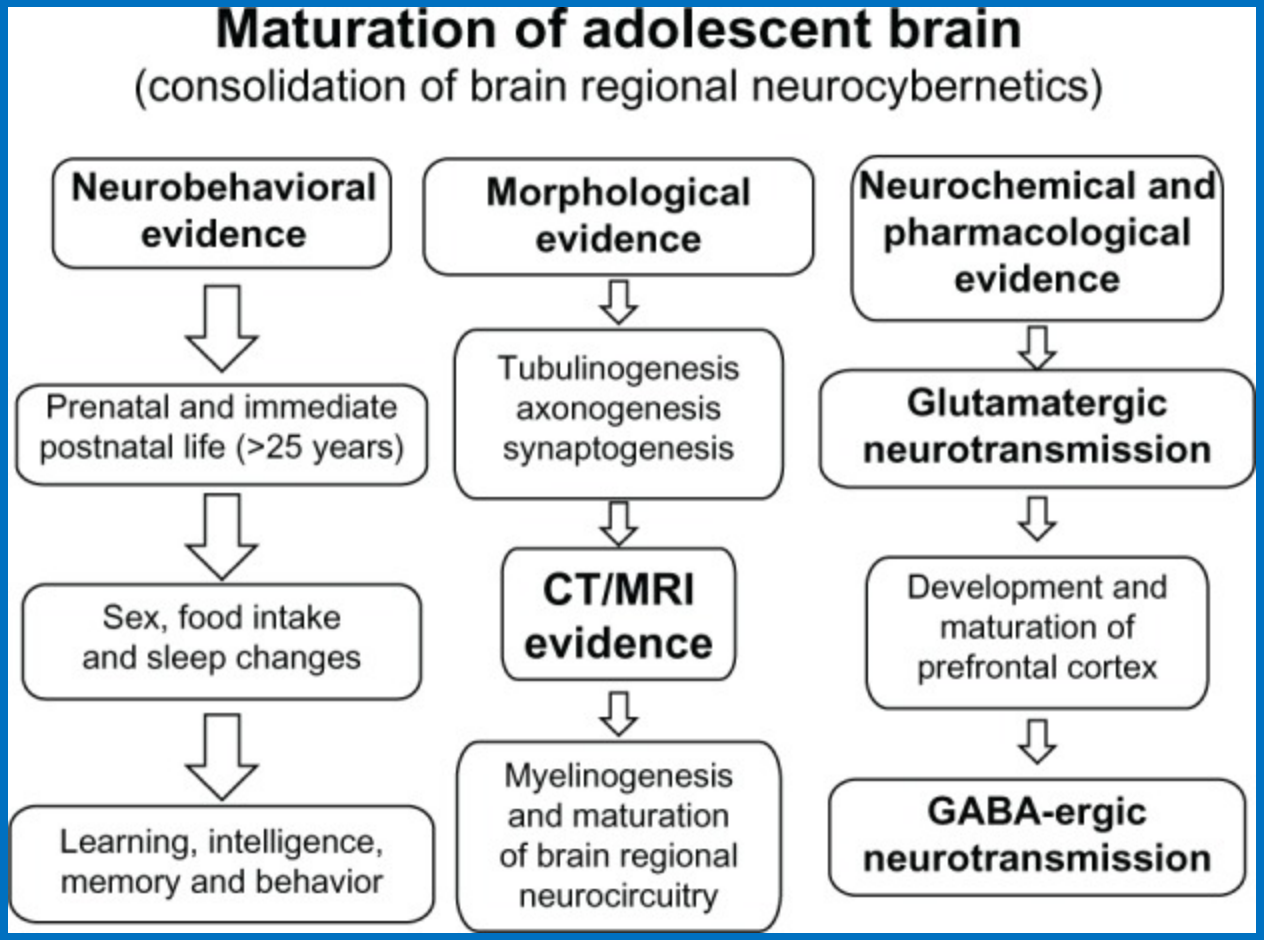
Reduced Gray Matter in the Frontal Lobes Linked to Smoking and Nicotine Addiction

- Left Ventromedial PFC Bio Marker for Nicotine Addiction
- Less Gray Matter Left VM PFC Increase Rule Breaking
- Gray Matter in the Right PFC Decreases After Someone Starts Smoking
- Right PFC Involved with Seeking Sensations
- Decrease Gray Matter Right VMPFC Will Strengthen Smoking Behavior and Decrease Inhibition

Longitudinal Assessments of Neurocognitive Performance and Brain Structure Associated With Initiation of Tobacco Use in Children, 2016 to 2021

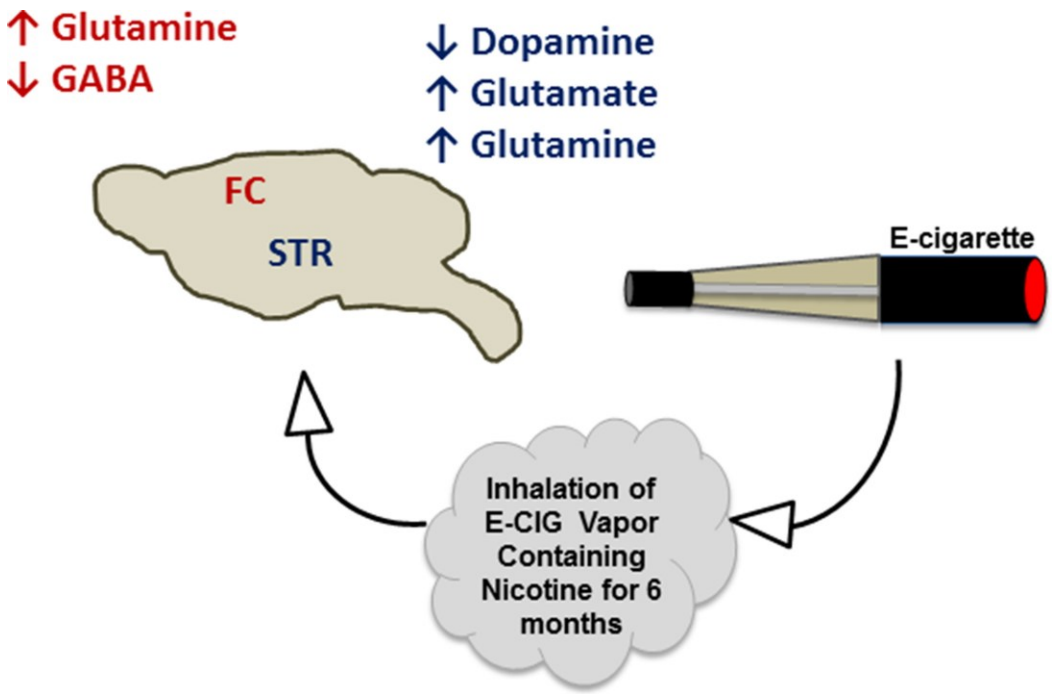
- Findings National Cohort Study 17,703 Children
- Early Age Initiation of Tobacco Use with Lower Crystalized Cognition
- Decreased Brain Development Lower Cortical Area and Volume

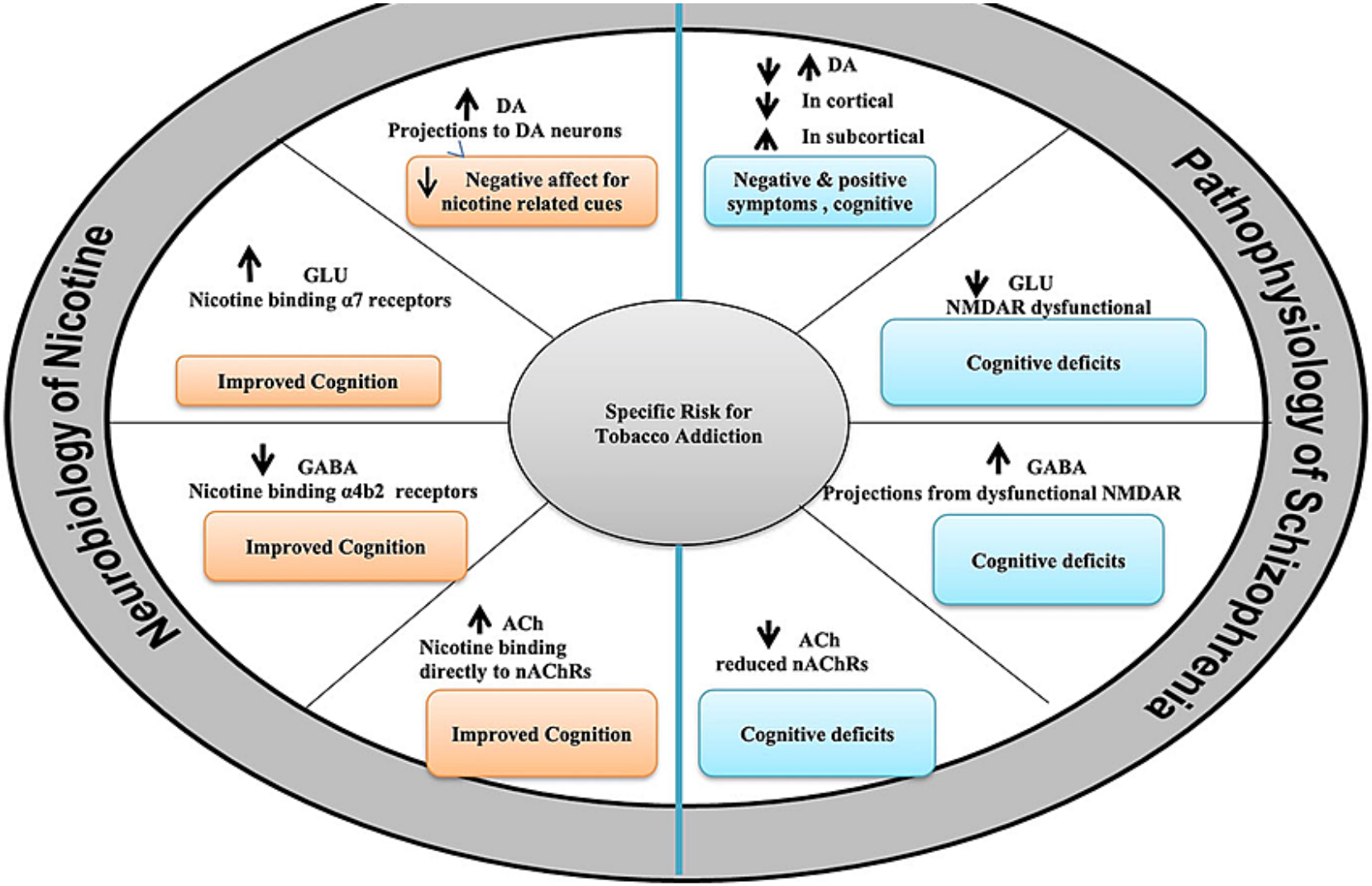

A Cortical area at baseline
Medial
Right
Left
SFG
PCG
rACG
iCG
PreCu
FG
PhG
mOFG
Lateral
PreCG
rMFG
SMG
STG
STS
MTG
IPL
-2.0
T
-4.5
B Cortical area at 2-y follow-up
Medial
Right
Left
SFG
cACG
PreCu
FG
mOFG
Lateral
cMFG
PreCG
STS
MTG
IPL
C Cortical volume at baseline
Medial
Right
Left
SFG
PCG
PreCu
rACG
PhG
FG
lOFG
mOFG
Lateral
cMFG
PreCG
rMFG
pOrIFG
SMG
STG
STS
MTG
IPL
-2.0
T
-4.5
D Cortical volume at 2-y follow-up
Medial
Right
Left
SFG
PCG
PreCu
PhG
FG
Ins
mOFG
Lateral
SPG
PreCG
cMFG
PostCG
rMFG
pOrIFG
lOFG
STS
MTG
IPL


Maturation of adolescent brain
(consolidation of brain regional neurocybernetics)
Neurobehavioral evidence
Prenatal and immediate postnatal life (>25 years)
Sex, food intake and sleep changes
Learning, intelligence, memory and behavior
Morphological evidence
Tubulinogenesis axonogenesis synaptogenesis
CT/MRI evidence
Myelinogenesis and maturation of brain regional neurocircuitry
Neurochemical and pharmacological evidence
Glutamatergic neurotransmission
Development and maturation of prefrontal cortex
GABA-ergic neurotransmission

- Some groups of middle and high school students use e-cigarettes at a higher percentage than others. For example, in 2024:
- More females than males reported current e-cigarette use.
- Current use of e-cigarettes varied by race and ethnicity.
- Non-Hispanic American Indian and Alaska Native students: 11.5%.
- Non-Hispanic Black or African American students: 7.0%.
- Non-Hispanic multiracial students: 6.6%.
- Hispanic or Latino students: 6.1%.
- Non-Hispanic White students: 5.9%.
- Non-Hispanic Asian students: 2.3%

Effect of Chronic Inhalation of Electronic Cigarette

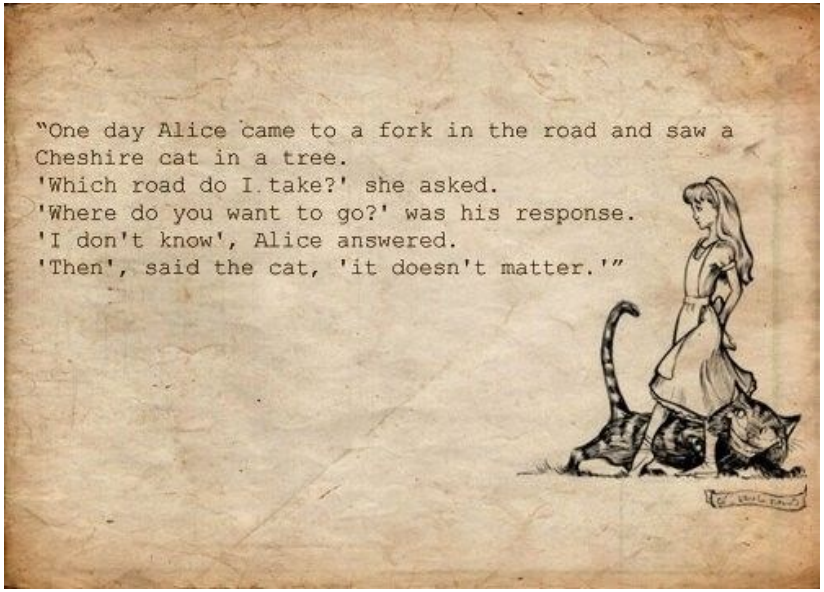



Neurobiology of Nicotine
Pathophysiology of Schizophrenia
Specific Risk for Tobacco Addiction
DA
Projections to DA neurons
Negative affect for nicotine related cues
GLU
Nicotine binding α7 receptors
Improved Cognition
GABA
Nicotine binding α4b2 receptors
Improved Cognition
ACh
Nicotine binding directly to nAChRs
Improved Cognition
DA
In cortical
In subcortical
Negative & positive symptoms , cognitive
GLU
NMDAR dysfunctional
Cognitive deficits
GABA
Projections from dysfunctional NMDAR
Cognitive deficits
ACh
reduced nAChRs
Cognitive deficits

Nicotine and the Developing Brain

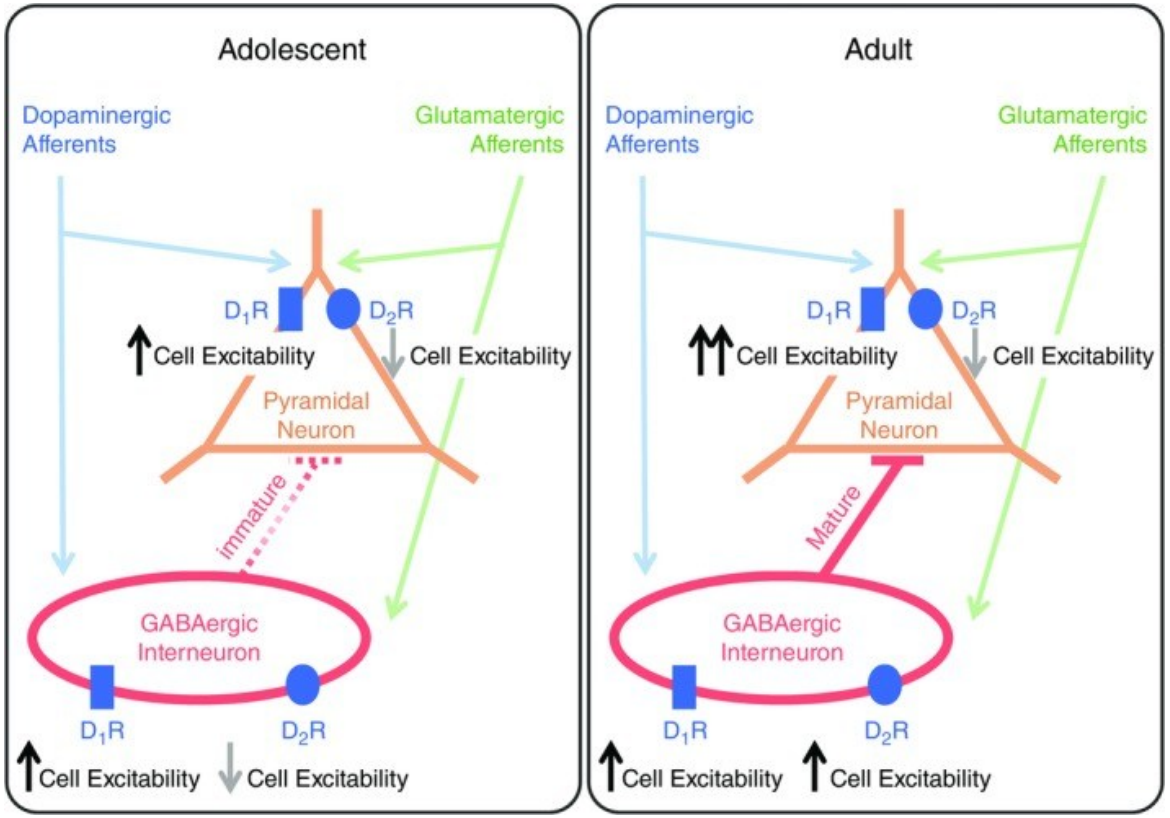
- Nicotine Highly Addictive
- Adolescent Brain Still Developing Until the Age of 25
- Cognitive Impairments
- Nicotine Interferes with Learning Attention and Memory
- Adolescent Exposure to Nicotine Lead to Cognitive Deficits

Prefrontal Cortex



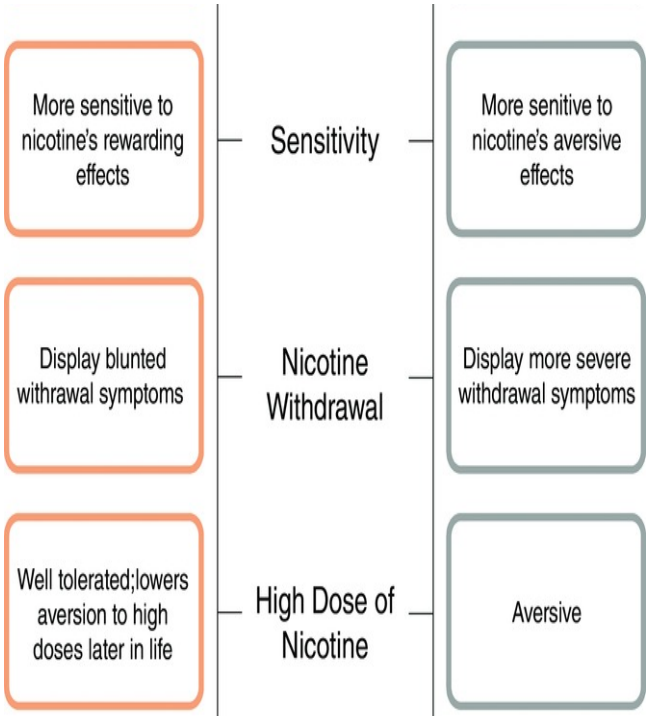
- Critical Thinking
- Decision Making
- Personality
- Moderating Social Behavior

- Vaping Affects the Prefrontal Cortex



Microcircuitry of the prefrontal cortex (PFC) showing developmental differences in dopamine function

Preclinical Studies of Rodent Models Indicate that Nicotine Produces Age Specific Response



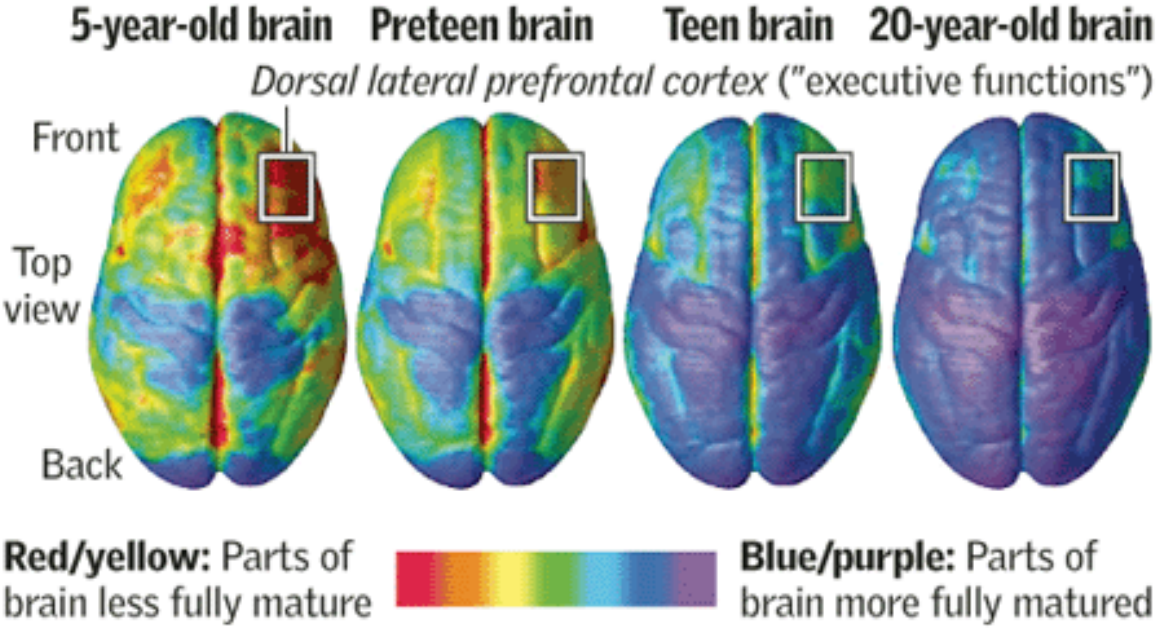
Adolescents Use Vaping to Regulate Distress

- Delvin Mattingly
  PhD University of Kentucky

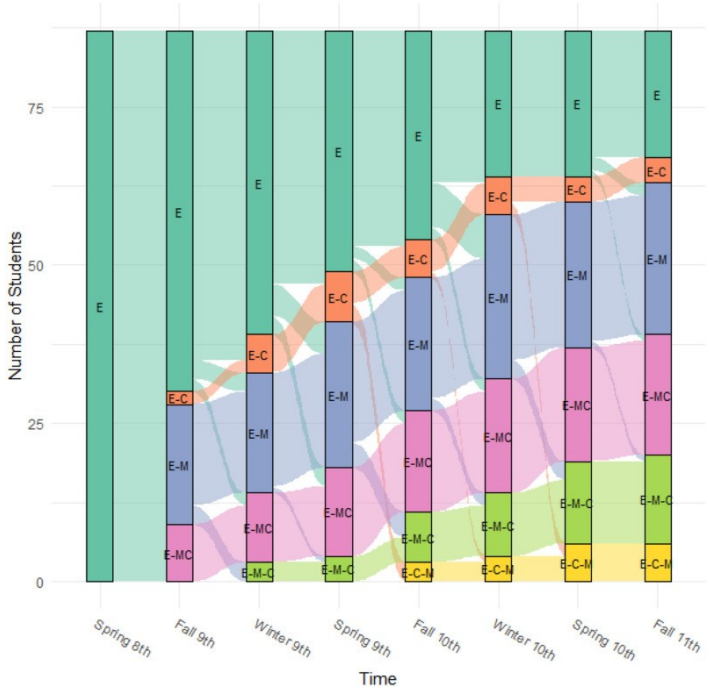
- National Youth Tobacco Study
- 22.2 percent Psychological Distress

Judgment last to develop

The area of the brain that controls "executive functions" — including weighing long-term consequences and controlling impulses — is among the last to fully mature. Brain development from childhood to adulthood:



Nicotine Vaping Precedes Cannabis Abuse



- 2020 Meta Analysis Nicotine Vaping Associated with a 6 Fold Increase Risk of ETOH Abuse and Binge Drinking

Vaping and psychotic experiences among college students in the United States

- Roughly 14 percent of students in the sample reported psychotic experiences in the past year
- About 14 to 12 percent of students reported vaping over the past month
- The who vaped were more likely to have reported psychotic experiences
- The association remained significant after adjusting for other substance abuse and mental heath

Nicotine and Cannabis

- **2 Most Commonly Vaped Substances**
- **E Cigarettes Prevalence 2020 19.46 Percent HS Students 4.7 percent middle**
- **Most Common Use of E Cigarette Use Relaxation**
- **Other Uses Flavor**

Vaping and the Brain

- E Cigarette Vapors
- Motor
- Learning
- Memory

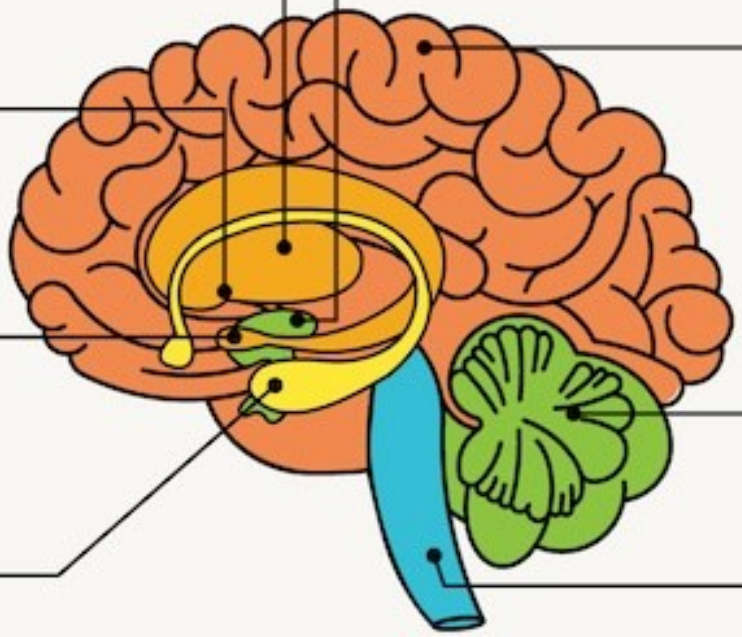
	Past-year self-injury $N = 10,757$ (%)	No past-year self-injury $N = 36,259$ (%)	p
Electronic cigarette use	2,901 (27.0)	5,854 (16.1)	<0.0001
Conventional cigarette use	1,747 (16.2)	3,088 (8.5)	<0.0001
Marijuana use	4,048 (37.6)	7,156 (19.7)	<0.0001
Alcohol use	6,615 (61.5)	20,571 (56.7)	<0.0001
Use of other substances	966 (9.0)	1,428 (3.9)	<0.0001

Non-Suicidal Self Injury

Mechanisms for Promoting Smoking Cessation

- blockade of glutamatergic transmission inhibited nicotine reward
- facilitation of GABAergic transmission inhibited nicotine reward
- blockade of glutamatergic transmission inhibited nicotine-seeking behavior
- facilitation of GABAergic transmission inhibited nicotine-seeking behavior
- glutamatergic and GABAergic medications may be promising for smoking cessation

Marijuana's Effects on the Brain



BASAL GANGLIA
Involved in motor control and planning, as well as the initiation and termination of action

VENTRAL STRIATUM
Involved in the prediction and feeling of reward

AMYGDALA
Responsible for anxiety, emotion, and fear

HIPPOCAMPUS
Important for memory

HYPOTHALAMUS
Controls appetite, hormonal levels, and sexual behavior

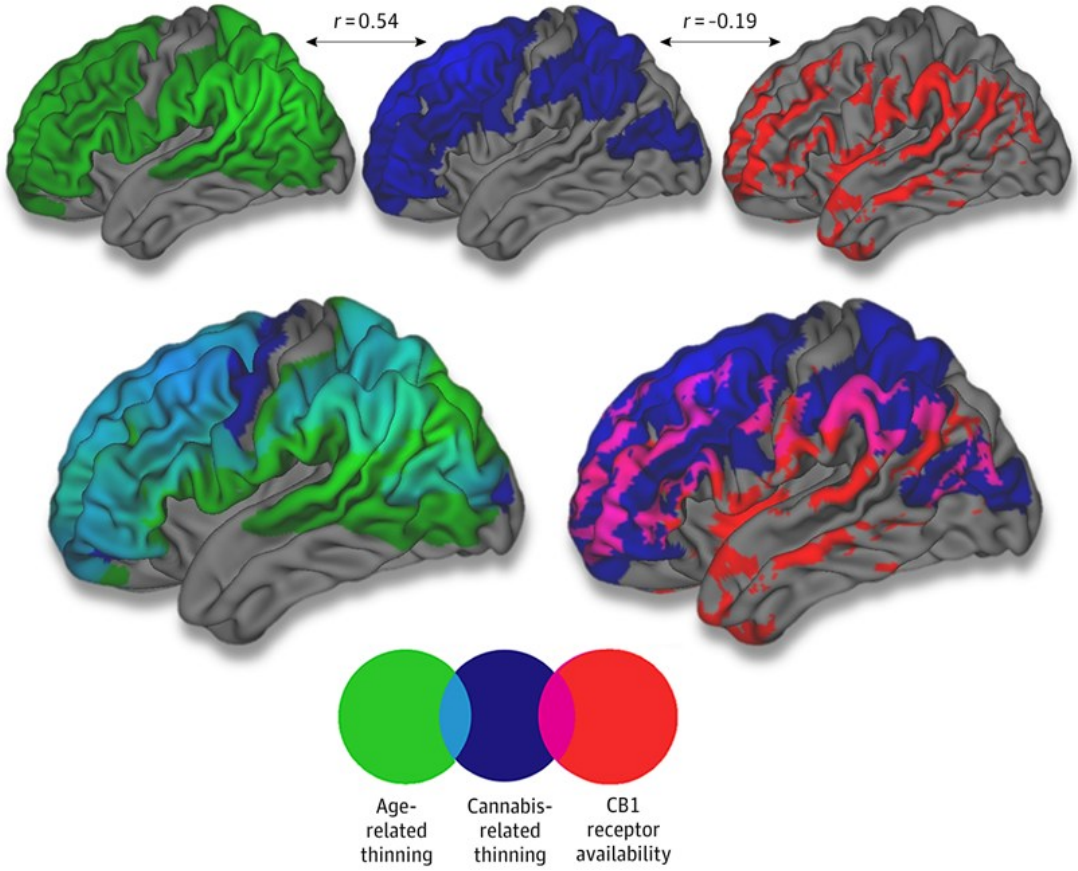
NEOCORTEX
Responsible for higher cognitive functions and the integration of sensory information

CEREBELLUM
Center for motor control and coordination

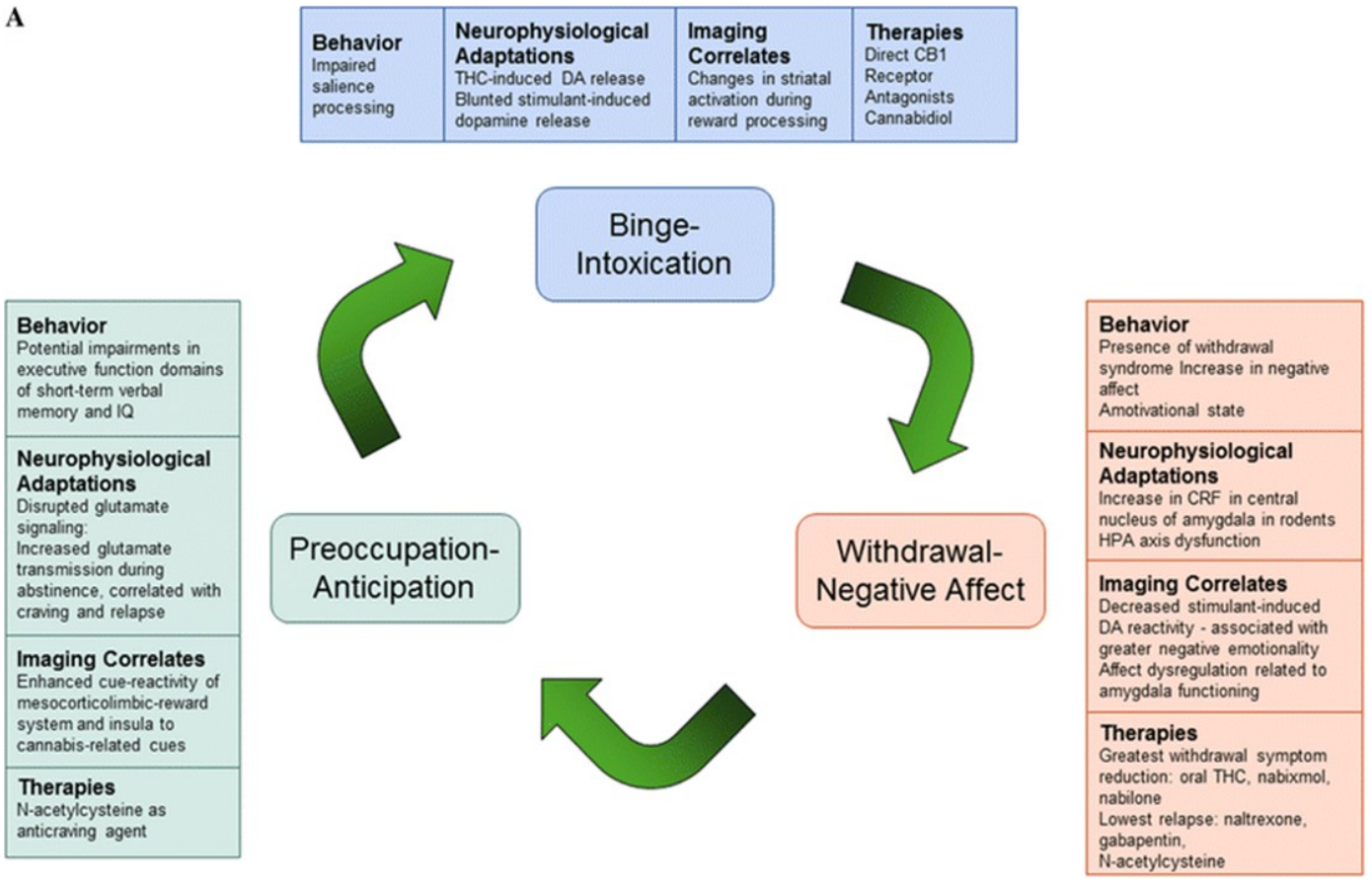
BRAIN STEM AND SPINAL CORD
Important in the vomiting reflex

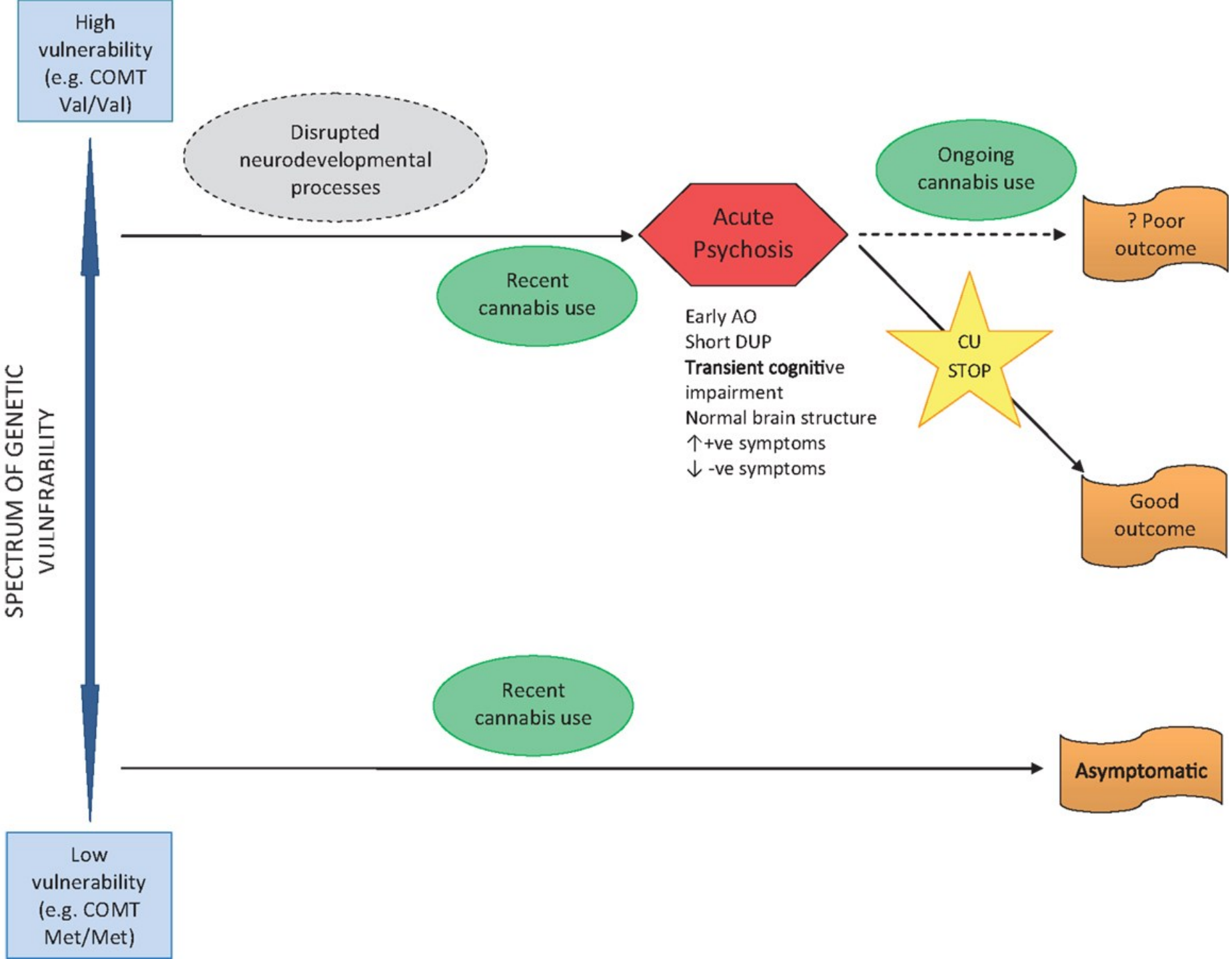
Association of Cannabis Abuse During Adolescence with Neurodevelopment

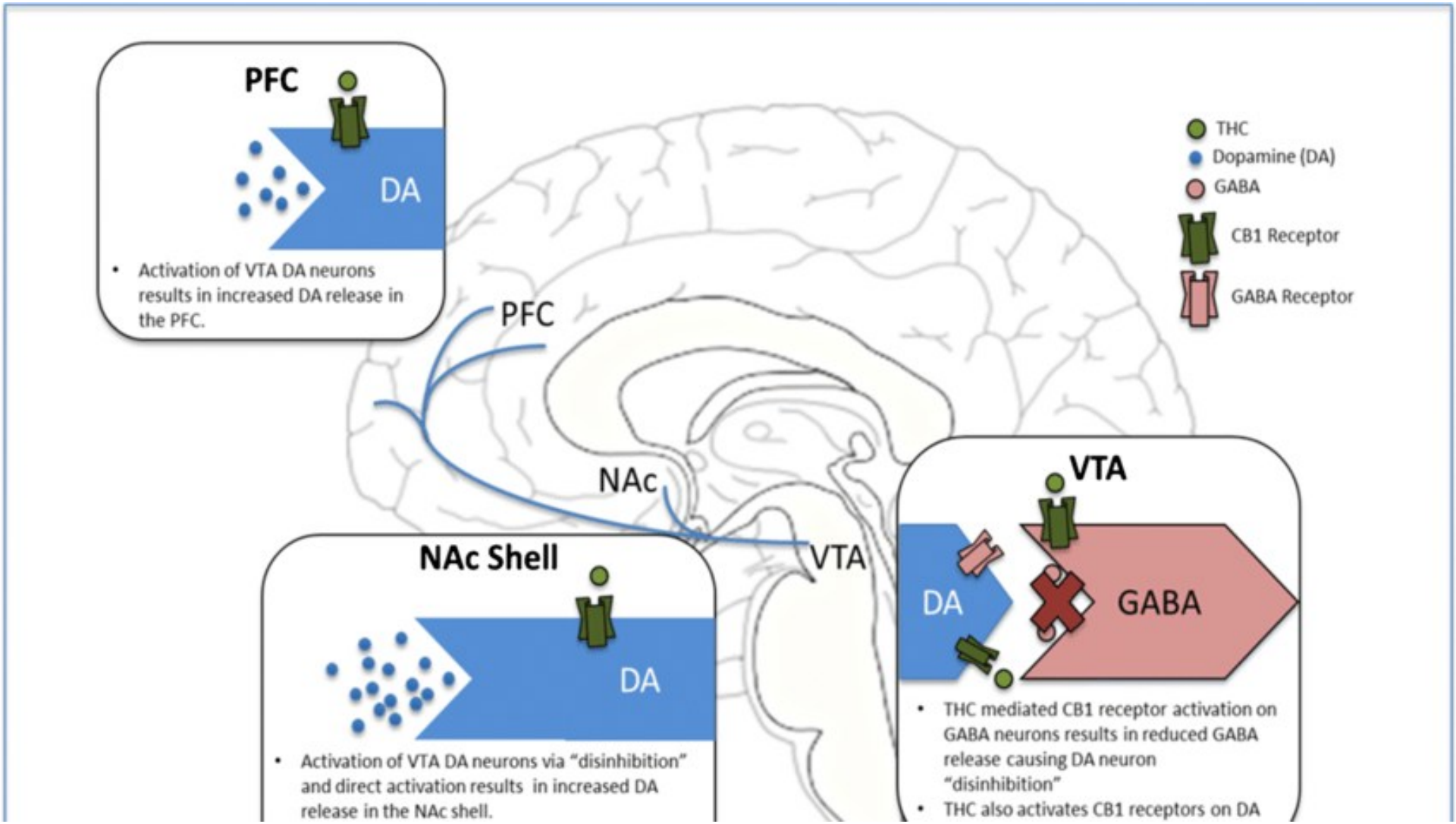
- Cannabis Accelerated Age Related Cortical Thinning 14-19 years
- Predominantly Prefrontal Regions
- Spatial Pattern of Cannabis Related Thinning PET SCAN of the Cannabinoid Receptor

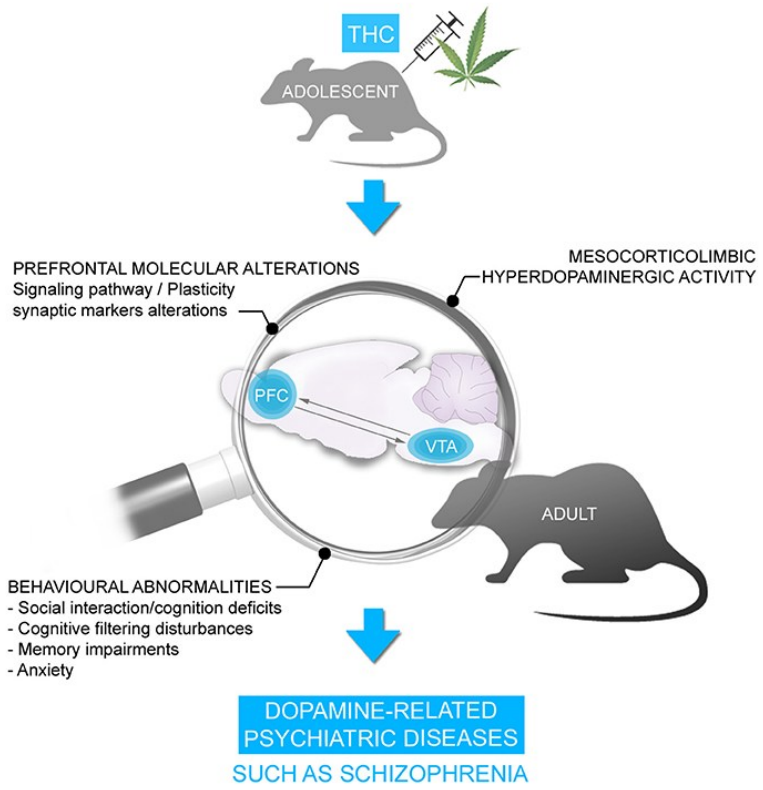


Cannabis Addiction Effects on the Brain

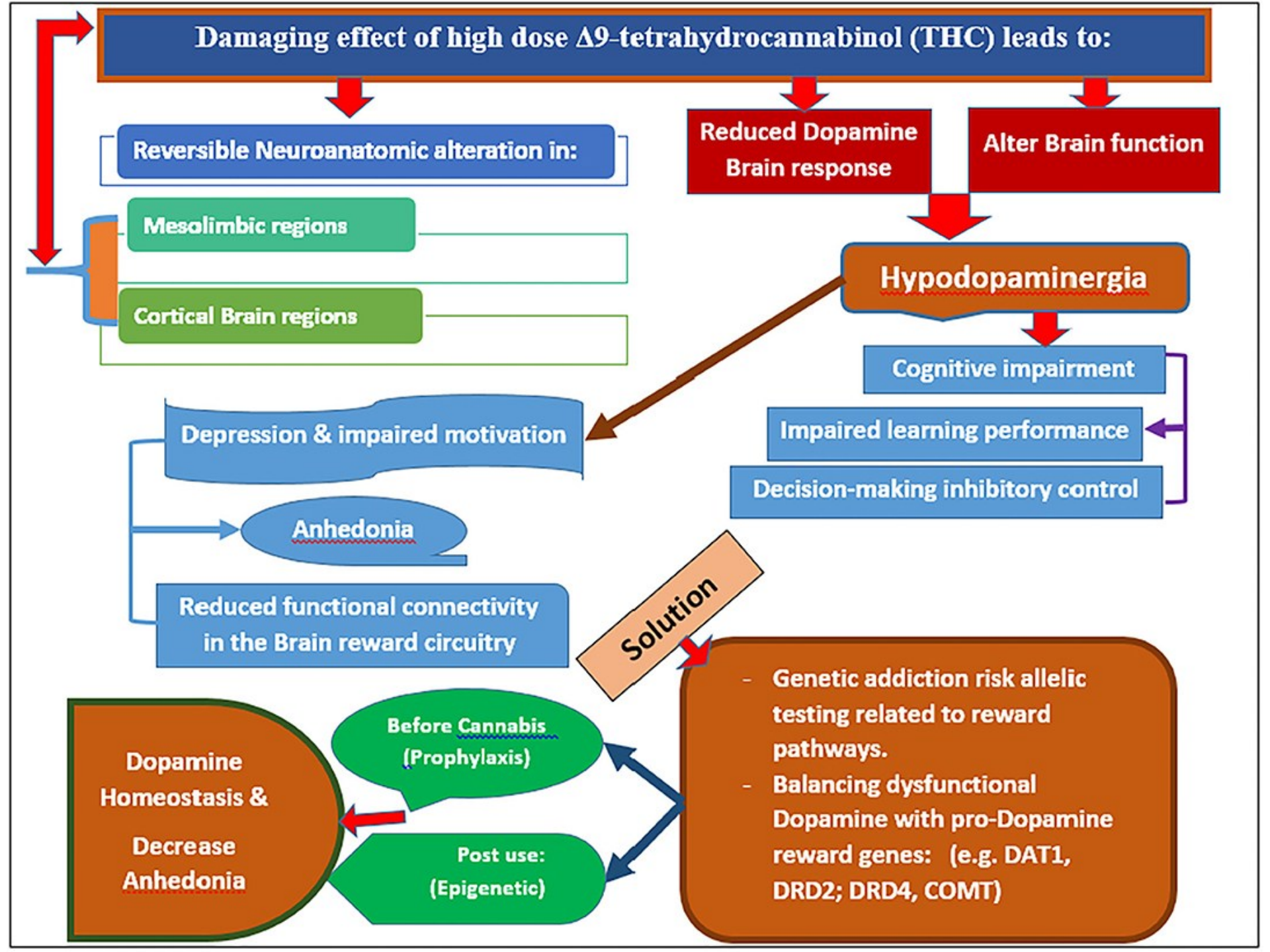



High vulnerability (e.g. COMT Val/Val)
Disrupted neurodevelopmental processes
Recent cannabis use
Acute Psychosis
Early AO
Short DUP
Transient cognitive impairment
Normal brain structure
↑+ve symptoms
↓ -ve symptoms
Ongoing cannabis use
? Poor outcome
CU STOP
Good outcome
SPECTRUM OF GENETIC VULNERABILITY
Recent cannabis use
Asymptomatic
Low vulnerability (e.g. COMT Met/Met)


PFC
DA
• Activation of VTA DA neurons results in increased DA release in the PFC.
PFC
NAc
VTA
NAc Shell
DA
• Activation of VTA DA neurons via "disinhibition" and direct activation results in increased DA release in the NAc shell.
THC
Dopamine (DA)
GABA
CB1 Receptor
GABA Receptor
VTA
DA
GABA
• THC mediated CB1 receptor activation on GABA neurons results in reduced GABA release causing DA neuron "disinhibition"
• THC also activates CB1 receptors on DA



- Chronic THC exposure during adolescence is associated with persistent behavioral disorders in adulthood including social interaction/cognition deficits, cognitive filtering disturbances, memory deficits and anxiety. These behavioral disorders were accompanied by alterations in signaling pathway and synaptic plasticity markers and hyperDAergic activity in the mesocorticolimbic pathway, resembling schizophrenia.


Damaging effect of high dose Δ9-tetrahydrocannabinol (THC) leads to:
Reversible Neuroanatomic alteration in:
Mesolimbic regions
Cortical Brain regions
Reduced Dopamine Brain response
Alter Brain function
Hypodopaminergia
Cognitive impairment
Impaired learning performance
Decision-making inhibitory control
Depression & impaired motivation
Anhedonia
Reduced functional connectivity in the Brain reward circuitry
Solution
- Genetic addiction risk allelic testing related to reward pathways.
- Balancing dysfunctional Dopamine with pro-Dopamine reward genes: (e.g. DAT1, DRD2; DRD4, COMT)
Before Cannabis (Prophylaxis)
Post use: (Epigenetic)
Dopamine Homeostasis & Decrease Anhedonia

Questions

- What type and brand of vape are you using? Where and how do you obtain your cartridges or vaping liquid? Do they come from a legitimate vendor (i.e., a store), or were they produced and sold in the illicit market?

Rationale

- Although data are still emerging, preliminary reports suggest that illicit market products may be associated with EVALI and other vaping-related harms.

Question

- When and at what age did you start vaping? Why did you start? Why do you continue to vape? What are some downsides of vaping for you?

Rationale

- Early onset of substance use is associated with greater lifetime risk of substance use disorder. Motivations for initiating and continuing vaping can help inform cessation counseling.

Questions

- How often do you vape in a day? How long after you wake up do you start vaping? Are you vaping at school and/or work, and if so, are you doing so regularly throughout the day? How many days a week do you vape?

Rationale

- Understanding the context in which youth vape can help clinicians offer effective cessation counseling. Frequent use throughout the day places youth at risk for developing withdrawal symptoms.

Questions

- What type of cartridges or liquids do you put in your vape? Do they contain nicotine? Tetrahydrocannabinol (THC)? Flavoring? If nicotine and/or THC, what is the concentration (or milligram content) of the cartridges/liquids?

Rationale

- Vaping nicotine and THC place youth at risk for nicotine and cannabis use disorders; higher concentration cartridges may be associated with greater risk. Vaping THC may also be associated with EVALI.

Withdrawal

- Question
- How long does a cartridge last you? How many cartridges do you go through in a typical week? If not using cartridges, how often do you refill your vaping device?

- Rationale
- More frequent use places youth at risk for withdrawal.

Question

- Have you tried quitting on your own? What happens if you stop vaping? Do you experience cravings (a strong feeling that you want to use again)?–If vaping nicotine:
- Do you develop symptoms of nicotine withdrawal (i.e., irritability, depressed mood, difficulty concentrating, feeling restless, increased appetite)?–If vaping THC: Do you develop symptoms of cannabis withdrawal (i.e., anxiety, hostility, difficulty sleeping, low appetite, depressed mood)? Have you had episodes of persistent vomiting? Paranoia? Psychotic symptoms like hearing voices or seeing things that are not really there?

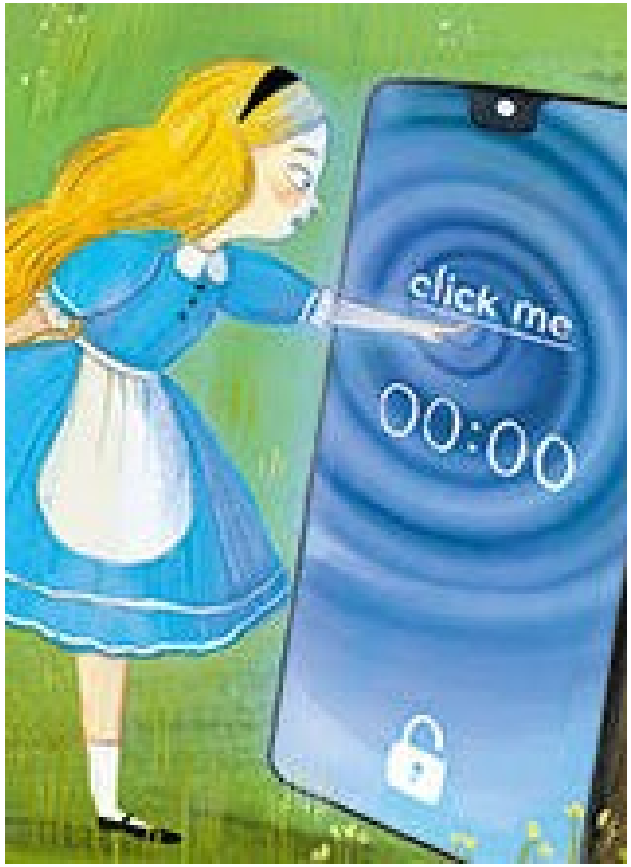
Vaping Pharmacotherapy Rx

- Bupropion SR Combined with Nicotine Replacement Therapy
- Varenicline Over 17

Vaping Rx

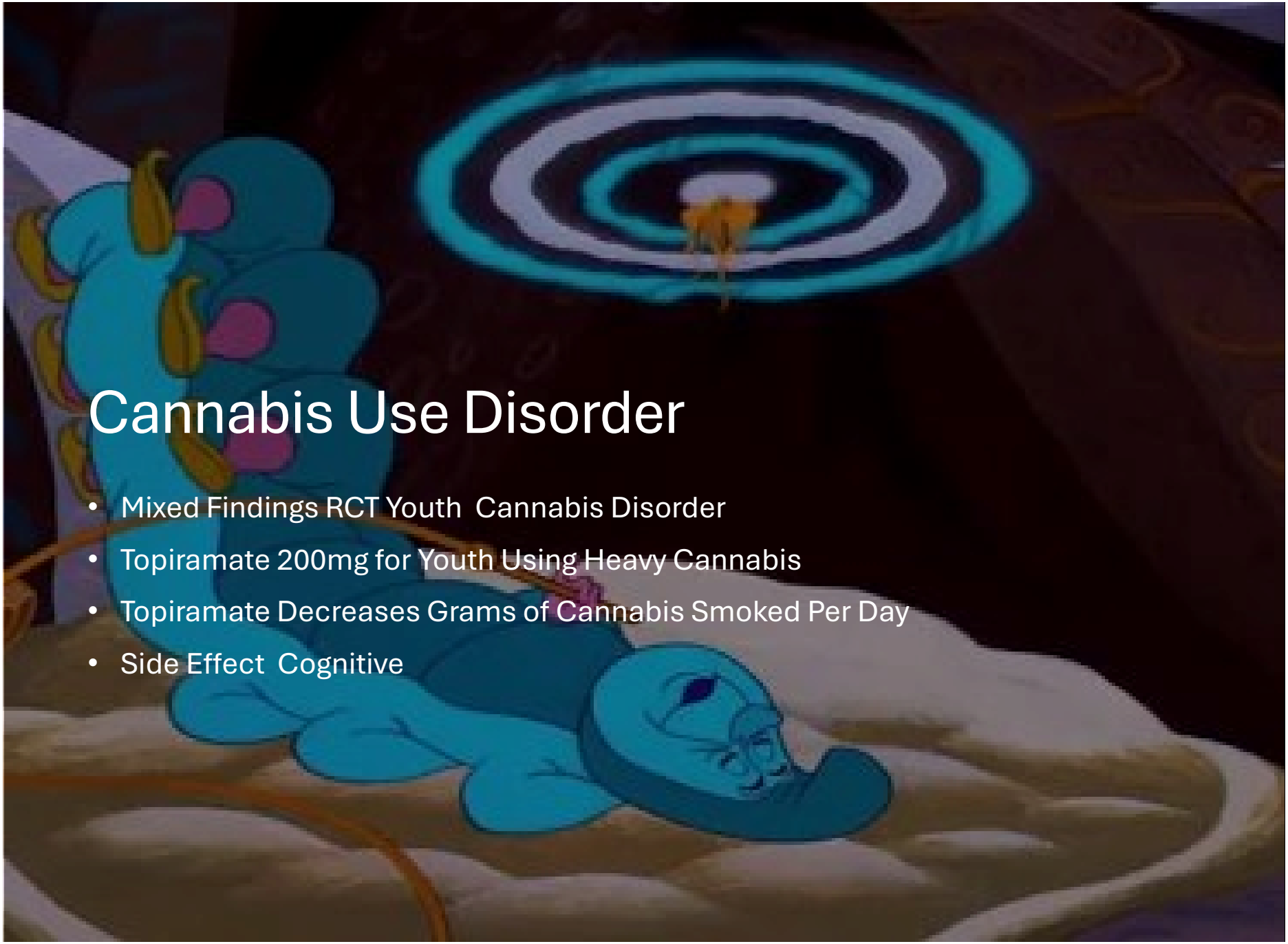
- Text Messaging Intervention
- 37.8 percent Decrease In Vaping For 7 months
- 287/759

- A Vaping Cessation Text Message Program for Adolescent E-Cigarette Users
- A Randomized Clinical Trial
- Amanda L. Graham, PhD



Cannabis Pharmacotherapy

- N-Acetylcysteine
- Gabapentin
- Topiramate



Cannabis Use Disorder

- Mixed Findings RCT Youth Cannabis Disorder
- Topiramate 200mg for Youth Using Heavy Cannabis
- Topiramate Decreases Grams of Cannabis Smoked Per Day
- Side Effect Cognitive

Rationale

- Cessation attempts are likely to be hampered by cravings and withdrawal. For nicotine, these symptoms can be reduced with pharmacotherapy.