Where does cannabis go in the body and how it may affect teenagers' brain?

Dr. Zerrin Atakan
Consultant Psychiatrist/Hon. Senior Lecturer
King's College London, IoPPN

1

Objectives

What will be covered:

- The content of the cannabis plant
- Endocannabinoid system
- Adolescent brain and the effects of THC
- Risk factors for psychosis

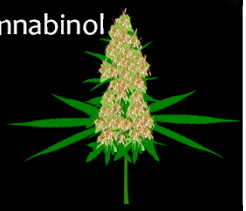
2

So what is so different about this plant?

3

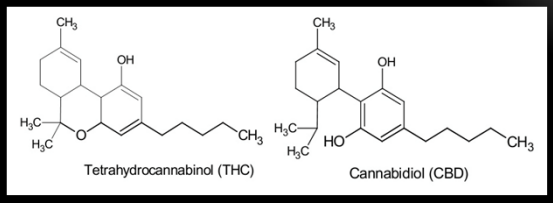
Cannabis plant

- A complex plant with ~143 compounds, ~100 terpenes and over all 400 chemicals
- First two main compounds are:
  - Delta-9-tetrahydrocannabinol (THC)
  - Cannabidiol (CBD)



4

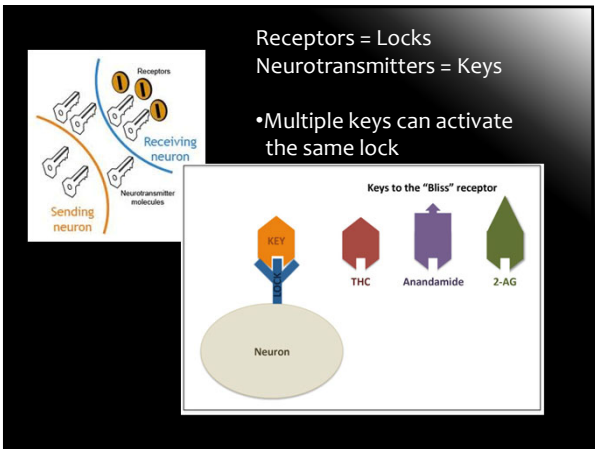
Delta-9-THC and cannabidiol with opposite effects



5

So, what happens when cannabis is taken? Where in the body does it go?

6



7

Endocannabinoid system - history

- 1988: A specific cannabinoid receptor was found in the rat brain
- 1990: CB1 and CB2 receptors are discovered
- 1992: The first neurotransmitter for this system is discovered (called "anandamide" from a Sanskrit word "ananda" meaning "bliss"
- 1993: The the second neurotransmitter discovered

8

Endocannabinoid system

- Found from humans to tuberculosis microbes to fruit flies
- This suggests that the gene must have been present early in evolution, and its conservation implies that this system serves very important biological functions

9

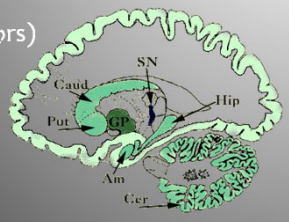
Where is the endocannabinoid system in the body?

10

ECS receptor distribution in the brain in humans:

(mostly CB1 receptors)

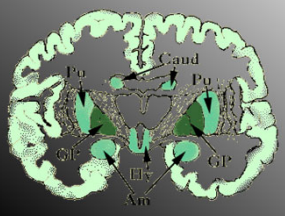
Cerebral cortex
Cerebellum
Limbic area



11

ECS receptor distribution in the brain in humans:

Limbic system
- Hippocampus
- Amygdala
- Hypothalamus

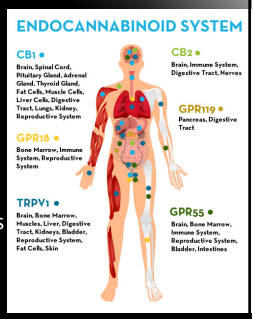


12

ECS receptor distribution in humans:

In the body (mostly CB2)

- Brainstem
- Spinal cord
- Spleen, heart and immune system
- Endocrine glands, leukocytes
- Parts of the reproductive, urinary and gastrointestinal tracts



13

Endocannabinoid system (ECS)

- One of the most widely distributed and currently researched systems
- Regulates neuronal, vascular, skeletal, metabolic, immune and reproductive systems
- Have effects on other neurotransmitter systems such as GABA, glutamate and dopamine, which are all associated with psychiatric conditions

14

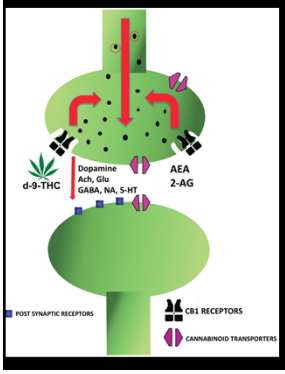
Therapeutic potential of this system

Svizenska et al, 2008

- Hypnotics
- Analgesics
- Anti-emetics
- Anti-asthmatics
- Anti-hypertensives
- Immunomodulatory drugs
- Neuroprotective agents
- Spasticity and other "movement disorders"
- Anti-glaucoma
- Eating disorders
- Alcohol withdrawal
- Bone growth
- Atherosclerosis
- Anti-epileptics
- Anti-psychotics

15

THC



When cannabis is used THC binds to CB1

16

Where does CBD go?

- CBD when taken with THC is known to reduce THC's effects
- CBD's exact mode of action is not yet known, but strongly inhibits CB1 agonists, by acting as a negative modulator at the receptor
- CBD targets beyond the endocannabinoid system, including some serotonin and opioid receptors (Pertwee, 2008)

17

So, what happens when young people use cannabis?

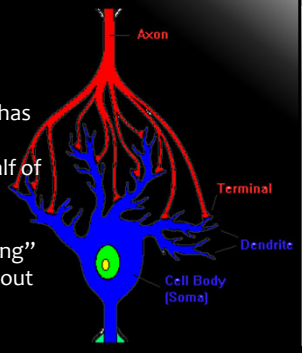
18

But first of all, what is so special about the teenager brain?

19

Nerve cells connect with each other via synapses

- At birth each cortical neuron has about 2,500 synapses
- At age 2 - 3 each neuron has about 15,000 synapses
- Adult brain has about half of these synapses, as old connections are deleted via a process called "pruning"
- Pruning is completed about age 20 - 21



20

Brain development

Brain development is an organized and highly dynamic multistep process and is;

- Genetically determined
- Epigenetically directed
- Environmentally influenced

Adolescence is characterized by

- Dramatic changes in brain growth and connectivity
- A critical period for the neurodevelopment of specific, mainly frontal cortical, brain regions

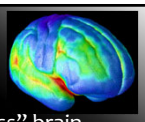
21

Brain development

- Brain growth among infants and children is focused essentially on volume
- In adolescence the focus shifts to creating efficient neuronal pathways
- Synaptic refinement is achieved by pruning some connections and keeping "useful" neurons by selection of certain synapses and dendrites
- Particularly the front part of the brain, Prefrontal Cortex (PFC) is considered one of the most functionally advanced areas
- PFC is mainly involved in higher order cognitive processing such as response selection, decision making and working memory

22

Adolescent brain



- Adolescent brain is a "work in progress" brain
- During this phase the brain goes through massive changes: loss of gray matter and increase in white matter
- Loss of gray matter, "pruning" leads to a more efficient neural network communication
- An interference at this phase might represent a risk for mental disorders
- Changes in synaptic pruning with cannabis use has been shown in animal studies

23

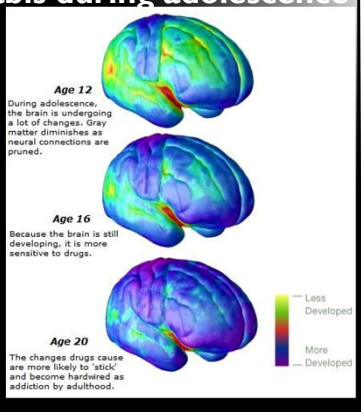
Endocannabinoids play an important role in neural development

- Animal studies confirm that endocannabinoid signalling is present during the gestational period and is integral for the morphogenesis of the neurons and axons
- Two processes may be adversely affected by exposure to cannabis during this period:
  - Synaptic pruning
  - White matter development

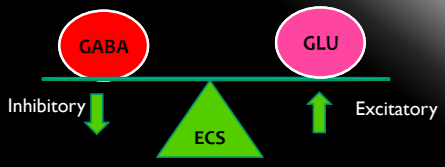
24

Use of cannabis during adolescence

- Interference with this process can affect attention, impulse control and executive functioning such as planning and decision making



25



- The good functioning of adult PFC functioning is dependent on a delicate balance between inhibitory GABA-ergic, and excitatory glutamatergic neurons
- Endocannabinoid system (ECS) controls this balance to prevent excessive release
- THC disrupts the protective effect of the ECS
- It has been postulated that THC induces psychotic states by disrupting the excitatory–inhibitory balance of neural networks

26

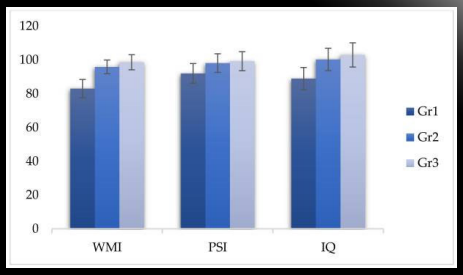
Effects of cannabis use on cognition during adolescence

Frolli et al, 2021:

- Three groups of 15-16 yr-olds
  - Group 1: Chronic and heavy cannabis users
  - Group 2: Occasional users
  - Group 3: Non-users
- Results: A significant decrease in performance in working memory tasks and processing speed by subjects using cannabis chronically (group 1), compared to the other two groups

27

The effect of cannabis use on cognition in teenagers



WMI: Working Memory Index; PSI: Processing speed Index; IQ: Intelligence quotient , Frolli et al, 2021

28

Earlier cannabis use vs. later cannabis use

A population survey of 36,309 people found (Ryan et al, 2020)

- No support for an association between cannabis use and the development of schizophrenia/psychosis among **adults aged 18-34** after adjusting for covariates such as history of trauma, sexual orientation, other substance use and family substance-related problems
- But they observed that cannabis use in **early and late adolescence** was consistently associated with schizophrenia/psychosis

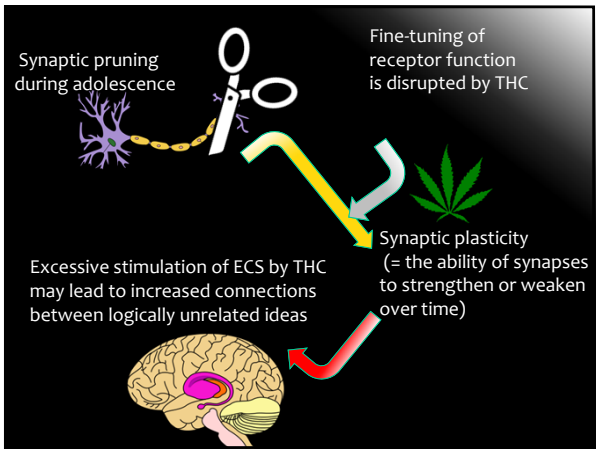
29

Can earlier use of cannabis bring forward the onset of a psychotic illness?

Systematic meta-analysis: cannabis use and earlier onset of psychosis; Large et al, 2011

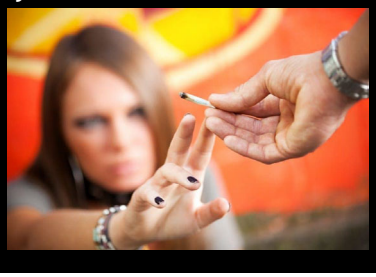
- 443 articles ➔ 83 studies met the inclusion criteria
- Meta-analysis of age at onset was 2.70 years earlier among samples of cannabis users (**p<.001**)

30



31

So why not every teenager who use cannabis does not develop a psychotic illness?..



32

Genetic studies

- As there is now a significant movement toward the legalization of cannabis around the world, it is important to know who is particularly vulnerable to the psychotogenic effects of cannabis in the young
- Gene-environment interaction studies have mainly focussed on genetic variants involved in the regulation of the dopaminergic system

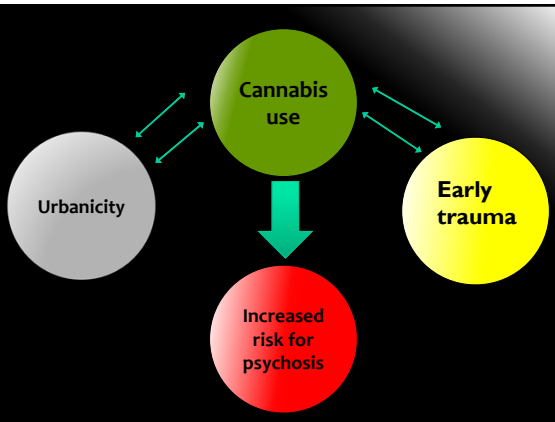
33

Genetic studies

Genes so far associated with an increased risk of development of a psychotic illness with cannabis use:

- COMT (Caspi et al, 2005) – the views are mixed
- AKT1 (van Winkel et al, 2011; di Forti et al, 2012; Bhattacharyya et al, 2012)
- DAT1 (Bhattacharyya et al, 2012)
- Possibly.. BDNF Val66Met (Decoster et al, 2011)
- CNR1 and NRG1 (Pelayo-Teran et al, 2012)
- ZNF804A gene (Soler et al, 2018)

34



Cougnard et al, 2007; Dominguez, et al 2011; Kuepper et al. 2011b)

35

Even healthy subjects are differently affected by THC

- 1/3 of our healthy volunteers developed transient psychotic symptoms after having 10 mg of THC, which lasted up to 3 hours

- The transiently psychotic group showed less activation than the non-psychotic group in certain parts of their brain (right middle temporal gyrus and cerebellum)

Atakan et al, 2013

36

At risk groups

Sensitivity to psychosis as determined by	Possible sensitivity factors	Study group
Predisposition to psychosis	Family history of psychotic illness	McGuire et al. 1995
	Presence of subclinical psychotic symptoms	Henquet et al. 2004
	Ultra-high risk groups	Peters et al. 2009
Personality	Schizotypal personality disorder	Barkus et al, 2006; Stirling et al. 2008; Anglin et al. 2012
Psychosis susceptibility genes	COMT	Caspi et al. 2005
	AKT1	van Winkel et al. 2011; DiForti et al. 2012, Morgan et al, 2016
	AKT1 and DAT1	Bhattacharyya et al. 2012, 2014

37

Strong evidence on the following factors for increased risk

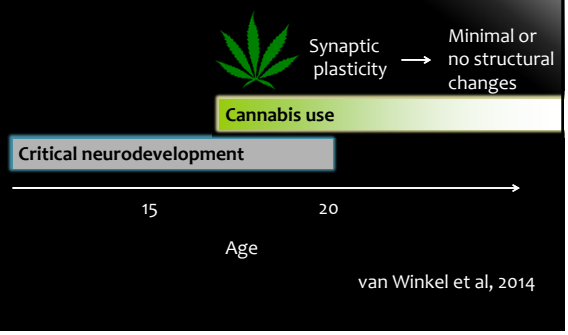
Statement	Consistency of evidence	Evidence from E NB G	Evid. grade
Younger age use associated with higher risk	+ + +	E NB	A+
THC interferes with synaptic plasticity	+ + +	NB	A
Those with familial risk have higher sensitivity	+ +	NB G	A
THC/CBD critical	+ +	E NB	A
Early life events and cannabis use	+	E NB	B

E=Epidemiological; NB= Neurobiological; G=Genetic

van Winkel et al, 2014

38

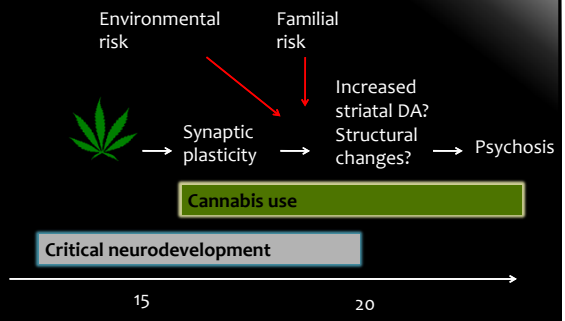
a) Genetically low risk individual



van Winkel et al, 2014

39

b) Genetically high-risk individual



40

Summary

- Cannabis is chemically a complex plant
- Endocannabinoid system (ECS) is essential for our survival and has many significant functions in the body and the brain
- Adolescent brain is a 'work in progress' brain and ECS has a significant role in developing the brain into adult form
- Heavy THC use during adolescence can disrupt the development of adult brain and may impact upon cognitive functioning and mental health

41

Summary (contd.)

- It is thought that THC induces psychotic states by disrupting the excitatory–inhibitory balance of neural networks
- However, not everyone who use cannabis develops a psychotic illness for number of reasons including; having genetic vulnerability, certain type of personality, living in urban areas and experiencing early trauma

42

43