consequences?
marijuana and the teen brain
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UCSD
in this talk

- what is marijuana?
- the brain on marijuana
- is the teen brain special?
- current research
what is marijuana?

cannabis sativa plant

leaves, stems, flowers

delta-9-tetrahydrocannabinol

$= \Delta^9$-THC

main psychoactive ingredient
Δ⁹-THC is the main psychoactive ingredient

Δ⁹-THC activates cannabinoid1 (CB1) receptor in the brain.

CB1 is expressed at high levels in many brain areas.

Two endogenous brain lipids have been identified as CB1 ligands.
endocannabinoids – ligands for CB₁

- N-arachidonylethanolamine
- anandamide (AEA)
- arachidonate-derived neuroactive lipids
- 2-arachidonoylglycerol
- 2-AG
what areas of the brain process marijuana?

- hypothalamus
- basal ganglia
- ventral striatum
- amygdala
- brainstem
- cortex
- hippocampus
- cerebellum
hormones
appetite
circadian rhythms
sexual behavior

brain areas:
- hypothalamus
- basal ganglia
- ventral striatum
- amygdala
- brainstem
- hippocampus
- cortex
- cerebellum
motor controlled planning

initiation of actions

termination of actions

habit pathway

hypothalamus
basal ganglia
ventral striatum
amygdala
brainstem
hypocampus
cortex
cerebellum
prediction

reward

addiction?
anxiety
emotion
fear

hypothalamus
basal ganglia
ventral striatum
amygdala

hypothalamus
cortex
basal ganglia
hippocampus
ventral striatum
amygdala
brainstem
cerebellum
vomiting reflex
pain sensation
sympathetic nervous system reactions

hypothalamus
basal ganglia
ventral striatum
amygdala
brainstem
cortex
hippocampus
cerebellum
cortex

hypothalamus
basal ganglia
ventral striatum
amygdala
brainstem

hippocampus
cerebellum

cortex

higher cognitive functions
sensation perception
judgment and pleasure
Hypothalamus, basal ganglia, ventral striatum, amygdala, cortex, hippocampus, cerebellum, brainstem.

Memory formation: facts, sequences, places.
- hypothalamus
- basal ganglia
- ventral striatum
- amygdala
- brainstem
- cortex
- hippocampus
- cerebellum

- motor control
- coordination
- motor learning
- doubles risk of car accident - DUI

DUI
Three Types of Implicit Learning

- Habituation
- Sensitization
- Classical Conditioning
Most simple form of learning

Initial response to stimuli:
very defensive -

Repeated exposure to stimuli:
Response is muted - Eventually ignored.

Purpose:
Animal needs to learn which stimuli to safely ignore

Eliminates inappropriate or exaggerated defense responses

Important for:
Organizing perception
Sensitization – mirror image of habituation

After a noxious stimulus

the sensitized animal respond more strongly to all stimuli.

Purpose:
Instead of ignoring a stimulus – it is a form of learned fear. Survival.

It teaches the animal to attend and respond more vigorously to almost any stimulus

Konrad Lorenz: “An earthworm that has just avoided being eaten by a blackbird ... is indeed well advised to respond with a considerably lowered threshold to similar stimuli because it is almost certain that the bird will still be nearby for the next few seconds.”
Aversive Classical Conditioning

A neutral stimulus must always precede the aversive stimulus – that way the animal will come to predict it.

Pavlov: shock a dog’s paw. The shock caused the animal to raise and withdraw its leg – a fear response.

Pavlov found that after several trials in which he paired the shock with a bell – first sounding the bell then the shock – the dog would withdraw his paw whenever the bell sounded.

Classical conditioning an association is formed between a pair of stimuli that occur in rapid sequence.

Teaches the animal to associate an unpleasant stimulus with a stimulus that ordinarily elicits no response.
Synaptic strength is not fixed – it can be altered in different ways by different patterns of activity.
Cellular basis of learning and memory

- Learning changes neural responsiveness
- Enhanced functioning of existing neural circuits or the establishment of new ones.
Changes in synaptic efficiency:

- **Normal synapse**
- Increase in release probability
- Increase in number of release sites
- Increase in number of vesicles
- Increase in receptor sensitivity
- Increase in the number of receptors
- Increase in number of dendritic spines
- Active receptor
- Hyper-sensitive receptor
- Silent receptor
- Synaptic vesicle
- Released
How do endocannabinoids affect synaptic transmission?

Voltage-dependent Ca\(^{++}\) channels open & Ca\(^{++}\) enters the terminal.

Xmtr is released from synaptic vesicle.

Xmtr binds to receptor and the channel opens.

Post-synaptic depolarization opens voltage-dependent Ca\(^{++}\) channels \(\rightarrow\) which activates endocannabinoid synthesis.
endocannabinoid signaling is critical during development
Brain maturation continues through adolescence.

- **Infancy**
- **Childhood**
- **Adolescence** (12-17 years old)
- **Adulthood**

Robust neurodevelopment continues through childhood and adolescence.

- Hippocampus
- Prefrontal cortex
- Synaptic pruning
- Receptor distribution
- Volumetric growth
- Myelination
CB₁ receptors increase dramatically from infancy to young adulthood.

- CB1 receptor expression changes over time
- Dramatic increase during development
- Frontal cortex, striatum & hippocampus

Mato et al., 2003
endocannabinoid ligand expression changes during adolescence.

- AEA and 2-AG expression changes
- AEA – onset of puberty for females in hypothalamus
- 2-AG expression changes in PFC & N. Accumbens

Disruption of normative endocannabinoid signalling during adolescence may have long-standing consequences on adult brain function.

Mato et al., 2003
Invited review

Trajectory of adolescent cannabis use on addiction vulnerability

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Long lasting consequences of cannabis exposure in adolescence

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Moreover, there is evidence for a role of the endocannabinoid system in neural development. Both cannabinoid receptors and endocannabinoid ligands can be detected in the brain during early developmental periods (Romero et al., 1997; Berrendero et al., 1999). The atypical distribution of cannabinoid CB1 receptors during the perinatal period seems to be related to a specific involvement of the endocannabinoid system in brain development. The system constituted by CB1 receptors and their putative endogenous ligands might influence the gene expression of several key genes for neural development as part of the specific function of the endocannabinoid system during this period (Fernandez-Ruiz et al., 2004). Moreover, in animal models, cannabinoid receptors have been shown to mature slowly, with maximal levels during adolescence which later drop to adult levels (Rodriguez de Fonseca et al., 1993; McLaughlin et al., 1994; Belue et al., 1995). Like dopamine receptors (Seeman, 1999), cannabinoid receptors may undergo postadolescent pruning. It is, therefore, conceivable that intake of exogenous cannabinoids, especially in vulnerable developmental periods, such as the adolescence, might induce residual effects.
Schizophrenia is a devastating illness.

1% of world population emerges: late adolescence or early adulthood

10% eventually commit suicide

most experience a lifetime of disability

high emotional family burden

Psychosis:

- Distortions in inferential thinking
- Perceptual disturbances
- Auditory hallucinations
- Voices distinct from one’s own thoughts
- Delusions - fixed, false beliefs that are firmly held in the face of contradictory evidence

Risk of developing schizophrenia

- Risk is directly proportional to being genetically related to someone affected by schizophrenia.

- Degree of risk conferred for each susceptibility gene is small.

- Twin studies: only 50% is accounted for by genes – the rest is environmental risk.
environmental events increase risk

- environmental events during development
- advanced paternal age at time of conception
- frequent cannabis use during adolescence

genetics + environment

- frequent cannabis use during adolescence
- environmental events during development
- advanced paternal age at time of conception
Schizophrenia is more than psychosis.

disturbances in brain function

perception
inferential thinking
language (fluency & production)
expression of emotion
capacity for pleasure
volition
attention

impairments

social

occupational
Does cannabis use increase the risk of schizophrenia?

Worldwide evidence documents that cannabis use is a modest statistical risk factor for the emergence of psychosis, ranging from psychotic symptoms such as hallucinations and delusions to clinically significant disorders such as schizophrenia. Prospective studies estimate that cannabis use is associated with a two-fold increase in later schizophrenia outcomes, and early, adolescent-onset cannabis use is associated with a higher risk (Arseneault et al., 2004), possibly because individuals who begin to use cannabis when the brain is still developing are most vulnerable to its deleterious effects (Ehrenreich et al., 1999; Pistis et al., 2004; Pope et al., 2003; Schneider and Koch, 2003). Nonetheless, the vast majority of young people who use cannabis do not develop psychosis, suggesting the hypothesis that, if cannabis is indeed causal, some individuals may be genetically vulnerable to its effects.
CORTICAL INHIBITORY NEURONS AND SCHIZOPHRENIA

David A. Lewis*, Takanori Hashimoto* and David W. Volk*

Abstract | Impairments in certain cognitive functions, such as working memory, are core features of schizophrenia. Convergent findings indicate that a deficiency in signalling through the TrkB neurotrophin receptor leads to reduced GABA (y-aminobutyric acid) synthesis in the parvalbumin-containing subpopulation of inhibitory GABA neurons in the dorsolateral prefrontal cortex of individuals with schizophrenia. Despite both pre- and postsynaptic compensatory responses, the resulting alteration in perisomatic inhibition of pyramidal neurons contributes to a diminished capacity for the gamma-frequency synchronized neuronal activity that is required for working memory function. These findings reveal specific targets for therapeutic interventions to improve cognitive function in individuals with schizophrenia.
Dysfunctional GABAergic inhibition in the prefrontal cortex leading to "psychotic" hyperactivation

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Abstract

**Background:** The GABAergic system in the brain seems to be dysfunctional in various psychiatric disorders. Many studies have suggested so far that, in schizophrenia patients, GABAergic inhibition is selectively but consistently reduced in the prefrontal cortex (PFC).

**Results:** This study used a computational model of the PFC to investigate the dynamics of the PFC circuit with and without chandelier cells and other GABAergic interneurons. The inhibition by GABAergic interneurons other than chandelier cells effectively regulated the PFC activity with rather low or modest levels of dopaminergic neurotransmission. This activity of the PFC is associated with normal cognitive functions and has an inverted-U shaped profile of dopaminergic modulation. In contrast, the chandelier cell-type inhibition affected only the PFC circuit dynamics in hyperdopaminergic conditions. Reduction of chandelier cell-type inhibition resulted in bistable dynamics of the PFC circuit, in which the upper stable state is associated with a hyperactive mode. When both types of inhibition were reduced, this hyperactive mode and the conventional inverted-U mode merged.

**Conclusion:** The results of our simulation suggest that, in schizophrenia, a reduction of GABAergic inhibition increases vulnerability to psychosis by (i) producing the hyperactive mode of the PFC with hyperdopaminergic neurotransmission by dysfunctional chandelier cells and (ii) increasing the probability of the transition to the hyperactive mode from the conventional inverted-U mode by dysfunctional GABAergic interneurons.

SYMPOSIUM REPORT

Defined types of cortical interneurone structure space and spike timing in the hippocampus

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The cortex encodes, stores & combines information about the *external* and *internal* environment in terms of rhythmic activity.
basket cell resets pyramidal cell firing

a single inhibitory pulse will synchronize two pyramidal cells


IPSPs in theta frequency caused tighter synchrony
A recent study found that cannabis use was significantly associated with a decrease in age of onset of schizophrenia (Sugranyes et al., 2009). This is concerning as the early onset of schizophrenia has been proven to be a negative outcome factor (Malla and Payne, 2005; Rabinowitz et al., 2006). A study in Spain found that patients presenting with first episode psychosis (average age 15.5 years) had a higher rate of positive symptoms and less negative symptoms if they were cannabis users compared with non-cannabis users (Baeza et al., 2009). In addition, the increases in cannabis use in the UK population over the last 30 years as reported by Hickman et al. (2007) were concluded by the authors to be mainly due to more prolonged use initiated at younger ages (Hickman et al., 2007). Thus, despite some variables factors such as the measurement of psychotic symptoms and control for confounding factors, it appears that there is a causal link between adolescent cannabis use and the development of psychoses such as schizophrenia. With a greater amount of adolescents consuming cannabis, it has become imperative to critically evaluate whether this age group is particularly vulnerable to developing psychoses such as schizophrenia compared with adolescents that do not consume cannabis, and to elucidate mechanisms responsible for this vulnerability.

Adolescent cannabis use and psychosis: epidemiology and neurodevelopmental models

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Impact of Cannabis Use on Brain Function in Adolescents

Research report

Altered prefrontal and insular cortical thickness in adolescent marijuana users

Melissa P. Lopez-Larson, Piotr Bogorodzki, Jadwiga Rogowska, Erin McGlade, Jace B. King, Janine Terry, Deborah Yurgelun-Todd

Genetic mediation of the link between schizophrenia and cannabis use

Neurophysiological and cognitive effects of smoked marijuana in frequent users

Carl L. Hart, Aaron B. Ilan, Alan Gevins, Erik W. Gunderson, Kemi Role, Richard W. Foltin

 Adolescent Cannabis Exposure Alters Opiate Intake and Opioid Limbic Neuronal Populations in Adult Rats

Cannabis use and risk of psychotic or affective mental health outcomes: a systematic review

Theresa H M Moore, Stanley Zammit, Anne Lingford-Hughes, Thomas R E Barnes, Peter B Jones, Margaret Burke, Glyn Lewis
Adolescent Cannabinoid Exposure Permanently Suppresses Cortical Oscillations in Adult Mice

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Regular marijuana use during adolescence, but not adulthood, may permanently impair cognition and increase the risk for psychiatric diseases, such as schizophrenia. Cortical oscillations are integral for cognitive processes and are abnormal in patients with schizophrenia. We test the hypothesis that adolescence is a sensitive period because of the active development of cortical oscillations and neuromodulatory systems that underlie them. The endocannabinoid system upon which marijuana acts is one such system. Here we test the prediction that adolescent cannabinoid exposure alters cortical oscillations in adults. Using in vitro local field potential, in vivo electrocorticogram recordings and cognitive behavioral testing in adult mice, we demonstrate that chronic adolescent, but not adult, cannabinoid exposure suppresses pharmacologically evoked cortical oscillations and impairs working memory performance in adults. The later-maturing prefrontal cortex is more sensitive to adolescent exposure than the earlier-maturing, primary somatosensory cortex. These data establish a link between chronic adolescent cannabinoid exposure and alterations in adult cortical network activity that underlie cognitive processes.

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Keywords: marijuana; development; schizophrenia; Δ⁹-tetrahydrocannabinol; novel object recognition; neural synchrony

INTRODUCTION

et al. 2004). The cortical endocannabinoid (eCB) system in
what now?

- hypothalamus
- basal ganglia
- ventral striatum
- amygdala
- cortex
- hippocampus
- cerebellum
- brainstem