adolescent brains and marijuana use

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PART 2
**what is marijuana?**

<table>
<thead>
<tr>
<th>cannabis sativa plant</th>
<th>leaves, stems flowers</th>
</tr>
</thead>
<tbody>
<tr>
<td>delta-9-tetrahydrocannabinol</td>
<td>main psychoactive ingredient</td>
</tr>
<tr>
<td>$\Delta^9$-THC</td>
<td></td>
</tr>
</tbody>
</table>
$\Delta^9$-THC is the main psychoactive ingredient

$\Delta^9$-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
- cerebellum
- brainstem
- cortex
- hippocampus
“Neuroscience, the scientific study of the biology of the brain, has made great strides over the past decade in revealing that remarkable changes occur in the brain during the second decade of life.

Contrary to long-held ideas that the brain was mostly grown up – “fully cooked” – by the end of childhood, it is now clear that adolescence is a time of profound brain growth and change.”

Weinberger, Elvevag, & Giedd, 2005
White matter:
- Increase during adolescence
- Increase into 50’s (frontal, temporal)
- Corpus callosum: greatest increase during adolescence

Gray matter:
- Increases volume until early teens
- Decreases until old age

Zits

Jerry Scott & Jim Borgman

Jeremy: You're sunburned!!

Mom: Yeah, I guess my back is a little pink.

Jeremy: How could you forget sunscreen? I handed it to you on your way out the door!

Mom: So you admit that this is your fault?

Jeremy: I beg your pardon?

Mom: You gave me the sunscreen, but you didn't tell me to use it. Poor followthrough on your part, Mom.
teen brain ... is different

- puberty changes everything
- mood swings, slammed doors, rash decisions
- brain is to blame – and the hormones
- do not have reasoning as adults
- prefrontal cortex – involved in complex decision making

Prefrontal cortex is one of the last parts of the brain to mature

Testosterone increases aggression and irritability.

Estrogen enlarges the hippocampus more in girls

Teen underdeveloped decision processing affects everything.

- All decisions
- Risk taking decisions – teens have higher levels of dopamine too
- Lack of impulse control – prefrontal and serotonin
- Teens prefrontal cortex is similar to a damaged adult’s prefrontal cortex
- Moral decision knowledge and doing disconnect
- Emotion control

Amygdala increases in size, which causes the teen’s emotional centers to be in hyper-drive.

How do endocannabinoids affect synaptic transmission?

1. **Pre-synaptic**
   - Voltage-dependent Ca++ channels open & Ca++ enters the terminal.
   - Xmtr is released from synaptic vesicle.

2. **Post-synaptic**
   - Xmtr binds to receptor and the channel opens.
   - Post-synaptic depolarization opens voltage-dependent Ca++ channels → which activates endocannabinoid synthesis.

**Question:** How do endocannabinoids affect synaptic transmission?
endocannabinoid signaling is critical during development
Brain maturation continues through adolescence.

- **infancy**
- **childhood**
- **adolescence 12-17 years old**
- **adulthood**

**Brain maturation continues**

- hippocampus
- prefrontal cortex
- synaptic pruning
- receptor distribution
- volumetric growth
- myelination

**robust neurodevelopment**
$\text{CB}_1$ 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
- delusions - fixed, false beliefs that are firmly held in the face of contradictory evidence

Voices distinct from one's own thoughts

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

Advanced paternal age at time of conception
Environmental events during development
Frequent cannabis use during adolescence
Schizophrenia is more than psychosis.

Impairments

- Social
- Occupational

Disturbances in brain function

- Perception
- Inferential thinking
- Language (fluency & production)
- Expression of emotion
- Capacity for pleasure
- Volition
- Attention
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; Pitsis 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 (γ-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.

Research article

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.

A single inhibitory pulse will synchronize two pyramidal cells.

- Basket cell resets pyramidal cell firing.
- 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

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Neurophysiological and cognitive effects of smoked marijuana in frequent users
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Research report
Altered prefrontal and insular cortical thickness in adolescent marijuana users
Melissa P. Lopez-Larson a,b,c, Piotr Bogorodzki d, Jadwiga Rogowska e, Erin McGlade a,c, Jace B. King a, Janine Terry a, Deborah Yurgelun-Todd a,b,c

Cannabis use and risk of psychotic or affective mental health outcomes: a systematic review
Theresa M. Moore, Stanley Zammit, Anne Lingford-Hughes, Thomas R.E. Barnes, Peter B. Jones, Margaret Burke, Glyn Lewis

Genetic mediation of the link between schizophrenia and cannabis use
Wim Veling

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