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INTER-AMERICAN DRUG ABUSE CONTROL COMMISSION

CICAD

Secretariat for Multidimensional Security

FIFTY-SEVENTH REGULAR SESSION
April 29 - May 1, 2015
Washington, D.C.

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28* April *2015
Original: English

MEDICAL MARIHUANA

RUBEN D. BALER
NATIONAL INSTITUTE ON DRUG ABUSE

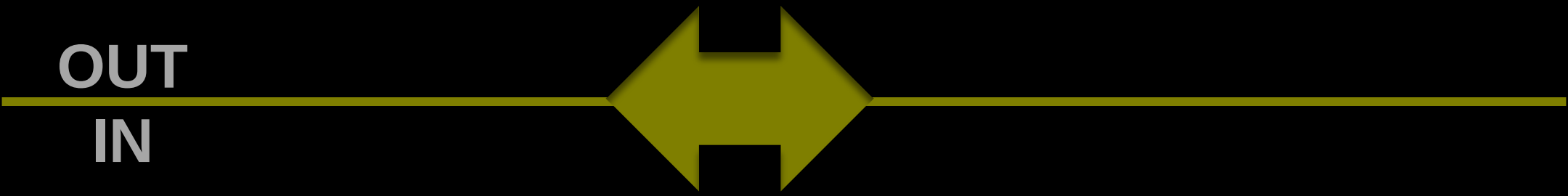
Medical Marijuana (?)

Ruben D. Baler, Ph.D.
Science Policy Branch

NIH National Institute on Drug Abuse

DEPARTMENT OF HEALTH & HUMAN SERVICES · USA

OPIOID SYSTEM



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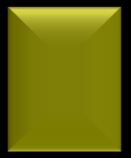
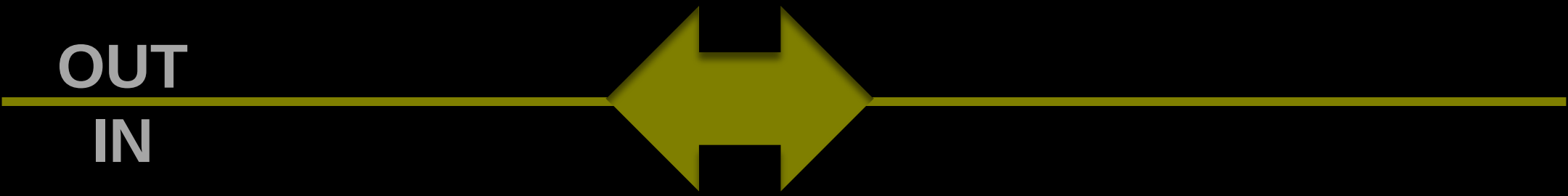


Dynorphin
Enkephalin
Endorphin



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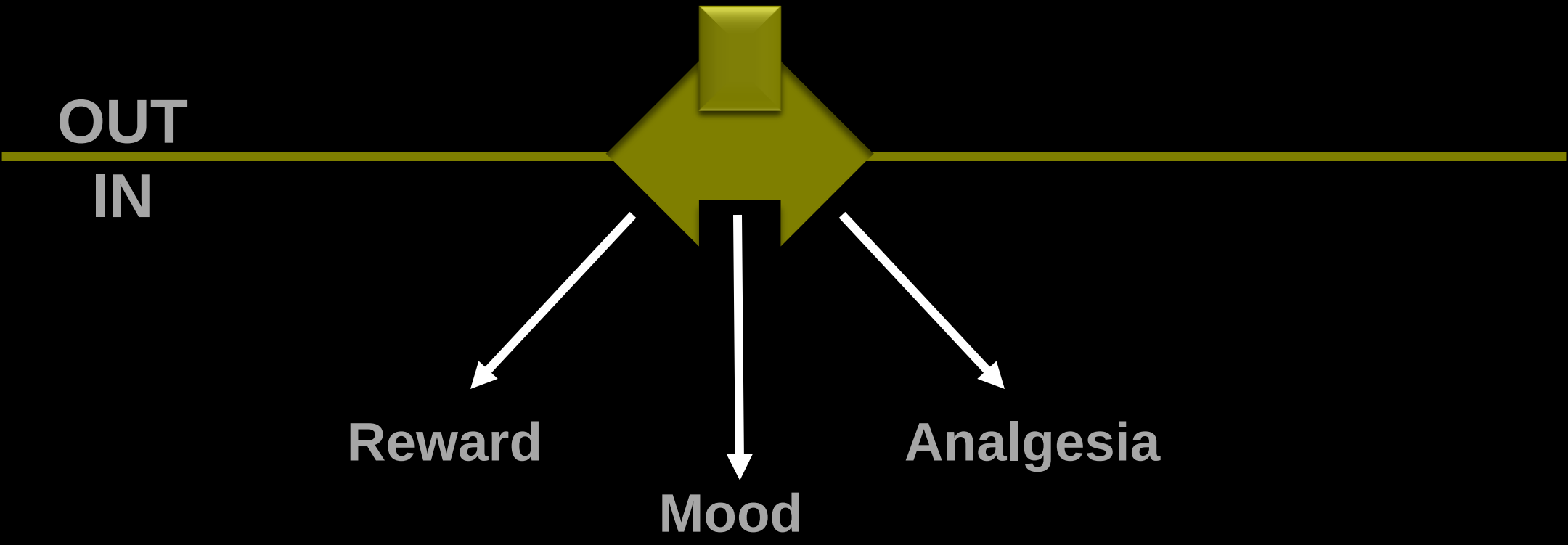
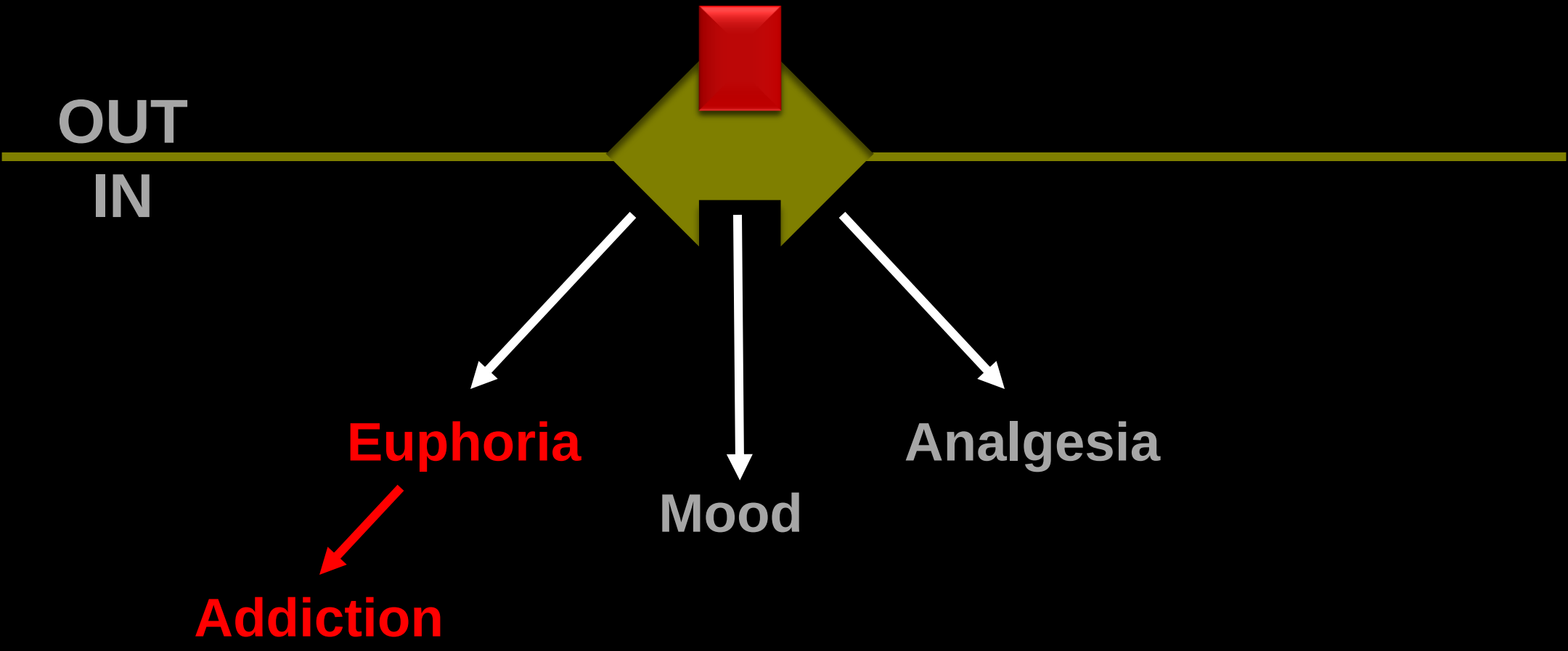
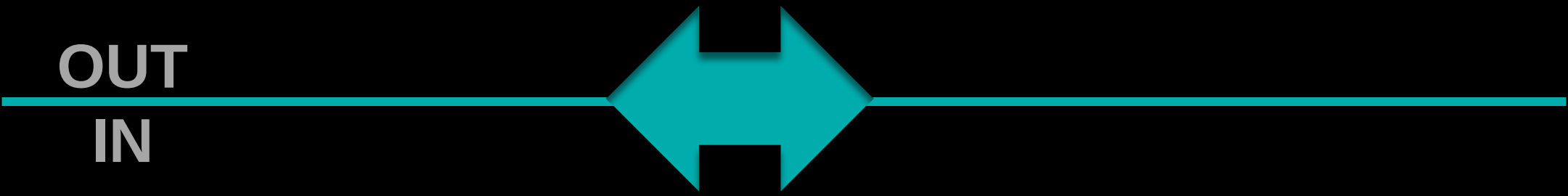


OPIOID SYSTEM

Heroin
Morphine
Vicodin

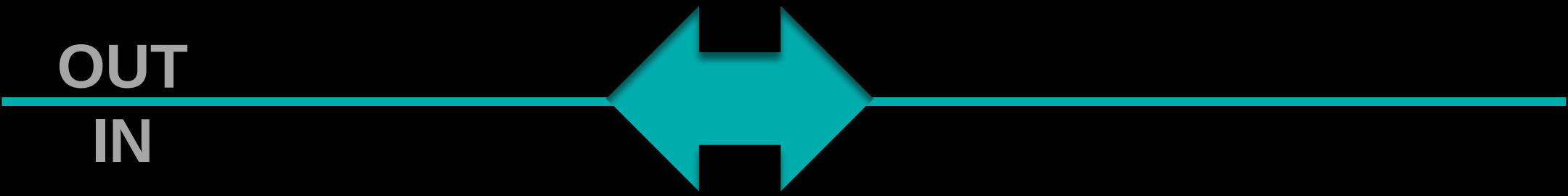


ENDOCANNABINOID SYSTEM

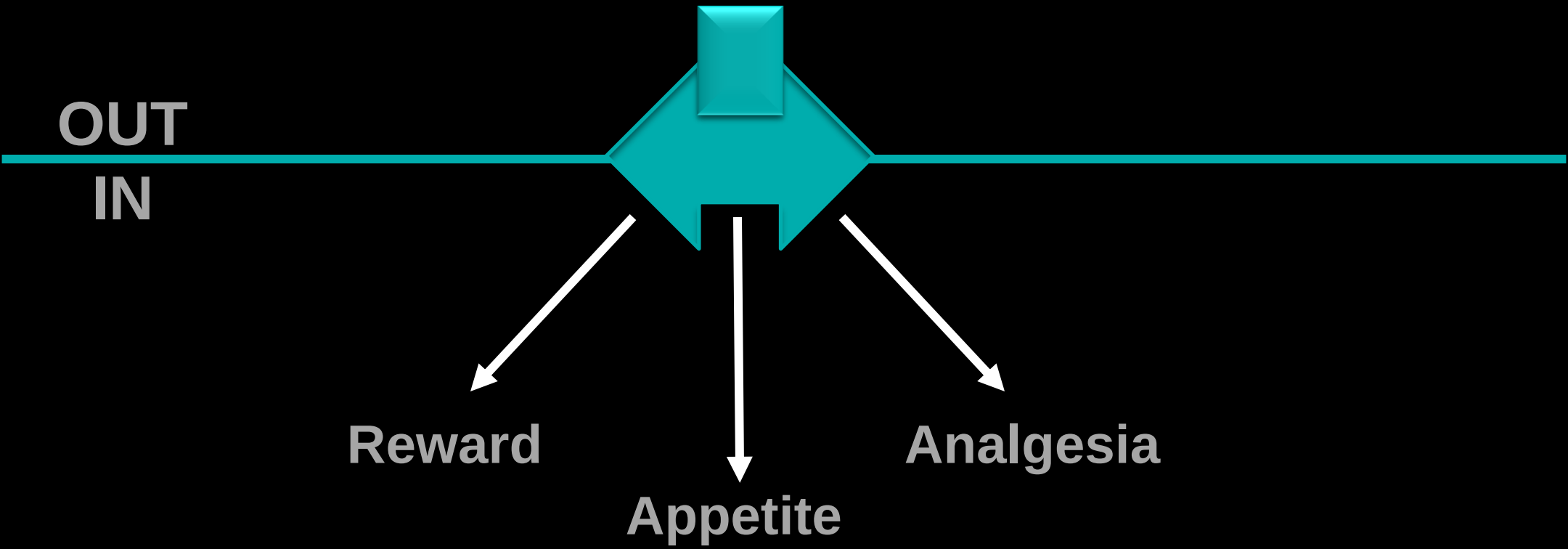


ENDOCANNABINOID SYSTEM

Anandamide
2-Arachidonyl glyceryl ether
Virodhamine

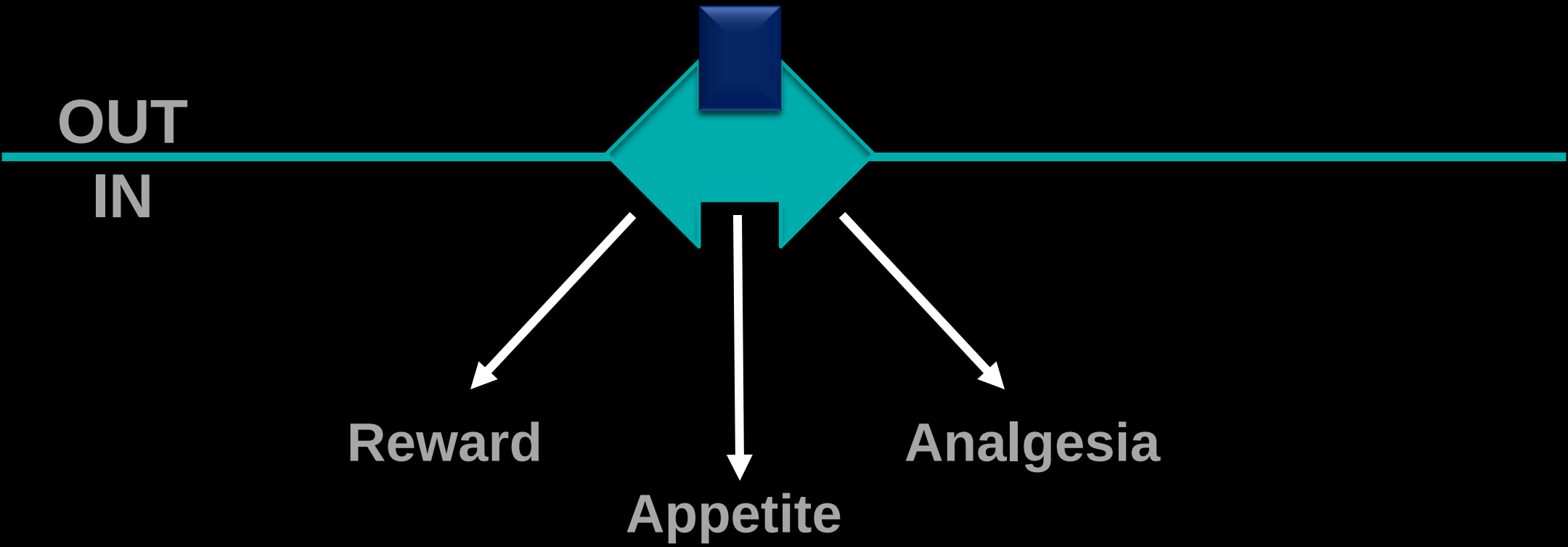


ENDOCANNABINOID SYSTEM

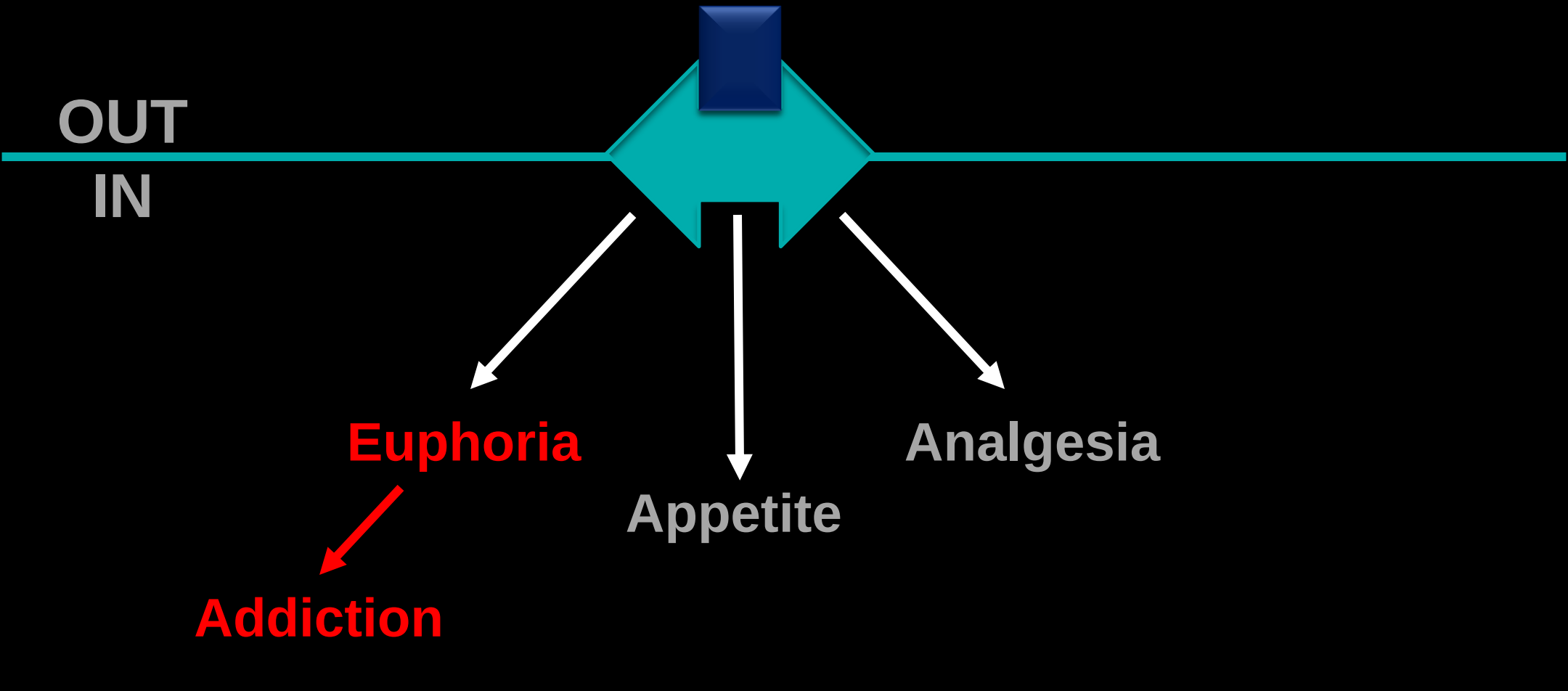


ENDOCANNABINOID SYSTEM

THC
CBD
JWH-018 (Spice)



ENDOCANNABINOID SYSTEM



Pure Cannabinoids (Sativex)

Pure Opioids (Vicodin)

Medicines in Marijuana

Promise lies in purified ingredients or synthetic compounds with more selectivity, less adverse effects

Applications: pain, nausea, wasting, muscle spasticity, addiction, inflammatory conditions, HIV, epilepsy.

NIH research (across NIDA, NCI, NINDS, NIAID, etc.) focuses on THC, CBD, and compounds that alter the function of the endocannabinoid system.

Glaucoma

Evidence of MJ benefits for glaucoma patients consistent with MJ's ability to temporarily decrease intraocular pressure. However, other, standard treatments are currently more effective.

Question: Could CBs also provide a neuroprotective benefit in patients with glaucoma?

Nausea

Treatment of the nausea and vomiting associated with chemotherapy was one of the first medical uses of THC and other cannabinoids.

Patients often state that MJ is more effective in suppressing nausea.

Question: How do we explain the paradoxical observation that repeated MJ use can cause increased vomiting (hyperemesis)?

AIDS-associated anorexia and wasting syndrome

Smoked or ingested cannabis can stimulate appetite, weight gain and improved mood and quality of life among AIDS patients.

However, no long-term or rigorous evidence of a sustained effect of cannabis on AIDS-related morbidity and mortality.

Question: Need better long term studies of safety, particularly of potential drug-drug interactions between CBs and retroviral therapies.

Chronic Pain

Marijuana has been used to relieve pain for centuries. Consistent with CBs actions on central CB1 and possibly peripheral CB1 and CB2 receptors, with important roles in various models of pain.

MJ may be effective in ameliorating neuropathic pain, even at very low levels of THC (1.29%).

Question: What would be the best strategy to separate the rewarding from the analgesic effects of various CBs?

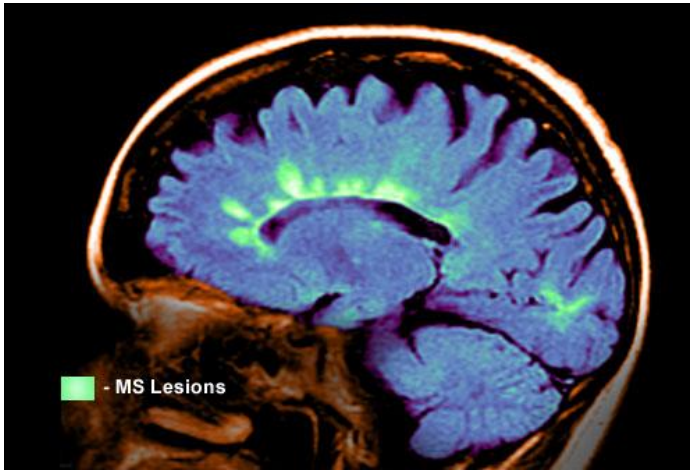
Inflammation

Cannabinoids (e.g., THC and cannabidiol) have substantial antiinflammatory effects because of their ability to induce apoptosis, inhibit cell proliferation, and suppress cytokine production.

Cannabidiol is particularly promising in this context because of its lack of psychoactive effects.

Question: Need more research on CBD for the treatment of rheumatoid arthritis and for inflammatory diseases of the gastrointestinal tract (e.g., ulcerative colitis and Crohn's disease).

Multiple Sclerosis



Nabiximols (Sativex, GW Pharmaceuticals), an oromucosal spray that delivers a mix of THC and CBD, appears to be an effective treatment for neuropathic pain, disturbed sleep, and spasticity in patients with multiple sclerosis.

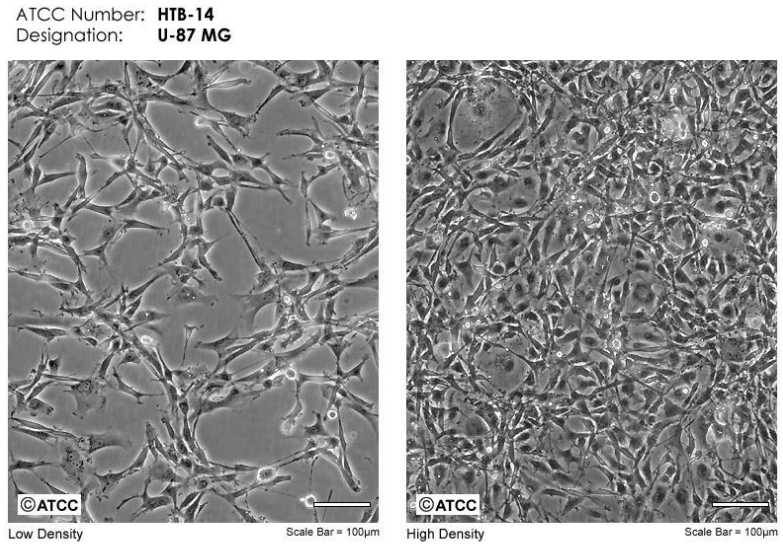
Question: Will Sativex ever gain FDA approval? Ongoing phase III clinical trials of Sativex in the US

Epilepsy

In a recent small survey of parents who use marijuana with a high cannabidiol content to treat epileptic seizures in their children, 11% (2 families out of the 19 that met the inclusion criteria) reported complete freedom from seizures, 42% (8 families) reported a reduction of more than 80% in seizure frequency, and 32% (6 families) reported a reduction of 25 to 60% in seizure frequency.

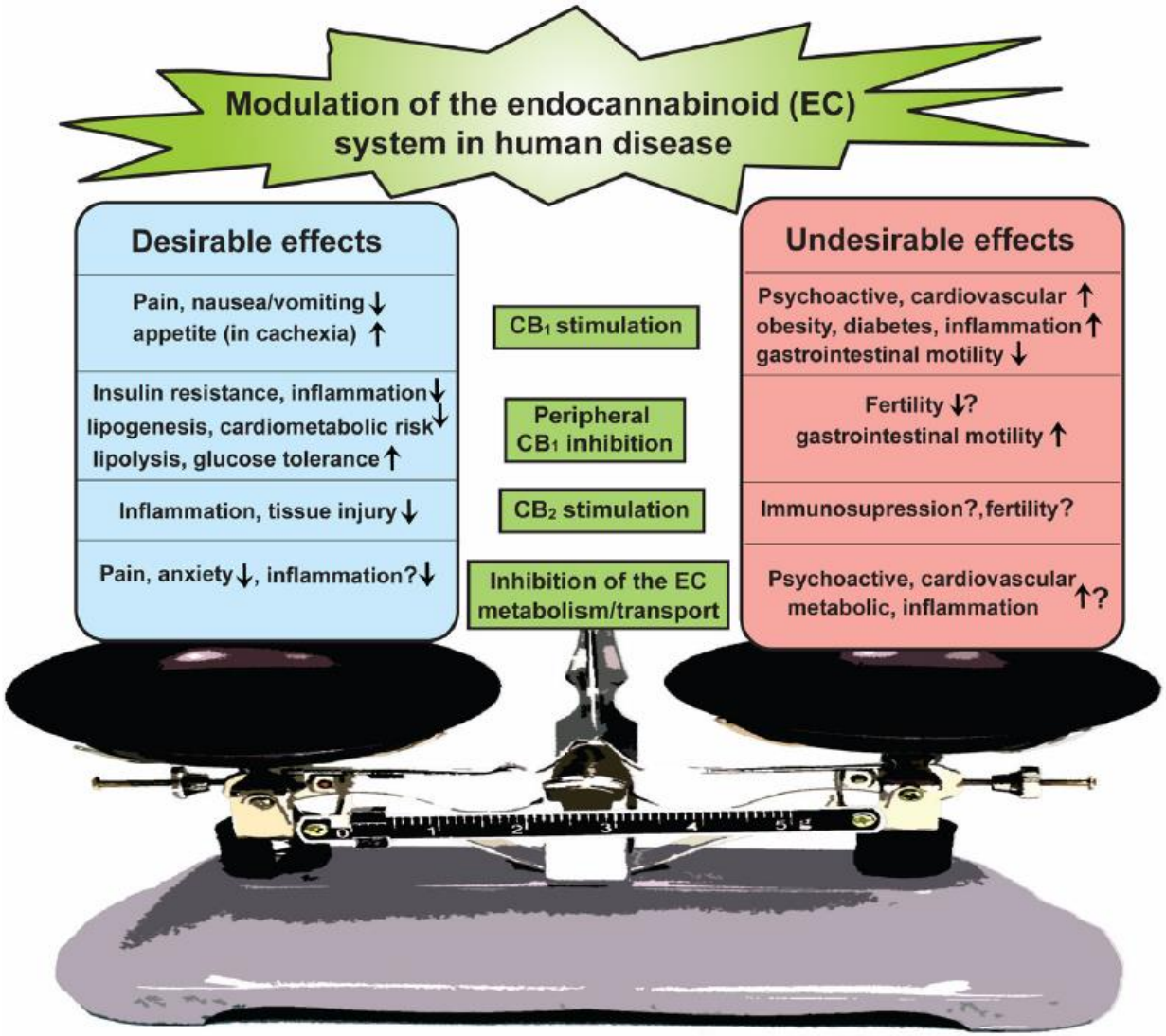
Question: We need larger studies on safety and efficacy.

Cancer



Recent in vitro studies showed that a combination of purified THC/CBD can enhance the anticancer effects of radiation in a mouse model of cancer. Evidence from one animal study suggests that extracts from whole-plant marijuana can shrink one of the most serious types of brain tumors. Research in mice showed that these extracts, when used with radiation, increased the cancer-killing effects of the radiation.”

Modulating the endocannabinoid system in human health and disease: successes and failures



Pacher et al. FEBS J. 280(9): 1918–1943 (2013)

Examples of current NIDA grants

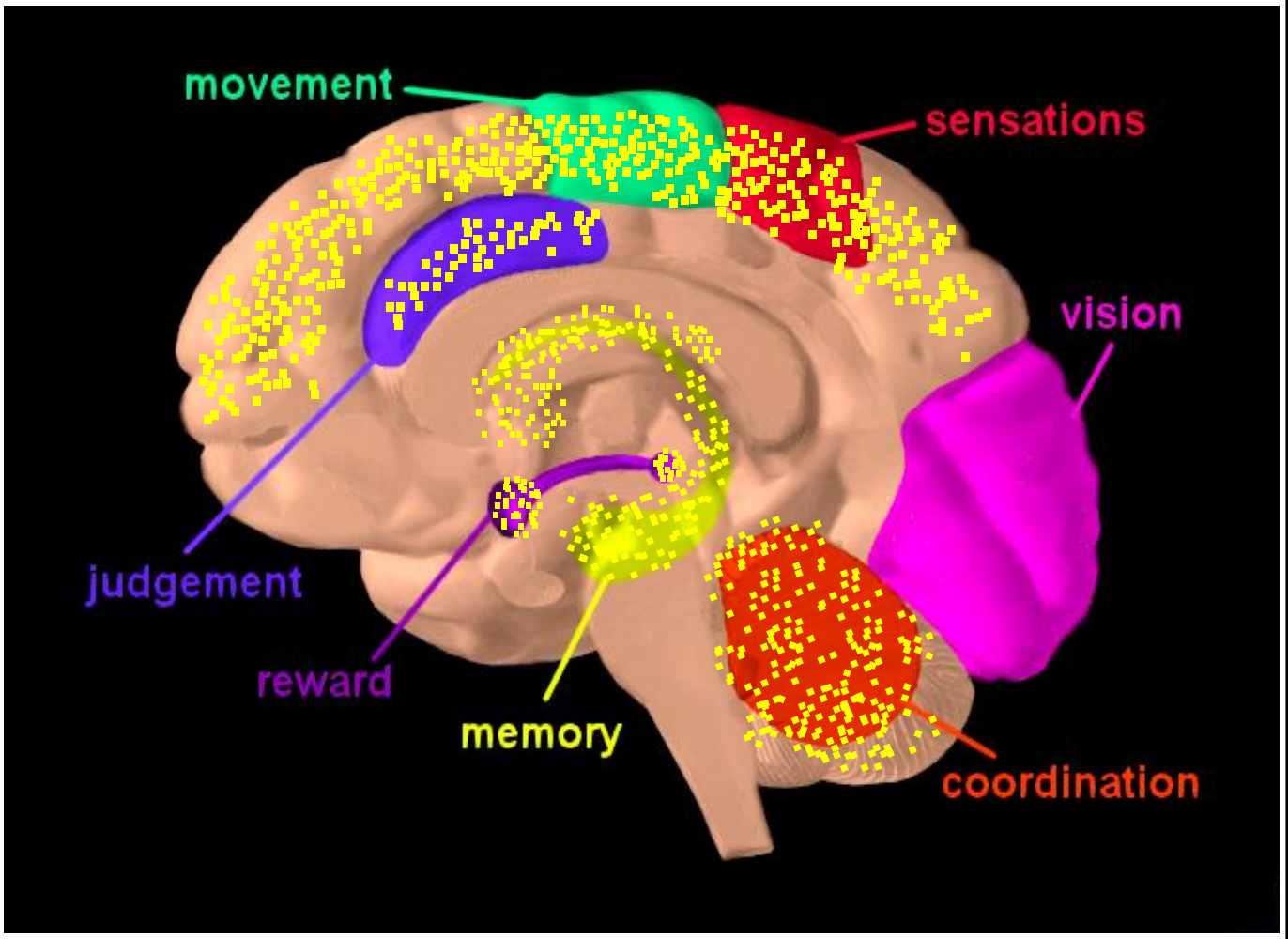
1R01DA035949-01A1	*SUNY*	*FABPS: NOVEL ROLES IN PAIN AND INFLAMMATION*
1R43DA036289-01	*ORGANIX, INC.*	*CBR AGONISTS FOR TREATMENT OF CHRONIC PAIN*
5R01DA033932-0	*U. of Kentucky*	*OR THE TREATMENT OF OPIOID DEPENDENCE*
1R44DA038932-01	*APHIOS Corp.*	*A CGMP MANUFACTURING PROCESS FOR CBD*
5P01CA077839-13	*Mayo Clinic*	*THE ROLE OF EC and ECR IN COLORECTAL CANCER*
3R01CA142115-05S1	*U. Arizona*	*CB2 FOR TX OF BREAST CANCER-INDUCED BONE PAIN*
1R01EY024717-01	*Northeastern U.*	*A NOVEL PHARMACOTHERAPY FOR GLAUCOMA*
1R01DA037255-01A1	*LSU*	*INTERACTIONS BETWEEN CBs AND SEX HORMONES*

NIH National Institutes of Health
Turning Discovery Into Health

MJ’s Adverse Effects on the Brain

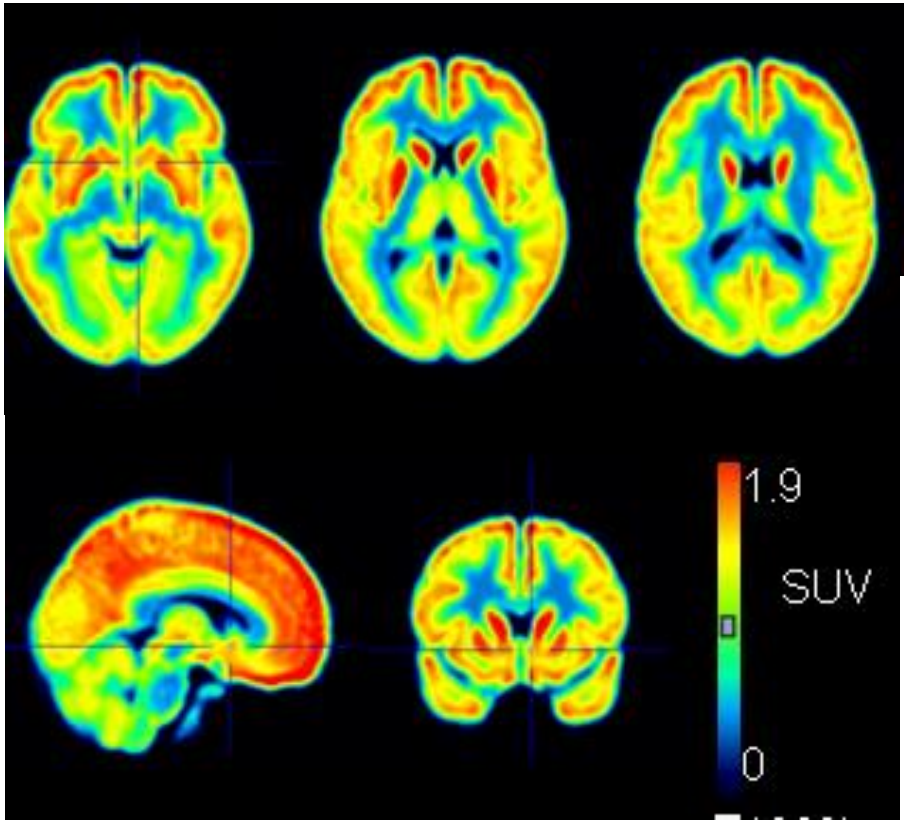
Cannabinoid Receptors Are Located Throughout the Brain and Regulate:

- Brain Development
- Memory and Cognition
- Motivational Systems & Reward
- Appetite
- Immunological Function
- Reproduction
- Movement Coordination
- Pain Regulation & Analgesia

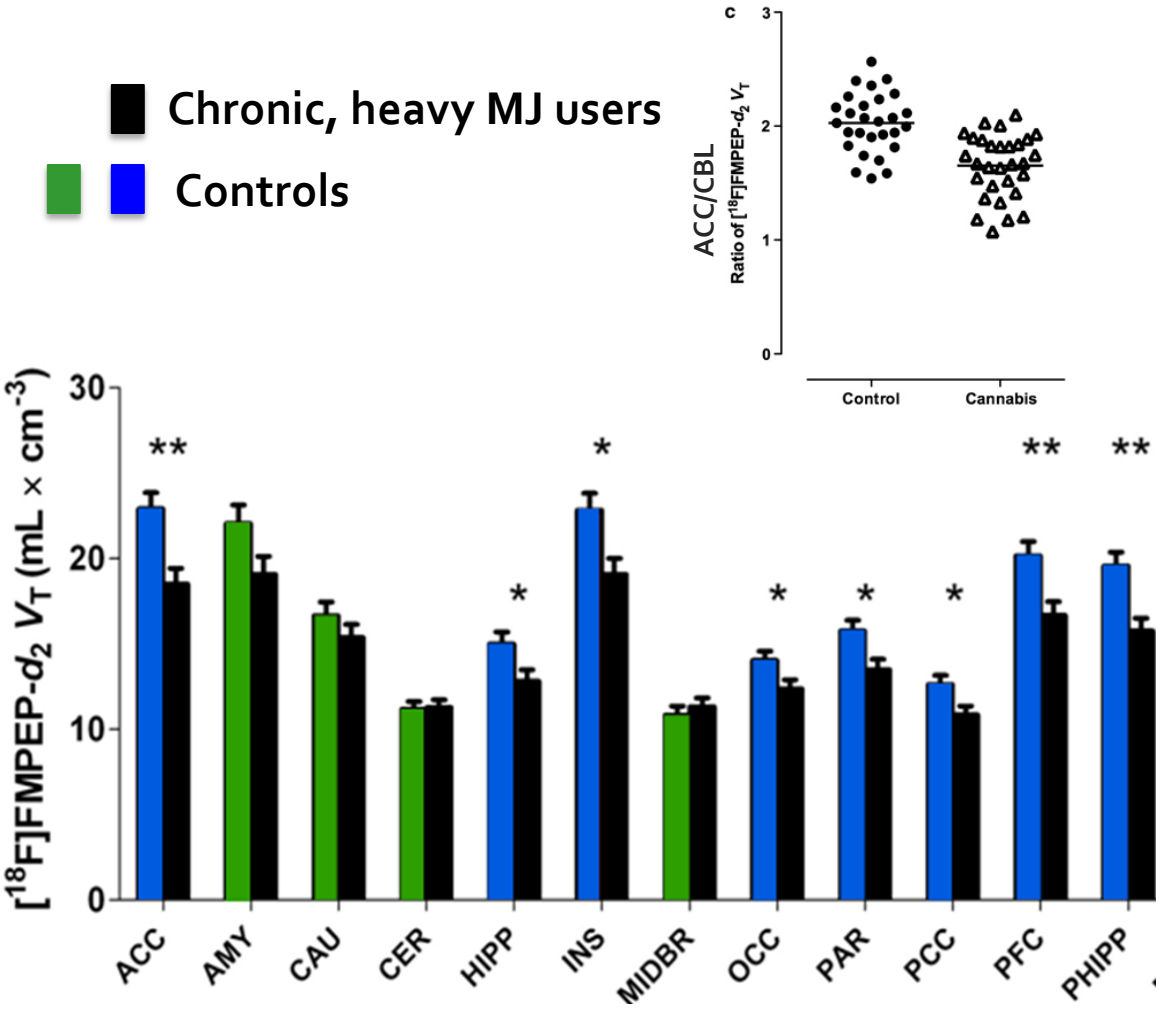


Lower CB1R in Heavy MJ Users

(partially reversible after 4 weeks of abstinence)

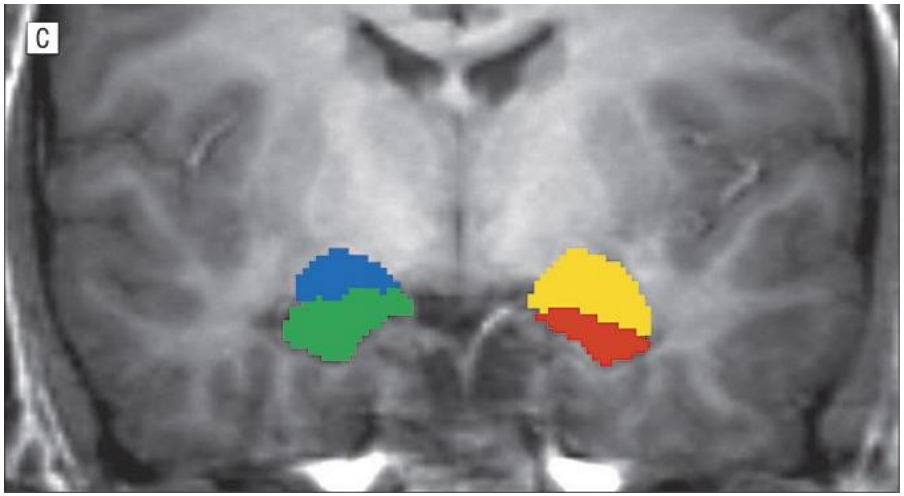


Selective inverse CB1R agonist [^{18}F]MK-9470
Van Laere et al., 2007.



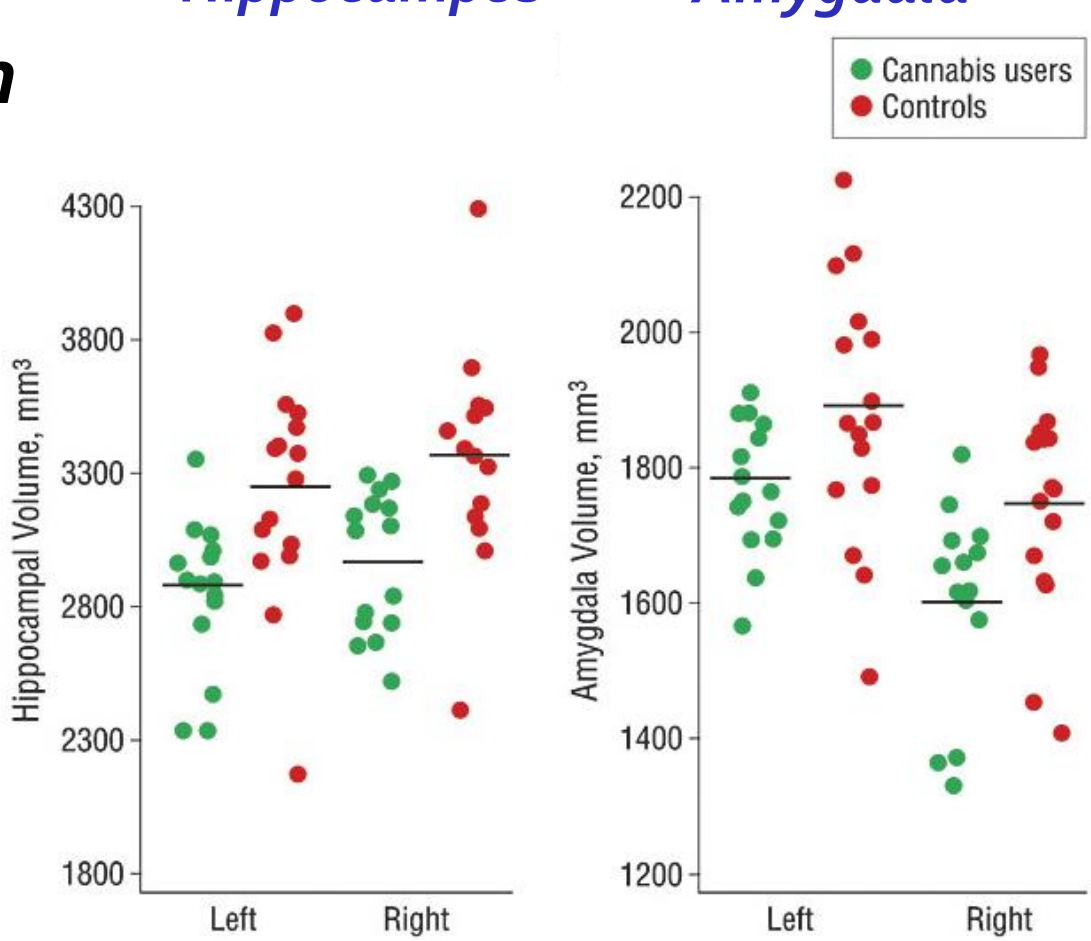
Hirvonen et al., Mol Psychiatry 2013

Smaller brain regions associated with long-term heavy marijuana use



L (yellow) and R (blue) amygdala
L(red) and R(green) hippocampus

Dysfunction of the hippocampus has been linked to reduced memory performance in heavy cannabis users.

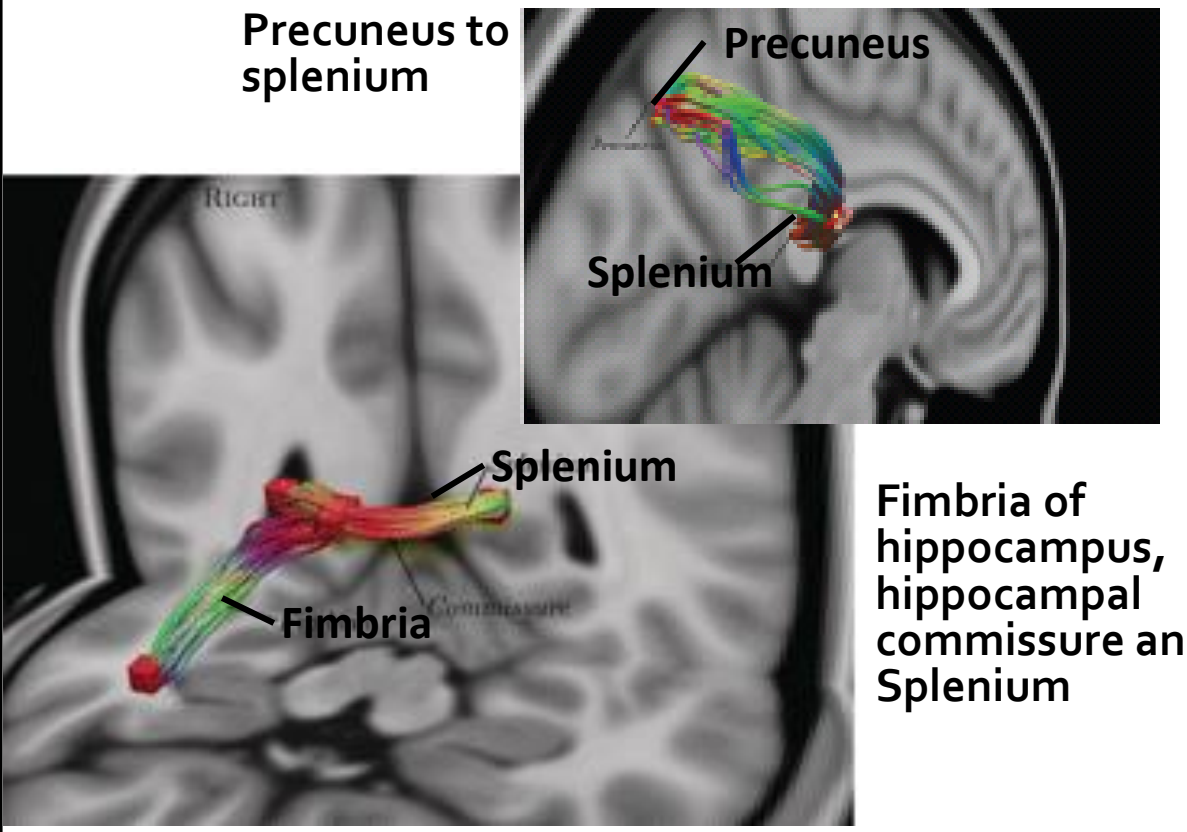


Hippocampal and amygdalar volumes are smaller in heavy MJ users

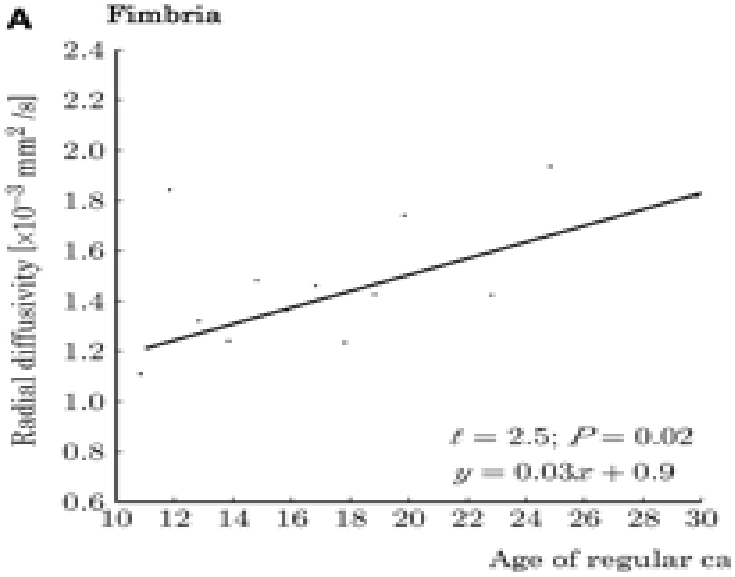
Yucel et al., Arch Gen Psychiatry. 2008 Jun;65(6):694-701.

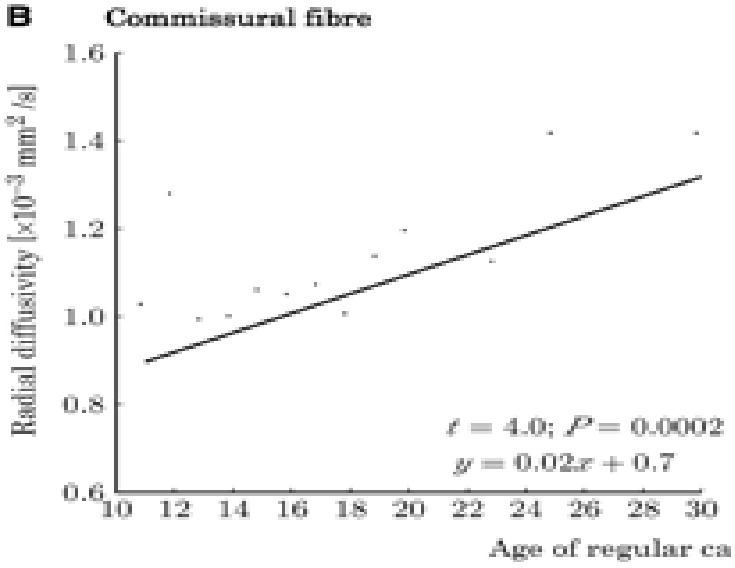
Early (<18y) Long-Term Cannabis Use Linked to Decreased Axonal Fiber Connectivity (no alcohol)

Precuneus to splenium



Fimbria of hippocampus, hippocampal commissure and Splenium





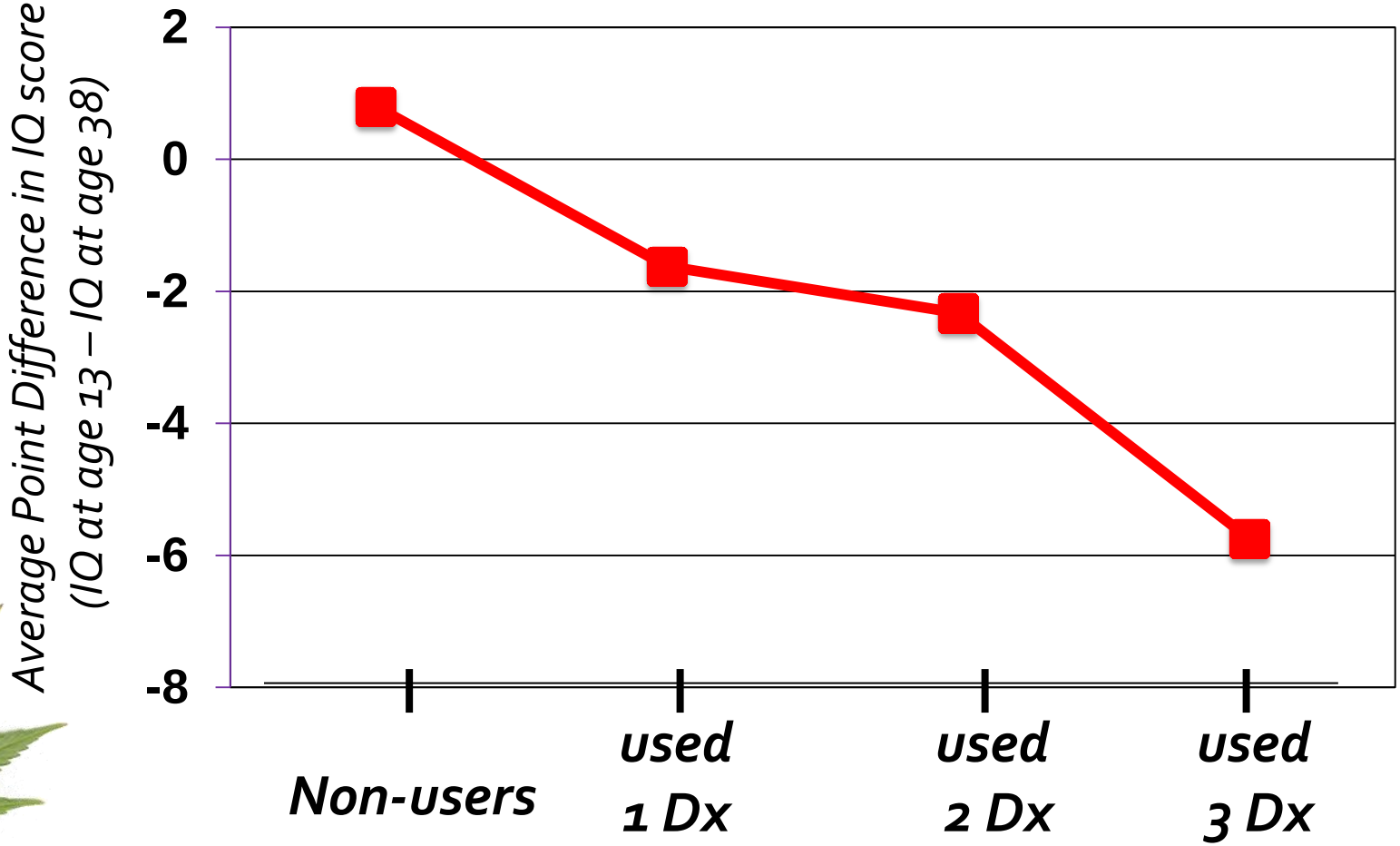
Axonal paths with reduced connectivity (measured with diffusion-weighted MRI) in cannabis users (n=59) than in controls (N=33). *Zalesky et al Brain 2012.*

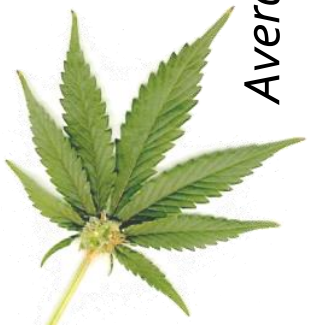
Early, chronic and heavy MJ use

- Down-regulation of CB1 receptors
- Smaller Amygdala and Hippocampus
- Decreased Connectivity

Persistent Marijuana Users Show A Significant IQ Drop between Childhood and Midlife

Followed 1,037 individuals from birth to age 38. Tested marijuana use at 18, 21, 26, 32 and 38. Tested for IQ at ages 13 and 38

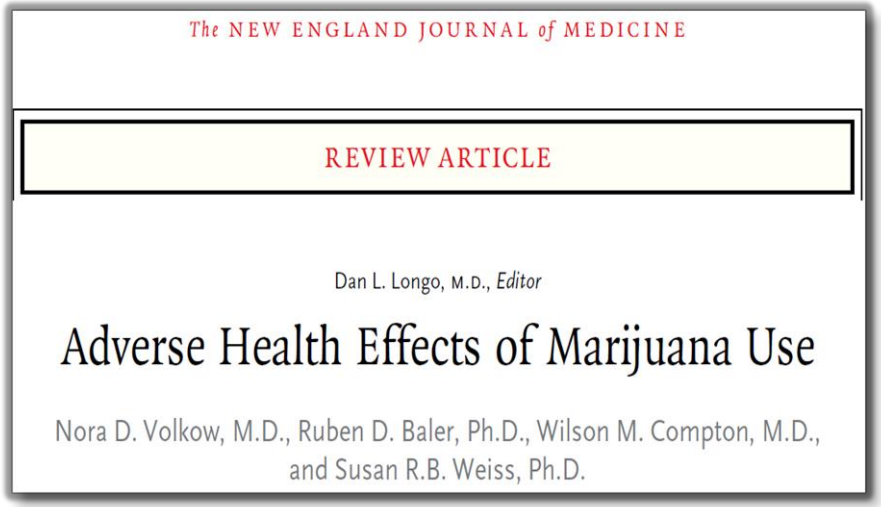




Source: Meier MH et al., PNAS Early Edition 2012

Adverse effects: The Big Picture

- Marijuana is the ***most commonly used*** illicit drug in the U.S.
- Marijuana use generally ***begins in adolescence***
- Use of marijuana can have a ***wide range of effects on an individual's brain, body and behavior*** including short and long term effects on functions such as:
  - ✓ *Brain development*
  - ✓ *Memory and cognition*
  - ✓ *Motivational systems/reward*
  - ✓ *Addiction*
  - ✓ *Lung health*


The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

Dan L. Longo, M.D., *Editor*

Adverse Health Effects of Marijuana Use

Nora D. Volkow, M.D., Ruben D. Baler, Ph.D., Wilson M. Compton, M.D., and Susan R.B. Weiss, Ph.D.

- Recent ***increases in both treatment admissions*** and in ***Emergency Department visits*** involving marijuana

Thank you

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