



Marijuana

The Science: What We Know About its Effects on Health

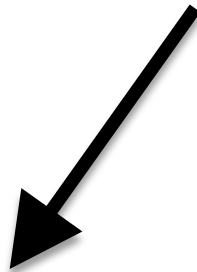
Rochelle D. Schwartz-Bloom, PhD

Professor of Pharmacology

Duke University Medical Center



~70 cannabinoids



THC

CBD

Δ 9-tetra-hydrocannabinol

cannabidiol



Marijuana Makes Most People Feel Good



THC

Pleasure
Euphoria
Relaxation
Analgesia*

Hunger

*analgesia is produced at intoxicating doses



Marijuana Makes Some People Feel Bad



THC

Anxious
Altered sensory perception
Time distortion
Disorientation



How Does Marijuana Work?



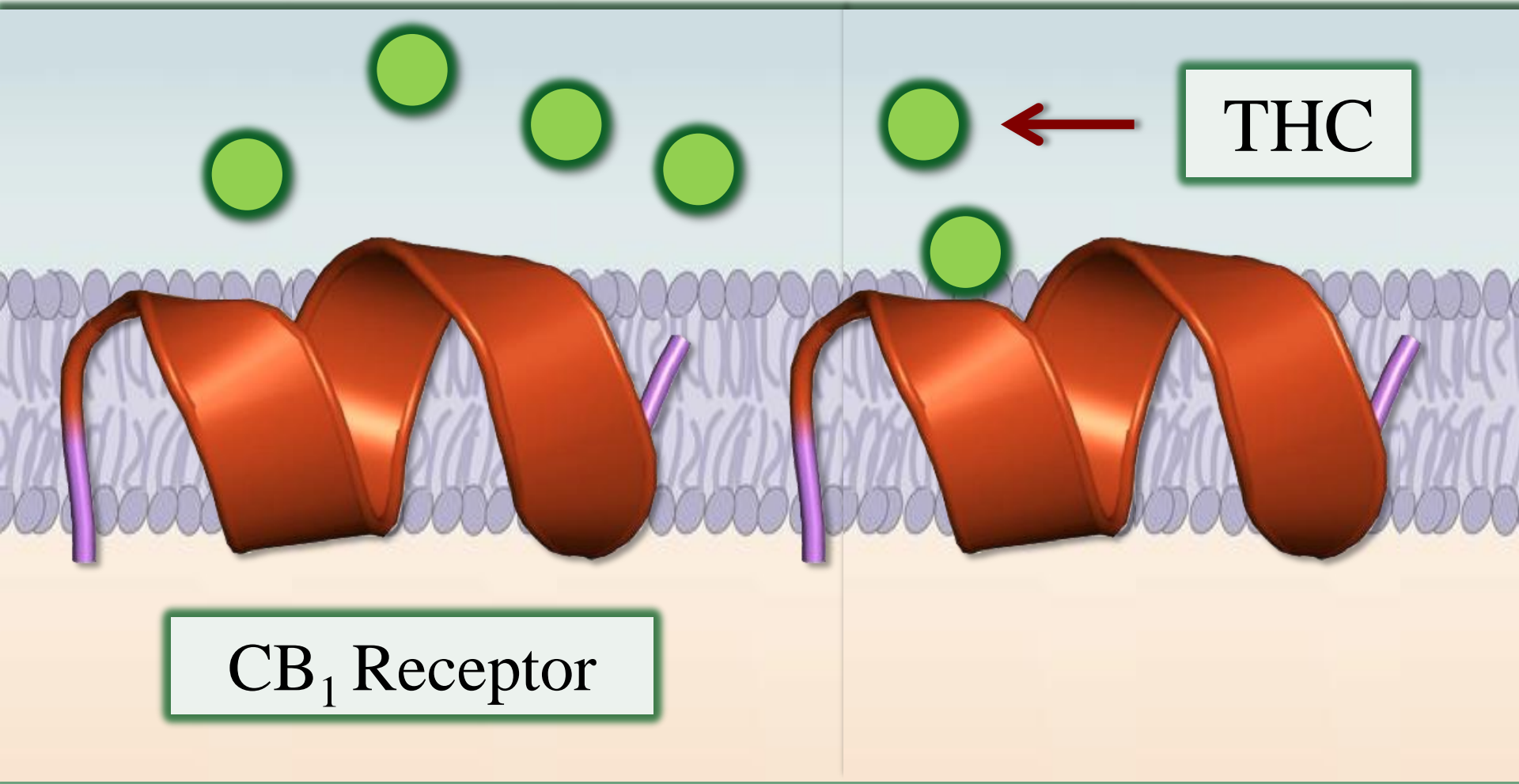
Normal Communication Between Neurons



Graham Johnson, 2004

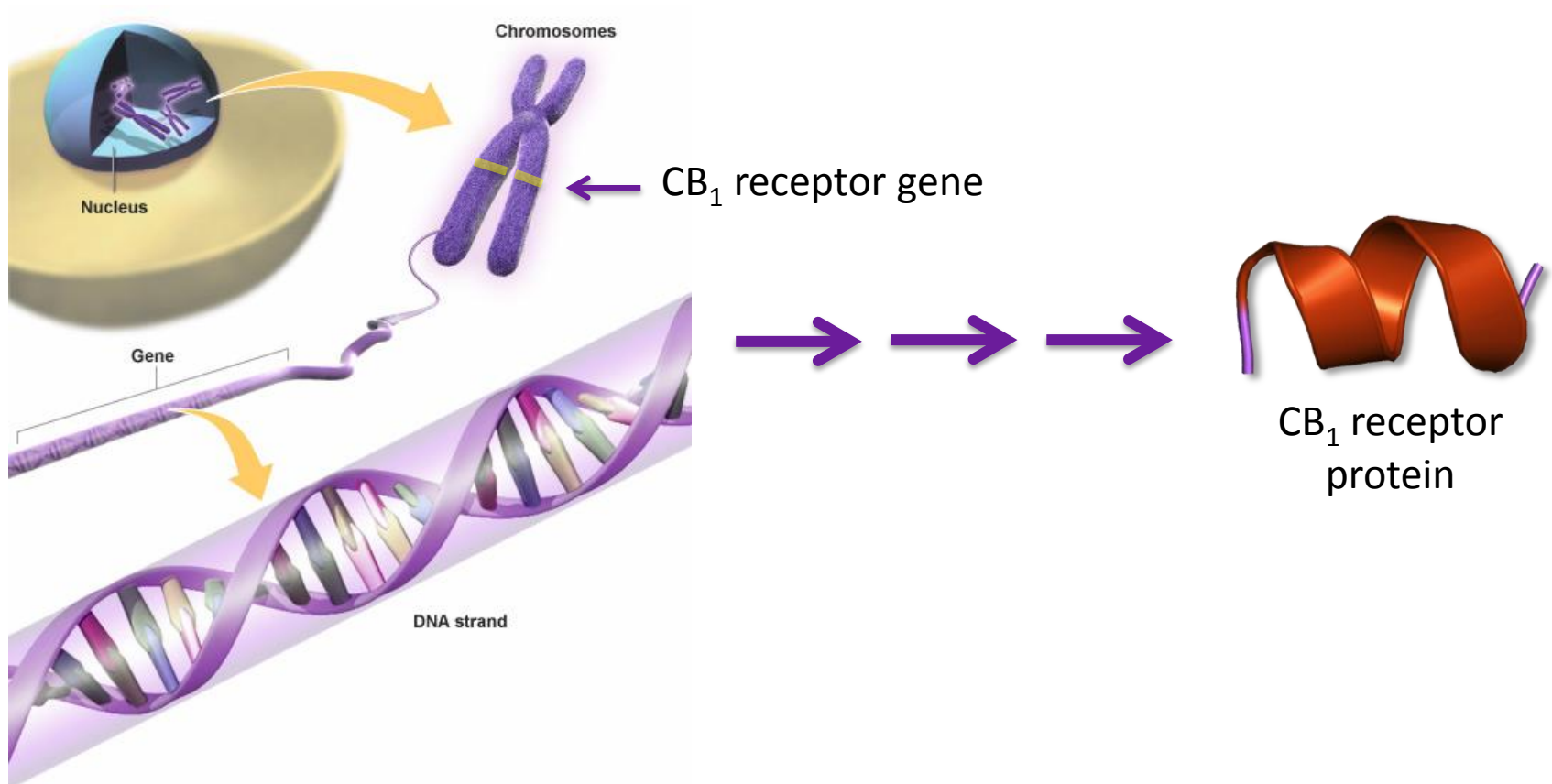


THC Binds to a Target: Cannabinoid Receptors





Proteins are Made under Instructions From Specific Genes





Most CB₁ Receptors are on Neuron Terminals



Graham Johnson, 2004



THC Inhibits Release of Neurotransmitters

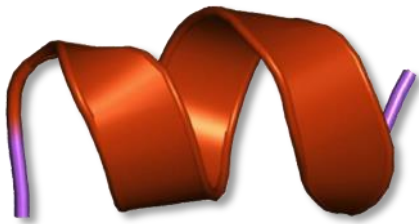


Graham Johnson, 2004



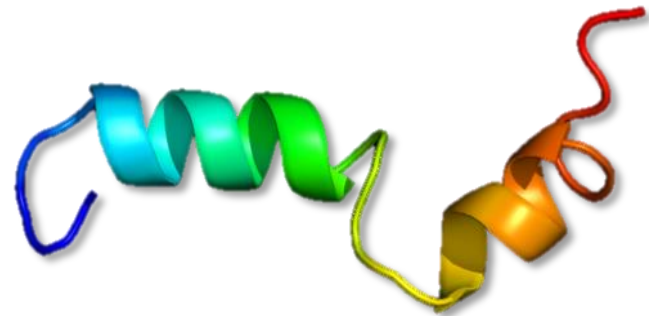
Cannabinoid Receptors Come in 2 “Flavors”

CB₁ Receptor



Mostly on neurons

CB₂ Receptor



Mostly on immune cells



Cannabinoid Receptors Come in 2 “Flavors”

CB₁ Receptor

Mood
Cognition
Appetite
Nausea

CB₂ Receptor

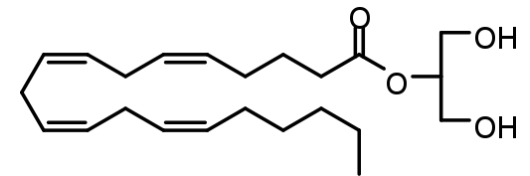
Immune cell migration
Inflammation
Fertility
Mood?



Why are the CB Receptors Even There?



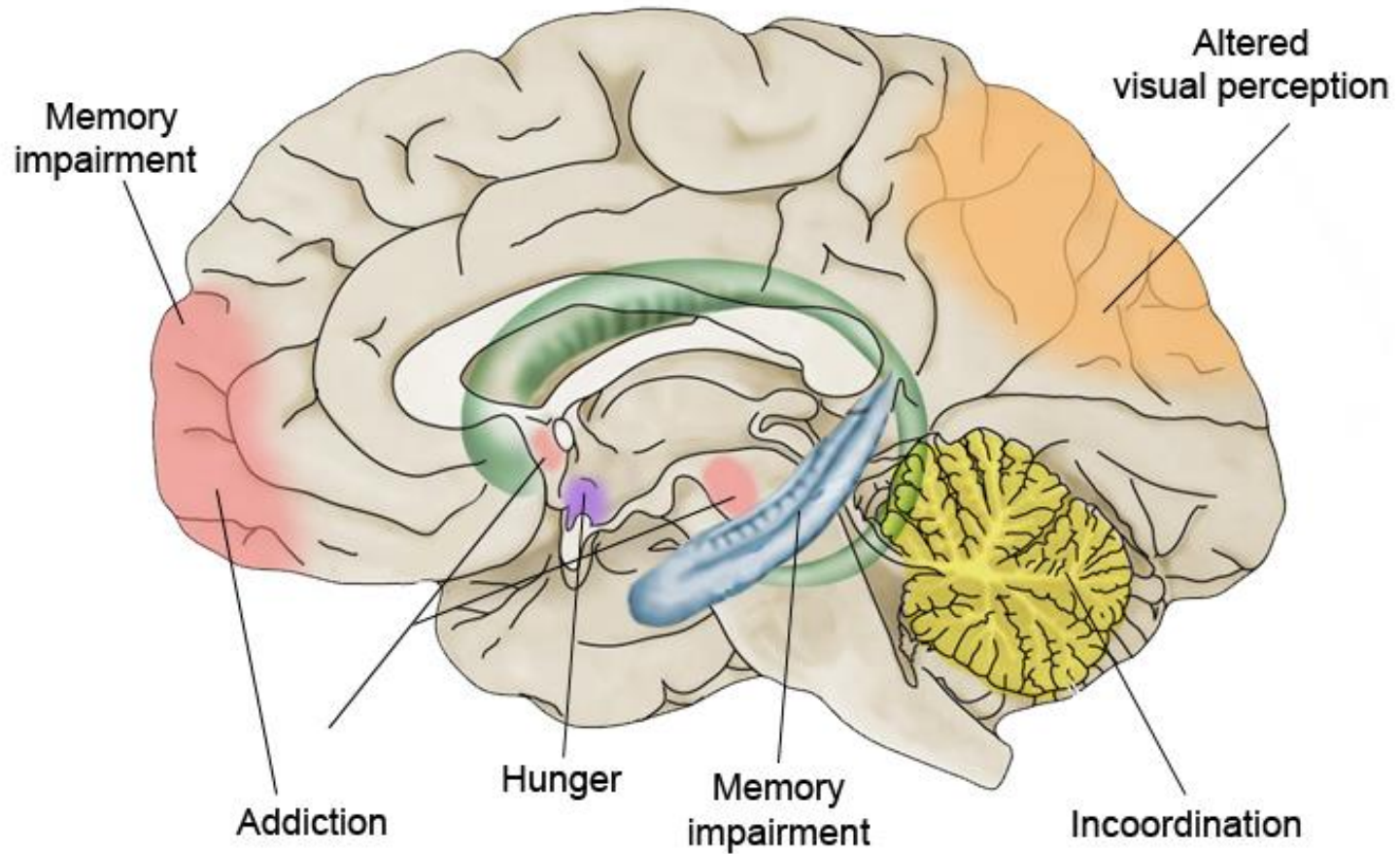
Graham Johnson, 2004



“Endocannabinoids”

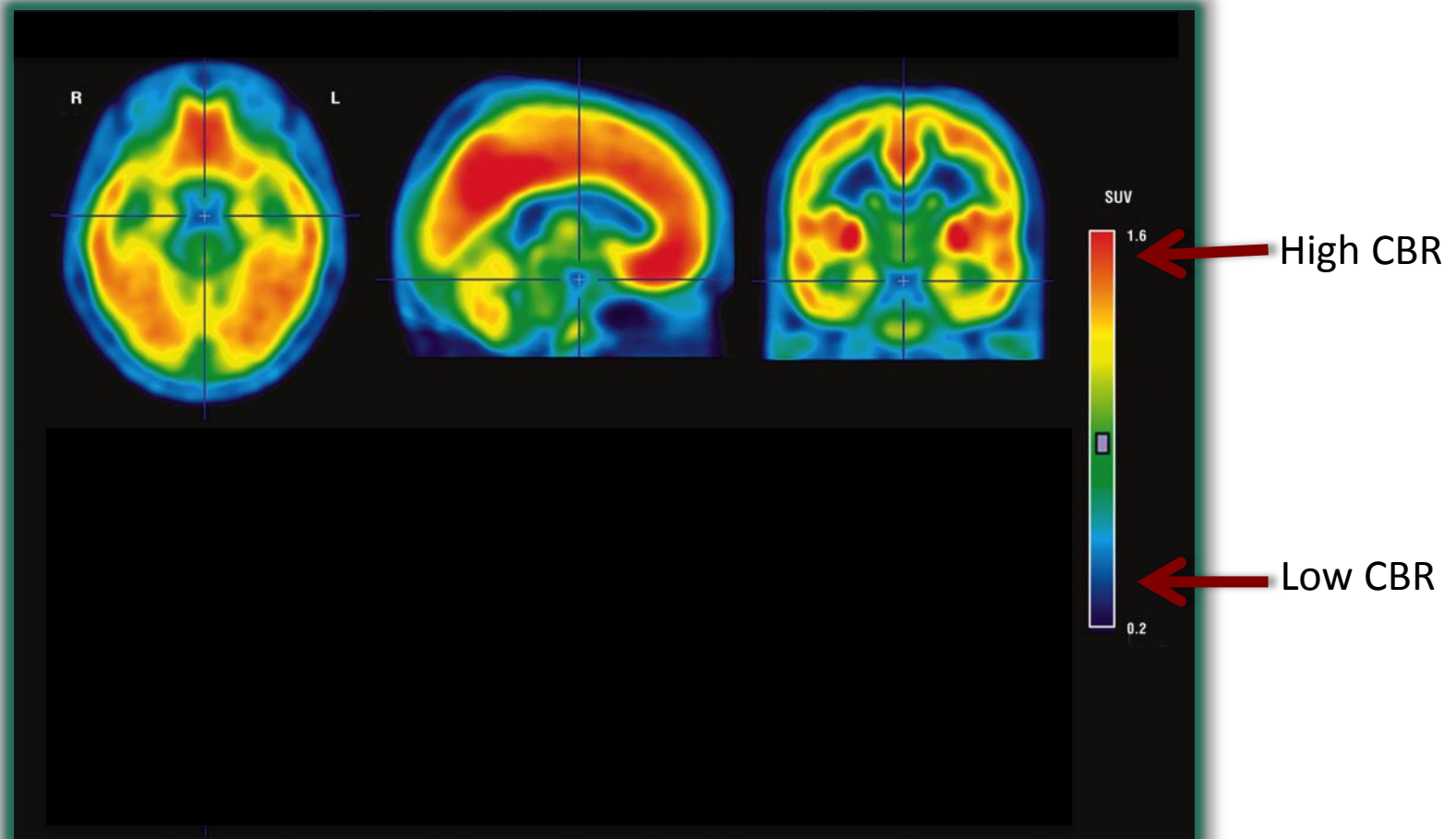


Marijuana's Effects in the Brain Depend on CB1 Receptor Location





PET Scans Show Location of CB₁ Receptors



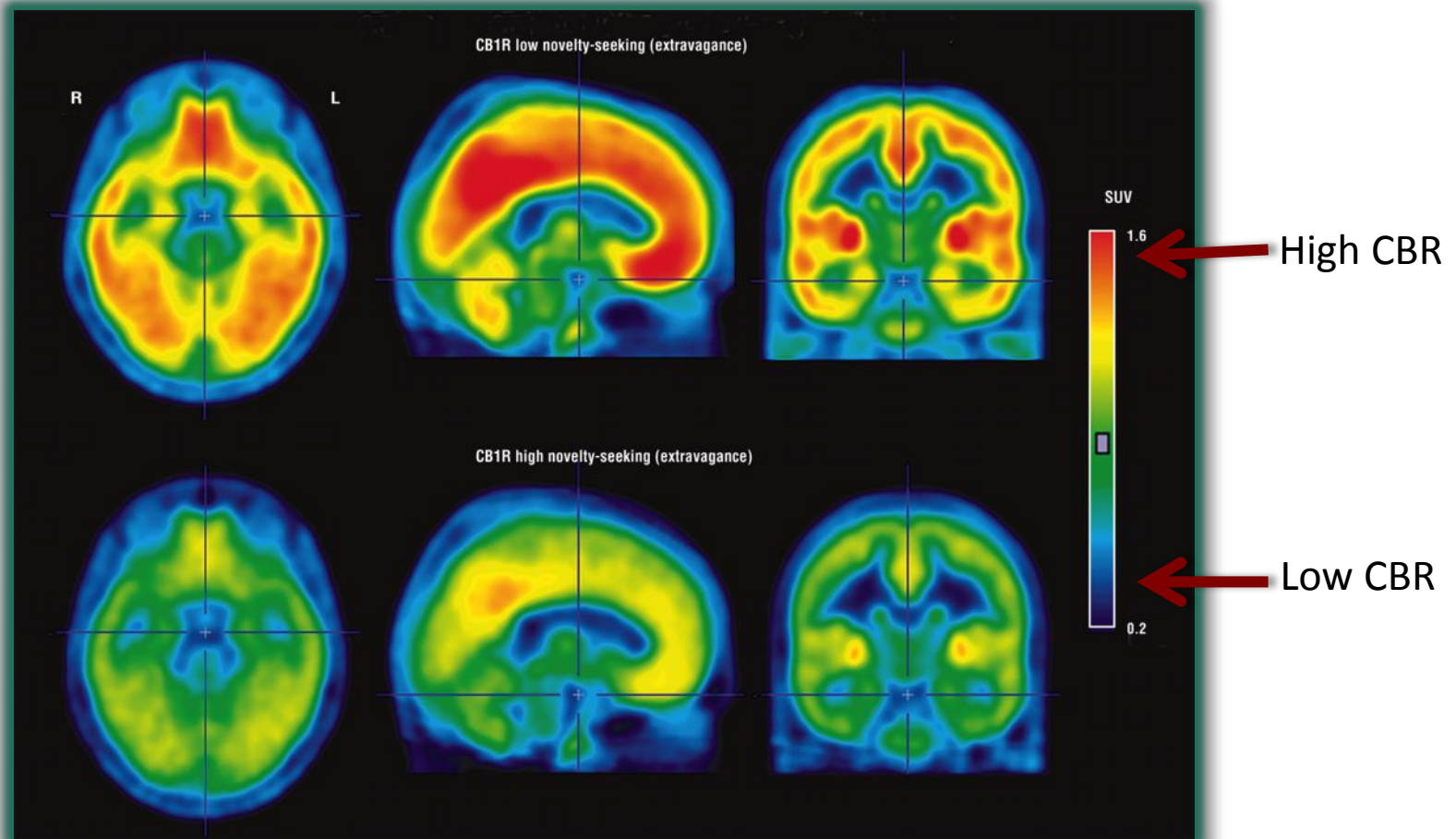
K Van Laer et al., 2009



High-Novelty Seekers have Low CB₁ Receptors

Low-novelty seekers

High-novelty seekers



K Van Laer et al., 2009



Smoking Marijuana Lowers CB₁ Receptors



J Hirvonen et al., 2012

Yellow = recovery of CB receptors



What About Cannabidiol?



THC & CBD Often Work in Opposition

THC

Euphoria
Anxiety
Psychosis
Cognitive impairment
Hunger



Recreational users

CBD

No euphoria
Anti-anxiety
Anti-psychotic
No cognitive impairment

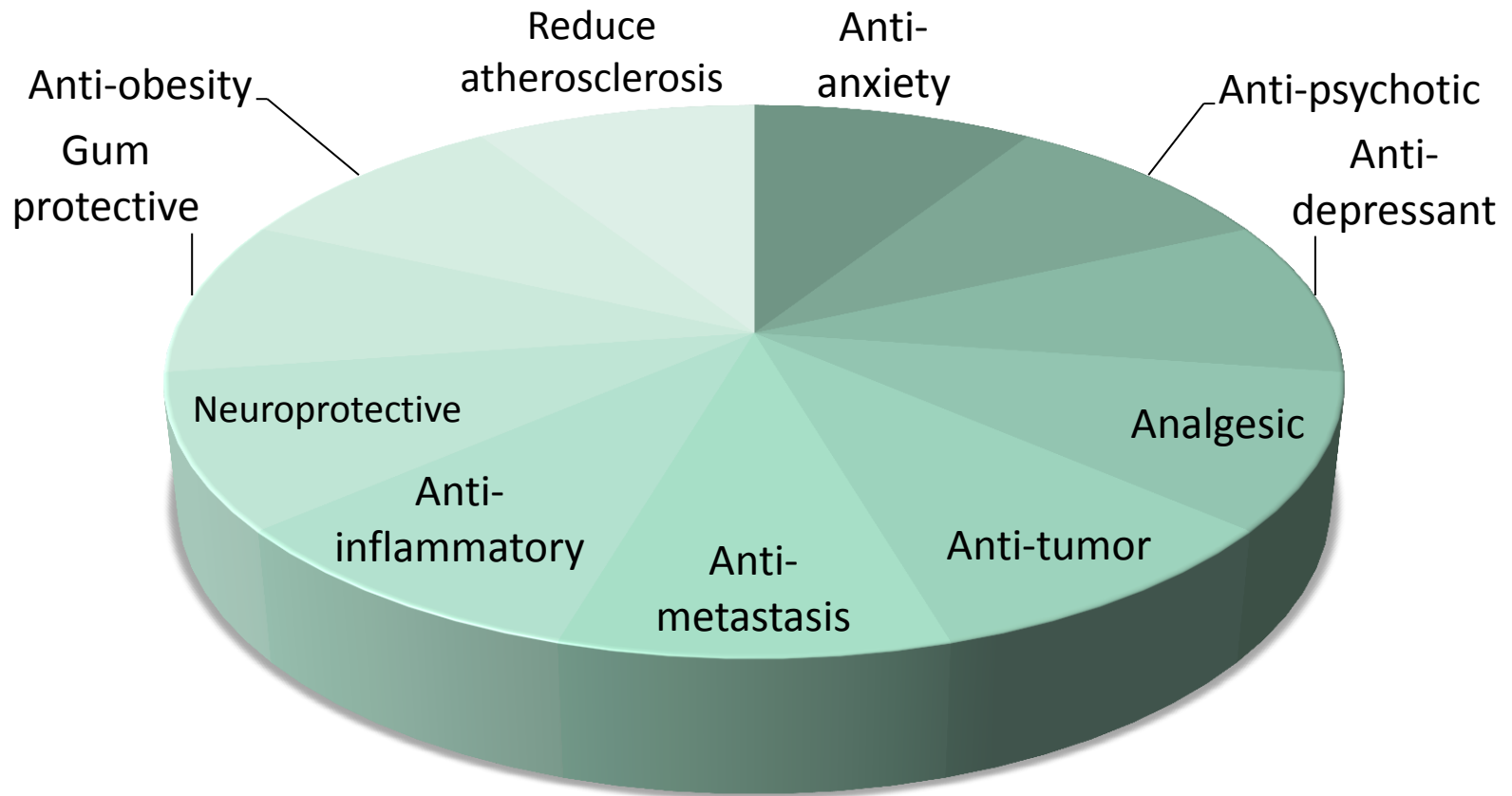


Drug companies



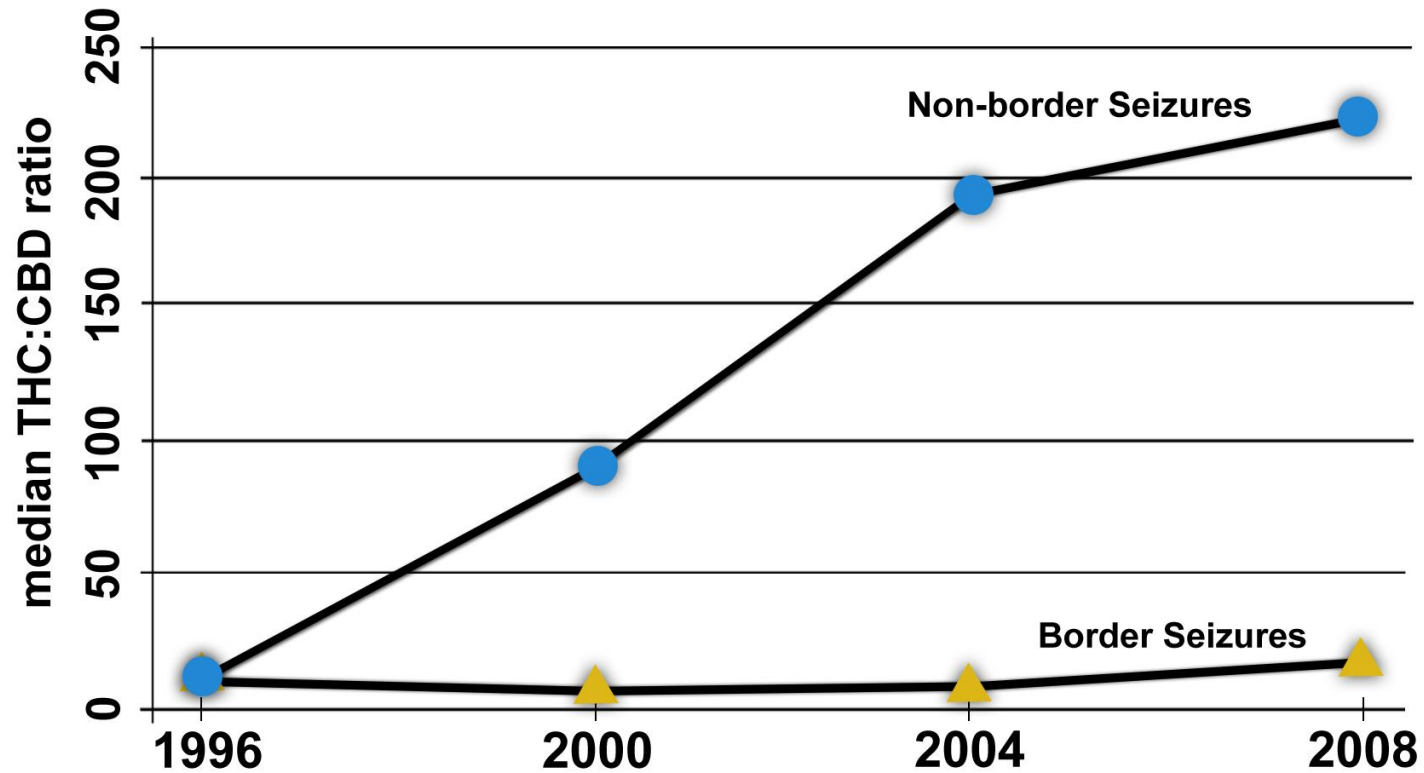
CBD

A Drug Developer's Dream





THC-to-CBD Ratio is Rising



THC concentration is rising and CBD concentration is dropping

JR Burgdorf et al. 2011



Growing “Maximum Yield” Medical Marijuana



Maximum yield marijuana formula for more THC and weight

<http://bigbudsmag.com/grow/article/hydroponics-marijuana-maximum-yield-formula-january-2012>



Sativex™: Oral Spray-THC:CBD = 1





Marijuana is Associated with Several Health Problems



Caveats of Human Studies & Marijuana

It is difficult to prove causation in humans
(animal models are very useful)

Association or correlation is not causation

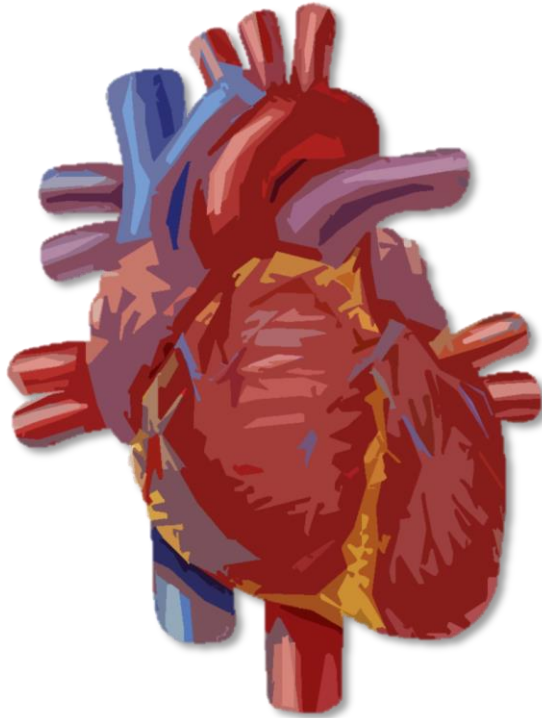
Failure to see an effect doesn't prove
it's not there

Many marijuana users also use alcohol or tobacco
(this can be controlled in analyses)

The best studies include longitudinal time-points,
varied doses and frequencies, & controls



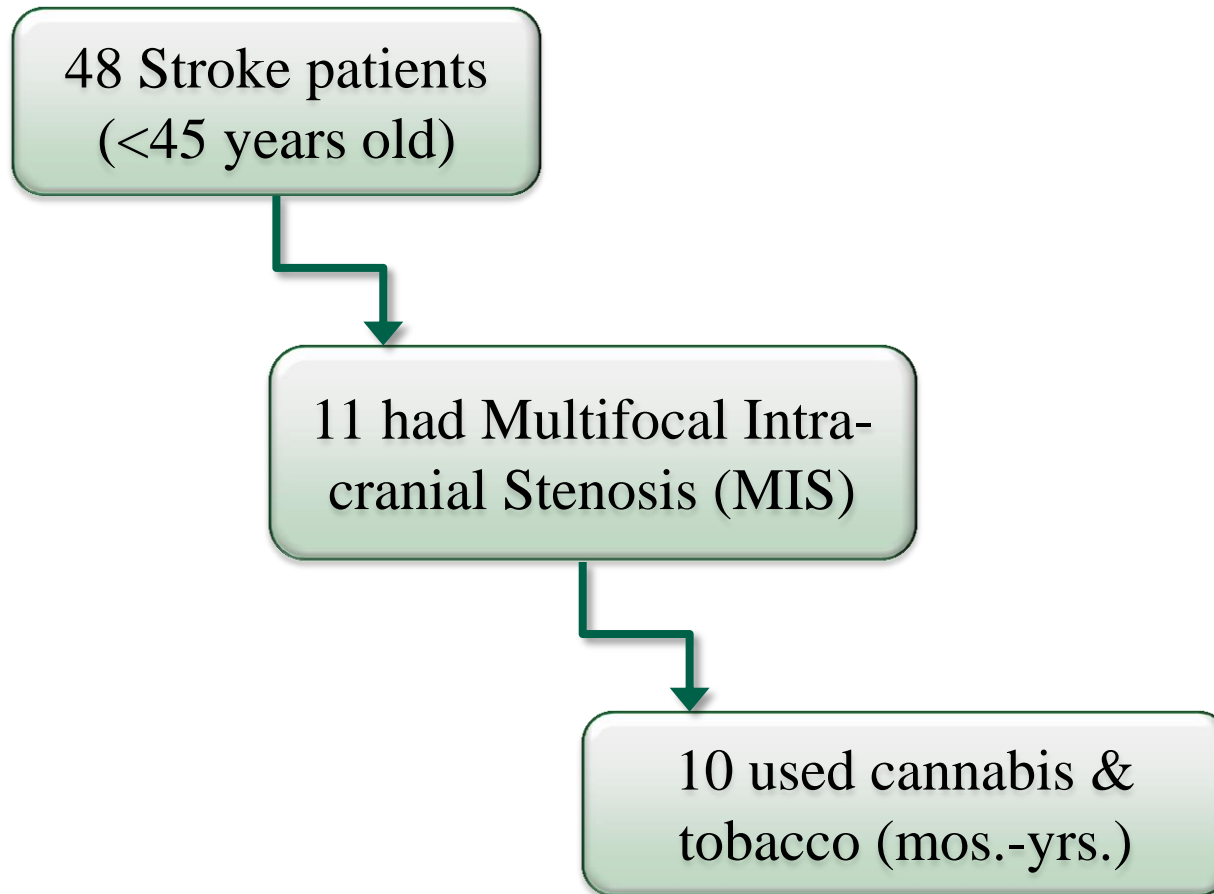
Marijuana & the Cardiovascular System



Increases heart rate
Increases blood pressure (supine)
Increases O₂ demand



Risk of Stroke is High in Young Adults using Marijuana & Tobacco



V Wolff et al. 2011



Occluded Brain Arteries can Recover with Cessation

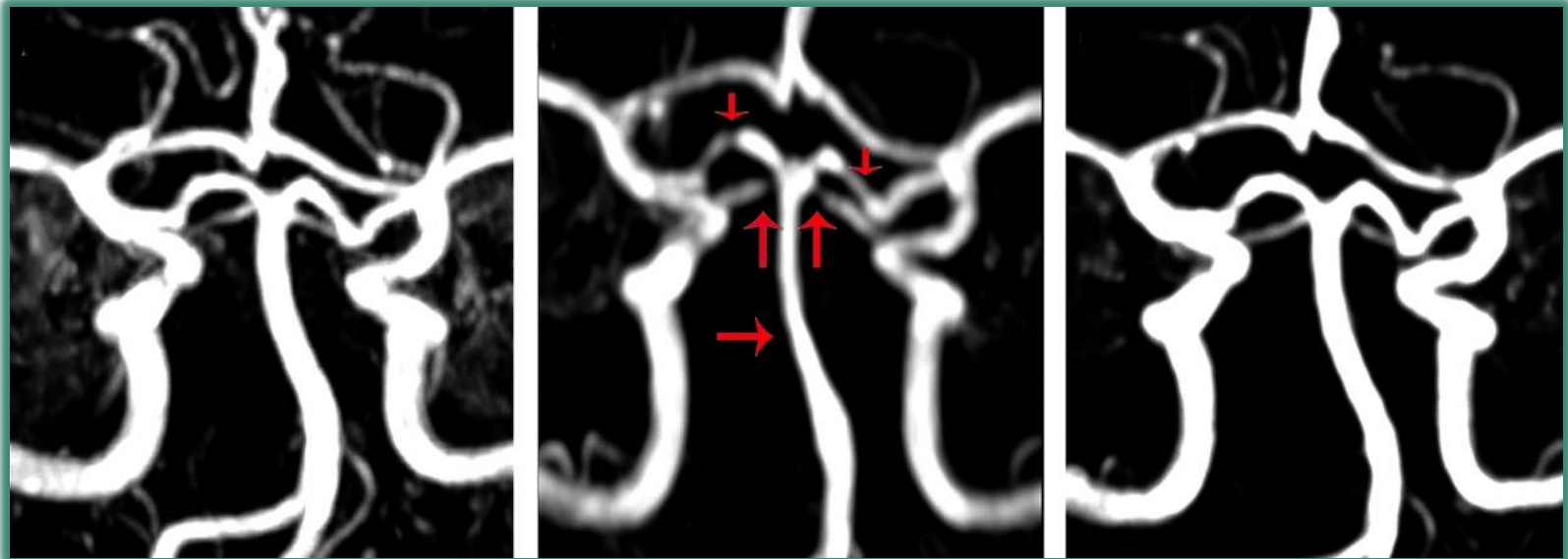
Started smoking MJ-age 20



Age 19

Age 21

3 months-no MJ



V Wolff et al. 2011



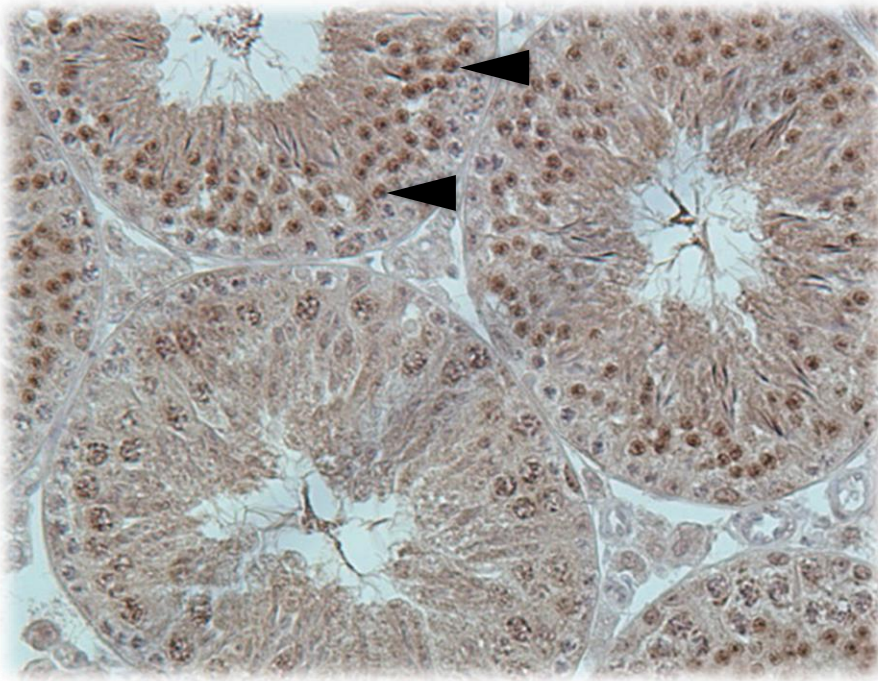
Marijuana & the Testicles





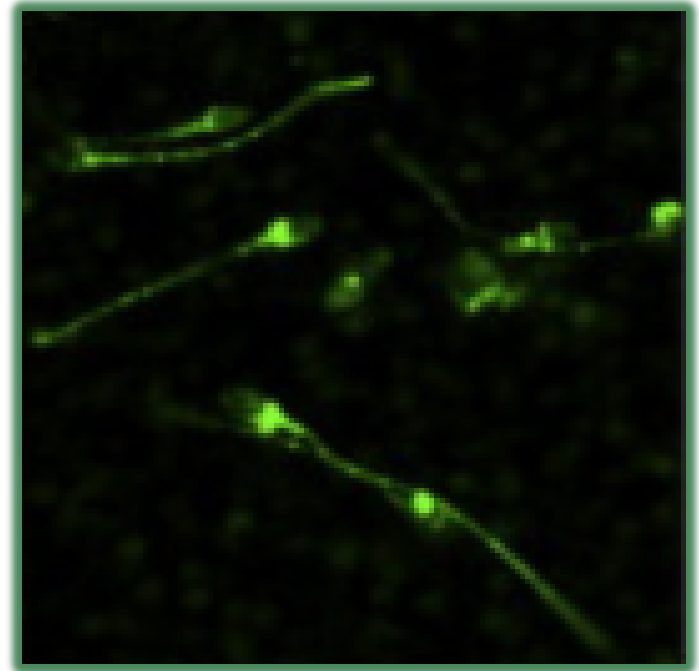
Marijuana & the Testicles

CB Receptors in testis



X Sun et al. 2009

CB Receptors on sperm



E Agirregiotia et al. 2010



Marijuana Significantly Increases Risk of Testicular Cancer (non-seminous)

Lacson, 2012

1986-1991

Ages 18-35

33% current users

2.5 x as likely if ever used

3 x as likely if a former user

3 x as likely if < 1/week

3 x as likely if < 10 years

6.5 x as likely if > 10 years

Trebert, 2011

1990-1996

Ages 18-50

< 10% current users

2 x as likely overall

3 x as likely if used daily

75% had 1st use < age 18

Dahling, 2009

1999-2006

Ages 18-44

100% current users

2 x as likely overall

3 x as likely if 1st use < age 18

3 x as likely if used weekly



Marijuana & the Lungs



Higher risk of bronchitis
Higher risk of respiratory infections
Increased risk lung cancer in heavy smokers



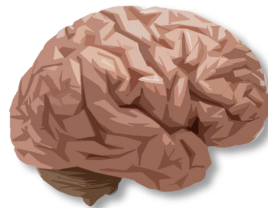
Marijuana & the Brain





Marijuana Use is Associated with Brain Disorders

- Cannabis Use Disorder
- Anxiety/Mood Disorders
- Cognitive dysfunction
- Psychosis/Schizophrenia





Marijuana & Brain Disorders

- Cannabis Use Disorder
- Anxiety/Mood Disorders

12-18 yr old users are 3-7 x as likely to have CUD than 22-26 yr old users

CUD is 2 x as likely in states with medical marijuana (2.6%)

Patients with mental illness are 3 x as likely to have CUD



Marijuana & Brain Disorders

- Cannabis Use Disorder
- Anxiety/Mood Disorders

14 yr olds using occasionally, weekly, or daily over 15 yrs are 2.5 x as likely to have anxiety disorder at age 29

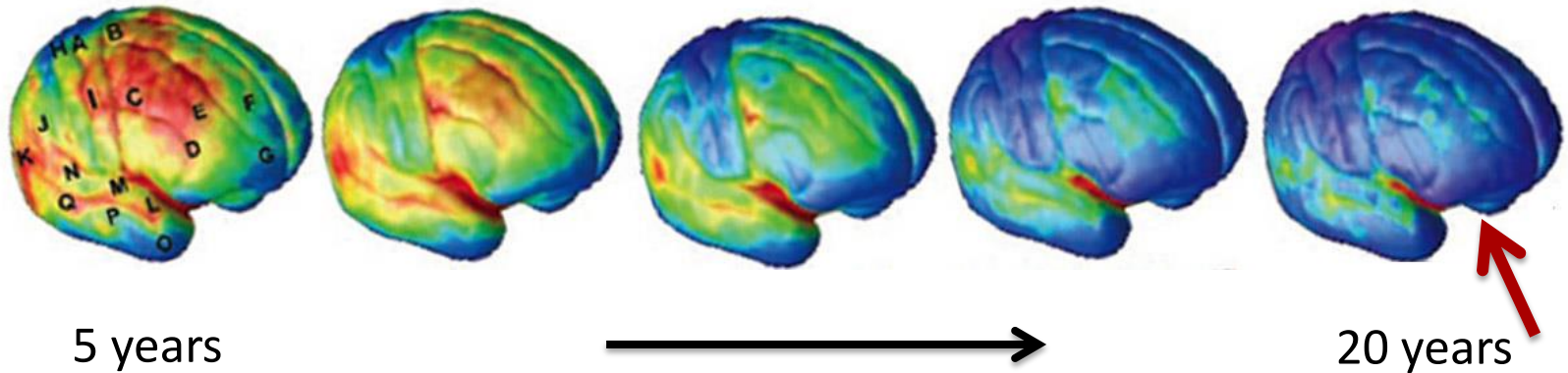
If non-using at age 29, they are still 2 x as likely to have anxiety disorder



Marijuana & Adolescents: Impacts on Brain Health



The Adolescent Brain: A Key Time for Maturation



5 years

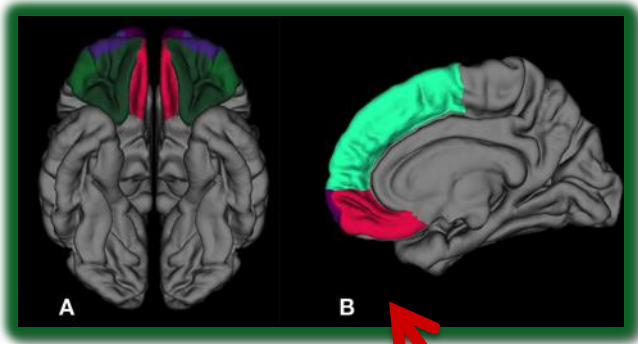
N Gogtay et al. 2004

20 years

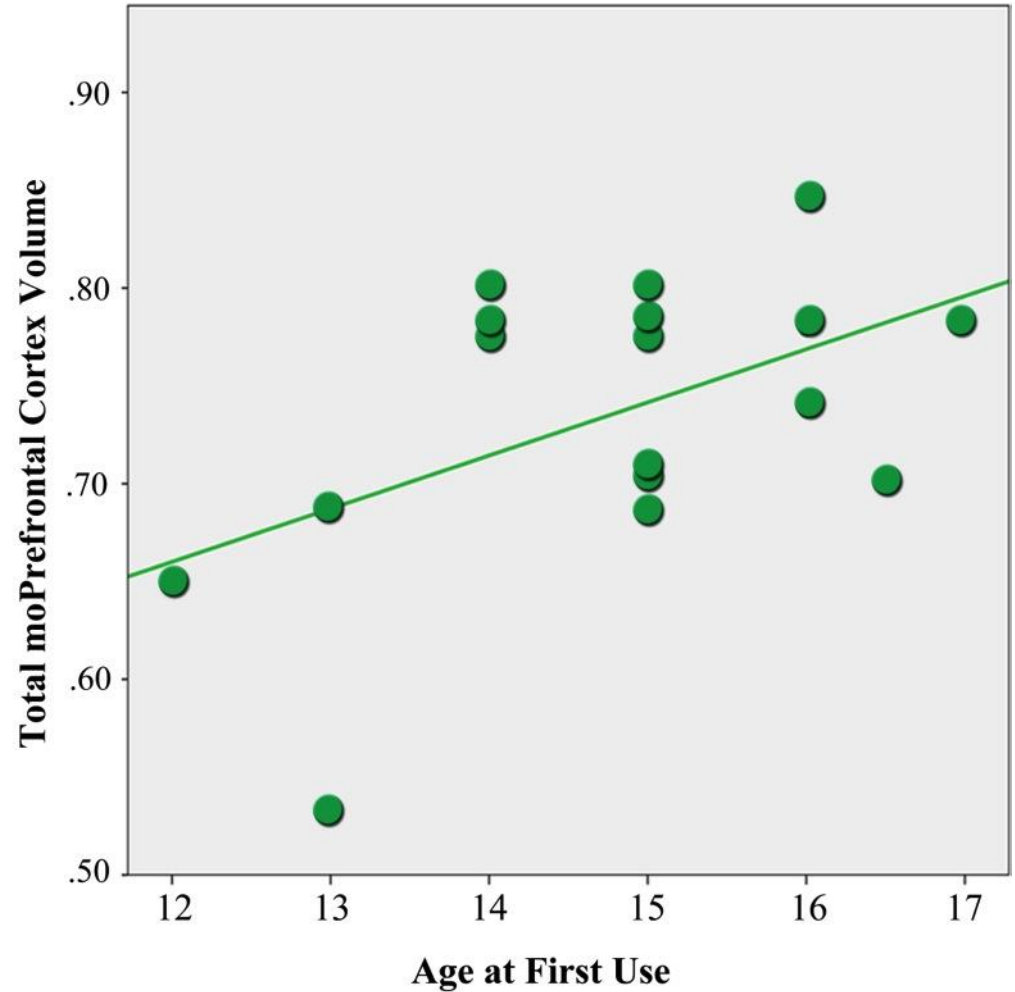
Decision-making
Judgment
Impulsivity
Memory



Earlier Use of Marijuana is Associated with Lower mo-Prefrontal Cortex Volume

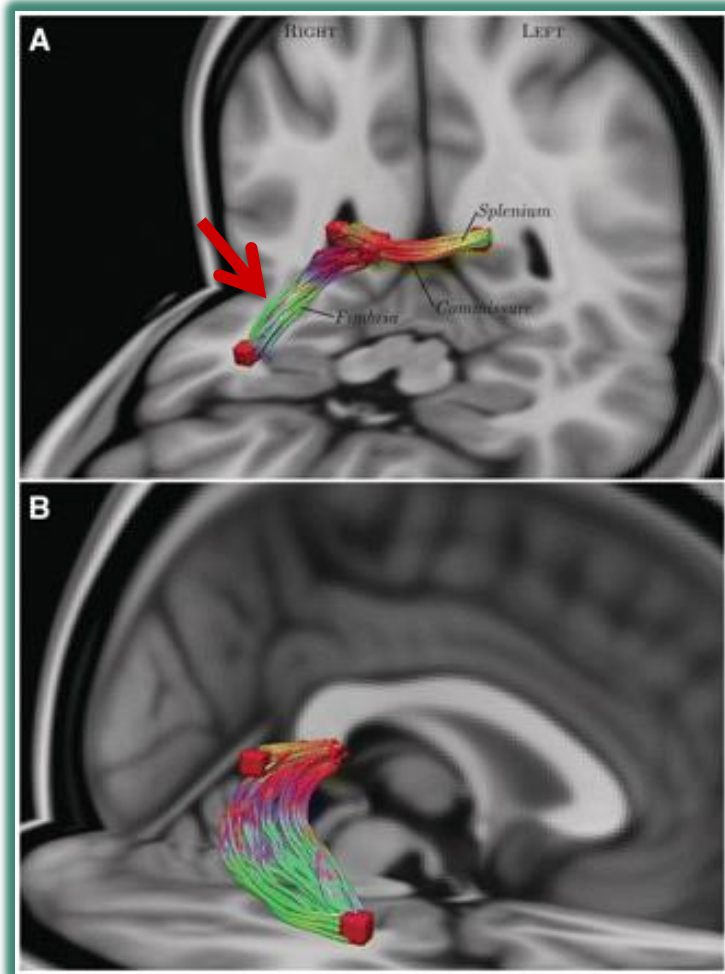


JC Churchwell et al. 2010

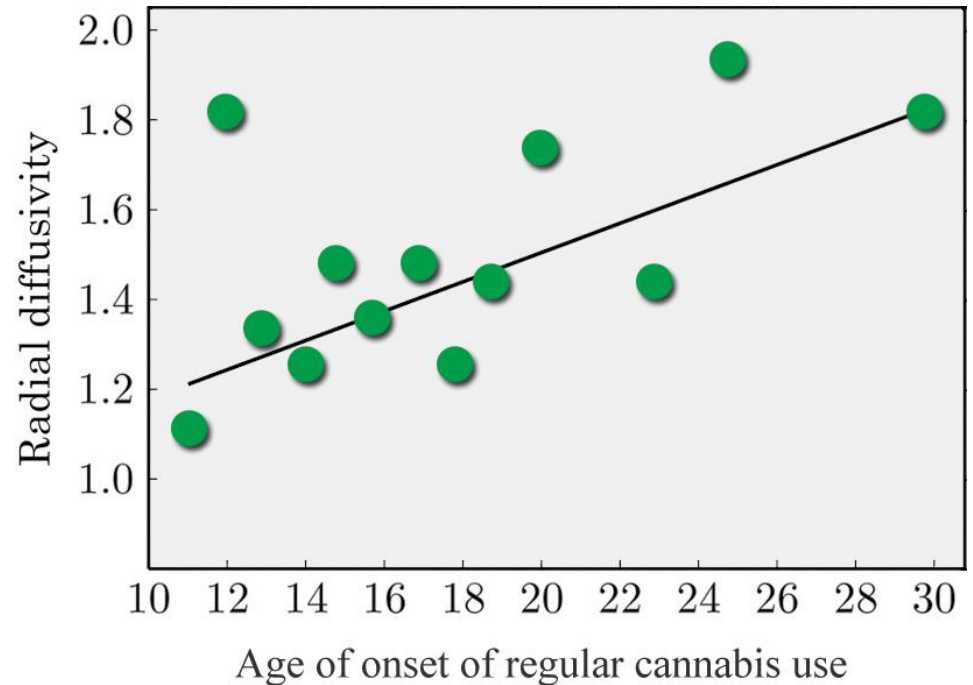




Earlier Use of Marijuana is Associated with Altered White Matter Tracts

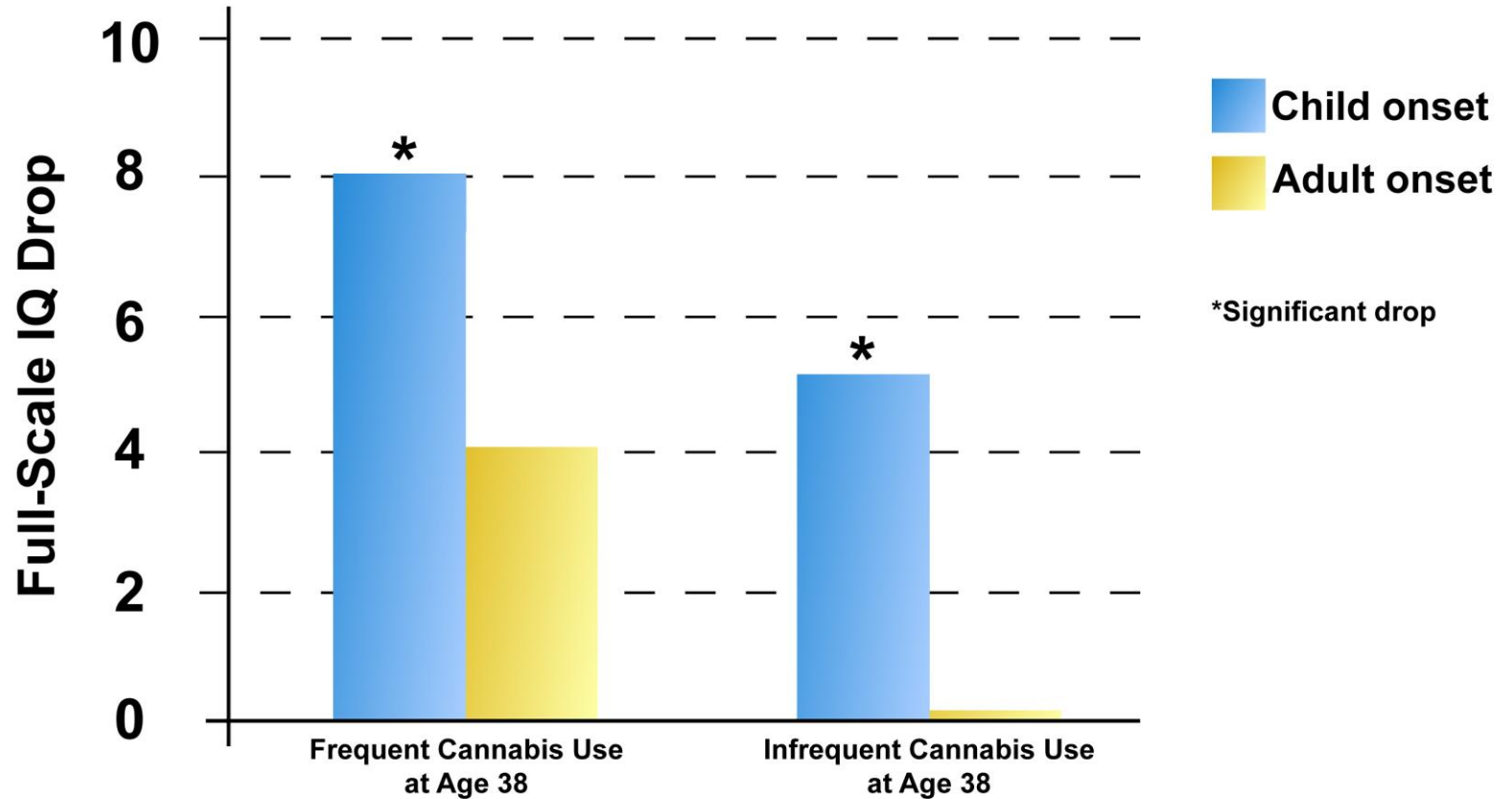


A Zalesky et al. 2012





IQ Drop Persists in Adults who use Marijuana Infrequently if they Smoked Weekly Before Age 18



MH Meier et al. 2012



Adults with Persistent Cannabis Dependence Show Mental Function Impairment at Age 38

Memory

Executive function*

Processing speed*

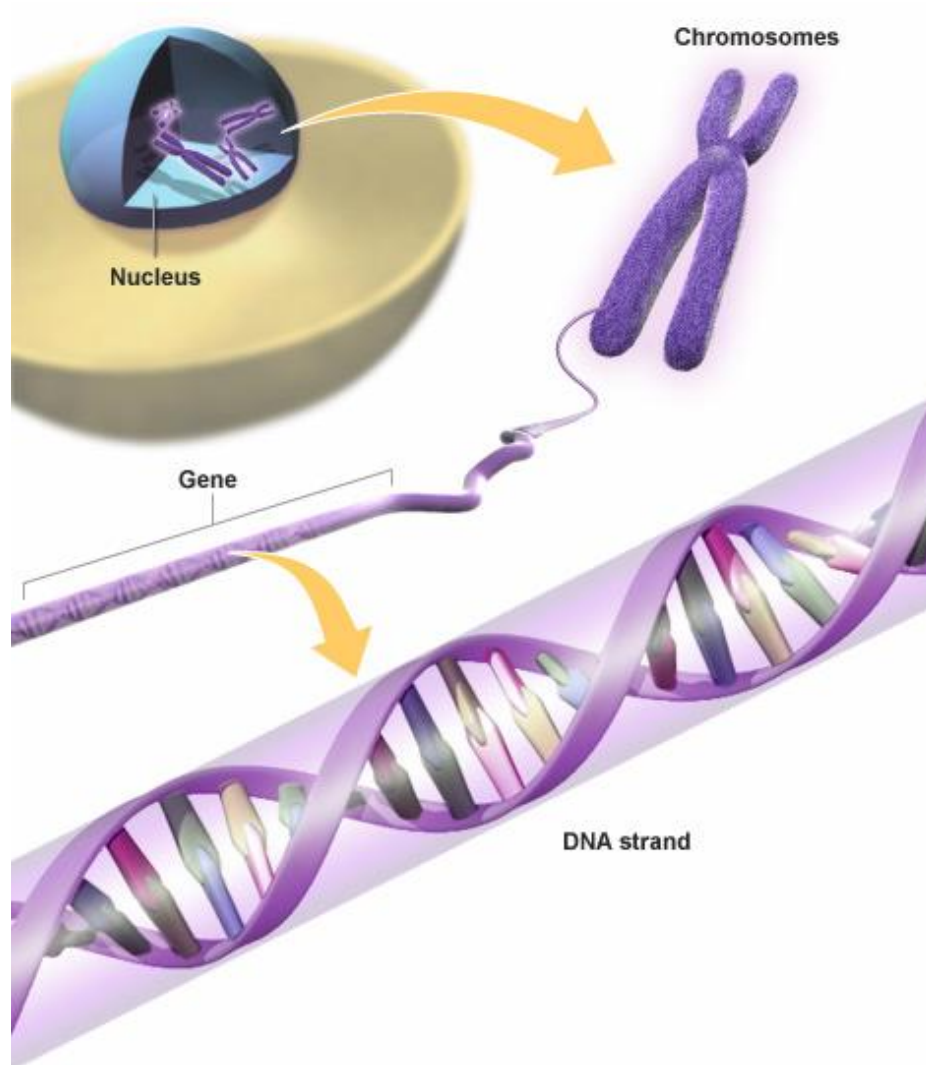
Perceptual reasoning

Verbal comprehension

**greatest impairment*



Marijuana, Genes, and Disease





Chromosomes: Half from Mom & Dad

from Mom

from Dad





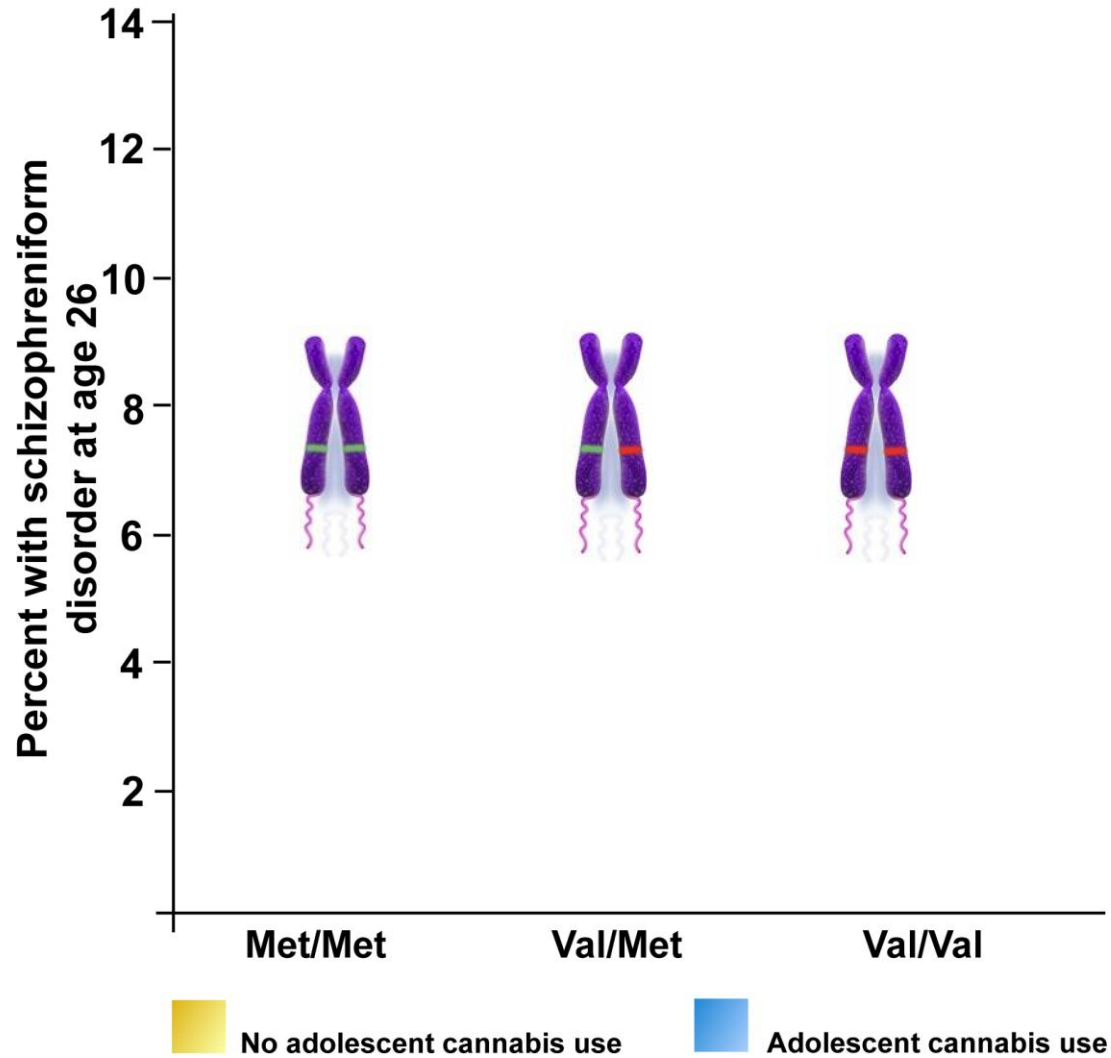
COMT Gene Variations: Risk of Schizophrenia

Chromosome 22





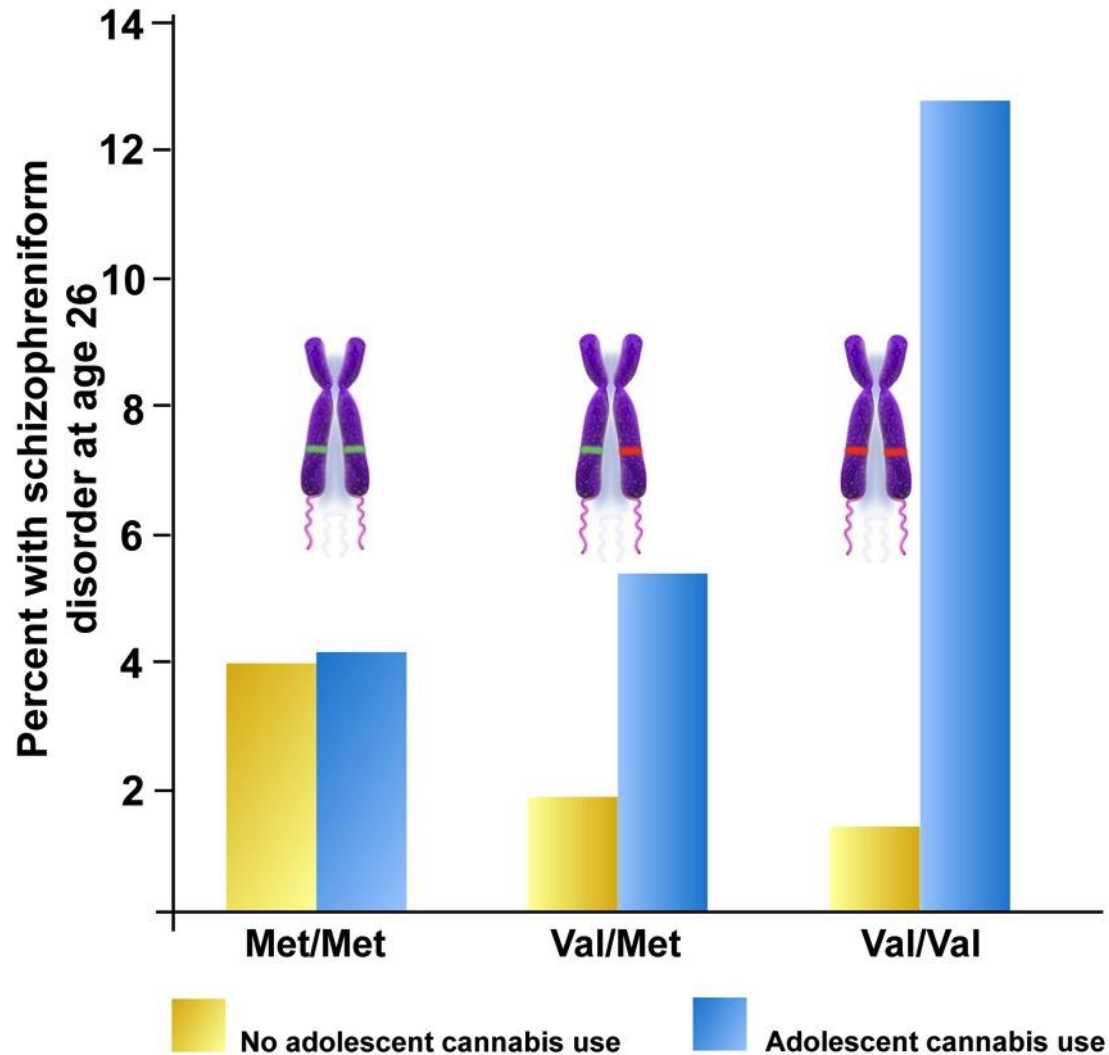
Study of Adolescents: Use of Cannabis and Risk of Schizophreniform Disorder, Based on Genetics



Caspi et al., 2005



Adolescents who Smoke Cannabis have Increased Risk of Schizophreniform Disorder, Depending on the COMT Gene



Caspi et al., 2005



Schizophrenia-related Genes on Chromosome #6



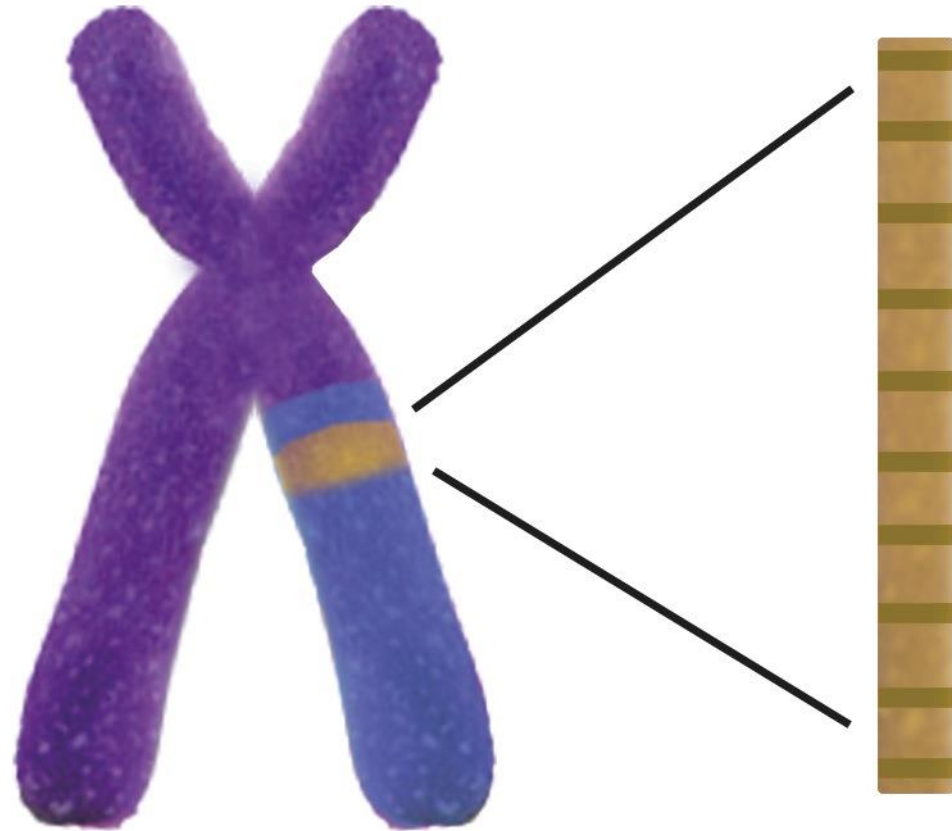


Gene for the CB1 Receptor is on Chromosome #6



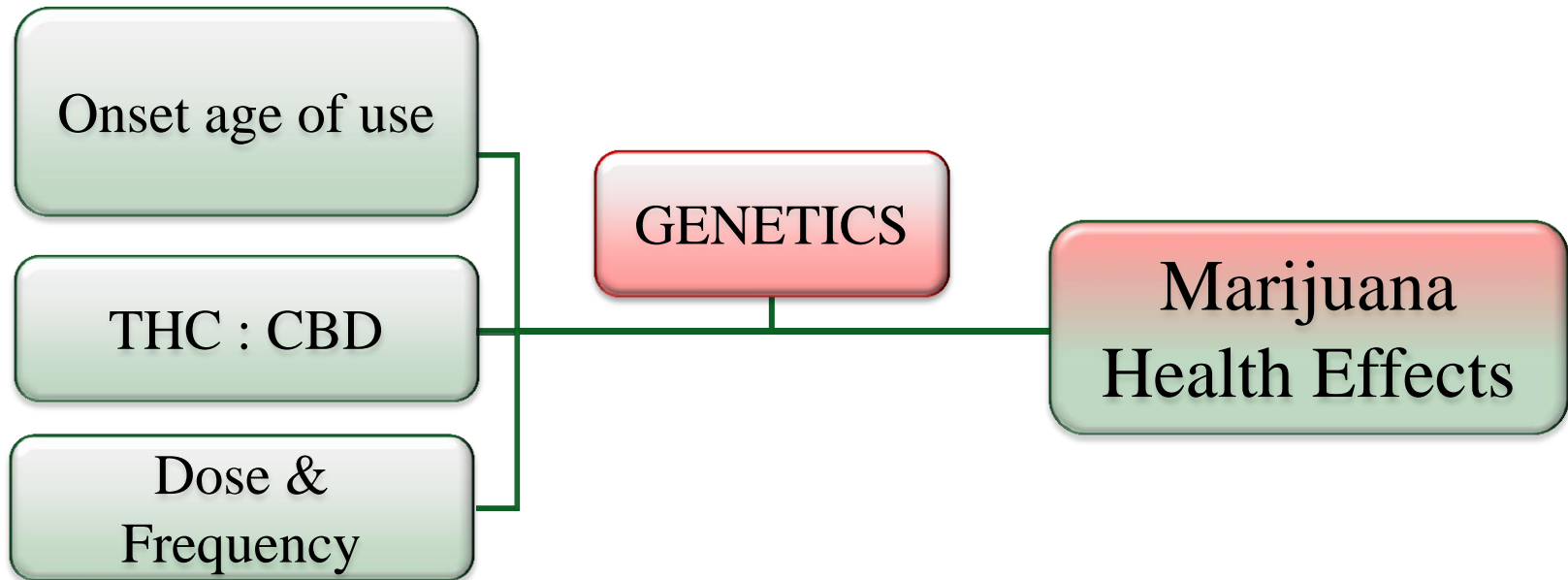


CB1 Receptor Gene Can Have Many Variations





Effects of Marijuana on Health are Influenced by Genetics





Take Home Messages

Marijuana's effects on the developing brain & other organs impacts future health

Delay the onset of marijuana use as long as possible



Cited Studies

Cannabinoid receptor pharmacology:

- RG Pertwee, AC Howlett, ME Abood et al, (2010) International Union of Basic and Clinical Pharmacology. LXXIX. Cannabinoid Receptors and Their Ligands: Beyond CB1 and CB2. *Pharmacologic Reviews* 62:588–631.

THC:CBD ratios:

- JR Burgdorf, B Kilmer, & R Liccardo Paculab (2011) Heterogeneity in the composition of marijuana seized in California. *Drug and Alcohol Dependence* 117:59– 61.

MJ effects on IQ and cognition:

- MH Meier, A Caspi, A Ambler et al., (2012) Persistent cannabis users show neuropsychological decline from childhood to midlife. *Proceedings National Academy of Sciences* 109 (40):E2657–E2664.

MJ effects on cardiovascular function:

- V Wolff, V Lauer, O Rouyer et al., (2011) Cannabis use, ischemic stroke, and multifocal intracranial vasoconstriction. *Stroke* 42:1778-1780.

MJ and anxiety disorders:

- L Degenhardt, C Coffey, H Romaniuk et al. (2012) The persistence of the association between adolescent cannabis use and common mental disorders into young adulthood. *Addiction* 108:124-133.

MJ effects on testicles and cancer:

- JR Daling, R Doody, X Sun et al, (2009) Association of marijuana use and the incidence of testicular germ cell tumors. *Cancer* 115:1215-1223.



Cited Studies

MJ effects on testicles and cancer:

- B Trabert, AJ Sigurdson, AM Sweeney et al., (2011) Marijuana use and testicular germ cell tumors. *Cancer* 117:848–853.
- JCA Lacson, JD Carroll, E Tuazon et al., (2012) Population-based case-control study of recreational drug use and testis cancer risk confirms an association between marijuana use and nonseminoma risk. *Cancer* 118:5374-5383.

MJ and lung cancer:

- M Hashibe, H Morgenstern, Y Cui et al, (2006) Marijuana use and the risk of lung and upper aerodigestive tract cancers: Results of a population-based case-control study. *Cancer Epidemiology Biomarkers & Prevention* 15:1829-1834.
- S Aldington, M Harwood, B Cox et al., (2008) Cannabis use and risk of lung cancer: a case–control study. *European Respiration Journal* 31:280–286.

MJ, genes, & schizophrenia:

- A Caspi, TE Moffitt, M Cannon, et al., (2005) Moderation of the effect of adolescent-onset cannabis use on adult psychosis by functional polymorphism in the COMT gene: longitudinal evidence of a gene x environment interaction. *Biological Psychiatry* 57:1117-1127.

MJ & brain structure changes:

- A Zaleski, N Solowij, M Yucel et al., (2012) Effects of long-term cannabis use on axonal fibre connectivity. *Brain* 135: 2245-2255.
- JC Churchwell, M Lopez-Larson,& DA Yurgelun-Todd (2010) Altered frontal cortical volume and decision making in adolescent cannabis users. *Frontiers in Psychology* 1:1-8.