Endocannabinoids, cannabinoids and cannabis

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Cannabis

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Cannabis

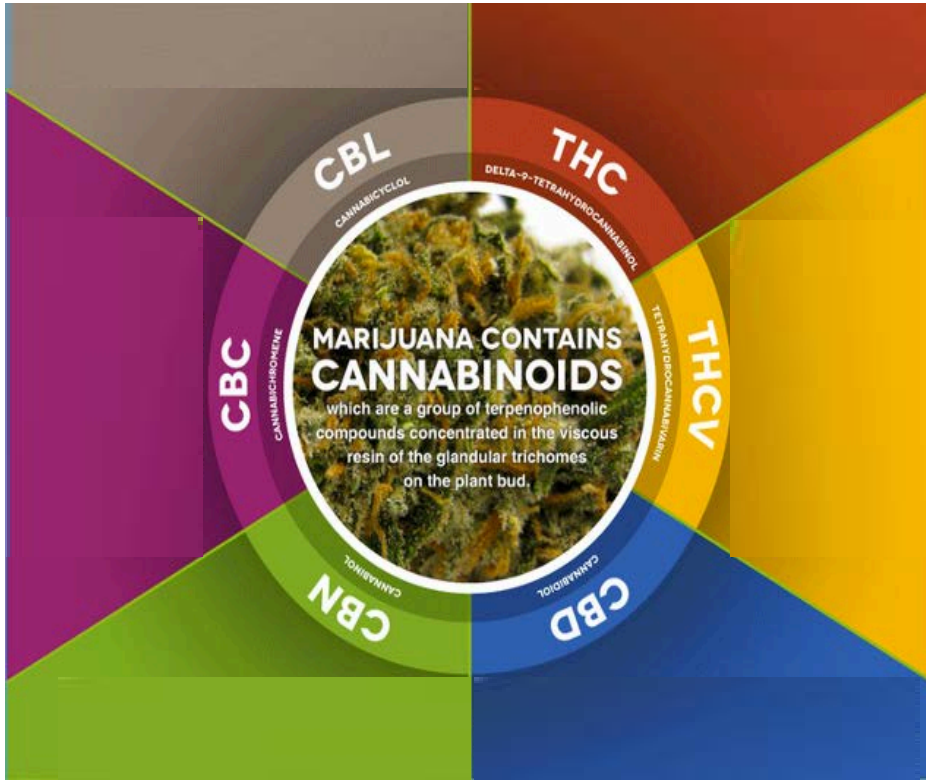
- Trichomes on cannabis plant
- Evolved to protect the plant
- Contain chemicals: ‘cannabinoids’

Cannabinoids

> 80 different cannabinoids

Δ9-tetrahydrocannabinol (THC) induces anxiety, memory impairment, 'stoned' and schizophrenia-like effects (D'Souza et al, 2004; 2008).

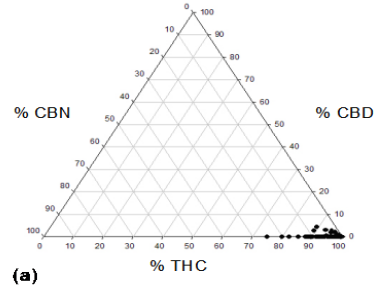
Cannabidiol (CBD) anxiolytic, reduces paranoia, neuroprotective (Zuardi et al. 2006; Hermann et al. 2007; Leweke et al, 2007).

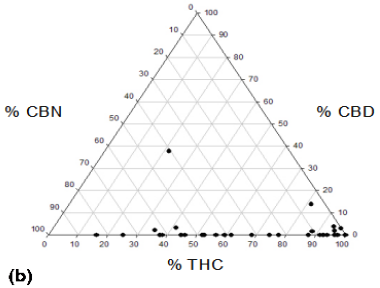


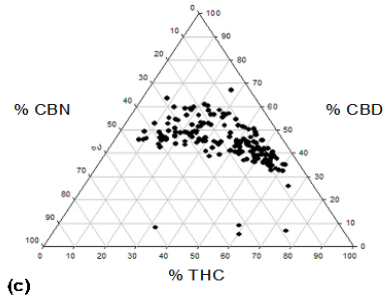
Afghani - BC bud – big bud – bomb – Blue velvet – boo-yah – bubble – bud – buddha – burger – Charis – chiba – chino – choke – cigga-weed – cigweed – combustible herbage – crippy – dank - dirt weed – ditch weed – doja – doob – dope – drat – draw – dro – dub – dube – Dutchie – endo – erve – gange – ganja – giggle stick – gonj – grass – green – green bud – hash - heim – herb – herbal refreshment – Holland's Hope – hog leg – hooter – hydro – indica – indo – jib — keef – kief – Kush – Mary Jane – Mexican dirt weed – MJ – Mr. J – Nepalese - Northern Lights – paca lolo – Purple Haze – pot – purp — Lebanese red - reggie – schwag –silver weed – skunk – smoke – soapbar tea – Thai stick – treats – tweed – wacky baccy – vortex - weed – White Widow - woolies – zombie

- Different types of cannabis vary in levels of cannabinoids

Levels of THC and CBD in 3000 cannabis seizures UK

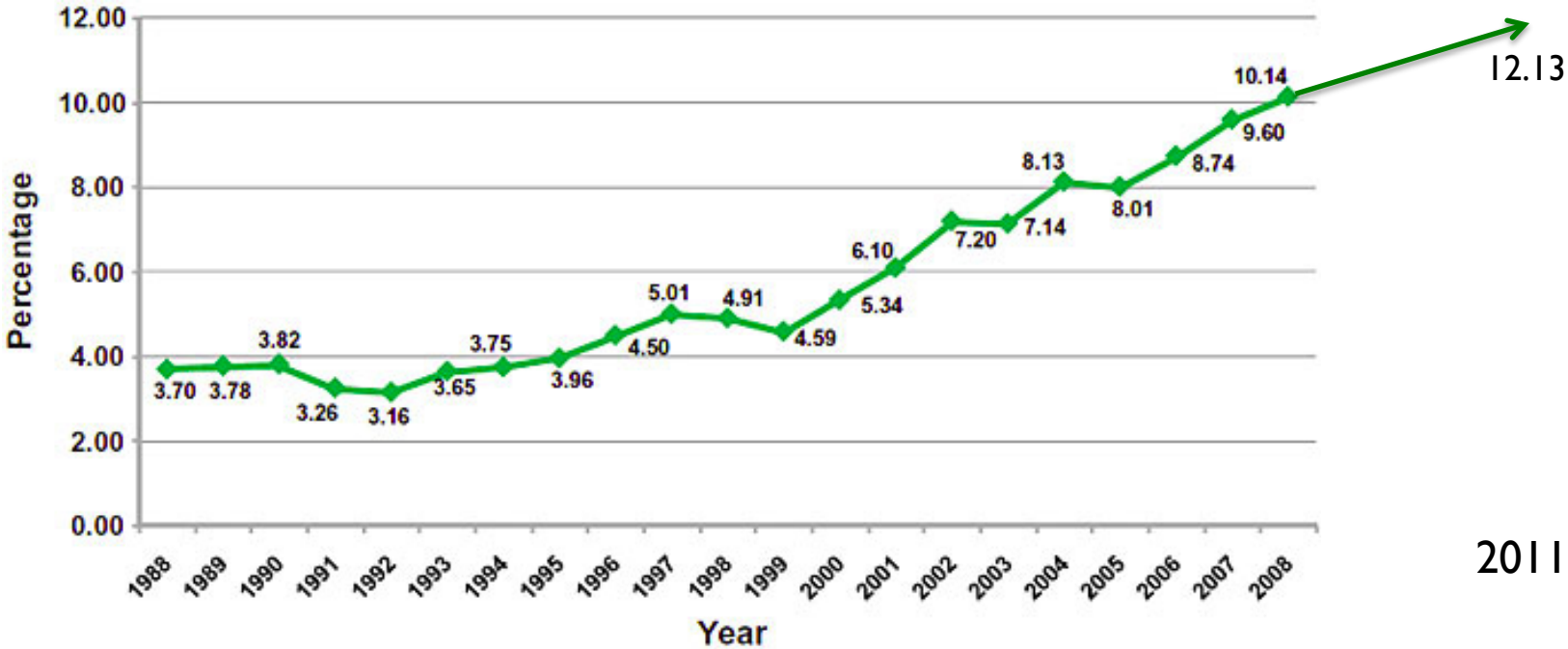




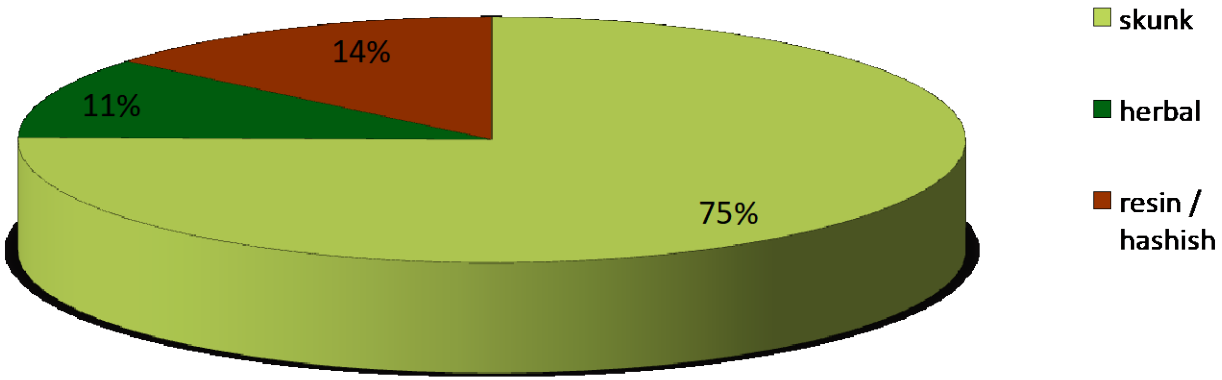


King and Hardwick, 2008

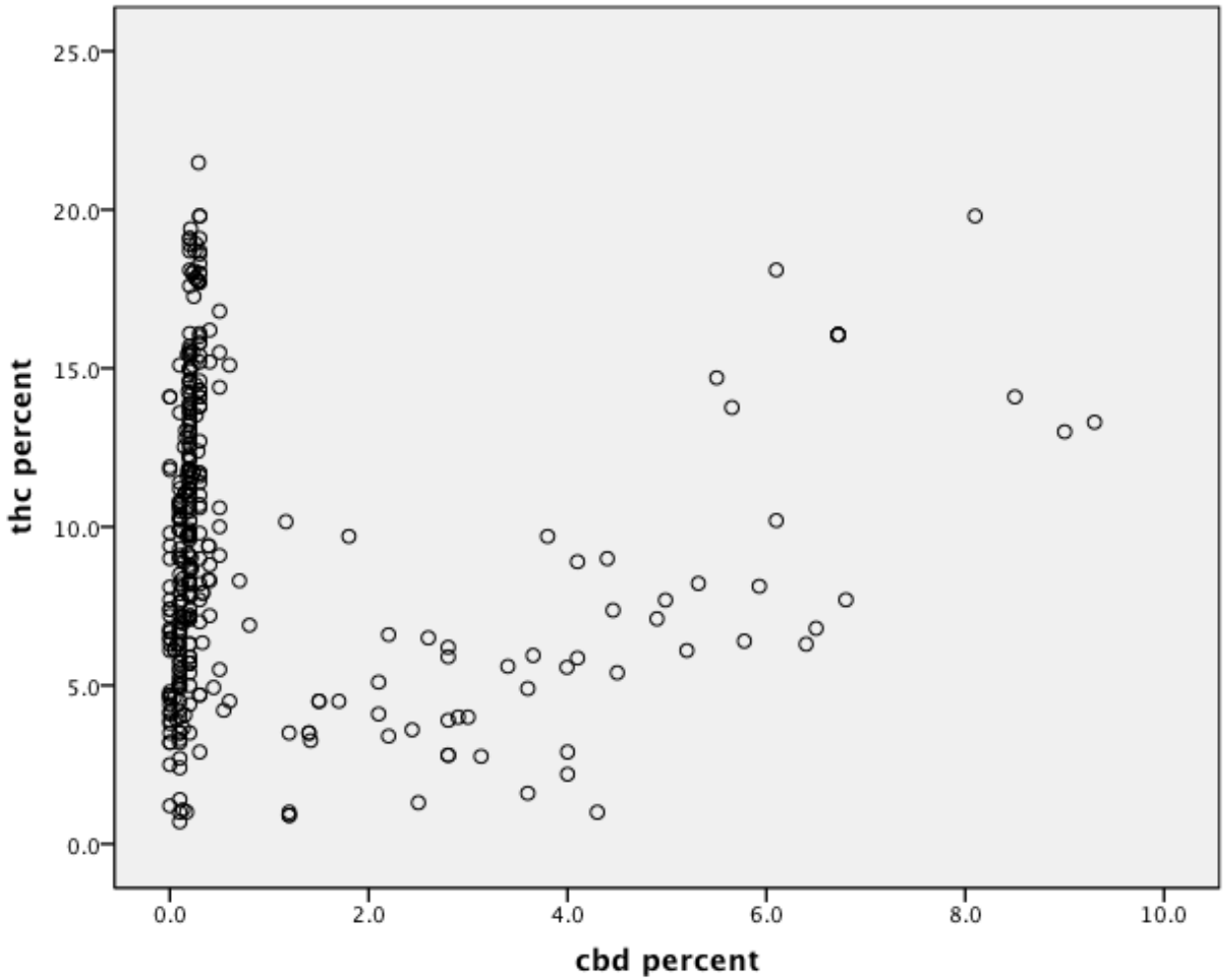
Increasing THC potency in UK cannabis seizures



Cannabis samples collected, n=422

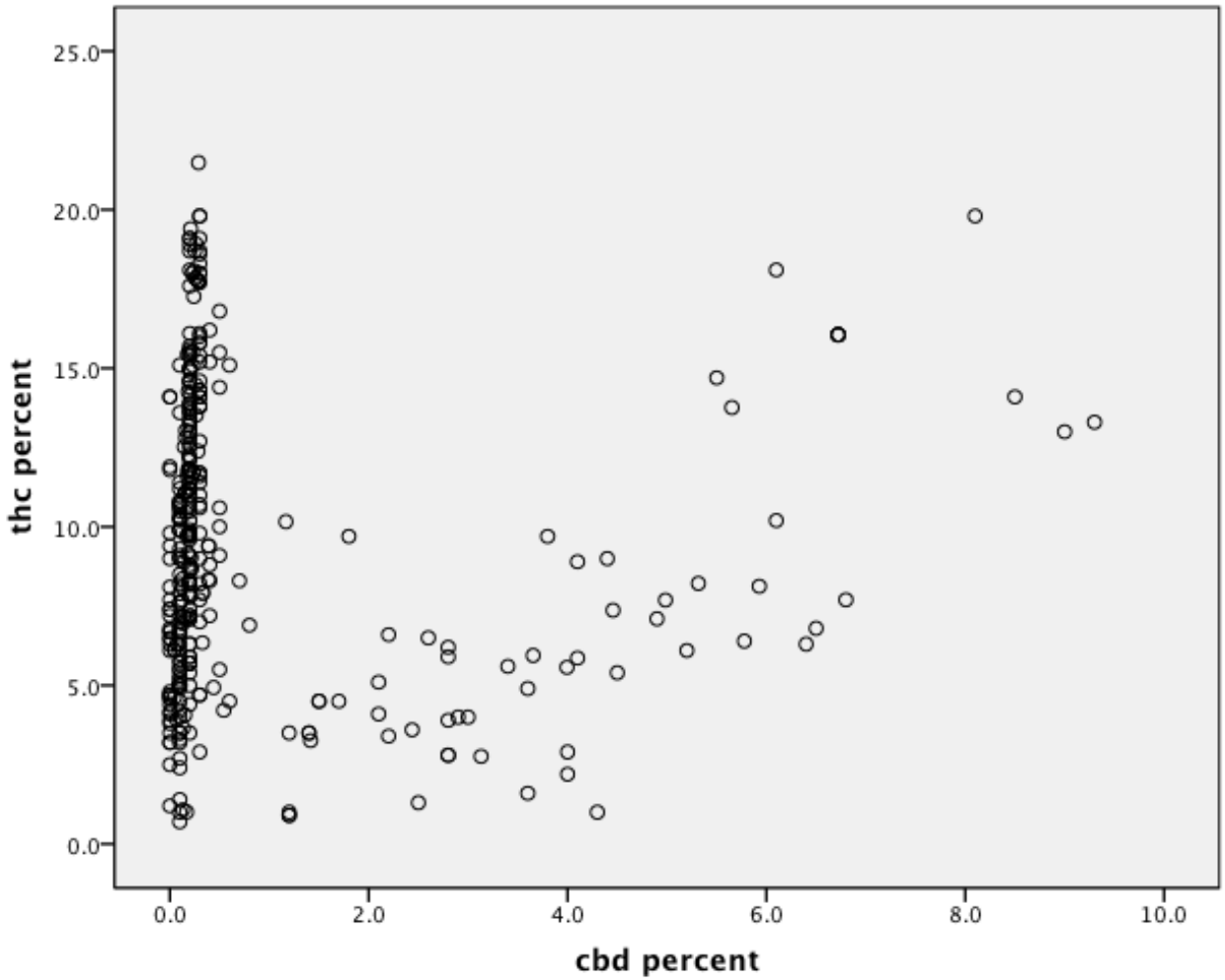


CBD and THC levels



n = 371

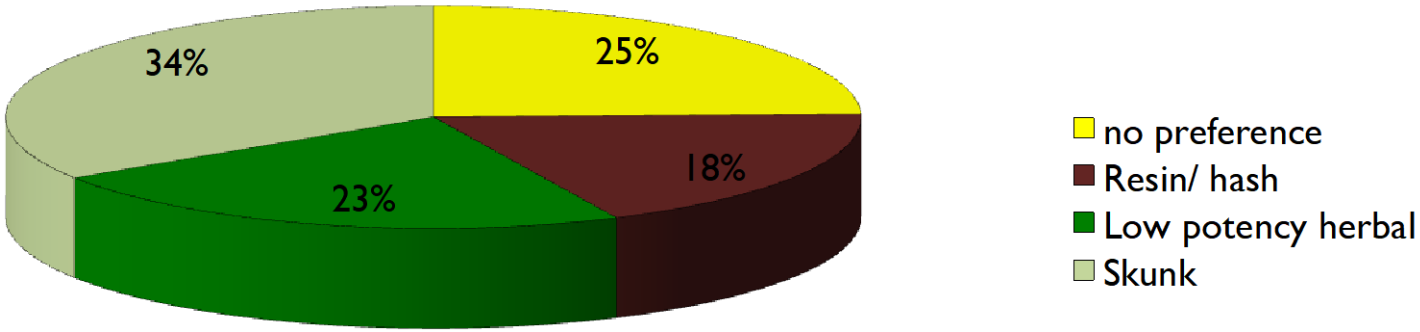
CBD and THC levels



n = 371

CBD levels are declining: why?

Preferences for types of cannabis in 16-23 year olds

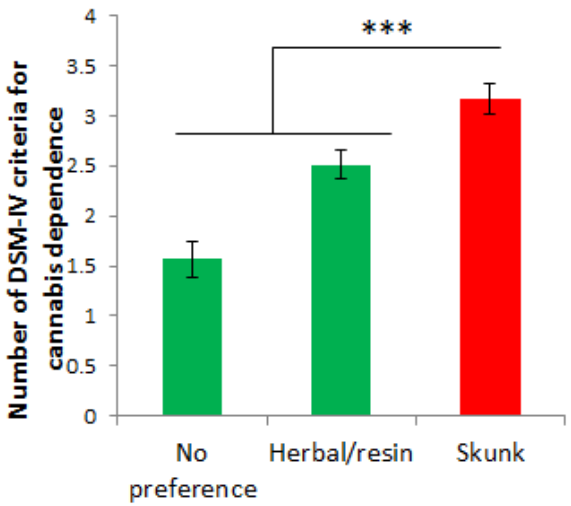


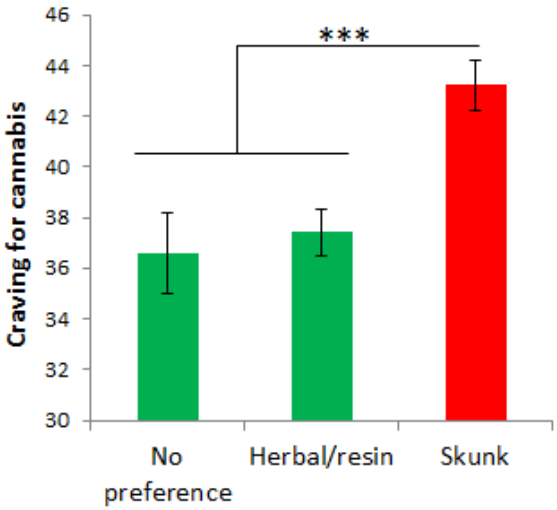
Where has the CBD gone?

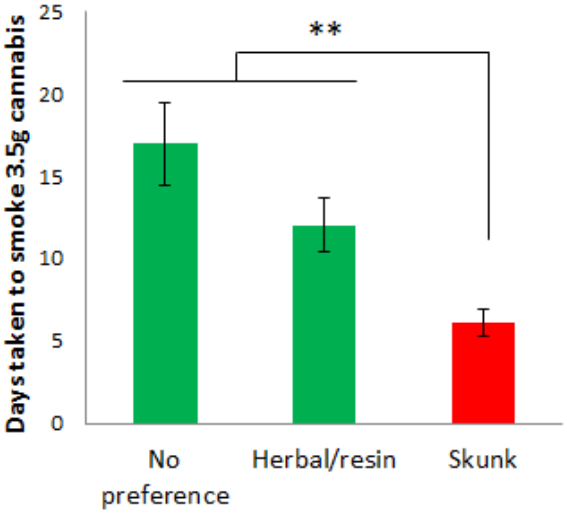
- Potter (2010)
- Majority of UK consumed cannabis now grown intensively in illegal 'farms'
- Intensive heating decreases levels of CBD in trichomes
- Hashish combines a variety of cannabis plants
  - Most cannabis seeds in UK now are a variety with no CBD

Skunk and cannabis use disorder

- Cannabis second only to heroin as reason for presentation at drug services across EU – 25% cases (EMCDDA, 2014)







‘Skunk’ use linked to psychosis

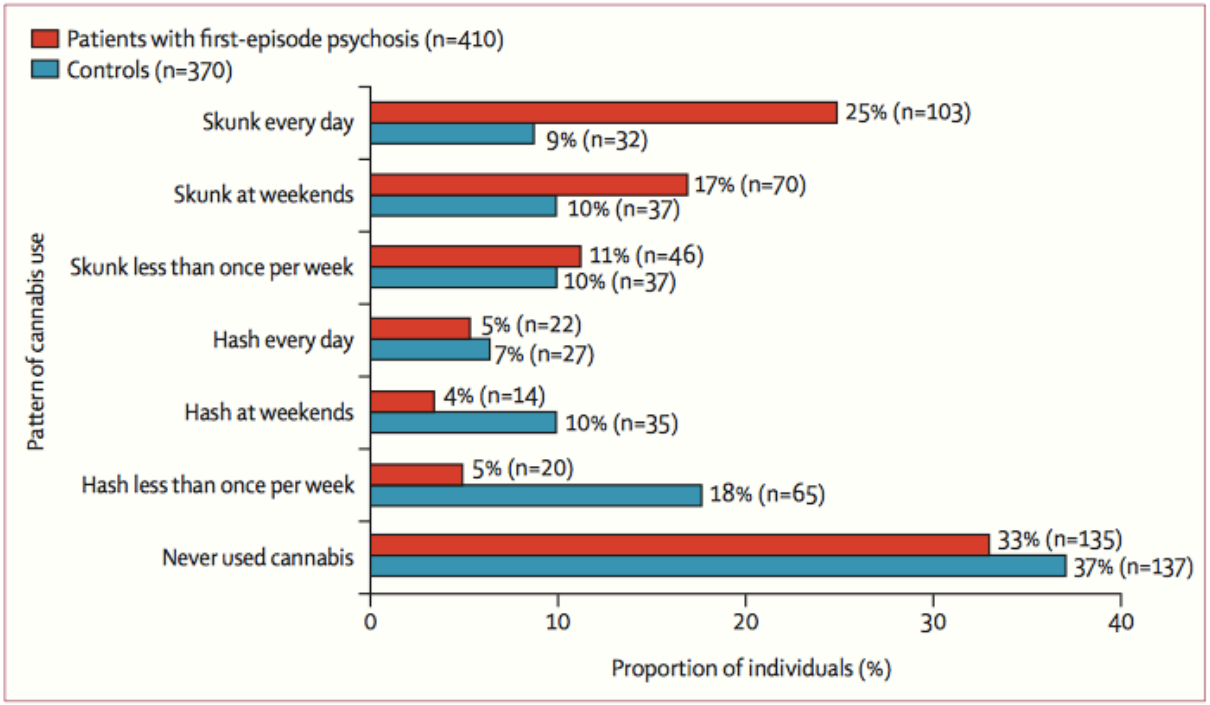


Figure 1: **Patterns of cannabis use between patients with first-episode psychosis and population controls**

Di Forti et al., 2015, Lancet Psychiatry

Research question

- Given that levels of cannabinoids vary in different cannabis preparations
- THC and CBD have opposing effects in the laboratory
- Skunk use is more prevalent in psychosis and cannabis use disorder

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Does CBD protect against the harmful effects of THC in cannabis users?

- Study 1: Cannabinoids in hair
- Study 2: Naturally occurring cannabinoids in hair and cannabis

Looking at cannabinoids in the hair…

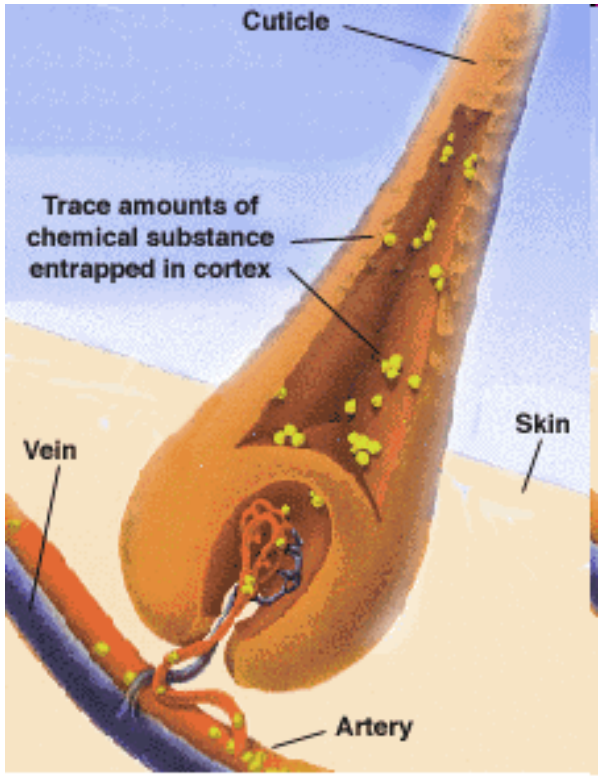


Illustration of Human Hair

Looking at cannabinoids in the hair…

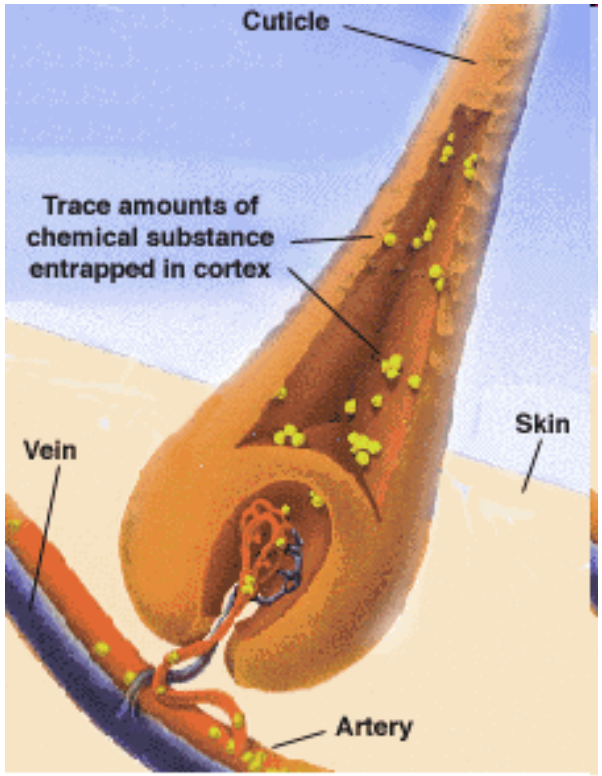


Illustration of Human Hair

Study 1: THC/CBD in hair

- Hair analysis
- 3cm hair samples ~ 3 months
- 132 people, mean age 27 years

Study 1:THC/CBD in hair

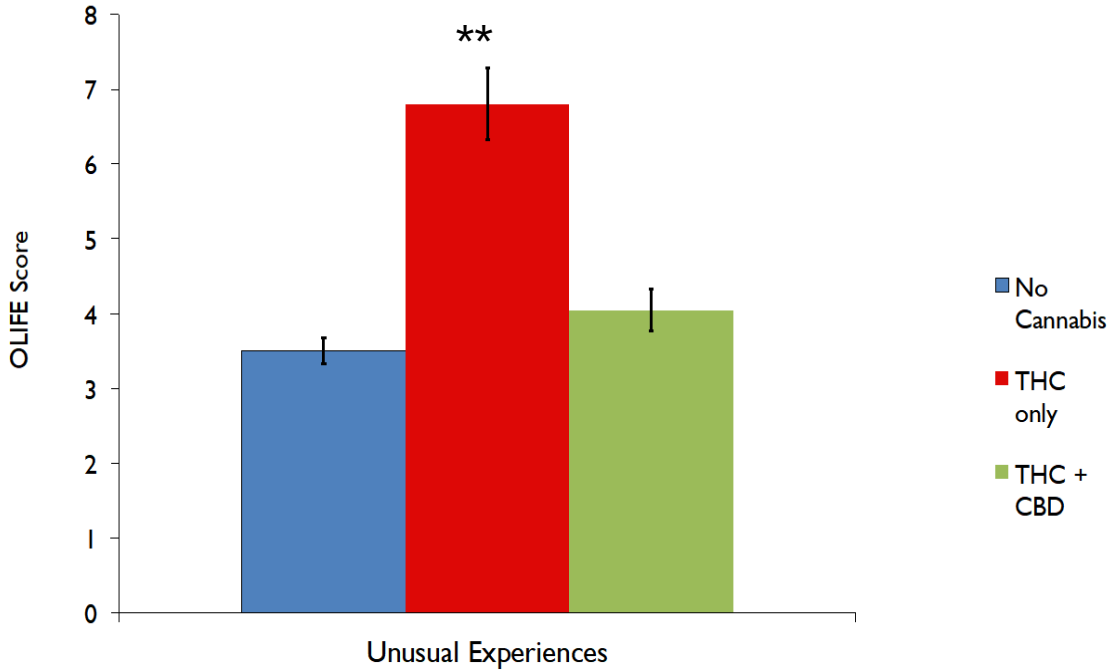
THC only n=20	CBD and THC n=26	Neither n=86

Psychotic-like experiences: O-LIFE

– Unusual Experiences ~ Paranoia, Illusions & Delusions

- When you look in the mirror does your face sometimes seem quite different from usual?
- Do think you could learn to read others minds if you wanted to?
- Do you sometimes think people are laughing about you behind your back?

THC/CBD in hair



Morgan & Curran, 2008 *British Journal of Psychiatry*

THC / CBD

- Cannabis users with THC only in hair experience higher levels of unusual experiences than THC+CBD

Interpretations:

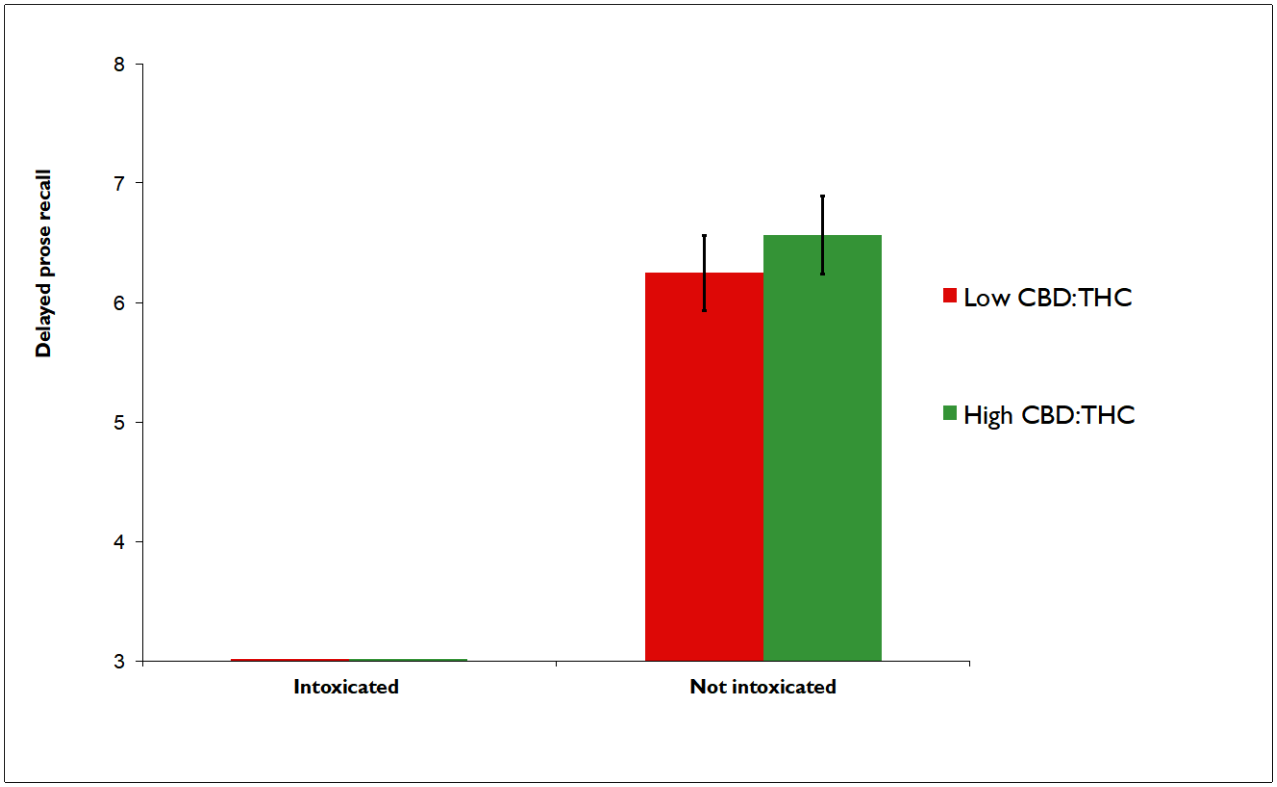
- Pre-existing group differences?
- Is CBD protective against psychotic-like effects of THC?

Study 2: Naturalistic study of the effects of cannabinoids

- n=626 individuals; 16-23 year olds
- Tested in own home, smoking own supply of cannabis
- Tested cannabis smoked for CBD and THC
- Looked at hair for chronic use

Day 0	**Stoned**	**Sober**
Day 7	**Sober**	**Stoned**

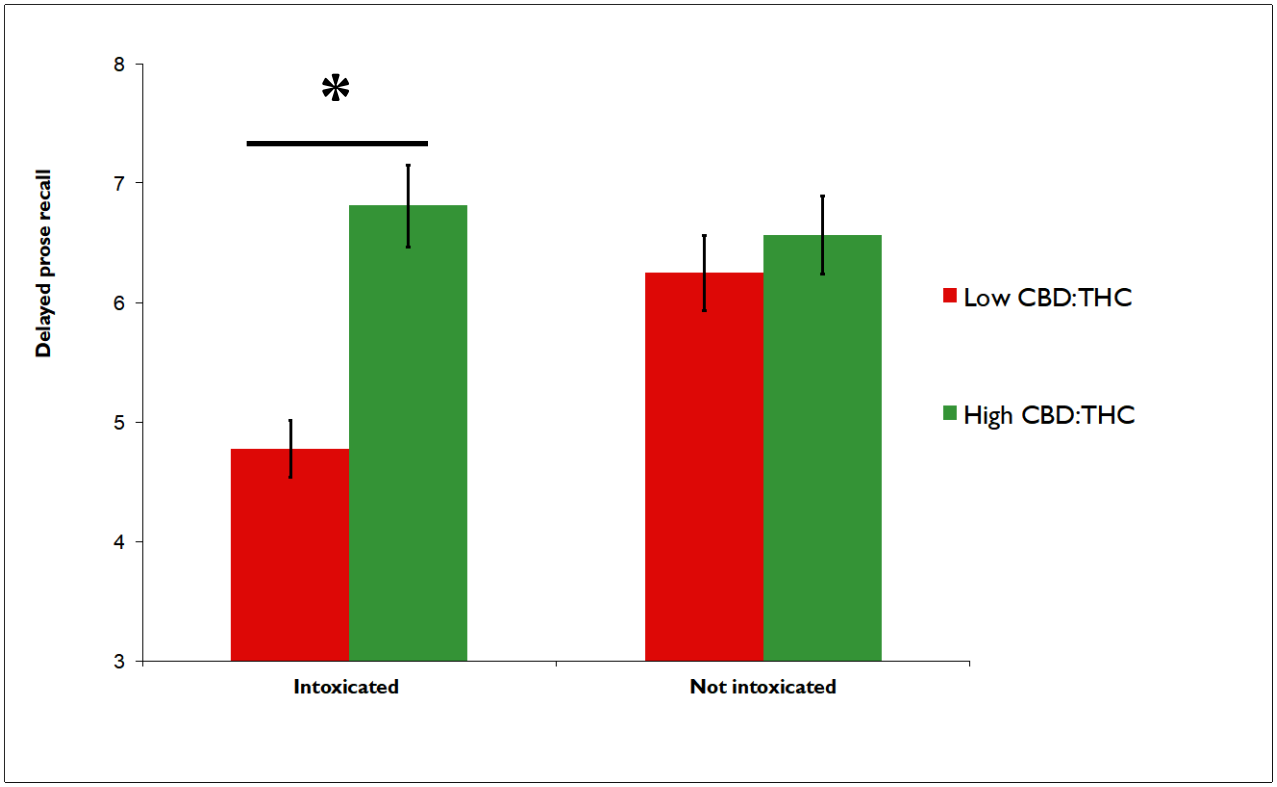
Acute effects: memory



Same amount of THC; differed in CBD

Morgan et al. (2010) British Journal of Psychiatry

Acute effects: memory



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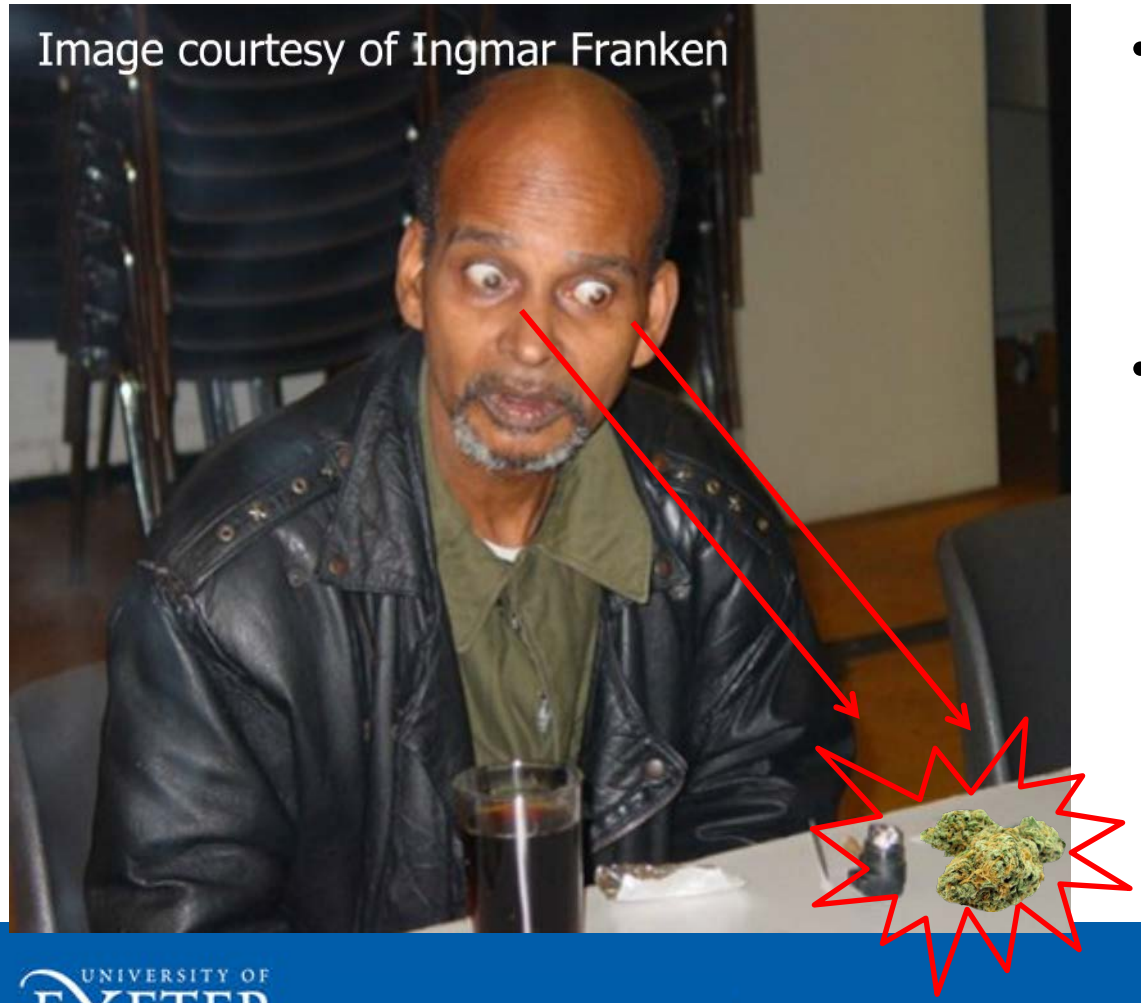
Attentional Bias



- Cues associated with drug use (e.g. cannabis, pipe, joint) grab the users' attention
- Increases drug craving and predicts relapse

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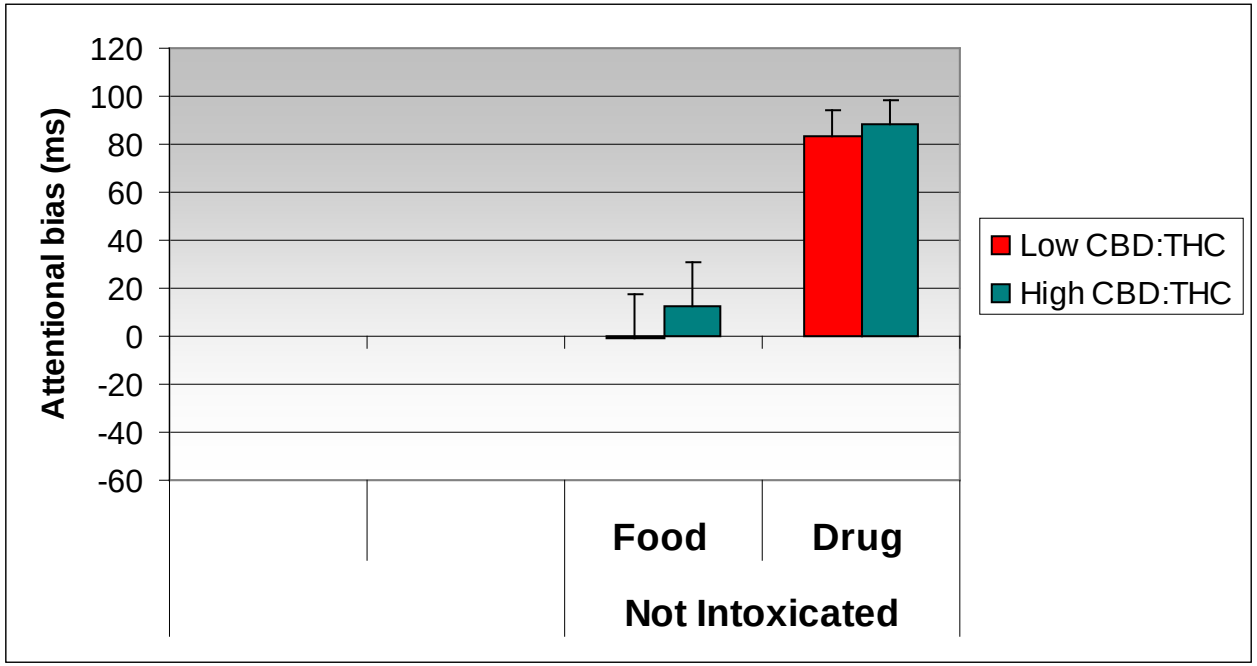
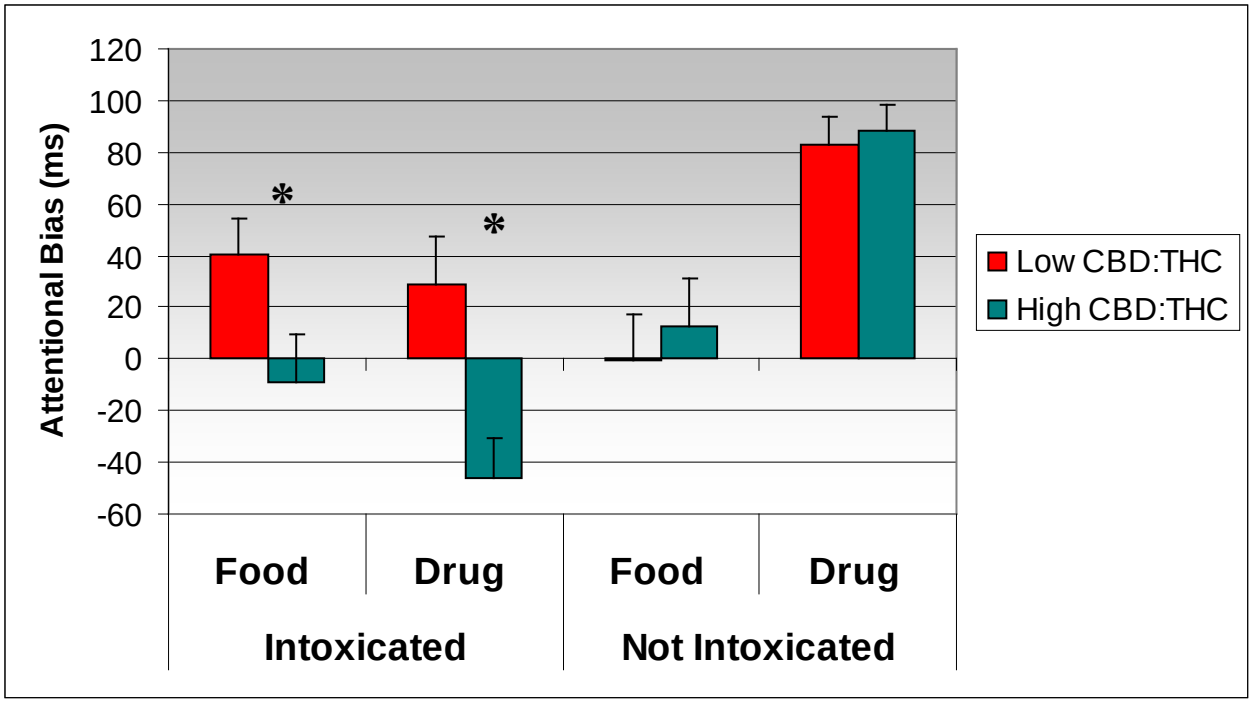
Attentional Bias



Stimulus exposure = 250ms

Morgan, Freeman, Schafer & Curran (2010) Neuropsychopharmacology

Attentional Bias



Morgan, Freeman, Schafer & Curran (2010)
Neuropsychopharmacology

Paranoia and 'stoned' effects

- Levels of CBD in cannabis smoked did not impact on acute psychotic like effects of cannabis
- No difference in 'stoned' ratings between high and low CBD groups

Morgan et al. (2011) Psychological Medicine

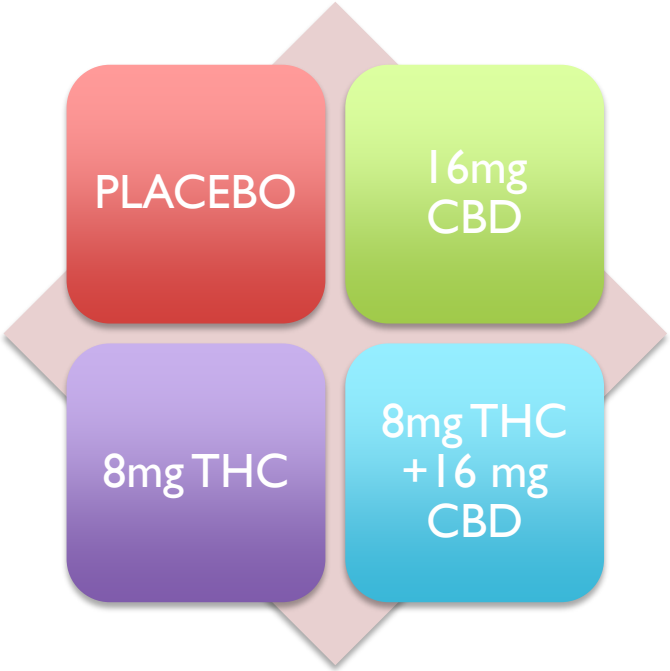
Acute effects of cannabinoids

- Acutely CBD protects from memory impairment of THC
- Greater attentional bias in people smoking low CBD cannabis

Chronic effects of cannabinoids on psychotic symptoms

- Looked at CBD and THC in hair
- Replicated previous findings Morgan & Curran (2008)
- Psychotic symptoms higher in those smoking cannabis with no CBD
  - Highest in *infrequent users* smoking high THC cannabis with no CBD

Acute effects of cannabinoids in cannabis smokers: laboratory study

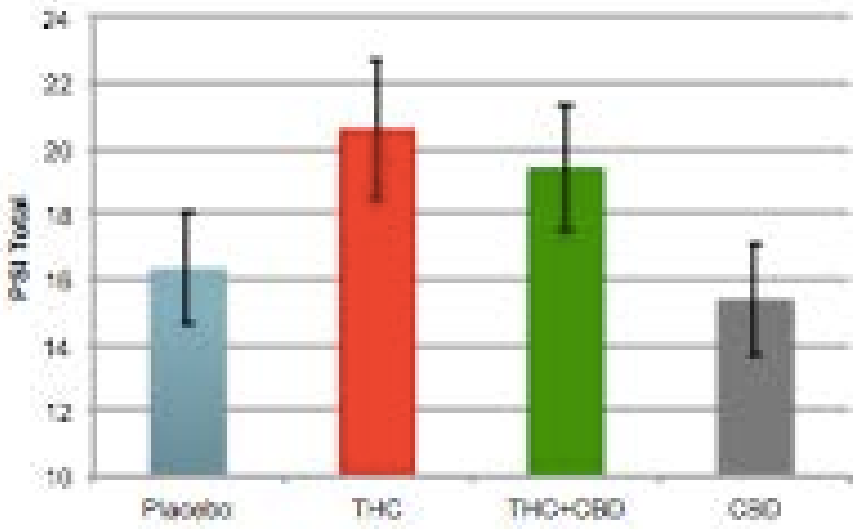


- 48 participants
- Selected to be:
  - 24 daily users
  - 24 less frequent
- Of those
  - 50% High psychosis proneness / *schizotypy* : (top quartile)
  - 50% Low psychosis proneness / *schizotypy* (bottom quartile)

Acute effects of cannabinoids in cannabis smokers: laboratory study

- Inhaled CBD and THC through a 'Volcano'
- Aimed to reverse the acute psychotic effects of THC in line with laboratory studies (Bhattarcharya et al., 2010)

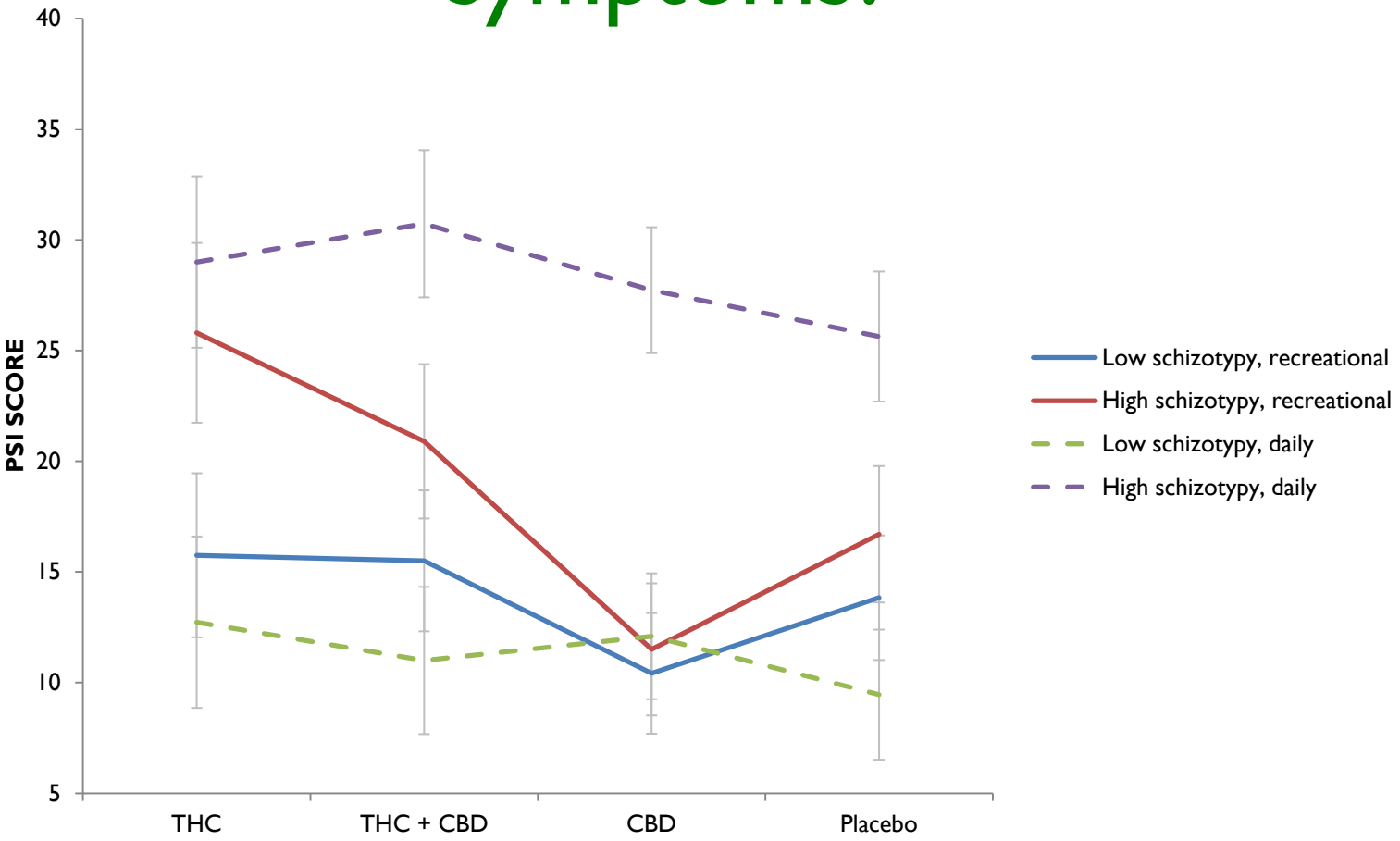
Study 3: Acute effects of CBD/THC in laboratory



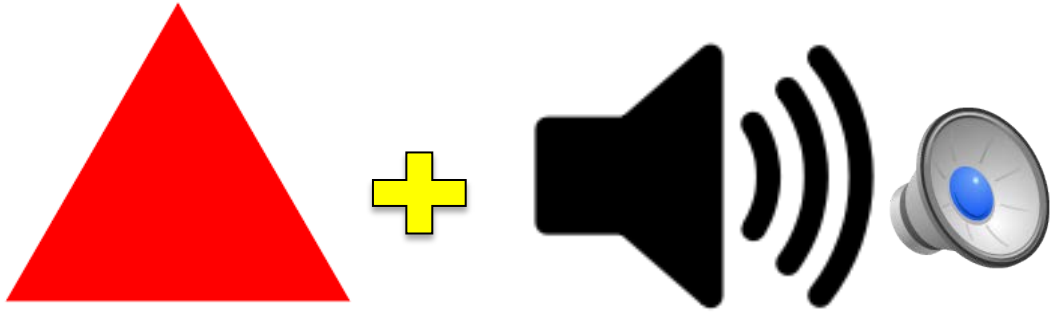
- Psychotic symptoms greater following THC

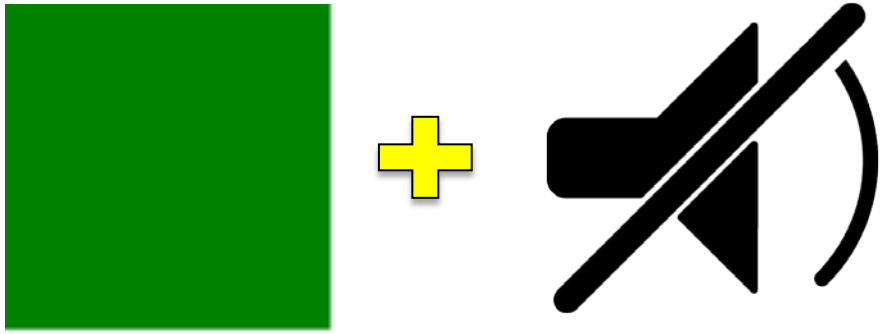
Study 3: Acute effects of CBD/THC in laboratory

CBD reduces THC induced psychotic symptoms?



CBD and memory in the laboratory





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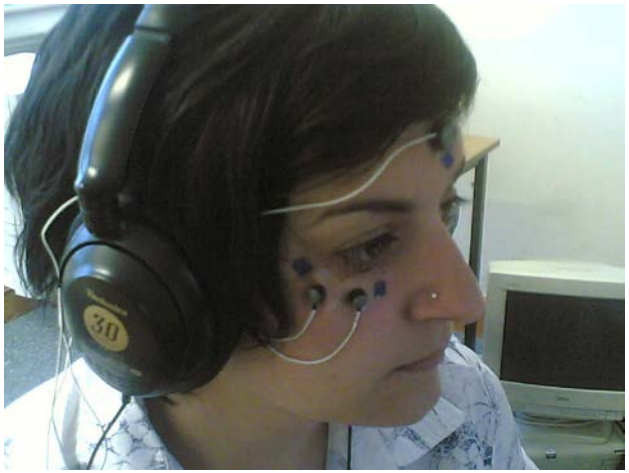
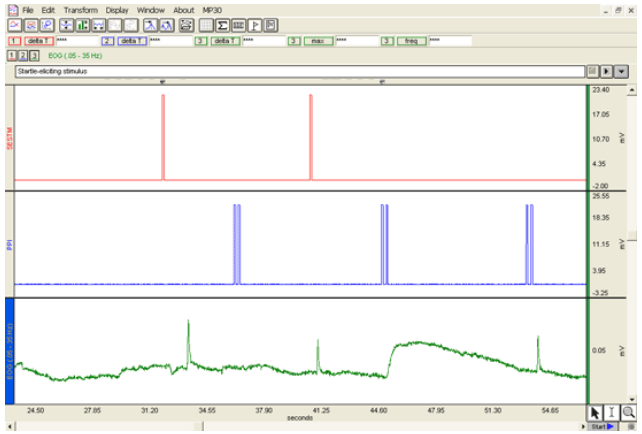
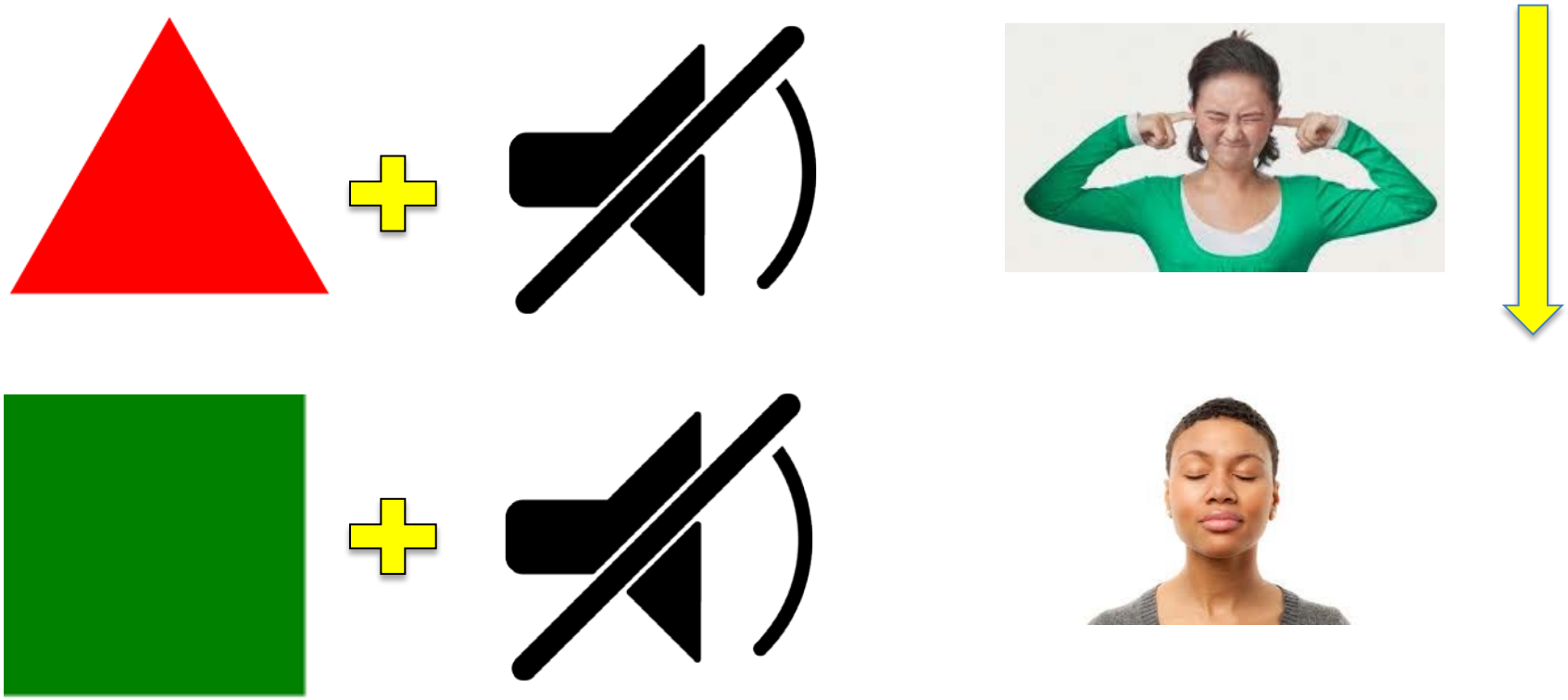




- Measure startle response from electrical impulses in skin

CBD in the laboratory

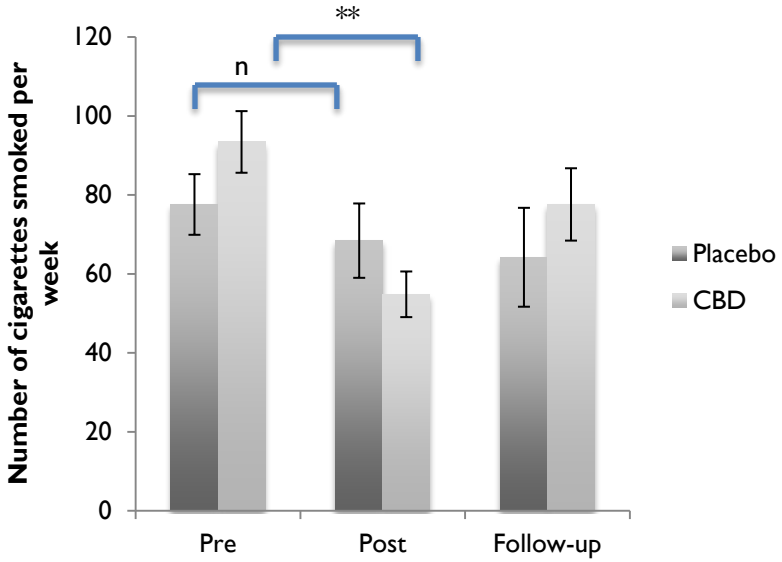


CBD in the laboratory

- CBD speeds up 'forgetting' of associations… 'extinction learning'
- Forgetting has important therapeutic implications in treatment of psychiatric disorders…
- Phobias – e.g. spider with fear response
- Substance use – e.g. drugs with pleasure

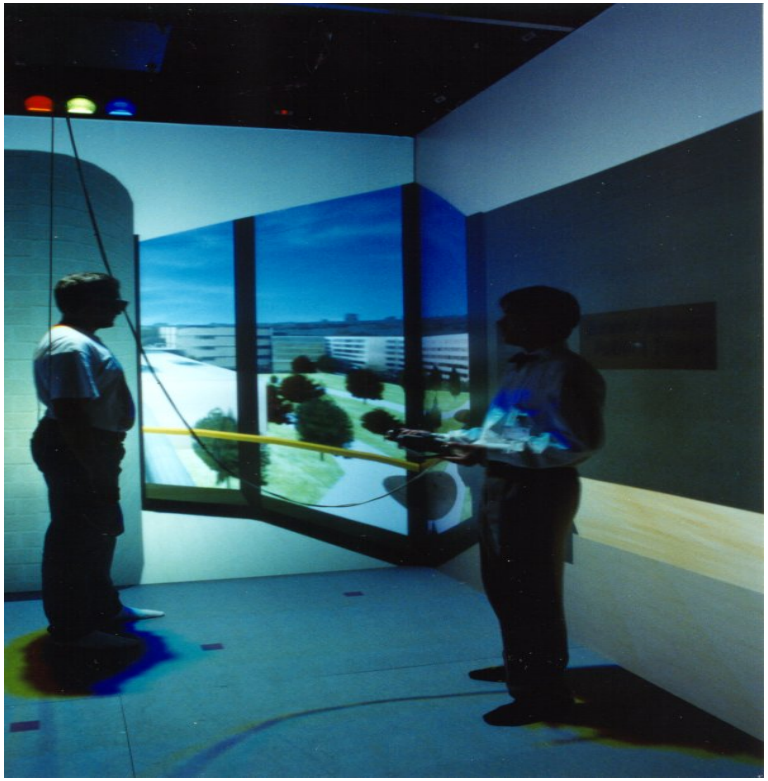
CBD to reduce cigarette smoking?

- n=24 smokers not actively quitting
- Half given CBD inhaler, half placebo
- Ad hoc use over a week
- 40% reduction in cigarette smoking in CBD group



Morgan et al., 2013 Addictive Behaviour

Use of CBD in therapy



How does cannabis act on the brain?

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Raphael Mechoulam

Asked Israeli police to give him 5kg cannabis.
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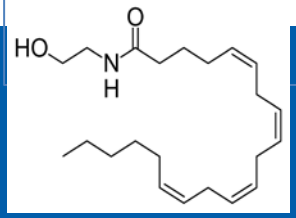
Raphael's team discovered the **'brain's own cannabis'** - **anandamide** (**ananda = bliss/ delight** in Sanscrit) & **2-AG**.



Endocannabinoids
brain

Phytocannabinoids
plant

Synthetic cannabinoids
manufactured

CB1 & CB2 receptors

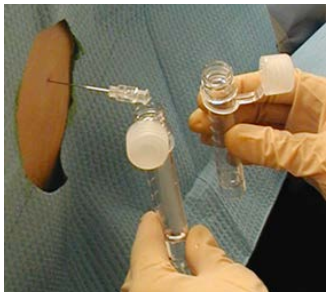
Pleasure, addiction, pain, appetite, memory, immune system, mental health

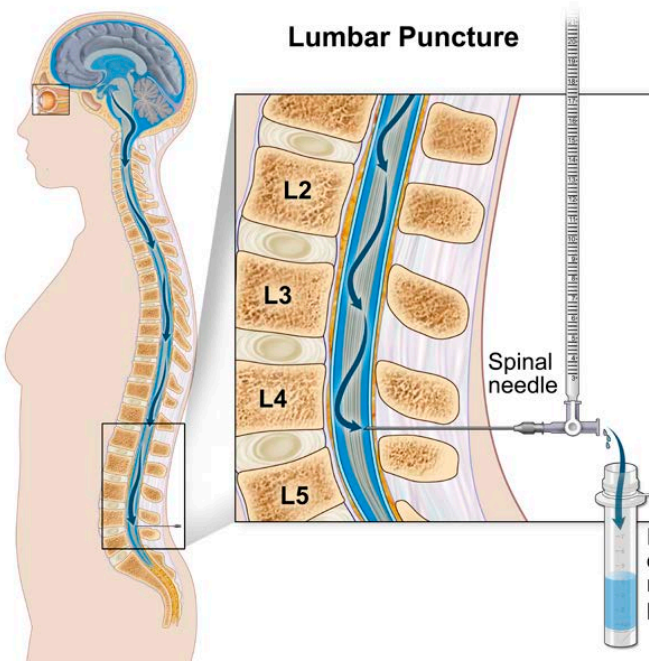
Endocannabinoids in psychosis

- AEA increased in antipsychotic-naïve first-episode psychosis (Leweke et al., 1999, Guiffrida et al. 2004)
- Drops off in chronic schiz
- Modulate excessive DA release?
- Downregulation of endocannabinoid signalling following repeated THC administration in rats *(DiMarzo et al., 2000)*

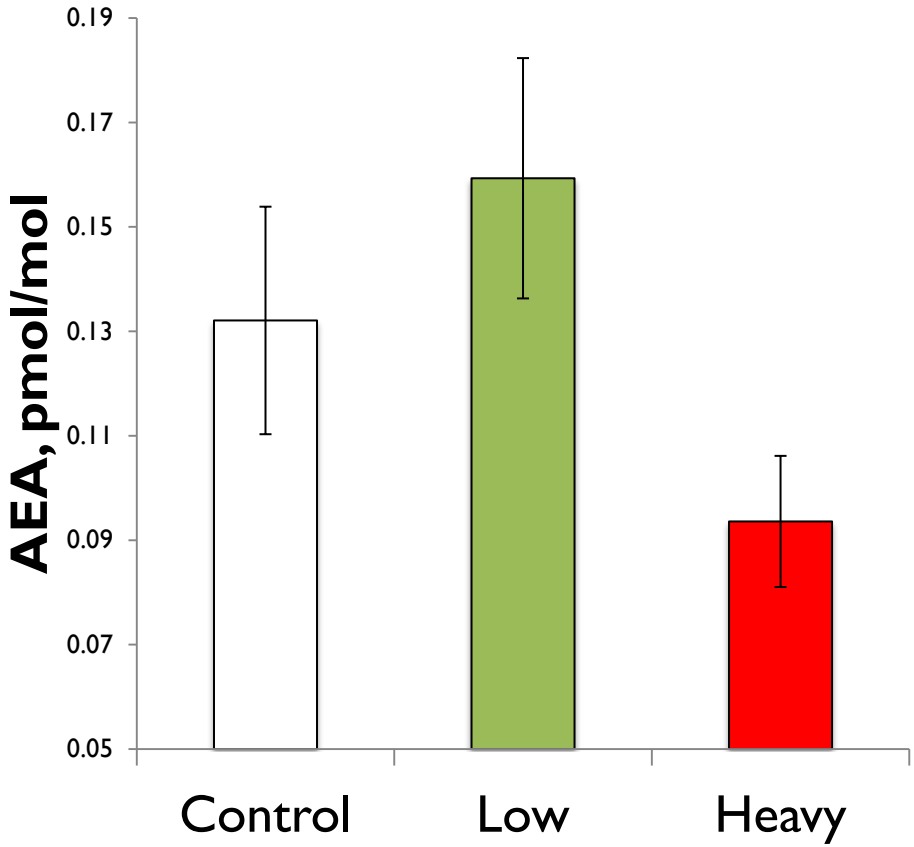
Looking at endocannabinoids in cannabis users

- AEA in blood does not correlate with brain
- Collected CSF from lumbar punctures
- 21 cannabis users (mean age 22.0±2.91)
- 13 matched controls (mean age 22.1±2.45)
- PSI to assess psychotic symptoms

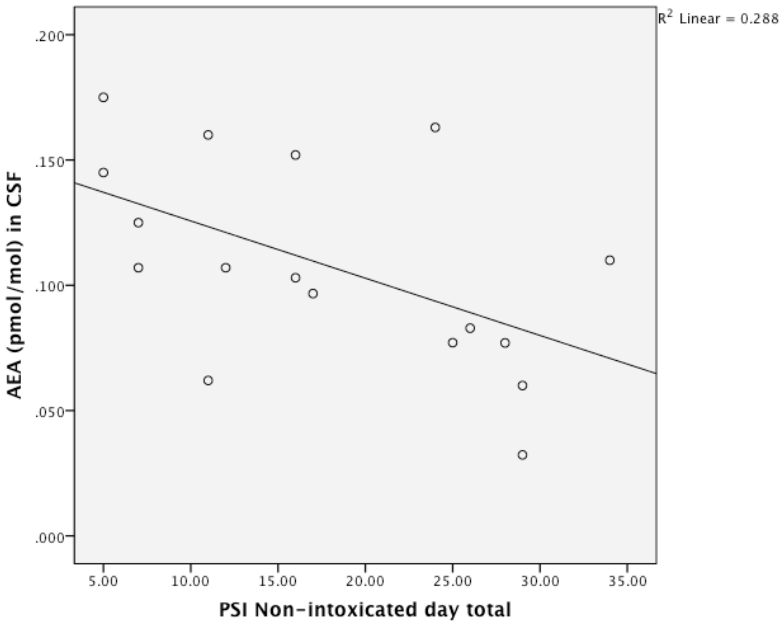




AEA in cannabis users



r= -0.536, p=0.02



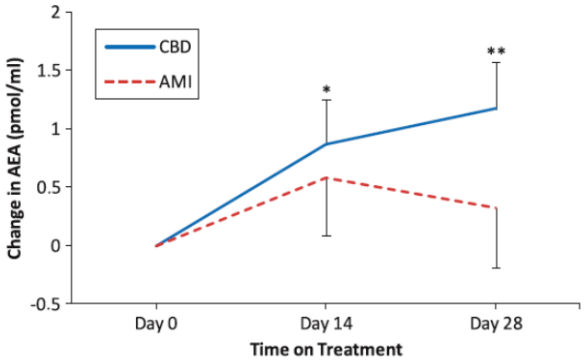
Morgan et al., 2013 Brit J Psych

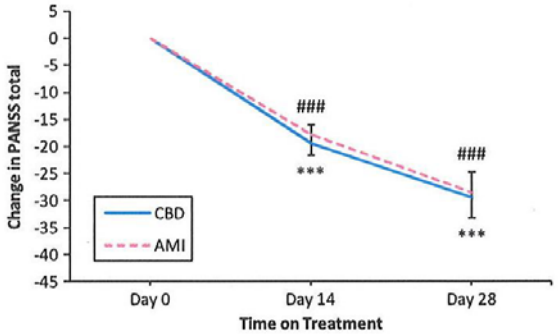
Endocannabinoids and psychosis

- Lower AEA in heavy users
  - Chronic downregulation of anandamide through repeated THC administration
  - How cannabis increases risk of psychosis?
- Negative correlation with symptom severity
  - Consistent with findings in psychosis

Endocannabinoids and Cannabinoids

- CBD may block the reuptake and hydrolysis of anandamide
- CBD increases levels of AEA in patients with schizophrenia
- CBD improves psychotic symptoms in patients with schizophrenia



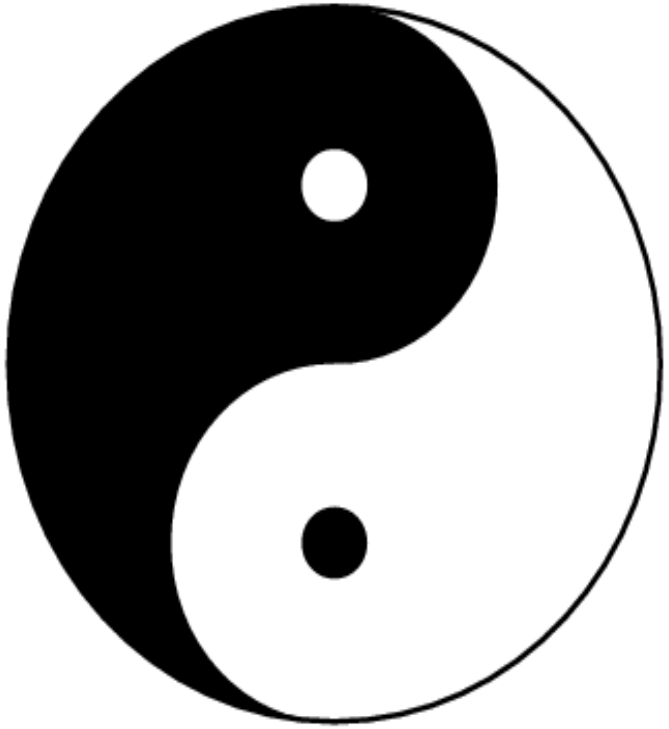


(Leweke et al., 2012 Translational Psych)

Conclusions

THC

- Induces anxiety
- Psychotic-like effects.
- Impairs memory and learning



CBD

- Reduces anxiety
- Anti-psychotic effects
- Enhances learning and blocks THC memory loss

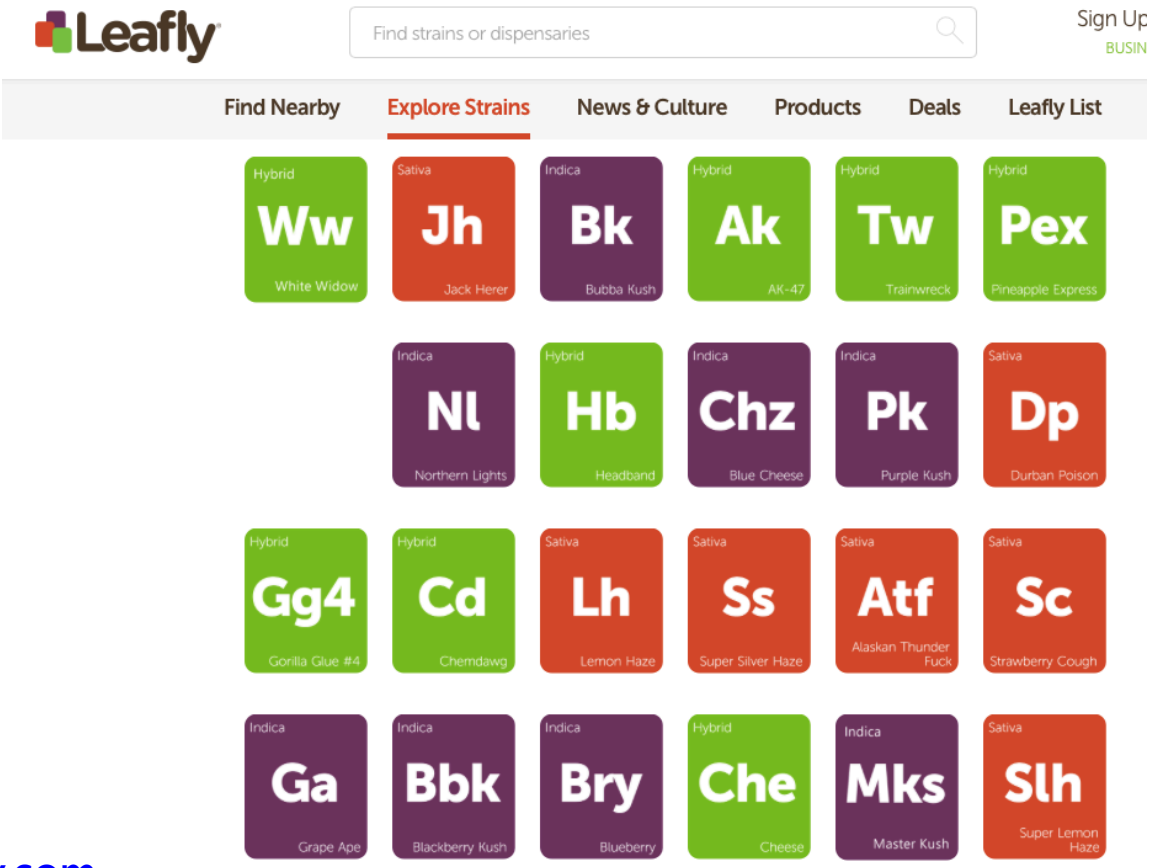
Conclusions

- CBD is emerging as an important medicine
- CBD levels are declining in street cannabis
  - Alongside increasing levels of THC may increase the harms of the drug
- Smoking hash / resin (if available) reduce the harm

What implications does our scientific understanding of cannabis have for debates about legalisation?

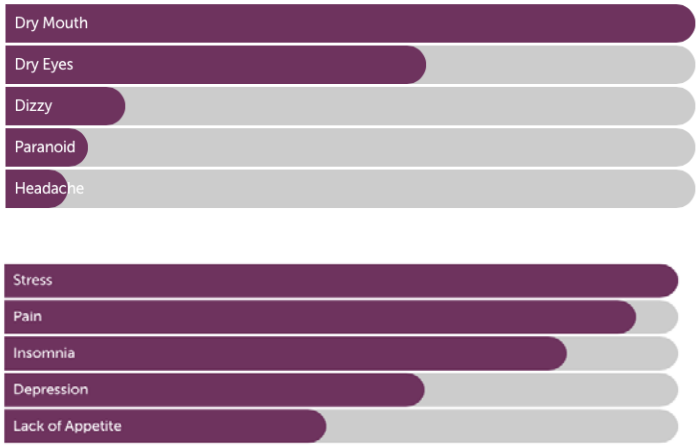
- Taking control of the cannabis market could allow rich CBD forms of cannabis to become widely available.
- This could help protect young people from the mental health harms of high THC/skunk forms.

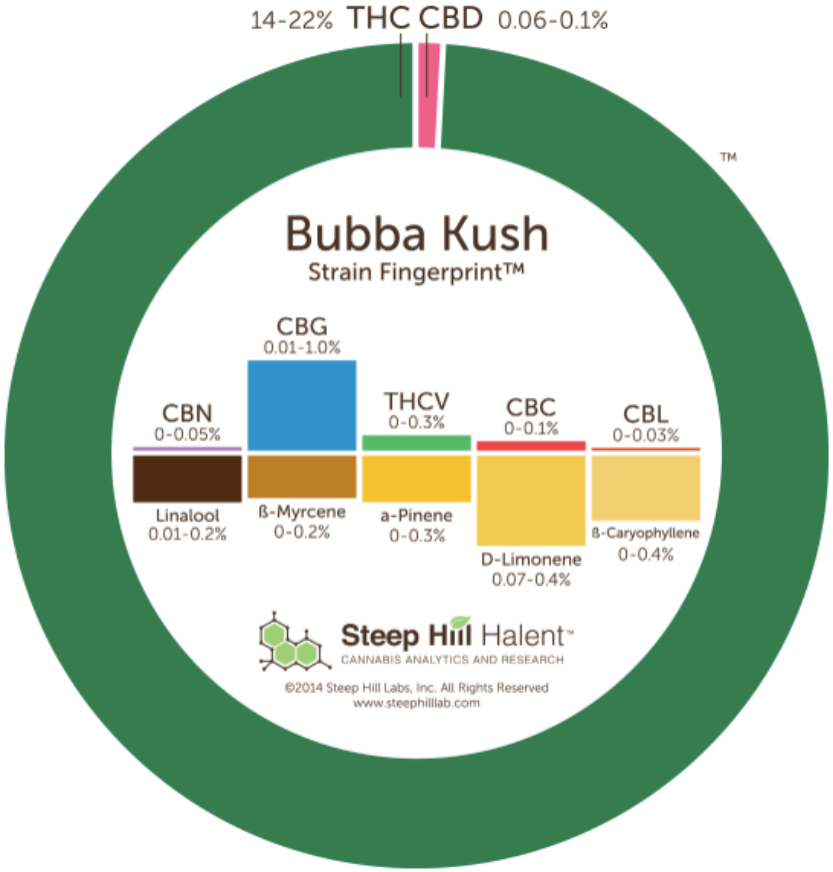
Medical Marijuana: US



www.leafly.com

Medical Marijuana US





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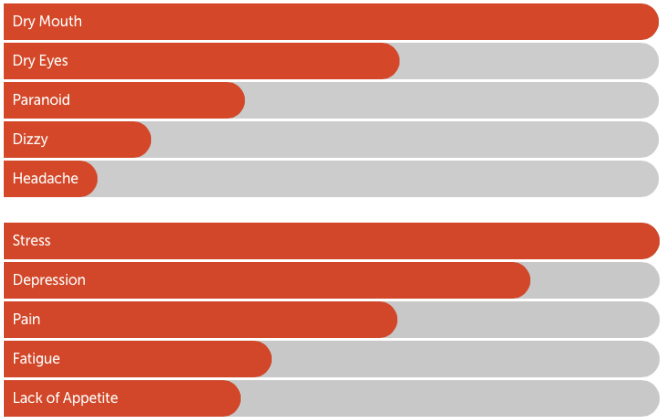
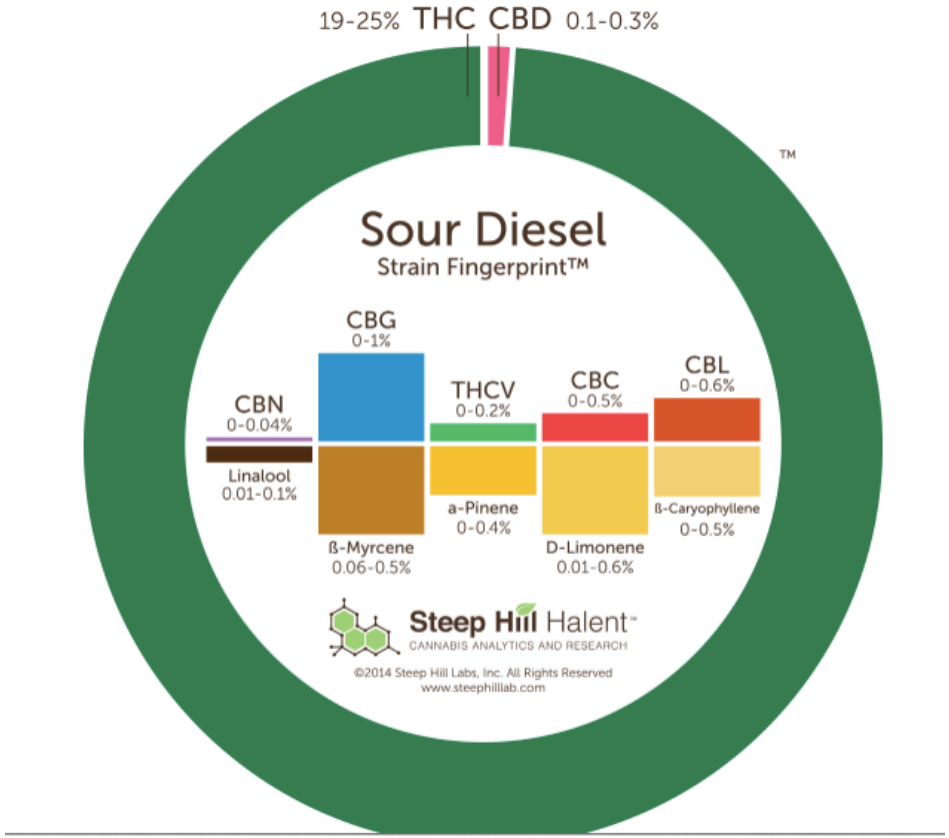
Medical Marijuana: US





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