**ECNP School of Neuropsychopharmacology**

**Oxford, United Kingdom**
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# Cannabis &

# Schizophrenia

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# Disclosure:

Grant Funding from
GW Pharmaceuticals.

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What are the effects of recreational cannabis use...

# Cannabis: The Downside

1. Acute psychotic episodes.
2. Chronic psychotic illness (schizophrenia).
3. Psychotic relapse, re-admission to hospital.
4. Cognitive impairment
5. Negative symptoms
6. Addiction

# Cannabis: The Downside

1. Acute psychotic episodes.

1840's Paris.
Dr Jean Moreau....

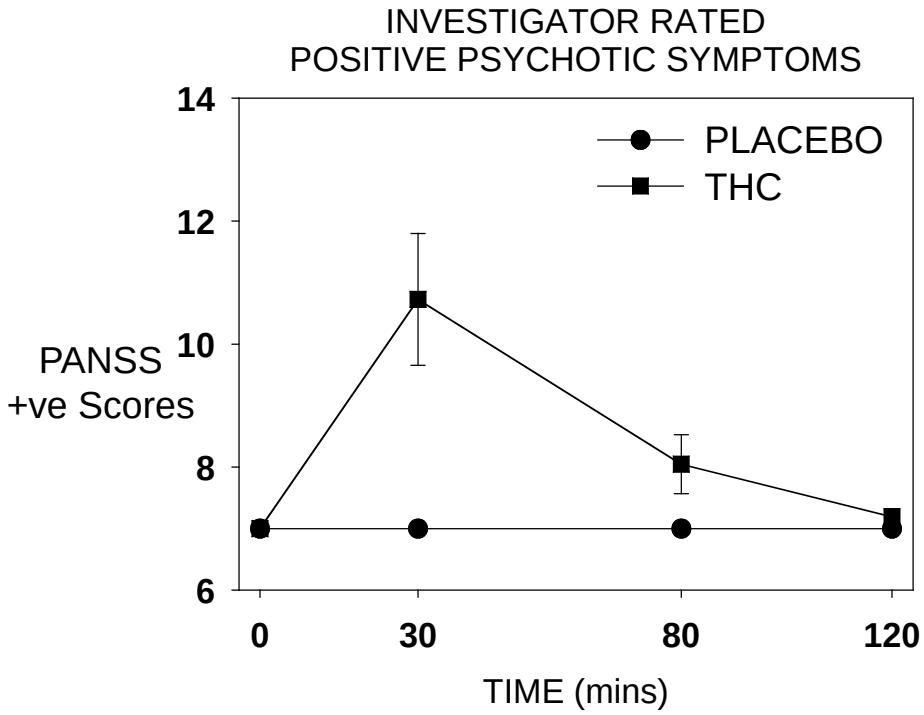
“Hashish gives to whoever submits to its influence the power to study in himself the mental disorders that characterise insanity,

or at least the intellectual modifications that are the beginning of all forms of mental illness”

Langlitz, N. (2006) Ceci n'est pas une psychose. Towards a Historical epistemology of Model Psychoses. *Biosocieties* **1,** 159-180

# Cannabis: The Downside

1. Acute psychotic episodes.




Morrison PD, Zois V, McKeown DA, Lee TD, Holt DW, Powell JF, et al. *Psychol Med* 2009;39(10):1607

# Cannabis: The Downside

1. Acute psychotic episodes.

In a recent study from Finland (n=18,478)

46% of people who had been hospitalized for an acute cannabis psychosis developed a chronic psychosis over the next 8 years.

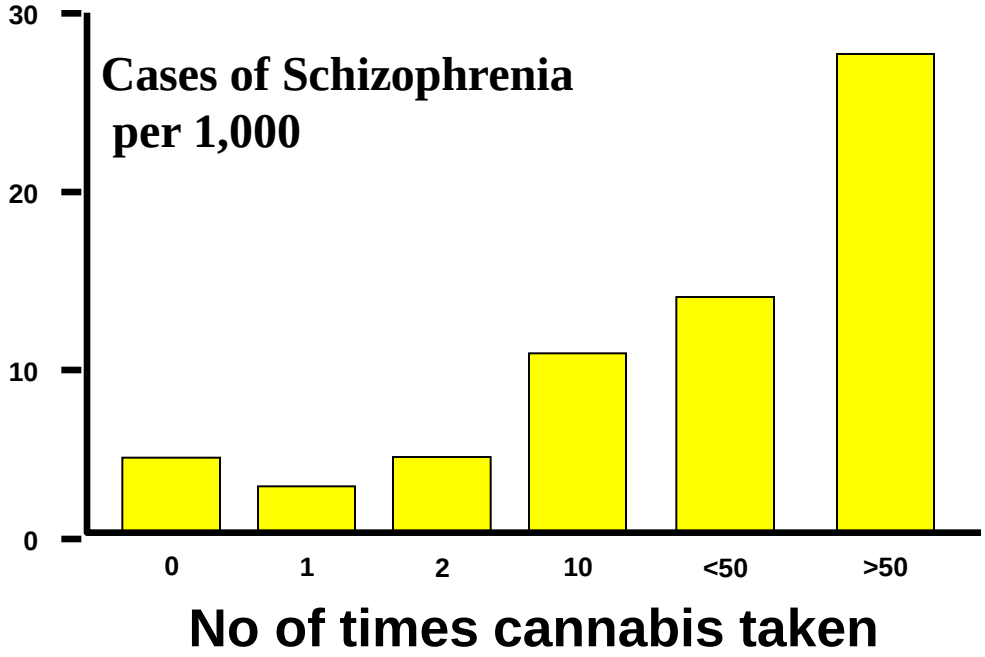
A red flag

Niemi-Pynttari et al *J Clin Psychiatry* 2013;74(1)

# Cannabis: The Downside

2. Chronic psychotic illness (schizophrenia).

## Cannabis consumption at age 18 and later risk of schizophrenia

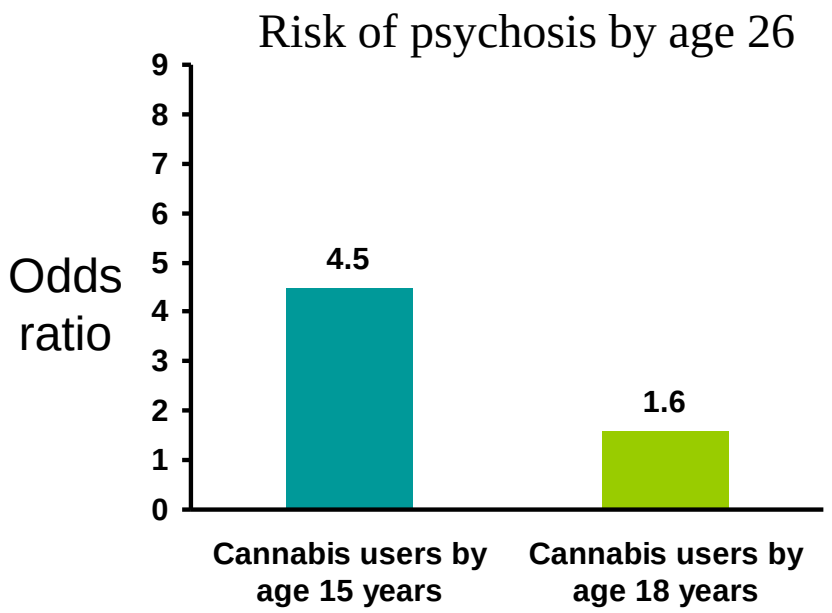



Andreasson et al (1987) *Lancet*

# Cannabis: The Downside

2. Chronic psychotic illness (schizophrenia).

Earlier exposure -> higher risk




Arseneault L, Cannon M, Poulton R, Murray R, Caspi A, Moffitt TE. *Bmj* 2002;325(7374):1212-3

# Cannabis: The Downside

2. Chronic psychotic illness (schizophrenia).

Interaction between
cannabis + genetic variants…

COMT – inconsistent

AKT1 - 2 positive studies

van Winkel R. et al. *Arch Gen Psychiatry* 2011;68(2):148-57.

Di Forti M, Iyegbe C, Sallis H, Kolliakou A, Falcone MA, Paparelli A, et al..
*Biol Psychiatry* 2012;72(10):811-6

# Cannabis: The Downside

3. Psychotic relapse, re-admission to hospital.

- A recurrence of positive symptoms

- Further hospitalization

Hides L, Dawe S, Kavanagh DJ, Young RM. *Br J Psychiatry* 2006;189:137-43.

# Cannabis: The Downside

4. Cognitive Impairment

Acute effects

- Prefrontal dysfunction

- Hippocampal dysfunction

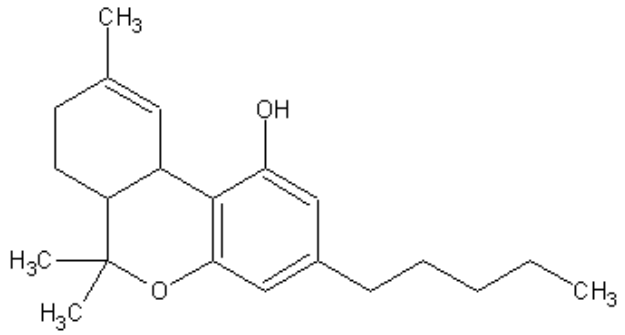
Longstanding effects *of repeated early exposure*

- Lower IQ

*"Individuals who started using cannabis in adolescence and used it for years thereafter showed an average 8-point IQ decline."*

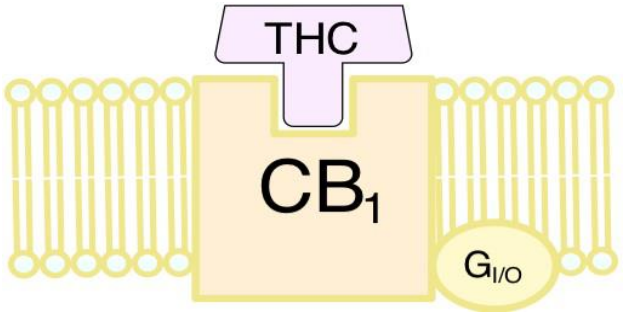
Meier MH, et al (2012) PNAS

# The THC:CBD Story...

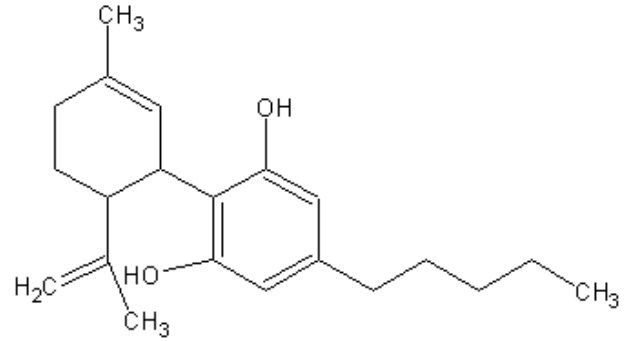



$\Delta^9$-Tetrahydrocannabinol

THC




Mechanism:
$CB_1$ partial agonist




Cannabidiol

CBD

Mechanism:
Multiple targets.

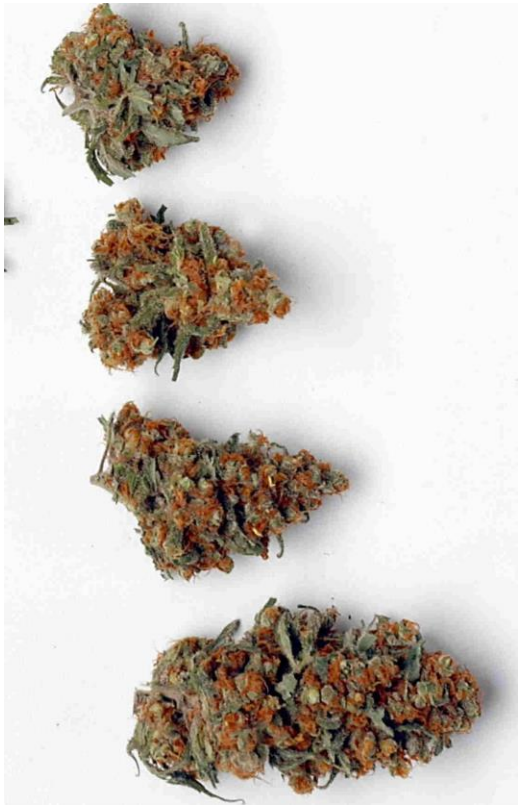
Doesn't bind to $CB_1$, but inhibits tissue responses to $CB_1$ agonists.

# The THC:CBD Story...

## Resin

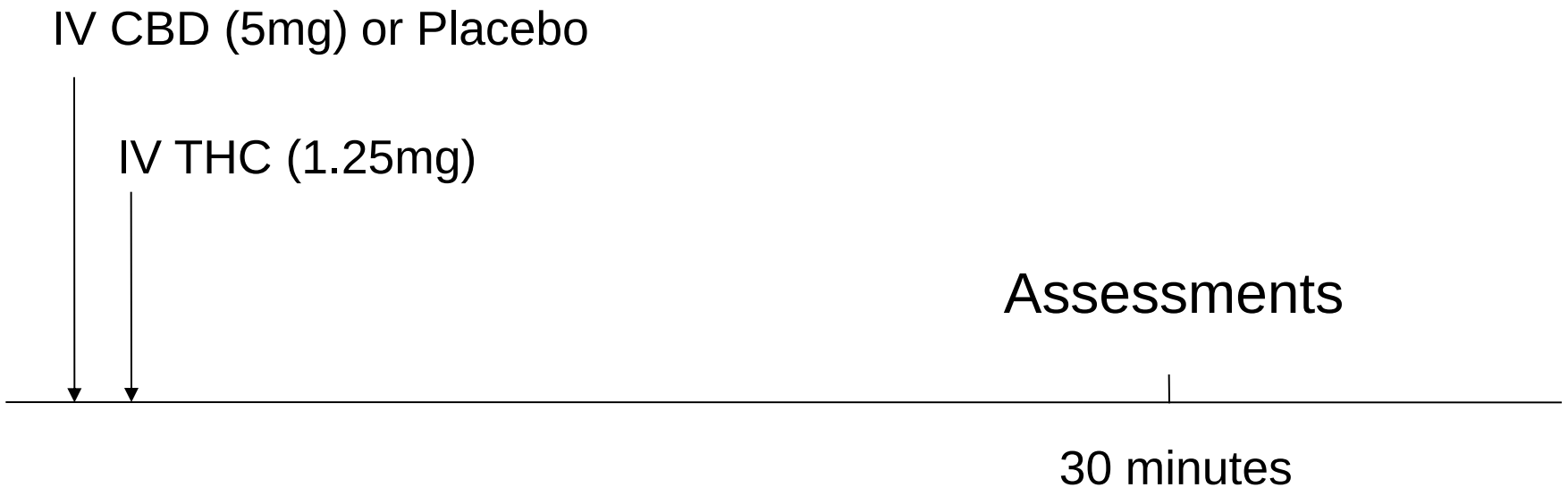
THC ~ 5%
CBD ~ 5%

## Skunk



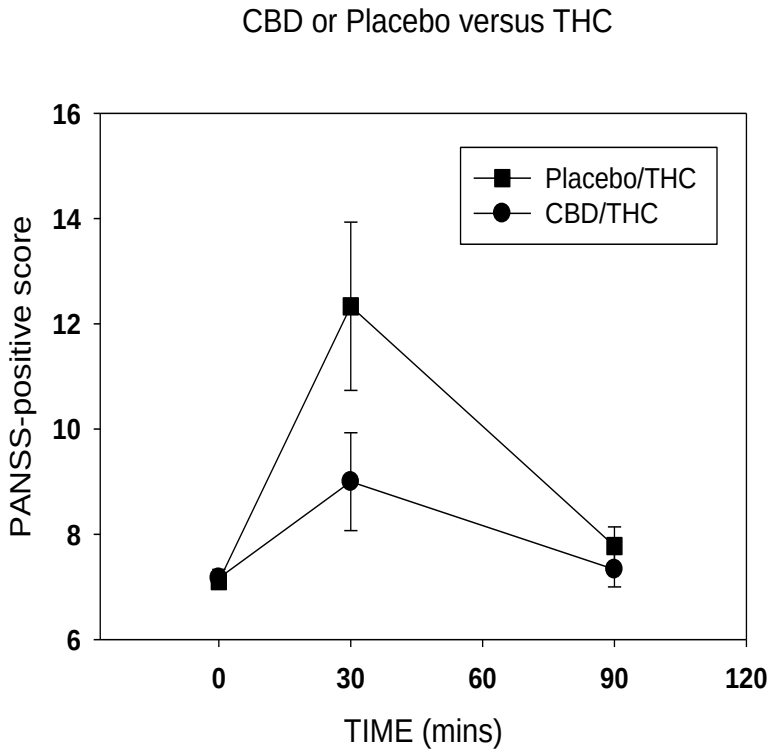
THC ~ 15%
CBD ~ 0%

# IV CBD *or* PLACEBO...
## *then IV THC*



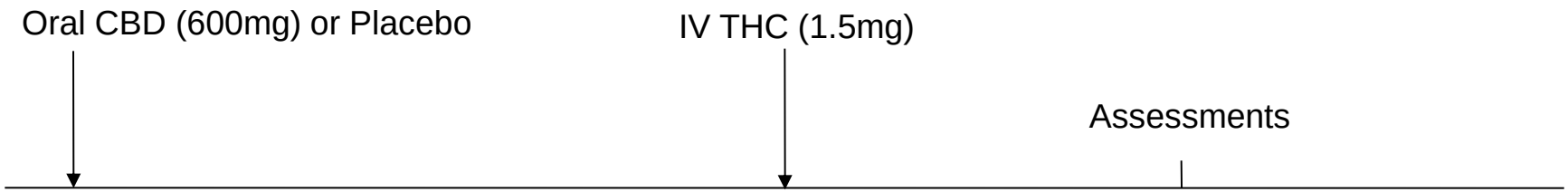
# IV CBD *or* PLACEBO...
## *then IV THC*

n=6

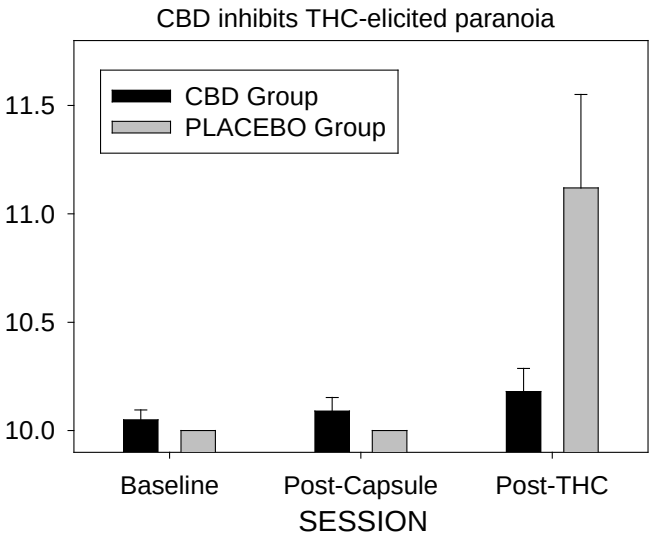


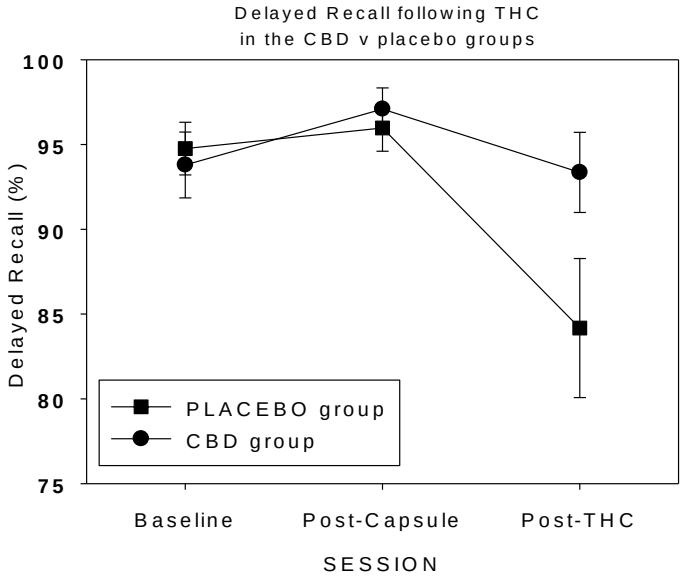

Morrison PD et al (2010) *J Psychopharm S3*

# **Oral** CBD *or* PLACEBO...
*then IV THC*



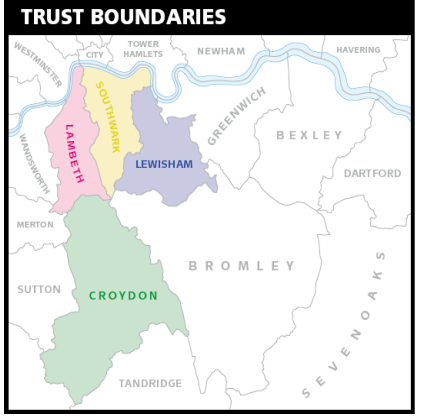

n=48

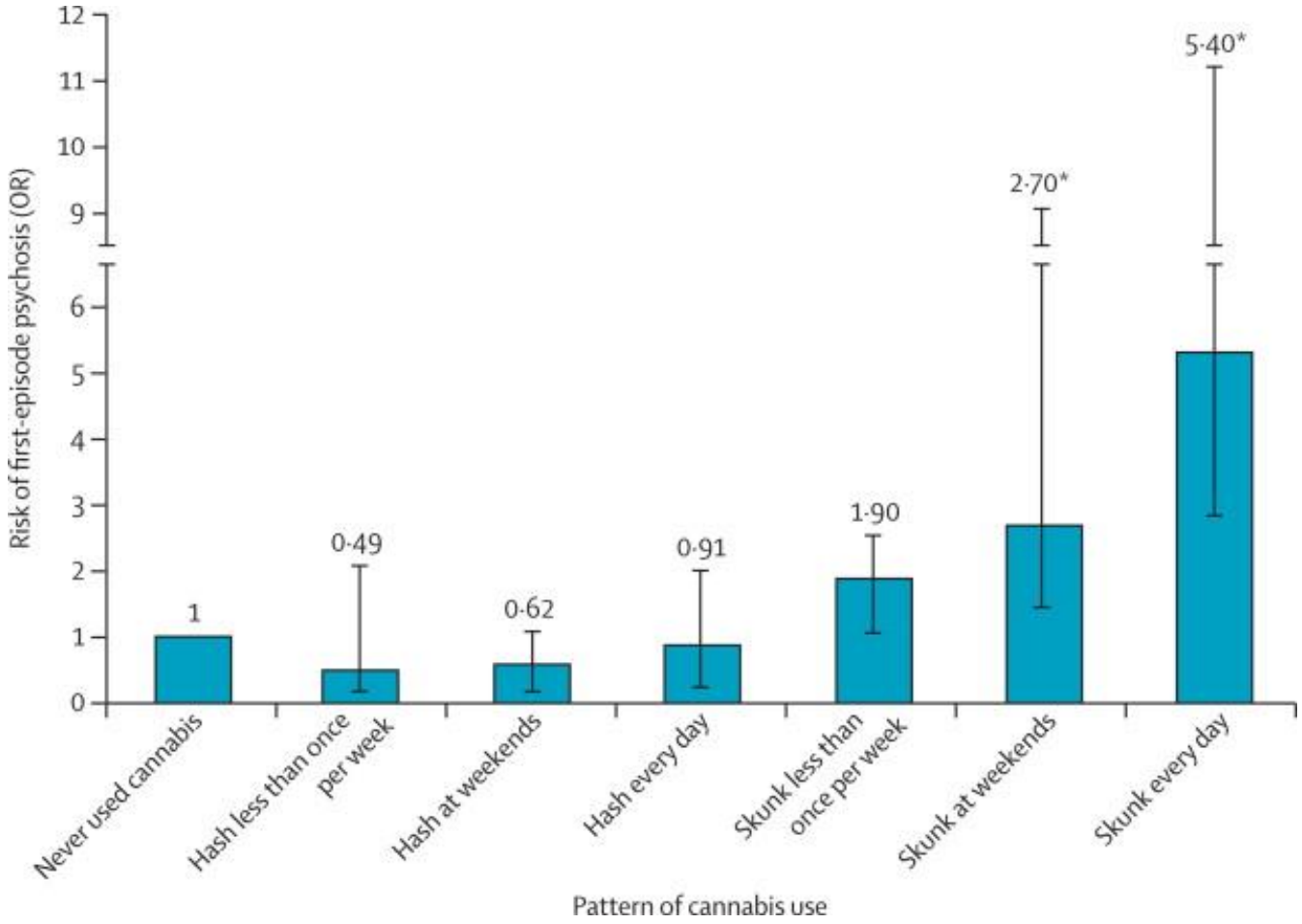



Englund A, Morrison PD, Nottage J, Hague D, Kane F, Bonaccorso S et al. *Journal of psychopharmacology* 2013;27(1):19-27.

# The THC:CBD Story...




*"Skunk accounts for 24% of cases of schizophrenia in South London..."*

DiForti et al (2015) Lancet Psychiatry

# CBD as an antipsychotic in F20

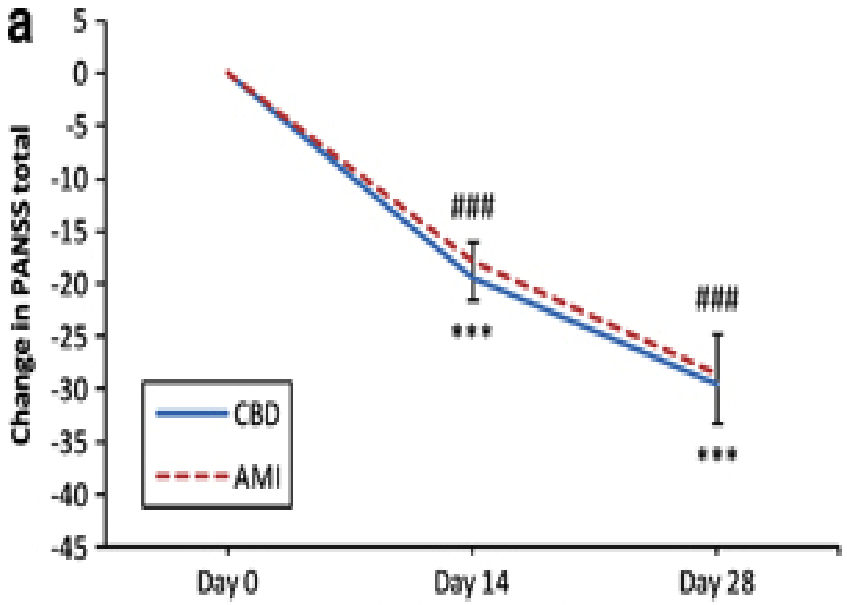
RCT (Leweke et al 2012)

AMI v CBD (200-800mg/d)

N = 2 x 21

4 week

Ami = CBD



# CBD as an antipsychotic in F20

RCT (GW 2015)

Add on Rx

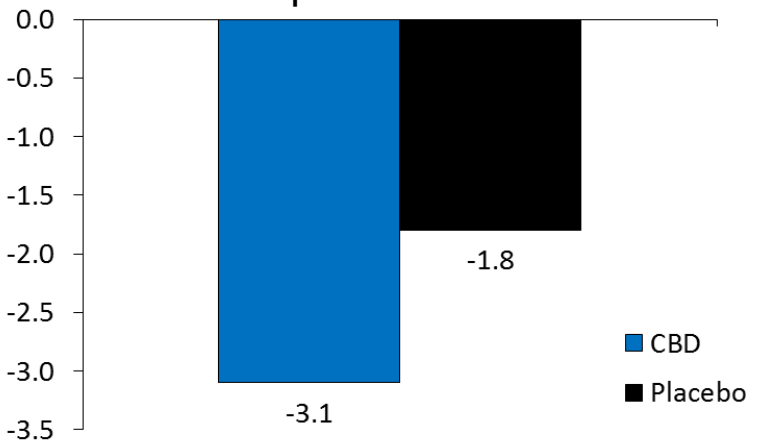
CBD 500mg bd v Placebo

N = 88

6 week

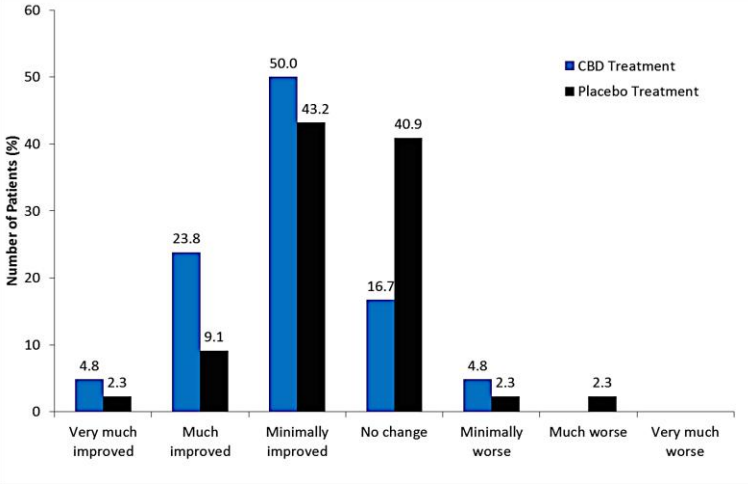
CBD > Placebo

PANSS positive scores



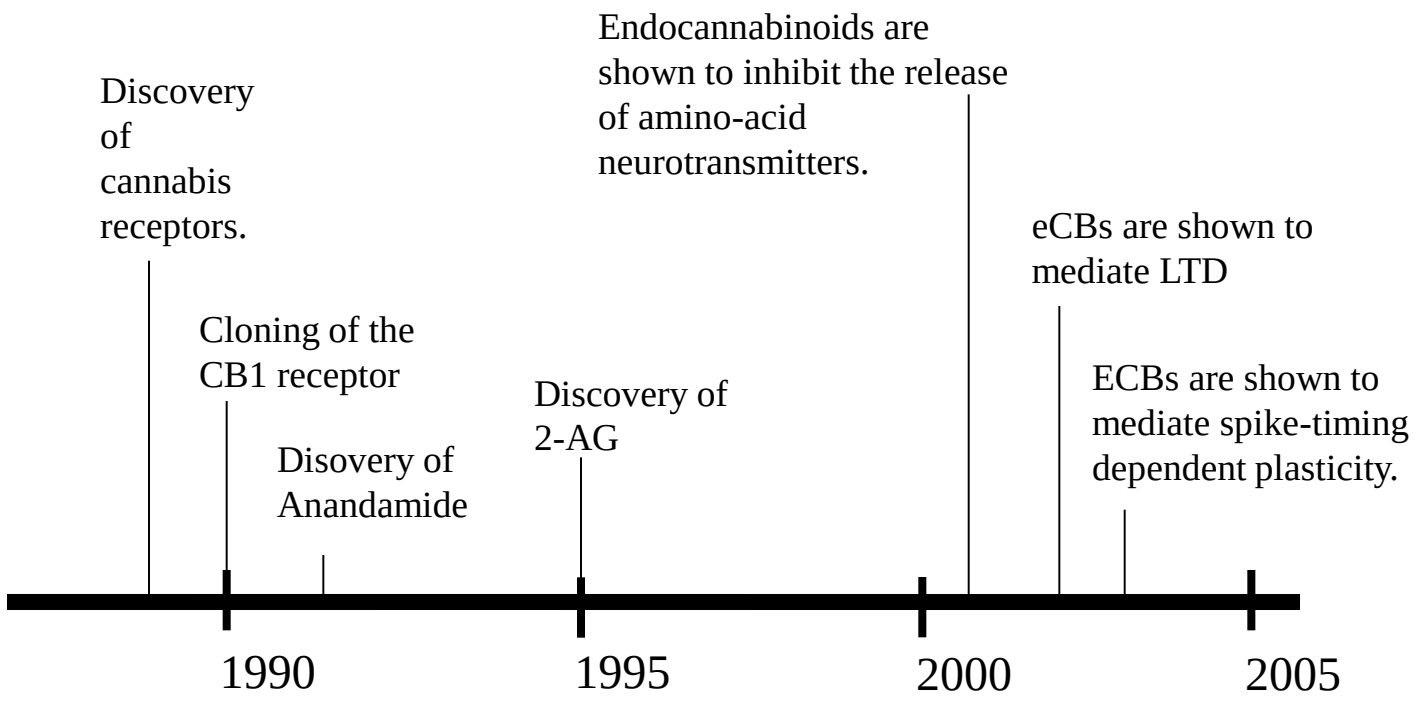

P=0.02

Clinical Global Impression




P=0.02

# Cannabinoid neurobiology...



# Cannabinoid neurobiology...

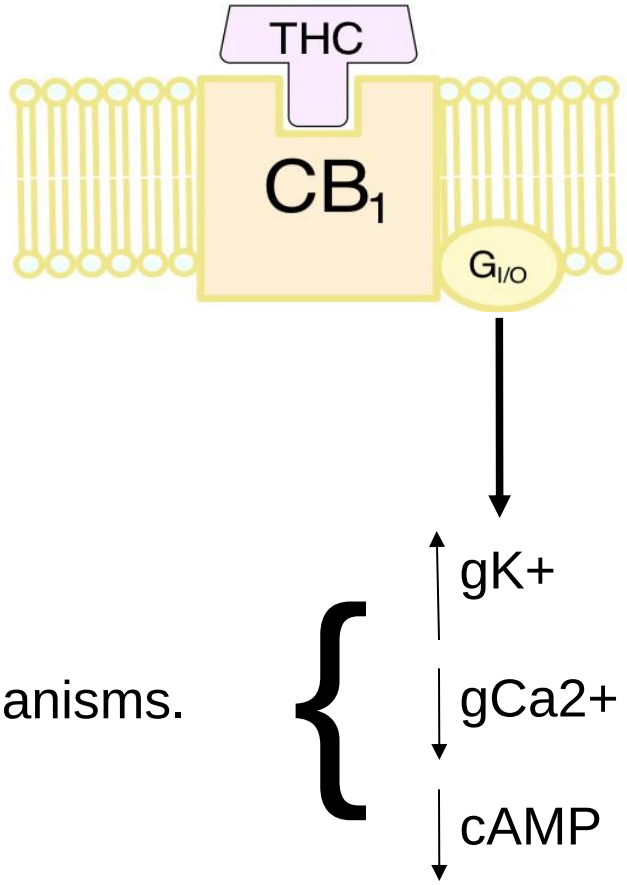
## $CB_1$ receptors

- Exogenous agonists,
THC, AM-2201

- Endogenous agonists
Anadamide, 2-AG

- G-protein coupled receptors

- Classic $G_{i/o}$ presynaptic mechanisms.



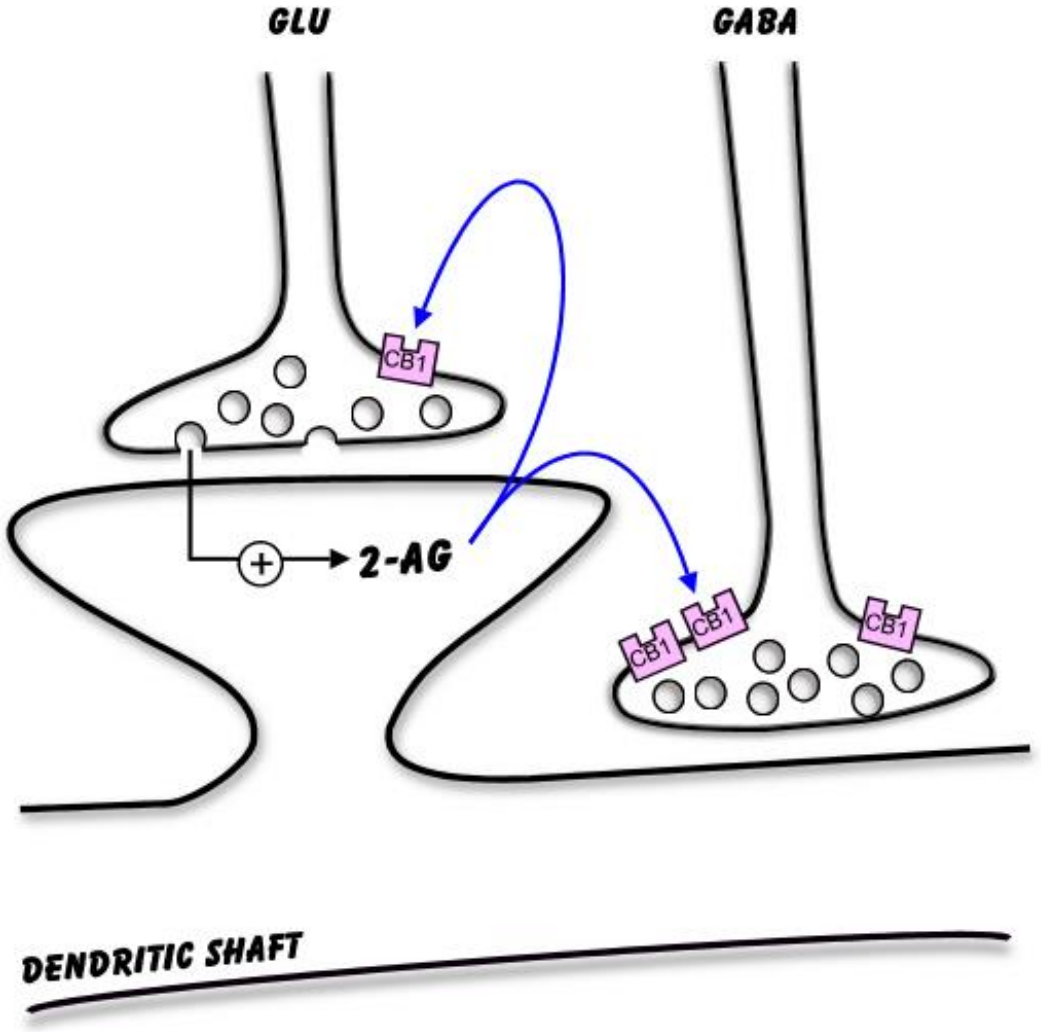

- Reduction of pre-synaptic
neurotransmitter release.

# Cannabinoid neurobiology...

## Retrograde Transmission

The eCB is released from the postsynaptic neuron…

And acts at presynaptic receptors.



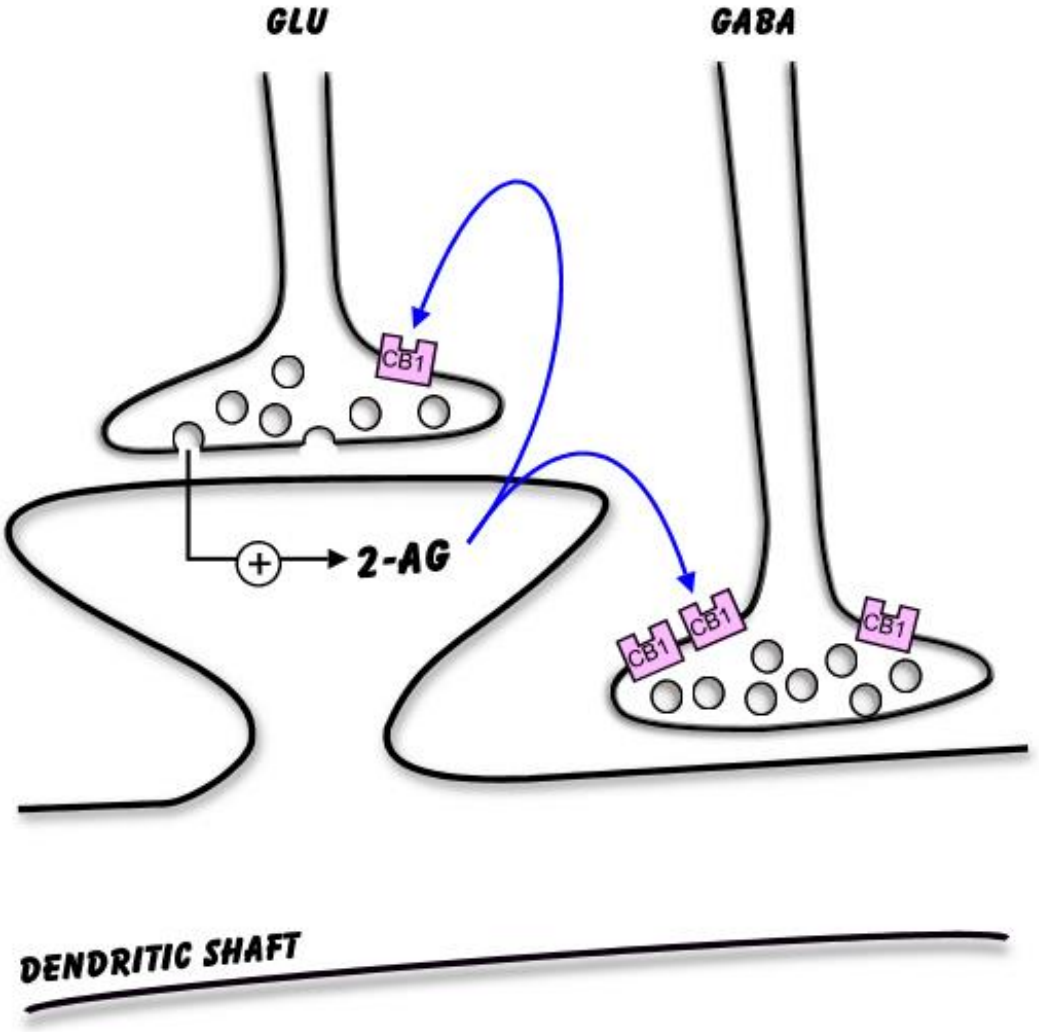

*Wilson, R.I. & Nicoll, R.A. Endogenous cannabinoids mediate retrograde signalling at hippocampal synapses. Nature **410**, 588-592 (2001).*

# Cannabinoid neurobiology...

## Retrograde Transmission

Principal output neurons in the cortex, striatum, hippocampus, cerebellum & amygdala,

fine-tune their inputs by endocannabinoid signalling.




*Wilson, R.I. & Nicoll, R.A. Endogenous cannabinoids mediate retrograde signalling at hippocampal synapses. Nature **410**, 588-592 (2001).*

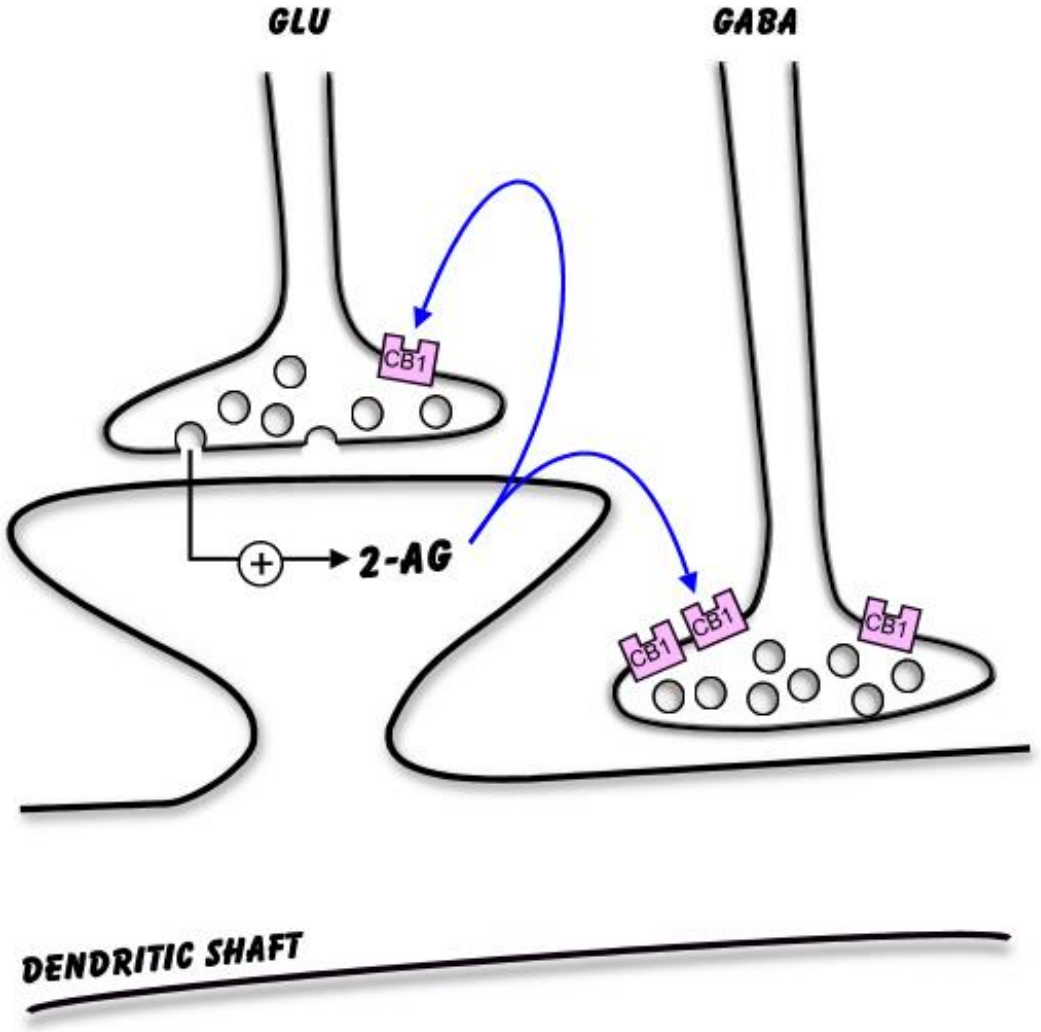
# Cannabinoid neurobiology...

## Retrograde Transmission

Fine-tuning can be short term or…long-term.

LTD: Long-term depression

2-AG mediated LTD is an important mechanism for learning and memory at synapses.




*Wilson, R.I. & Nicoll, R.A. Endogenous cannabinoids mediate retrograde signalling at hippocampal synapses. Nature **410**, 588-592 (2001).*

# Cannabinoid neurobiology...

## Retrograde Transmission

2-AG synthesis?

Depends on coincident pre- and post-synaptic events.

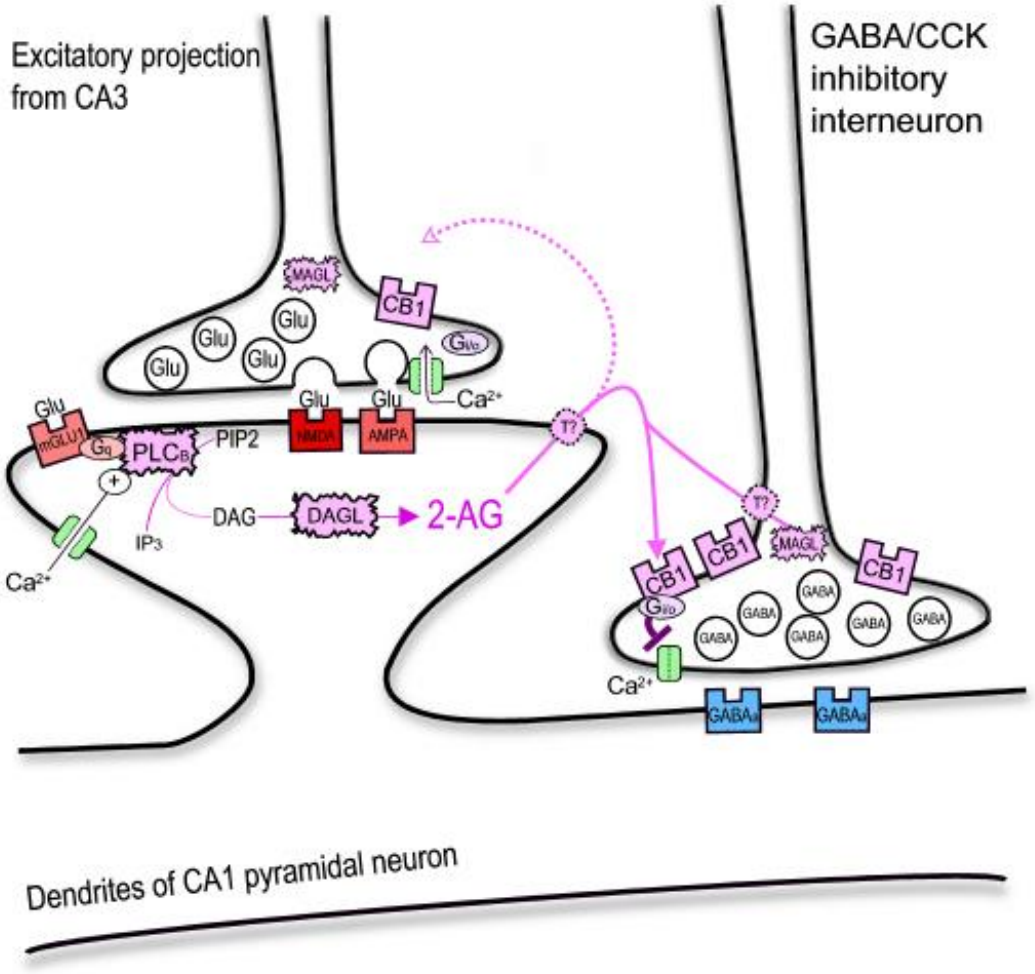
1. Pre-synaptic AP

*-> mGLU activation*

**AND**

2. Post-synaptic AP

*-> Ca2+ channel opening*




Murray RM, Morrison PD, DiForti M & Henquet C., (2007) Nature Reviews Neuroscience

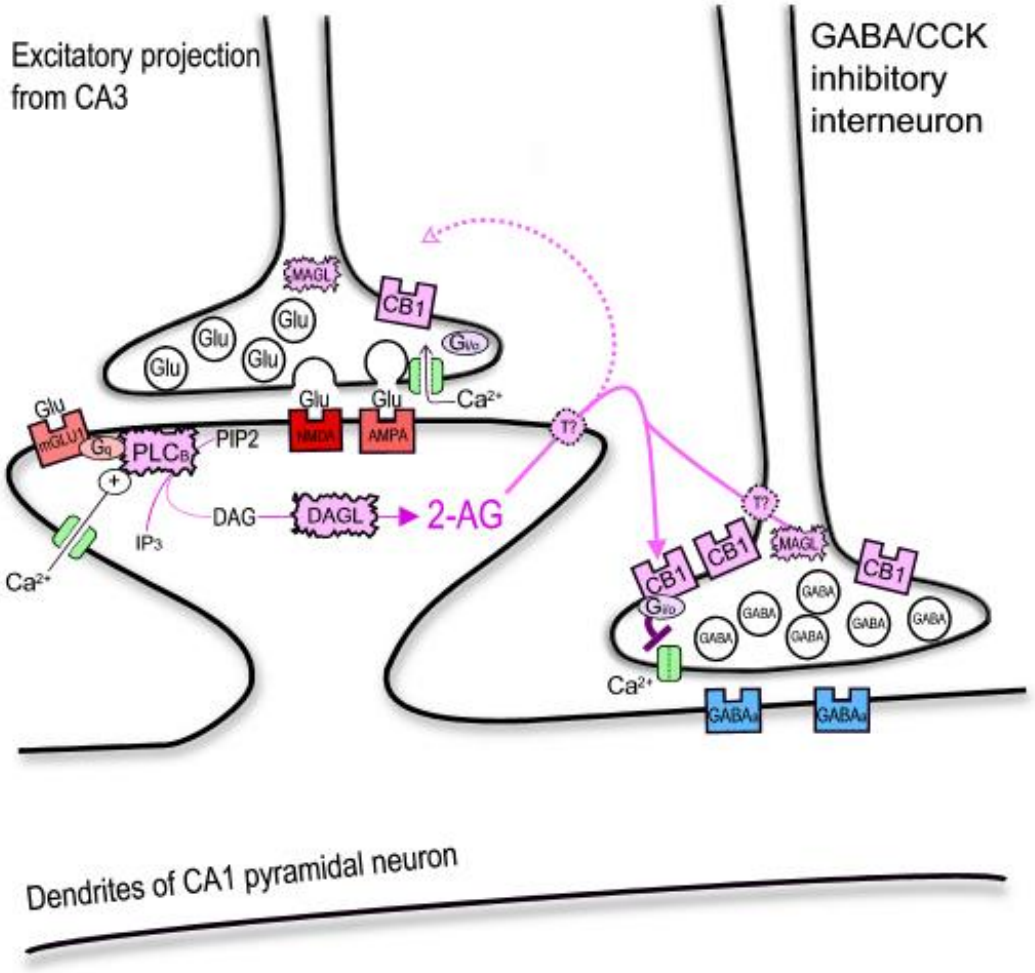
# Cannabinoid neurobiology...

Retrograde

Transmission

2-AG signalling is a vital component for learning and memory in the hippocampus.

2-AG sets the strength of synaptic inputs to principal neurons.




Murray RM, Morrison PD, DiForti M & Henquet C., (2007) Nature Reviews Neuroscience

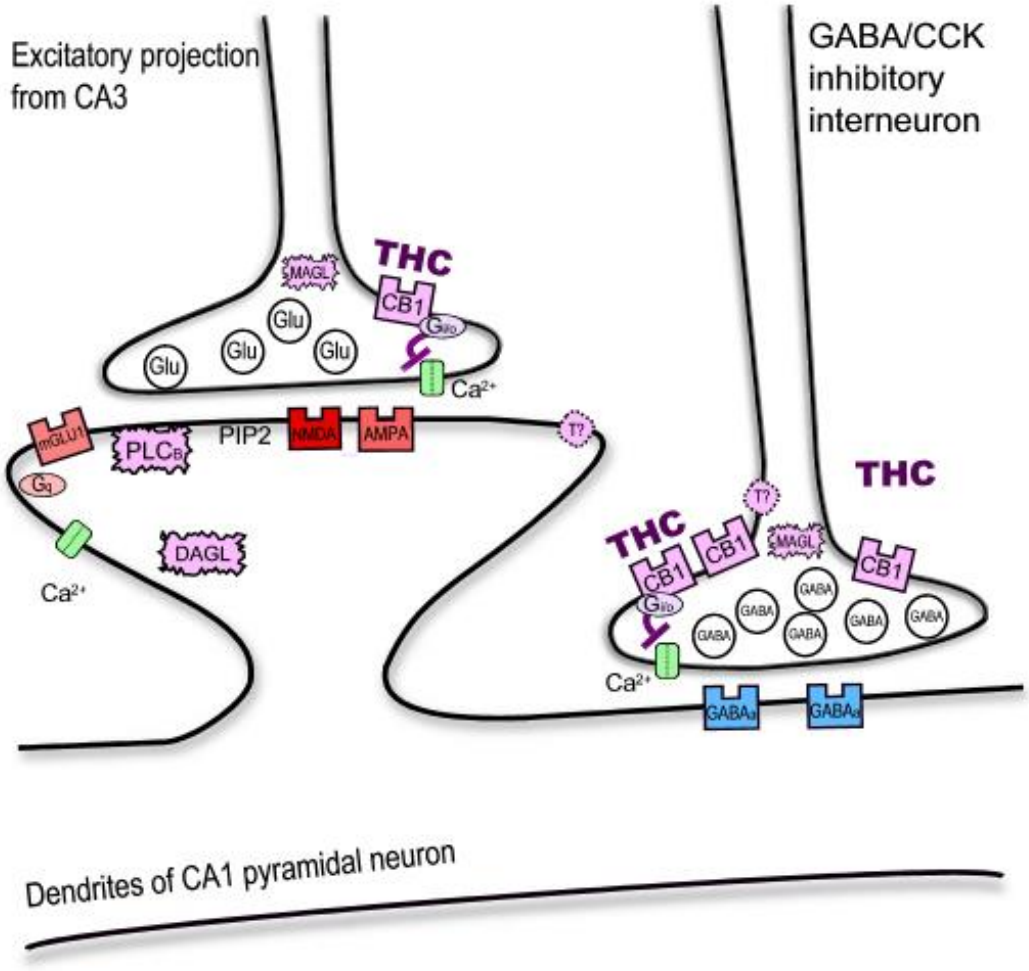
# Cannabinoid neurobiology...

## Effect of THC

THC disrupts fine-grained eCB signalling.

Indiscriminate targeting of CB1 receptors at a multitude of GABA and glutamate terminals.

No rapid removal of THC from the synapse as is the case for eCBs.




Murray RM, Morrison PD, DiForti M & Henquet C., (2007) Nature Reviews Neuroscience

# Cannabinoid neurobiology...

## Effect of THC

Disruption of local glutamate and GABA circuits.

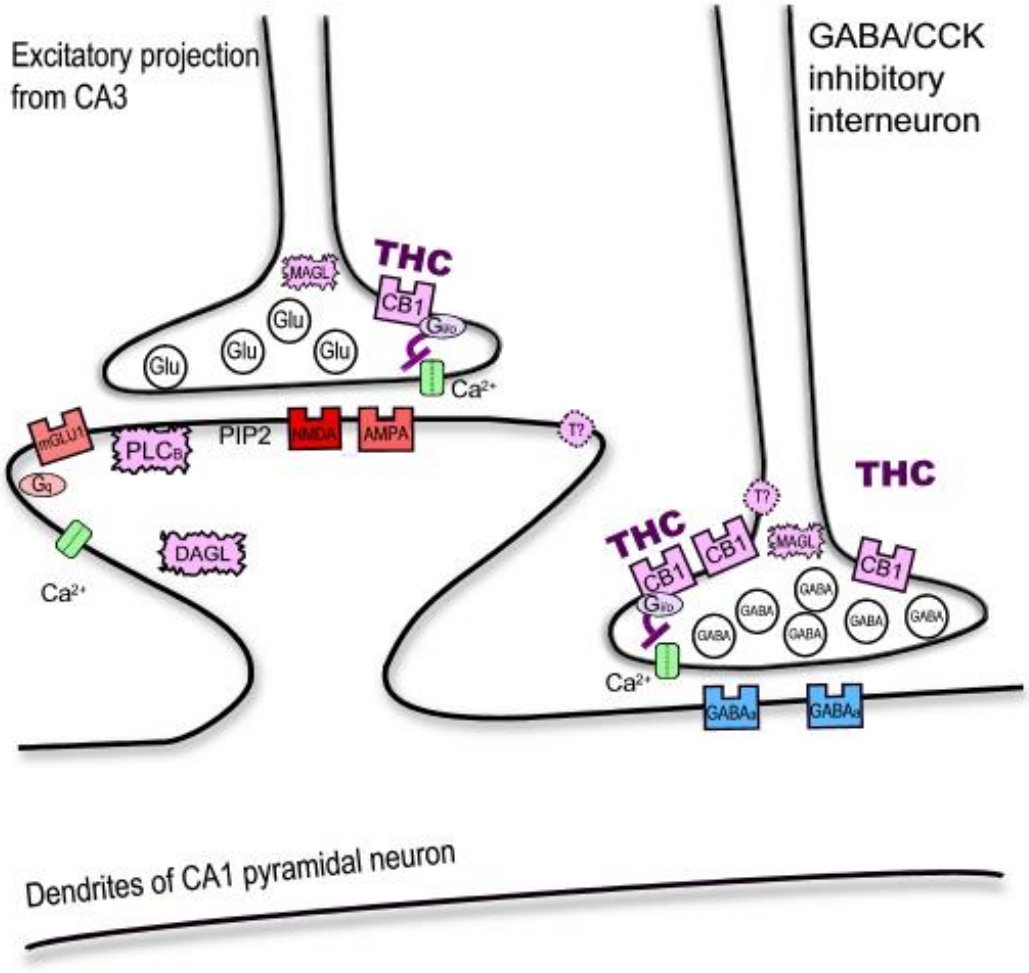
- ↓ theta waves
- ↓ synchronised firing of neurons

Disruption of plasticity

- ↓ LTP

Impaired processing.

Impaired learning & memory



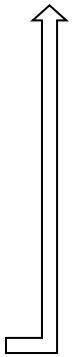

Murray RM, Morrison PD, DiForti M & Henquet C., (2007) Nature Reviews Neuroscience

# Cannabinoid neurobiology...

## Effect of THC

-Impaired cognition

Disruption of the dynamics of glutamate and GABA networks.



-Psychosis

???

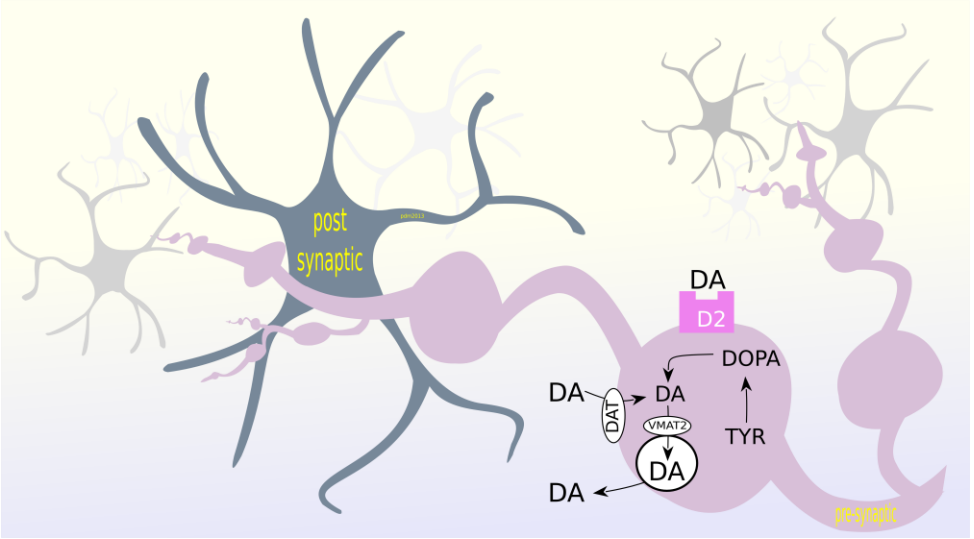
As above ?
Dopamine ?

# Cannabinoid neurobiology...

## Dopamine (DA)?

3 PET/SPET challenge studies.

*- No evidence for THC induced ↑ DA release.*




1 PET study of F-DOPA in cannabis users v controls.

*- No evidence for ↑ F-DOPA uptake in cannabis users.*

*- Instead ↓ F-DOPA uptake in cannabis users was found(!)*

Bloomfield MA et al (2014) Biol Psych

Unlikely that THC-psychosis is driven by THC-induced dopamine release.


Barkus E, Morrison PD, Vuletic D, Dickson JC, Ell PJ, Pilowsky LS, et al*Journal of psychopharmacology* 2011;25(11):1462-8.

Bossong MG, van Berckel BN, Boellaard R, Zuurman L, Schuit RC, Windhorst AD, et al.. *Neuropsychopharmacology* 2009;34(3):759-66

Stokes PR, Mehta MA, Curran HV, Breen G, Grasby PM. *NeuroImage* 2009;48(1):186-90.

# Cannabinoid neurobiology...

## Glutamate & GABA networks

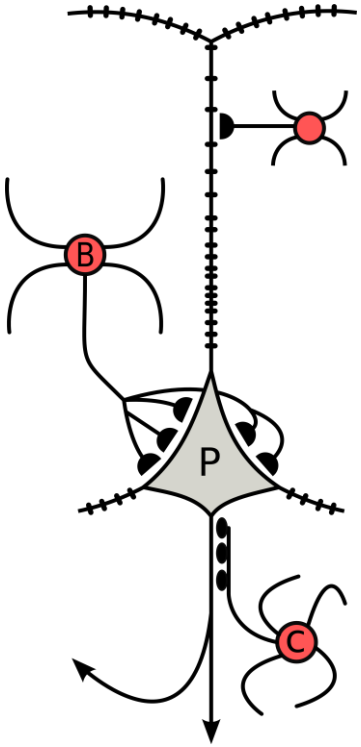
Several THC, EEG challenge studies

Consistent findings…

- *Abnormal theta waves*

- *Abnormal gamma waves*

*Associations between EEG changes and THC-induced psychosis.*




Emerging evidence that THC psychosis stems from disrupted network dynamics.

Morrison PD et al *Neuropsychopharmacology* 2011; **36**(4)**:** 827-836.

Cortes-Briones et al (2015) Neurropsychopharmacology

Nottage J., et al (2015) Psychopharm (Berl.)

## Summary

1. Early, heavy patterns of cannabis use are a risk factor for mental health.
2. Skunk carries a particularly high risk.
3. The absence of CBD in skunk is an important factor.
4. A history of acute cannabis-induced psychosis must be regarded as a red flag, warning against further use.
5. THC appears to have little effect on dopamine release in the striatum.
6. By disrupting the intricacies of fast amino-acid based neurotransmission, THC impairs network oscillations and synaptic plasticity with functional consequences.
7. CBD appears to have antipsychotic properties.

**Funding**

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NHS
National Institute for Health Research

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NHS Foundation Trust