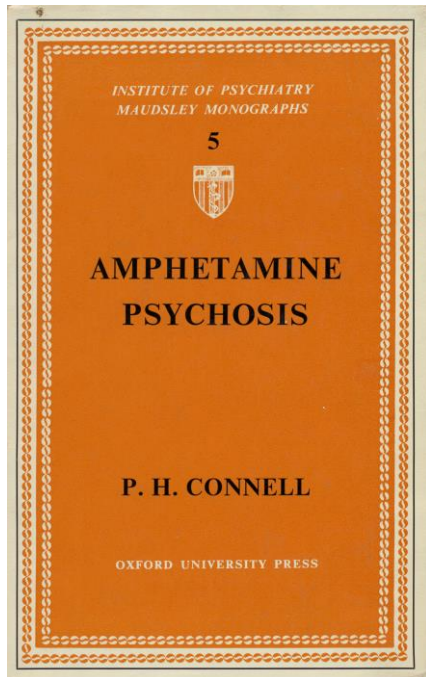


Marijuana, high potency cannabis, and synthetic cannabinoids: increasing risk for psychosis?

Robin M Murray and Marta Di Forti
Institute of Psychiatry,
London, UK

robin.murray@kcl.ac.uk

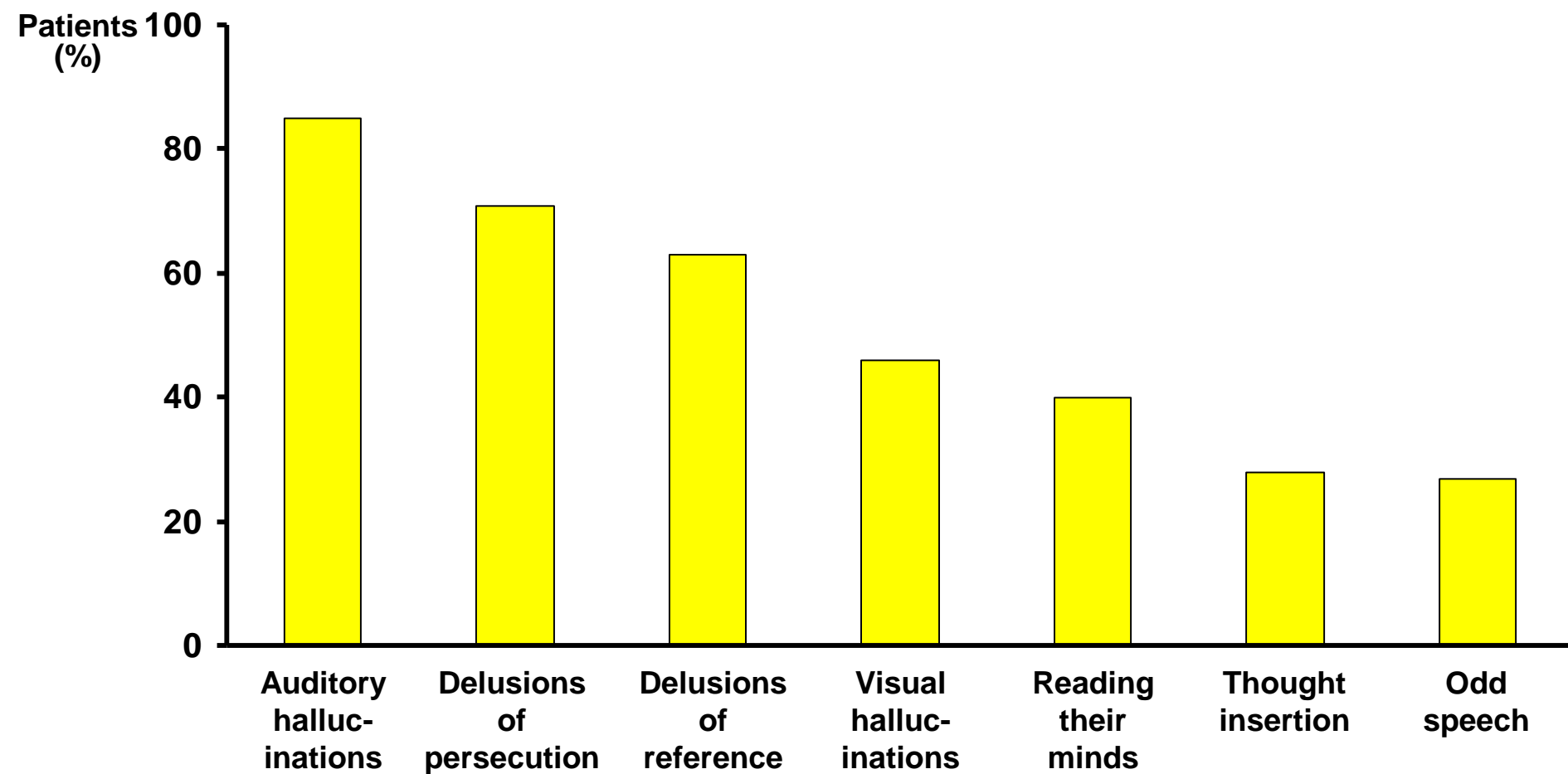
Drug Use can increase risk of Schizophrenia



Callaghan et al followed up methamphetamine abusers admitted to hospital in California and showed that they had a ninefold increase of subsequent schizophrenia

American Journal of Psychiatry, 2012

Psychopathology of individuals with methamphetamine psychosis



n=163

Chen et al 2003

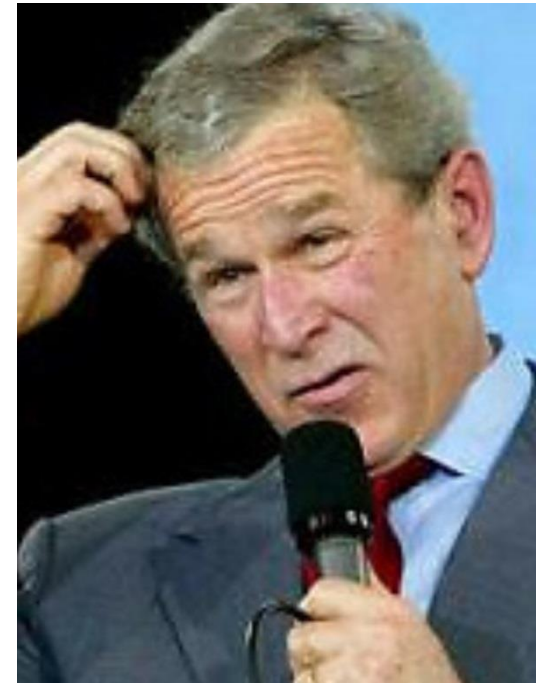
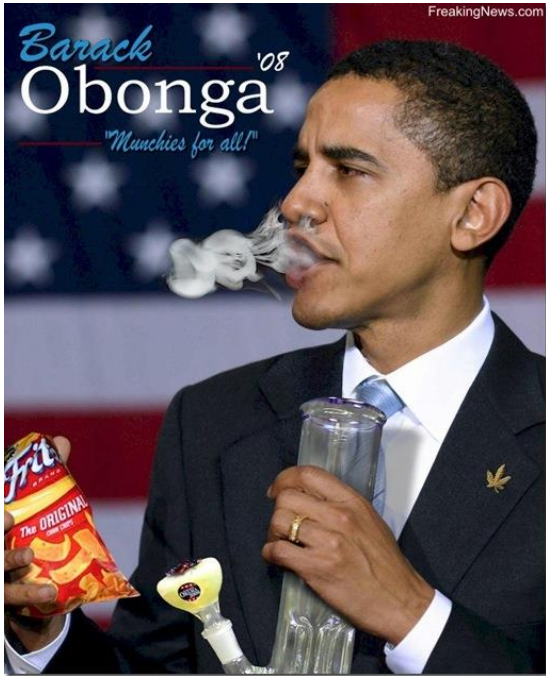
Other stimulants which increase risk of psychosis



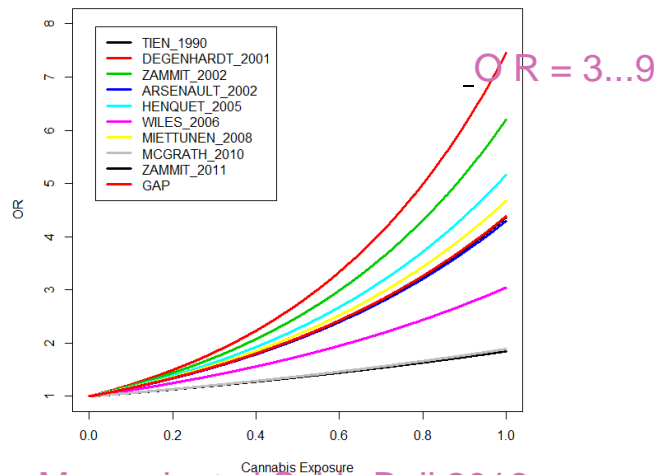
Khat - Cathinone

Methylmethylecathinone (MMCat or miew-miew)

Which drug do you have to use to become President?



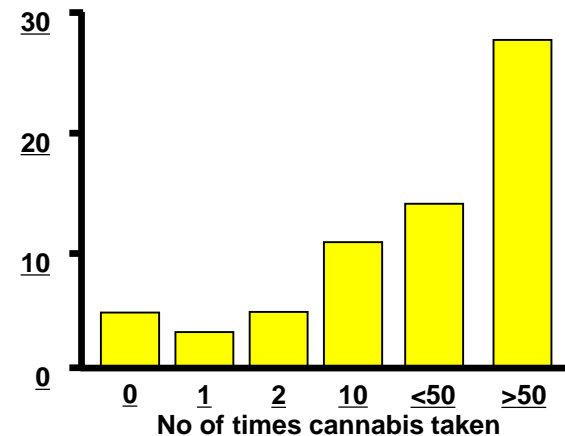
Risk of psychosis in relation to extent of cannabis use



Marconi et al Schiz Bull 2016

Swedish Army Study of Andréasson et al 1987

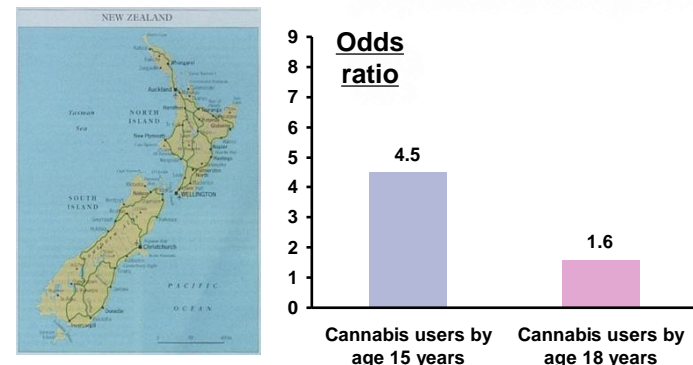
Cases of Sz per 1,000



Cohort Studies

Country	<u>n</u>	<u>FU</u>	OR
Sweden	50,053	25 yrs	3.1
NL	4,045	3 yrs	2.8
NL	4,045	3 yrs	12.0
NL	18,000	Retro	3.2
NZ (Chr)	1,265	3 yrs	1.8
NZ (Dun)	1,253	15 yrs	3.1
Germany	2,436	4 yrs	1.7
UK	8,500	18 mths	1.5
Australia	3,800	14 yrs	2.2

Risk of schizophreniform psychosis at age 26 years



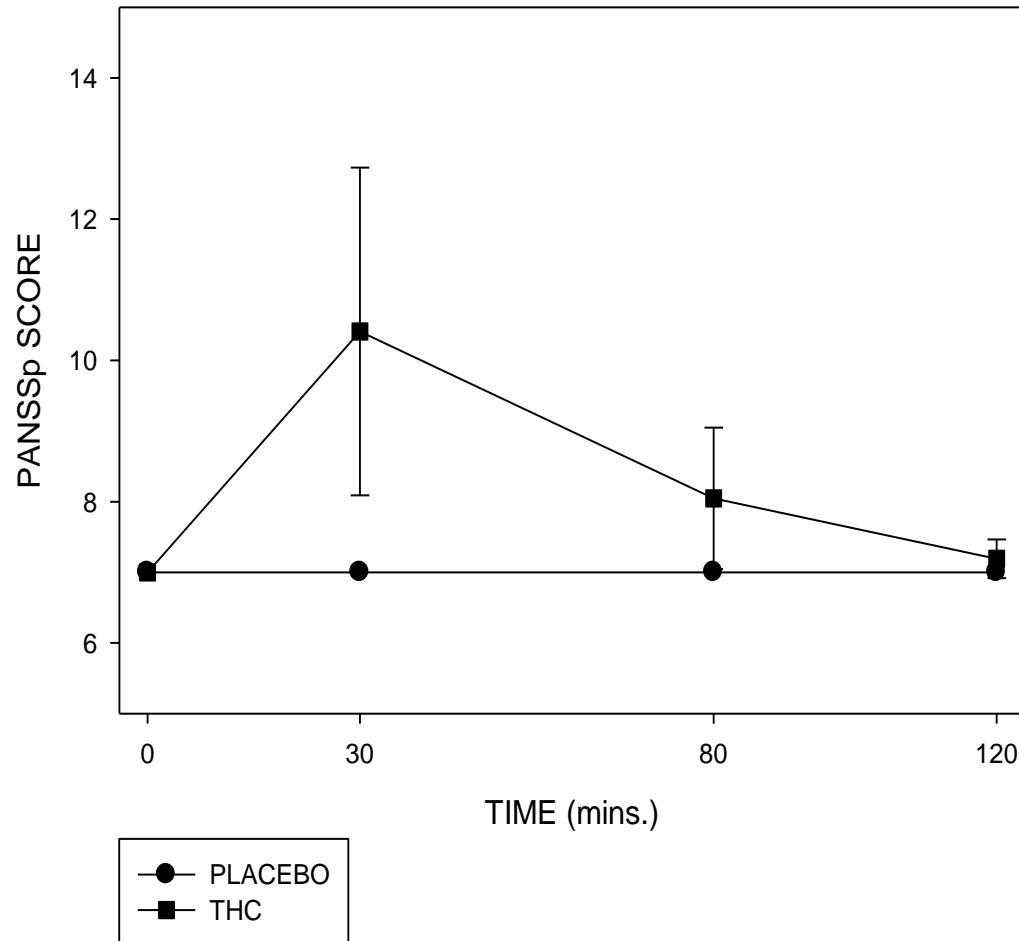
Arseneault et al BMJ 2002

IV administration of 2.5 mg of Tetrahydrocannabinol (THC) induces transient psychotic symptoms.

INVESTIGATOR RATED POSITIVE PSYCHOTIC SYMPTOMS



Morrison et al, 2009



121 schizotypal individuals were randomised to receive THC or placebo



Mean (S.D.) Paranoia
Score

after Placebo 6.8 (9.8)

after THC 15.6 (17.3)

The ingredients of cannabis

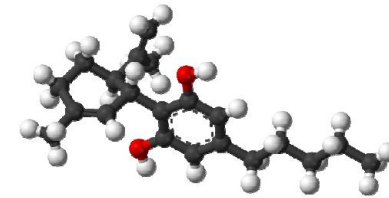
Tetrahydrocannabinol (THC)
– partial agonist at CB1



Impairment of
attention, memory and learning
Hallucinations and
paranoid ideas

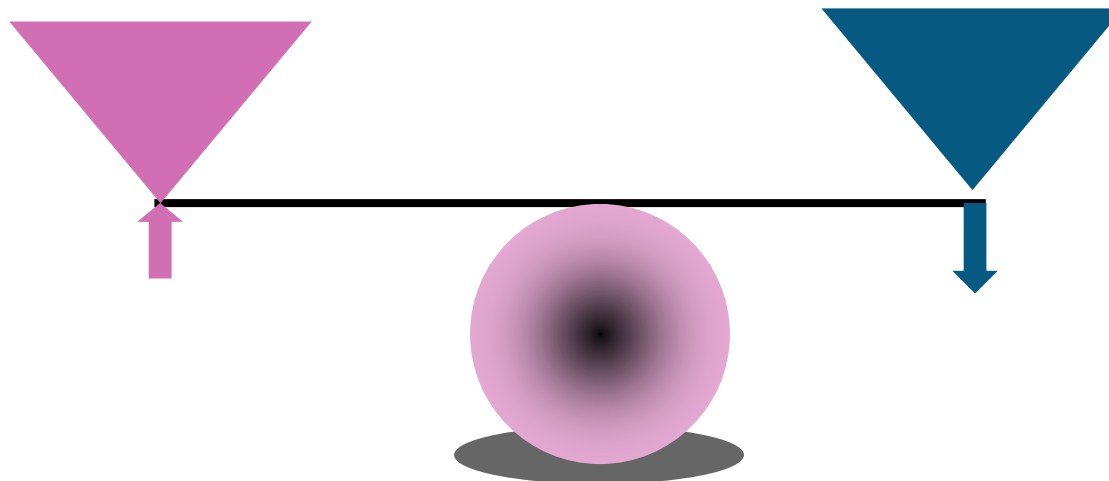
THC

Cannabidiol (CBD)



Is not hallucinogenic
Has anxiety relieving properties
Antipsychotic actions?
Antagonise effects of THC?

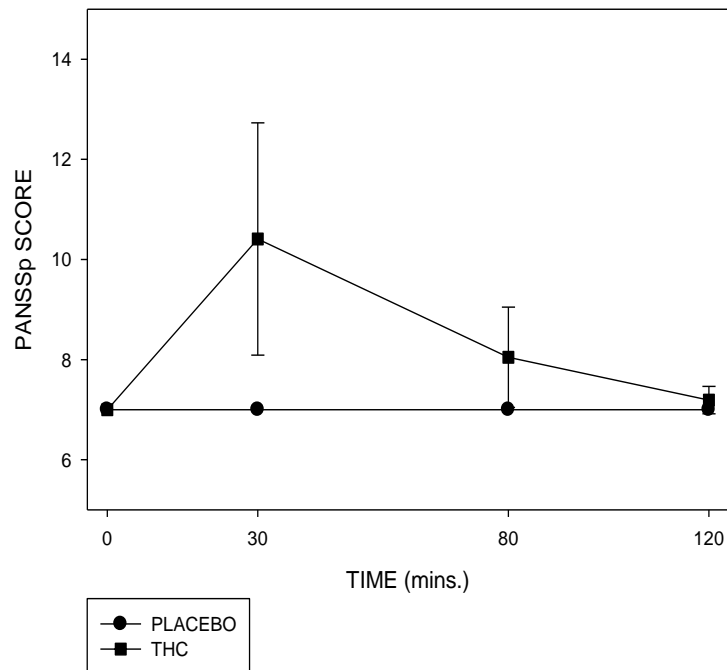
CBD





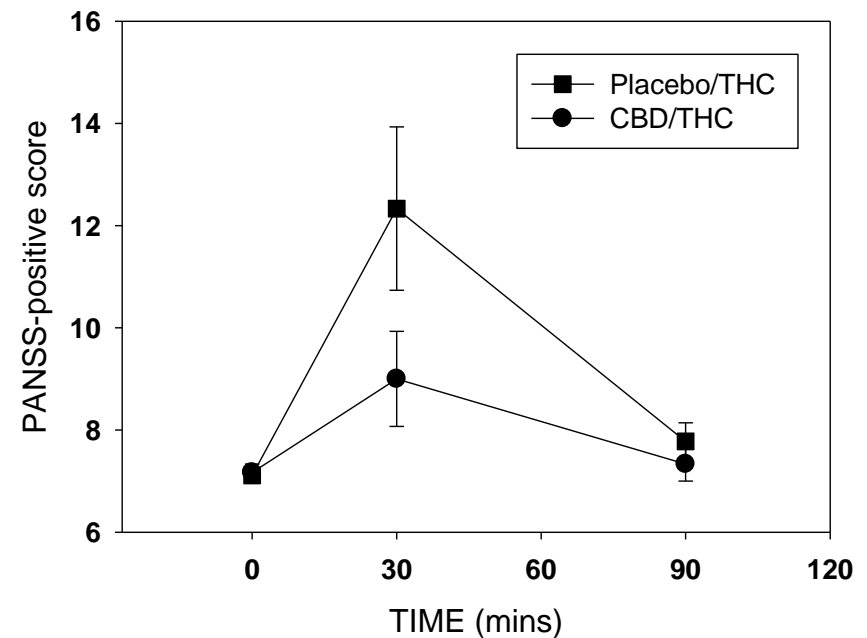
Psychotogenic effect of acute administration of 2.5 mg of IV Tetrahydrocannabinol (THC) .

INVESTIGATOR RATED POSITIVE PSYCHOTIC SYMPTOMS



THC induces transient psychotic symptoms

CBD or Placebo versus THC



Cannabidiol (CBD) blocks the effects of THC

Cannabidiol as an Antipsychotic?

Present

GW Pharmaceuticals Announces Positive Proof of Concept Data in Schizophrenia 15 September 2015

Placebo-controlled trial of addition of Cannabidiol (CBD) to standard antipsychotic in 88 patients with schizophrenia who had previously failed to respond adequately.

CBD was consistently superior to placebo, with the most notable differences being in the PANSS positive sub-scale ($p=0.018$).



Increase in the potency of cannabis – the development of skunk!

When Ronald Reagan began a crackdown on illegal drugs, Tom Watson (the Skunkman) fled the USA in 1985 and brought his seeds to Amsterdam where he could experiment with his plants more openly.

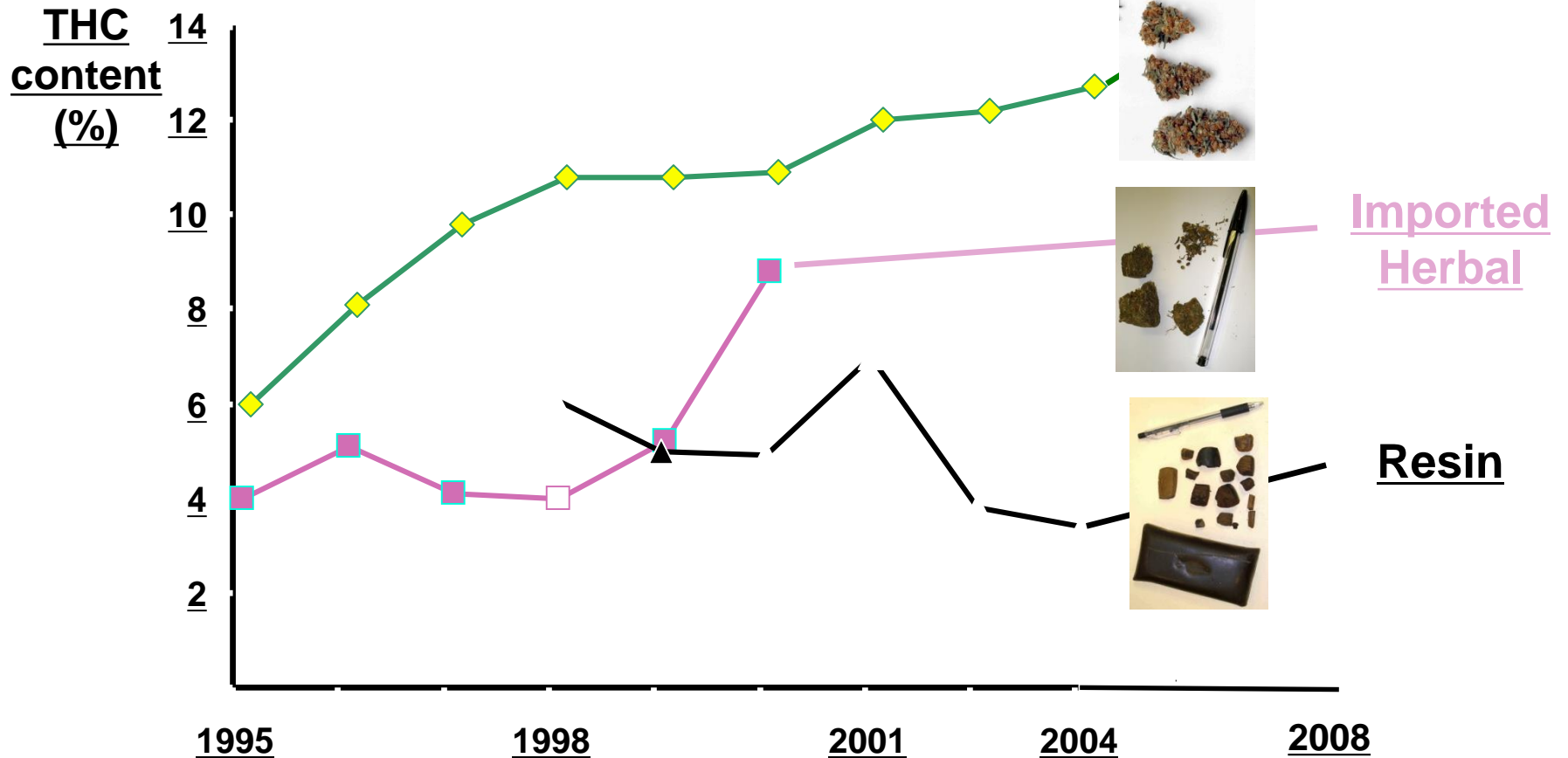
Indoor cultivation of cannabis was just starting to take off in the Netherlands, so he joined up with local cannabis experts to “breed” more potent plants

The Skunkman is said to be the father of “skunk”—a smelly hybrid of three previously uncrossed cannabis genetic lines.





Cannabis potency in England



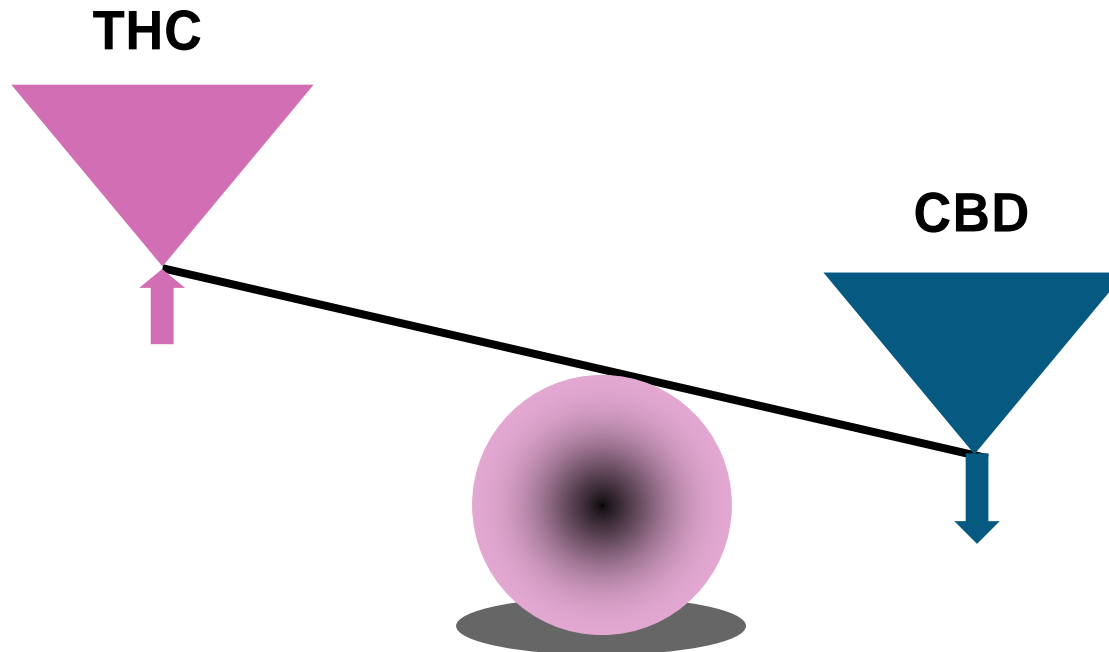
The ingredients of cannabis

THC causes

Impairment of attention,
memory and learning
Hallucinations and
paranoid ideas

Cannabidiol (CBD)

Is not hallucinogenic
Has anxiety relieving properties
No adverse effect on cognition





Case-control study of cannabis and psychosis

TRUST BOUNDARIES



- 410 patients in their 1st episode of psychosis.

- 370 population-based healthy controls
(screened for psychosis)

All interviewed using the cannabis experience questionnaire



Di Forti et al, BJPsych 2009; Schiz Bull 2013



Patterns of Cannabis Use

	Ever used (%)	Daily (% users)	Skunk (% users)
First episode Psychosis (n=410)	63.3	46.1	80.9
Controls (n=370)	63.4	18.7	42.6
	NS	<0.001	<0.001

Skunk and its frequency of use

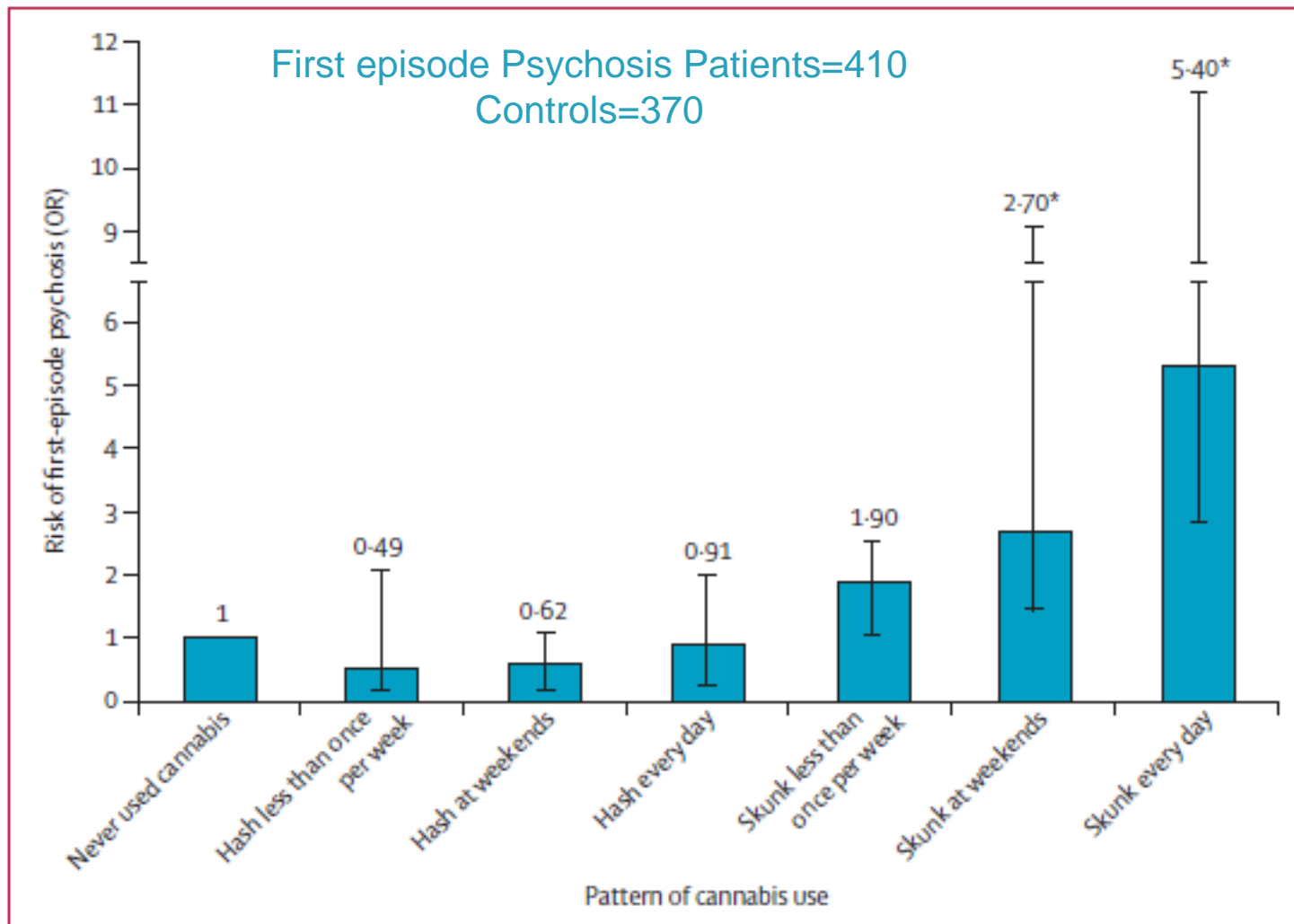


Figure 2: Probability of individuals having a psychotic disorder by pattern of cannabis use

OR adjusted for age, gender, ethnic origin, education, employment status, and tobacco use. OR=odds ratio.

* $p < 0.05$.

Proportion of patients in south London with first-episode psychosis attributable to use of high potency cannabis: a case-control study

+ Monday, February 16, 2015

FINAL



The best for sport
David Luiz interview: I had to con Chelsea
Six Nations: Why Joseph is giving England the X-factor

Total Football plus 16 pages of sport



Indian Summers vs Casual Vacancy
Who won the Sunday TV battle?

News page 11

No 49,680 £1.40



The Daily Telegraph

NATIONAL NEWSPAPER OF THE YEAR

telegraph.co.uk

Cannabis causing a quarter of psychosis

New York bows to Beckham



Labour may ban private government contracts

By Ben Riley-Smith
Political Correspondent

PRIVATE companies motivated by profit should be stripped of billions of pounds' worth of government contracts, Ed Miliband's top policy chief has said. Jon Cruddas, who is writing Labour's general election manifesto, said there should be "no more outsourcing" of public services to firms making money rather than achieving a "social purpose". The Labour frontbencher also said it was "staggering" that 20 companies received £10 billion of government money to help deliver services in the public sector.

His comments undermine the Labour leadership's attempts to prove it is anti-business, after weeks of public

Are cannabis using schizophrenics different from non using schizophrenics?

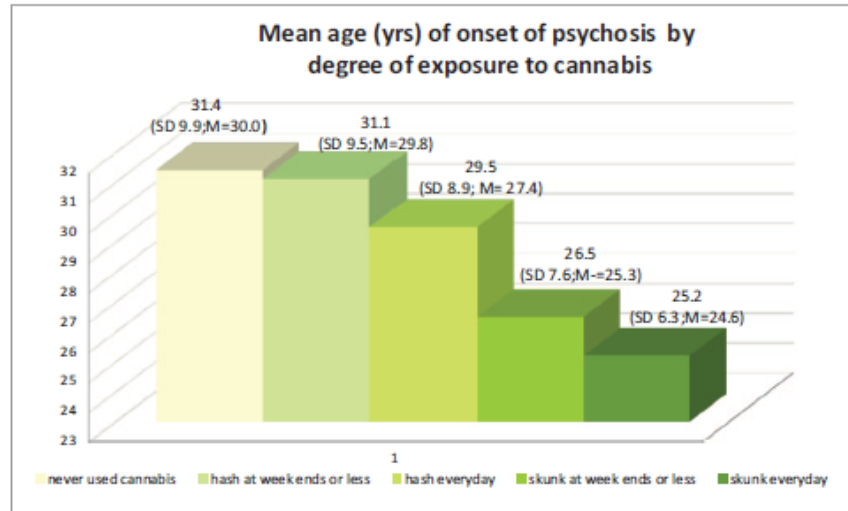
Users have an earlier onset

Users have a higher IQ

Users have better pre-morbid social
functioning

If cannabis using psychotic patients are a discrete group, they should be different from non-using psychotic patients

Users had an earlier onset of psychosis

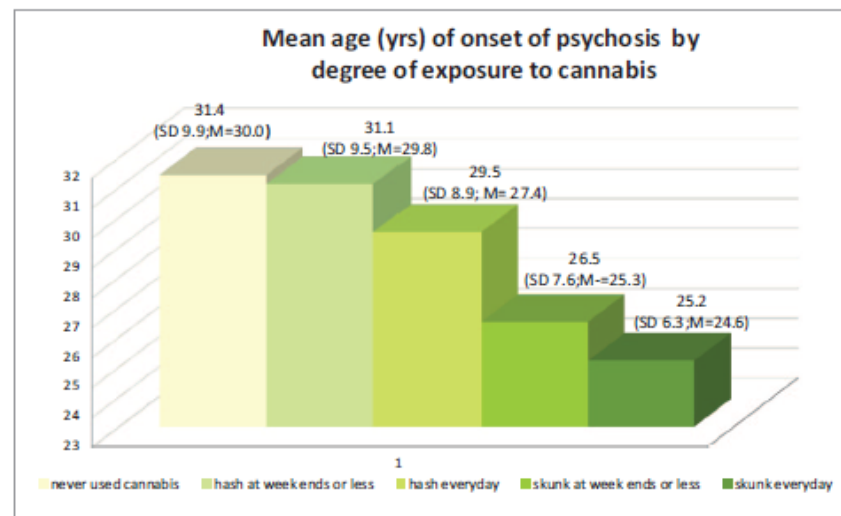
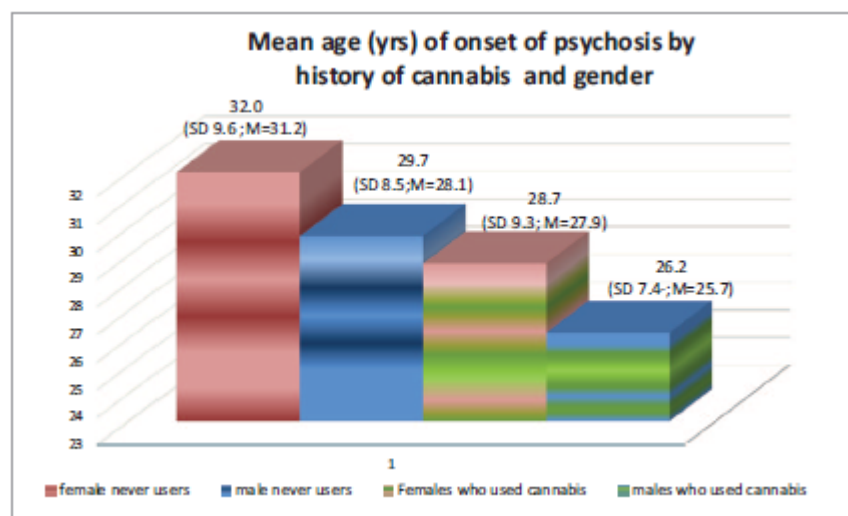


Users had a higher pre-morbid IQ and better pre-morbid social function

Continued users had a worse outcome

Daily Use, Especially of High-Potency Cannabis, Drives the Earlier Onset of Psychosis in Cannabis Users

Marta Di Forti^{*,1}, Hannah Sallis², Fabio Allegri³, Antonella Trotta¹, Laura Ferraro⁴, Simona A. Stilo⁵, Arianna Marconi¹, Caterina La Cascia⁴, Tiago Reis Marques¹, Carmine Pariante⁶, Paola Dazzan¹, Valeria Mondelli⁶, Alessandra Paparelli¹, Anna Kolliakou¹, Diana Prata¹, Fiona Gaughran¹, Anthony S. David¹, Craig Morgan⁵, Daniel Sthal⁷, Mizanur Khondoker⁷, James H. MacCabe^{1,8}, and Robin M. Murray^{1,8}



ONLINE FIRST

Cannabis Use and Earlier Onset of Psychosis

A Systematic Meta-analysis

Matthew Large, BSc(Med), MBBS, FRANZCP; Swapnil Sharma, MBBS, FRANZCP;
Michael T. Compton, MD, MPH; Tim Slade, PhD; Olav Nielssen, MBBS, MCrim, FRANZCP

Context: A number of studies have found that the use of cannabis and other psychoactive substances is associated with an earlier onset of psychotic illness.

Data Synthesis: Meta-analysis found that the age at onset of psychosis for cannabis users was 2.70 years younger (standardized mean difference = -0.414) than for nonusers; for those with broadly defined substance use, the age

Daily use and skunk use bring onset further

Continued versus discontinued cannabis use in patients with psychosis: a systematic review and meta-analysis



Tabea Schoeler, Anna Monk, Musa B Sami, Ewa Klamerus, Enrico Foglia, Ruth Brown, Giulia Camuri, A Carlo Altamura, Robin Murray, Sagnik Bhattacharyya

Lancet Psychiatry 2016

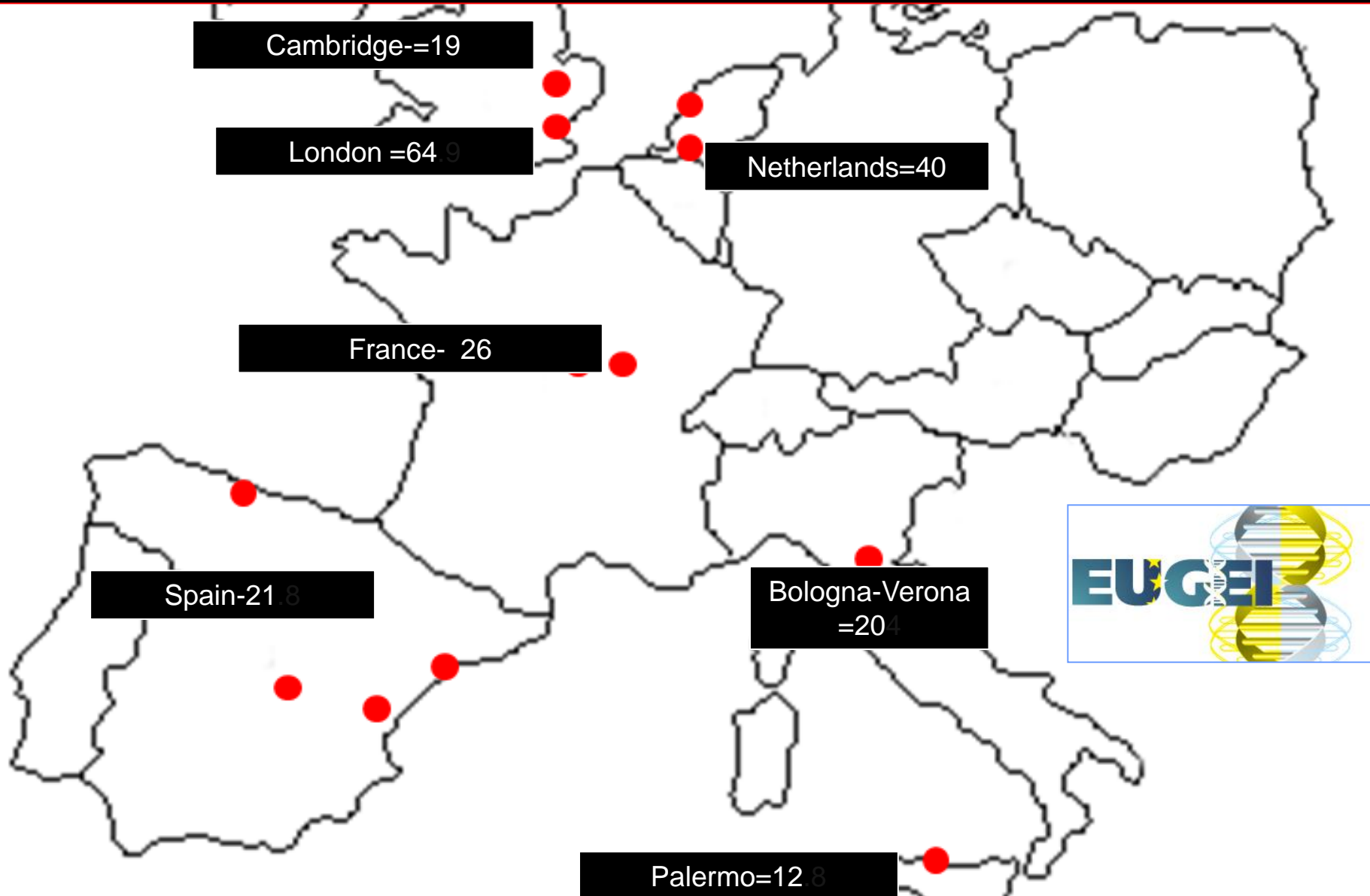
Published Online

January 14, 2016

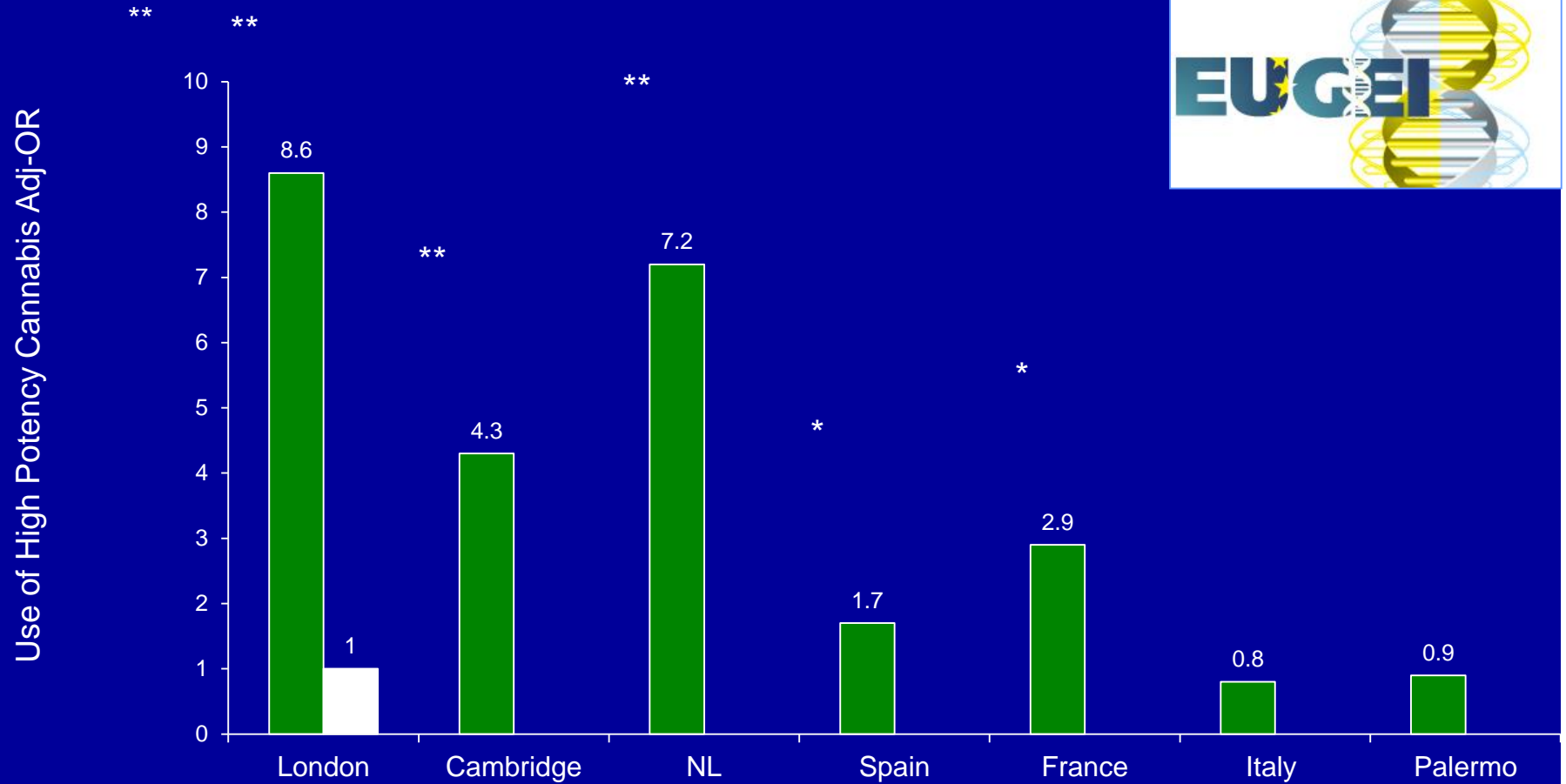
[http://dx.doi.org/10.1016/S2215-0366\(15\)00363-6](http://dx.doi.org/10.1016/S2215-0366(15)00363-6)

Interpretation Continued cannabis use after onset of psychosis predicts adverse outcome, including higher relapse rates, longer hospital admissions, and more severe positive symptoms than for individuals who discontinue cannabis use and those who are non-users. These findings point to reductions in cannabis use as a crucial interventional target to improve outcome in patients with psychosis.

Incidence of First Episode Psychosis across 16 sites - ranged from 12.0 per 100,000 person years in Palermo to 63.9 per 100,000 in London

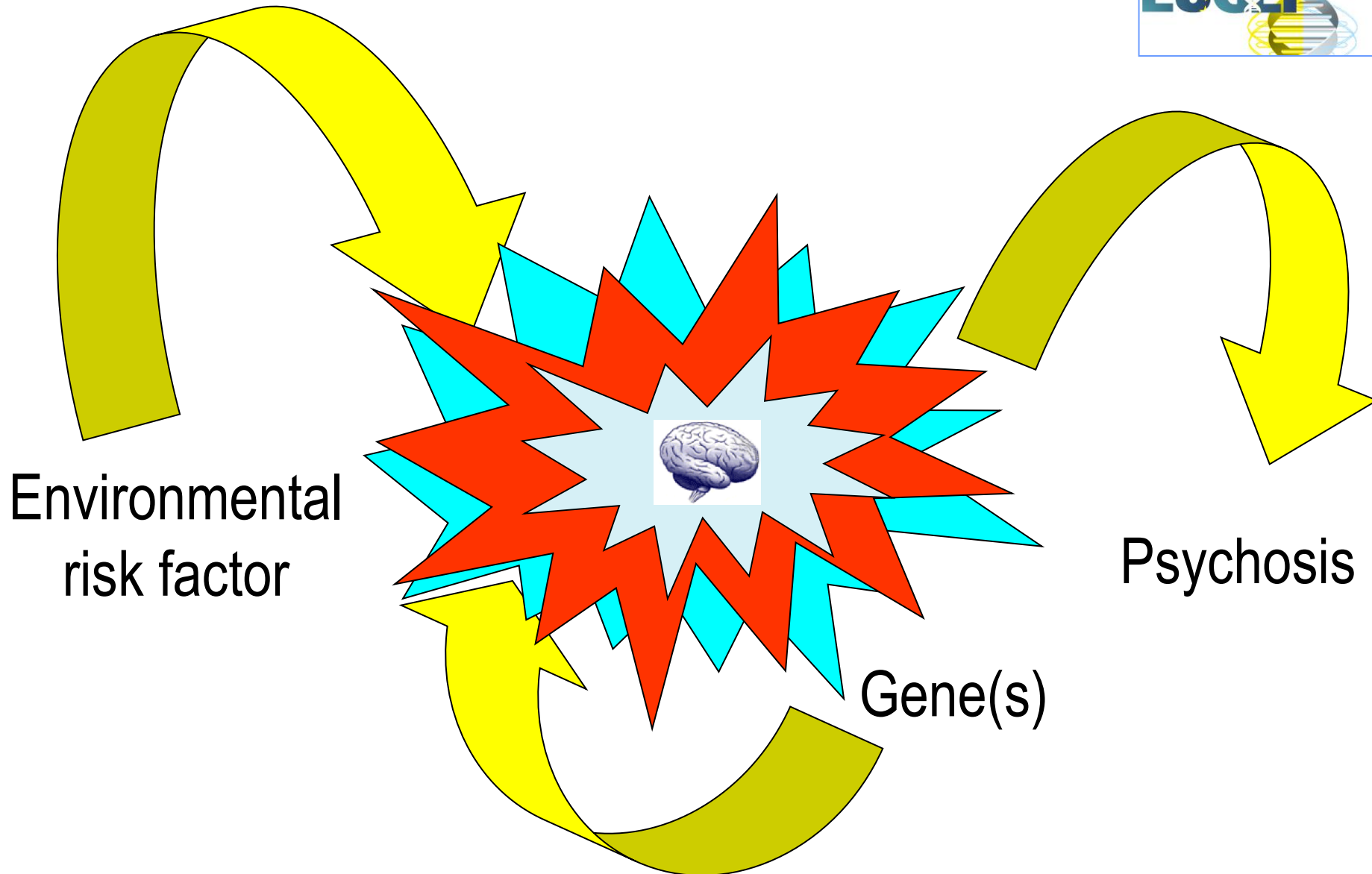


Use of High Potency Cannabis (TCH>10%) in 1600 Cases of First Episode Psychosis and 1383 Populations Controls



**p<0.001 *p<0.05 OR Adj for age, gender, ethnicity, other drugs

Gene-Environment Interaction



Gene-Environment Interaction

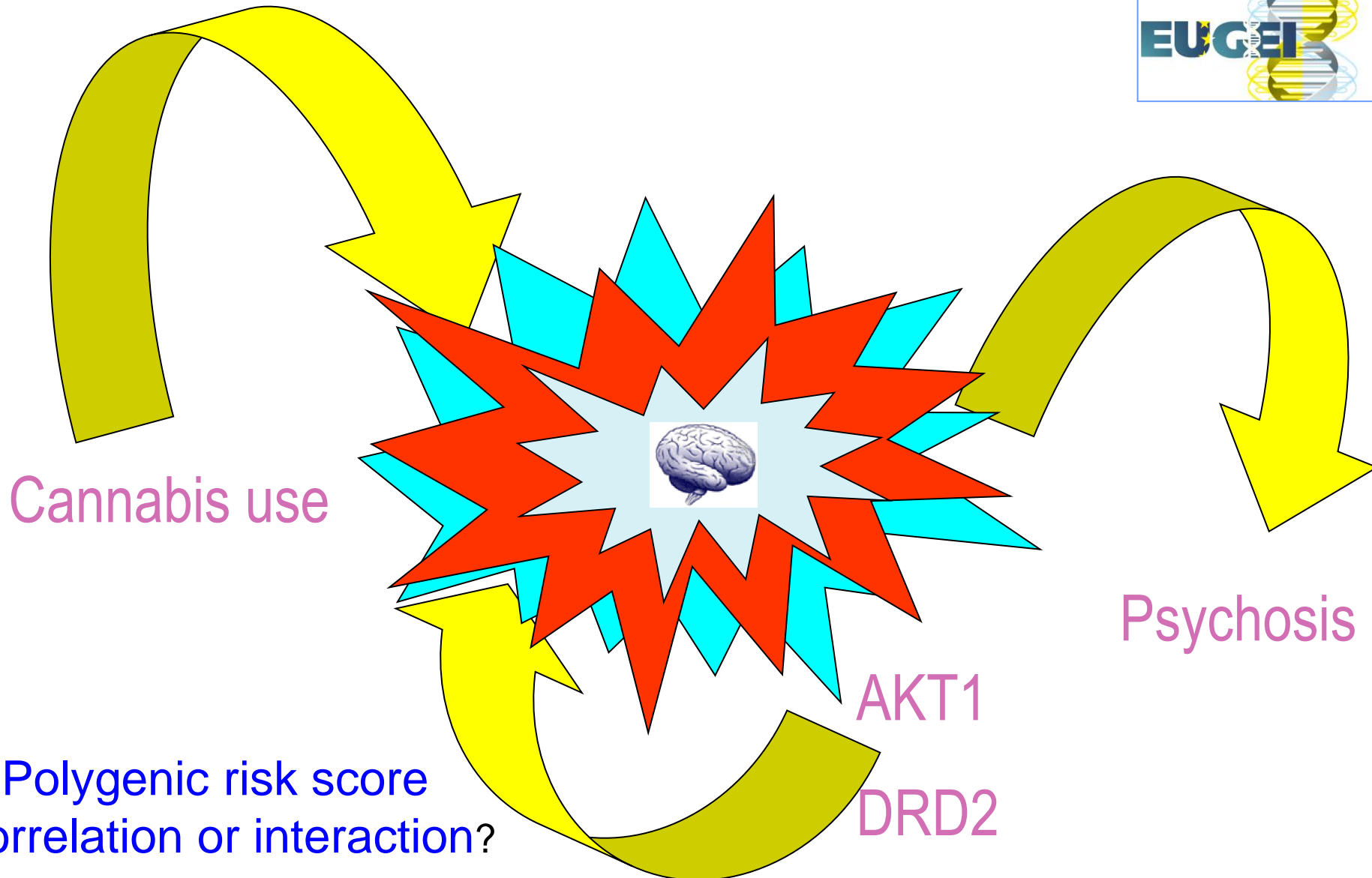
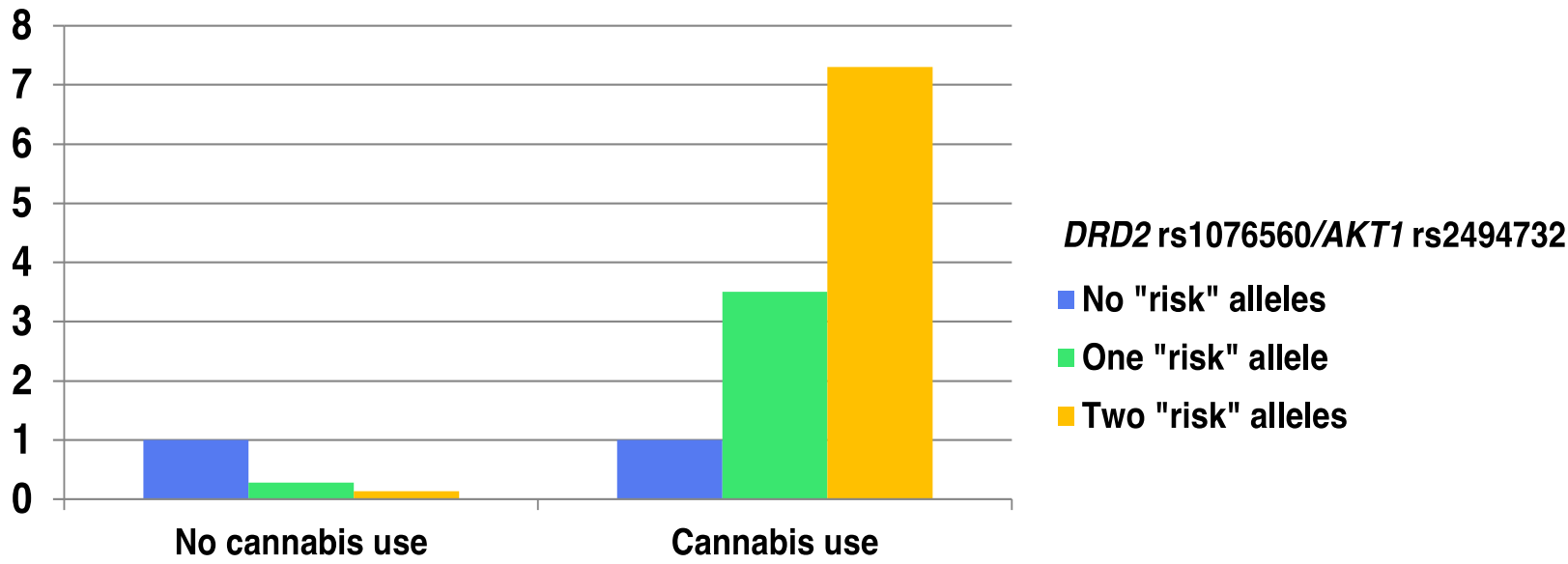


Figure 1a. Interaction between *DRD2* rs1076560/*AKT1* rs2494732 and lifetime cannabis use on psychosis risk



<i>DRD2</i> rs1076560/ <i>AKT1</i> rs2494732	No cannabis use			Cannabis use		
	Adj OR *	95% CI	P value	Adj OR *	95% CI	P value
No “risk” alleles	1	-	-	1	-	-
One “risk” allele	0.29	0.09, 0.88	0.03	3.50	1.14, 10.77	0.03
Two “risk” alleles	0.14	0.03, 0.63	0.01	3.07	1.58, 33.64	0.01

The arrival of synthetic cannabinoids puts the psychotogenic effect beyond doubt





Spicing things up: synthetic cannabinoids

Max Spaderna • Peter H. Addy • Deepak Cyril D'Souza

While THC is a partial agonist at the CB1 Receptor, synthetic Cannabinoids are full agonists. Therefore they have much more powerful effects

Users are 30 times more likely to seek emergency treatment than users of regular cannabis
Winstock A, Global Drug Survey 2014

Hum. Psychopharmacol Clin Exp 2013; **28**: 379–389.
Published online in Wiley Online Library
(wileyonlinelibrary.com) DOI: 10.1002/hup.2312

SPECIAL ISSUE ON NOVEL PSYCHOACTIVE SUBSTANCES

“Spiceophrenia”: a systematic overview of “Spice”-related psychopathological issues and a case report

Duccio Papanti^{1,2a}, Fabrizio Schifano³, Giulia Botteon^{1,2}, Francesca Bertossi⁴, Jason Marnix⁵, Daniela Vidoni⁶, Matteo Impugnatiello³, Elisabetta Pascual-Fabici^{1,7} and Tommaso Bonavito^{1,4}



Strange fame for an Academic



In 1984 Professor JW Huffman in Clemson Univ, USA began developing cannabinoid compounds to aid in research into multiple sclerosis, AIDS, and chemotherapy. Over twenty years, Huffman and his team developed 450 synthetic cannabinoid compounds.

In the late 2000s, Huffman's cannabinoid compounds began being sold in Germany as marijuana alternatives known as K2 and SpiceJWH-018 etc.

“It bothers me that people are so stupid as to use this stuff”.

CAUTION:

For fragrance purposes only.

Not for consumption.

Keep out of reach of children and pets.

Never leave burning incense unattended
and make sure all ashes fall in ashtrays
or burners.

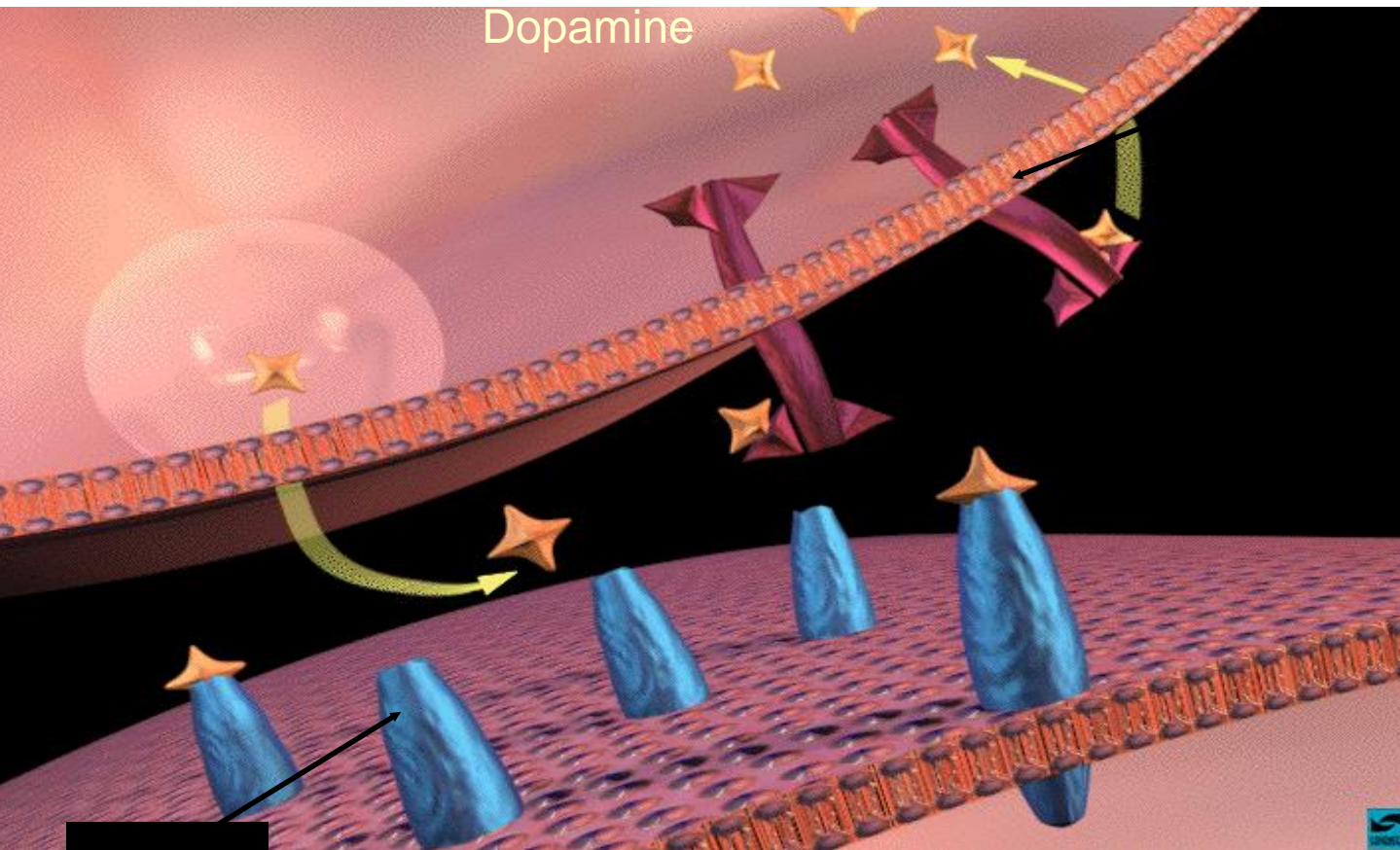
Burn in a well-ventilated area.

Smoke inhalation may cause
light-headedness and be harmful
to your health.

Excess Synthesis
of Striatal Dopamine



Psychosis



Striatal
dopamine
neuron

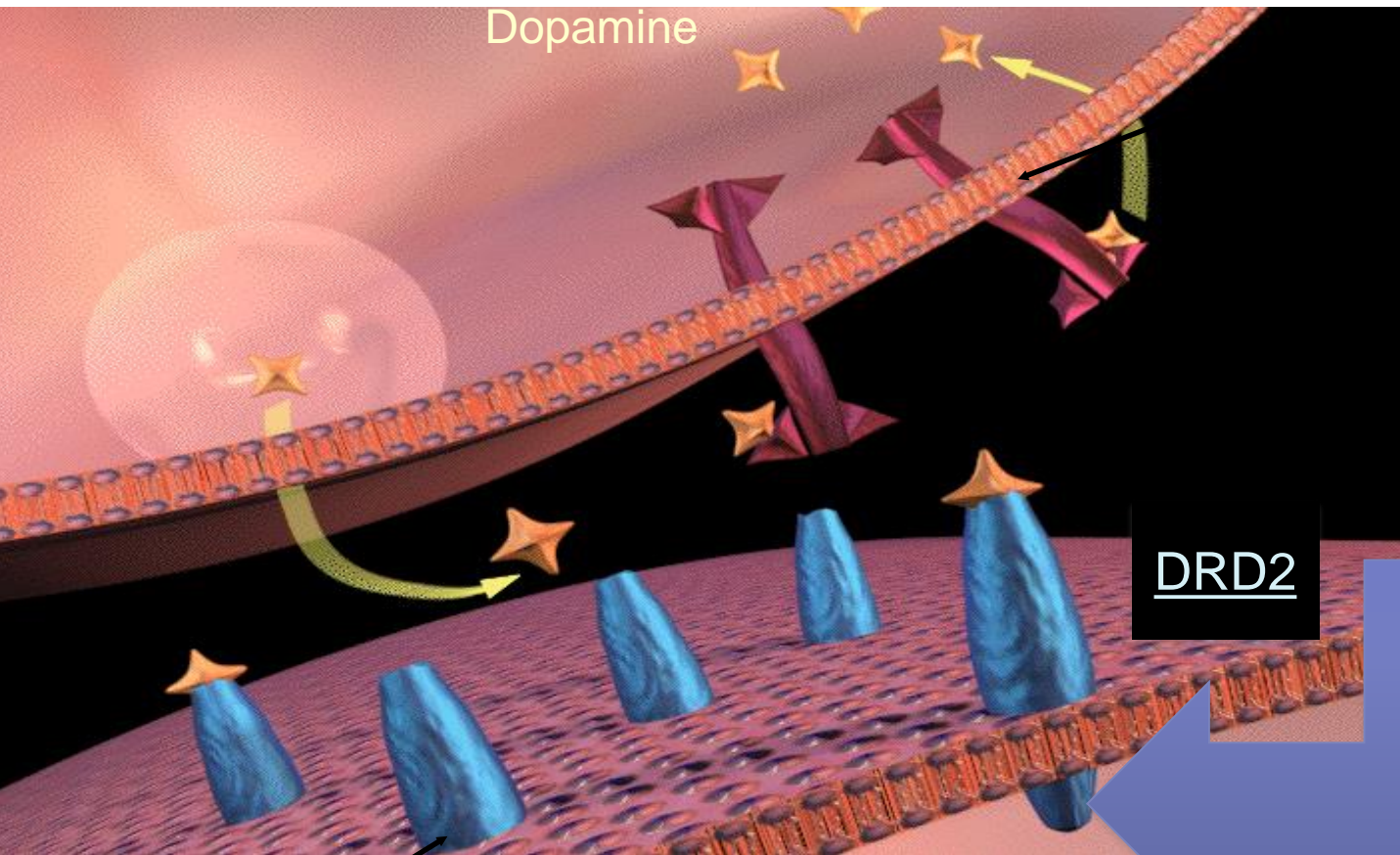
DRD2

Post-synaptic receptor

Excess Synthesis
of Striatal Dopamine



Psychosis



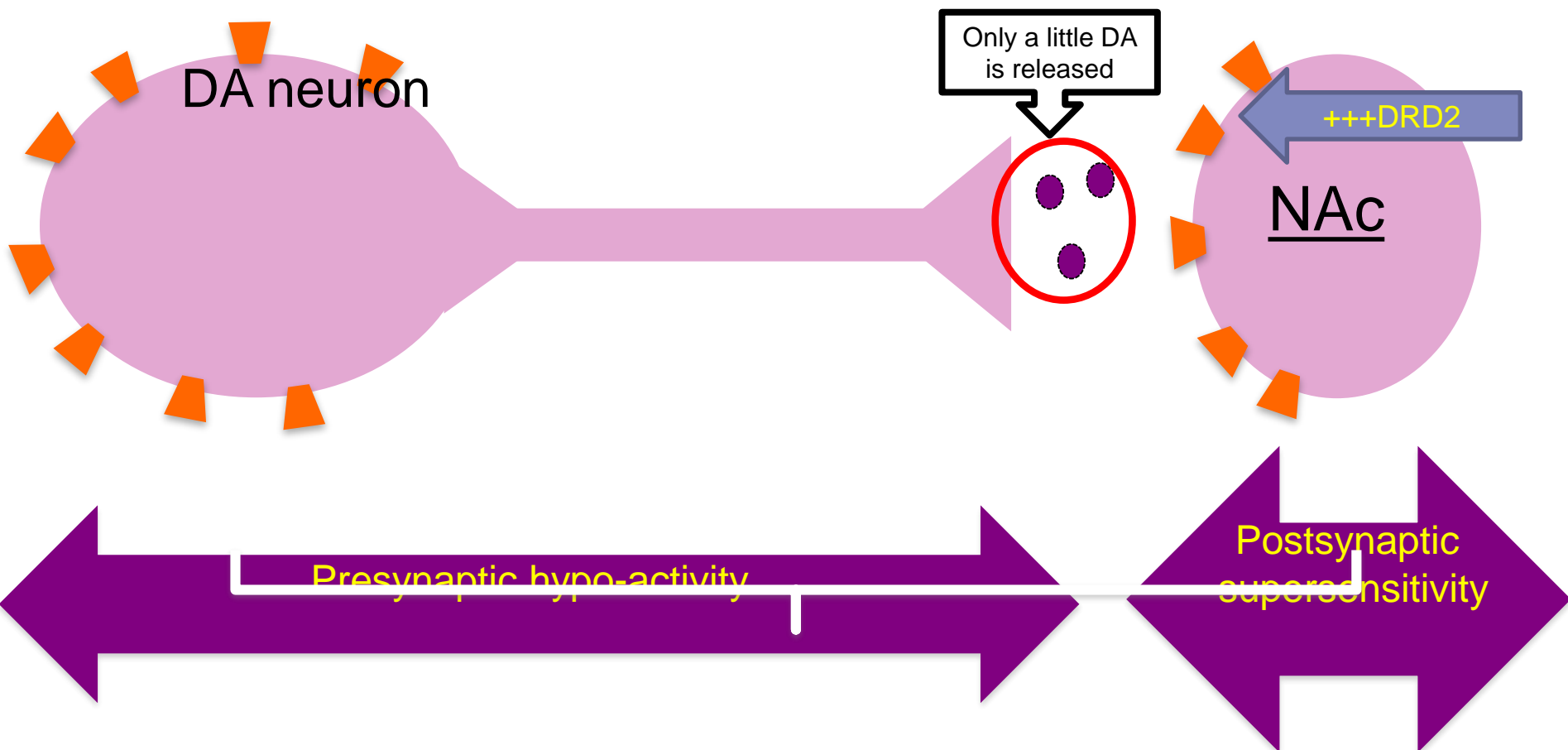
**Striatal
dopamine
neuron**

DRD2

Post-synaptic receptor

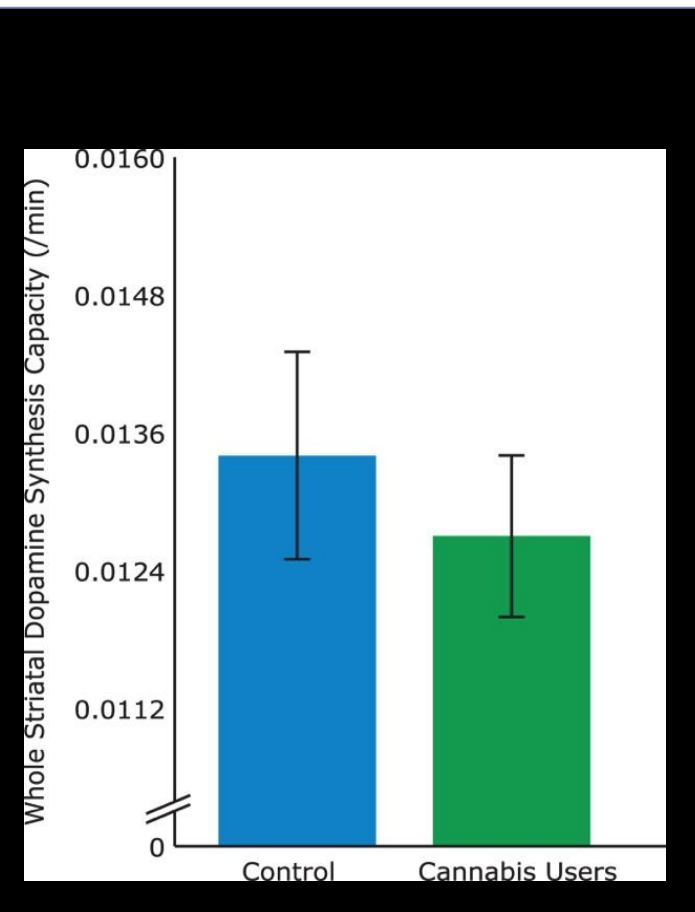
AKT1 is a Kinase
Protein involved in
the transmission of
the DRD2 signaling

Effect of chronic THC on DA transmission in rats



Nathalie Ginovart et al. Neuropsychopharmacology 2012

Striatal dopamine synthesis capacity in regular cannabis users vs. nonusers



Abi-Dhargum group showed that in cannabis-induced psychosis, striatal DA was low but even a small increase precipitated psychotic symptoms

COMMENTARY

Different Dopaminergic Abnormalities Underlie Cannabis Dependence and Cannabis-Induced Psychosis

Robin M. Murray, Mitul Mehta, and Marta Di Forti

Chronic cannabis use induces low striatal dopamine – similar to other drug dependencies, but also the concurrent development of post-synaptic super-sensitivity

Conclusions

- 1) Administering THC can induce an acute psychosis; this effect is moderated by CBD.
- 2) Heavy use of cannabis, especially high potency varieties, is associated with greater later risk of psychosis.
- 3) Cannabis-using psychotic patients have an earlier onset, and better premorbid function than non-using psychotic patients; they have a worse outcome if they continue to use cannabis
- 4) There is preliminary evidence that some people are genetically vulnerable

Thanks to:
The GAP and EU-GEI
Teams, and especially
Paul Morrison
Amir Englund
Marco Colizzi
Evangelos Vassos
Jim Van Os

and all our patients

