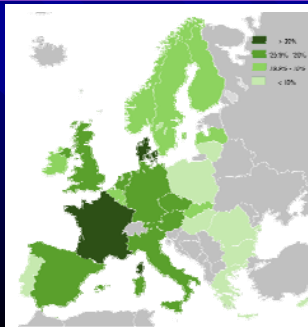


## (Developmental) Cannabis use



EMCDDA, 2006

NEWS FEATURE PERSONAL GENOMES

NATURE 453 15 November 2008



## The case of the missing heritability

## Sz Heritability = 80%

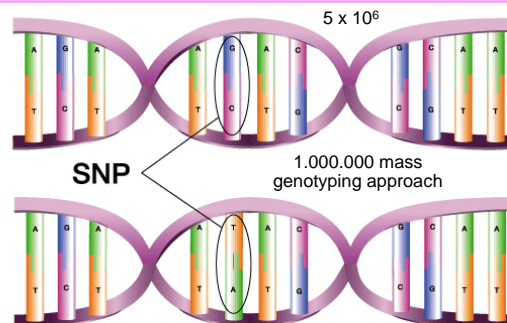


100% genetically identical

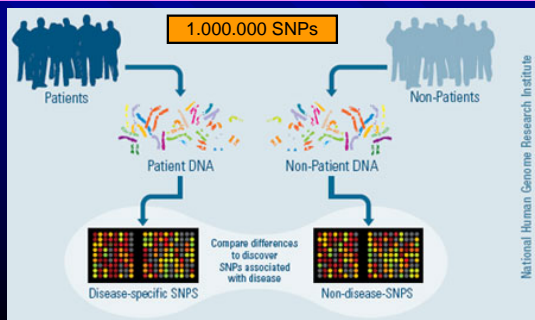


50% genetically identical

## Common Variants: DNA Sequence Variation (SNP)



## Genome-wide Association



## Common Genetic Variation and Schizophrenia

nature

Vol 460 | 6 August 2009 | doi:10.1038/nature08186

LETTERS

Explain <5% of heritability...

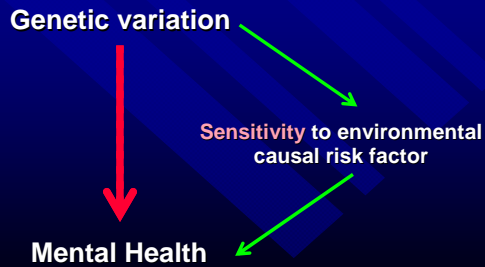
## Common variants conferring risk of schizophrenia

A list of authors and their affiliations appears at the end of the paper

Schizophrenia is a complex disorder, caused by both genetic and environmental factors and their interactions. Research on pathogenesis has traditionally focused on neurotransmitter systems in the brain, particularly those involving dopamine. Schizophrenia has been considered a separate disease for over a century, but in the absence of clear biological markers, diagnosis has historically been

3,634 controls from the Netherlands; set 2, 3,330 cases and 6,892 controls from Denmark (Aarhus), Denmark (Copenhagen), Germany (Bonn), Germany (Munich), Hungary, the Netherlands, Norway, Russia and Sweden; set 3, 287 cases and 3,907 controls from Finland; set 4, 667 cases and 1,042 controls from Spain (Santiago) and Spain (Valencia) (Supplementary Table 3).

## Heritability Includes Differential Sensitivity



Van Os et al. Nature, in press

## GxE: Ecogenetics



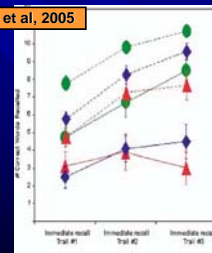
## Dutch Traditions



10% acute psychotic symptoms

## Differential Sensitivity?

D'Souza et al, 2005



SZ (n=13)

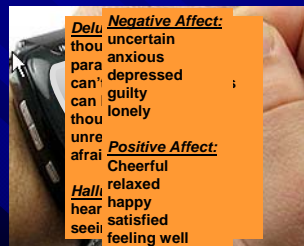
Ctr (n=22)

● Placebo  
◆ 2.5mg THC  
▲ 5mg THC

## Why Do Patients Use?



- Random event sampling
- 10 times per day
- 6 days per week



Positive Affect (0-1)?  
 Negative Affect (1-7)?

Delespaul, 1995; Myin-Germeys et al, 2001

## Why Do Patients Continue: ESM Study

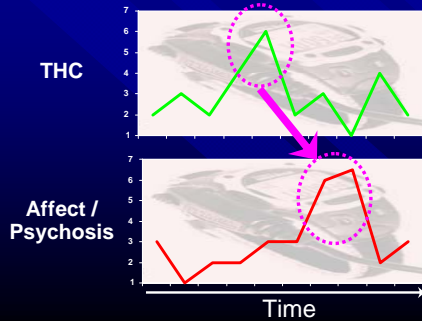
THC, Affect, Psychosis

THC, Affect, Psychosis

THC, Affect, Psychosis

THC, Affect, Psychosis

## ESM Time Relationships



## An ESM study of cannabis and symptoms

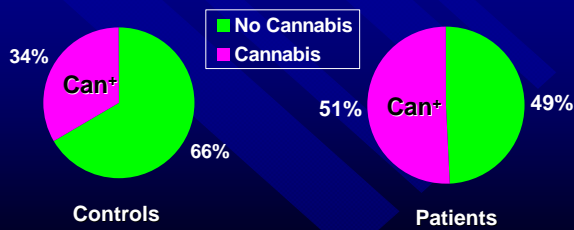
Sample

- 1. patients (38)
- 3. controls (42)

ESM study

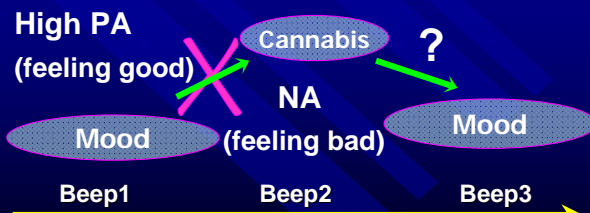
Henquet et al, BJPsych, in press

## % Cannabis moments during sampling



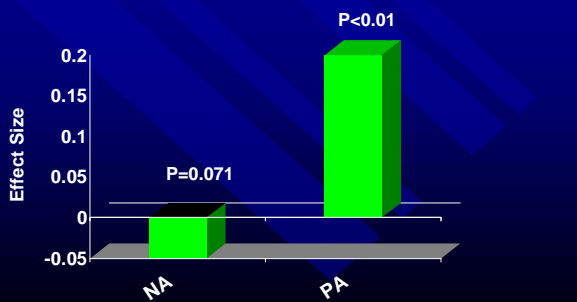
Henquet et al, BJPsych, in press

## ESM Self-medication (patients)



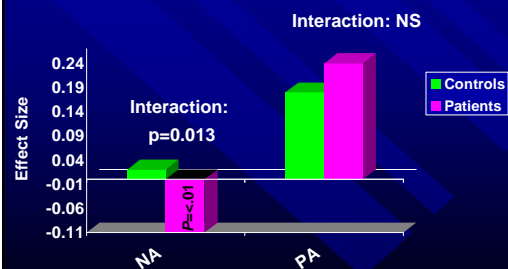
Negative affect: 'uncertain', 'anxious', 'depressed', 'guilty', 'lonely'  
Positive affect: 'relaxed', 'cheerful', 'satisfied', 'happy', 'globally well'

## Main effects Cannabis on Mood

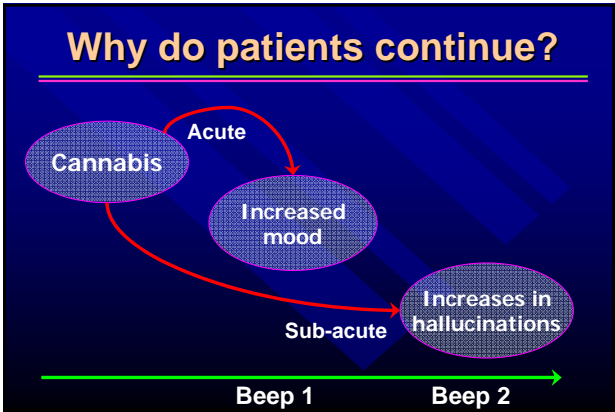
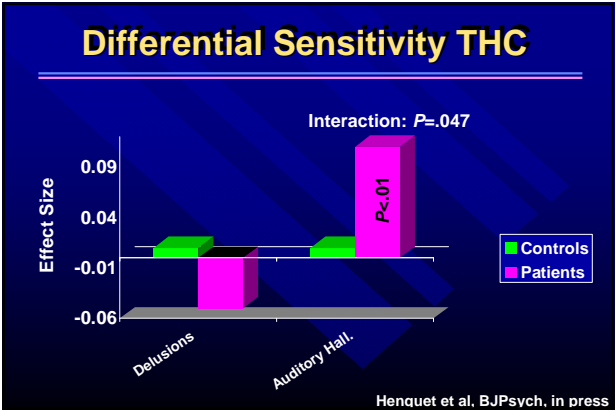
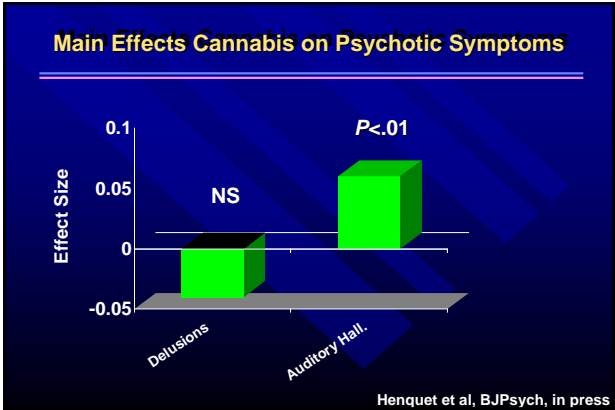


Henquet et al, BJPsych, in press

## Differential Sensitivity THC



Henquet et al, BJPsych, in press

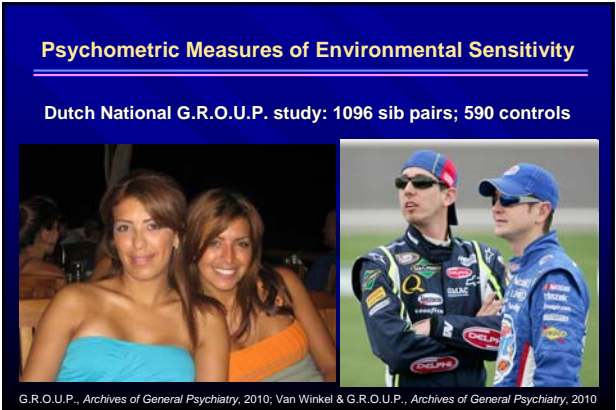
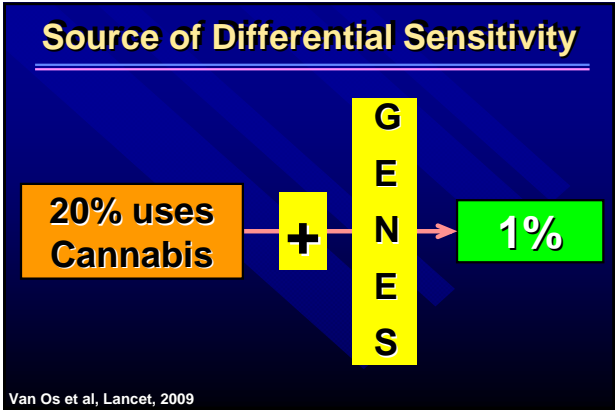


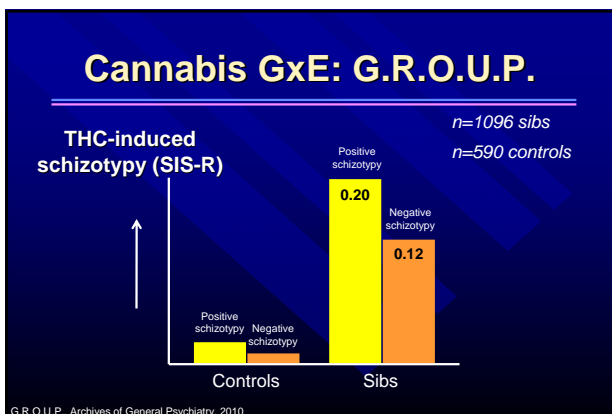
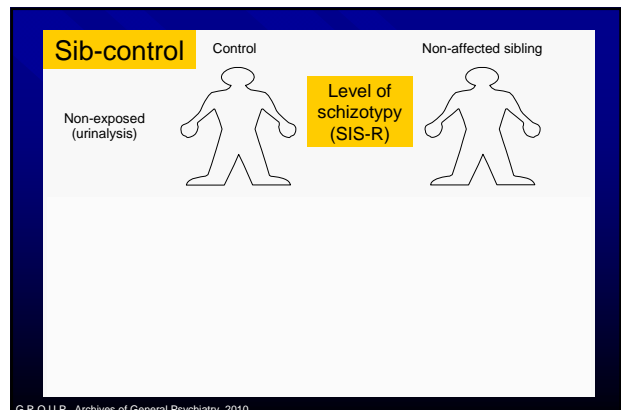
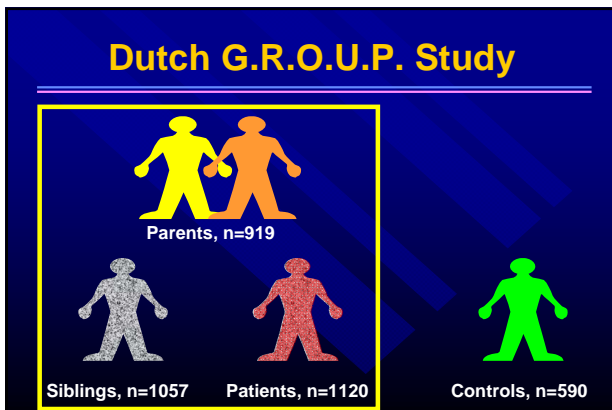
### Cannabis & Psychosis

Country	n	FU	OR (95% CI)	Outcome
Sweden	50,053	5 yrs	2.1 (1.2, 3.7)	narrow
NL	4,045	3 yrs	2.8 (1.2, 6.5)	broad
NL	4,045	3 yrs	12.0 (2.2, 64.3)	narrow
Israel	9,724	4-15 yrs	2.0 (1.3, 3.1)	narrow
NZ (Chr)	1,265	3 yrs	1.8 (1.2, 2.6)	broad
NZ (Dun)	1,253	15 yrs	3.1 (0.7, 13.3)	narrow
Germany	2,436	4 yrs	1.7 (1.1, 1.5)	broad

Random effects meta-analysis: 1.9, 1.6-2.3; test heterogeneity  $P=0.28$

Henquet et al, Schiz Bull, 2005





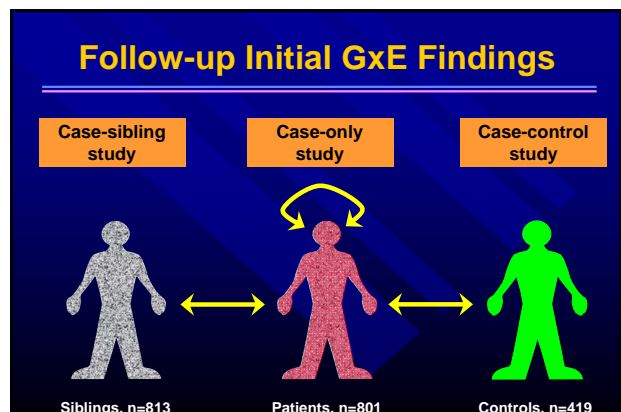
- Association with schizophrenia:**  
RGS4, NRG1, DTNBP1, PIP5K2A, G72/DAOA, DISC1, HT2A, AKT1, LRRTM1, FGF2, FGFR1, GPM6A, PRODH, GRM3, GABRA6, GAD1, NOS1, RGS2, ROBO1, CHRM3, TBX1
- Relevant for dopaminergic neurotransmission**  
COMT, ANKK1, DRD1, DRD2, DRD3, SLC6A3, PPP1R1B, SLC18A2
- Directly related to cannabinoid signaling**  
CNR1
- Responsivity to environmental stress**  
ADRA2C, FKBP5
- Adaptive neuronal survival**  
BDNF, P2RX7, NPY, NQO1, GST-1, GST-2
- Epigenetic regulation of environmental influences**  
MTHFR, MTR, MTRR, DNMT3B, EHMT1, EHMT2, PRDM2
- van Winkel & G.R.O.U.P., Arch Gen Psychiatry, 2010

SNP	Gene	Risk variant	HWE	Effect size	P
(p-value)					
rs1799732	DRD2	deletion	0.65	0.24	0.0312
rs1800498	DRD2	C	0.94	0.20	0.0147
rs2058725	GAD1	G	0.20	0.26	0.0349
rs379850	GAD1	G	0.83	0.22	0.0113
rs1801133	MTHFR	C	0.07	0.19	0.0339
rs806379	CNR1	T	0.04	T	0.0428
rs806308	CNR1	T	0.86	0.25	0.0036
rs1018381	DTNBP1	T	0.40	0.34	0.0119
rs1421292	G72/DAOA	A	0.30	0.21	0.0112
rs1130233	AKT1	A	0.47	0.37	0.0003***
rs2494732	AKT1	C	0.43	0.42	0.0001***
rs673871	LRRTM1	T	0.74	1.17	0.0001***
rs372055	PRODH	A	0.20	0.24	0.0246
rs5746832	TBX	G	0.40	0.21	0.0343
rs3037354	NPY	deletion	0.41	0.19	0.0368
rs4606	RGS2	G	0.23	0.25	0.0340

Cannabis x Gene=Schizotypy  
in 740 sibs

Bonferroni correction

Van Winkel & GROUP, Arch Gen Psychiatry, 2010



SNP	Gene	At-risk paradigm (n=740)				Case-only paradigm (n=801)					
		Distribution (%)	Effect size (β) <sup>†</sup>	SE	P	Risk variant	Distribution (%)	Effect size (β) <sup>#</sup>	Risk variant	SE	P
rs1130233	AKT1	G/G 54.9	.37	.17	.0003	A	G/G 54.9	.13	—	.08	.109
		A/G 39.0					A/G 39.0				
		Explained 19% variance positive schizotypy in exposed sibs									
rs2494732***	AKT1	T/T 32.5	.42	.22	.0001	C	T/T 34.4	.19	C	.07	.005
		Explained 2% variance positive schizotypy in entire sample									
rs673871	LRR1M1	C/C 17.3				C/C 19.0					
		A/A 78.4	1.17	.57	.0001	T	A/A 78.1	-.31	(A)	.17	.067
		A/T 20.0					A/T 21.3				
		T/T 1.6					T/T 0.6				

Van Winkel & GROUP. Arch Gen Psychiatry. In press

### Biological Plausibility?

Beaulieu et al 2007

Ozaita et al 2007

Regulation of PI3K/Akt/GSK-3 pathway by cannabinoids in the brain

Akt-GSK-3 signaling cascade in the action of dopamine

## Hennep and I