Why is Vulnerability so Common?

Vulnerability = Plasticity

Personal vulnerability
Gene Z

ENVIRONMENT A
Illness

ENVIRONMENT B
Resilience

Ecological Variation Drinking Patterns

Spirits
Beer
Wine
Binge
Regular

Impact Alcohol on Genetic Risk CHD

Risk-increasing
Protective

Substance Use and Public Health

The environment and schizophrenia

Perspectives on genetic susceptibility

Behavioral syndromes can be understood as disorders of adaptation to social contexts. Although heritability is often confounded, some is associated with environmental factors such as early life adversity, growing up in an urban environment, minority group position and cumulative use, suggesting that exposure may have an impact on the developing social brain during sensitive periods. Genetic risk, or at least of genetic influence, may also be a factor in the genetic-environmental interaction that determines how expression of vulnerability in the general population may occur or not.
Sz Heritability = 80%

100% genetically identical

50% genetically identical

Common Variants: DNA Sequence Variation (SNP)

1.000.000 mass genotyping approach

Genome-wide Association

1.000.000 SNPs

Common Genetic Variation and Schizophrenia

Explain <5% of heritability….
Heritability Includes Differential Sensitivity

Genetic variation

Sensitivity to environmental causal risk factor

Mental Health

Van Os et al, Nature, In press

GxE: Ecogenetics

Dutch Traditions

10% acute psychotic symptoms

Differential Sensitivity?

Sz (n=13)

Ctr (n=22)

Placebo

2.5mg THC

5mg THC

Why Do Patients Use?

Positive Affect (1-7)?

Negative Affect (1-7)?

THC, Affect, Psychosis

Delespaul, 1995; Myin-Germeys et al, 2001

Why Do Patients Continue: ESM Study

THC, Affect, Psychosis

THC, Affect, Psychosis
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

No Cannabis
Cannabis

34%
66%

51%
49%

Controls
Patients

Cannabis
High PA
(felling good)

Cannabis
NA
(felling bad)

Mood

Beep1
Beep2
Beep3


ESM Self-medication (patients)

Main effects Cannabis on Mood

Effect Size

P<0.01
p=0.071

Differential Sensitivity THC

Interaction: NS

Interaction: p=0.013

Henquet et al, BJPsych, in press
Main Effects Cannabis on Psychotic Symptoms

- Delusions
- Auditory Hall.

Effect Size

0.1
0.05
0
-0.05
NS
NS

Interaction: P<.047

Differential Sensitivity THC

- Delusions
- Auditory Hall.

Effect Size

0.09
0.04
0
0.06
-0.01

Why do patients continue?

Cannabis & Psychosis

<table>
<thead>
<tr>
<th>Country</th>
<th>n</th>
<th>FU</th>
<th>OR (95% CI)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sweden</td>
<td>50,053</td>
<td>5 yrs</td>
<td>2.1 (1.2, 3.7)</td>
<td>narrow</td>
</tr>
<tr>
<td>NL</td>
<td>4,045</td>
<td>3 yrs</td>
<td>2.8 (1.2, 6.5)</td>
<td>broad</td>
</tr>
<tr>
<td>NL</td>
<td>4,045</td>
<td>3 yrs</td>
<td>12.0 (2.2, 64.3)</td>
<td>narrow</td>
</tr>
<tr>
<td>Israel</td>
<td>9,724</td>
<td>4-15 yrs</td>
<td>2.9 (1.3, 3.1)</td>
<td>narrow</td>
</tr>
<tr>
<td>NZ (Chr)</td>
<td>1,265</td>
<td>3 yrs</td>
<td>1.8 (1.2, 2.6)</td>
<td>broad</td>
</tr>
<tr>
<td>NZ (Dun)</td>
<td>1,253</td>
<td>15 yrs</td>
<td>3.1 (0.7, 13.3)</td>
<td>narrow</td>
</tr>
<tr>
<td>Germany</td>
<td>2,436</td>
<td>4 yrs</td>
<td>1.7 (1.1, 1.5)</td>
<td>broad</td>
</tr>
</tbody>
</table>

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

Source of Differential Sensitivity

- 20% uses Cannabis
- G E N E S

Psychometric Measures of Environmental Sensitivity

Dutch National G.R.O.U.P. study: 1096 sib pairs; 590 controls
Dutch G.R.O.U.P. Study

Parents, n=919
Siblings, n=1057
Patients, n=1120
Controls, n=590

Cannabis GxE: G.R.O.U.P.

THC-induced schizotypy (SIS-R)

Positive schizotypy
Negative schizotypy

Controls
Sibs

0.20
0.12

n=1096 sibs
n=590 controls

Association with schizophrenia:
RGS4, NRG1, DTNBP1, PIP5K2A, G72/DAOA, DISC1, HT2A, AKT1, LRRRTM1, FGF2, FGR1, GRMA, PRODH, GRM6, 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, NOQ1, GST-1, GST-2

Epigenetic regulation of environmental influences
MTHFR, MTR, MTRR, DNMT3B, EHMT1, EHMT2, PRDM2

Follow-up Initial GxE Findings

Case-sibling study
Case-only study
Case-control study

Cannabis x Gene=Schizotypy in 740 sibs

Bonferroni correction
Beaulieu et al 2007
Ozaita et al 2007

Biological Plausibility?

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

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

Hennep and I