Schizophrenia: Of neurodevelopment and other things...

Professor David Castle
Chair of Psychiatry, St. Vincent’s Hospital Melbourne
The University of Melbourne

david.castle@svhm.org.au
Kraepelin (1896): dementia praecox, a disorder of young men associated with early onset & a poor outcome.

Bleuler (1911): Schizophrenia: “splitting of the psychic functions” –

1º Symptoms
- Autism
- Affect
- Association
- Ambivalence

2º Symptoms
- Delusions
- Hallucinations
Crow (1980)  
Type I - delusions & hallucinations: associated with dopamine excess.  
Type II - affective flattening, social withdrawal: associated with structural brain abnormalities  

Andreasen (1982)  
Positive - delusions & hallucinations  
Negative - affective flattening & social withdrawal  

Liddle (1987)  
- Reality Distortion  
- Psychomotor Poverty  
- Disorganisation
The Long Term Course of Psychotic Disorders

Figure 2. Graded course of illness in first-admission schizophrenics as indicated by episodes of illness, symptomatology and social impairment at assessments during five years (n=49). Reproduced from Shepherd M, Watt D, Falloon I, Smeeton N. The natural history of schizophrenia: a five-year follow-up study of outcome and prediction in a representative sample of schizophrenics. Psychological Medicine Monograph Supplement 15. Cambridge: Cambridge University Press, 1989.
Figure 1
A Longitudinal Perspective

Figure 1. Early course of schizophrenia: Phases and definitions

- Birth
- Premorbid phase
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- Onset of illness
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- Relapse phase

Vulnerability to schizophrenia

Deficit processes, primary

Deficit processes, secondary

A = duration of untreated psychosis
B = duration of untreated illness
What causes schizophrenia?

“Genetics (well yes, of course) vs Environment, and G/E interactions”

- OC’s
- Early Head Injury?
- Season of birth (late winter, early spring)
- Influenza (2nd trimester) and maybe other infections..
- 1st trimester starvation
- In utero anaemia
- In utero low vitamin D
- Urban birth
- Migration
- Ethnic Minorities
- Cannabis: of this later….
Brain Abnormalities in Schizophrenia

Ventricular size in patients and controls.
- Each point represents average of four measurements on photographs.
Brain Abnormalities in Schizophrenia (2)
“It is proposed that schizophrenia is a neurodevelopmental disorder in which a fixed brain lesion from early life interacts with certain normal maturational events that occur much later”

(Weinberger, 1987)
How can an early brain lesion remain quiescent until adulthood?

- Perinatal hypoxic damage may cause spastic diplegia or hemiplegia in a 2-year-old, while at age four athetosis might develop.

- Temporal lobe hamartomas produce absences and autonomic phenomena in childhood, and not psychic experiences, which are very rare before adolescence.

- Stereotactically lesions of rat brains manifest only with maturity.
Other Clinical Parameters of ND Schizophrenia

- MPA’s - males?
  - FH pos?
- dermatoglyphics
What about sex?

(Castle et al, 1992)

Rates for DSM-III–R schizophrenia, by gender.
“Neurodevelopmental” Schizophrenia

- Early onset
- OC’s
- FH +ive
- Poor premorbid functioning
- Negative symptoms
- Severe course
- MPA’s
- Structural brain abnormalities?
“Mid Life”
Schizophrenia

- Akin to paranoid subtype
- ? protective effect of oestrogens
“Very Late Onset” Schizophrenia

- usual onset >60 years
- vastly more females
- high rates of florid delusions & hallucinations but low rates of disorganisation or negative symptoms
- associations with
  - social isolation
  - premorbid paranoid personality
  - FH schizophrenia (but < early onset cases)
  - sensory deprivation
Psychomimetic Properties of Cannabis Sativa

- Psychoactive moiety is delta-9-tetrahydrocannabinol
- Action via CB1 receptors (Huestis et al, 2001)
- Dopamine release in limbic system
- Blockade of Dopamine D2 receptors blocks some but not all psychotic effects
RED LIGHT DISTRICT à la carte
VIDEO SCREENS 5 FLOORS POOL BAR
Smoking Kills
Psychomimetic Properties of Cannabis Sativa

(Ames et al, 1958): 12 medical volunteers

- alteration in sense of self
- altered sense of passage of time
- euphoria
- transient paranoid ideation
- visual hallucinations (eyes closed)

(Isbell et al, 1967): delta-9-THC in human subjects

- Dose-response relationship
- Some idiosyncratic response at low dose
Psychosis-proneness and cannabis

(Verdoux et al, 2003)

- Experience sampling
- Acute effects of cannabis more extreme in people with “psychosis proneness”
Cannabis Psychosis

- Numerous reports of short-lived psychosis bearing temporal relationship to cannabis ingestion.

- Hypomanic features with excitement and hallucinations; negative symptoms rare.

- ? Whether discrete entity or precipitation of psychosis in vulnerable individuals
Cannabis-induced Psychosis & Subsequent Schizophrenia

(Arendt et al, 2005)

- 535 patients with cannabis-induced psychosis
  - followed for 3 years
  - 44.5% schizophrenia spectrum disorders

Note: - young males most vulnerable
  - diagnosis > 1yr in 47.1% of patients
Cannabis and the Course of Schizophrenia (1)

- High rates of cannabis use in schizophrenia patients (~50%)

- Use associated with more severe symptoms, greater chance of relapse, and worse outcome.
Cannabis and the Course of Schizophrenia

(Negrete et al, 1986): 137 (25 cannabis users) patients with schizophrenia over 6 months.

Cannabis patients:
- higher relapse rate
- more delusions/hallucinations

(Linszen et al, 1994): 24 cannabis users vs 69 non users

cannabis users:
- more an earlier relapse
Mental Health Institute

Keep off the grass
Motivation for Use

Why such high rates of use?
Spencer, Castle, Michie (2002); Schizophrenia Bulletin 28:233-247

- Determine reasons for substance use amongst people with psychosis
- Determine the influence these motives have on quantity, context, problems and dependence
- Determine the role motives play in mediating the relationship between psychotic symptoms and substance use
Coping with Unpleasant Affect – 37% of variance

- Because it helps when you feel nervous
- It helps when you feel depressed
- To forget your worries
- To feel more motivated
- To make it easier to sleep
- To help me concentrate
- Because you feel more self confident and sure of yourself
- To relieve boredom
- To decrease restlessness
- To slow down racing thoughts
Why Do People With Psychotic Illness Abuse Drugs? (3)

Conformity & Acceptance – 8% of variance

- So you won’t feel left out
- To be liked
- To help you talk to others
- To be sociable
- To be part of a group
Why Do People With Psychotic Illness Abuse Drugs? (4)

Relief of positive symptoms and side effects – 6%

- To get away from the voices
- To reduce side effects of medication
- Because your friends pressure you to do it
- To decrease suspiciousness and paranoia
Referred and Assessed for Eligibility (n=83)

Excluded as did not meet inclusion criteria. Refused to participate (n=10)

Randomised (n=63)

Allocated to intervention group (n=32)
Received allocated intervention (n=32)

Lost to follow-up
- Left the metropolitan area (n=3)

Analysed (n=29)

Allocated to control group (n=31)
Received allocated intervention (n=31)

Lost to follow-up
- Unable to contact (n=3)

Analysed (n=29)
Drug Abuse Screening Test (DAST)
Severity of Dependence Scale

SDS – Score of 4+ is indicative of dependence

<table>
<thead>
<tr>
<th></th>
<th>Intake</th>
<th>3 months</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Treatment</strong></td>
<td>7.42</td>
<td>3.85</td>
</tr>
<tr>
<td><strong>Controls</strong></td>
<td>6.75</td>
<td>5.20</td>
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</table>

**Interaction Effect**
Time p<0.01

n = 28
n = 29
Does Cannabis Cause Schizophrenia?

Bradford Hill’s criteria for causality:

- **Strength** of association
- **Consistency** of association
- **Specificity** of association
  - specificity of **cause**
  - specificity of **effect**
- **Temporality** of association
- **Biological gradient**
- **Experimental evidence**
- **Plausible hypothesis**
Swedish Conscript Study

(Andreason et al, 1987)

45,570 male Swedish conscripts 1969/70

questionnaire re background & drugs
(7% refusal rate on drug question)

psychological assessment

follow-up through 1987
(register of psych care; death register

cannabis best predictor (RR 2.3) of later sz after

- psych Dx at conscription
- parental divorce
Dose – Response Relationship

Rates of schizophrenia after different levels of cannabis consumption
NEMESIS Study

(Van Os et al, 2002)

- 5104 m & f Dutch general population (59 had psychosis) assessed at 1 and 3 years
- Cannabis use at baseline associated with psychotic symptoms (RR 2.76; 1.2 - 6.5)
- Dose-response effect
- Confounders controlled for:
  - Age & sex
  - Marital status
  - Urban dwelling
  - Ethnicity & discrimination
Dunedin Study

(Arsenault et al, 2002)

- Cohort study 1037 males & females followed from birth to 26yrs (96% follow-up)
- Cannabis use at 15yrs associated with later schizophreniform psychosis (10% vs 3%); RR 3.12 (0.7 – 13.3)
- Confounders controlled for:
  - social class
  - prior psychotic symptoms (age 11yrs)
- Interaction between psychotic symptoms at age 11, Cannabis use at 18, and psychotic symptoms at 26
An Amotivational Syndrome? (2)

(Tennant & Groesbeck, 1972)

Study of US soldiers in West Germany (45% habitual cannabis users)

- no discernible effect on 392 subjects of smoking up to 10g per month

- 110 men smoking 50-600g month (500-6000 joints):
  - apathy
  - lethargy
  - impaired concentration
  - impairment of STM

(9 followed up for 2 years – 6 showed no residual Sx)

conclusion: reversible sub-acute encephalopathy
SPIDERS ON DRUGS

MARIJUANA

BENZEDRINE

CAFFEINE

EXCLUSIVE OFFER!

FREE “Spiders on Drugs” T-shirt with every subscription!

NewScientist
A Longitudinal Perspective

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Is it possible predict who will go on to develop psychosis?

- Signs and symptoms very non-specific
- Transition rates very dependent upon sampling base (law of diminishing returns)

Yung et al, 2005

- Much reduced transition rate in more recent samples

Yung et al, 2010

- 115 UHR patients (from 464 eligible) + 78 ‘monitored’ (not randomised)
- Randomised to CT + risperidone, CT + PBO, supportive care + PBO
- 6 month relapse rates:
  - CT + risperidone: 8 (7%)
  - ‘monitored’ group: 4 (5%)
  - No difference in relapse between any group
The Long Term Course of Psychotic Disorders

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<tr>
<th>Group</th>
<th>Description</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>One episode only - No impairment</td>
<td>22%</td>
</tr>
<tr>
<td>2</td>
<td>Several episodes with no or minimal impairment</td>
<td>35%</td>
</tr>
<tr>
<td>3</td>
<td>Impairment after the first episode with subsequent exacerbation and no return to normality</td>
<td>8%</td>
</tr>
<tr>
<td>4</td>
<td>Impairment increasing with each of several episodes and no return to normality</td>
<td>35%</td>
</tr>
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180 1st episode patients followed over 3 years
57% remitted but 43% at least one relapse
Special intervention benefit for 60%, but 40% “treatment reluctant” and did badly
Any gains made were lost after intervention stopped
Predictors of poor outcome
  - lack of insight (OR 3.00)
  - non-compliance (OR 2.23)
  - cannabis use (OR 2.28)
LEO, London (Craig et al, 2004)

- **RCT vs. TAU**
- **18 month** outcomes better for global functioning, hospitalisation rates, vocational and social parameters
- no difference in relapse rates after controlling for baseline ethnicity and prior psychotic episodes
- **5 year** follow-up gains lost: indeed, once intervention stopped, patients did even worse than controls
OPUS, Denmark (Bertelsen et al, 2008)

- RCT vs TAU
- 2-year outcomes better for homelessness, psychotic symptoms, substance use, global functioning
- High attrition rates and non-blinded assessments = bias
- 5-year follow-up gains lost in terms of symptoms, substance use and global functioning
EPPIC Australia (Henry et al, 2010)

- 723 1st episode patients followed over 7 years; no control group
- Schizophrenia and schizophreniform combined (n=347)
- Only 22% achieved social/vocational recovery and only 15% achieved social, vocational and symptomatic recovery
‘Faith before facts’ (Bosanac, Patton, Castle, 2010)
‘Emperors new clothes’ (Castle, 2010)

- Seems very clear any early gains are lost
- Puts paid to ‘prevention’ assertion
- Merely shows good treatment good for patients!
- No justification for youth focus (many patients onset after 25)
- No justification for specialised services, indeed:
  - Can achieve good fidelity using integrated model (Petrakis et al, 2010)
  - Silo effect
  - Un-useful transition problems to adult services
Factors Associated with a Poor Outcome in Schizophrenia

<table>
<thead>
<tr>
<th>Factors Not Subject to Amelioration</th>
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<tbody>
<tr>
<td>male gender</td>
</tr>
<tr>
<td>early onset of illness</td>
</tr>
<tr>
<td>strong family loading for schizophrenia</td>
</tr>
<tr>
<td>Insidious onset of illness</td>
</tr>
<tr>
<td>long prodrome</td>
</tr>
<tr>
<td>poor pre-morbid functioning</td>
</tr>
<tr>
<td>lack of affective symptoms at onset</td>
</tr>
<tr>
<td>prominent negative symptoms at onset</td>
</tr>
<tr>
<td>lack of obvious precipitating factors at onset</td>
</tr>
<tr>
<td>structural brain abnormalities (somewhat inconsistent findings)</td>
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</tbody>
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(Castle & Buckley, 2008)
**Factors Associated with a Poor Outcome in Schizophrenia**

Factors Potentially Addressed by Optimal Clinical Care

- long duration of untreated psychosis (debated)
- suboptimal treatment of psychotic symptoms
- suboptimal treatment of comorbid symptoms
- poor medication adherence
- medication side effects (e.g. neuroleptic-induced deficit syndrome)
- substance abuse
- suboptimal family environment

*(Castle & Buckley, 2008)*
What Can Be Done to Optimise Outcomes? (c)

Individual Issues Needing to be Addressed

- Persistent symptoms
- Comorbid mood & anxiety disorders
- Substance abuse
- Medication adherence
- Relationships
- Vocational
- Healthy lifestyle
Catchment Area
“Very early intervention”

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Vulnerability to schizophrenia

Deficit processes, primary

Deficit processes, secondary

A

B
Very early intervention?

How early is really early enough?

- Risk begins at conception
- Poor antenatal and postnatal care of mothers with psychosis
- Parenting issues, engagement issues, etc etc.

Gilmore et al, 2010
- Structural brain abnormalities demonstrable even as infants (males)

McGrath, 2010
- Clearer determination of environmental risk factors opens up potential for ‘prevention’

University of Melbourne initiative (Castle, Everall, Judd, Pantelis, etc.)
- Proposed prospective study: “Nurturing the Vulnerable Brain”
- Multifaceted approach addressing antenatal, postnatal, parenting etc.
- Proximal and distal outcomes (biological, neurobehavioural, psychosocial, cognitive, etc.)
Very early intervention?

- Nurturing the vulnerable brain