Cannabis and schizophrenia

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BENITO MENNI
Complex Assistencial en Salut Mental

Does there have to be a neurochemistry of psychosis?

- Psychotic symptoms come and go
  - Ameliorated by drug treatments
  - Exacerbated by some drugs of abuse
- Psychotic symptoms do not resemble symptoms of neurological disease
  - Except perhaps epilepsy
- In a general sense psychotic symptoms do resemble the effects of certain drugs
  - Opiates, hallucinogens, anticholinergic drugs

The dopamine hypothesis
Heroic failure

- Neuroleptic drugs are dopamine antagonists
  - All drugs which are effective in schizophrenia block dopamine receptors
- Amphetamine is a dopamine agonist
  - Known to cause psychosis since the 1930s

Does amphetamine psychosis resemble schizophrenia?

- 42 patients who developed psychotic states while taking amphetamine.
  - 34 using drug regularly
  - 8 had taken only a single large dose
- Typically delusions of reference and persecution ± auditory hallucinations in clear consciousness
  - Other hallucinations uncommon and/or minor.
  - Formal thought disorder evident in some cases
  - No mention of catatonic symptoms or negative symptoms
- In 77% recovery within a week
  - Almost all the remaining cases remitted within 2-4 weeks

(Connell, 1958)

Does everyone who takes amphetamine develop psychosis?

- Griffith et al (1968, 1972)
  - 4/4 previous users with no history of psychosis developed delusions after 1-5 days
- Angrist and Gershon (1970)
  - 2/4 previous users with no history of psychosis developed psychosis (FTD in one case)
  - Other two minor symptoms only
- Chen et al (2005)
  - 174/435 (40%) of methamphetamine users in custody had a history of psychosis
  - Rate sig. higher in those with family history of schizophrenia (7% vs 1.9%)

The decisive test of the dopamine hypothesis

Radioactively label Neuroleptic drug

Inject into drug-naive schizophrenics and controls

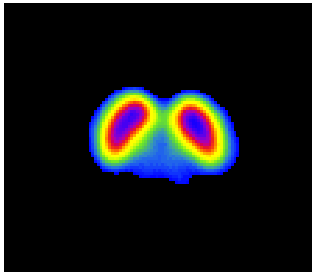


Image DA receptors

- The Hopkins study
  - 10 drug-naive patients + 11 age and sex matched controls
  - D2 receptor binding 41.7 pmol/g vs 16.6 pmol/g

    (Wong et al, 1986)
- The Karolinska study
  - 15 drug-naive patients + 14 age and sex matched controls
  - D2 receptor binding 25.1 pmol/g vs 24.6 pmol/g

    (Farde et al, 1987)
- Further studies on drug-naïve patients
  - All negative

    (Martinot et al, 1990, Hietala et al, 1994; Pilowsky et al, 1994)

The glutamate hypothesis
A cautionary tale

'Although hallucinations, agitation, paranoia, and paranoid delusions occur after PCP administation, the most striking and consistent behavioral effects of PCP are alterations in body image, disorganization of thought, negativism and apathy.'

'The symptoms…are thus similar to the "four A's" proposed by Bleuler to represent the primary symptoms of schizophrenia."

'PCP interacts selectively with a specific binding site (PCP receptor) that is associated with the N-methyl-D-aspartate (NMDA)-type excitatory amino acid receptor.'

(Javitt & Zukin, 1991)

Does phencyclidine cause psychosis?

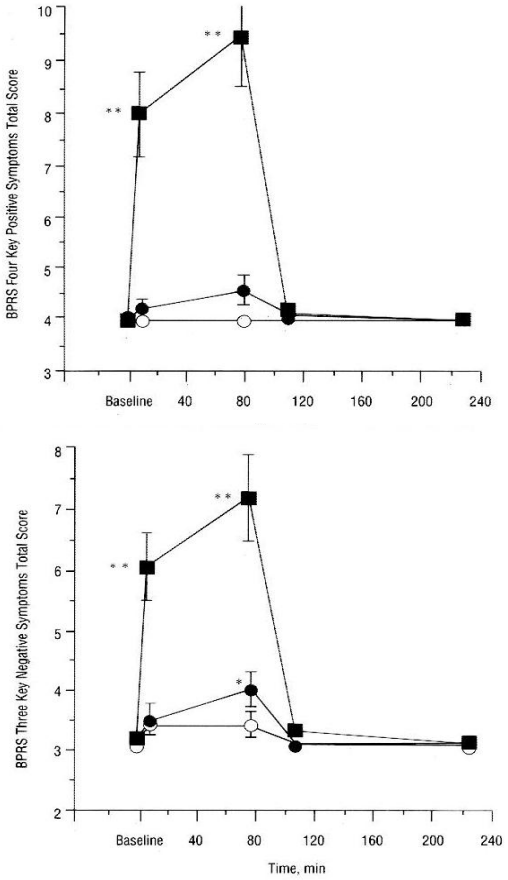
- Delirium
  - Confusion, often with delusions, hallucinations, disturbed behaviour
- Psychotic states resembling schizophrenia
  - Apparently in clear consciousness
  - Could last several weeks
  - Mania also documented

(Pearlson et al, 1981; Javitt & Zukin, 1991)

- Catatonia
  - Standing motionless and stiff, eyes open staring blankly, arms or head in bizarre positions.
  - Many mute, some showed echolalia, or would hear a word or phrase and repeat it continuously

(McCarron et al, 1981)

A modern study of ketamine in normal volunteers



Dose dependent increases in positive and negative scores on the BPRS

'Formal thought disorder was also noticeable on the high-dose ketamine day with loosening of association, derailment, stilted speech, and other alterations'

(Krystal et al, 1994)

Lone voices of doubt

- Body image disturbances and illusions would tend to be rated on the 'hallucinatory behaviour' item of the BPRS….Thinking may become tangential and circumstantial on ketamine, but this could be said of many drugs with intoxicating effects.

  (Deakin, 2000)

- No study of ketamine in normal volunteers has ever produced auditory hallucinations

  (Murray, 2009)

A phenomenological study of ketamine in normal subjects

- Cabinets don't look hard, everything looks rounded, edges not sharp.
- Colours are blurred into one
- You appear like a 2D image
- My legs look very big and funny shaped, like another person's.
- Things feel more liquid when I touch them.
- Disconnected from arms.
- Feels as though my arms are crossed when by sides.
- Feeling like I am made of sandpaper.
- I feel like I'm shrunken inside.
- Like a statue, sitting in one position, frozen. I couldn't move when I tried to.
- Time stopped, feels like I've been here for hours.

(Pomarol-Clotet et al, 2006)

The ketamine experience, continued

- No subject showed hallucinations
  - As in all other studies
- No subject showed convincing thought disorder
  - Only circumstantiality and manifestations of poor concentration
- Reduced speech and 'flattened' affect in half
  - May have been due to sedation
- Referential ideas in half
  - 'It was like they were saying one thing but what they're actually trying to do is discover what's going on somewhere else.'
  - 'People at the scanner were maybe spies. I was convinced.'
  - 'I feel like I'm not being told everything. Something's going to happen and I haven't been told.'
  - 'It's like that film [The Truman Show]'

Glutamate agonists as a treatment for schizophrenia

- Meta-analysis of18 trials of glycine or d-cycloserine
  - No effect on positive symptoms
  - Effect of glycine on negative symptoms (ES -0.66)

(Tuominen et al, 2005)

- Multicentre trial of glycine/d-cycloserine in 157 schizophrenic patients
  - No effect on negative symptoms for either drug

(Buchanan et al, 2007)

- Large multicentre trial of metabotropic glutamate receptor, LY2140023
  - As effective as olanzapine

(Patil et al, 2007)

- Further multicentre trial of LY2140023
  - No better than placebo

The cannabis connection

Third time lucky?

'Andreasson et al (1987), who examined almost 50,000 young Swedish male conscripts, found that men who had smoked cannabis by the age of conscription had double the risk of schizophrenia in the ensuing 15 years.

In addition, they found that men who had smoked cannabis on at least 50 occasions were six times more likely to later receive a diagnosis of schizophrenia.

These findings were confirmed in a follow-up study of the cohort 25 years later (Zammit et al, 2002).'

(Murray et al, 2007)

The state of the evidence
Meta-analysis of 7 studies

- Increased risk of any psychotic outcome[1] in individuals who had ever used cannabis
  - OR =1·41 (CI 1·20–1·65).
- Risk greater in people who used cannabis most frequently
  - OR = 2·09 (CI 1·54–2·84).
- Risk of psychotic disorder[2] also increased
  - OR = 2·58, 1·08–6·13
- Findings for depression, suicidal thoughts, and anxiety less consistent

(Moore et al, 2007)

[1]studies pooled under the assumption of a continuum of psychosis
[2]presence of psychotic symptoms with concurrent evidence of impaired functioning

Can acute cannabis intake cause psychosis?

- 12 soldiers in Vietnam with *disorientation, impaired memory, confusion, reduced attention span* and disordered thinking with labile effect and hallucinations. The symptoms resolved within a week.

  (Talbott & Teague, 1969)

- Sudden onset of *confusion*, generally associated with delusions, hallucinations (usually visual) and emotional liability ... *amnesia*, *disorientation*, depersonalisation and paranoid symptoms.

  (Chopra & Smith, 1974)

- Grandiosity, excitement, hostility, uncooperativeness, *disorientation*, hallucinatory behavior and unusual thought content.

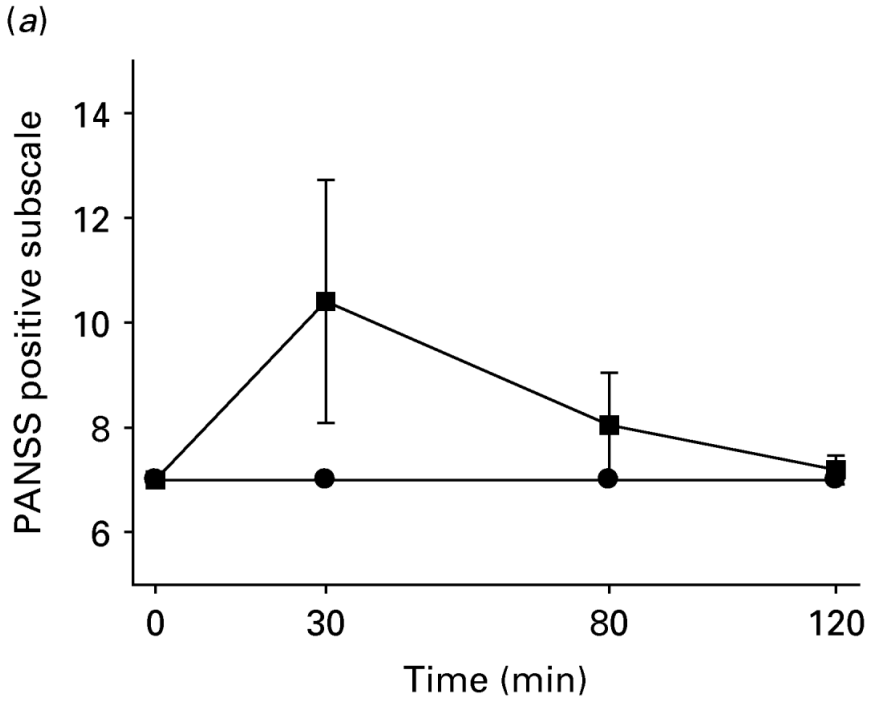
  (Chaudry et al, 1991)

Psychotic symptoms caused by ‘skunk’

‘All three described psychotic experiences after smoking one "regular sized joint." These consisted of paranoid delusions and visual illusions in all three cases, visual and auditory hallucinations in two cases, and pronounced derealisation and depersonalisation together with thought broadcast in one case. Two users described associated severe anxiety. The experience lasted for a variable period (half an hour, one day, and three days).’

(Wylie et al, 1995)

THC in normal volunteers



- 19 healthy subjects given IV THC or placebo under double-blind conditions
- PANSS positive scores increased by a mean of 3.7 points (range 0–17), returning to baseline levels by 120 min

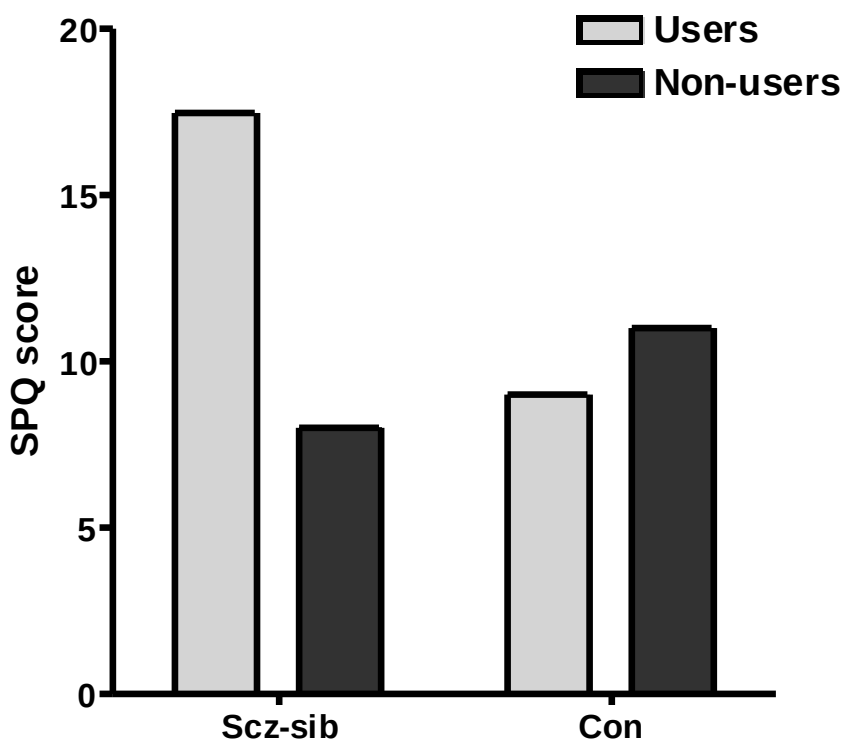
(Morrison et al, 2009)

What volunteers actually report

- Delusions
  - 'I thought you could read my mind, that's why I didn't answer'
  - 'I thought you all were trying to trick me by changing the rules of the tests to make me fail'
  - 'I thought you were turning the clock back to confuse me'
  - 'I could hear someone on typing on the computer ...and I thought you all were trying to program me'
  - 'I felt as if my mind was nude'
  - 'I thought you all were giving me THC thru the BP machine and the sheets`
  - 'I felt I could see into the future...I thought I was God'
- Perceptual changes
  - 'The AC that I couldn't hear before suddenly became deafening`
  - 'I thought I could hear the dripping of the i.v. and it was louder than your voice`
- Changes in thinking
  - 'I couldn't keep track of my thoughts... they'd suddenly disappear'
  - 'It seemed as if all the questions were coming to me at once... everything was happening in stacatto'
  - 'My thoughts were fragmented... the past present and future all seemed to be happening at once'

(D'Souza et al, 2004)

Cannabis and family history of psychosis



- 36 non-psychotic siblings of adolescents with schizophrenia
  - 72 controls
  - 25 adolescents with ADHD
- Rated using Schizotypal Personality Questionnaire
  - Also Strengths and Difficulties Questionnaire, GAF

Endocannabinoid: a candidate for the neurochemistry of schizophrenia?

- There is at least one endogenous cannabinoid (anandamide)
- Released by dendrites, acts by retrograde signalling
- Cannabinoid (CB1) receptors are localised on axons and presynaptic terminals of 'classical' neurotransmitters
- High concentrations in basal ganglia and cerebellum, also neocortex, olfactory brain and ?hippocampus
- Interacts with glutamate, dopamine, GABA, serotonin and ACh
- Roles in nociception, movement, memory, neuroendocrine regulation and possibly brain development

Why doesn't cannabis cause schizophrenia more often?

- Cannabis affects other neurotransmitter(s) relevant to schizophrenia
  - eg dopamine, ?glutamate
- Cannabis interacts with some aspect of the genetic predisposition to schizophrenia

(Henquet et al, 2008)

- Cannabis interferes with brain maturational processes in adolescence

(DeLisi, 2008)

- Cannabis worsens a putative cognitive endophenotype of schizophrenia

(Solowij & Michie, 2007)

Murray on cannabis and psychosis

- At first, cannabis use produces euphoria and other typical effects
- After a period of regular use, however, in certain individuals, the effect changes from euphoria to depression
- He/she becomes more withdrawn, starts seeing significance in neutral events
- Full-blown psychosis supervenes
  - And at this stage the process becomes irreversible

Status of neurochemical theories of schizophrenia, 2008

	Dopamine	Glutamate	Endocannabinoid
The drug induces a schizophrenia-like state	√	**X**	√
Drugs with opposite effects improve schizophrenic symptoms	√	**?**	**-***
There is evidence of corresponding neurochemical abnormality in the schizophrenic brain	**X**	**X**	**-***

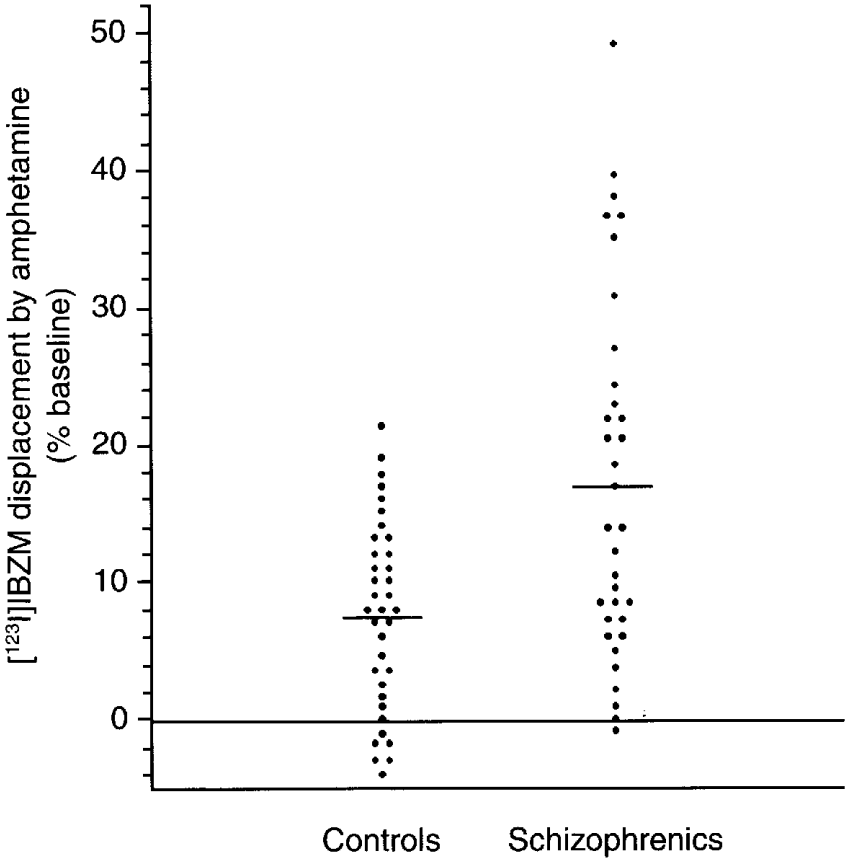
*No substantive evidence either way

Is glutamate abnormal in the schizophrenic brain?

Study	Sample	Assay	Prefrontal cortex	Temporal cortex	Hippocampus	Striatum
Deakin et al (1989)	14 patients 14 controls	[3H] Asparate	increased	normal		
Akbarian et al (1996)	15 patients 15 controls	mRNA levels	normal	normal		
Humphries et al (1996)		mRNA levels	?			
Sokolov et al (1998)	21 patients 9 controls	mRNA levels	decreased			
Kornhuber et al (1989)		[3H]MK-801*	normal	normal	normal	Increased in putamen
Noga et al (1997)	8 patients 8 controls	[3H]MK-801*	-	-	-	normal
Wiessman et al (1991)		[3H] * TCP	?normal	?normal		normal
Simpson et al (1989; 1992)	19 patients 22 controls	[3H] Asparate *	?increased		normal	?decreased
Kerwin et al (1990)	7 patients 8 controls	3H glutamate			normal	
Ishimaru et al (1993)	13 patients 10 controls	[3H]glycine*	normal	normal		
Mueller et al (2004)	15 patients 15 controls	mRNA	increased	normal		
Gao et al (2000)	12-18 patients 13-19 controls	mRNA			normal	
Dracheva et al (2001)	26 patients 13 controls	mRNA	?normal			

(Similar findings for kianate and AMPA receptors)

Hope for the dopamine hypothesis?



- Drug free schizophrenic patients release 2x more DA in response to amphetamine challenge

  (Laruelle et al, 1996)
- Correlated with increase in positive symptoms
- Replicated in two further studies

  (Breier et al, 1997

  Abi-Dargham et al, 1998)
- *But* only 7 out of 34 patients in Laruelle´s combined sample were drug-naive