

Responses to
IV THC:
*An overabundance of
meaningful co-incidences.*

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The Club de Haschischins

‘Hashish gives to whoever submits to its influence the power to study in himself the mental disorders that characterise insanity...’

Moreau De Tours JJ. *Du Haschich et de l'Aliénation Mentale* (1845)



“An indication that the drug is beginning to work...is uncontrollable laughter... the most trivial remark assumes new meaning”.

“In this state, one final supreme thought breaks into consciousness – ‘I have become God’ ”

Baudelaire C. *Les Paradis Artificiels*

(1860)



Cannabis in the English-speaking world...



Cannabis in the English-speaking world...



Does cannabis increase the risk of psychotic illness ?

Country	N	Follow up	OR	Study Design	Reference
USA	4,494	NA	2.4	Population based	<i>Tien et al, 1990</i>
Sweden	50,053	25 yrs	2.1	Cohort	<i>Andreasson et al, 1987 Zammit et al, 2002</i>
Netherlands	4,045	3 yrs	2.8	Population based	<i>Van Os et al, 2002</i>
Israel	9,724	4-15 yrs	2.0	Population based	<i>Weiser et al, 2002</i>
New Zealand (Christchurch)	1,265	3 yrs	1.8	Birth-cohort	<i>Fergusson et al, 2003</i>
New Zealand (Dunedin)	1,253	15 yrs	3.1	Birth-cohort	<i>Arsenault et al, 2002</i>
Netherlands	1,580	14 yrs	2.8	Population based	<i>Ferdinand et al 2002</i>
Germany	2,436	4 yrs	1.7	Population based	<i>Henquet et al, 2005</i>
United Kingdom	8,580	18 months	1.5	Population based	<i>Wiles et al, 2006</i>

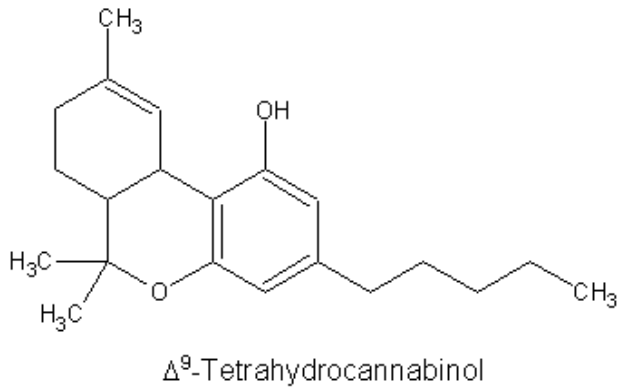
Murray RM et al *Nature Rev Neurosci* (2007)

Cannabis sativa...

Contains over 60 cannabinoid molecules.

THC

Δ^9 -Tetrahydrocannabinol

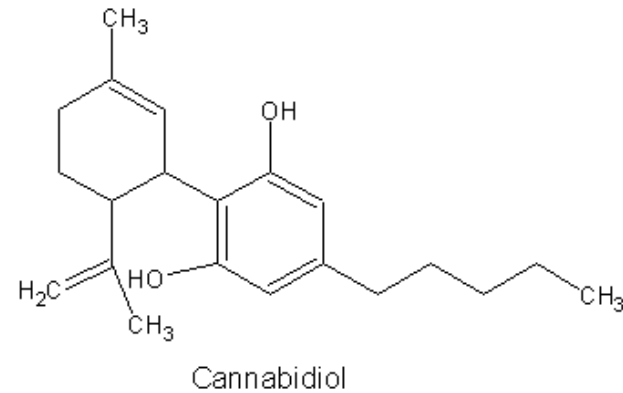


Pro-psychotic

Anxiogenic

CBD

Cannabidiol



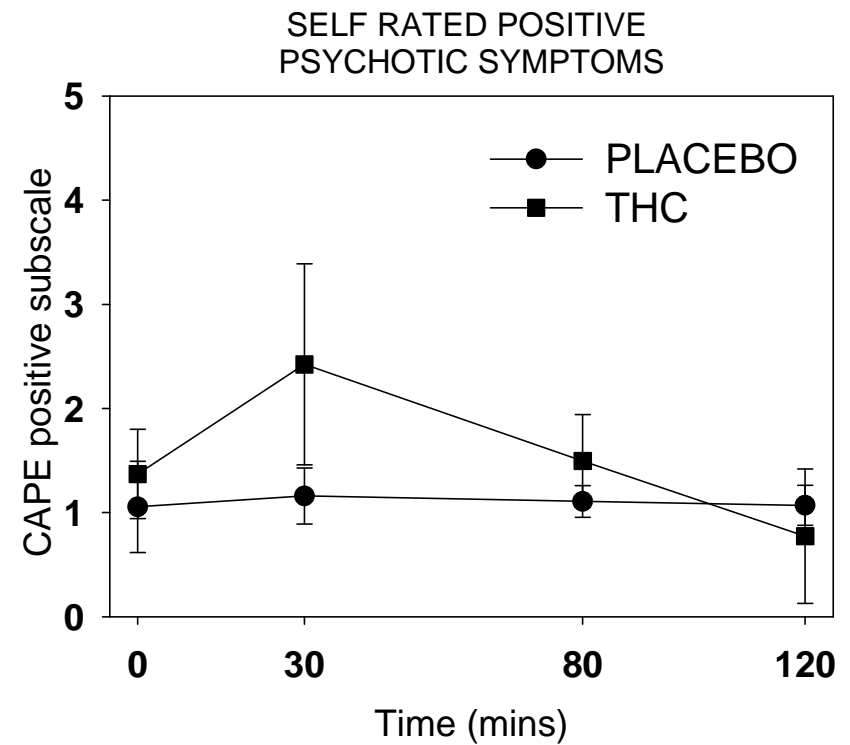
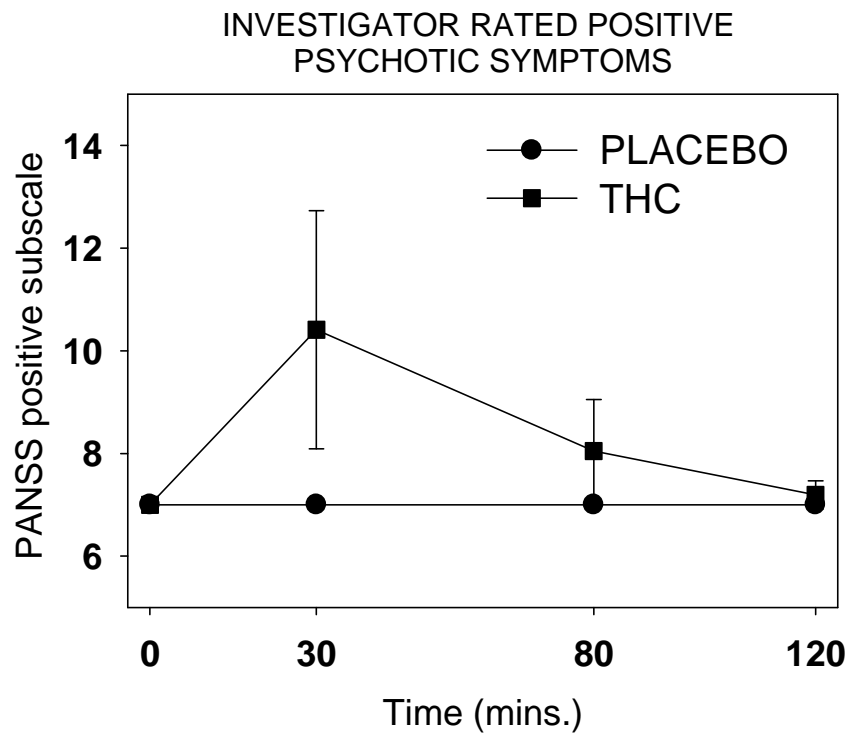
Anti-psychotic ?

Anxiolytic

The effects of pure THC...

Intravenous THC 2.5 mg

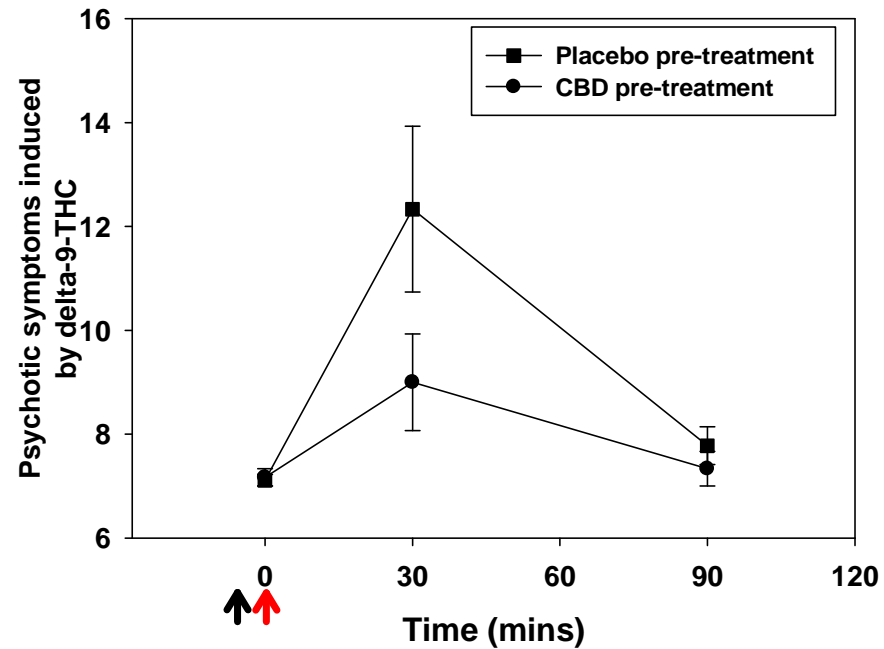
n=22



The effects of pure THC...

Following pre-treatment with placebo or CBD

Preliminary findings



$n=6, p=0.1$

The effects of pure THC...

“A feeling of great insight...I must write down this fantastic theory.... of course it's all nothing”

.....

“Every occurrence, cough, object, test has deeper and connected meaning...All deliberate, planned....some sort of prank, to make a fool of people.”

.....

“It was like you guys were having a conversation outside, saying- ‘the dude in there is off his rocker’ ”

.....

“It was threatening and sinister. I'm still a bit unsure of you. Your re-assurances sound insincere.”

Stimulants and ketamine can also evoke ideas of reference, suspiciousness and delusions.

Hallucinations are not prominent in ketamine or THC models. (but are part of stimulant sensitization).

Connell P *Maudsley monograph* 1958.

Griffith JD et al *JAMA* 1968.

Pomarol-Clotet E et al *BJ Psychiatry* 2006.

Krystal J et al *Arch Gen Psych* 1994

Mckenna PJ 2006

“Patients feel uncanny and there is something suspicious about everything. Everything gets a new meaning.”

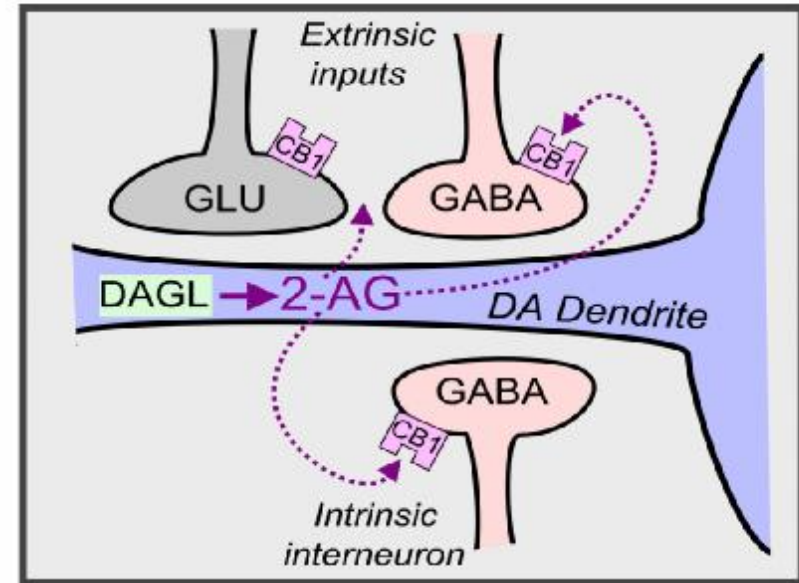
Jaspers K *General Psychopathology* 1913

Mechanisms?

Mechanisms?

- Endocannabinoids modulate the excitability of midbrain dopamine neurons.
- THC appears to switch off inhibitory inputs to dopamine neurons.

Is the increased excitability of dopamine neurons important in THC-psychosis?



Mechanisms?

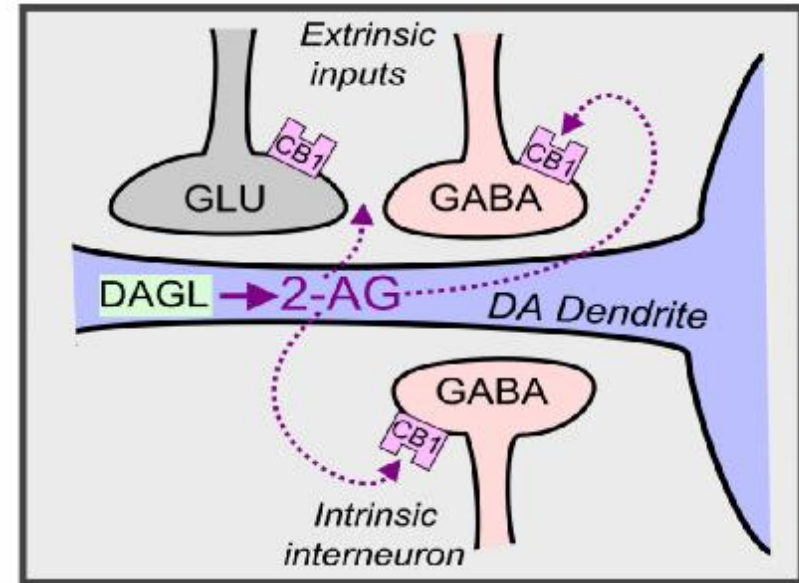
But:

-D2 antagonists were unable to inhibit
THC-elicited acute psychosis in
patients & in healthy controls.

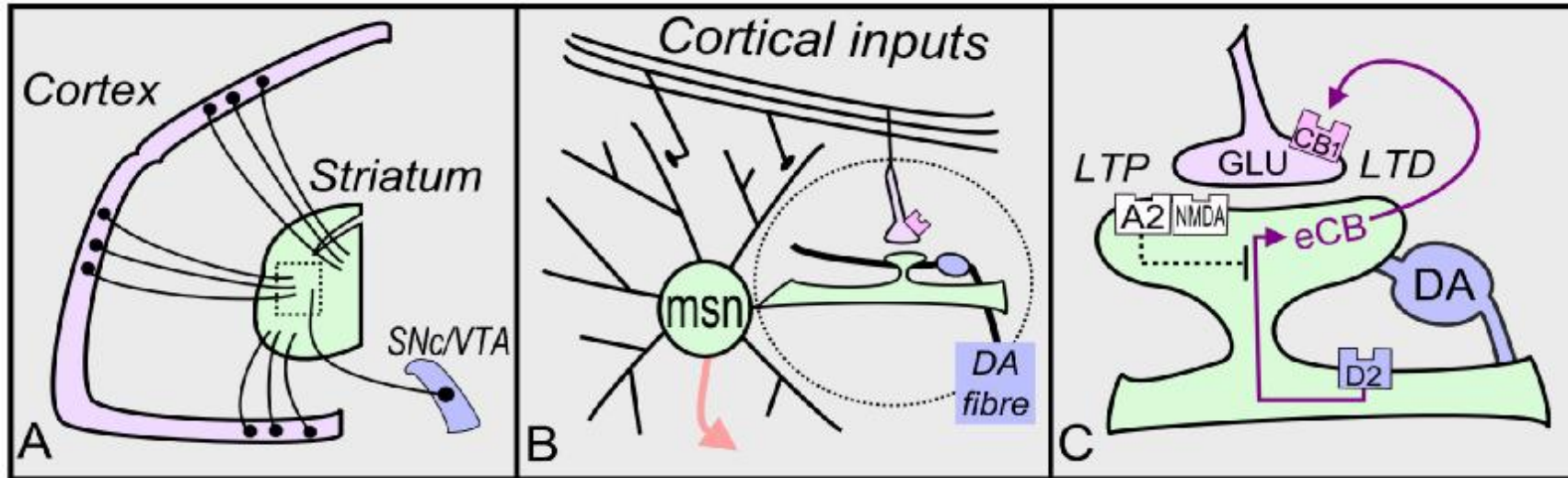
D'Souza DC et al.

Biol Psychiatry 2005,

Psychopharmacology 2008.



Mechanisms?



Dopamine regulates plasticity in the striatum via the release of endocannabinoids.

Kreitzer AC & Malenka RC *Nature* 2007

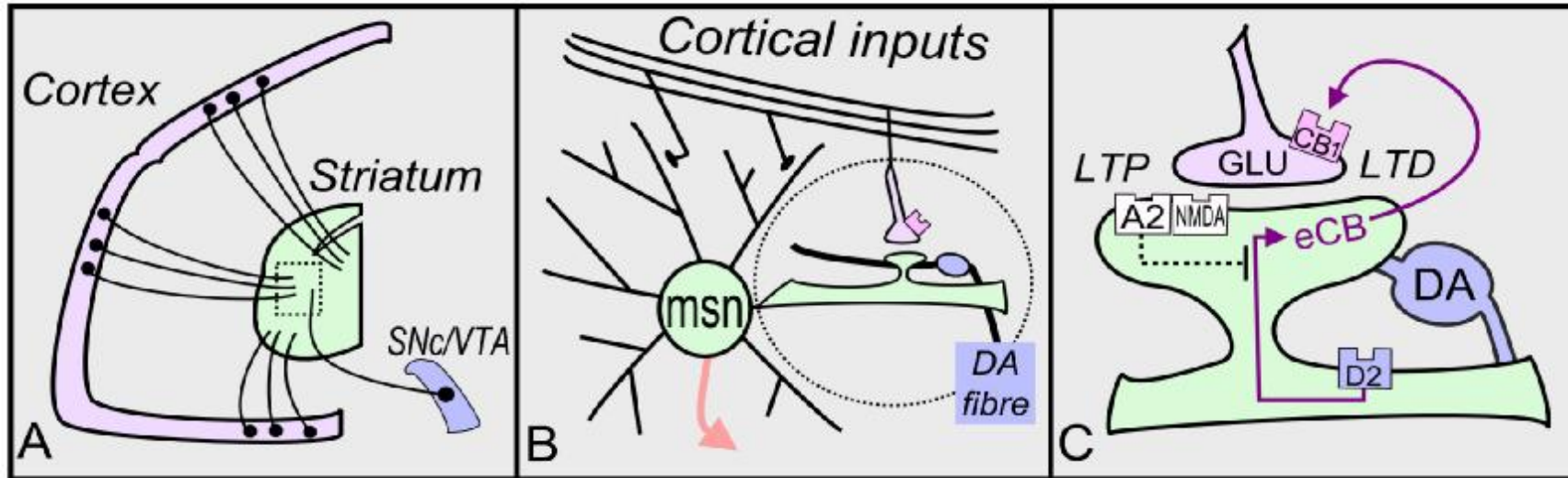
Yin HH & Lovinger DM *PNAS* 2006.

Shen W et al *Science* 2008.

Are the pro-psychotic effects of excess D2 stimulation mediated via retrograde endocannabinoid signaling?

Morrison PD & Murray RM
Schizophrenia Bulletin (July 2009)

Mechanisms?



- Cannabidiol (CBD), which uncouples CB1 receptors from their intracellular effectors inhibits L-DOPA induced psychosis.

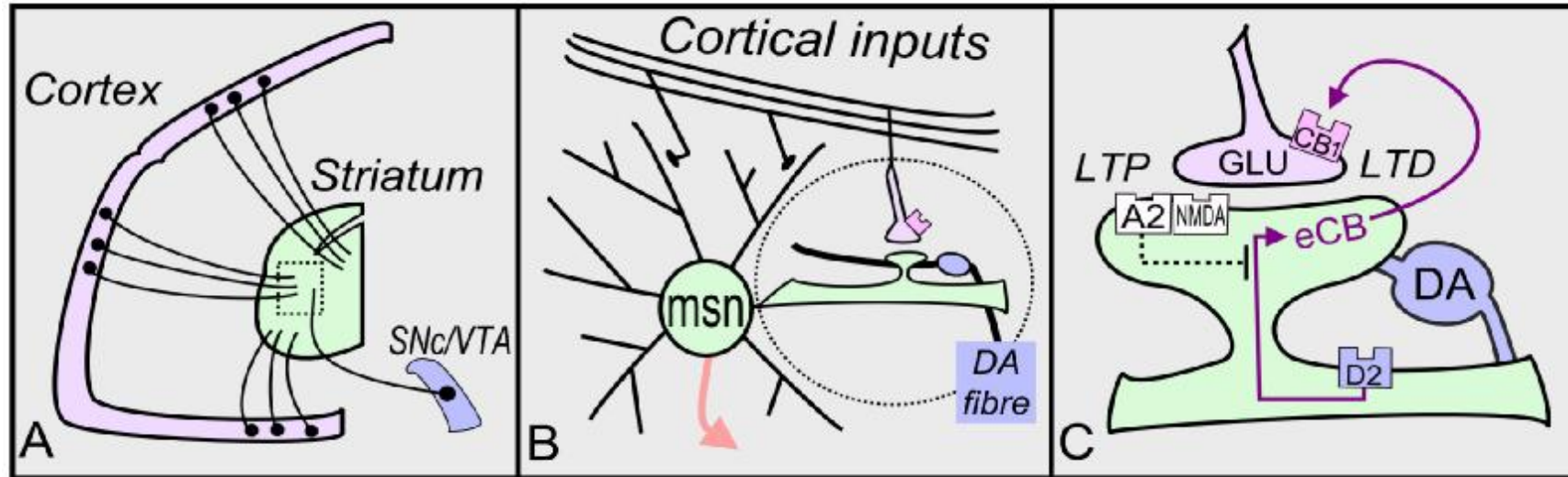
Zuardi A et al *J Psychopharmacol.* 2008.

- Microinjection of the potent CB1 antagonist (SR147778) into the ventral striatum inhibits sensitization to methamphetamine.

Chiang YC, Chen JC *J Neurochem.* 2007.

Morrison PD & Murray RM
Schizophrenia Bulletin (July 2009)

Mechanisms?



-In patients, dipyradomole was shown to augment the anti-psychotic properties of haloperidol.

Akhondzadeh S. J et al *Clin Pharm Ther.* 2000.

-Conversely, adenosine receptor antagonists, such as the methylxanthines, can induce a transient exacerbation of psychotic symptoms.

Lucas PB et al *Biological psychiatry.* 1990.

Zaslove MO et al *Br J Psychiatry.* 1991.

Morrison PD & Murray RM
Schizophrenia Bulletin (July 2009)

Mechanisms?

-MSNs compete with each other via lateral inhibition.

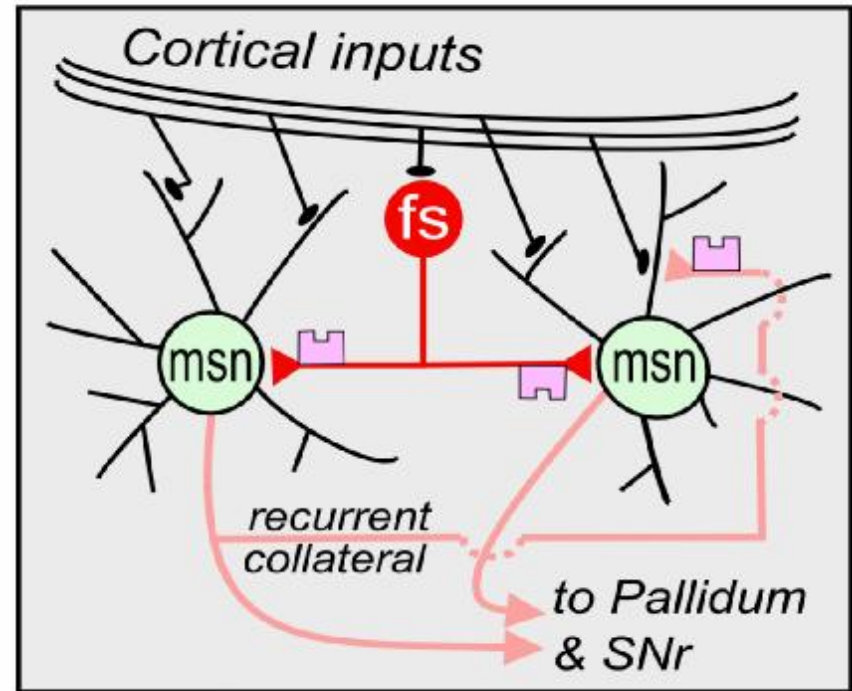
Wickens JR et al *Prog Brain Res* 2007.

-Endocannabinoids relax mutual inhibition between MSNs.

Freiman I et al *J Physiol* 2006.

-eCBs are vital for habit learning

Hilario MR et al 2007



Mechanisms?

-Cocaine depresses GABA-ergic currents via D2 to eCB signalling.

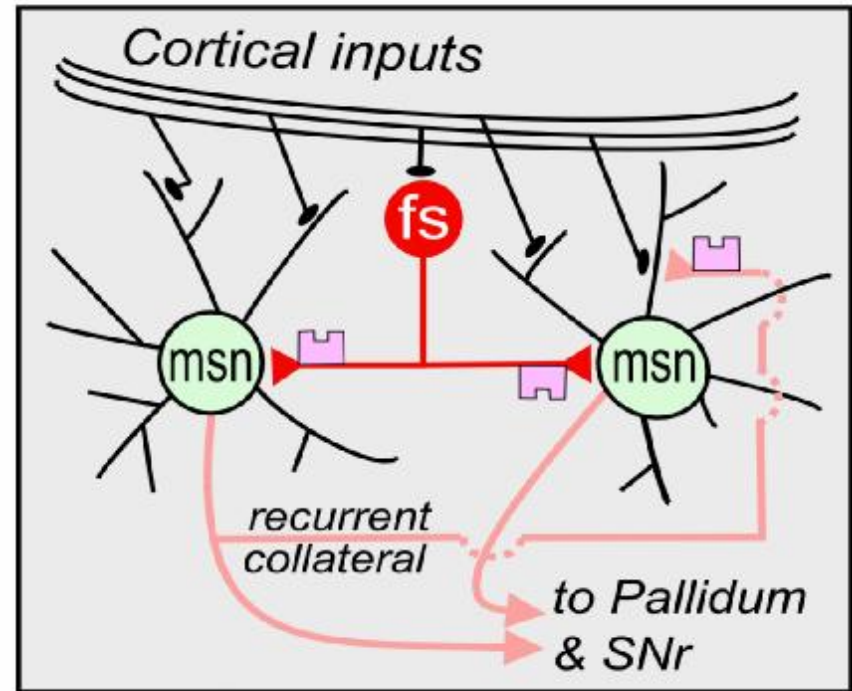
Centonze D et al *Neuropsychopharmacology* 2004

-Repeated doses of cocaine sensitise CB1 receptors on GABA-ergic terminals to CB1 agonists.

Centonze D et al *Eur J Neurosci.* 2007

-Stimulation of A2A receptors facilitates GABA-ergic signalling between MSNs.

Shindou T et al *Journal of neurophysiology.* 2008



Morrison PD & Murray RM
Schizophrenia Bulletin (July 2009)

Summary

- Cannabis can have a major impact on the highest faculties.
- Increased connectivity between ideas.
- At extremes, these new associations can be un-understandable.

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- Direct midbrain DA mechanism?- *unlikely*.
- Direct effect in the striatum?

.....

- CB1 receptor effects appear to be downstream of D2
- Pharmacological convergence of pro- and anti-psychotic molecules at MSN synapses.

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-Do THC and stimulants relax the mutual inhibition between MSN assemblies to such an extent that associations are formed between co-incident psychomotor streams that would otherwise remain separate?



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