Does drug use cause reduced occupational attainment, vice versa, or are caused by a third variable?

- Greater cannabis (& alcohol) use in adolescence predicted reduced occupational performance in adulthood.
- Consistent with the idea that drug use caused reduced performance
- *the cause (cannabis use) preceded the effect (reduced performance*)
- When estimates of third variables (e.g. parental income, personality, intelligence, educational attainment, etc.) were removed, the association between drug use and occupational performance remained **significant**.
- This is consistent with a causal relationship between adolescent drug use & reduced adult occupational attainment; so, poorer long term economic prospects may be considered as a harm produced by drug use

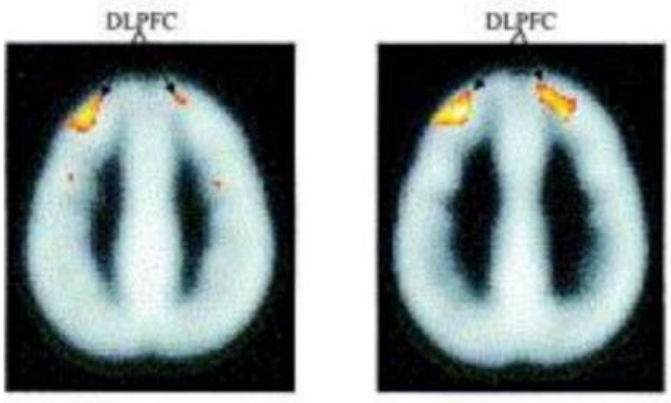
NEUROPATHOLOGY

- Etiology/causes of neuropathy is obscure. It could be:
  • psychoactive ingredient of the consumed compound
  • adulterants within the substance
  • secondary illnesses incurred by poor lifestyle
  • infections/disease from the route of administration
  • accidents under intoxication, violent assault, and/or self-harm.

Neuropathology: Nicotine

Brody et al (2004)

- Smoking associated with a decreased matter volume in the frontal cortex
- Brain volume negatively correlated with years of smoking
- As years of smoking increases frontal brain volume decreases!!



Showing brain regions with lower grey matter density in smokers (left) compared to nonsmokers (right).
Brody et al. 2004, Biological Psychiatry, 55, 77

Serotonin: MDMA

MDMA (ecstasy) has high affinity for blocking 5-HT reuptake from the synaptic cleft

- Serotonin agonist
- Hallucinogens (psilocybin, mescaline, peyote, LSD) & Stimulants (cocaine, amphetamine) also block 5-HT reuptake
- MDMA has a high affinity of 5-HT
- Suggests that positive mood may be a *common element amongst these drugs which helps maintain their recreational use.*

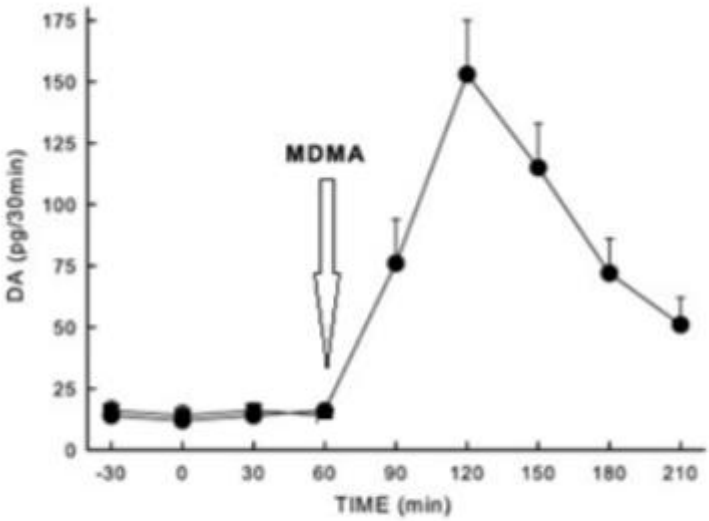
MDMA: addictive potential

MDMA (& hallucinogens) also release dopamine in the **nucleus accumbens**

- it is the dopamine enhancing effect of the drug which determines their addictive potential (Ritz & Kuhar, 1989)
- MDMA'S relatively lower affinity for releasing dopamine compared to amphetamine & cocaine may explain why these compounds are ranked as having a lower addiction potential than other drugs with higher dopamine affinity (Nutt et al. 2007)

Drug	Dependence score
Heroin	3
Cocaine	2.39
Tobacco	2.21
Street methadone	2.08
Barbiturates	2.01
Alcohol	1.93
Benzodiazepines	1.83
Amphetamine	1.67
Ketamine	1.54
Cannabis	1.51
Methylphenidate	1.25
LSD	1.23
GHB	1.19
Ecstasy	1.13
Khat	1.04
Solvents	1.01
Anabolic steroids	0.88

(Nutt et al. 2007. Lancet. 369. 1047).



(Gudelsky et al 2008 Pharmacology Biochemistry and Behavior, 90, 198)

Endorphins (Opioids): Pain & Pleasure

Endorphins: (neuropeptide) play a key role in pain reduction (analgesia) & subjective pleasure (euphoria).

- receptors are called opioid receptors because they respond to opioids/opiates
- receptors are located throughout the spine & sensory-motor pathways of the brain
- either open K+ channels or close Na+ channels reducing the likelihood of action potentials carrying pain signals.
- Endorphins are released by the pituitary gland during a fight or flight response to stress
- reduce pain sensation

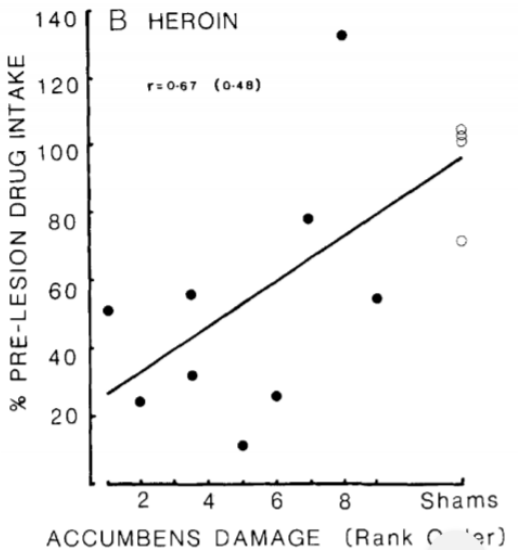
- Endorphins are **also located within the VTA of the mesolimbic dopamine pathway**
- they **inhibit inhibitory GABA** neurons causing an **increase** in dopamine release in the nucleus accumbens (*Spanagel et al. 1990)*

Heroin & Dopamine

Release of dopamine in the nucleus accumbens is crucial to maintain heroin self-administration.

Zito et al. (1985):

- rats self-administered heroin until their behaviour had stabilized
- lesioned the nucleus accumbens & measured the percent decline in self-administration behaviour relative to the pre-lesion baseline.
- Animals ranked as having the greatest accumbens damage (2-4) showed the smallest percent of self-administration relative to pre-lesion (20-60%),
- whereas animals ranked as having little accumbens damage & sham animals who had no damage, showed self-administration rates which were closer or matched their prelesion baseline
- **Nucleus accumbens is essential for heroin self-administration.**

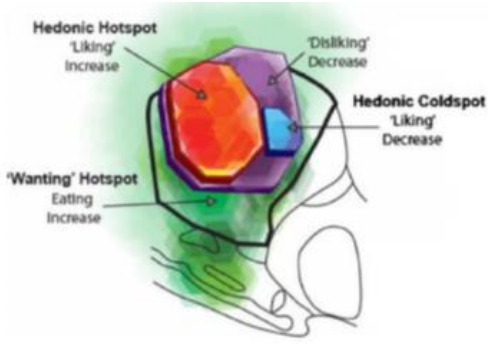


Endorphins: Pain & Pleasure: Hedonic reactions procedure: an animal model of subjective emotional experience.

- a sweet (pleasant) or bitter (unpleasant) solution is squirted into a rat's mouth
- facial reaction is recorded with a close-up camera. Facial reactions to pleasant & unpleasant solutions
- Liking is associated with a licking reaction
- Disliking is associated with a gaping reaction.

Berridge & Kringelbach (2008):

- explore the neural mechanisms underpinning subjective reactions to opiates
- whether injections of opiates into different locations within the nucleus accumbens increased sweet liking ('liking increase') decreased bitter disliking ('disliking decrease') or decreased sweet liking.
- In response to opiates, a large region (purple) decreased disliking, a smaller region (red) increased liking, and a very small region (blue) decreased liking.
- Accords with human subjective reports of opiates that unpleasantness melts away & pleasure is overwhelming



Acetylcholine

- Plays a role in cognitive capacity.
- sensitivity to sensory events, memory, speed of responding etc.
- Evidence: Alzheimer's disease is marked by broad impairments in cognitive capacity & **characterised by destruction of acetylcholine cell bodies** (Auld et al. 2002)
- These cells project broadly across the cortex, they are believed to modulate higher cortical functions as a whole

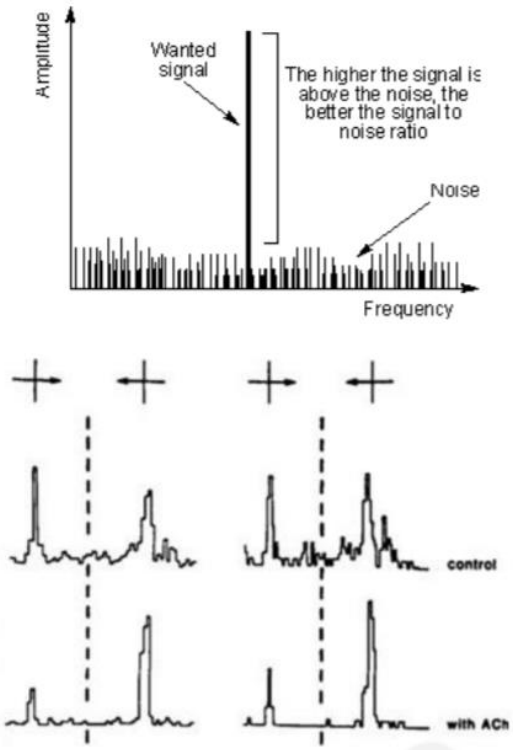
Acetylcholine: cognitive function

Acetylcholine functions as a cognitive enhancer, improving **attention** & reactivity to environmental events.

- At the cellular level, acetylcholine increases the signal to noise ratio in the firing rate response to stimulation
- cells have a background firing rate, & increase this rate in response to appropriate stimulation (AKA 'tuning').
- The difference between the signal & the noise (background) is crucial for detection & responding to environmental events

Sillito & Kemp (1983):

- Cells in the visual cortex of anesthetised cats are tuned to respond preferentially to bars of light moving across the visual field in a particular direction (left or right).
- Selectivity of this tuning is weak in the control (anesthetised) animals.
- However, when acetylcholine is applied (Ach) the tuning of the cells become much more selective to the preferred stimulation.



Acetylcholine: Nicotine

• Nicotine is an acetylcholine agonist.

-**binds to acetylcholine receptor**s on the postsynaptic cell

-these receptors **are coupled to sodium channels**, which open in response to binding, exciting the cell & thus *increasing the probability of an action potential.*

-Nicotine also binds to pre-synaptic acetylcholine receptors located on the terminal button of cells which express endorphins (Berrendero, 2010) & dopamine (Sidhpura et al., 2007; Nisell et al., 1994).

-Cells in the VTA (mesolimbic dopamine pathway) increase firing rate in response to tobacco smoke (TS).

-activation (of DA in the VTA) is essential for nicotine to maintain self-administration behaviour (David et al., 2006).