Imaging Addiction

David Nutt
Prof of Neuropsychopharmacology
Imperial College London

d.nutt@imperial.ac.uk
Questions

• Where in the brain is addiction mediated?
  
  Van Ree JM (1977) Multiple brain sites involved in morphine antinociception. J.Pharm.Pharmacol. 29: 765-767

• What neurotransmitter mechanisms underlie addiction?
  
  • dopamine –or– endorphins
  
Re-living opiate memories activate the anterior cingulate cortex

left anterior cingulate and medial pre-frontal gyri

All subjects (n=12)

Activation centered on Talairach co-ordinates -10,46,24 mm

Peak t = 4.52 (p<0.005 corrected for multiple comparisons)

Daglish et al 2001
Brain changes are long lasting

![Graph showing the size of effect over the duration of abstinence (months)]
Heroin craving and urge to use associated with orbitofrontal cortex activation

- Area of rCBF that co-varies with the composite score (craving & urge to use)
- Peak $t = 5.19$ ($p<0.05$ corrected for multiple comparisons)

Daglish et al 2001
Alcohol similar regions but less intense

**Opiate** study

**Alcohol** Study (-18, 48, 28mm)

Lingford-Hughes et al 2009
Another alcohol visual cue study

Craving correlated with activation in L nucleus accumbens, orbitofrontal cortex and anterior cingulate.

George et al 2004
Cocaine cues also activate anterior cingulate activation

fMRI of cocaine cue exposure & craving.

Pts: + craving         Pts: no craving            Controls

Activation of anterior cingulate cortex is seen in abstinent cocaine addicts while watching a 'cocaine video' whether or not they experienced craving

Wexler et al. 2001
Nicotine: cue exposure and craving

Heavy smokers [>20/d] compared with non-smokers.

- cue exposure
  - anterior cingulate cortex
  - anterior temporal lobe

- craving
  - orbitofrontal cortex
  - anterior insular cortex
  - R sensorimotor cortex

Brody et al 2002
Food cue exposure in anorexic patients activates similar areas

Food exposure in patients with anorexia nervosa

Anterior cingulate activation in active and recovered patients

fMRI

Uher et al
Brain regions of addiction

Same as those involved in other appetitive and motivational processes

- Anterior Cingulate $\rightarrow$ arousal and attentional processes
- Orbitofrontal cortex $\rightarrow$ response/impulse control

Theory – addiction is excessive activation of normal functional behavioural circuits

= More rather than different
Neurotransmitters and addiction

Dopamine or endorphins?
Dopamine (DA) systems in the human brain

- Cognition
- Schizophrenia
- Parkinson's disease
- Attention deficit

Reward learning
- Depression
- Drug abuse

Movement
- Parkinson's disease

Hormone control - prolactin

Frontal lobes

THE DOPAMINERGIC PATHWAYS

A. Substantia nigra
B. Ventral tegmental area
C. To amygdala
D. Tubero-infundibular DA system
E. Nucleus accumbens (ventral striatum)
F. To the striatum (caudate nucleus, putamen and globus pallidus)
G. Frontal cortex

Stefan et al
Rewarding effects of **stimulants** are associated with increases in brain dopamine

Volkow et al 1999
## Studies reporting dopamine release using [11]C-raclopride PET

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Size of dopamine release</th>
<th>Paper</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methylphenidate</td>
<td>-21% in controls, -9% in cocaine users</td>
<td>Volkow et al 1999</td>
</tr>
<tr>
<td>Smoking</td>
<td>-30% (recently revised down to 8% and only in COMT val/val sub group)</td>
<td>Brody et al 2004, 2006</td>
</tr>
<tr>
<td>Video game*</td>
<td>-12% (left) &amp; -14% (right)</td>
<td>Koepp et al 1999</td>
</tr>
<tr>
<td>Placebo (expecting apomorphine)</td>
<td>-17% to -19%</td>
<td>Fuente-Fernandez et al 2001 2002</td>
</tr>
<tr>
<td>Caffeine</td>
<td>-5%</td>
<td>Kaasinen et al 2004</td>
</tr>
<tr>
<td>Alcohol</td>
<td>~10%</td>
<td>Boileau et al 2003 (v v drunk)</td>
</tr>
<tr>
<td>Cannabis</td>
<td>~4%</td>
<td>Bossong et al 2008</td>
</tr>
</tbody>
</table>

* recent study by same group suggest motor activity rather than reward
Testing the dopamine theory

opioids
hydromorphone and heroin
Daglish et al 2008 Brit J Psychiatry

nicotine
Montgomery et al 2007 Synapse: 637-45
Heroin 50mg iv produces a good high.

![Graph showing VAS scores over time after administration of heroin and diamorphine.](image-url)
No dopamine Response - $^{11}$C-Raclopride

- No significant change in Raclopride binding
Individual binding data
with internal validation [accidental]
Nicotine had clear pharmacological effects = elevated heart rate

Nicotine 2mg via nasal spray
But... no change in binding

<table>
<thead>
<tr>
<th>Region</th>
<th>Control</th>
<th>Nicotine</th>
<th>% Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lateral Striatum</td>
<td>2.1 ± 0.2</td>
<td>2.1 ± 0.3</td>
<td>0.6% ± 7.2</td>
</tr>
<tr>
<td>Associative Striatum</td>
<td>2.4 ± 0.2</td>
<td>2.4 ± 0.2</td>
<td>1.0% ± 5.0</td>
</tr>
<tr>
<td>Sensorimotor Striatum</td>
<td>2.7 ± 0.2</td>
<td>2.7 ± 0.2</td>
<td>1.1% ± 4.5</td>
</tr>
</tbody>
</table>

note recent Brody paper fails to replicate their original nicotine dopamine findings except in post-hoc analysis of COMT status
So if it's not dopamine is it endorphins?

Endorphins and their receptors
two PET tracers

Carfentanyl $\mu$

Diprenorphine $\mu, \kappa, \delta$
Increased $^{11}$C-carfentanil binding in cocaine abstinence

Cocaine craving correlated with mu receptor levels in first scan in:
- Amygdala
- Anterior Cingulate
- Frontal cortex
- Temporal cortex

Increase in [11C]diprenorphine binding in early opioid abstinence

Opioid patients and controls VD for a priori regions

<table>
<thead>
<tr>
<th>Region</th>
<th>Control</th>
<th>Opioid</th>
<th>p &lt; 0.05</th>
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</thead>
<tbody>
<tr>
<td>R Posterior Orbital</td>
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<tr>
<td>L Posterior Orbital</td>
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<tr>
<td>R Lateral Orbital</td>
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<td>L Lateral Orbital</td>
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<tr>
<td>R Medial Orbital</td>
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<tr>
<td>L Medial Orbital</td>
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<tr>
<td>R Anterior Orbital</td>
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<tr>
<td>L Anterior Orbital</td>
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<tr>
<td>R Thalamus</td>
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<tr>
<td>L Thalamus</td>
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<tr>
<td>R Putamen</td>
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<tr>
<td>L Putamen</td>
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<tr>
<td>R Nucleus Accumbens</td>
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<tr>
<td>L Nucleus Accumbens</td>
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<tr>
<td>R Caudate Nucleus</td>
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<td>L Caudate Nucleus</td>
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<td>R Anterior Cingulate</td>
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<tr>
<td>L Anterior Cingulate</td>
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<tr>
<td>R Amygdala</td>
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<tr>
<td>L Amygdala</td>
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<tr>
<td>Brainstem</td>
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<td>Global mean</td>
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Mean 11C-diprenorphine VD (±SD)

Psychopharmacology Unit

Williams et al – 2007
Correlation of elevations in striatal $\mu$-opioid receptor availability in detoxified **alcoholic** patients with alcohol craving

Heinz et al 2005
Increase in opiate receptor availability in the brain in early abstinence from alcohol and opiates.

<table>
<thead>
<tr>
<th>Subject Type</th>
<th>Control n = 28</th>
<th>Alcohol dependent n = 11</th>
<th>Opiate dependent n = 10</th>
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* : significantly different to control $p<0.05$

Bristol studies  Williams et al Brit J Psychiatry 2007
Alcohol dependence – early abstinence

Increase in diprenorphine binding correlates with craving

Increased availability of opioid receptors in left caudate nucleus (above) and whole brain ($r=0.753$, $p=0.019$) is associated with greater craving for alcohol

Psychopharmacology Unit

Williams et al 2008
Conclusions

• addiction uses the same brain circuits as other motivated behaviours
  • but “highjacks” them to detriment of normal function

• dopamine and endorphins appear to play important roles in addiction
  • dopamine for stimulants ? alcohol
  • endorphins for craving and drug liking
So how can we communicate these facts?

And what are the health and social policy implications?
INTRODUCTION

The European College of Neuropsychopharmacology (ECNP)

• is a unique and remarkably broad interdisciplinary platform
• aims to apply new knowledge on fundamental disease mechanisms to clinical applications and vice versa
• bridges the gap between basic research, clinical science and medical practice
• paves the way for improved pharmacological treatments, which will improve the quality of life of people suffering from mental disorders
Silencing the scientists
Should Nutt have been sacked?
Page 6
What did I say to get me sacked?

“alcohol more harmful than cannabis”

“we should consider the Dutch model of regulated access to cannabis”
So Jan

I have clearly learned to take your uncompromising approach to issues

Maybe you could give me a lesson or two in political strategy?

Now you have time on your hands!

Wishing you a very happy retirement