Food and drug rewards in humans: insights from functional brain imaging.

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Acknowledgements

Roger Gunn
John Aston
Keith Worsley
Isabelle Boileau
Dana Small
Saima Malik
Takuya Hayashi
Chawki Benkelfat
Marco Leyton
Dharma McBride
Jens Pruessner
Robert Pihl
Michael Meaney
Mirko Diksic
Krzysztof Welfeld
Igor Sibon
Nothing in Biology Makes Sense Except in the Light of Evolution.

- Theodosius Dobzhansky (1900-1975)
Is hunger an addiction?

- Homeostasis
- Thirst determined by internal state
- Water can’t be stored
- Water doesn’t induce craving
- Easily available

- Homeostasis does not fully explain hunger
- Calories can be stored
- Obtained through effort
- Food can induce craving even when satiated *
- Hunger is learned *

* Features of addiction
Is hunger an addiction?

• **DO Hebb (1949)**
  - Attributes the idea of hunger as an addiction to AJ Carlson (1916).
  - “Salted peanuts” paradox.
  - Hunger and learning:
    - Initial effect of hunger is disruptive.
    - Infant learns that eating relieves unpleasant effects (e.g. stomach contractions).
    - Eventually hunger becomes an organized behaviour

• **RA Wise (1978)**
  - Dopamine blockade reduces the reinforcing and rewarding effects of food.
  - Dopamine codes the “yumminess” of food.
  - Addictive drugs act on brain circuitry that originally developed to serve feeding behaviour.
"I applied a brief train of 60-cycle sine-wave electrical current whenever the animal entered one corner of the enclosure. The animal [...] came back quickly after a brief sortie which followed the second stimulation. By the time the third electrical stimulus had been applied the animal seemed indubitably to be coming back for more."

Olds, 1973, pg 31
Schultz’ Model

- Dopamine release:
  - Unexpected reward
  - Stimuli predictive of reward
- No dopamine release following aversive stimuli.

DA is a learning signal that encodes the difference between expected and actual reward.

“Sensitization causes excessive cue-triggered "wanting" for an associated reward, which might lead to compulsive drug pursuit and addiction”

Robinson & Berridge, 1993
Compulsion and control

Reflexive system

Impulsive system

Attention / arousal

Bechara, Nat Neurosci 2005
Questions

• Is the response of the dopamine system to “natural” and drug rewards similar?

• Is the dopamine system changed by drug taking / addiction?

• Are there differences in the dopamine system in individuals vulnerable to addiction.

• Interactions between frontal lobes and ascending monoaminergic systems.
Craving

- Plays a role in relapse amongst ex-drug users.
- Often triggered by the environment in which drugs were taken.
- May involve dopamine (since dopamine antagonists may block it).
- Drug craving can be induced in a laboratory setting by cues (e.g. videos, scripts).
Cocaine craving (FDG PET)

- Cocaine cues compared to neutral cues.
- FDG PET to measure glucose metabolism.
- In cocaine addicts cocaine cues activate DLPFC and amygdala.

Grant et al. 
PNAS 1996 93:12040-12045
# Imaging studies of cue-induced craving

<table>
<thead>
<tr>
<th>Study</th>
<th>Imaging modality</th>
<th>Addictive substance</th>
<th>Drug cue</th>
<th>DLPFC</th>
<th>OFC</th>
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<td><strong>Drug users currently not seeking treatment</strong></td>
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<tr>
<td>Bonson et al. (2002)</td>
<td>PET</td>
<td>Cocaine</td>
<td>Video, script, paraph.</td>
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<td>Video, tactile</td>
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<td>Due et al. (2002)</td>
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Wilson et al. Nat Neurosci
A fMRI study of cigarette craving

<table>
<thead>
<tr>
<th>20 SUBJECTS</th>
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<tr>
<td>Right-handed</td>
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<tr>
<td>-10 Male</td>
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<tr>
<td>-10 Female</td>
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<td>-2 scans (one month apart)</td>
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<tr>
<th>EXPECTANT GROUP (10)</th>
<th>ABSTINENT</th>
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<td>- No smoking 12 hrs. prior to scan</td>
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<td>- Smoke after scan</td>
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<th>NON-EXPECTANT GROUP (10)</th>
<th>NON-ABSTINENT</th>
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<tr>
<td>- No smoking 12 hrs. prior to, or 4 hrs. after scan</td>
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<tr>
<td>- Smoke before scan but no smoking 4 hours after scan</td>
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McBride et al. Neuropsychopharm 2006
Subjective Reports of CRAVING

Smoking - Neutral

McBride et al. Neuropsychopharmacology 2006
Effect of expectancy / abstinence

Smoking video > Haircut video

Lack of activation in non-expectant condition: inhibition of response to conditioned cues?

Ascending Reticular Activating System (AROUSAL)

McBride et al. Neuropsychopharm 2006
Expectancy effects

- **DLPFC** (20, 58, 34)
  - Exp - Nonexp
  - Affected by craving, as in previous studies.

**McBride et al. Neuropsychopharmacology 2006**
Expectancy affects DLPFC response

- Contingency
- Context
- Cue
- Internal state (craving)

- Stress
- Alcohol
- Nicotine

McBride et al. Neuropsychopharmacology 2006
Effect of stress

1) Stress task

2) Control task
Effect of stress

Non-stress

Stress
Effect of stress

Non-stress

Stress

Hippocampus

OFC
Effect of stress

Non-stress

Stress

Caudate
Cue-induced brain activation

- ACC, mPFC, dorsomedial thalamus
  - Activated during expectancy only
  - Arousal, Attention, Self-referential emotions

- DL-PFC
  - Modulated by expectancy and craving
  - Activity reflects influence of internal state, motivation and drive, external contingencies.
  - May be involved in planning to smoke and in over-riding the urge to smoke, depending on context.

- Role of cues
  - Cigarette cues are arousing, especially when cigarettes are available.
Brain response to “food cues”

- Event-related fMRI
- Images displayed 5s, 15s apart.
Food minus scenery (hungry subjects)

Expecting to eat

- OFC *
- Amygdala
- Insula *
- Visual

Expecting not to eat

lateral PFC
Gut - brain interactions

Broberger
J Intern Med 2005
Gut - brain interactions

Cota et al.  
Neuron 2006

Abizaid et al.  
JCI 2006
Effect of ghrelin

• Ghrelin is an orexigenic peptide hormone
• Increases hunger and food intake
• Acts on hypothalamus, but there is increasing evidence that it also acts directly on other areas: dopamine neurons, hippocampus…
• 12 non-hungry subjects tested:

Malik et al. submitted
Effect of ghrelin on response to food pictures

Saline

Ghrelin

Posterior insula

Amygdala

Malik et al. submitted
Right amygdala

Increase in amygdala activation correlates with increase in hunger

Malik et al. submitted
Ghrelin effects on visual areas

Left pulvinar

Right pulvinar

Malik et al. submitted
Ghrelin effects

Malik et al. submitted
Ghrelin effect - correlations

Malik et al. submitted
## Food picture recall and rating

<table>
<thead>
<tr>
<th></th>
<th>Pictures seen in the <em>saline</em> condition</th>
<th>Pictures seen in the <em>ghrelin</em> condition</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recall task</strong></td>
<td>81.8 ± 10.8</td>
<td>88.8 ± 7.3</td>
<td>0.014*</td>
</tr>
<tr>
<td>(Did you see this food picture in the scanner?)</td>
<td></td>
<td></td>
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<tr>
<td><strong>Picture rating task</strong></td>
<td>6.7 ± 0.84</td>
<td>6.8 ± 0.88</td>
<td>0.479</td>
</tr>
<tr>
<td>(Rate picture on a scale of 1 - 9)</td>
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*Malik et al. submitted*
Amygdala/OFC: predictive hedonic evaluation

Gottfried et al. Science 2003
Amygdala/OFC: predictive hedonic evaluation

Gottfried et al. Science 2003
Ghrelin

• A “metabolic” feeding signal.
• Increases response to food cues in brain areas involved in motivation, hedonic evaluation, memory.
• “Incentive salience”.
• Metabolic feeding signals act on hedonics and motivation.
Compulsion and control

Reflexive system

Impulsive system

Attention / arousal

Bechara, Nat Neurosci 2005