ADDICTION IN THE AGE OF BRAIN SCIENCE

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Substance use accounts for almost 1/10 of global disease burden

Degenhardt et al, Lancet 2013
What is the nature of the problem we are dealing with?

• A life-style choice among others?
• A character defect?
• A social construct?

Your answer is likely to influence your approach

• Arrest and incarcerate?
• Confront and control?
• Get with the program?
• Diagnose, develop personalized treatments, manage?
• Can neuroscience inform the answers?
"Only" a (large) minority of people exposed to drugs develop addiction

![Diagram showing estimated proportion of drug users who have become drug dependent.](diagram.png)

Anthony et al., Exp Clin Psychopharmacol 1994

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The core phenomenon of addiction: Seeking and taking drug despite adverse consequences

"compulsivity"  
"aversion resistant drug seeking"

Daily Mail, 2014
Genetics contribute to individual susceptibility, at a level similar to other complex diseases

- Largely non-shared environment
- Stress
- Early life trauma
- Exposure to interpersonal violence
- Peers who use drugs
- Availability and cost of addictive substances

- In contrast to genetics, these are modifiable risk factors!
The contribution of genetic susceptibility changes across the life span

Adapted from Kendler et al. 2008

No size fits all:
Addiction is the end stage of multiple trajectories

Experience:
- no addiction without drug
- kindling – like process
- stress interacts with drug

Genes
- heritability ≈ 50 – 80% (Goldman et al. 2005)
- numerous susceptibility loci
- each of small effect (e.g Treutlein et al. 2009)

Adapted from Heilig et al, Nat Rev Neurosci 2011
The bottle is half full:

Remarkable progress has been made in the understanding of circuitry that promotes drug seeking in model organisms
The bottle is half empty:

Neuroscience has so far had limited impact on unmet patient needs in addictive disorders

Relapse rates have barely budged in close to half a century

Hunt, J Clin Psychol 1971
The standard model of addiction: "the hijacked brain"

Cocaine
DA
Alcohol
Heroin
Nicotine

Courtesy of the National Inst on Drug Abuse

The standard model of addiction: stimulants

Volkow et al. JPET 1999

Nora Volkow
The standard model of addiction: alcohol

We need to get beyond the standard model
Unclear whether all addictive substances trigger a release of dopamine

The example of alcohol:
It can trigger a cascade that leads to dopamine release...

Alcohol → Endogenous opioid release → Dopamine release → "Reward"
But alcohol-induced dopamine release is largely restricted to males

Urban et al., Biol Psychiat 2010

Even in males, dopamine release in ventral striatum seems to depend on genetics

Ramchandani et al., Mol Psychiat 2011
And either way, "reward system" activation by alcohol burns out in heavy drinkers

Alcohol activates ventral striatum in light social drinkers →

This activation is markedly lower in heavy social drinkers →

(and is absent in alcoholics)

Gilman et al, Neuropsychopharmacology 2010

In fact, over time, addiction largely transitions from a reward-seeking to a relief-seeking disorder

Meinhardt and Sommer, Addict Biol 2015
Over time, stress becomes an increasingly important trigger for craving and relapse.

Kwako et al. Psychopharm 2014

Brain stress systems are pathologically upregulated in addiction.
**Brain stress systems are pathologically upregulated in addiction**

- a Schematic localization
- b Control non-selected rat
- c Alcohol-dependent non-selected rat
- d Alcohol-prefering msP rat

*Heilig et al., Nat Rev Neurosci 2011*

**Blocking a key brain stress-signal, CRF, blocks stress-induced relapse in alcohol dependent rats**

Self-administration

Extinction (~ 15 days)

Foot-shock stress (10 min)

30 min reinstatement session

Gehlert et al., J Neurosci 2007
A key role for corticotropin-releasing factor in alcohol dependence

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After this, we thought only translation remained

But translation has proven hard...

The Corticotropin Releasing Hormone-1 (CRH1) Receptor Antagonist Pexacertan in Alcohol Dependence: A Randomized Controlled Experimental Medicine Study

Laura E. Kwaal, Primavera A. Spagnole, Melanie L. Schwaetzi, Annika Thorsell, David T. George, Reza Momtahan, Daniel E. Rio, Marilyn Hurstis, Sebastian Anzani, Maria Concheiro, Rajita Saha and Markus Heilig

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Nothing!
CRF1 antagonists have now failed in clinical development for:

- Depression (Binneman et al 2008, GSK on file)
- Generalized anxiety disorder (GAD) (Coric et al 2010)
- PTSD (GSK / NIMH consortium, unpublished)
- Alcohol addiction (Kwako et al 2015, Schwandt et al. 2016)

Humans may not be a good model for a rat
Have we missed some key aspects of addiction, one lever, and one brain at a time?

The bigger picture

Drug... or drug?
The bigger picture

A drug to die for

Serge Ahmed

A drug to die for

Bozarth and Wise, JAMA 1985

Choosing drug over an alternative

Ahmed, Current protocols in neuroscience 2013:

The bigger picture

Family background
Traumatization

Education
Work
Housing

Socioeconomic status

Network
Drugs in the environment

Relationships

Sense of meaning
Sense of control

DNA-sequence
Exposure
Epigenetics

Gene expression
Development
Neuron
Transmitter
Synapse
Action potential
Reward
Stress

Brain

Stress

18
The most important stressors that trigger relapse in people are social

A brain signature of social exclusion stress

Eisenberger et al, Science 2003; Way et al, PNAS 2009
We take rejection very personally in the insula

Perini et al., in preparation

The brain signatures for physical and social pain overlap in the anterior insula

Wager et al. NEJM 2013
The insula of patients with an addictive disorder shows increased responses to social exclusion stress

Maurage et al, Neuropsychopharm 2012

An experimental anti-stress medication that attenuated insula responses...

Placebo

LY686017

George et al, Science 2008
…was also able to block social stress-induced craving

George et al, Science 2008

The insula: a detector of ”homeostatic emotions”

• Aversive interoceptive states – pain, nausea etc.

• But also: risky decision-making, uncertainty, empathy and social stress
Insula and addiction

- Insula activation is associated with craving across multiple drug categories (Naqvi an Bechara. TINS 2008, Garavan Brain Struct Func 2010; Naqvi et al. 2014)

- Insula has one of the highest levels of µ-opioid receptors in the human brain (Baumgartner et al, Neuroimage 2006)


Myric et al, Neuropsychopharm 2004

Damage to the insula in humans disrupts addiction to cigarette smoking

Naqvi et al., Science 2007; TINS 2008
Pronounced loss of von Economo neurons in the anterior insula of patients with alcohol addiction


A vicious circle

Craving
Marginalization
Social exclusion
Relapse
Impaired social function
The message from the neuroscience lab

- Promote opportunities and social integration
  - Jobs
  - Housing
  - Motivational Enhancement
  - Contingency Management
  - Community Reinforcement
  - Pharmacotherapies
  - Continuing care

...instead of

- Control
- Repression
- Marginalization