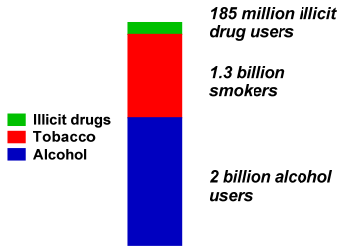
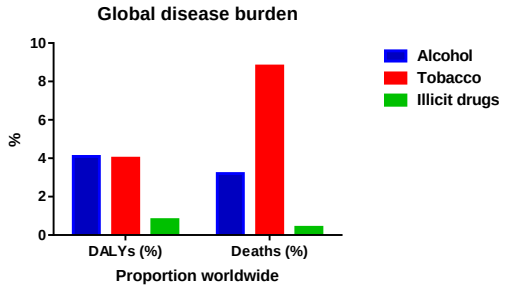
ADDICTION IN THE AGE OF BRAIN SCIENCE

Markus Heilig, MD PhD
Center for Social and Affective Neuroscience
Linköping University
SWEDEN

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 we dealing with?

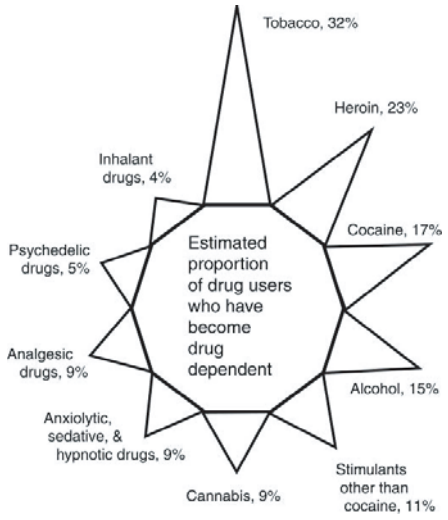
- A life-style choice among others?
- A character defect?
- A social construct?

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 anwers?**

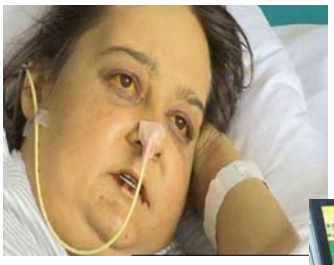
ATTORNEY GENERAL JEFF SESSIONS REFORMING OBAMA'S LAX POLICIES ON CRIME, DRUG TRAFFICKING

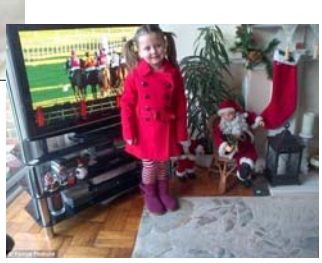
”Only” a (large) minority of people exposed to drugs develop addiction



Anthony et al., Exp Clin Psychopharmacol 1994

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

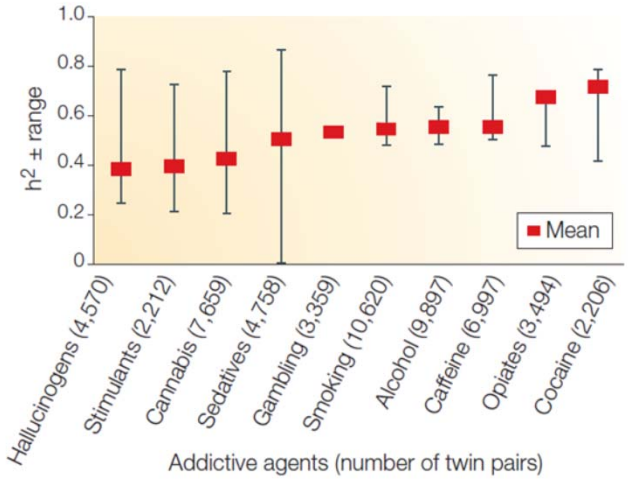




”compulsivity”
”aversion resistant drug seeking”

Daily Mail, 2014

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



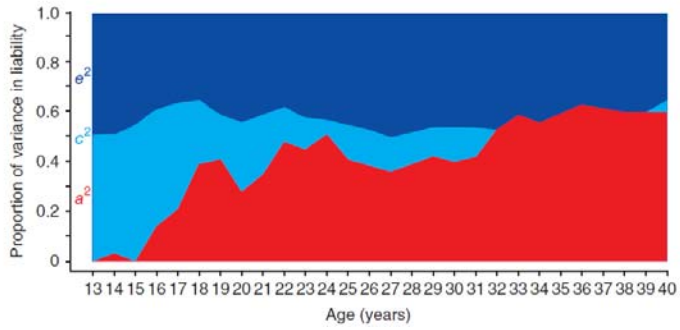
Orosz et al. Nature Reviews Neurosci 2005

Environment contributes 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



Genetics

Familial (shared) environment

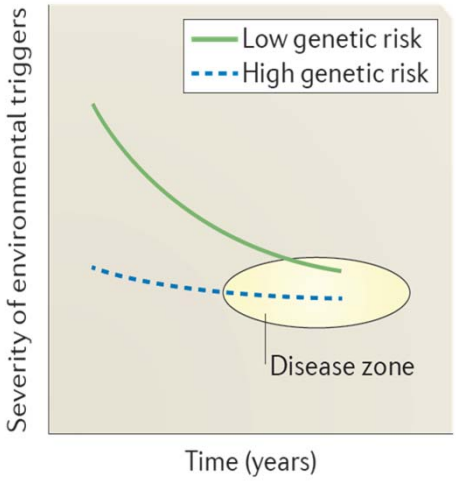
Individual (non-shared) environment

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

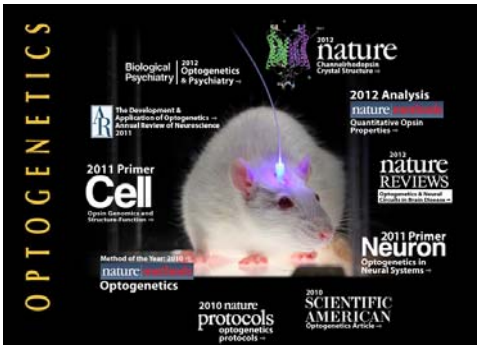
Genes
- heritability ≈ 50 – 80% *(Goldman et al. 2005)*
- numerous susceptibility loci
- each of small effect *(e.g Treutlein et al. 2009)*



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



LETTER

doi:10.1038/nature12024

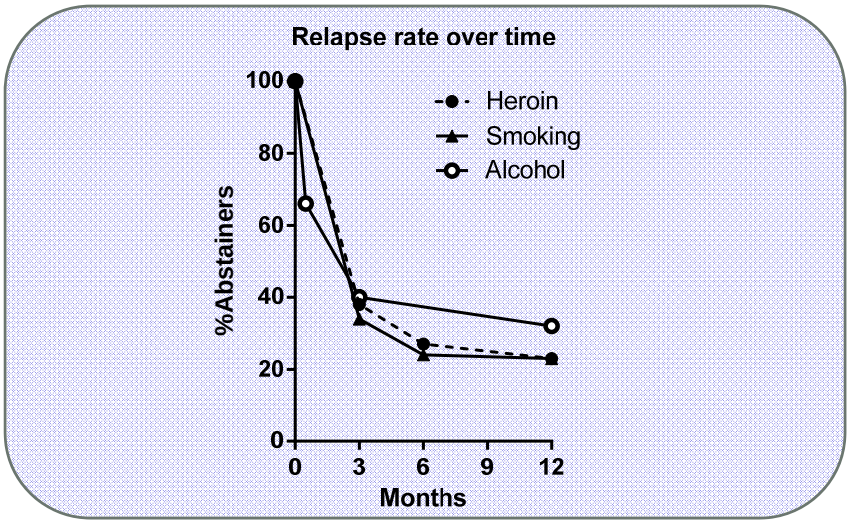
Rescuing cocaine-induced prefrontal cortex hypoactivity prevents compulsive cocaine seeking

Billy T. Chen[1], Hau-Jie Yau[1], Christina Hatch[1], Ikue Kusumoto-Yoshida[1], Saemi L. Cho[2], F. Woodward Hopf[2,3] & Antonello Bonci[1,3,4]

The bottle is half empty:

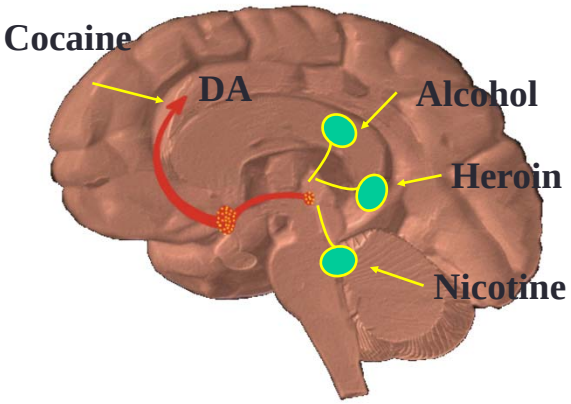
Neuroscience has so far had limited impact on unmet patient needs in addictive disorders

Relapse rates have barely budged in close to half a century



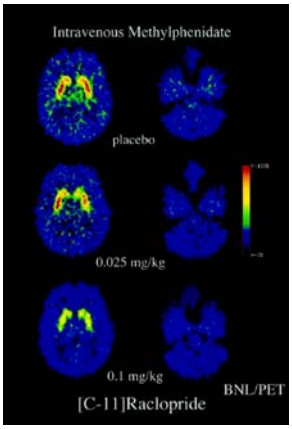
Hunt, J Clin Psychol 1971

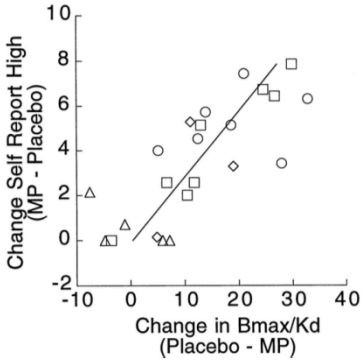
The standard model of addiction: ”the hijacked brain”



Courtesy of the National Inst on Drug Abuse

The standard model of addiction: stimulants



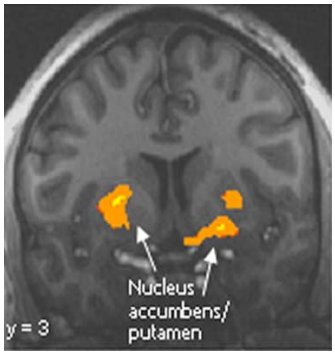


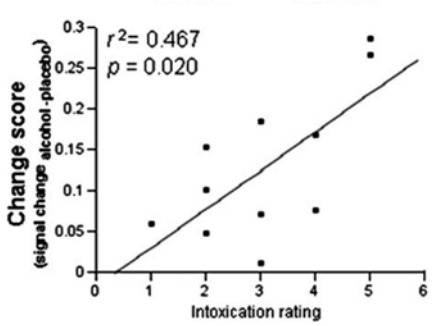
Nora Volkow

Volkow et al. JPET 1999

The standard model of addiction: alcohol

Dan Hommer

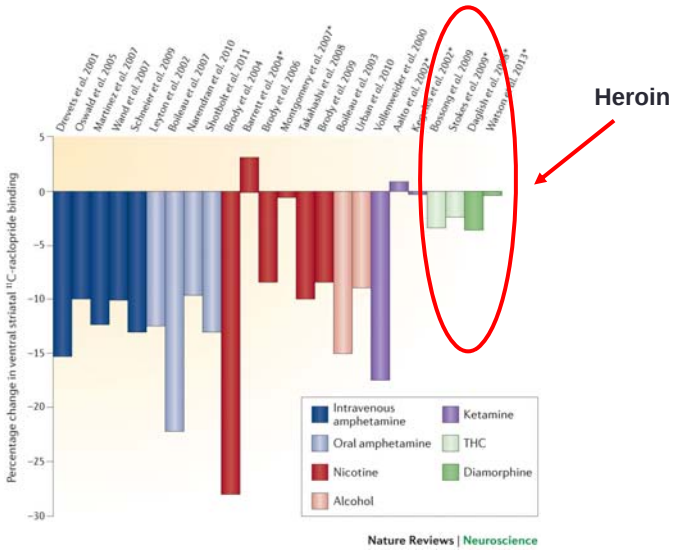




Gilman et al., J Neurosci 2008

We need to get beyond the standard model

Unclear whether all addictive substances trigger a release of dopamine

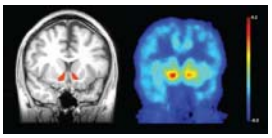


Nutt et al, Nat Rev Neurosci 2015

The example of alcohol: It <u>can</u> trigger a cascade that leads to dopamine release…

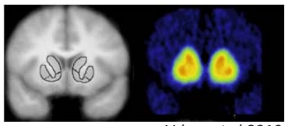
Alcohol

Endogenous opioid release



Mitchell et al 2012

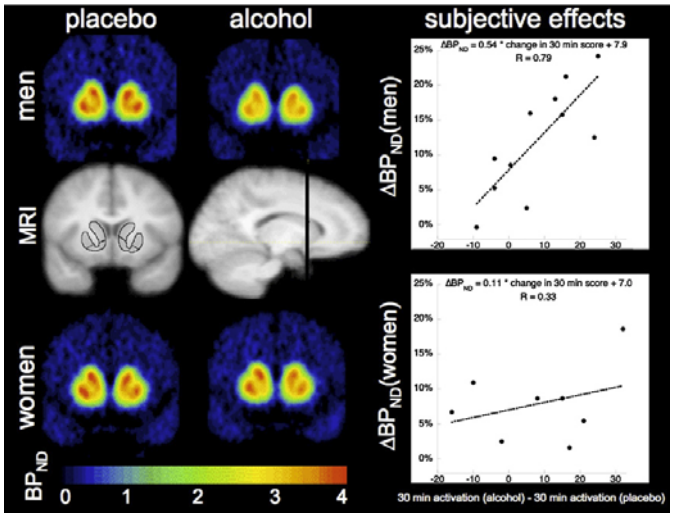
Dopamine release



Urban et al 2010

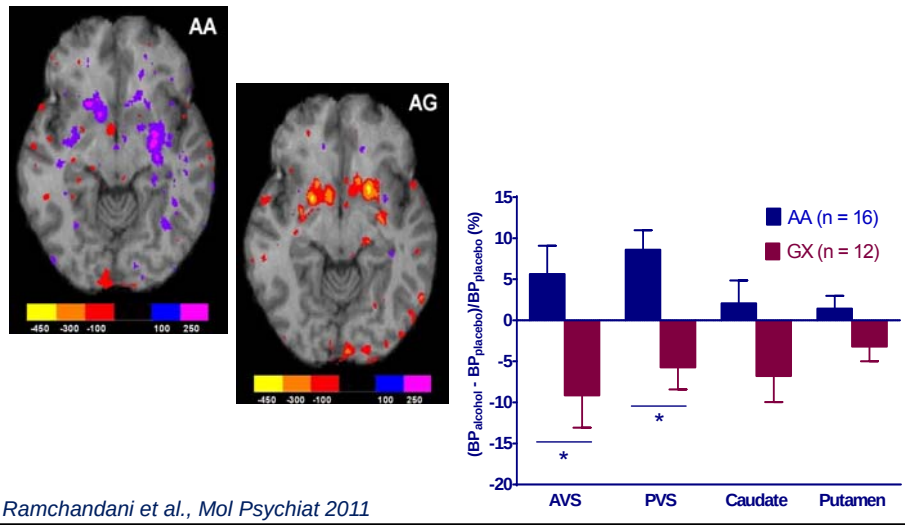
”Reward”

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



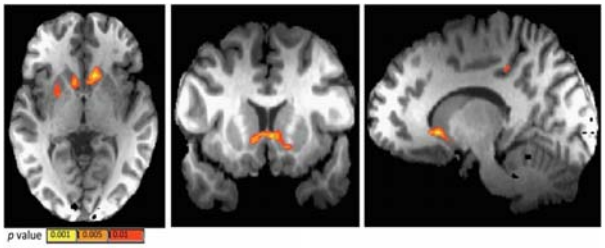
Ramchandani et al., Mol Psychiat 2011

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** →

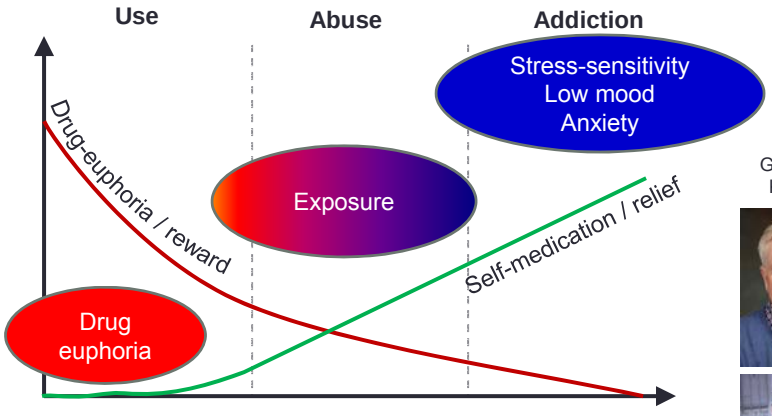
(and is absent in alcoholics)



Neuropsychopharmacology

Gilman et al, Neuropsychopharm 2010

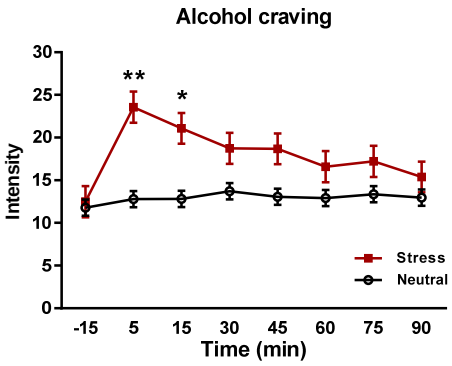
In fact, over time, addiction largely transitions from a reward-seeking to a relief-seeking disorder



George Koob

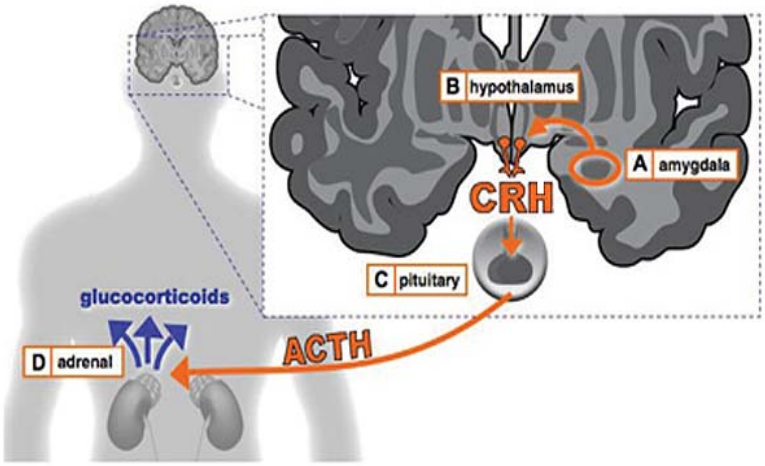
Meinhardt and Sommer, Addict Biol 2015

Over time, stress becomes an increasingly important trigger for craving and relapse

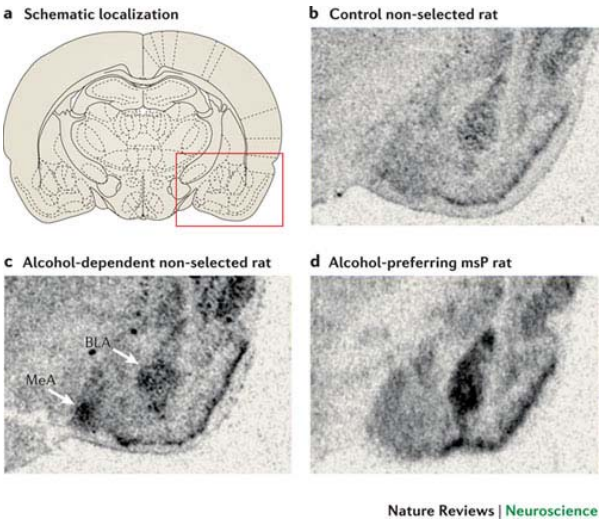


Kwako et al. Psychopharm 2014

Brain stress systems are pathologically upregulated in addiction

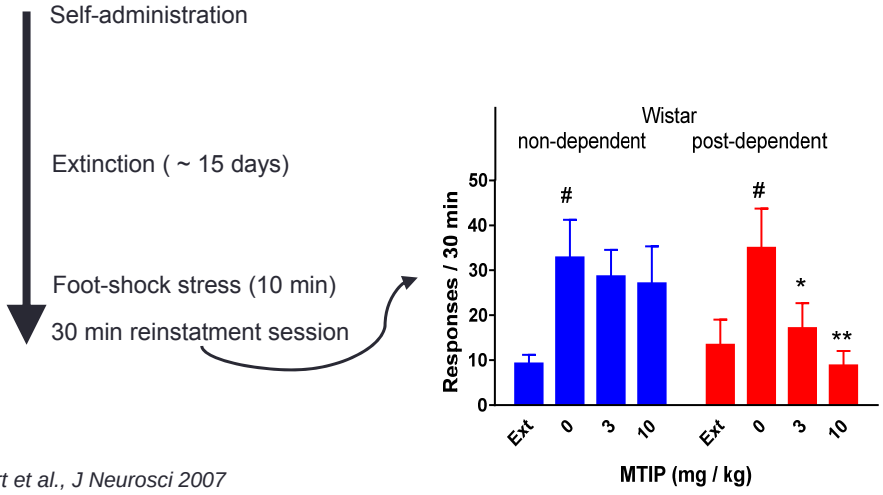


Brain stress systems are pathologically upregulated in addiction



Heilig et al, Nat Rev Neurosci 2011

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



Gehlert et al., J Neurosci 2007

Review TRENDS in Neurosciences Vol.30 No.8

A key role for corticotropin-releasing factor in alcohol dependence

Markus Heilig[1] and George F. Koob[2*]

[1] Laboratory of Clinical and Translational Studies, National Institute of Alcohol Abuse and Alcoholism (NIAAA), NIH, 10 Center Dr., 1/5334, Bethesda, MD 20892, USA
[2] Committee on the Neurobiology of Addictive Disorders, The Scripps Research Institute, 10550 North Torrey Pines Road, SP30-2400, La Jolla, CA 92037, USA

After this, we thought only translation remained

But translation has proven hard…

Neuropsychopharmacology (2015) 40, 1053–1063

www.neuropsychopharmacology.org

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

Laura E Kwako[1], Primavera A Spagnolo[1], Melanie L Schwandt[1,2], Annika Thorsell[1,2], David T George[1], Reza Momenan[1], Daniel E Rio[1], Marilyn Huestis[3], Sebastien Anizan[3], Marta Concheiro[3], Rajita Sinha[4] and Markus Heilig*[,1]

[1]Laboratory of Clinical and Translational Studies, National Institute on Alcohol Abuse and Alcoholism, NIH, Bethesda, MD, USA; [2]Department of Clinical and Experimental Medicine, Linköping Univ., Linköping, Sweden; [3]Chemistry and Drug Metabolism Section, National Institute on Drug Abuse, NIH, Baltimore, MD, USA; [4]The Yale Stress Center, Department of Psychiatry, Yale University School of Medicine, New Haven, CT, USA

Nothing!

Original Article

Neuropsychopharmacology accepted article preview 25 April 2016; doi: 10.1038/npp.2016.61

The CRF1 Antagonist Verucerfont in Anxious Alcohol Dependent Women: Translation of Neuroendocrine, but not of Anti-Craving Effects

Melanie L Schwandt[1,5], Carlos R Cortes[1,5], Laura E Kwako[1], David T George[1], Reza Momenan[1], Rajita Sinha[2], Dimitri E Grigoriadis[3], Lorenzo Leggio[4] and Markus Heilig[1]

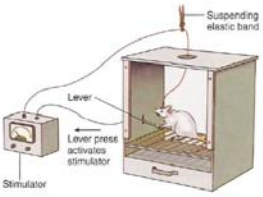
(Almost) Nothing!

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?

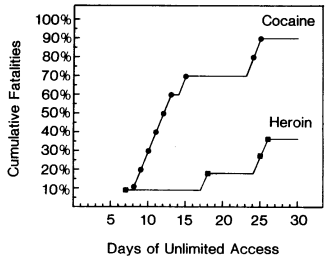


The bigger picture

The bigger picture

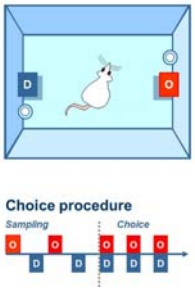
Serge Ahmed

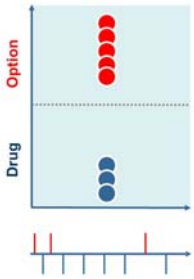
A drug to die for



Bozarth and Wise, JAMA 1985

Choosing drug over an alternative





Ahmed, Current protocols in neuroscience 2013:

The bigger picture

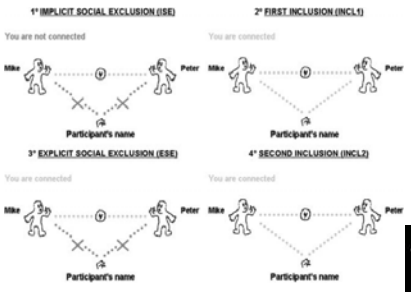
Family background
Traumatization
Education
Work
Housing
Socioeconomic status
Drugs in the environment
Network
Relationships
Sense of meaning
Sense of control

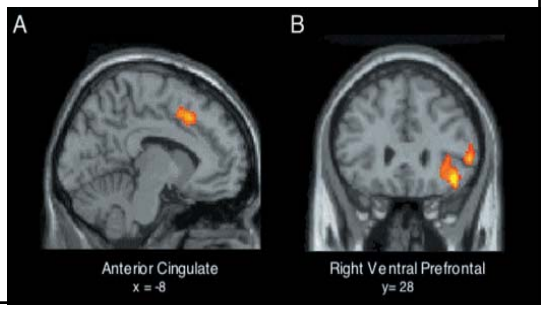
?

DNA-sequence
Exposure
Epigenetics
Gene expression
Development
Neuron
Transmitter
Synapse
Action potential
Brain
Reward
Stress

The most important stressors that trigger relapse in people are social

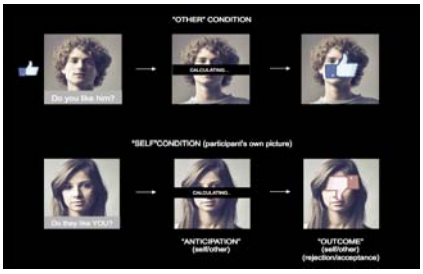
A brain signature of social exclusion stress

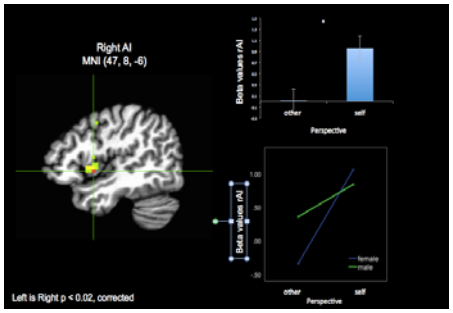




Eisenberger et al, Science 2003;
Way et al, PNAS 2009

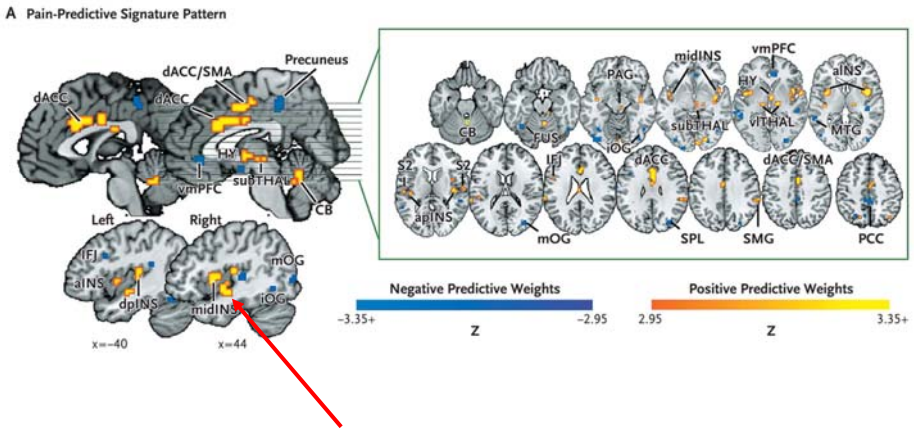
We take rejection very personally in the insula





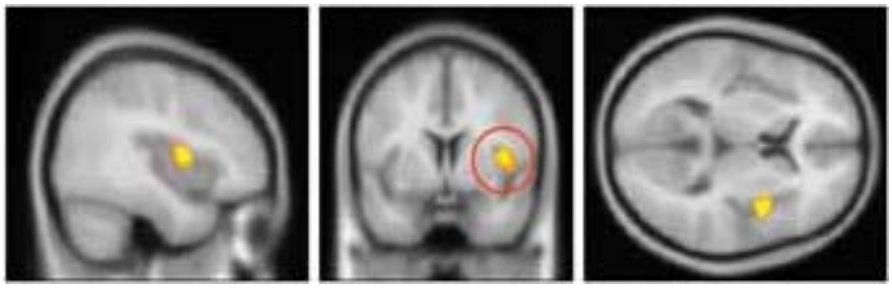
Perini et al, in preparation

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

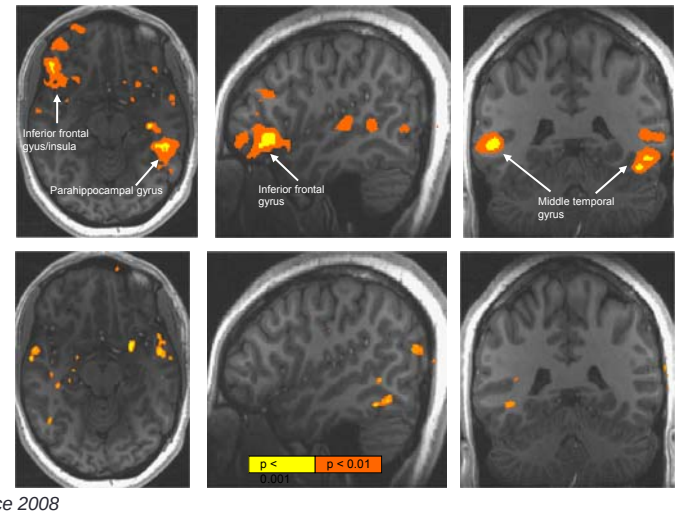


Maurage et al, Neuropsychopharm 2012

An experimental anti-stress medication that attenuated insula responses…

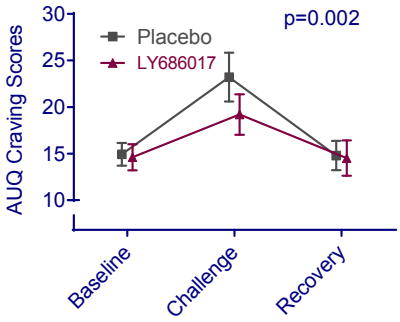
Placebo

LY686017



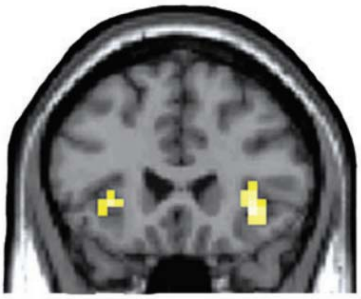
George et al, Science 2008

…was also able to block social stress-induced craving



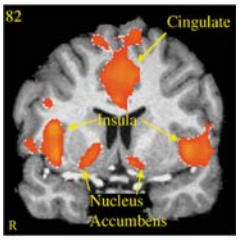
George et al, Science 2008

The insula: a detector of ”homeostatic emotions”

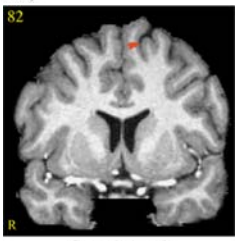


- Aversive interoceptive states – pain, nausea etc.
- But also: risky decision-making, uncertainty, empathy and social stress

Insula and addiction



Alcoholics (n=10)

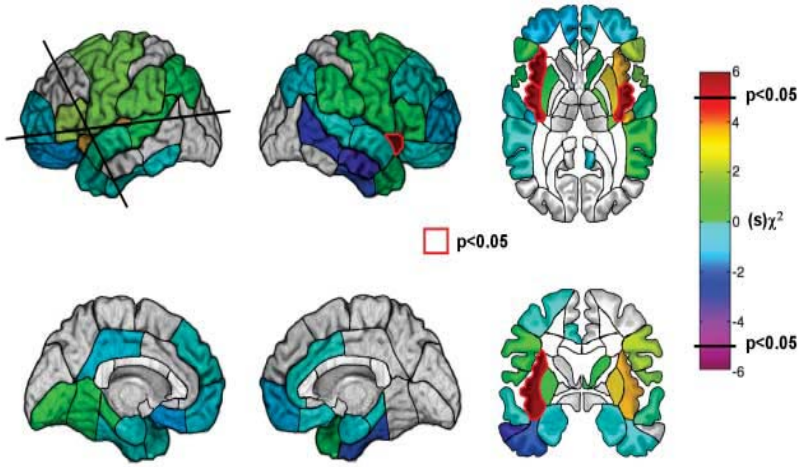


Controls (n=10)

- 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)*
- Inactivation of insular cortex in rats eliminates drug seeking *(Contreras et al., Science 2007, Forget et al. Biol Psych 2010)*

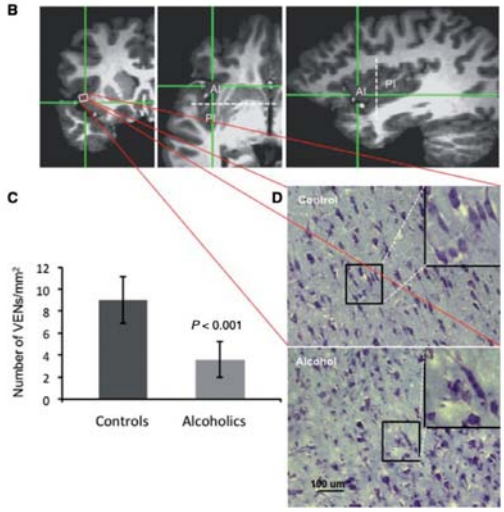
Myric et al, Neuropsychopharm 2004

Damage to the insula in humans disrupts addiction to cigarette smoking



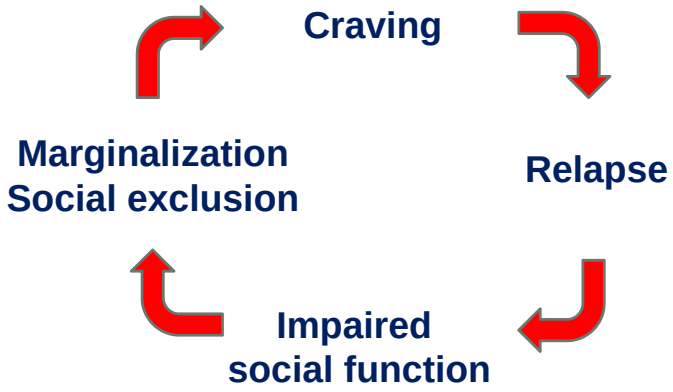
Naqvi et al., Science 2007; TiNS 2008

Pronounced loss of von Economo neurons in the anterior insula of patients with alcohol addiction



Senatorov et al, 2015, Heilig et al. Nat Rev Neurosci 2016

A vicious circle



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