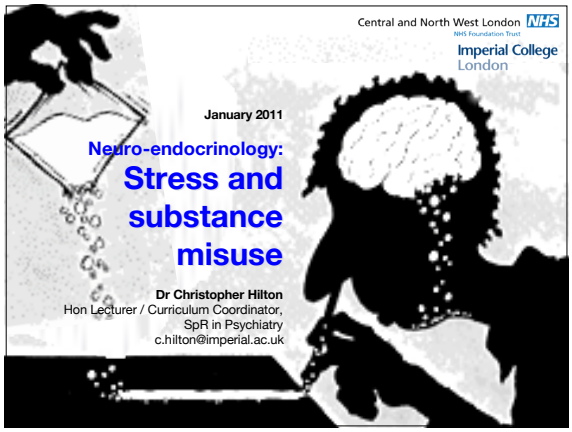


Lecture context, aims and objectives

Course aims and content:

- To provide an understanding of the body's **response to stressful stimuli**, including analysis of the regulation of the **HPA axis**… the **central actions of stress hormones**

- Assess impact of **early life exposure to stress** and glucocorticoid hormones on disease susceptibility later in life

- Highlight scope for **new therapeutic approaches**

Lecture context, aims and objectives

Related topics:

- Hypothalamus - coordinator of the stress response
- Behavioural and autonomic responses to stress
- HPA axis and depression
- **Stress and substance misuse**
- Glucocorticoids, stress and hypertension
- Corticosteroids in perinatal life
- Glucocorticoid exposure and early human development

Lecture context, aims and objectives

By the end of this lecture students should be better able to:

- Define key concepts in **addiction** and **stress**
- Describe a simplified model of central **stress** and **reward pathways**
- Interpret pre-clinical research into **stress** and **addiction**
- Revise psychological concepts of **reinforcement** and **conditioning**
- Consider mechanisms by which **stress** may contribute to **substance abuse** and **relapse**

Introduction

For some individuals the **use** of addictive substances moves from being **occasional or limited** to **chronic / dependent state** where individuals have **loss of control** over their intake of the substance

ICD-10 differentiates
use / intoxication
harmful use
dependence

Dependence syndrome - ICD-10

Three or more at once in the last year:

- Strong desire or compulsion — **CRAVING**
- Neglect of other activities

- Difficulty controlling use (amount, termination)
- Persistent use despite adverse consequences — **LOSS OF CONTROL**
- Tolerance
- Withdrawal symptoms — **NEGATIVE PHYSICAL AND AFFECTIVE STATE WHEN ACCESS TO DRUG PREVENTED**

Introduction

"Tobacco, alcohol and drug use and mental health"
UK ONS 2002

48% population drinks > twice a week
26% assessed as hazardous
7% assessed as dependent

27% reported ever using drugs
1.7% reported ever using IV
6% using in last month
4% assessed as dependent

Introduction

"Tobacco, alcohol and drug use and mental health"
UK ONS 2002

Likelihood of hazardous or dependent drug or alcohol use increased with higher **psychiatric symptom scores.**

Smoking, drinking and drug-taking (esp dependence) was associated with **stressful life-events**
eg: recent divorce, unemployment homelessness. Care?

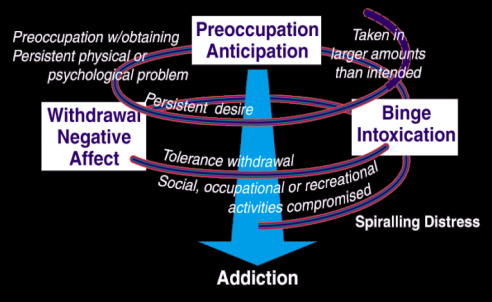
Neurobiology of addiction

Drug addiction is a chronic relapsing brain disorder characterized by neurobiological changes that lead to a **compulsion to take a drug** with **loss of control over drug intake**

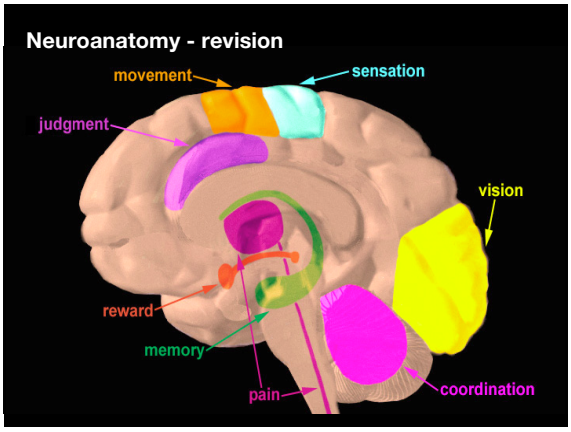
Transition from **recreational** to **obsessive use**

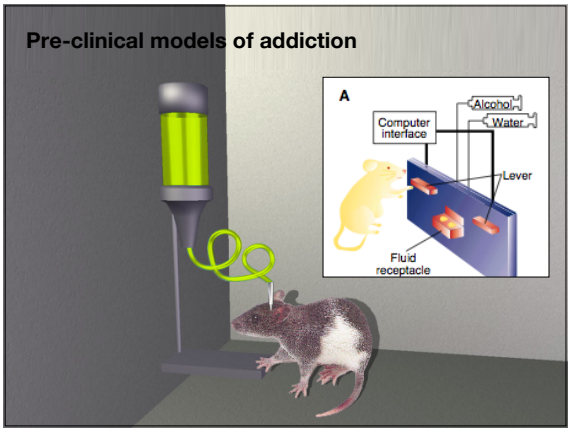
From **positive** to **negative** reinforcement

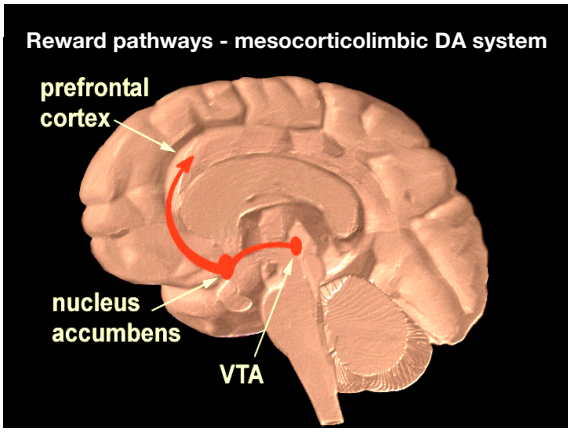
Spiral of dependence

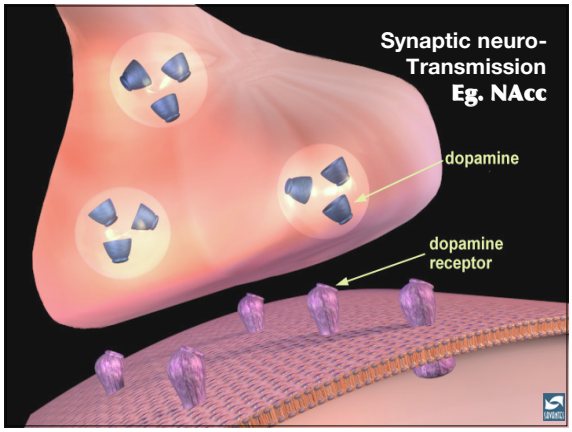


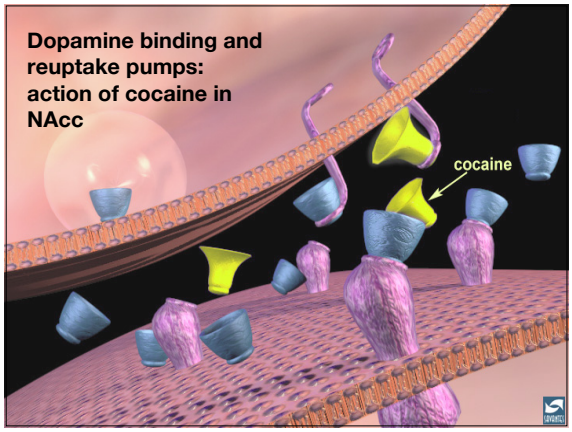
Koob GF and Le Moal M, *Science*, 1997


Neuroanatomy - revision
movement
sensation
judgment
vision
reward
memory
pain
coordination


Pre-clinical models of addiction
A
Alcohol
Water
Computer interface
Lever
Fluid receptacle

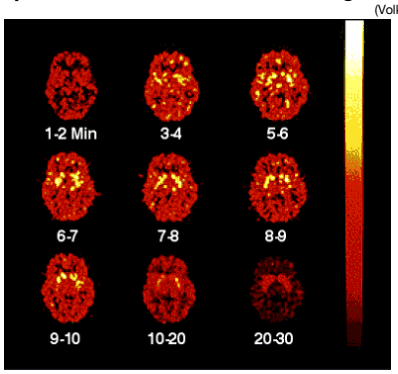

Reward pathways - mesocorticolimbic DA system
prefrontal cortex
nucleus accumbens
VTA





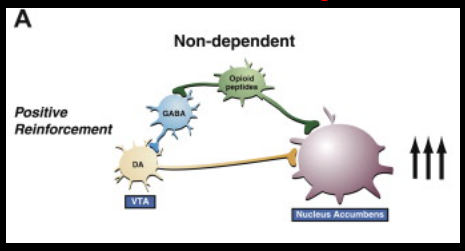
Time lapse PET scan of cocaine binding

(Volkow, 1989)

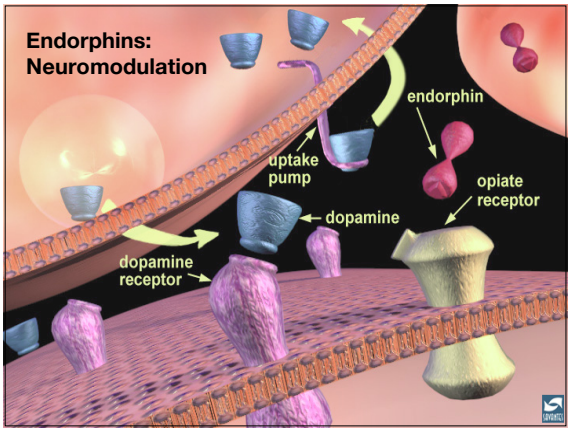


Neurobiology of addiction

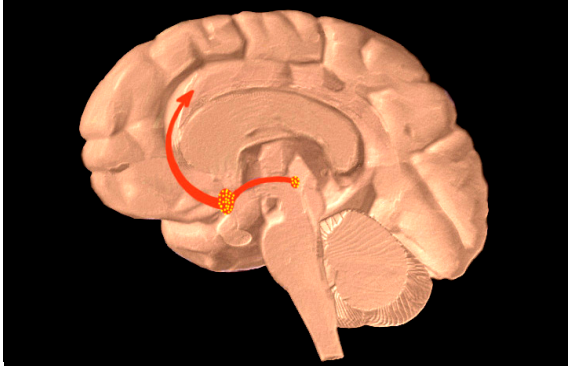
Positive reinforcement - It feels good



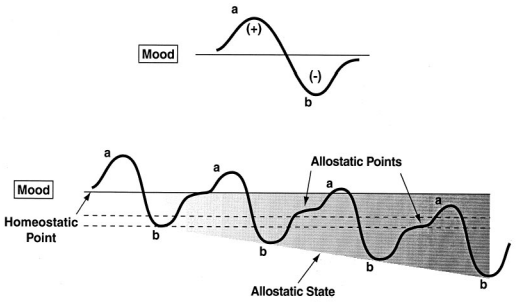
Koob, G. Neurobiological substrates for the dark side of compulsivity in addiction. Neuropharmacology. 56, (2009) 18-31



Reward pathways and negative reinforcement



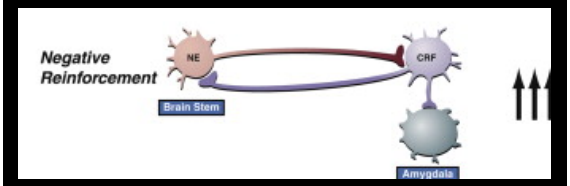
Affective allostasis:
Positive pathways disrupted



Koob

Neurobiology of addiction

Negative reinforcement - not doing it feels bad
Activation of stress circuit



Koob, G. Neurobiological substrates for the dark side of compulsivity in addiction. Neuropharmacology. 56, (2009) 18-31

Stress and the brain

- Harmful, threatening or challenging events
- Acute - novel stimulus, short lived
  - allows learning / adaptation
- Chronic - early trauma / abuse
  - adult illness / unemployment

- Perception
- Interpretation / appraisal
- Response
  - Physiological
  - Cognitive
  - Behavioural

Stress and the brain

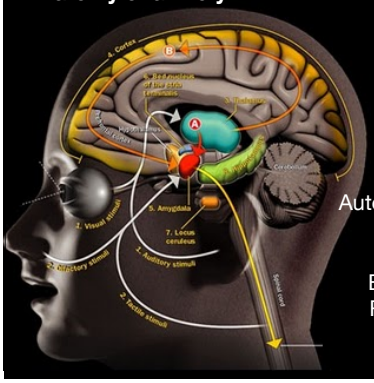
• Produce conditioned or unconditioned emotional reactions according to appraisal of situation. Eg: anger, fear, anxiety, excitement, pleasure, sadness

• Amygdala / limbic system and PFC contribute to determining significance

• Response produced via activation of HPA axis and autonomic system - Adrenaline / cortisol / endorphins

• Fight, fright, flight

Anatomy of anxiety



Limbic / Amygdala

Hypothalamus
Pituitary
Adrenals

Autonomic activation
Locus Coeruleus

Endorphin release
Reward activation

Stress and the brain

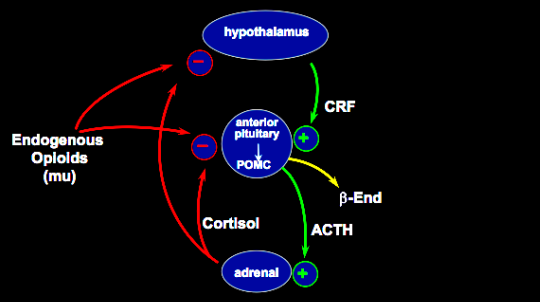
• Produce conditioned or unconditioned emotional reactions according to appraisal of situation. Eg: anger, fear, anxiety, **excitement**, **pleasure**, sadness

• Stress increases reward pathways (DA) including through endogenous opioid release / neuromodulation

• ? 'Adrenaline junkies'

HPA axis activation and endorphin release

Kreek



Stress and substance misuse

Tension reduction / self medication
Reduce -ve affect and increase +ve affect
(reinforces drug taking)

Stress activates reward pathways

Sensitisation to reinforcing properties of drugs

Endorphins

Stress and substance misuse - WITHDRAWAL

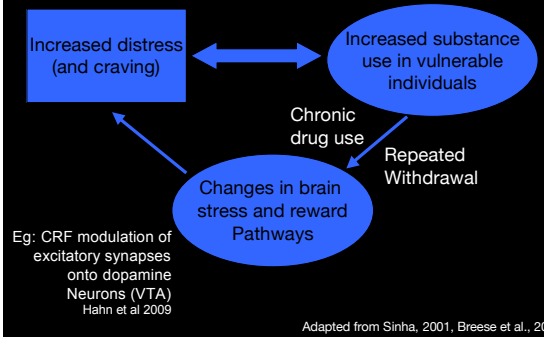
Drug withdrawal associated with:
Increased CRH in CSF
Increased plasma ACTH
Increased Cortisol (NA, Adr)

In early abstinence:
Blunted synACTHen test (etoh)

Hyperresponsivenes of HPA
in response to metyrapone (crack)

= Negative affect
Cure? - more drugs

Stress-induced neuroadaptation



Eg: CRF modulation of excitatory synapses onto dopamine Neurons (VTA)
Hahn et al 2009

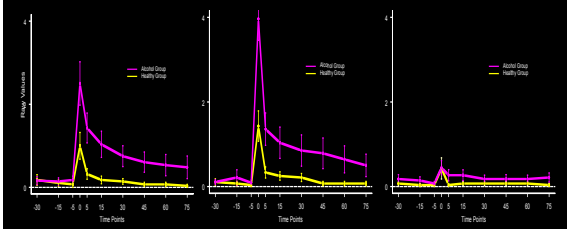
Adapted from Sinha, 2001, Breese et al., 2005

Models of relapse triggers

- Drug induced reinstatement
- Cue induced reinstatement
- Stress induced reinstatement

Stress and Cue-Induced Alcohol Craving in Abstinent Alcoholics

STRESS ALCOHOL CUE NEUTRAL



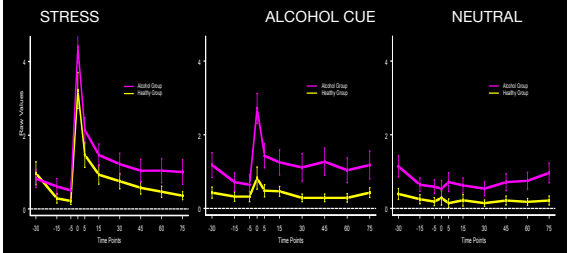
Group Difference: F{1,55}= 81.13, p<.0001(AD> HC in S and Cue Response, p<.0001)

Group X Condition: F{2,110}=12.07, p<.0001

Group X Timepoints: F{7,385}=3.95, p<.0004

Sinha et al., 2005

Stress and Cue-Induced Anxiety in Abstinent Alcoholics

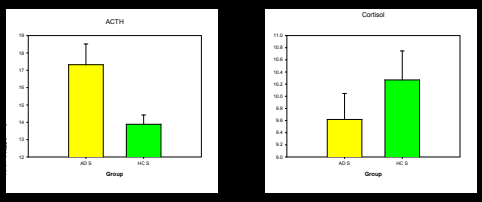


Group Difference: F{1,55}= 82.5, p<.0001(AD> HC in S and Cue Response, p<.0001; baseline Group Difference: AD > HC (p<.007)

Group X Condition: F{2,110}= 5.01, p<.008 (no increase in anxiety in cue condition for controls but greater increases in anxiety in AD subjects in all three conditions)

Sinha et al., 2005

Altered Stress-Induced ACTH and Cortisol Responses in Abstinent Alcoholics



Cases > Controls (p<.05)

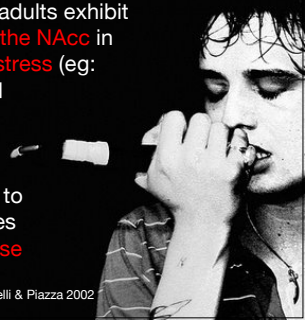
Cases < Controls (p<.05)

Junghanns et al., 2003; Sinha et al., unpublished

Models of chronic stress in infancy

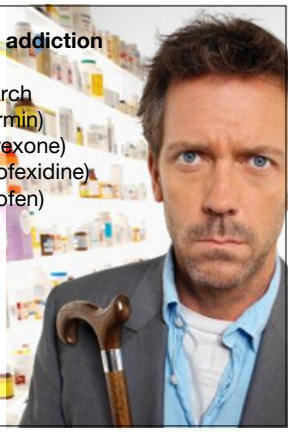
Animals exposed to adverse early life events (eg: maternal separation) as adults exhibit increased DA release in the NAcc in response to acute mild stress (eg: tail pinch) and enhanced locomotor responses to stress or cocaine.

? Altered resposiveness to mesolimbic DA influences vulnerability to drug abuse



Piazza 1991, Rouge-Point 1993,96, Marinelli & Piazza 2002

Treatment strategies for addiction



Biological - areas of research
- CRF antagonists (antalarmin)
- Opioid antagonists (naltrexone)
- CNS Alpha 2 Agonists (lofexidine)
- GABAergic agents (baclofen)

Psychological
- CBT / MI
- 12 Step
- Relaxation

Social / environmental
- Cues / peers

Summary

We have reviewed **reward** and **stress** pathways.

Stress (acute, in infancy or chronic) increases **risk of substance use, dependence and relapse**

Hypothesised mechanism: altered stress pathways in substance misuse and altered reward pathways in stress

Treatment outcomes may be improved by targeting stress through **pharmacotherapy** or **psychosocial** factors

Neuro-endocrinology:

Stress and substance misuse

References:

Neurobiology of substance misuse
Anything by George Koob

Eg: Koob G. The neurobiology of addiction: a neuroadaptational view for diagnosis. Addiction (2006) 101 (Suppl. 1) 23-30

Stress and substance misuse
Sinha, R. How does stress increase risk of drug abuse and relapse? Psychopharmacology (2001) 158:343:359