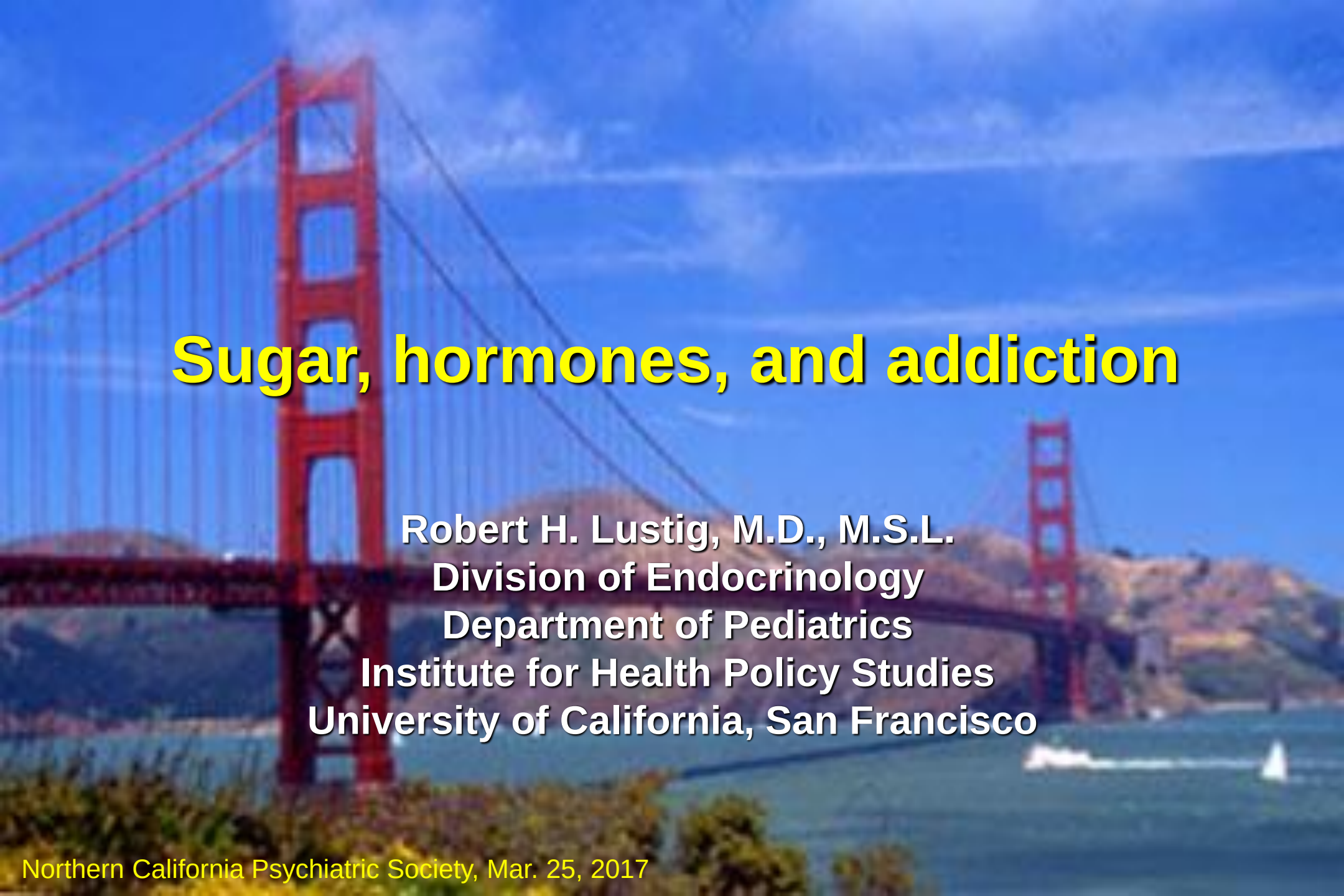


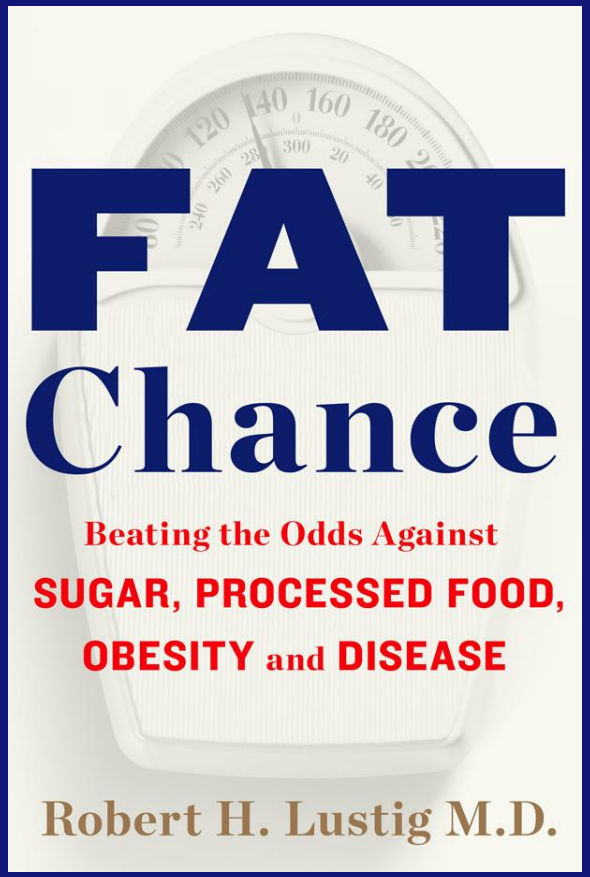
Sugar, hormones, and addiction

Robert H. Lustig, M.D., M.S.L.
Division of Endocrinology
Department of Pediatrics
Institute for Health Policy Studies
University of California, San Francisco

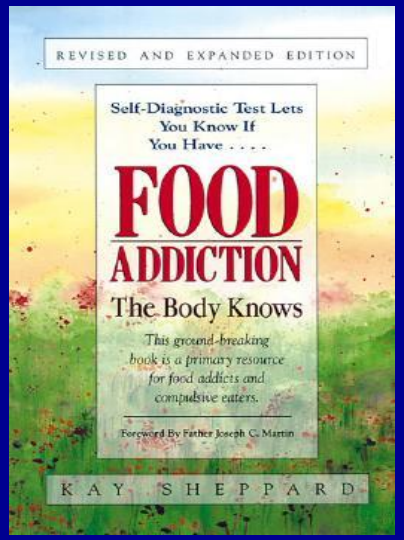
Northern California Psychiatric Society, Mar. 25, 2017

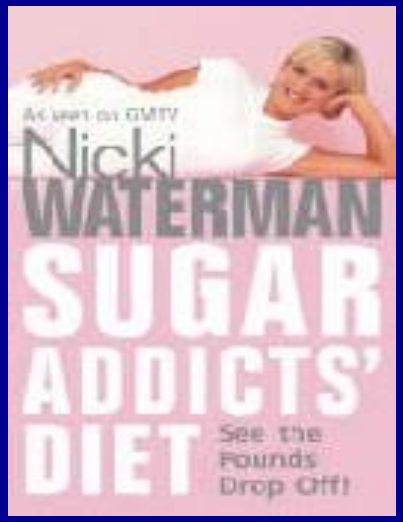
- **No disclosures**

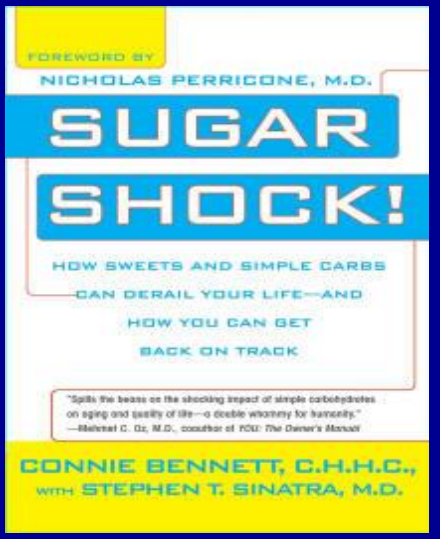
(except I wrote a book)

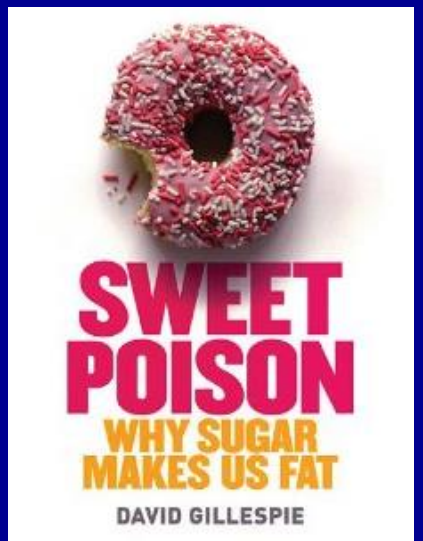


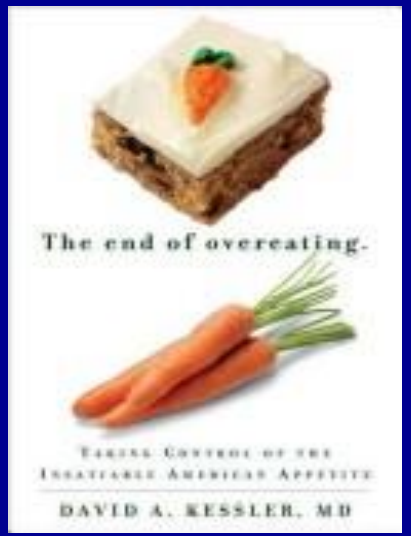
Is food addictive?
The lay public seems to know….

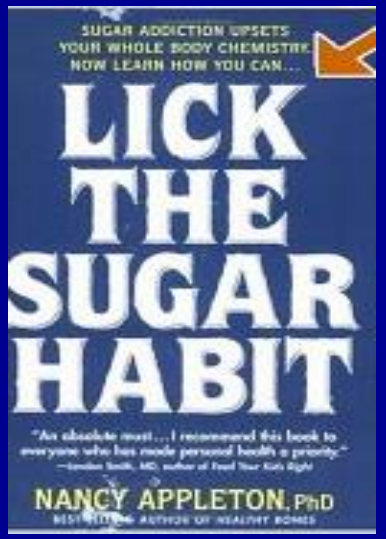












Similarities between obesity and addiction

	food	drug
potency as a reinforcer[a]	++	oral, ++ snorted, +++ smoked, injected ++++
delivery	oral	oral, snorted, smoked, injected
mechanisms reward	somatosensory (palatability) chemical (glucose)	chemical (drug)
relevance of kinetics	not investigated	the faster the stimulation the more powerful its reinforcing effects
regulation of intake	peripheral and central factors	mostly central factors
adaptations	physiologic	supraphysiologic
physiological role	necessary for survival	unnecessary
learning	habits conditioned responses	habits conditioned responses
role of stress	+++	+++

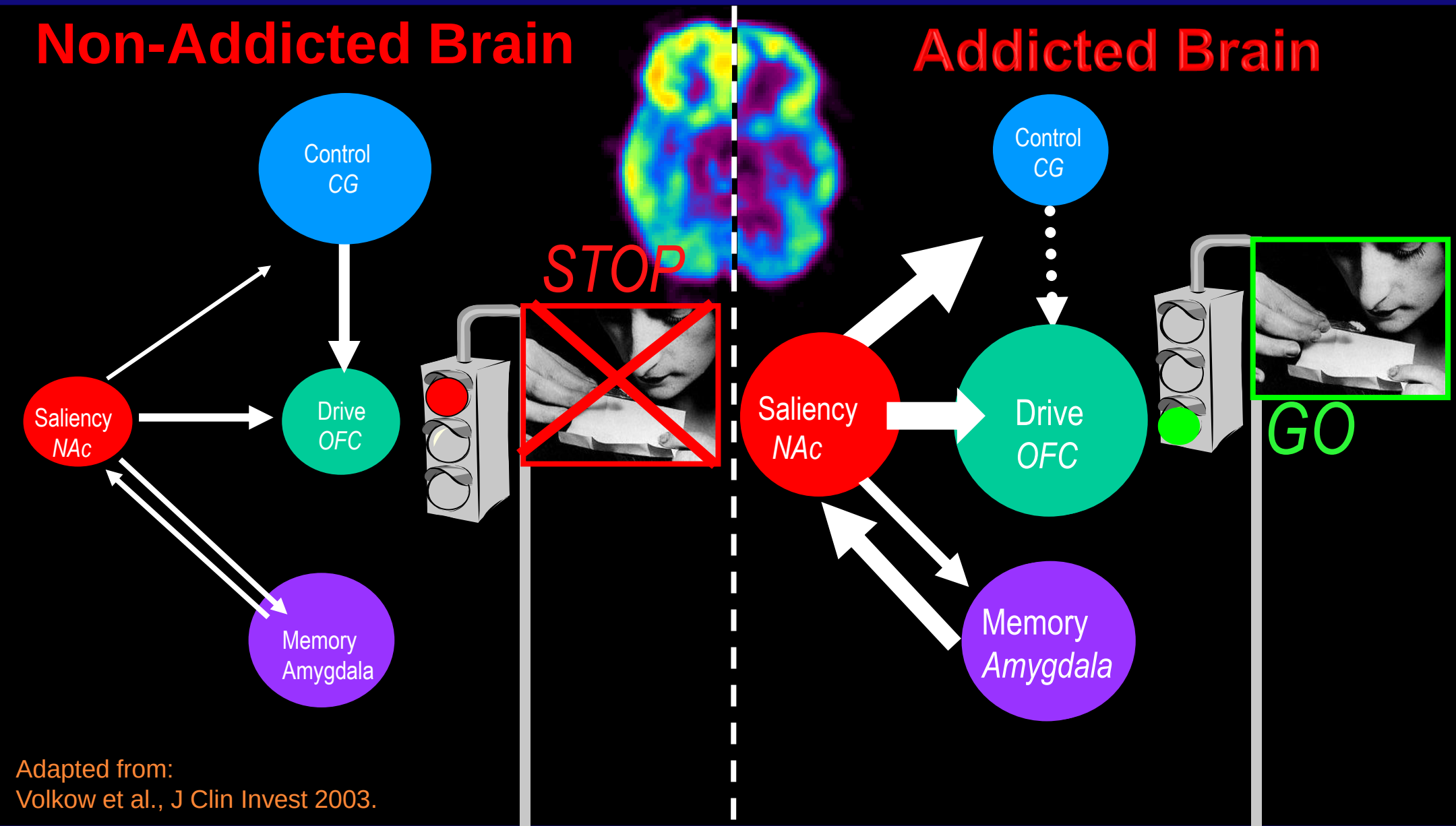
Volkow et al. Philos Trans R Soc Lond B Biol Sci. 2008 363:3191, 2008

Similarities between obesity and addiction

disrupted functions	implicated brain region
impaired inhibitory control	prefrontal cortex
to drug intake in addiction	anterior cingulate gyrus
to food intake in obesity	lateral orbitofrontal cortex
enhanced reward	nucleus accumbens
to drugs in addiction	ventral pallidum
to food in obesity	hypothalamus
conditioning/habits	amygdala
to drugs and drug cues in addiction	hippocampus
to food and food cues in obesity	dorsal striatum
Enhanced motivation/drive	medial orbitofrontal cortex
to consume drugs in addiction	mesencephalic dopamine nuclei
to consume food in obesity	dorsal striatum
emotional reactivity	amygdala
	ventral cingulate gyrus

Volkow et al. Philos Trans R Soc Lond B Biol Sci. 2008 363:3191, 2008

Neuroendocrine circuits in addiction



Adapted from:
Volkow et al., J Clin Invest 2003.

Yale Food Addiction Scale

- In 2009, the Yale Food Addiction Scale (YFAS) was created to study food addiction by applying the DSM-IV criteria for substance dependence to eating behaviors

Sample items:

- "I find myself continuing to consume certain foods even though I am no longer hungry"
- "I eat to the point where I feel physically ill"
- "I find that when I start eating certain foods, I end up eating much more than planned"

Gearhardt et al. Arch Psychiatr 2009

YFAS correlates with neuroimaging

- YFAS related to greater responsivity of reward regions (caudate, ACC, medial OFC, amygdala)
  and lower responsivity of an inhibitory control region (lateral OFC)

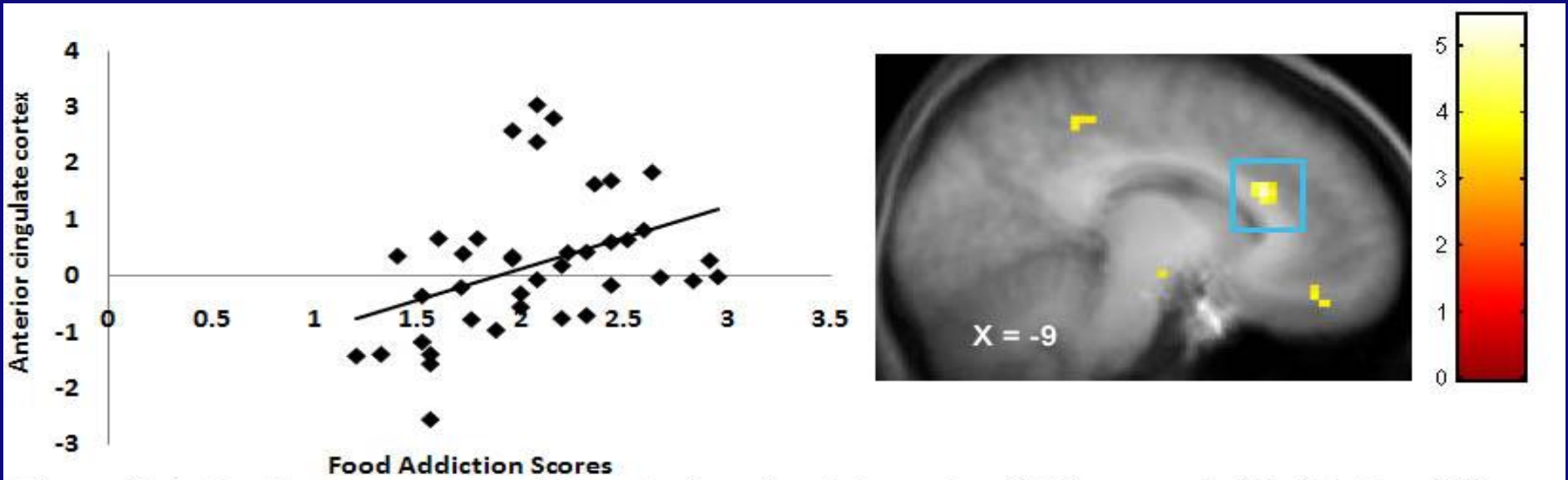


Figure 2. Activation in a region of the anterior cingulate cortex (MNI x,y,z: -9, 24, 27, Z = 4.64; pFDR <.001) during milkshake cues vs tasteless solution cues as a function of Yale Food Addiction Scale scores, with the graph of parameter estimates from that peak.

Palatable food cues trigger these areas as well

- Greater reward region response to palatable food cues predicts future weight gain
- Similar effects for substance use onset

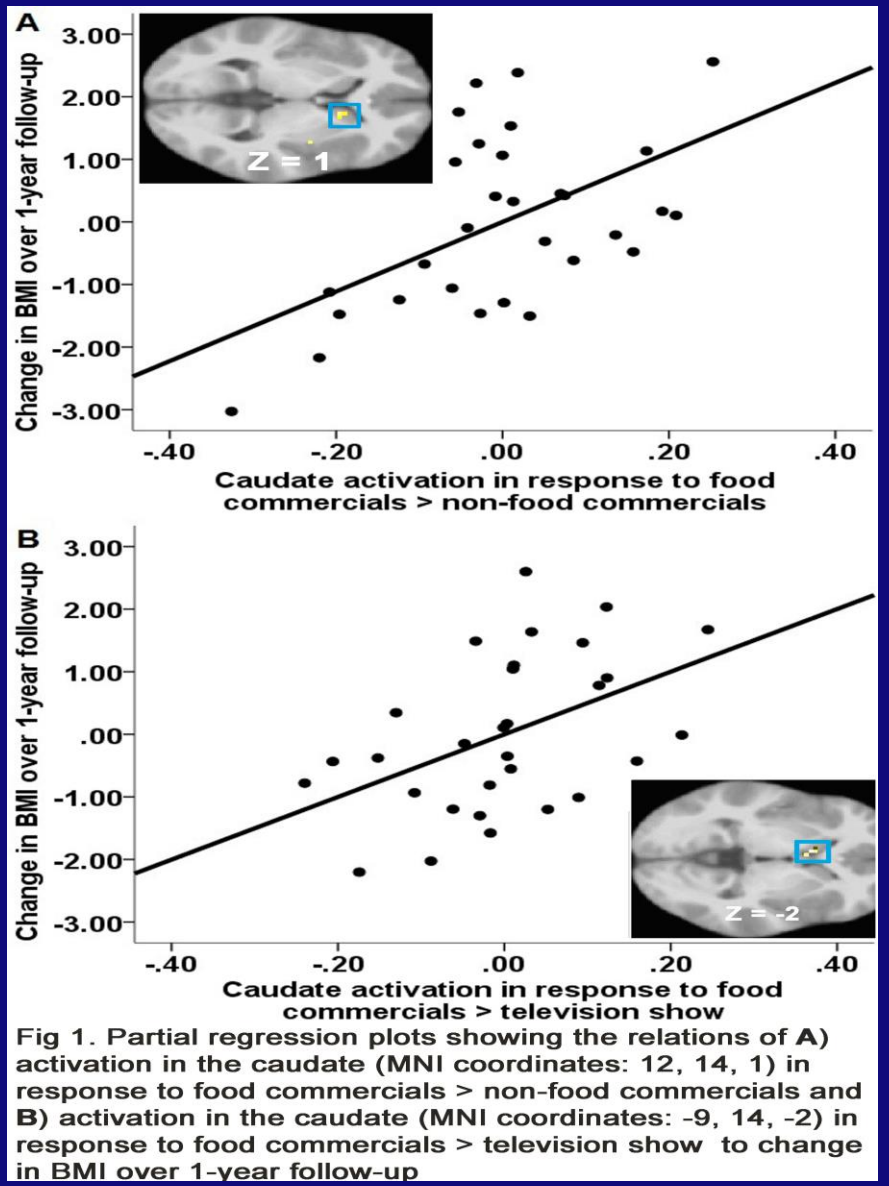


Fig 1. Partial regression plots showing the relations of **A)** activation in the caudate (MNI coordinates: 12, 14, 1) in response to food commercials > non-food commercials and **B)** activation in the caudate (MNI coordinates: -9, 14, -2) in response to food commercials > television show to change in BMI over 1-year follow-up

Chouinard et al. 2010; Demos et al. 2012; Stice et al. 2010; Yokum et al. 2011; Stice et al. 2013

Overlap between Binge Eating Disorder and Addiction

- 79 women with BED

  92.4% met the DSM-IV criteria for substance dependence when questions substituted "substance" with "binge eating"

  (Cassin and von Ranson, Appetite 48:687, 2007)

- Bariatric surgery candidates with BED had addictive personality scores similar to what has been reported for individuals with substance dependence disorder

  (Lent and Swencionis, Eat Behav 13:67, 2012)

OPINION

Obesity and the brain: how convincing is the addiction model?

Hisham Ziauddeen, I. Sadaf Farooqi and Paul C. Fletcher

Abstract | An increasingly influential perspective conceptualizes both obesity and overeating as a food addiction accompanied by corresponding brain changes. Because there are far-reaching implications for clinical practice and social policy if it becomes widely accepted, a critical evaluation of this model is important. We examine the current evidence for the link between addiction and obesity, identifying several fundamental shortcomings in the model, as well as weaknesses and inconsistencies in the empirical support for it from human neuroscientific research.

Nature Rev Neurosci 13:279, 2012

CORRESPONDENCE

Tossing the baby out with the bathwater after a brief rinse? The potential downside of dismissing food addiction based on limited data

Nicole M. Avena, Ashley N. Gearhardt, Mark S. Gold, Gene-Jack Wang and Marc N. Potenza

Nature Rev Neurosci 13:514, 2012

CORRESPONDENCE

Food addiction: is there a baby in the bathwater?

Hisham Ziauddeen, I. Sadaf Farooqi and Paul C. Fletcher

Nature Rev Neurosci 13:514, 2012

Neuroscience and Biobehavioral Reviews 47 (2014) 295–306

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

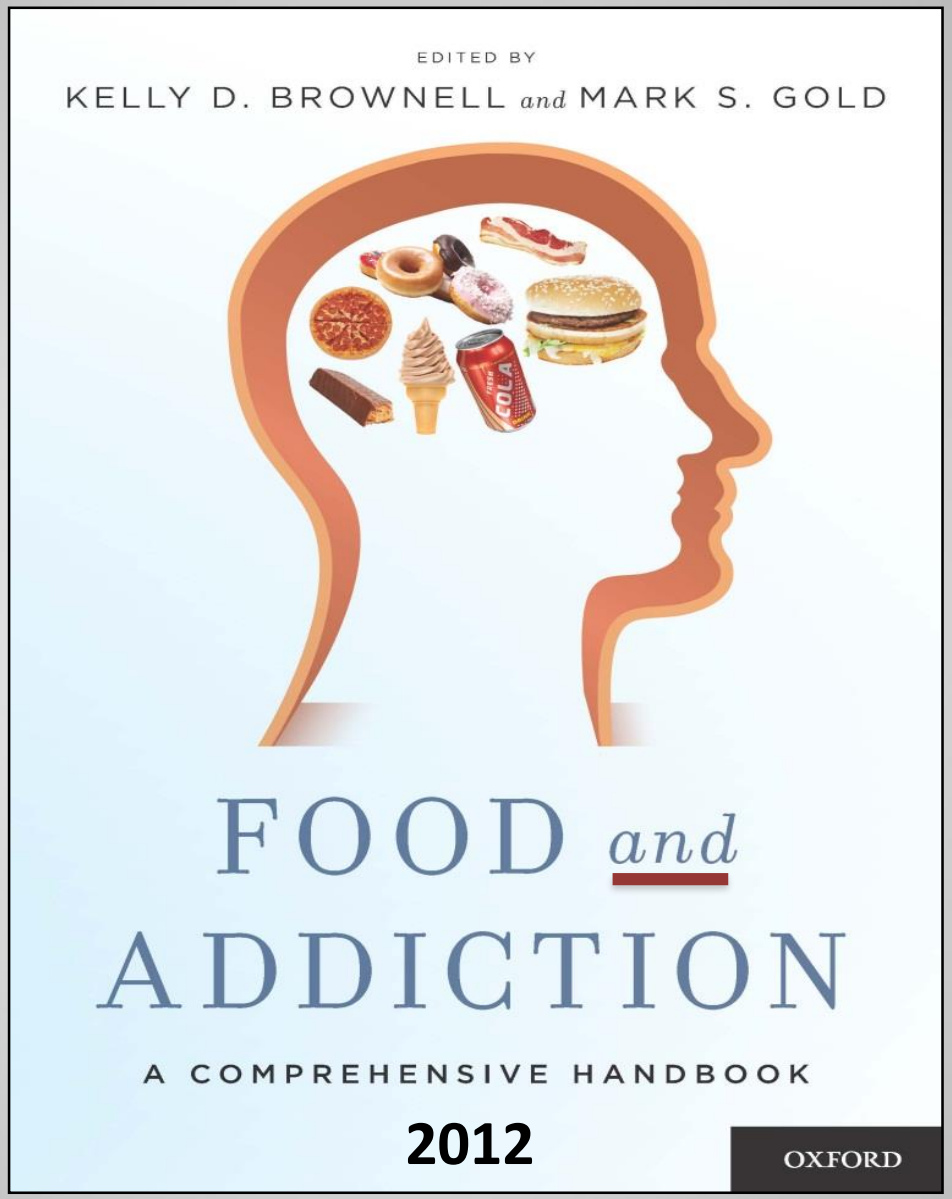
Review

"Eating addiction", rather than "food addiction", better captures addictive-like eating behavior

Johannes Hebebrand[a], Özgür Albayrak[a], Roger Adan[b], Jochen Antel[a], Carlos Dieguez[c,d], Johannes de Jong[b], Gareth Leng[e], John Menzies[e,*], Julian G. Mercer[f], Michelle Murphy[f], Geoffrey van der Plasse[b], Suzanne L. Dickson[g]

[a] Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy, Universitätsklinikum Essen (AöR), Wickenburgstr. 21, D-45147 Essen, Germany
[b] Department of Translational Neuroscience, Brain Center Rudolf Magnus, University Medical Center Utrecht, Universiteitsweg 100, 3584 CG Utrecht, The Netherlands
[c] Department of Physiology, School of Medicine, University of Santiago de Compostela, 15782 Santiago de Compostela, Spain
[d] CIBER Fisiopatología de la Obesidad y Nutrición (CIBERobn), Spain
[e] Centre for Integrative Physiology, University of Edinburgh, Hugh Robson Building, 15 George Square, Edinburgh EH8 9XD, UK
[f] Rowett Institute of Nutrition and Health, University of Aberdeen, Greenburn Road, Bucksburn, Aberdeen AB21 9SB, UK
[g] Department Physiology/Endocrine, Institute of Neuroscience and Physiology, The Sahlgrenska Academy at the University of Gothenburg, Medicinaregatan 11, SE-405 30 Gothenburg, Sweden

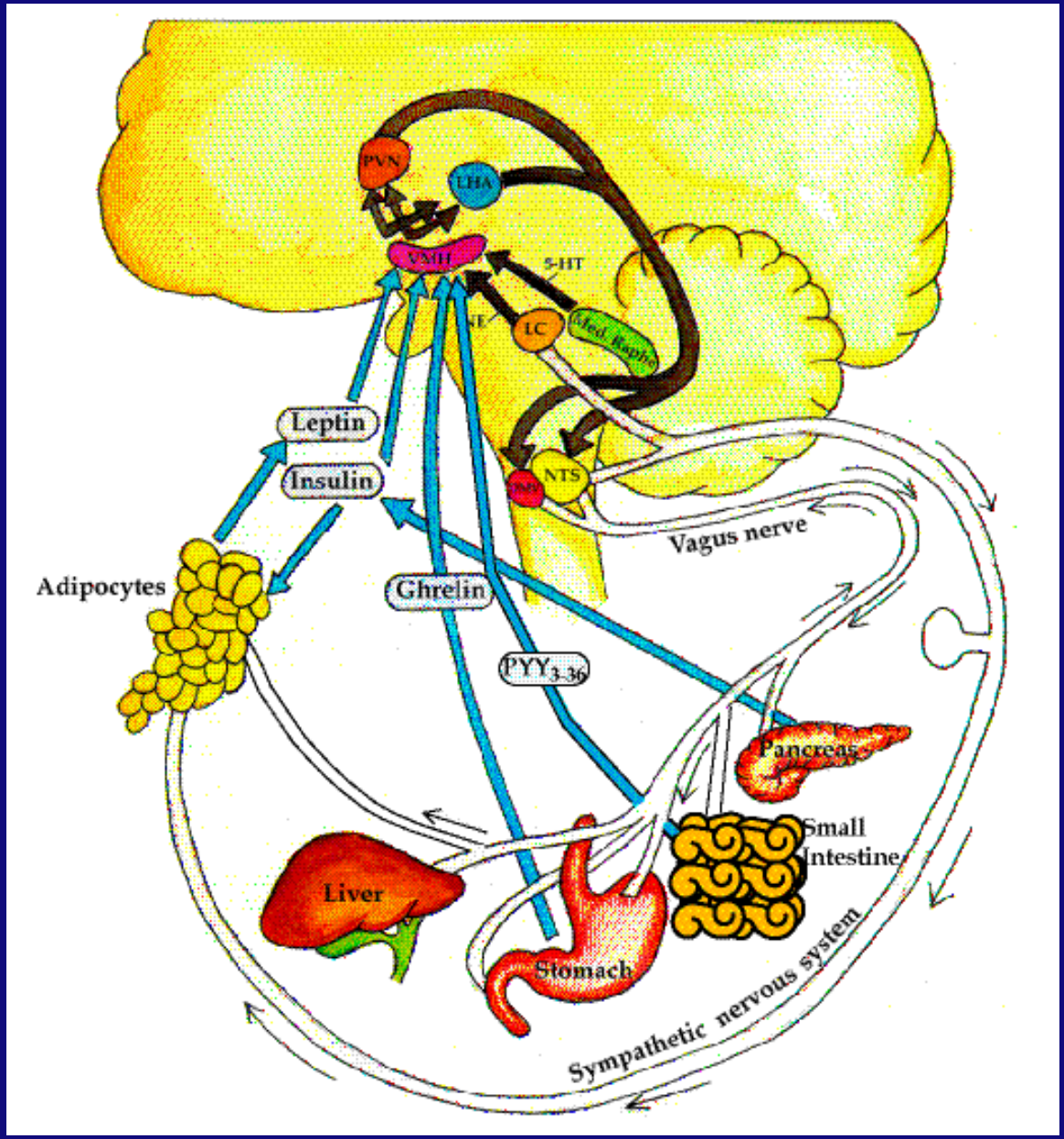
Puts the onus on the individual, not the food


EDITED BY
KELLY D. BROWNELL and MARK S. GOLD
FOOD and ADDICTION
A COMPREHENSIVE HANDBOOK
2012
OXFORD

Indirect effects on the reward system:

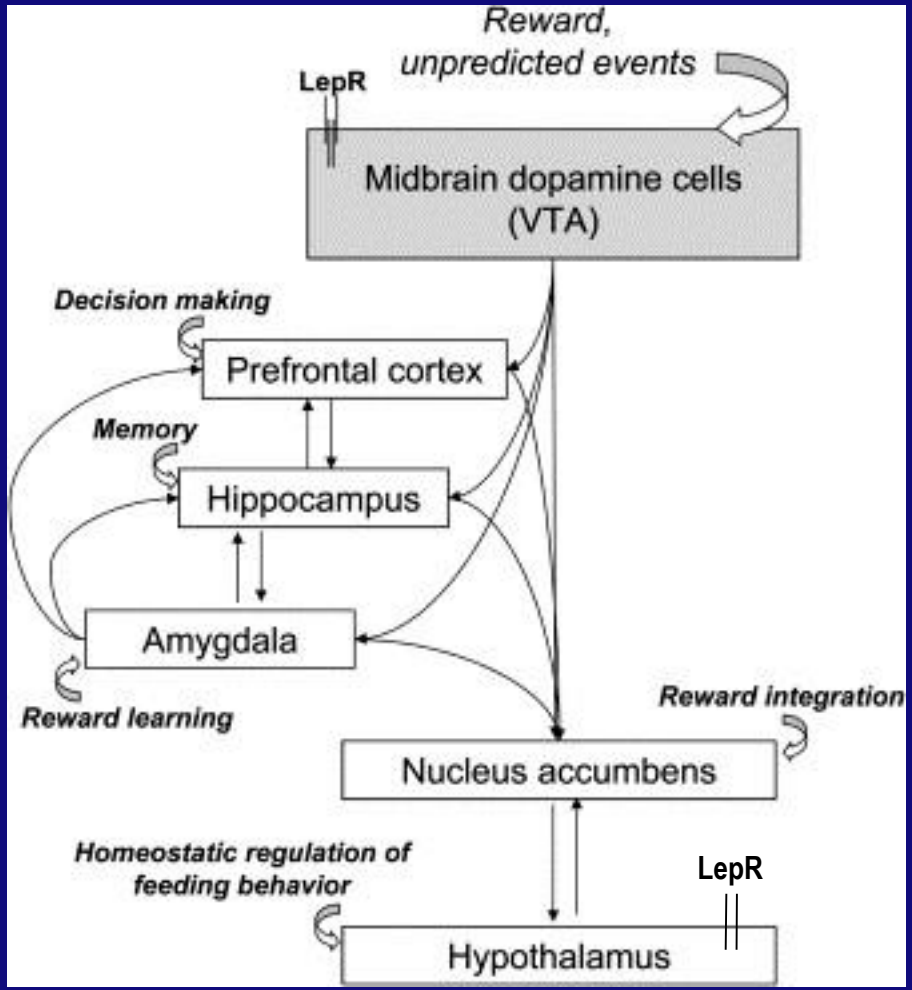
Leptin and Insulin

The neuroendocrinology of energy balance



Lustig, Endo Clin NA, 2001

The integration of the starvation and addiction pathways



Cota et al. Neuron 51:678, 2006

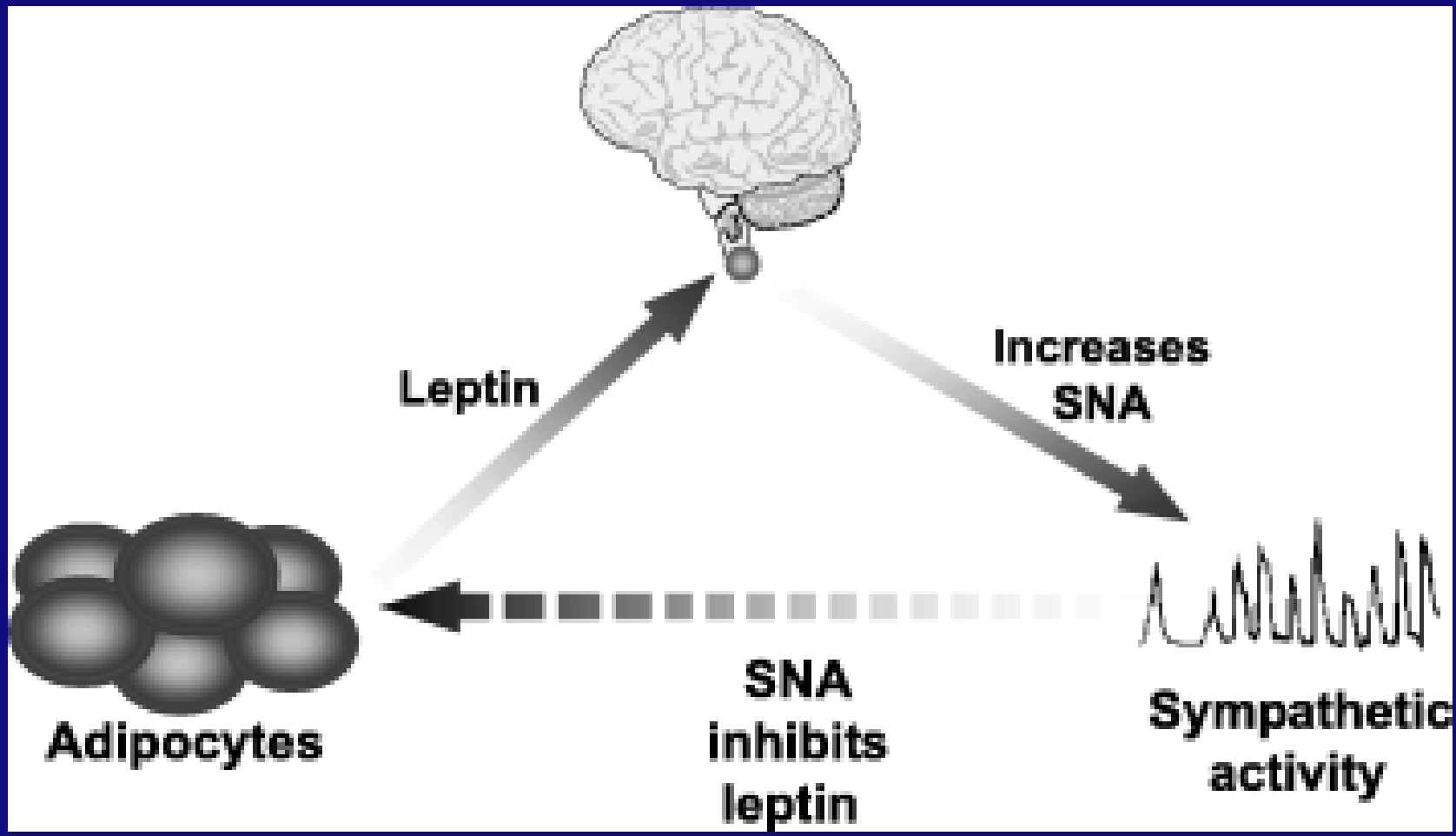
PARADOX:

If you give a 5 year old kid a cookie:

PARADOX:

If you give a 5 year old kid a cookie:

Leptin is supposed to keep us in energy balance



Mark et al. Acta Physiol Scand 177:345, 2003

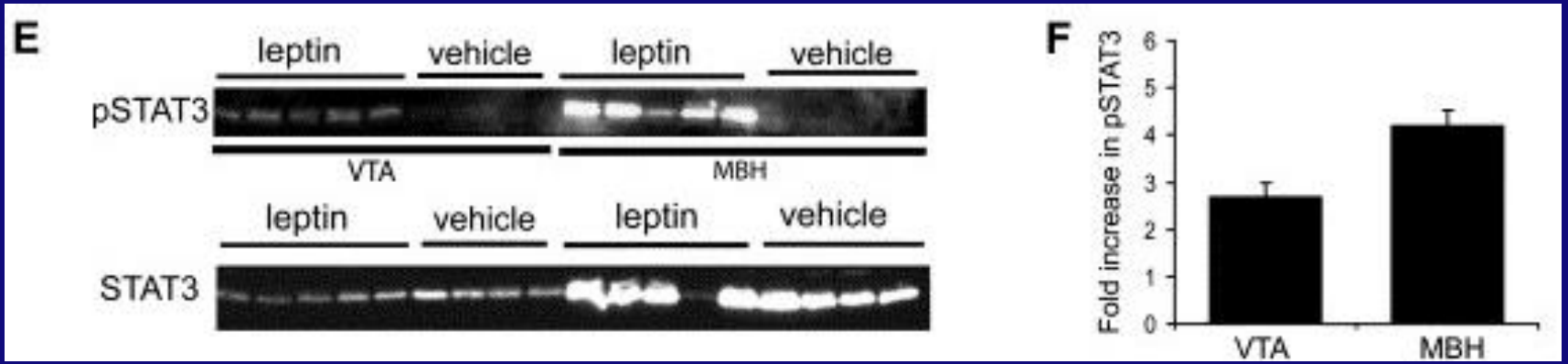
PARADOX:

But if you give a 5 year old obese kid a cookie:

PARADOX:

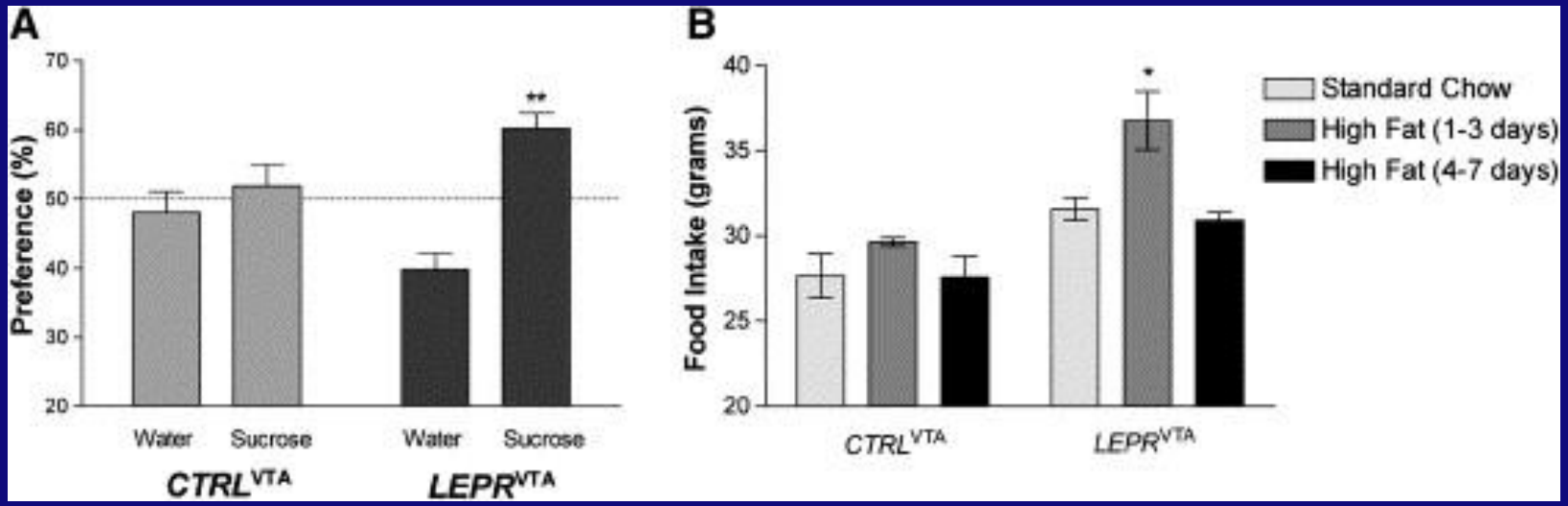
But if you give a 5 year old obese kid a cookie:

Leptin upregulates pSTAT-3 in the VTA and in the hypothalamus



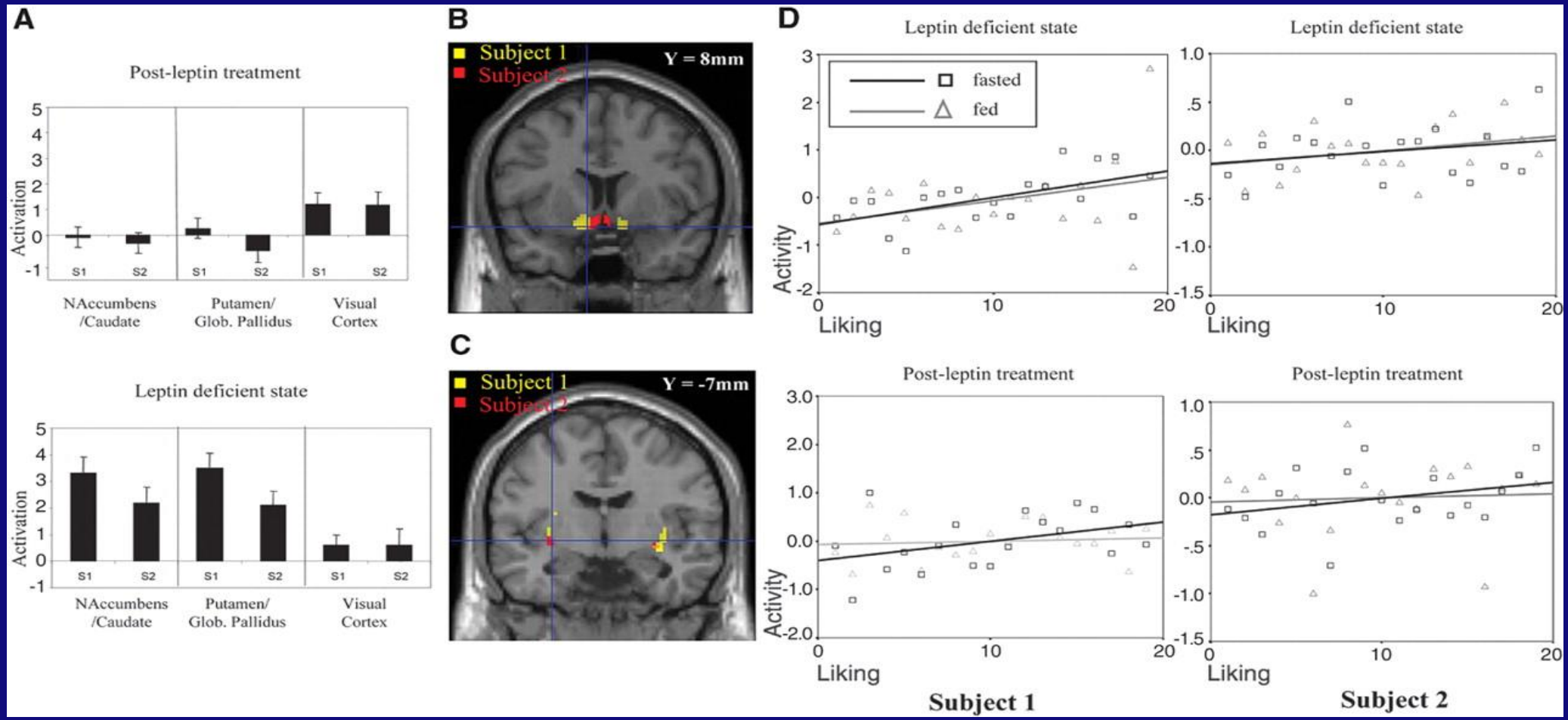
Fulton et al. Neuron 51:811, 2006

RNA-i mediated knockdown of leptin receptor in the VTA increases palatability of sucrose and fat



Hommel et al. Neuron 51:801, 2006

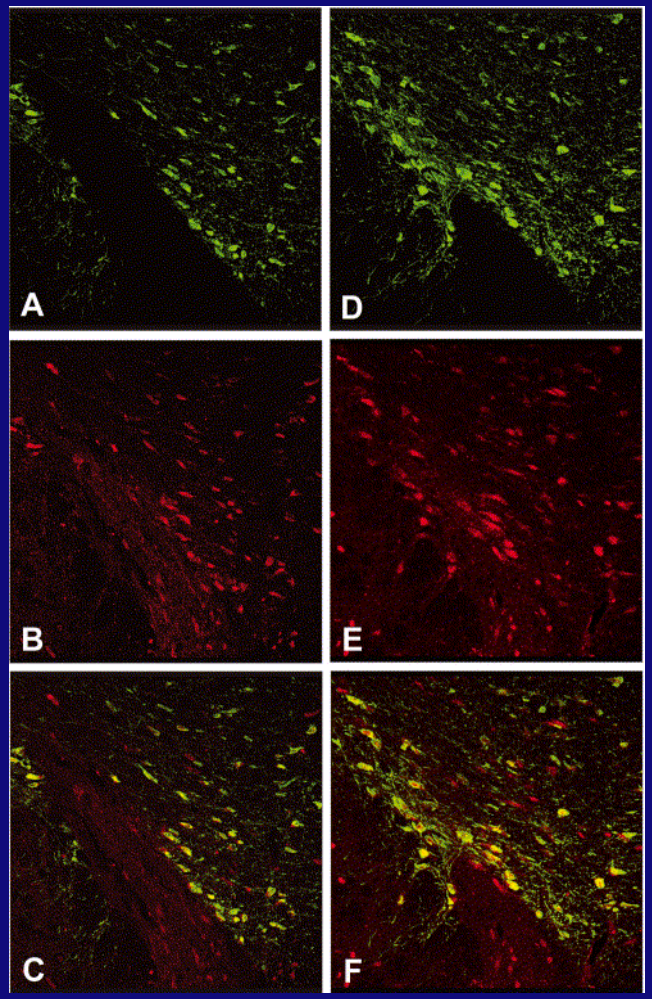
Leptin regulates brain responses to food images



Farooqi et al., Science 317:1355, 2007

Insulin and leptin receptors in dopaminergic neurons of the Ventral Tegmental Area (VTA)

Leptin receptor



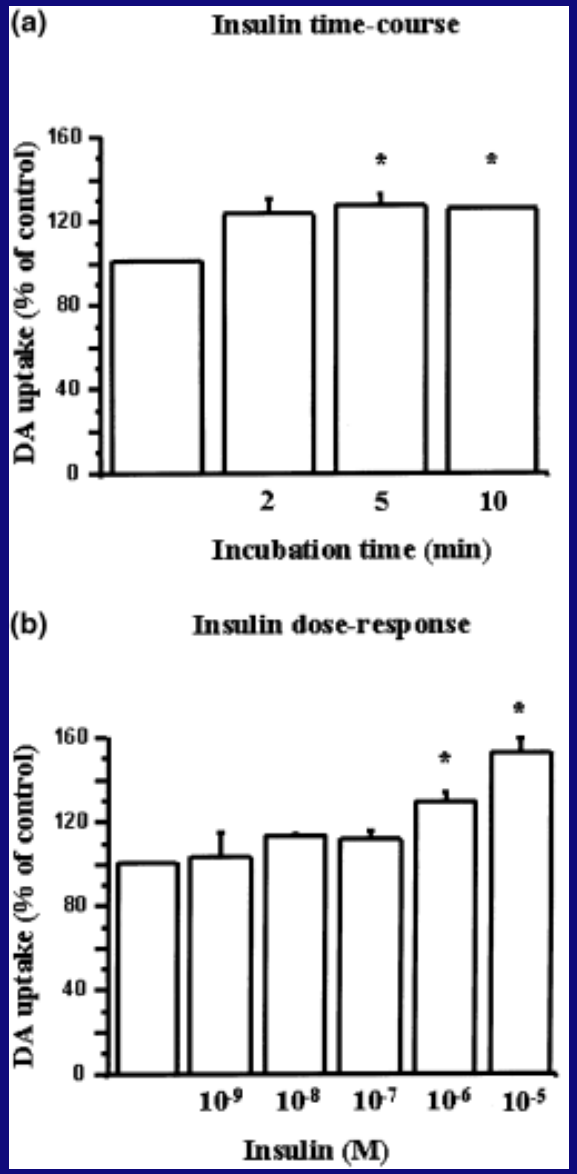
Tyrosine hydroxylase
(enzyme that makes dopamine)

Insulin receptor

Co-localization

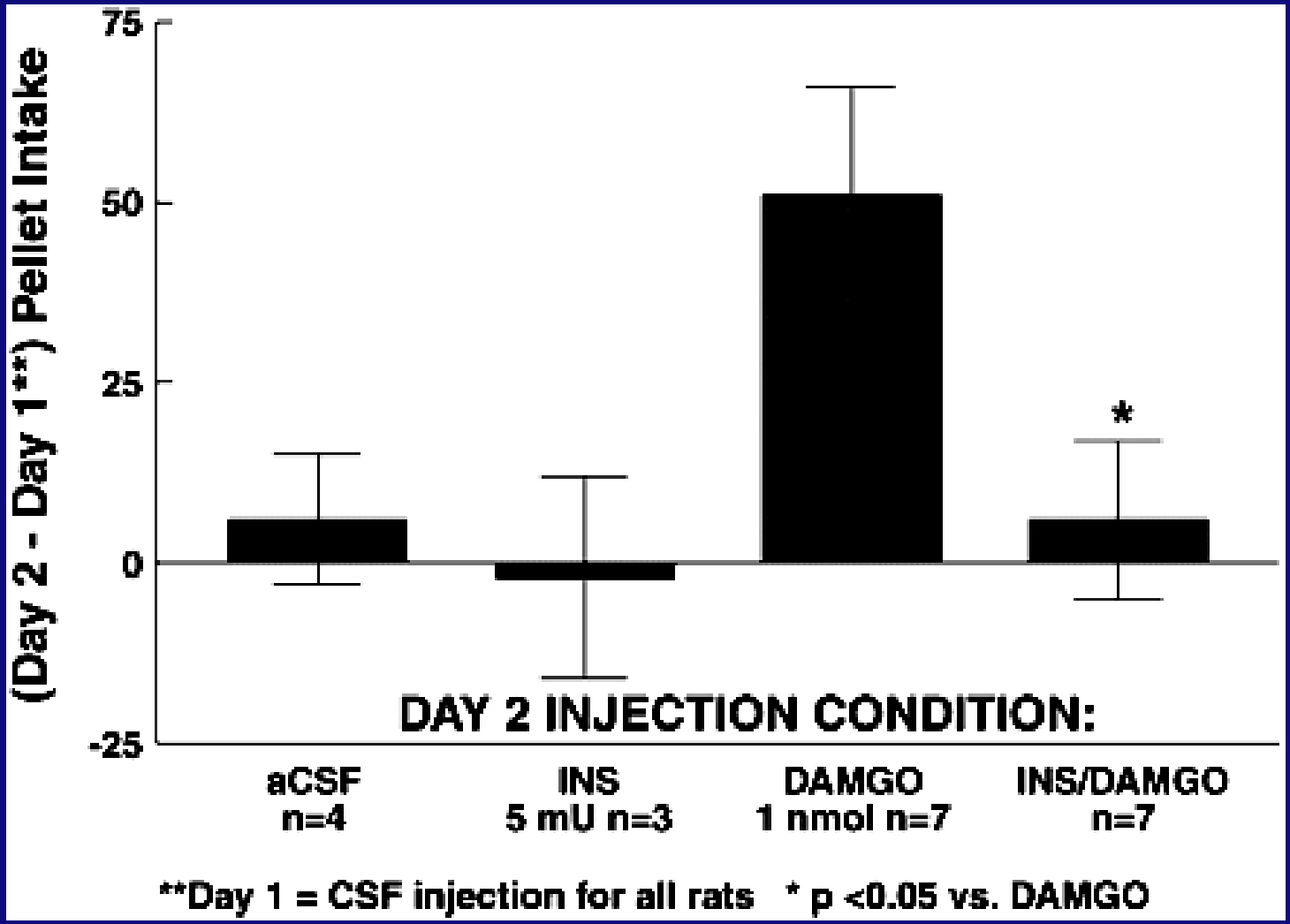
Figlewicz et al. Brain Res 964:107, 2003

Insulin stimulates [^{3}H]dopamine uptake in FLAG-hDAT cells



Carvelli et al. J Neurochemistry 81:859, 2002

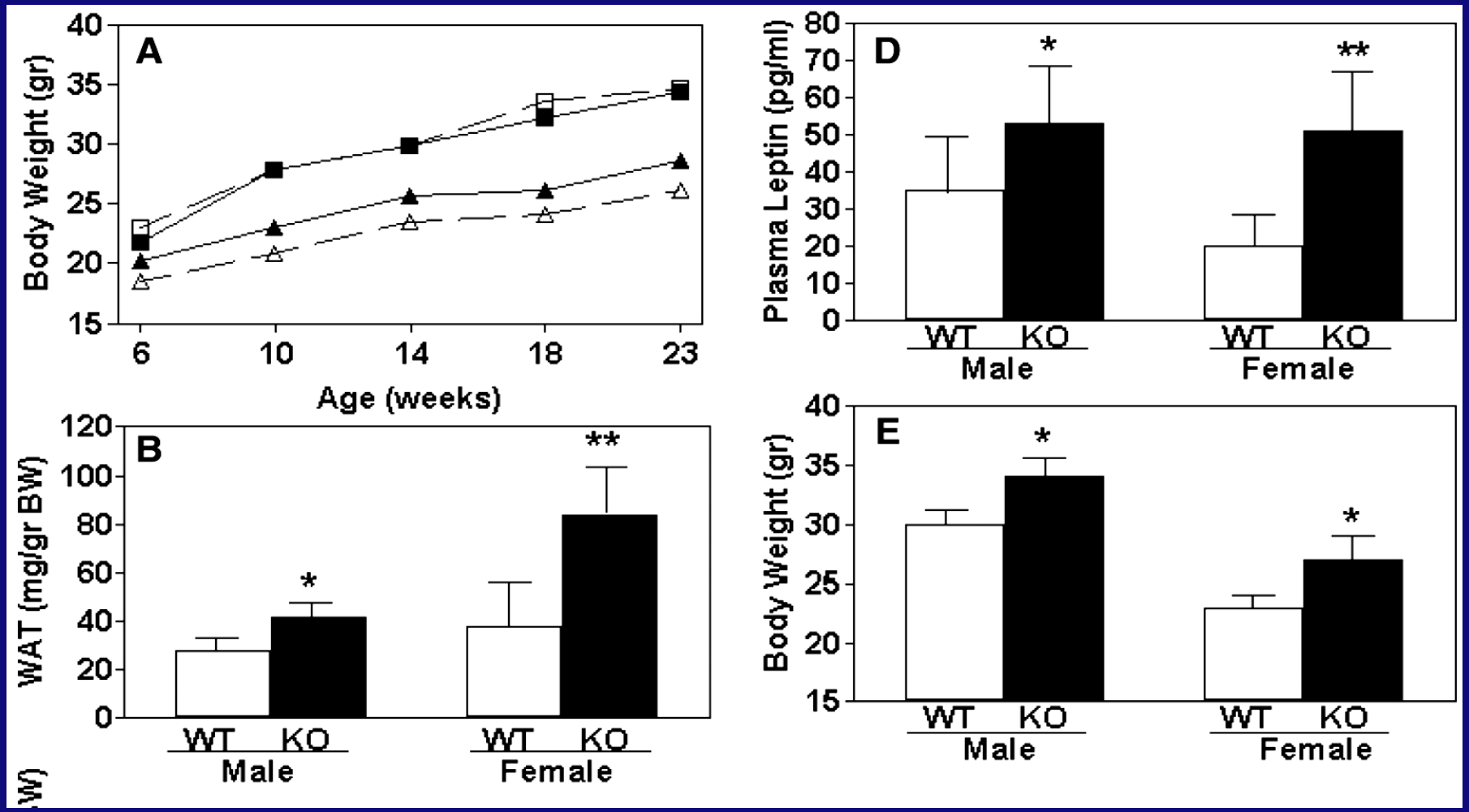
Insulin infusion into the Ventral Tegmental Area (VTA) blocks acute opiate effects on food intake



Figlewicz et al. Am J Physiol 284:R882, 2003

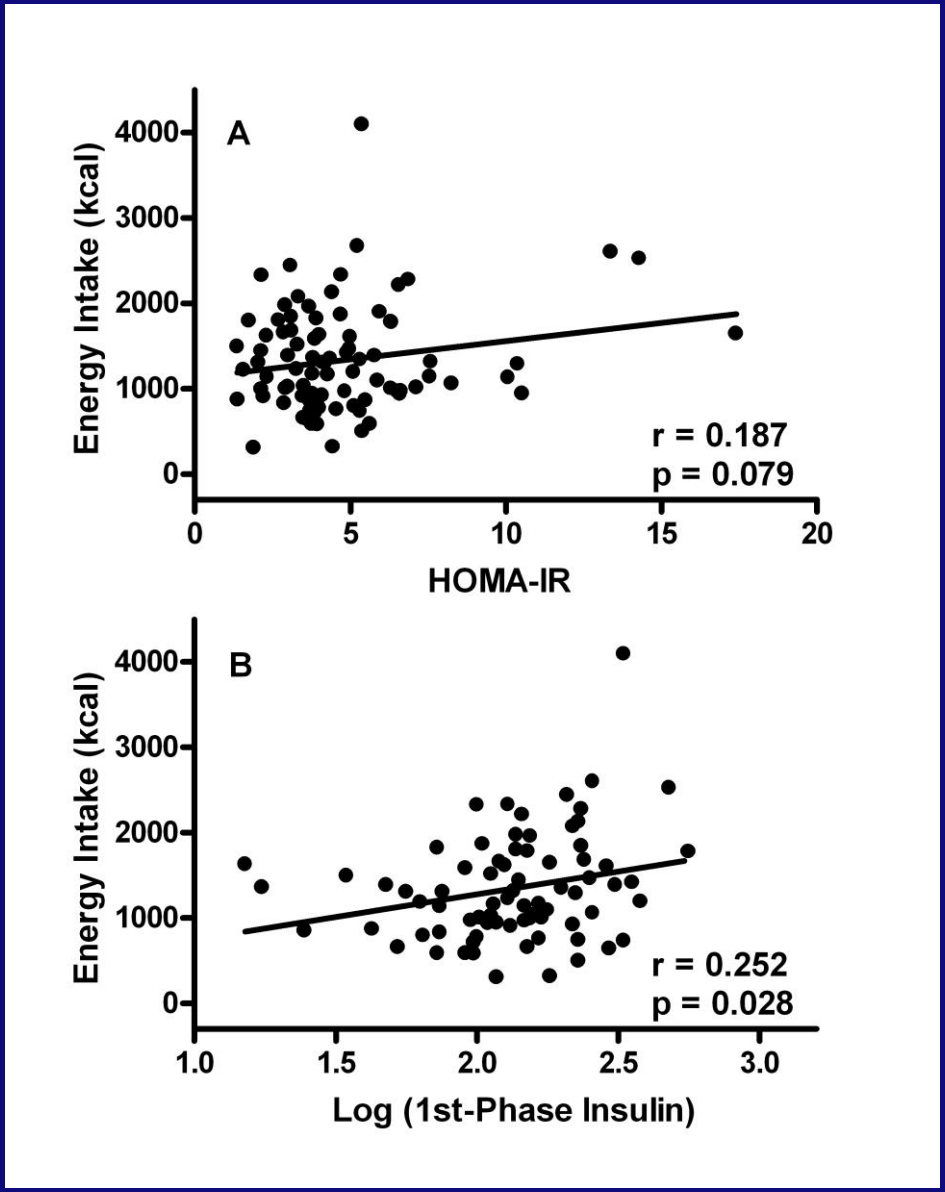
What does CNS insulin resistance do to reward?

The NIRKO (Brain Insulin Receptor Knockout) Mouse



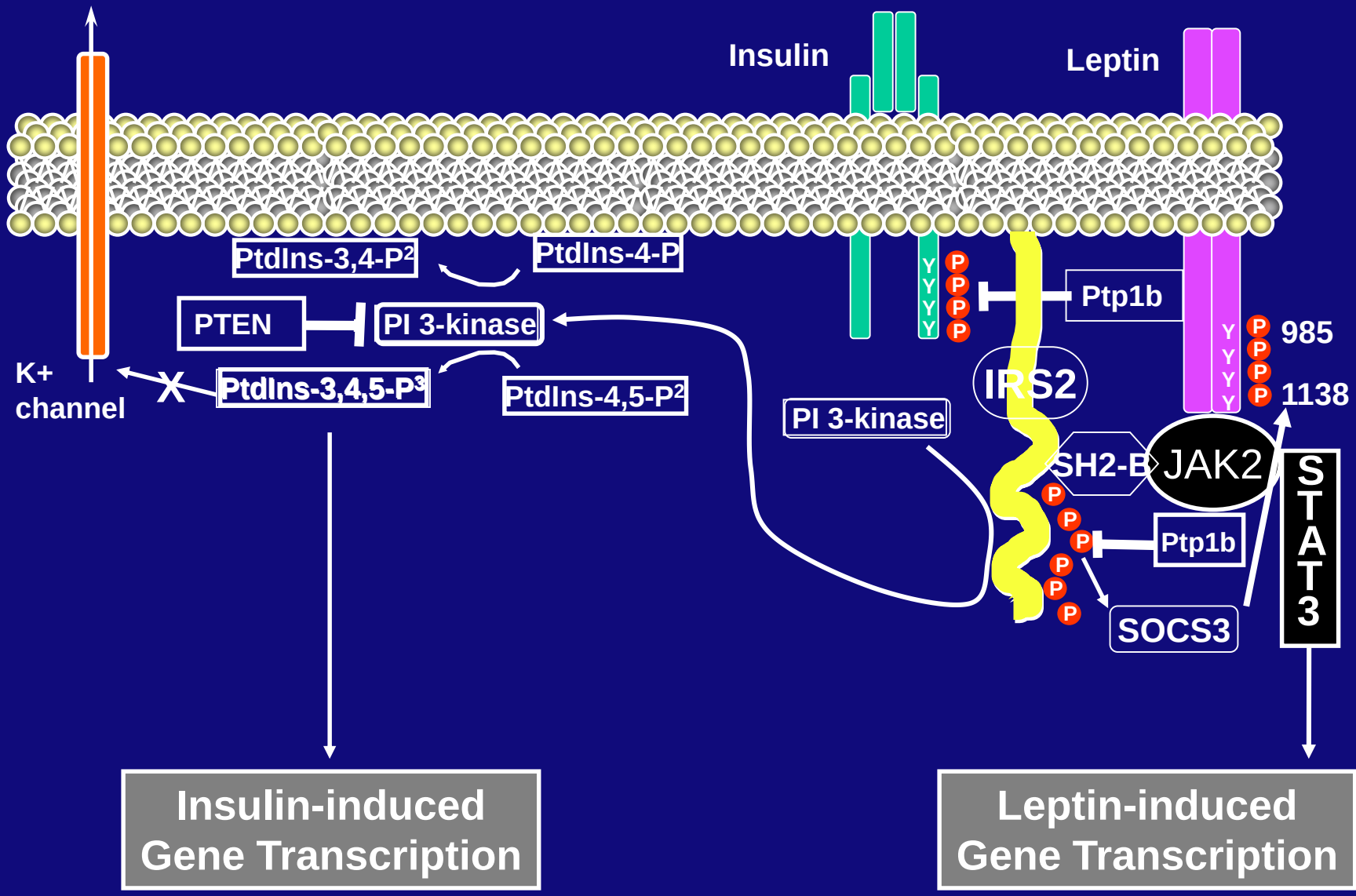
Brüning et al. Science 289:2122, 2000

Hyperinsulinemia correlates with energy intake in obese children



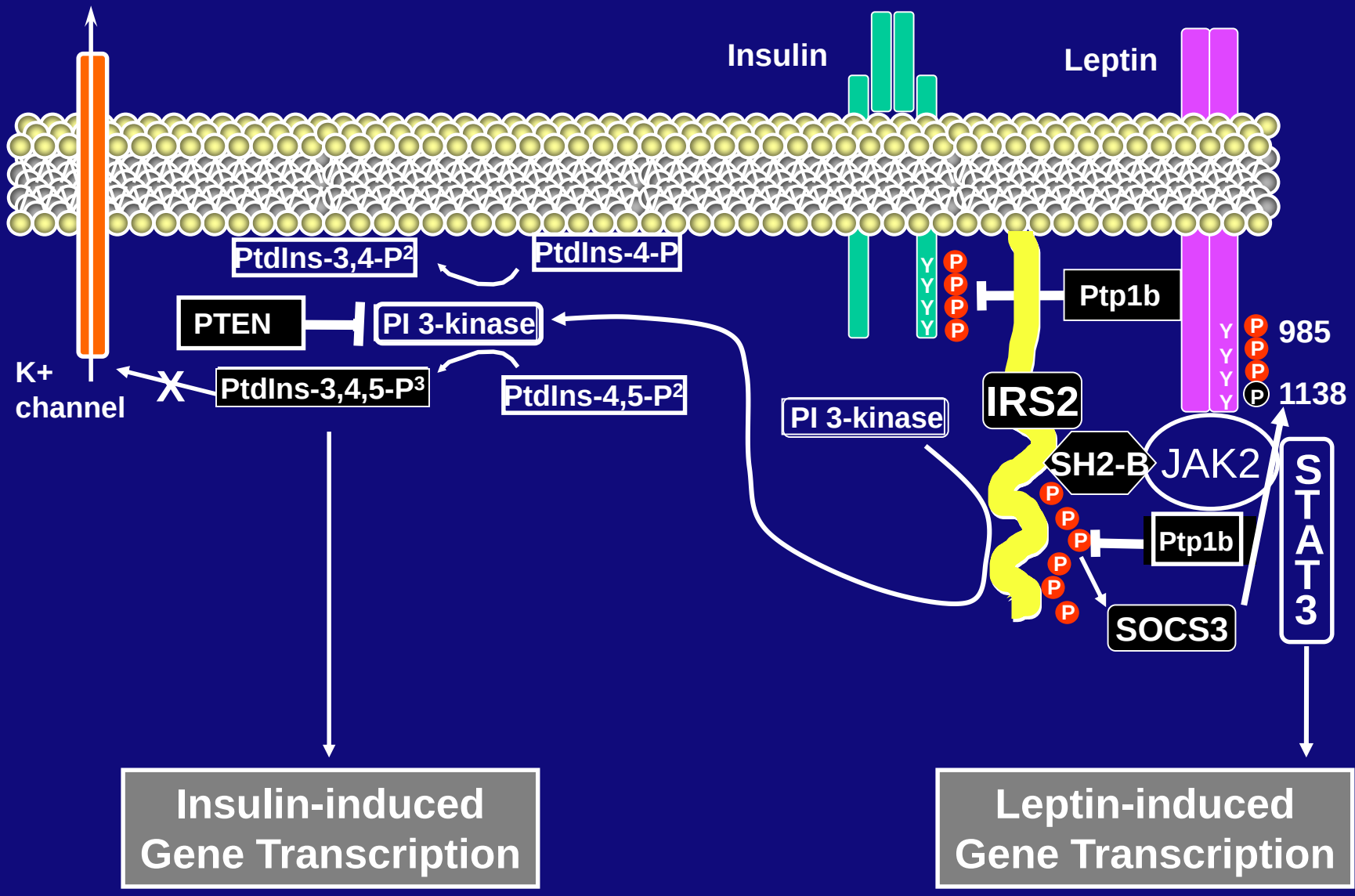
Han et al. J Pediatr 152:612, 2008

Knockout studies of leptin resistance: leptin pathway



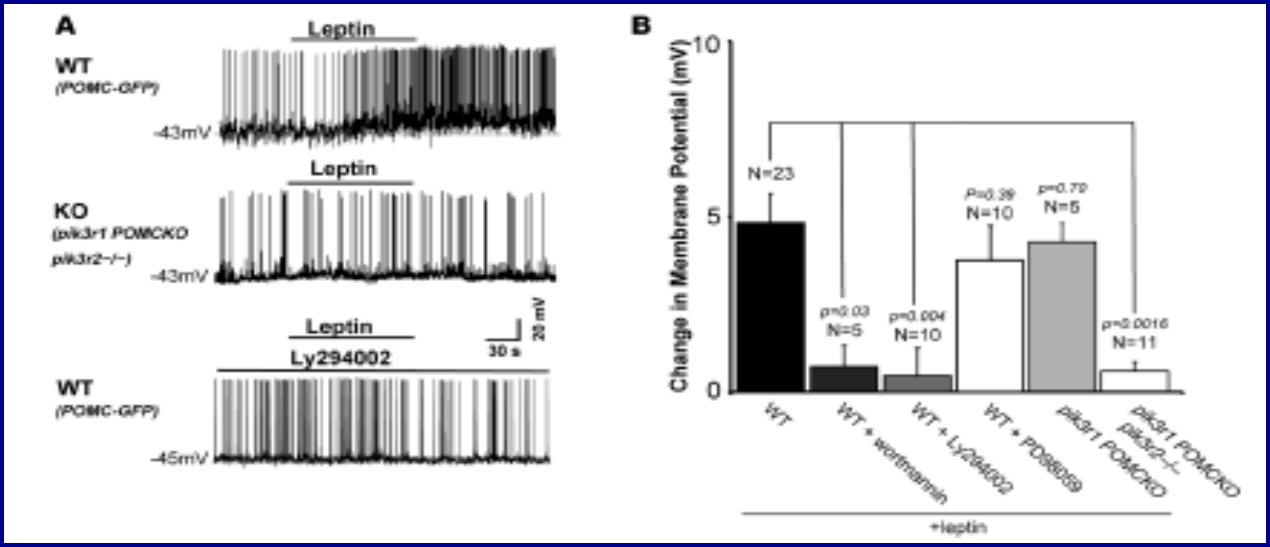
Lustig, Nature Clin Pract Endo Metab 2:447, 2006

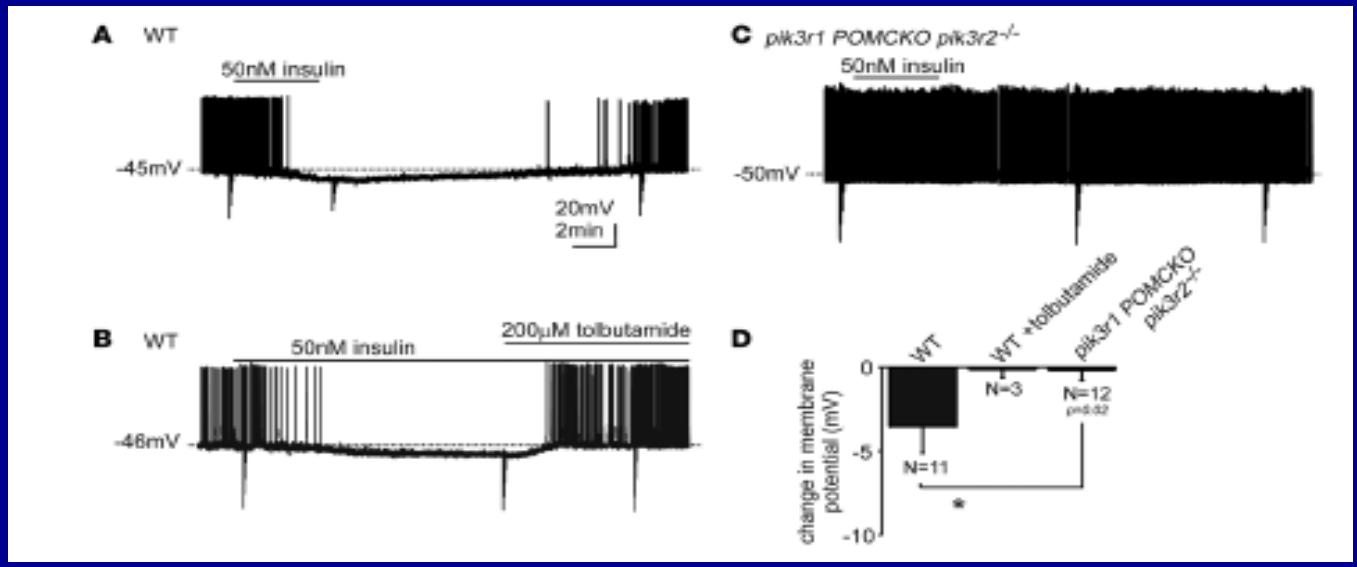
Knockout studies of leptin resistance: insulin pathway



Lustig, Nature Clin Pract Endo Metab 2:447, 2006

Leptin depolarizes, while insulin hyperpolarizes POMC neurons through a PI3K-mediated mechanism





Hill et al. J Clin Invest 118:1796, 2008

Hyperinsulinemia blocks leptin signaling

Insulin inhibits leptin receptor signalling in HEK293 cells at the level of janus kinase-2: a potential mechanism for hyperinsulinaemia-associated leptin resistance

M. Kellerer[1], R. Lammers[1], A. Fritsche[1], V. Strack[1], F. Machicao[1], P. Borboni[3], A. Ullrich[2], H.U. Häring[1]

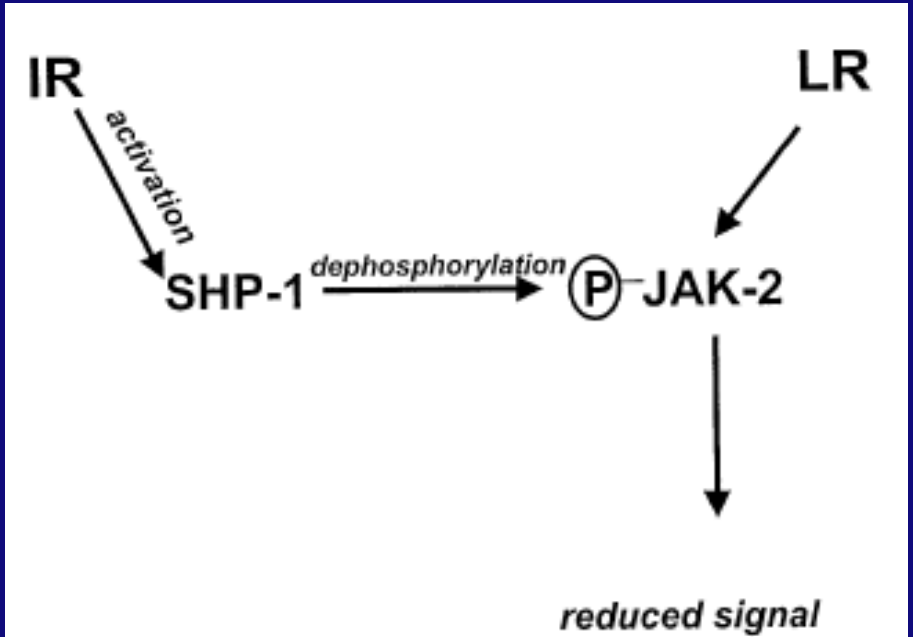


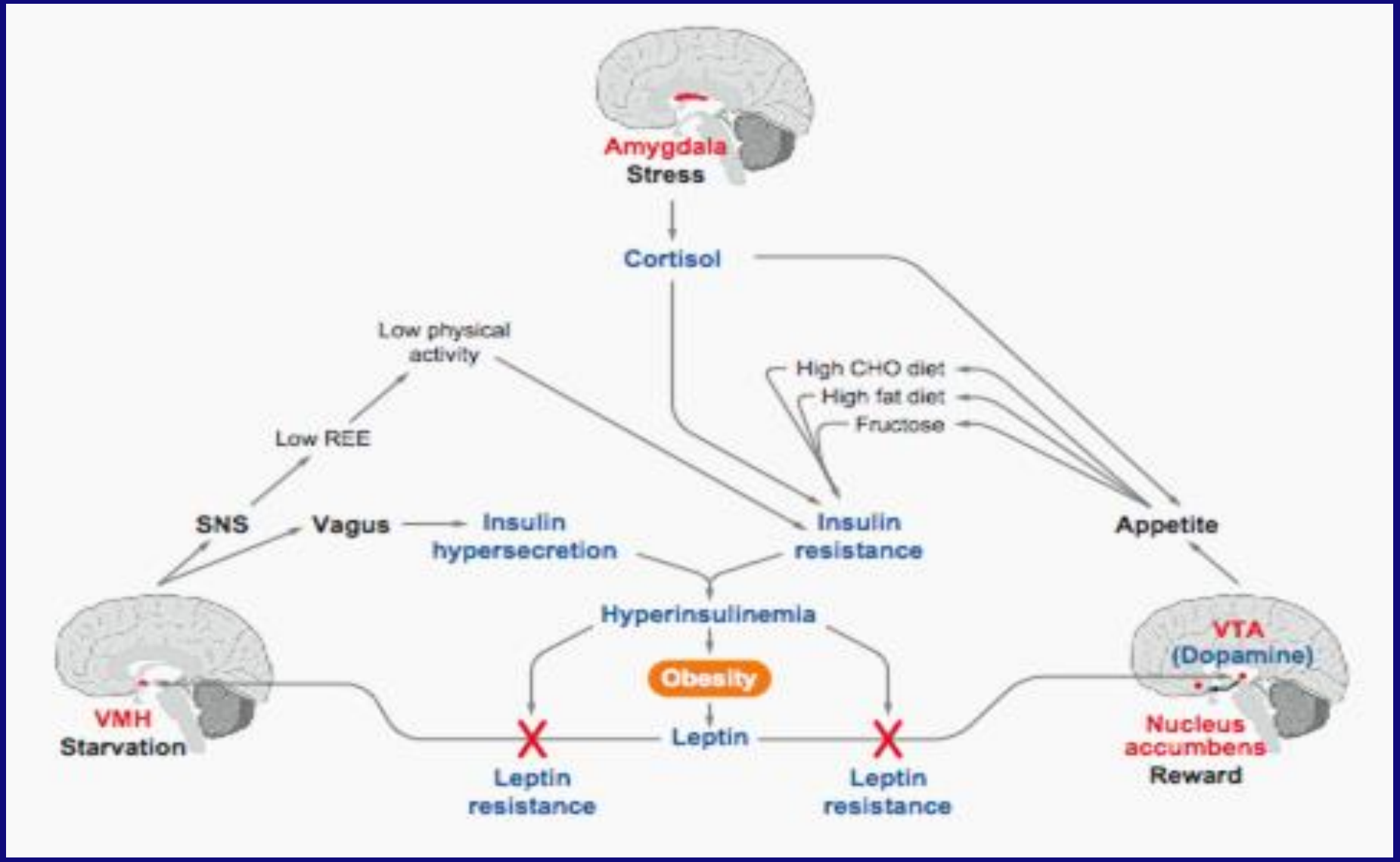
Fig. 9. Model for the signalling pathway leading to reduced leptin signalling

Kellerer et al. Diabetologia, 44:1125, 2001

Chronic hyperinsulinemia promotes obesity by:

- driving energy into adipose tissue
- interfering with leptin signaling in the VMH (starvation)
- interfering with leptin extinguishing of dopamine clearance in the NA (addiction)

The "limbic triangle"



Mietus-Snyder and Lustig, Ann Rev Med 59:147, 2008

Direct effects on the reward system:

- Controlled by the Ventral Tegmental Area and Nucleus Accumbens

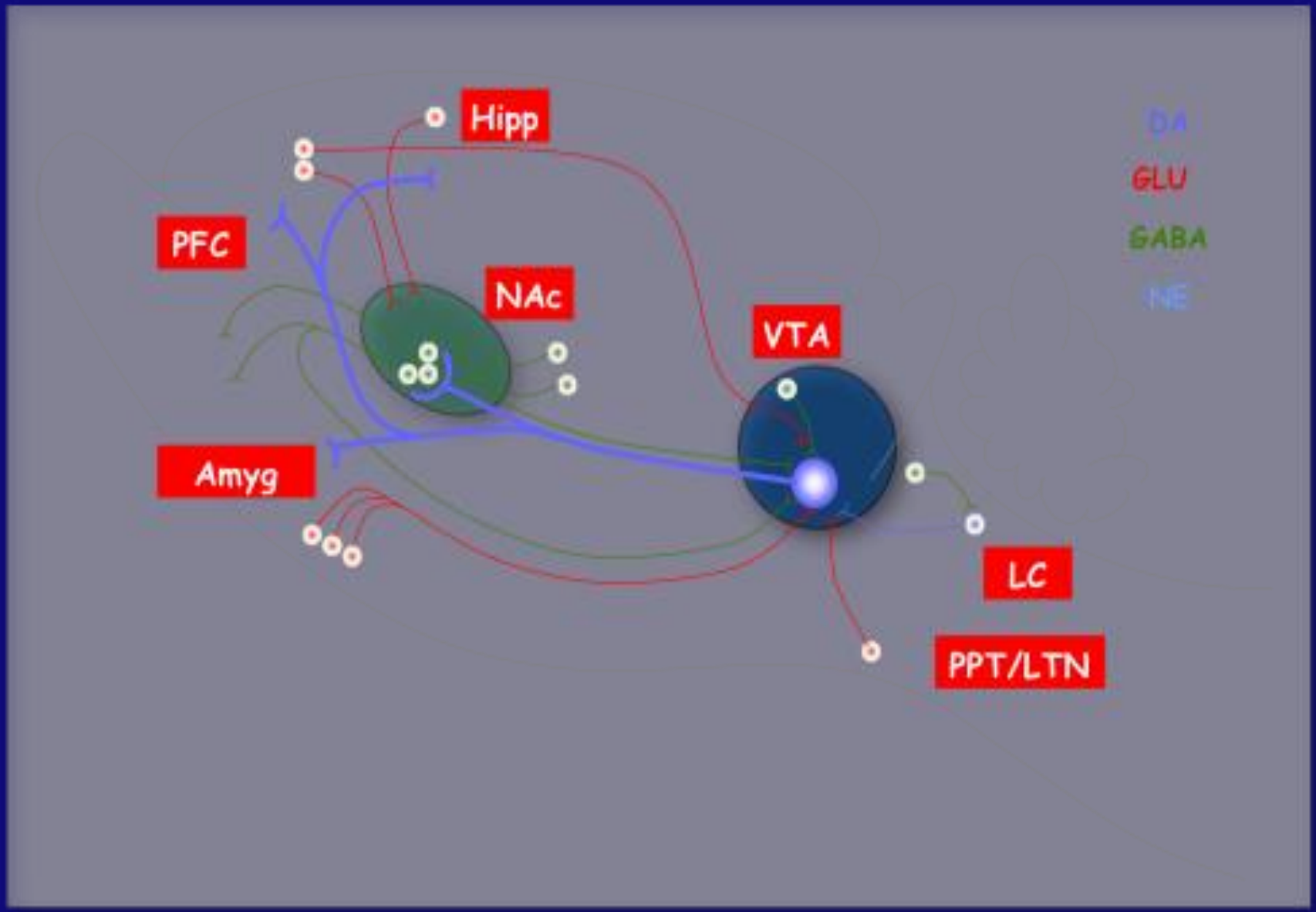
- dopamine

- endogenous opioids (mu and delta receptors)
- acetylcholine
- stress

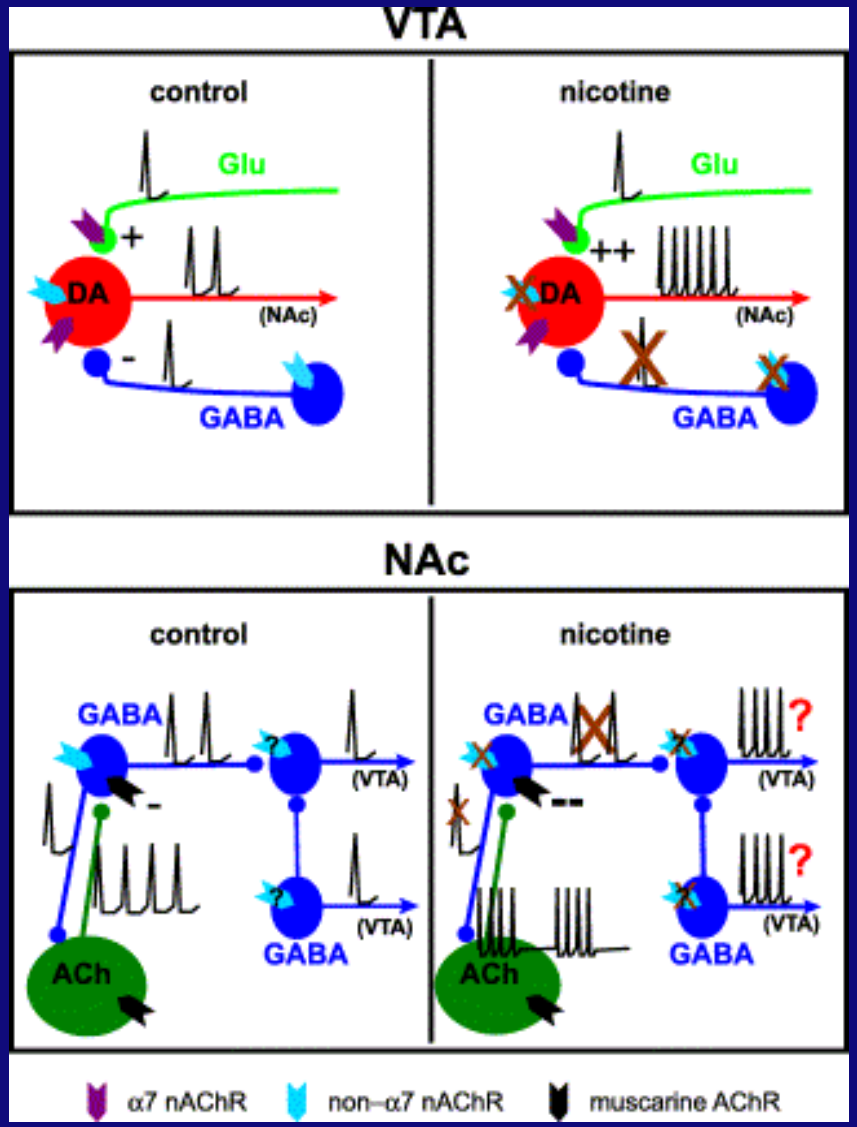
all equally important, but will not be discussed

The mesolimbic reward system in rodents

(Luscher, 2004)

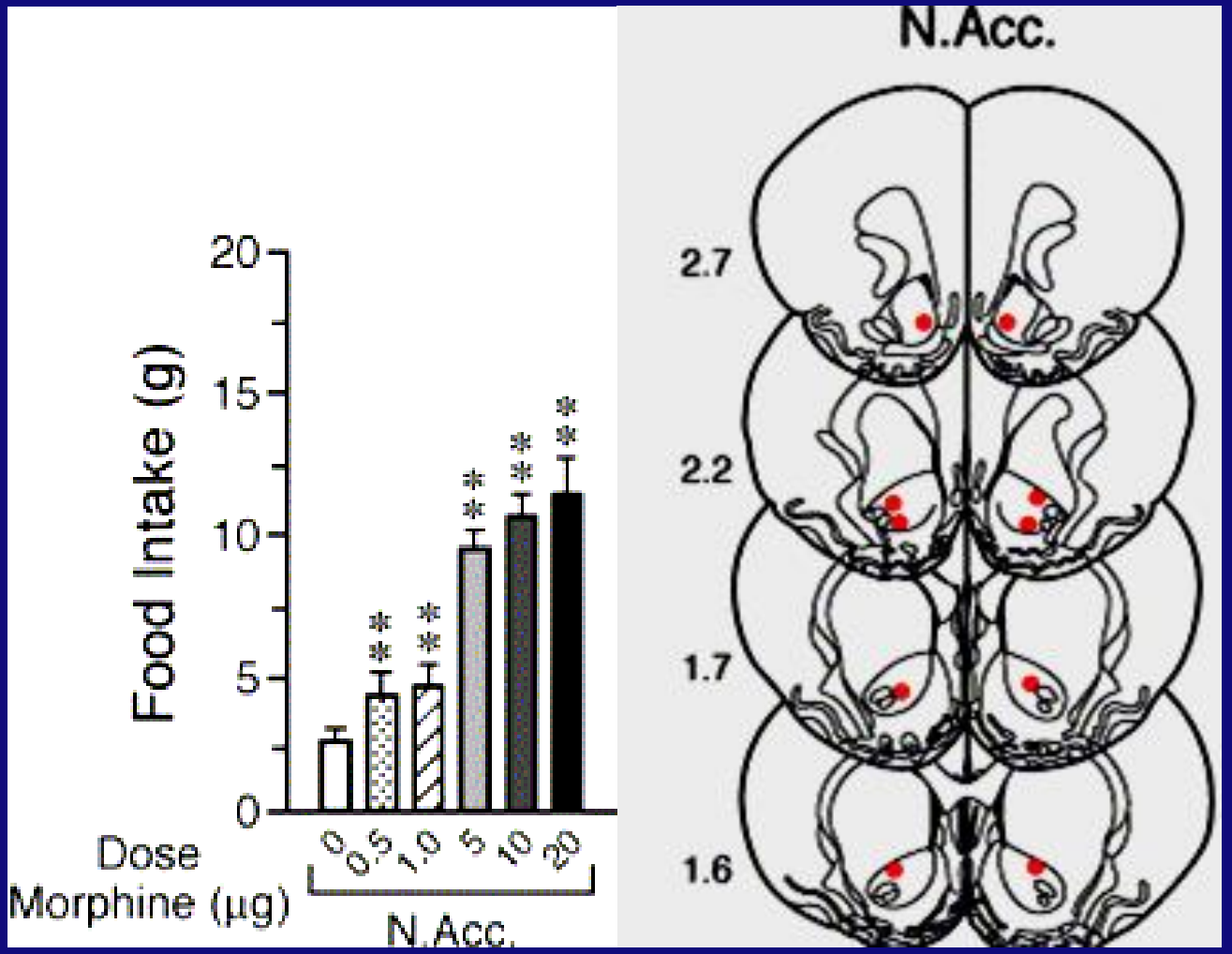


The Ventral Tegmental Area and the Nucleus Accumbens: Sites of opiate and nicotine effects on reward



Mansvelder et al. Eur J Pharmacol 480:117, 2003

The Ventral Tegmental Area and the Nucleus Accumbens: Sites of opiate and nicotine effects on reward



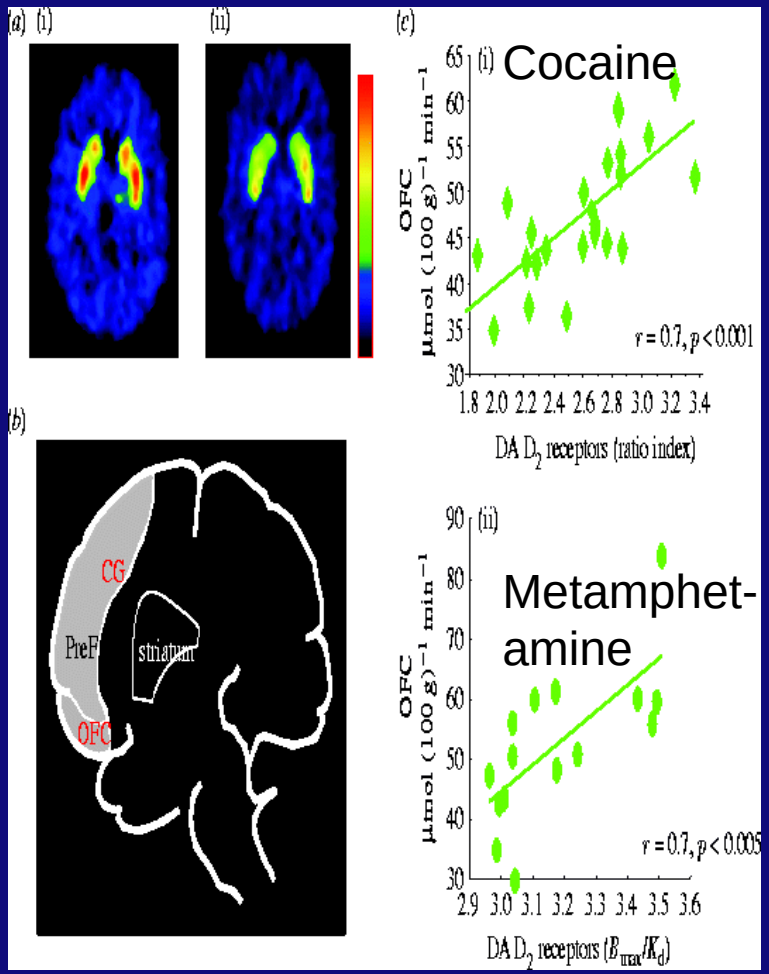
Kelly et al. Physiol Behav 76:365, 2002

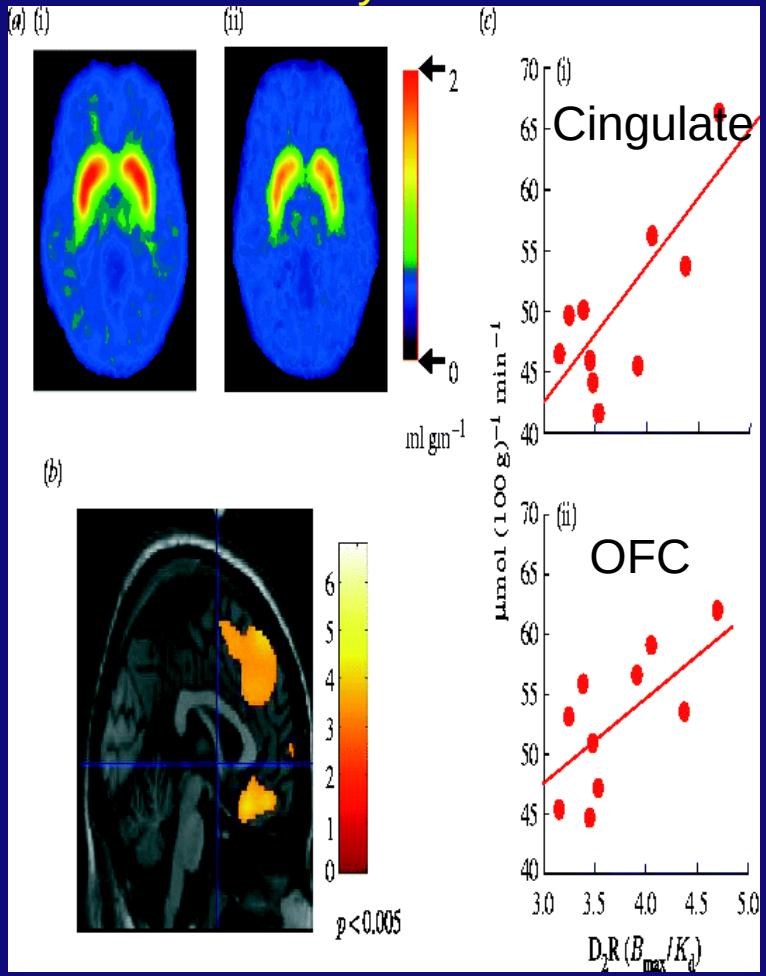
D_2 receptor binding correlates with glucose metabolism both in drug addiction and obesity

CTL Cocaine

CTL Obesity

D2 receptors





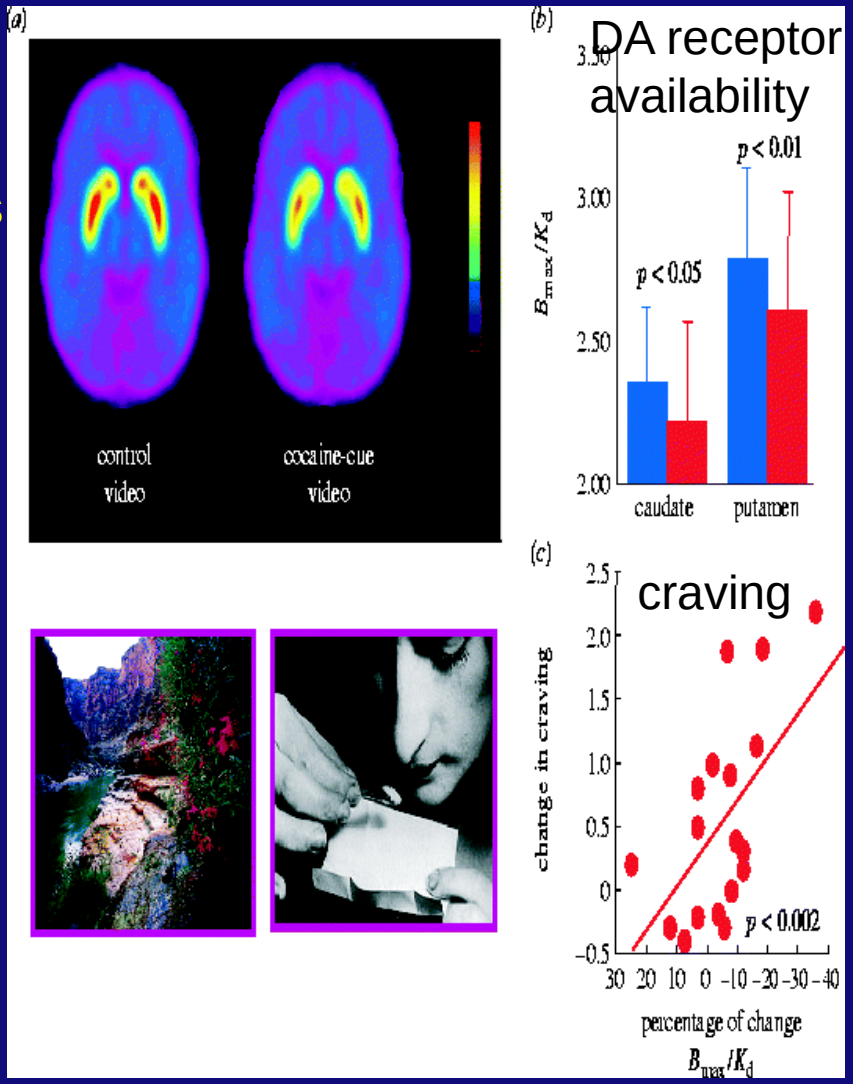
Volkow et al. Philos Trans R Soc Lond B Biol Sci. 2008 363:3191, 2008

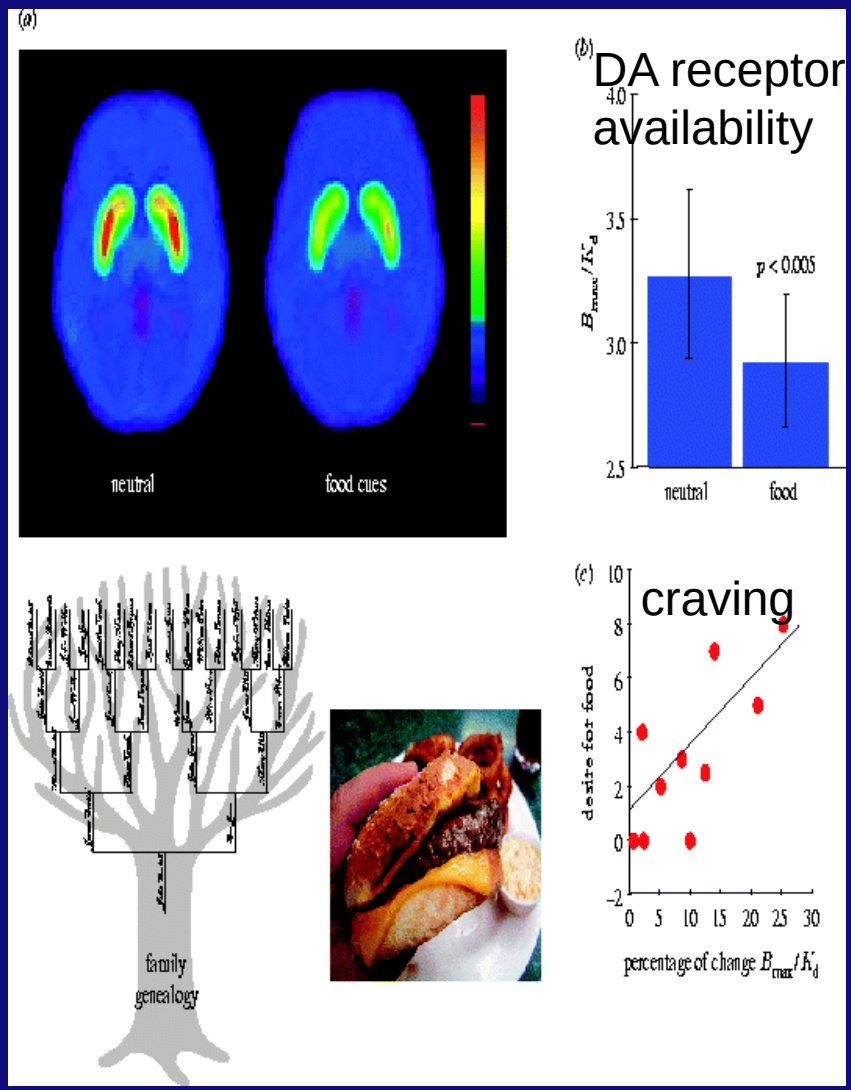
D_2 receptor binding availability indicates craving both in drug addiction and obesity

Cocaine-addicted

Control subjects

D_2 receptors

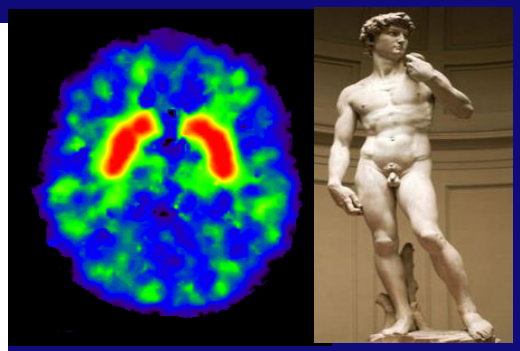




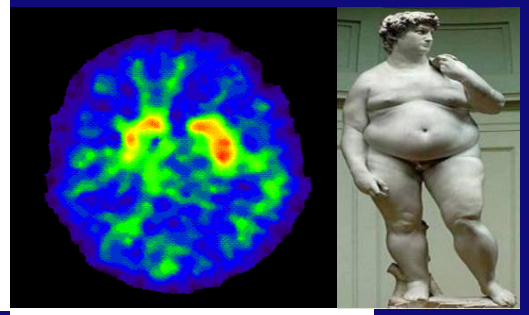
Volkow et al. Philos Trans R Soc Lond B Biol Sci. 2008 363:3191, 2008

Decreased D_2 Receptors in Obese Human, Monkey and Rodent

Human

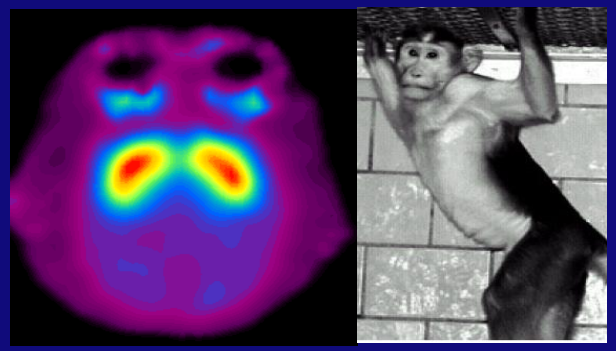


BMI = 23

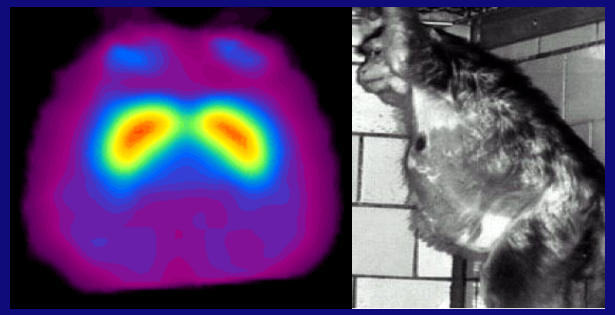


BMI = 50

Bonnet macaques

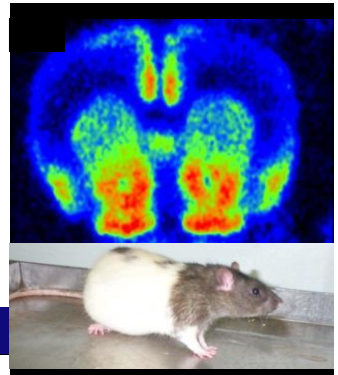


BMI = 23

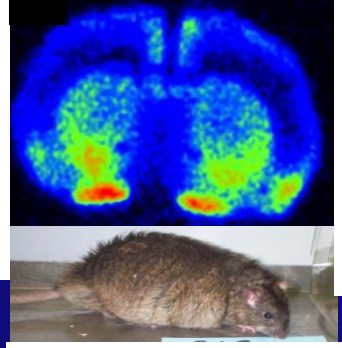


BMI = 42

PET [^{11}C]raclopride

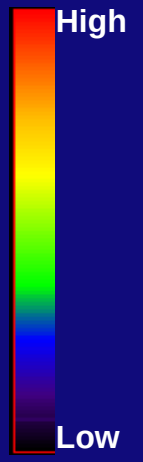


Weight = 400 g



Autoradiography

[^{3}H]spiperone



Wang et al. J Nucl Med. 49(Suppl 1):208P, 2008; Thanos et al. Synapse. 62:50, 2008

Evidence of down-regulation of D_2 receptors

- Women who gained weight showed a reduction in striatal response to “sweet” vs. women who were weight stable or weight losers

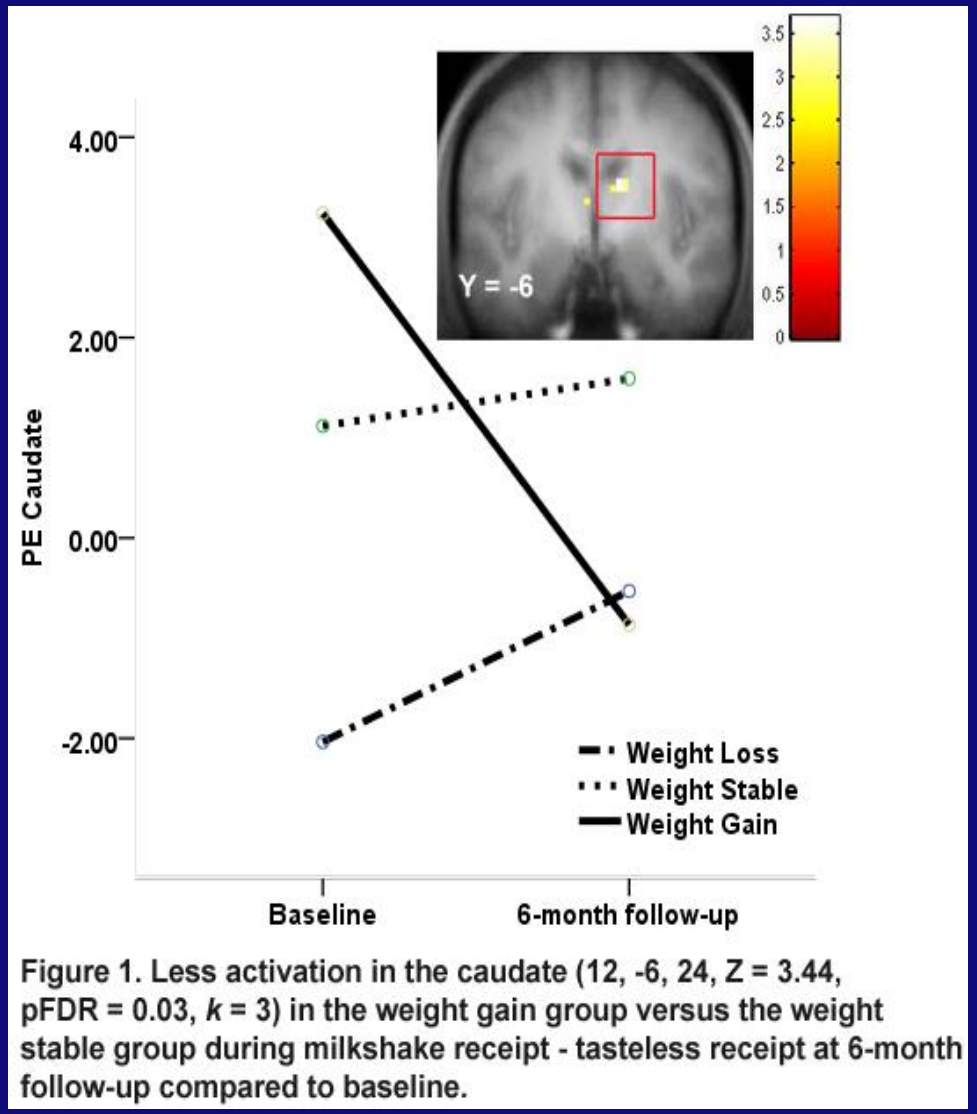
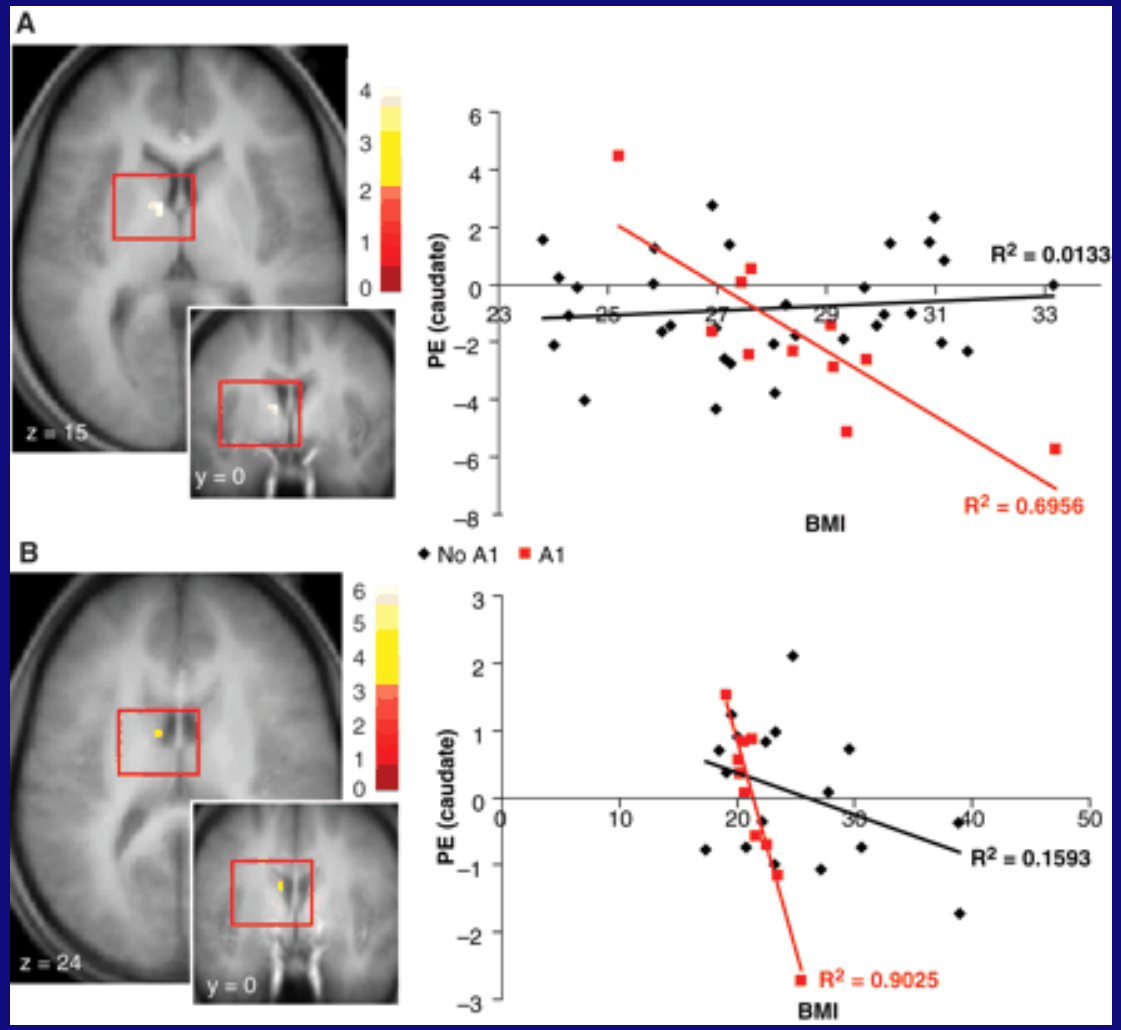


Figure 1. Less activation in the caudate (12, -6, 24, Z = 3.44, pFDR = 0.03, *k* = 3) in the weight gain group versus the weight stable group during milkshake receipt - tasteless receipt at 6-month follow-up compared to baseline.

Stice et al., J Neurosci. 2010 30:13105,.2010

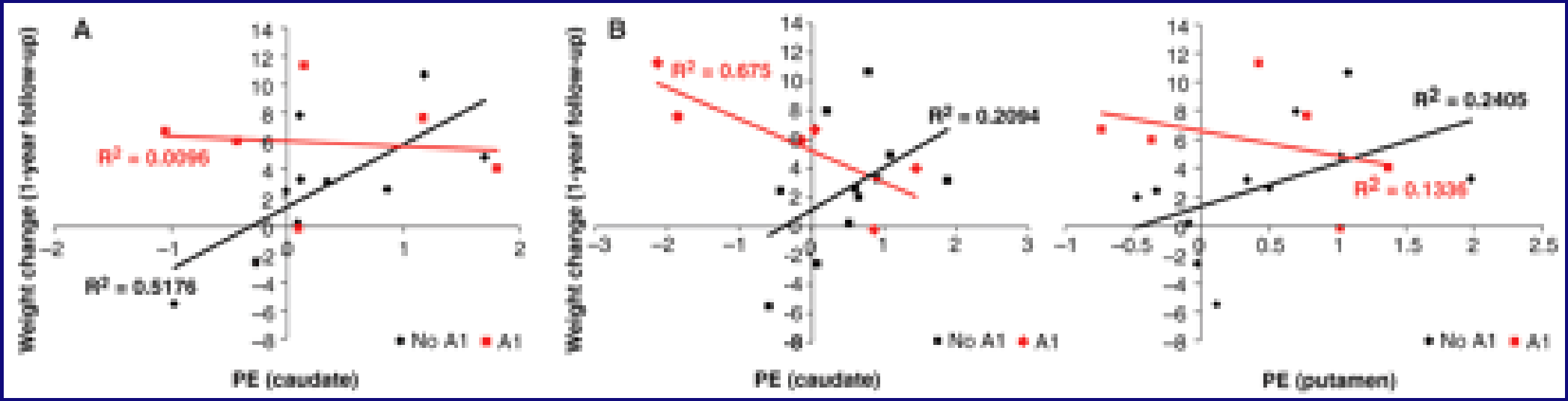
Blood oxygen level-depdendent fMRI: hypofunctioning dopaminergic activity in caudate, esp. with the Taq 1A allele (assoc. with low D2 receptors)



Stice et al. Science 322:449, 2008

Genetics of D_2 receptors and weight gain

Weight gain over one year correlated negatively with DA activity in those with the TaqA1 allele, and positively in those without the A1 allele



Stice et al. Science 322:449, 2008

Direct effects on the reward system:

Is fast food addictive?

Garber and Lustig, Curr Drug Abuse Rev 4:190, 2011

NeuroFAST
www.neurofast.eu

CONSENSUS

NeuroFAST consensus opinion on food addiction

- **Current evidence does not allow us to conclude that a single food substance** via a single specific neurobiological mechanism (e.g. specific brain receptors or specific neuronal pathways) can account for the fact that people overeat and develop **obesity**.
- **In humans, there is no evidence that a specific food, food ingredient or food additive causes a substance-based type of addiction** (the only currently known exception is caffeine which via specific mechanisms can potentially be addictive).

NeuroFAST
www.neurofast.eu

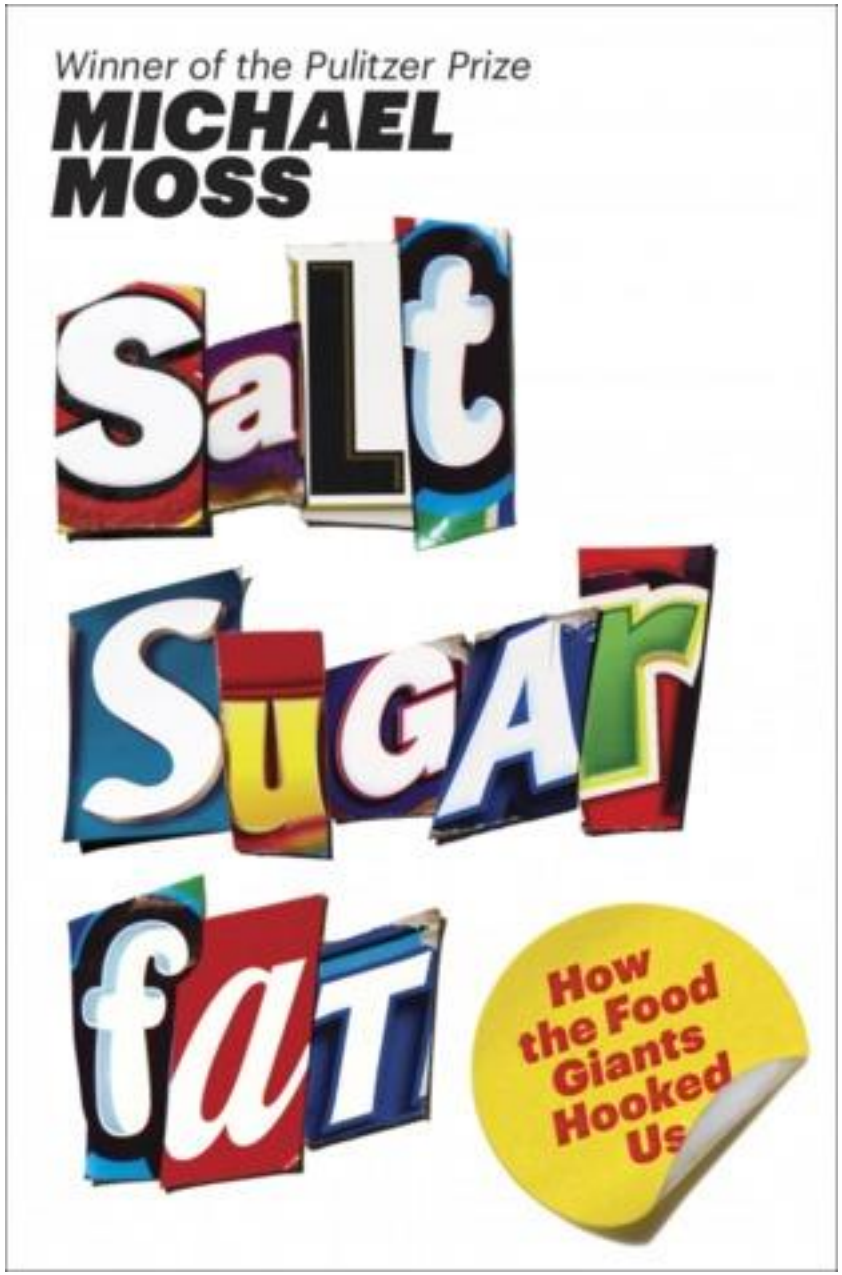
CONSENSUS

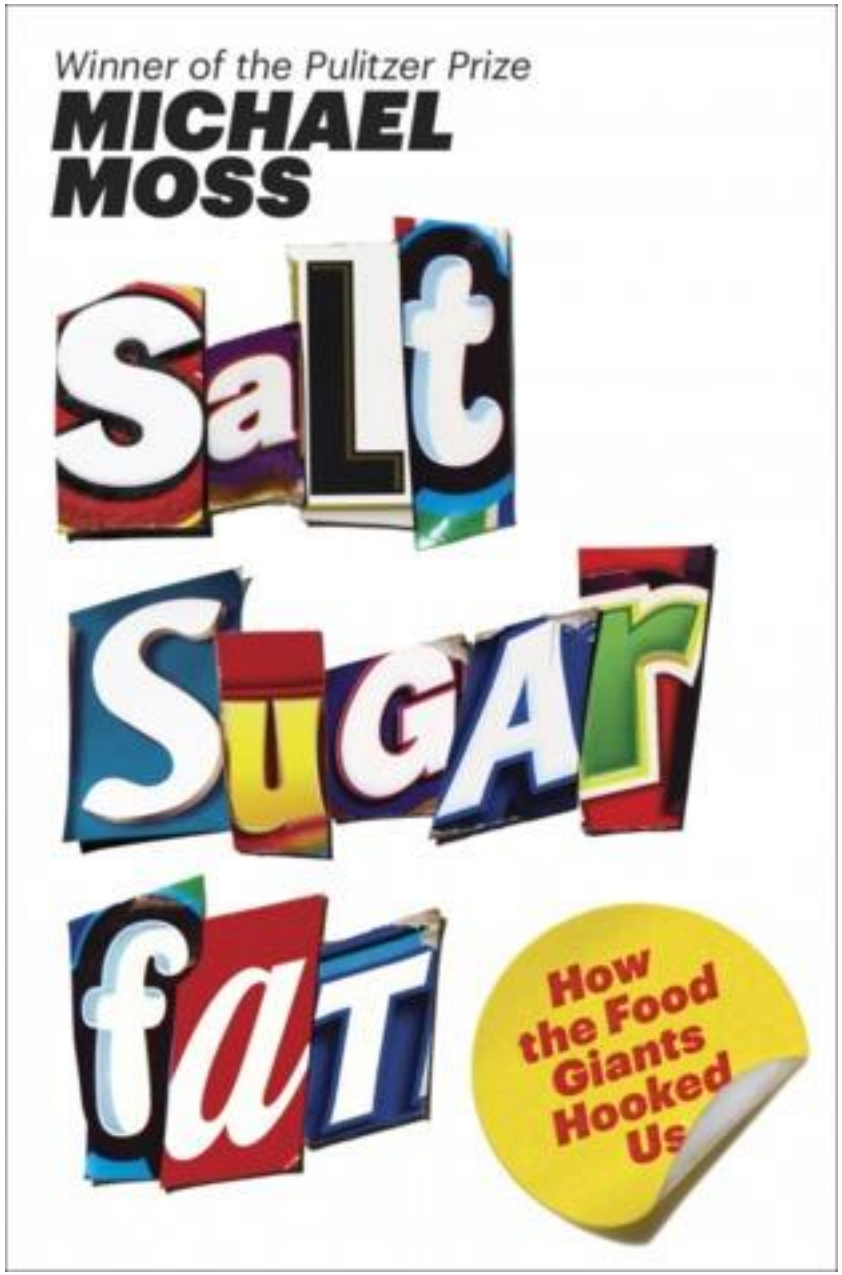
NeuroFAST consensus opinion on food addiction

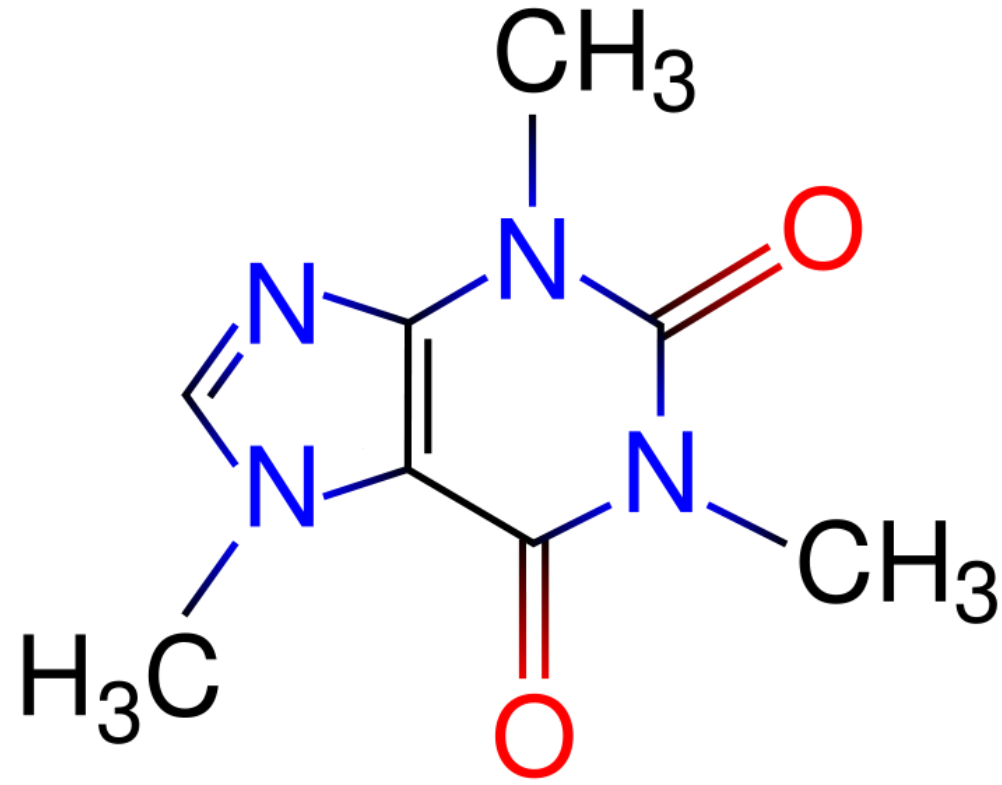
- Within this context **we specifically point out that we do not consider alcoholic beverages as food**, despite the fact that one gram of ethanol has an energy density of 7 kcal.

- **Addictive (over)eating is clearly distinct from substance use disorders** that cause addiction via specific mechanisms (e.g. nicotine, cocaine, cannabinoids, opioids, etc).

So, NeuroFAST exempts both alcohol and caffeine, even though both are in food


Winner of the Pulitzer Prize
MICHAEL MOSS
SALT
SUGAR
FAT
How the Food Giants Hooked Us


Winner of the Pulitzer Prize
MICHAEL MOSS
SALT
SUGAR
FAT
How the Food Giants Hooked Us

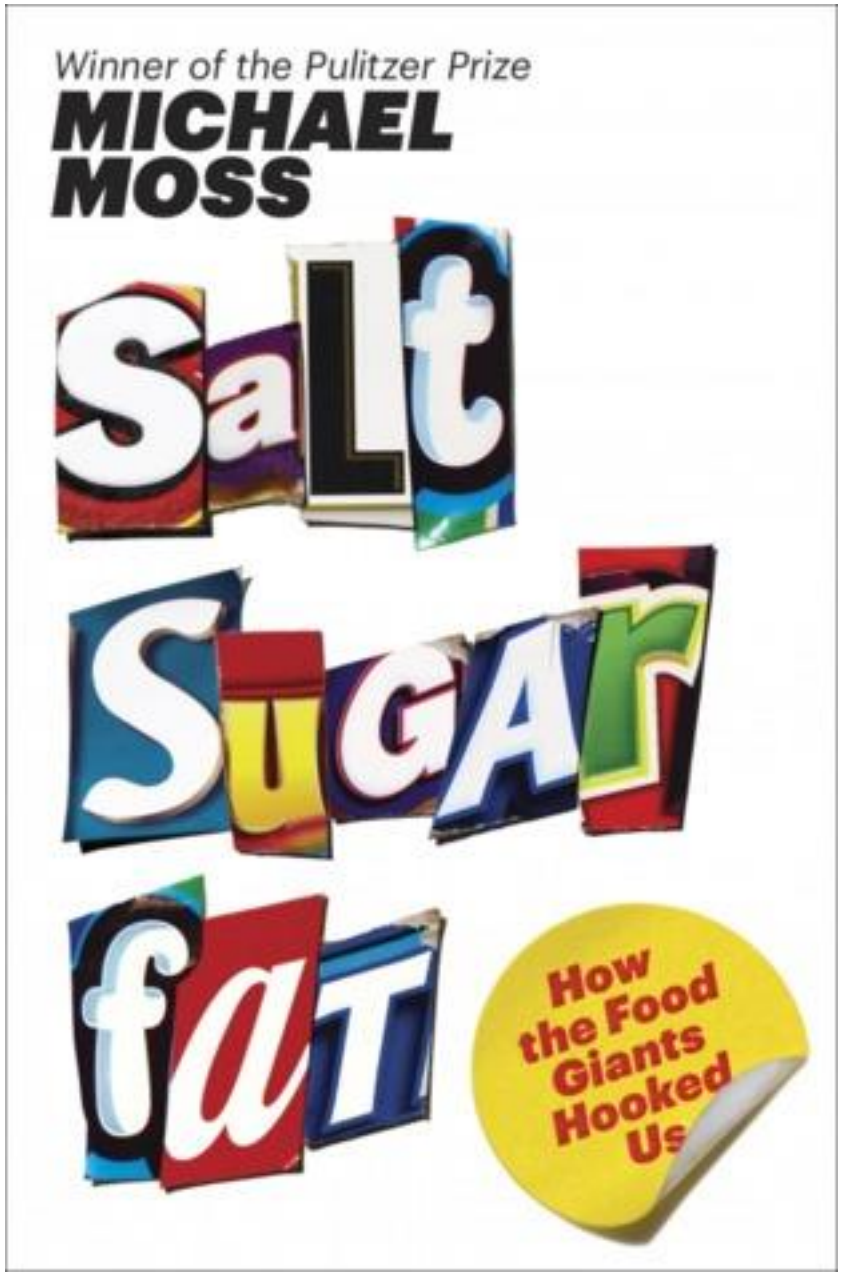

CH3
N
O
N
N
N
CH3
H3C
O

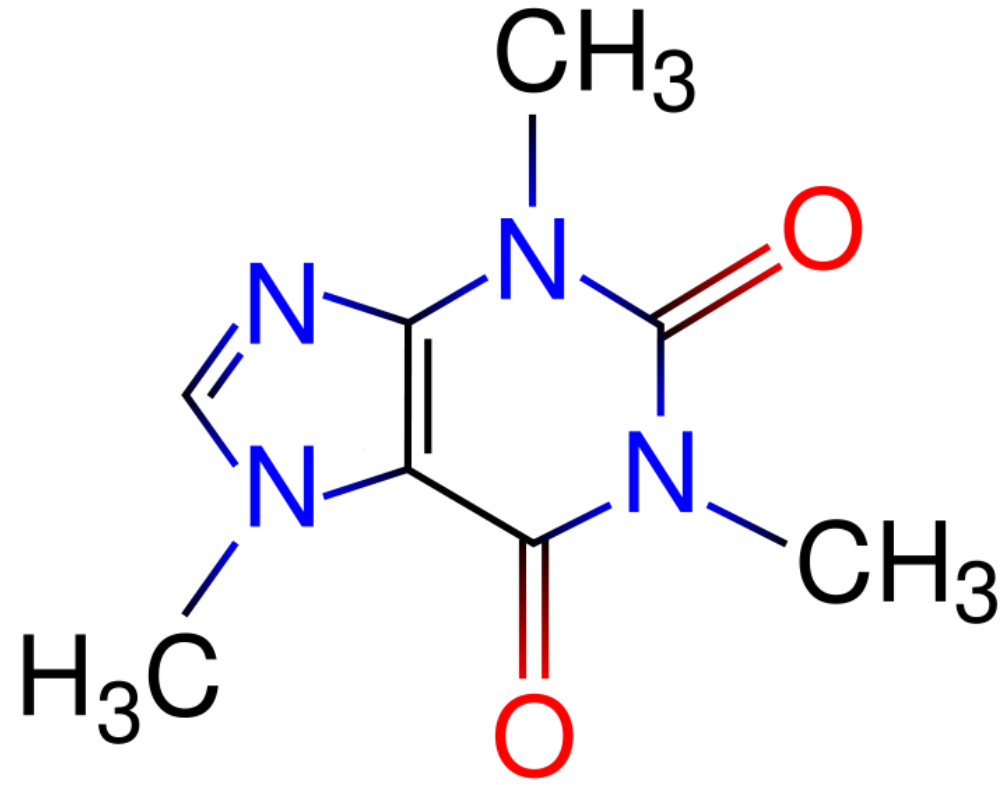
Caffeine

Salt

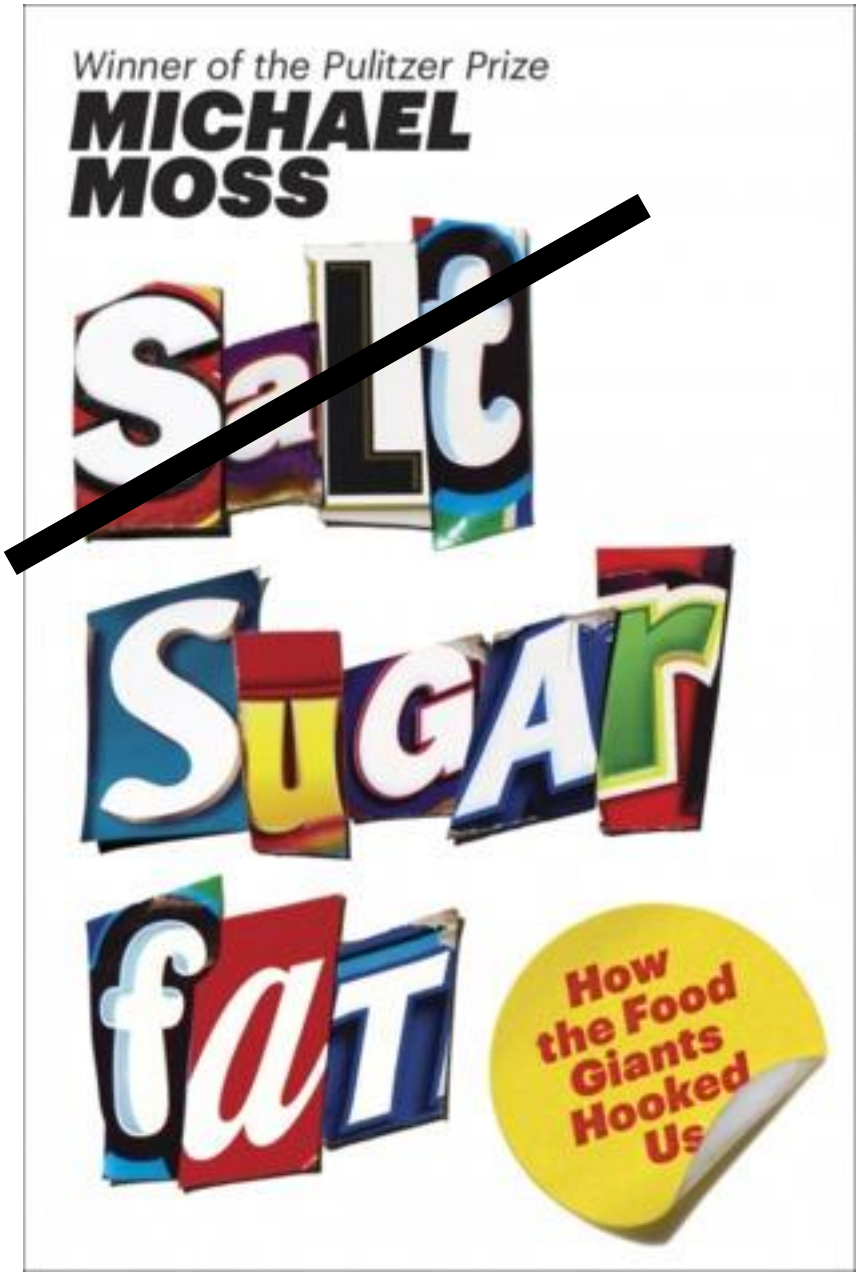
- In rodents, dopamine signaling (reward) in response to salt, bingeing, cross-sensitization with amphetamines

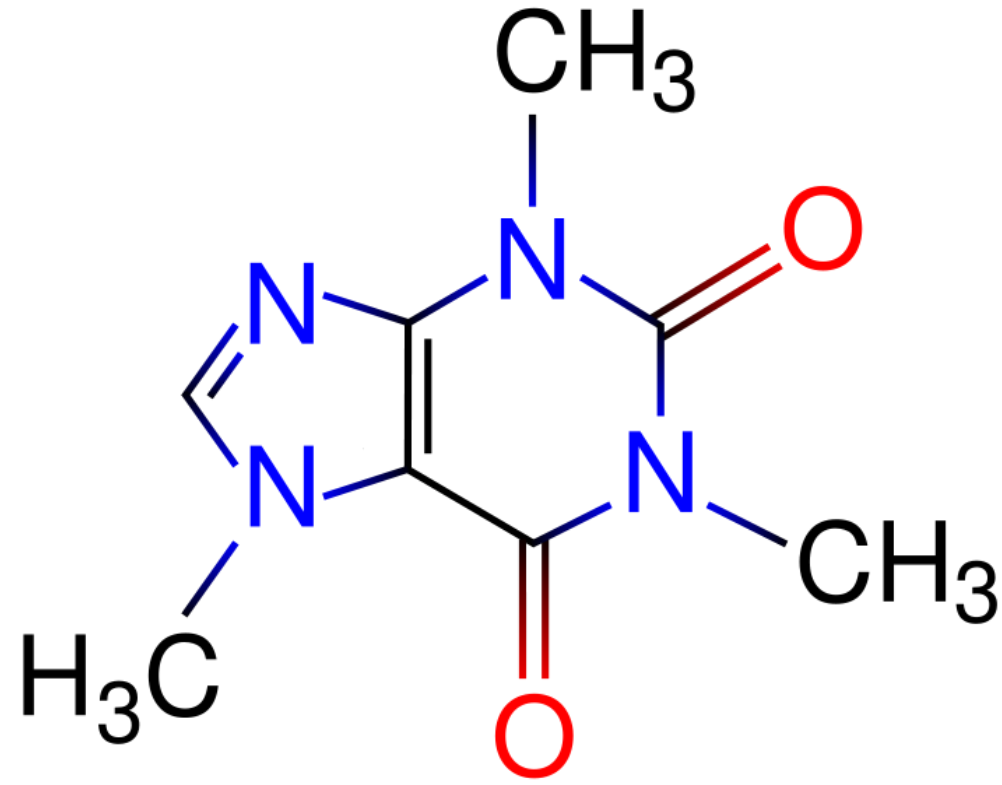
- In humans,
  - Lower threshold physiologically fixed
  - Higher levels attributed to “preference”, can retrain
  - Salt-losing congenital adrenal hyperplasia


Winner of the Pulitzer Prize
MICHAEL MOSS
SALT
SUGAR
FAT
How the Food Giants Hooked Us


CH3
N
O
N
N
N
CH3
H3C
O

Caffeine

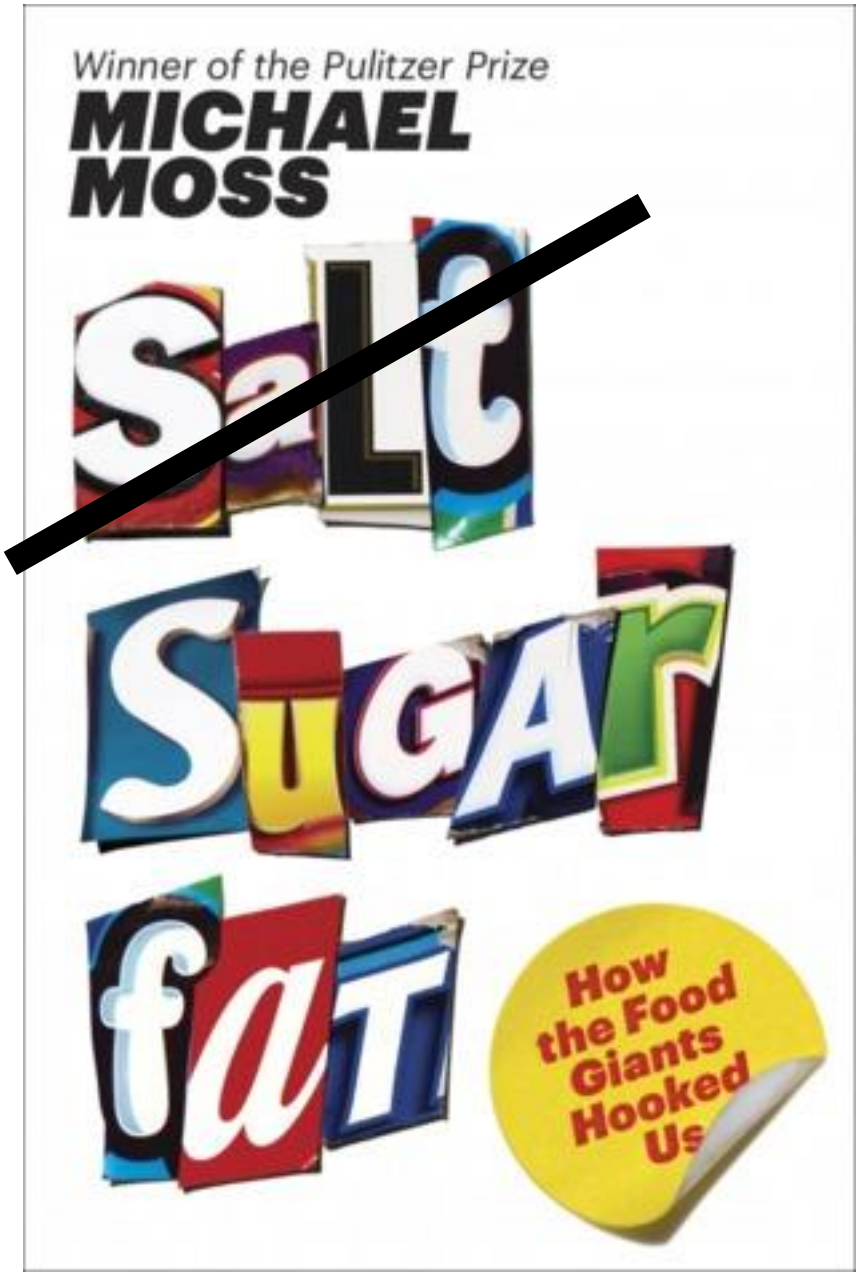

Winner of the Pulitzer Prize
MICHAEL MOSS
SALT
SUGAR
FAT
How the Food Giants Hooked Us

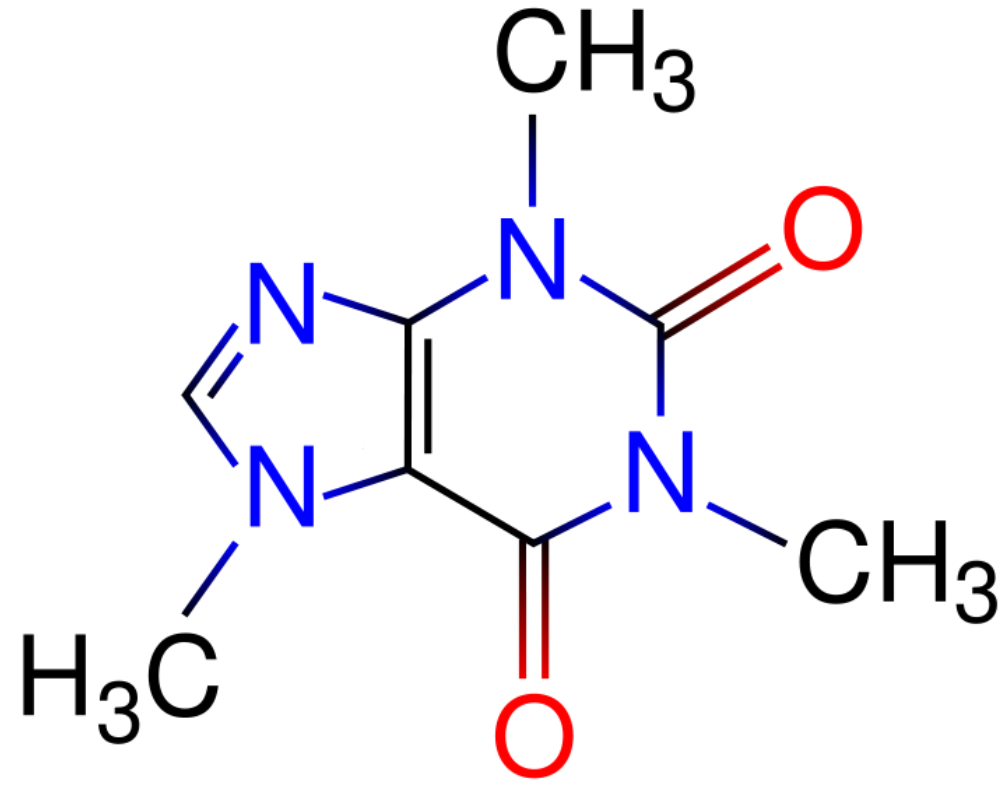

CH3
N
O
N
N
N
CH3
H3C
O

Caffeine

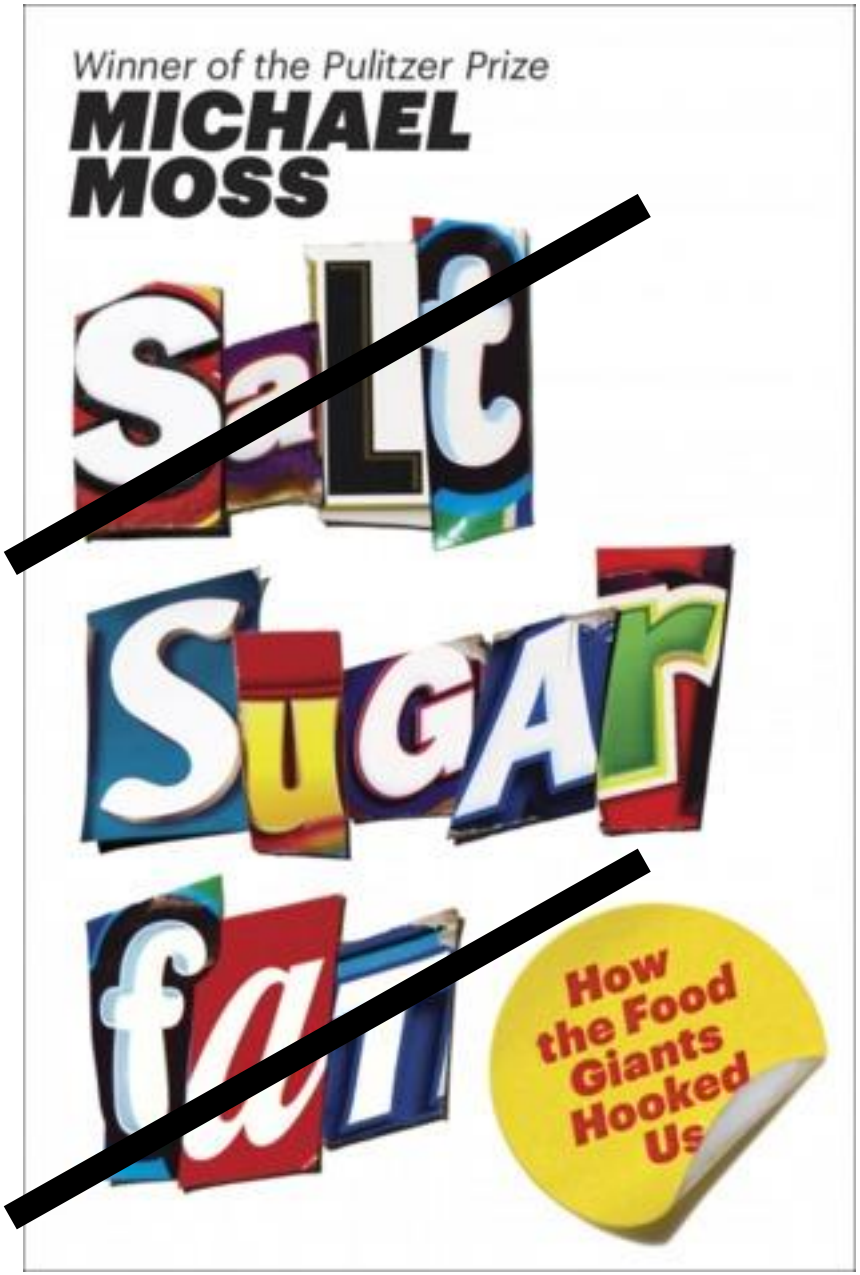
Fat

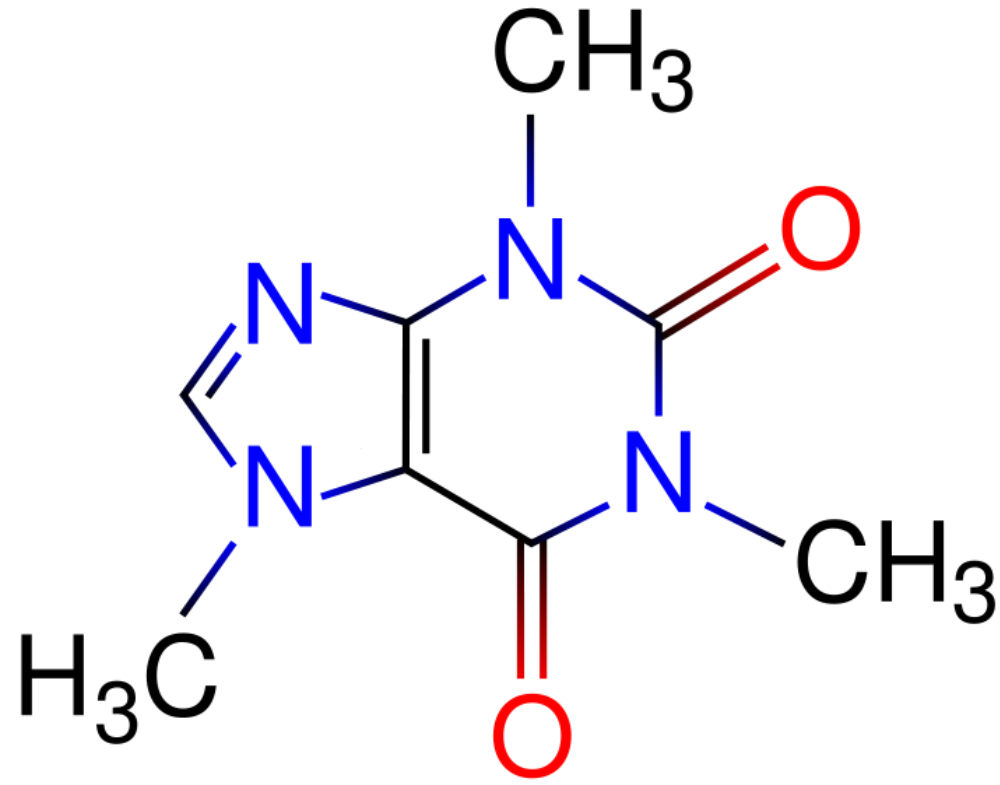
- Rodents binge but no signs of dependence
- In humans, binge foods are high fat but also high carb/sugar (e.g. pizza, ice cream)
  - Likely synergy, adding sugar increases preference for fatty foods [Drewnowski et al.]
- Atkins diet does not show dependence
- Energy density: stronger association with obesity, metabolic syndrome


Winner of the Pulitzer Prize
MICHAEL MOSS
SALT
SUGAR
FAT
How the Food Giants Hooked Us


CH3
N
O
N
N
N
CH3
H3C
O

Caffeine

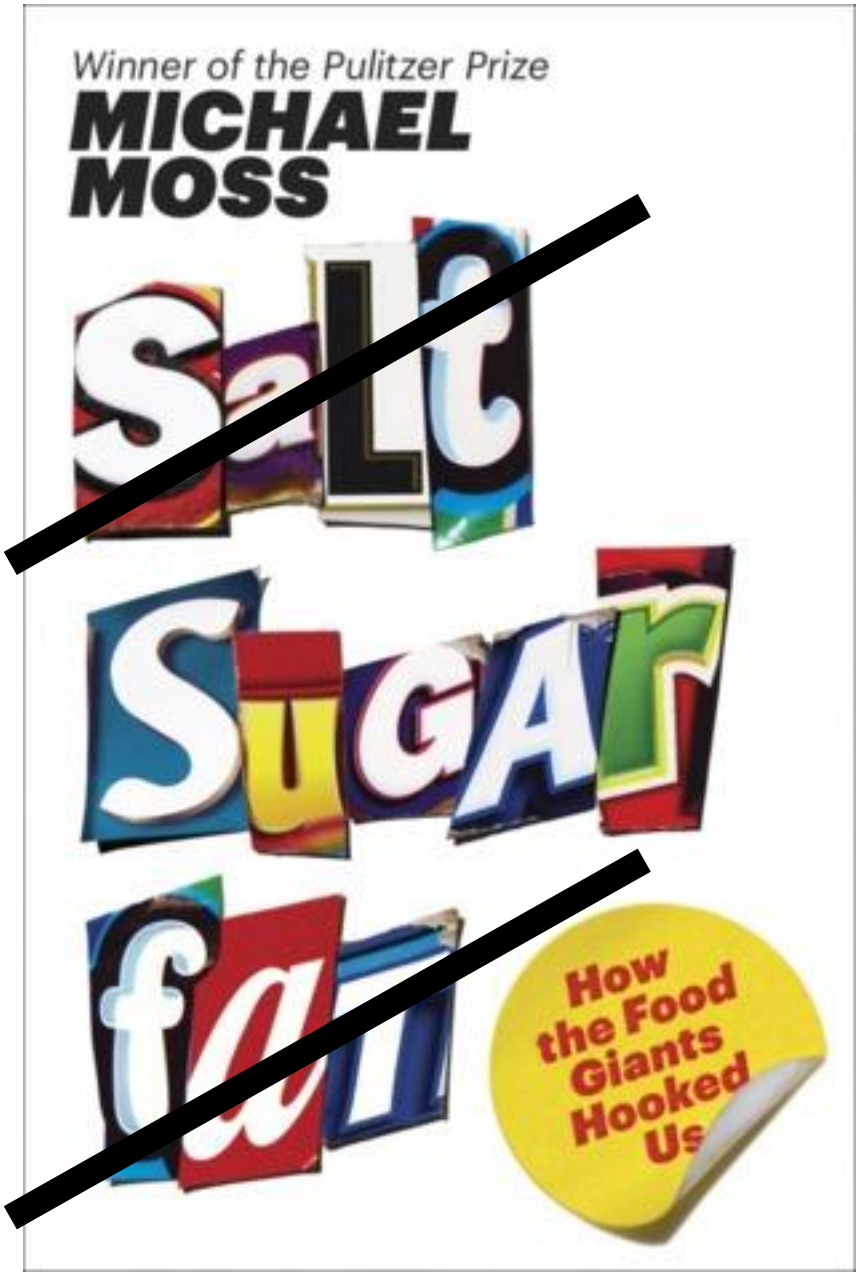

Winner of the Pulitzer Prize
MICHAEL MOSS
Salt
Sugar
fat
How the Food Giants Hooked Us

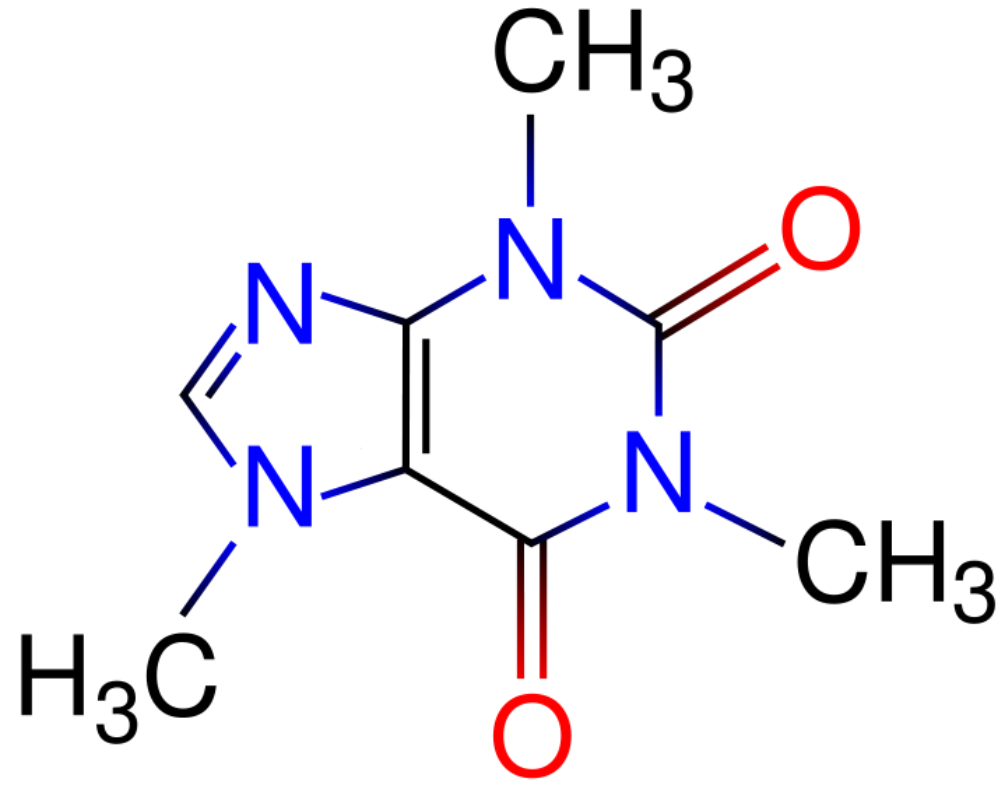

CH3
N
O
N
N
N
CH3
H3C
O

Caffeine

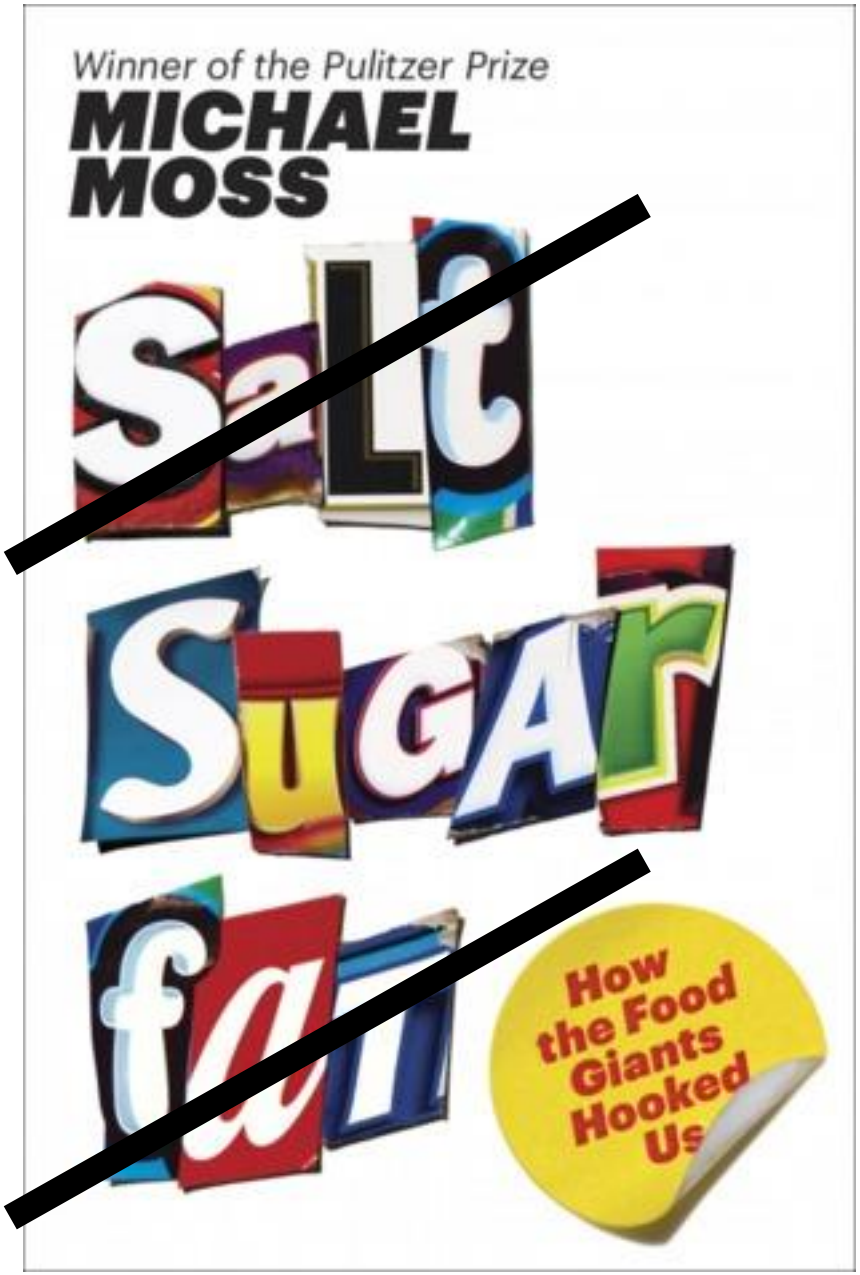
Caffeine

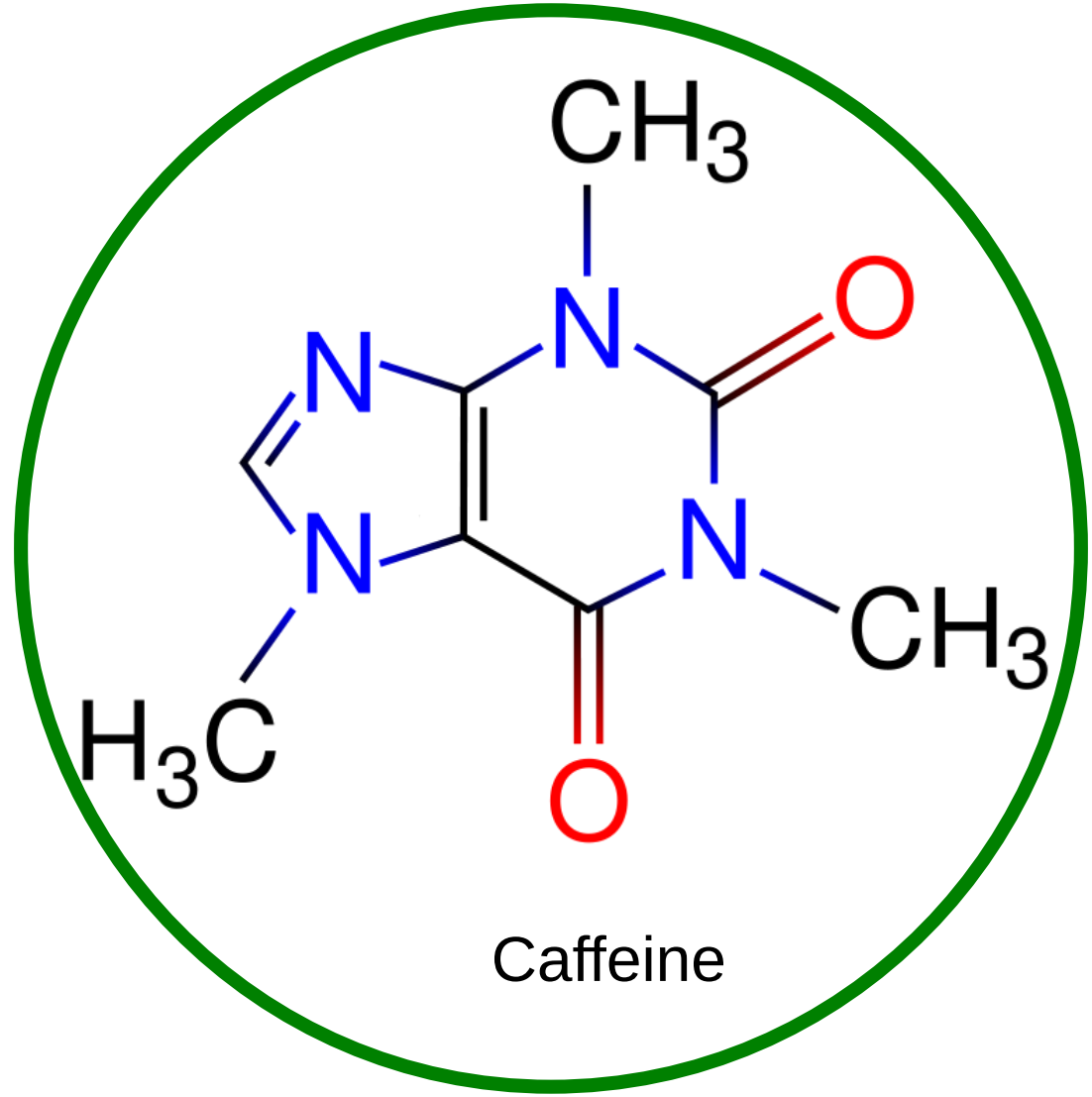
- “Model drug” of dependence
- In humans, dependence shown in children, adolescents and adults
  - 30% who consume it meet DSM criteria for dependence
  - Physiologic addiction established: headache (increased cerebral blood flow). Impaired task performance, fatigue


Winner of the Pulitzer Prize
MICHAEL MOSS
Salt
Sugar
fat
How the Food Giants Hooked Us


CH3
N
O
N
N
N
CH3
H3C
O

Caffeine


Winner of the Pulitzer Prize
MICHAEL MOSS
Salt
Sugar
fat
How the Food Giants Hooked Us


CH3
N
O
N
N
N
CH3
H3C
O
Caffeine

Direct effects on the reward system:

Is sugar (fructose) addictive?

Garber and Lustig, Curr Drug Abuse Rev 4:190, 2011

Sugar 'not addictive' says Edinburgh University study

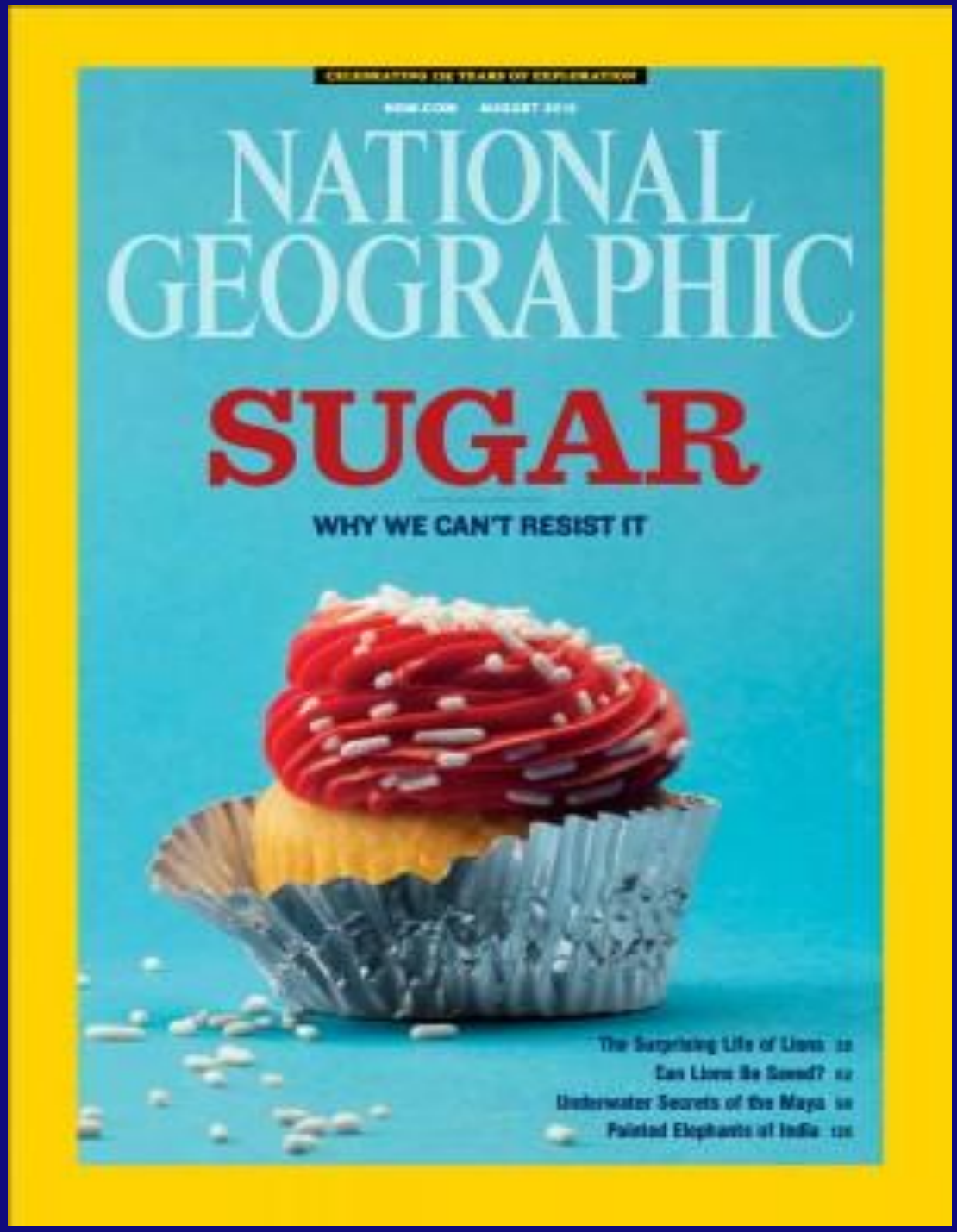
9 September 2014 | Edinburgh, Fife & East Scotland

Hebebrand et al. 2014
Neurofast (a review, not a study)

The research suggested people don't become addicted to individual foods but rather the act of eating

Sugar and opioids

Sweet-Ease increases endogenous opioids to reduce pain, Even in neonates


NATIONAL GEOGRAPHIC
SUGAR
WHY WE CAN'T RESIST IT
The Surprising Life of Lions
Can Lions Be Saved?
Underwater Secrets of the Maya
Painted Elephants of India

Is there really such a thing as sugar addiction?

Need to look for similarities to drugs of dependence

- nicotine
- morphine
- amphetamine
- cocaine
- cannabis
- ethanol

What makes a milkshake so rewarding?

- Normal weight young adult subjects, fMRI
- Milkshakes with graded doses of fat vs. sugar
- The fat stimulated the somatosensory cortex (e.g. mouthfeel)
- Only sugar stimulated the nucleus accumbens
- Adding more fat was not additive to the effect of sugar on reward

Stice et al. Am J Clin Nutr 98:1377, 2013

RESEARCH ARTICLE

Dissociable Behavioral, Physiological and Neural Effects of Acute Glucose and Fructose Ingestion: A Pilot Study

Bettina Karin Wölnerhanssen[1☯]*, Anne Christin Meyer-Gerspach[1☯], André Schmidt[2,3], Nina Zimak[1], Ralph Peterli[4], Christoph Beglinger[1], Stefan Borgwardt[2,3]

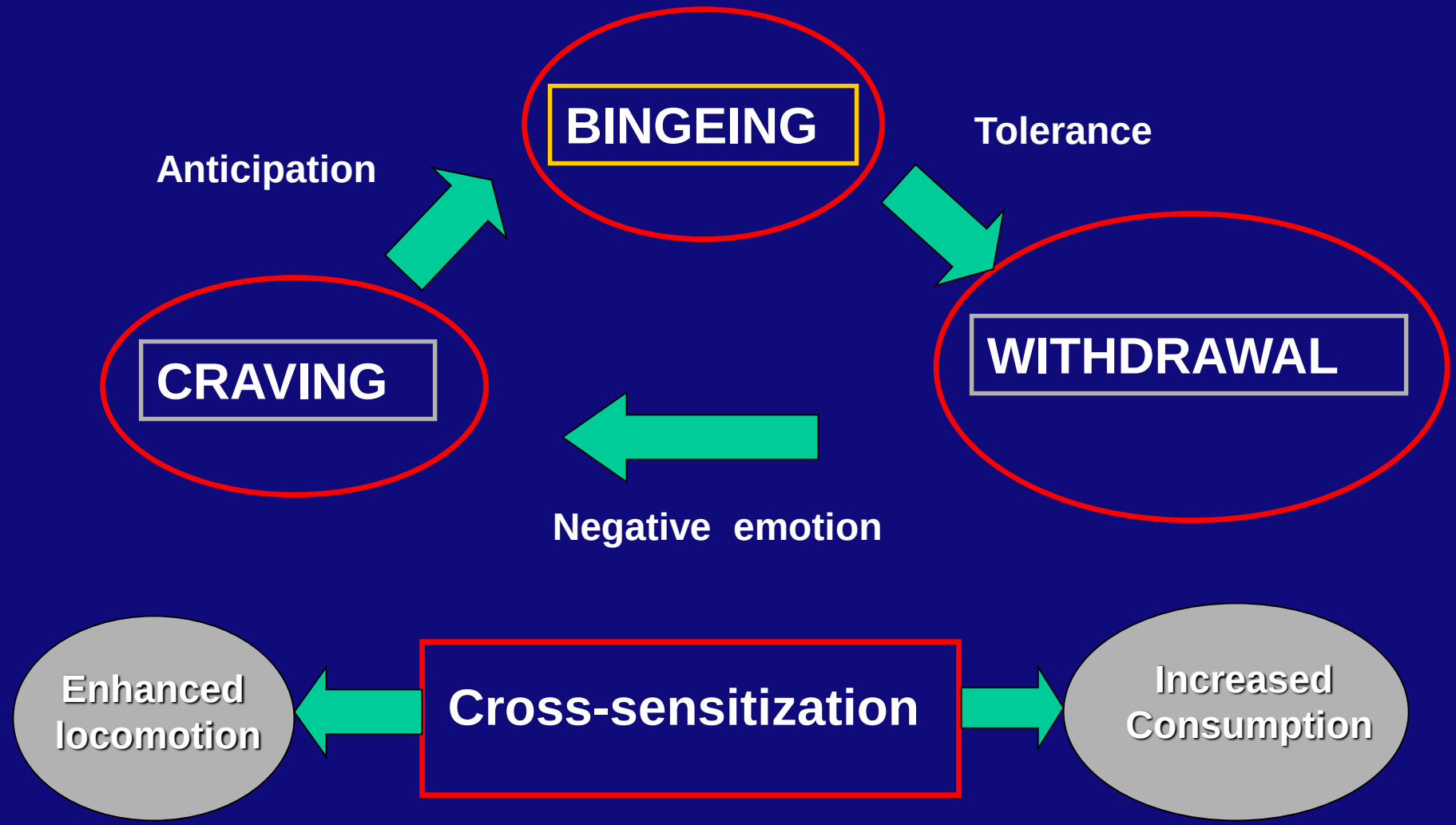
1 Department of Gastroenterology, University Hospital of Basel, Basel, Switzerland, 2 Medical Image Analysis Center, University Hospital of Basel, Basel, Switzerland, 3 Department of Psychiatry, University Hospital of Basel, Basel, Switzerland, 4 Department of Surgery, St. Clara Hospital, Basel, Switzerland

No satiety or fullness with fructose compared with glucose
No insulin rise with fructose compared with glucose

fMRI:
Glucose: caudate, putamen, precuneus, lingual gyrus
Fructose: amygdala, hippocampus, parahippocampus, orbitofrontal cortex
precentral gyrus

PLoS One 10(6):e0130280, 2014

Criteria for addiction



Avena et al. Neurosci Biobehav Rev 32:20, 2008 (Courtesy Dr. B. Hoebel)

Rat model of addiction

Daily Intermittent Sucrose and Chow

Rats are food deprived for 12 h,

then given 12-h access to rodent chow and a 10% sucrose solution starting 4 h into the active cycle.

DARK ONSET

(active)

LIGHT ONSET

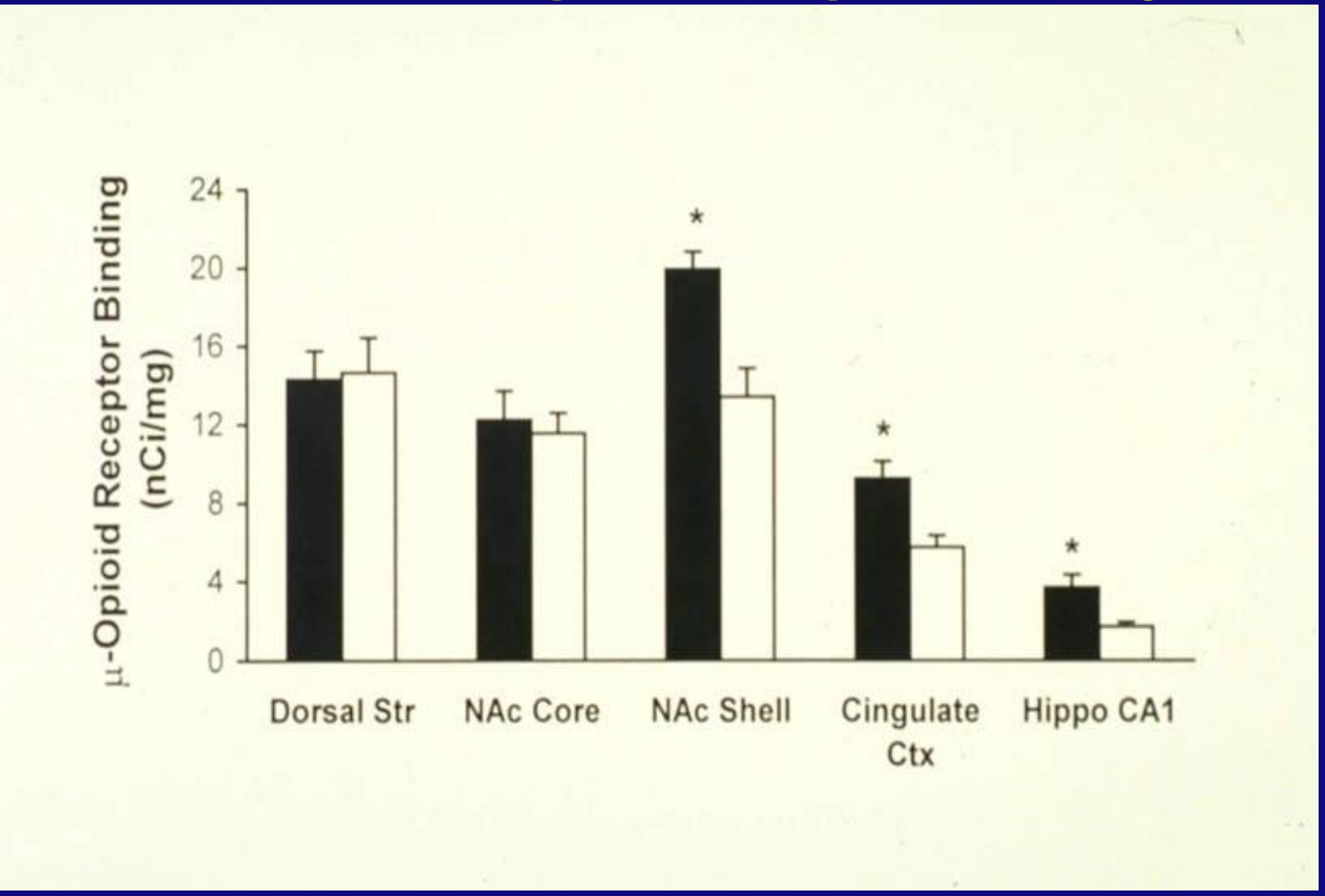
(resting)

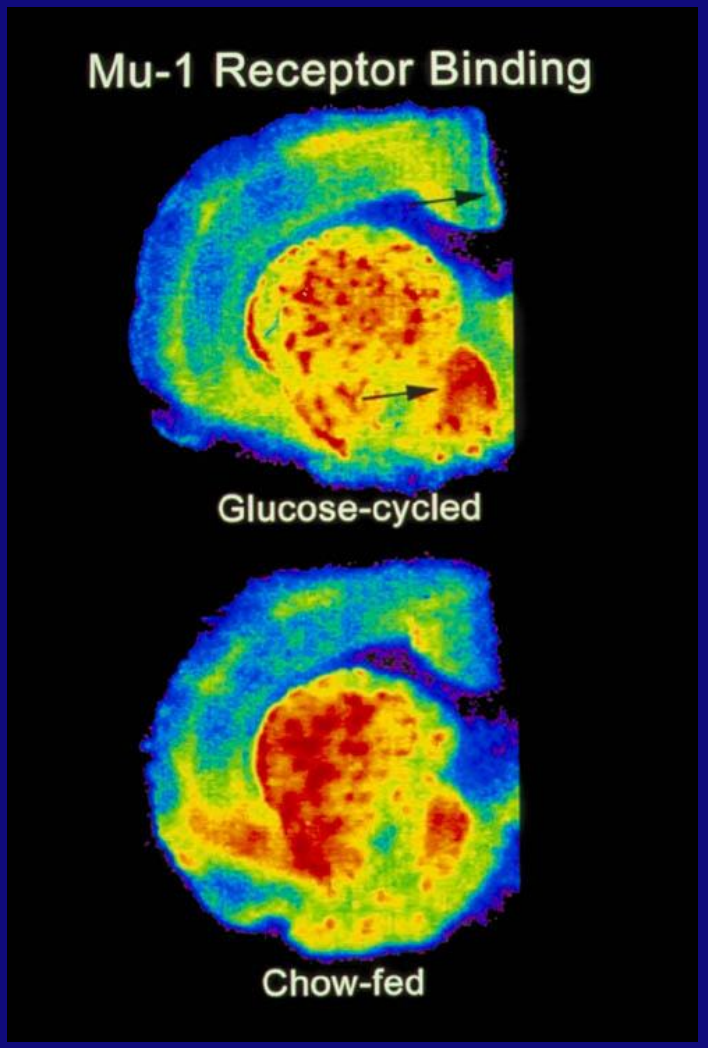
Avena et al. Neurosci Biobehav Rev 32:20, 2008 (Courtesy Dr. B. Hoebel)

Sugar and addiction

- Bingeing

Increased mu-opioid receptor binding in the accumbens shell





Avena et al. Neurosci Biobehav Rev 32:20,2008 (Courtesy Dr. B. Hoebel)

Opiate-like effects of sugar on gene expression in reward areas of the rat brain

Changes in mRNA levels in sucrose-dependent rats are similar to those in morphine-dependent rats

- reduction in dopamine 2 receptor mRNA
- reduction in opioid mRNAs
- increase in dopamine 3 receptor mRNA

Suggest that sucrose and morphine might activate similar pathways, either directly in the forebrain, or in regions which project to the forebrain

Spangler et al. Mol Brain Res 124, 134, 2004

Sugar and addiction

- Withdrawal

Naloxone-precipitated withdrawal on a plus-maze

Avena et al. Neurosci Biobehav Rev 32:20, 2008 (Courtesy Dr. B. Hoebel)

Sugar and addiction

- Withdrawal

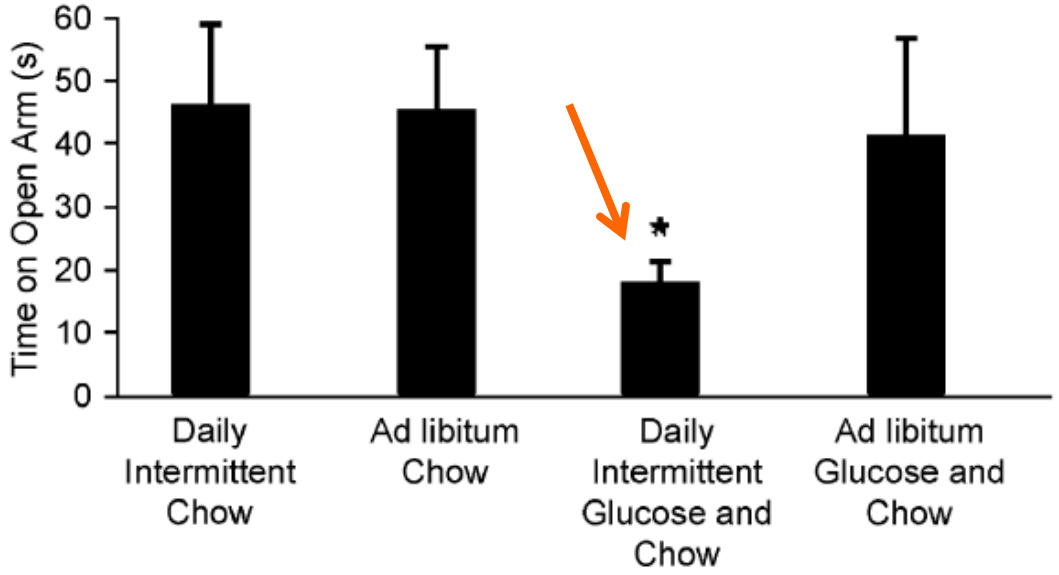


Fig. 2. Time spent on the open arms of an elevated plus-maze. Four groups of rats were maintained on their respective diets for one month and then received naloxone (3 mg/kg, s.c.). The Daily Intermittent Glucose and Chow group spent less time on the open arms of the maze. $*p<0.05$ compared with the Ad libitum Chow group. From Colantuoni et al., 2002.

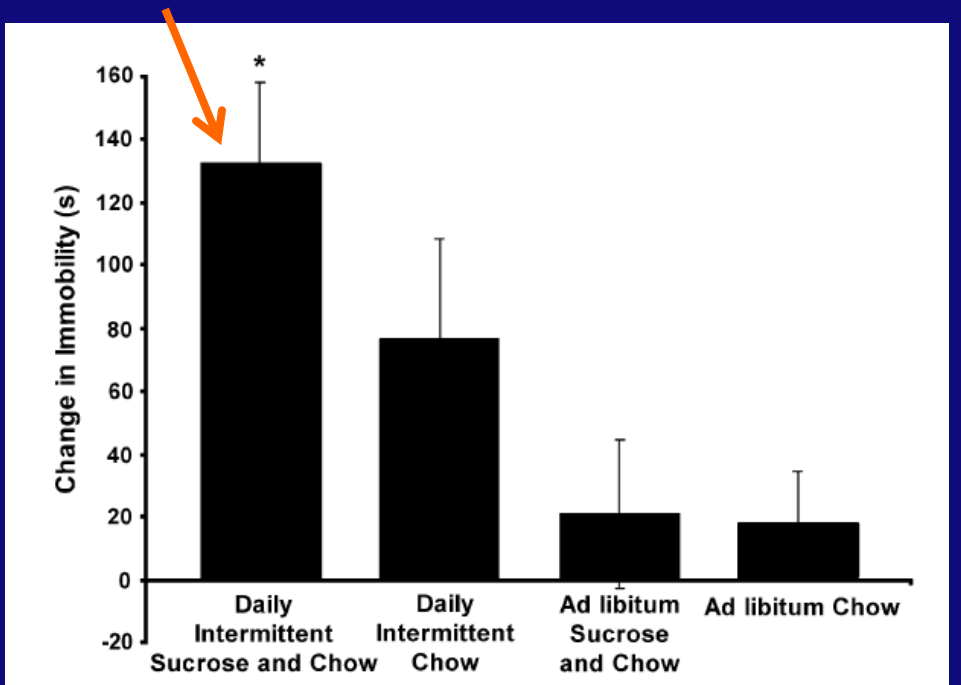
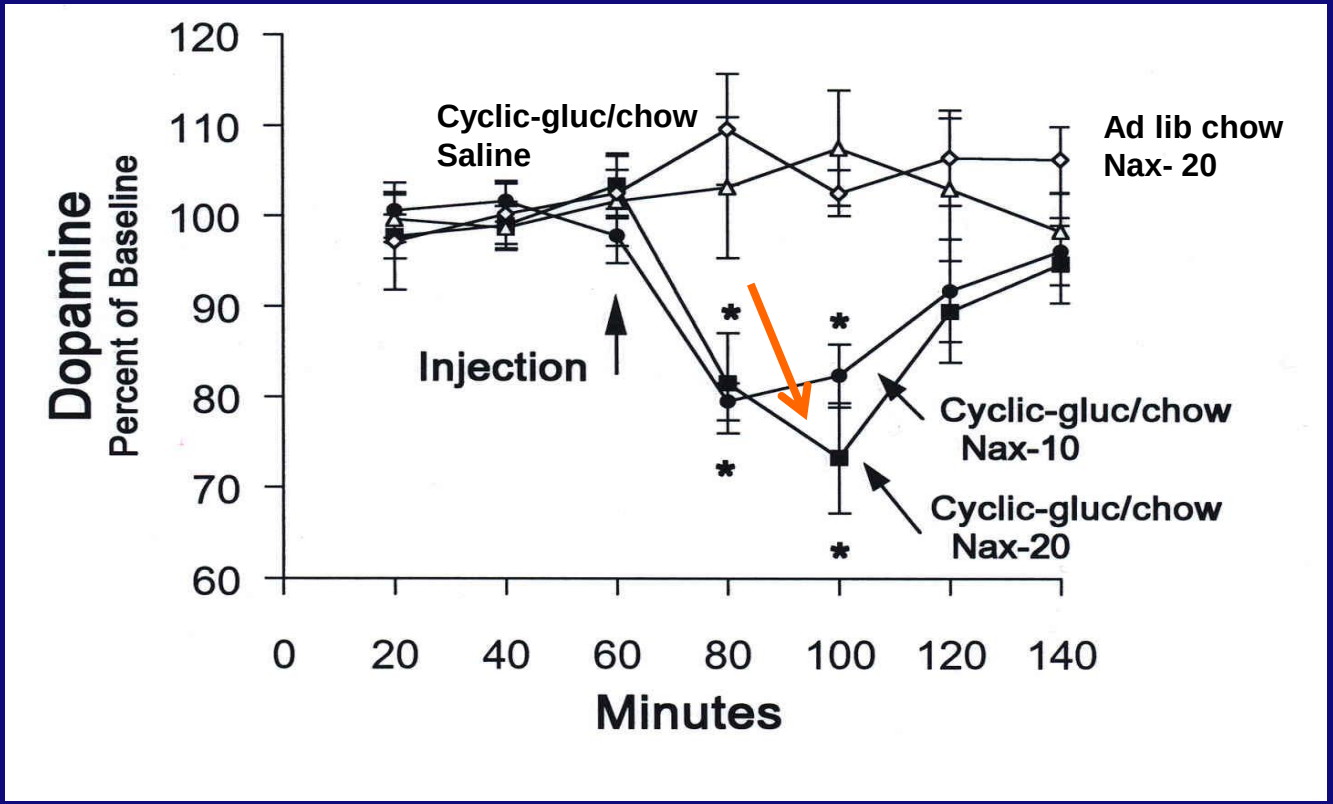


Fig. 3. Rats that have been maintained on Daily Intermittent Sucrose and Chow are more immobile than control groups in a forced-swim test during naloxone-precipitated withdrawal. $*p<0.05$ compared with Ad libitum Sugar and Chow and Ad libitum Chow groups.

Avena et al. Neurosci Biobehav Rev 32:20, 2008 (Courtesy Dr. B. Hoebel)

Sugar and addiction

- Withdrawal



Avena et al. Neurosci Biobehav Rev 32:20, 2008 (Courtesy Dr. B. Hoebel)

Sugar and addiction

- Craving

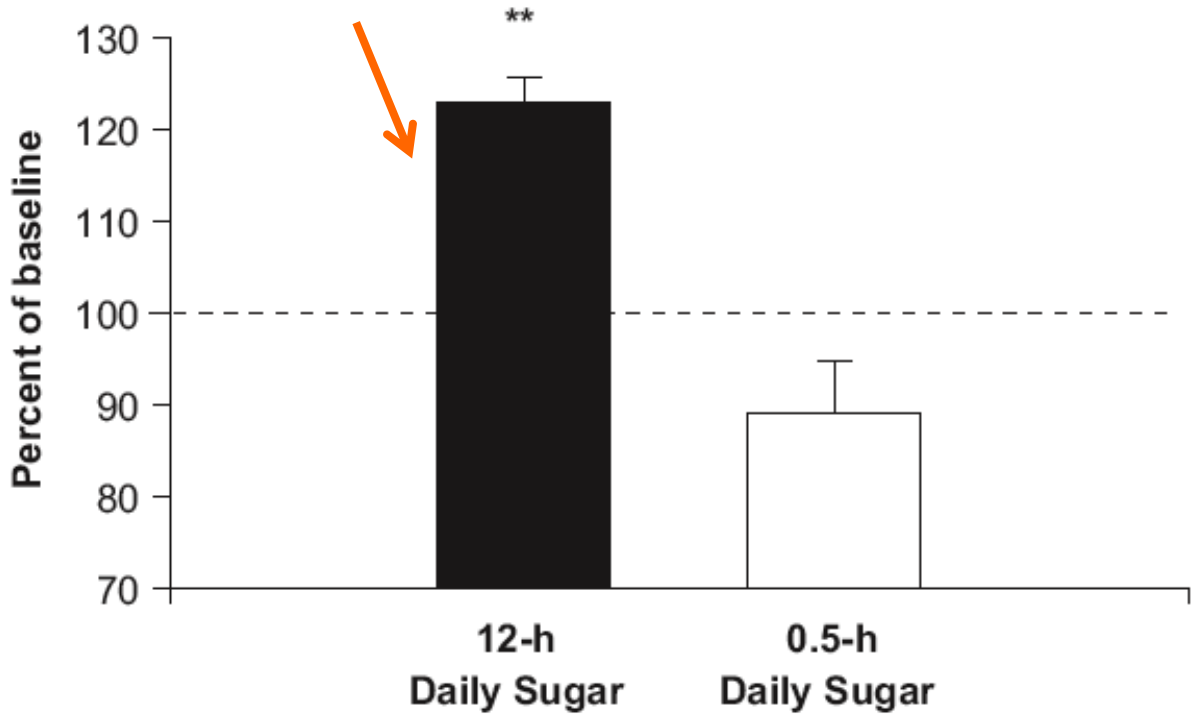
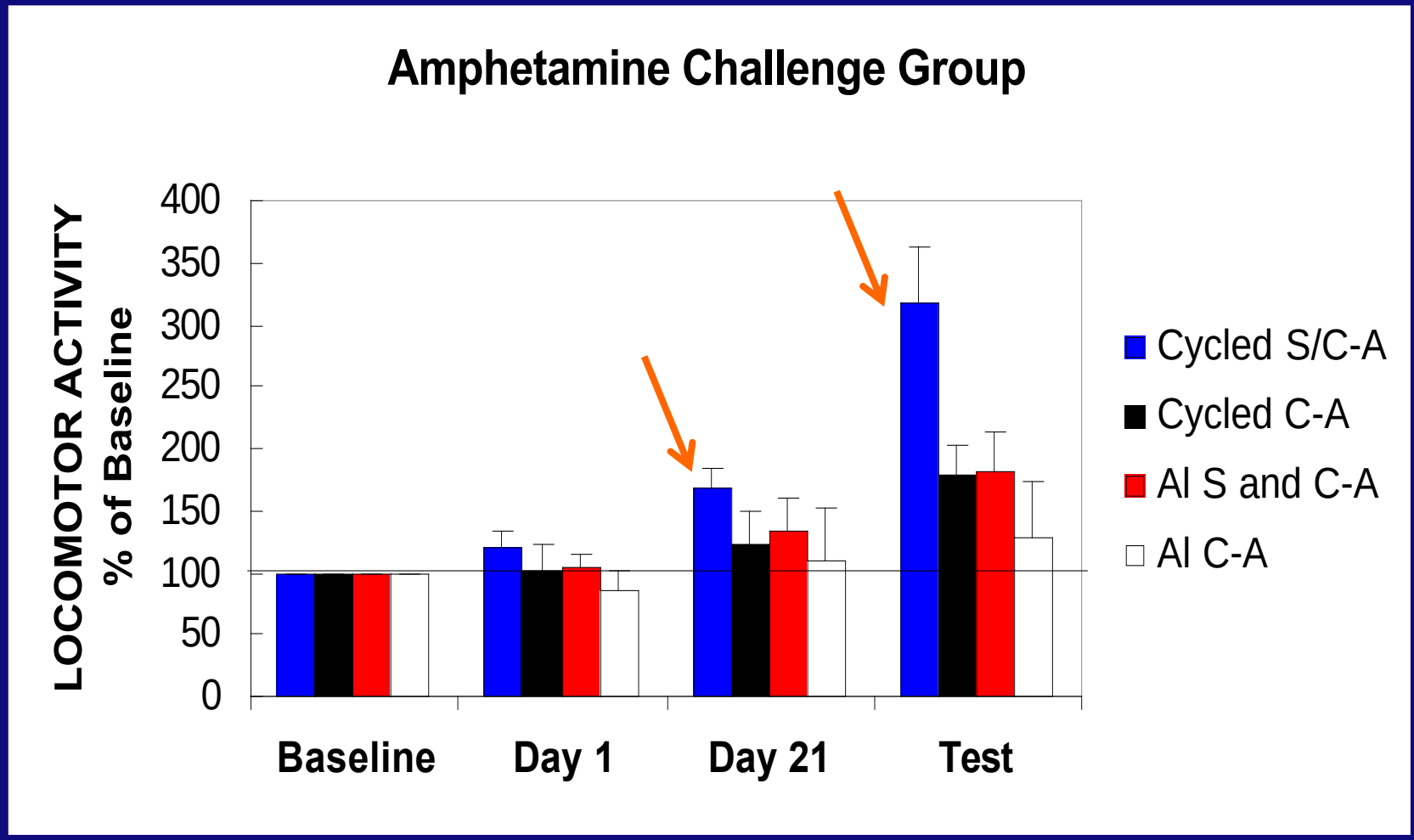


Fig. 4. After 14 days of abstinence from sugar, rats that previously had 12-h daily access significantly increased lever pressing for glucose to 123% of pre-abstinence responding, indicating increased motivation for sugar. The group with 0.5-h daily access did not show increased responding after abstinence. $^{**}p < 0.01$. From Avena et al., 2005.

Avena et al. Neurosci Biobehav Rev 32:20, 2008 (Courtesy Dr. B. Hoebel)

Sugar and addiction

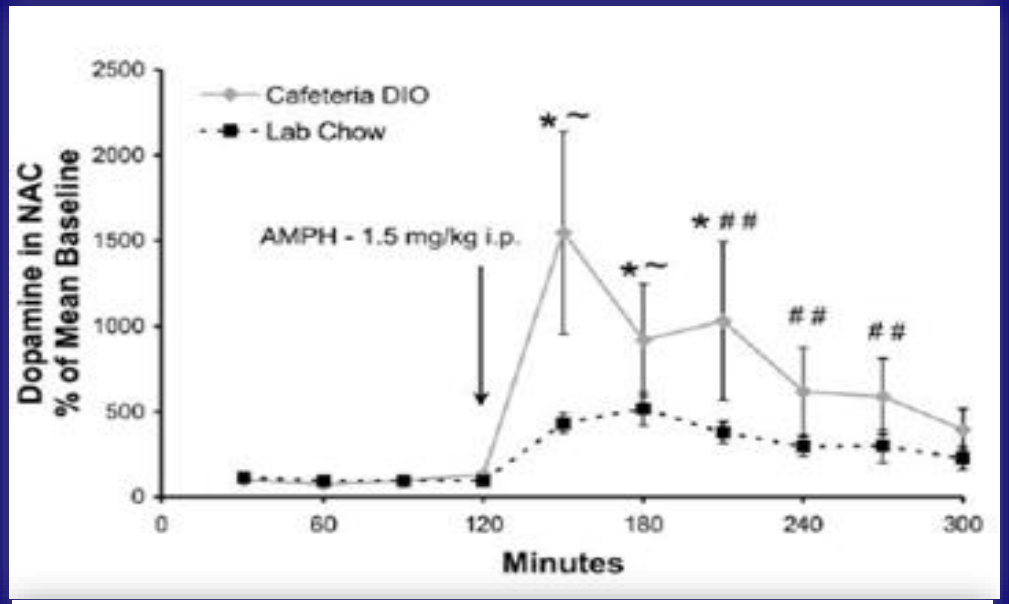
- Cross-sensitization with other drugs of abuse



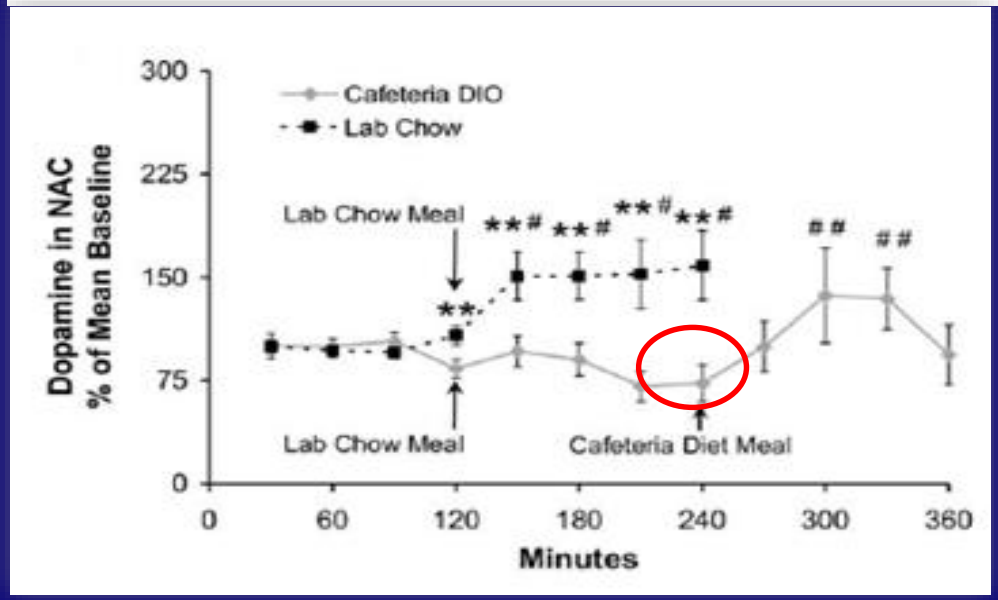
Avena et al. Neurosci Biobehav Rev 32:20, 2008 (Courtesy Dr. B. Hoebel)

Sugar and addiction

- Cross-sensitization with other drugs of abuse



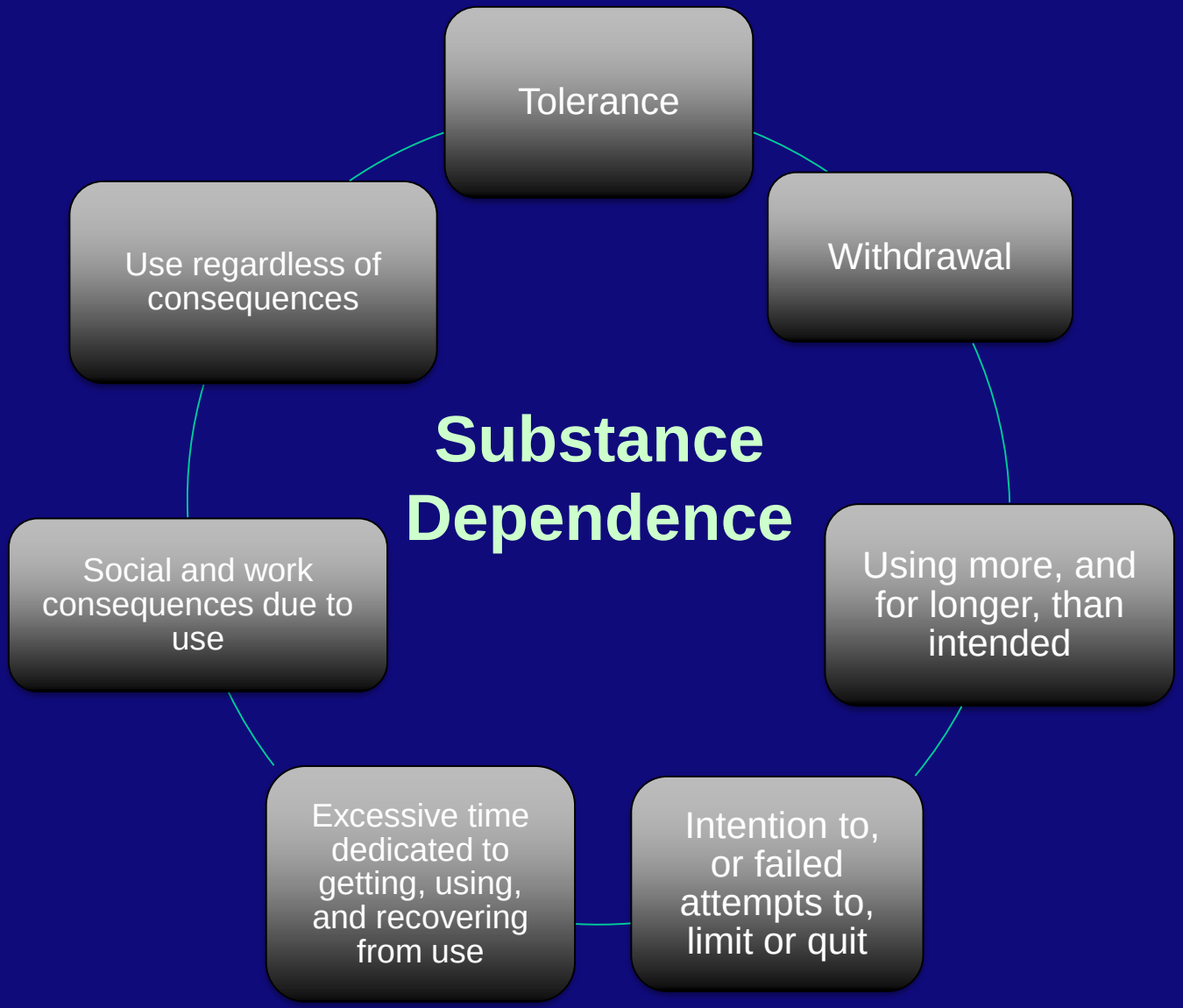
Rats with access to a Cafeteria-style (junk food) diet are hyper-responsive to amphetamine in terms of dopamine release.



However, they do not respond to a lab chow meal. These rats need junk food to release accumbens dopamine.

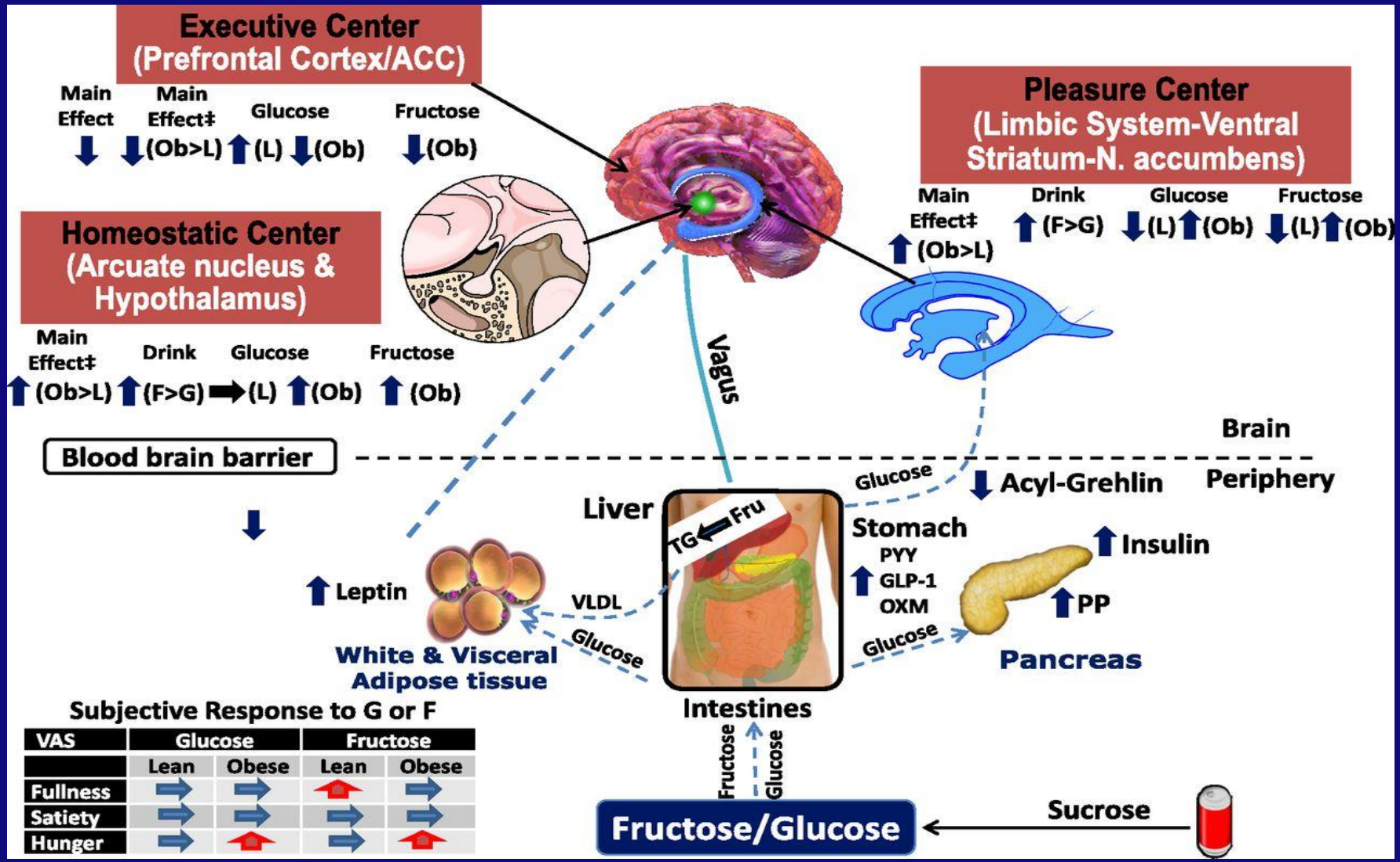
Geiger et al. Neuroscience 159:1193, 2009

Defining an addiction: DSM IV criteria




SUPER SIZE ME
A Film of Epic Portions
www.supersizeme.com

Effects of fructose and glucose on the brain in normal and obese adolescents



Jastreboff et al. Diabetes 65:1929, 2016

How about humans?
The DSM-V criteria for addiction

2 of the 11 following criteria within a 12-month period:

1. Tolerance
2. Withdrawal

Physiologic

3. Craving or a strong desire to use
4. Use resulting in a failure to fulfill major role obligations (work, school, home);
5. Recurrent use in physically hazardous situations (e.g. driving);
6. Use despite social or interpersonal problems caused or exacerbated by use;
7. Taking the substance in larger amounts or over a longer period than intended;
8. Attempt to quit or cut down;
9. Time spent seeking or recovering from use;
10. Interference with life activities;
11. Use despite negative consequences.

Psychologic (Dependence)

NeuroFAST
www.neurofast.eu

CONSENSUS

NeuroFAST consensus opinion on food addiction

•**In humans, there is no evidence that a specific food, food ingredient or food additive causes a substance-based type of addiction** (the only currently known exception is caffeine which via specific mechanisms can potentially be addictive).

• Within this context **we specifically point out that we do not consider alcoholic beverages as food**, despite the fact that one gram of ethanol has an energy density of 7 kcal.

Alcohol and caffeine are really "food additives"

If:

— it’s about obesity; or

— it’s about eating addiction; or

— no specific food is addictive,

then the food industry has “carte blanche”;
and there is no option for societal intervention

Is sugar a “food”?

FDCA: 321.201(f) The term "food" means (1) articles used for food or drink for man or other animals, (2) chewing gum, and (3) articles used for components of any such article.

Is sugar a “food”?

FDCA: 321.201(f) The term "food" means (1) articles used for food or drink for man or other animals, (2) chewing gum, and (3) articles used for components of any such article.

Webster: a material consisting essentially of protein, carbohydrate, and fat used in the body of an organism to sustain growth, repair, and vital processes and to furnish energy; also: such food together with supplementary substances (as minerals, vitamins, and condiments)

Is sugar a “food”?

FDCA: 321.201(f) The term "food" means (1) articles used for food or drink for man or other animals, (2) chewing gum, and (3) articles used for components of any such article.

Webster: a material consisting essentially of protein, carbohydrate, and fat used in the body of an organism to sustain growth, repair, and vital processes and to furnish energy; also: such food together with supplementary substances (as minerals, vitamins, and condiments)

Sugar provides only energy, but that should make it a food, right?

Can you name an energy source that is:

Can you name an energy source that is:

Not necessary for life

Can you name an energy source that is:

Not necessary for life

There is no biochemical reaction in the body that requires it

Can you name an energy source that is:

Not necessary for life

There is no biochemical reaction in the body that requires it

Is not nutrition

Can you name an energy source that is:

- Not necessary for life
- There is no biochemical reaction in the body that requires it
- Is not nutrition
- When consumed in excess it is toxic

Can you name an energy source that is:

- Not necessary for life
- There is no biochemical reaction in the body that requires it
- Is not nutrition
- When consumed in excess it is toxic
- We love it anyway, and it’s addictive

Can you name an energy source that is:

Not necessary for life

There is no biochemical reaction in the body that requires it

Is not nutrition

When consumed in excess it is toxic

We love it anyway, and it’s addictive

Answer: Ethanol

American Dietetic Association

RESEARCH

Review

Fructose: Metabolic, Hedonic, and Societal Parallels with Ethanol

ROBERT H. LUSTIG, MD

Aside from sugar, are there other energy sources that aren't foods?

Alcohol
Trans-fats

These are NOT foods;

Trans-fats was recently reclassified by the FDA (2013)

Neither one is currently considered Generally Recognized as Safe (GRAS)

The FDA has reclassified Trans-Fats and Nitrates as

NOT GRAS

Could we reclassify sugar as a food additive,

and therefore NOT GRAS?

Could we get sugar reclassified as a “food additive”?

Being addictive doesn’t get you off the GRAS list: **e.g. caffeine**

GRAS is defined (FDCA, 321(s)) as “generally recognized, among experts qualified by scientific training and experience to evaluate its safety, as having been adequately shown through scientific procedures (or, in the case of a substance used in food prior to January 1, 1958, through either scientific procedures or experience based on common use in food) to be safe under the conditions of its intended use.”

So GRAS is about “toxicity”, not addiction.

The current level of consumption (90-100 lb/yr) was never intended.

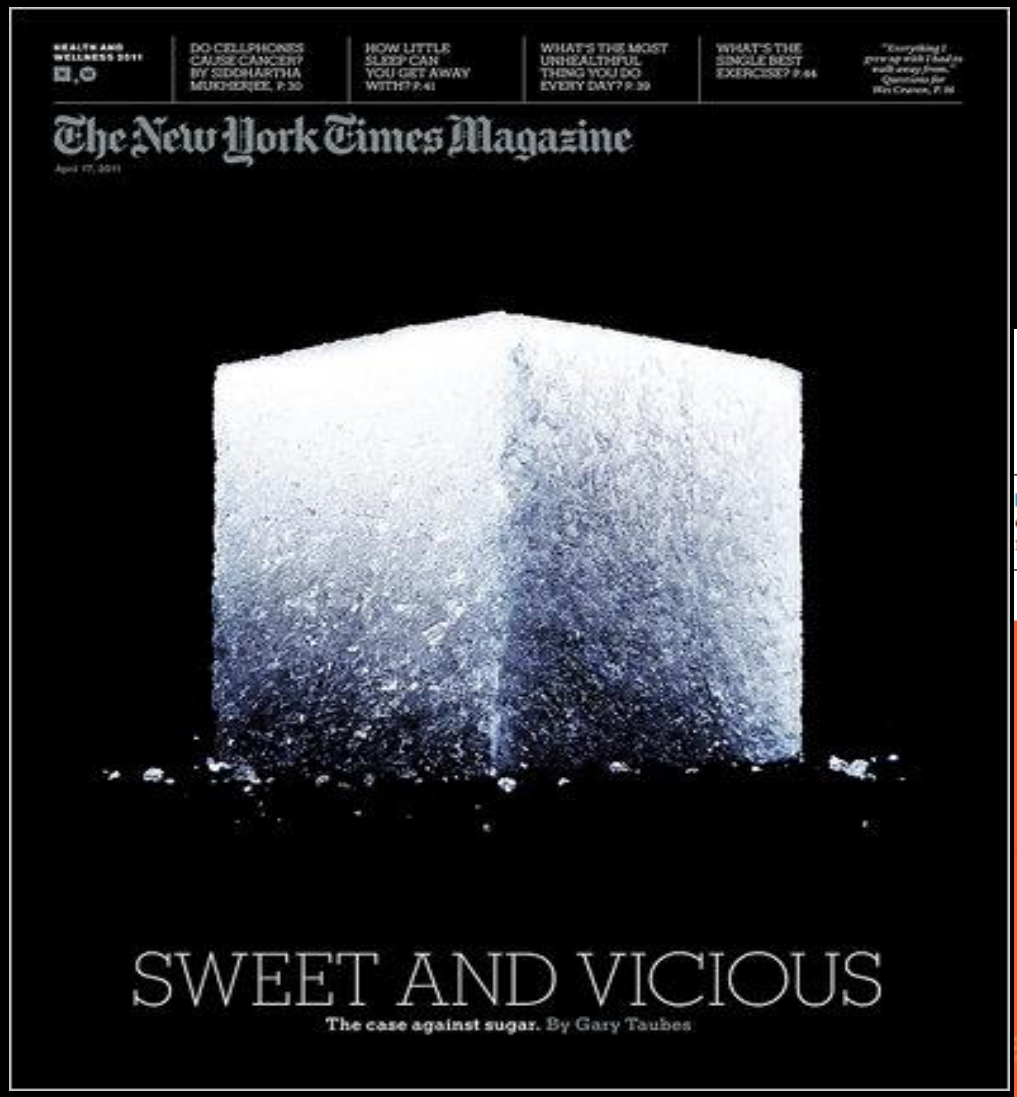
Sugar known to India 1200 BCE

Sugar on FDA's GRAS list since its inception in 1958

Last evaluation by FDA 1986 (before HFCS glut)
Avg. consumption:
51 gm/day sugar
25.5 gm fructose
(HALF AS MUCH AS WE CONSUME TODAY)

Result: Inconclusive

Glinsmann et al. J. Nutr 116:1/S, 1986



New York Times, April 17, 2011

Nature 487:27-29, Feb 1, 2012

COMMENT

ECOLOGY Komodo dragons and elephants could reduce fire risk in Australia **p.30**

NEUROSCIENCE The source of the self is in the brain's wiring, not individual neurons **p.31**

LITERATURE How Charles Dickens drew on science, but left room for wonder **p.32**

OBITUARY Philip Lawley and the discovery that DNA damage can cause cancer **p.36**

The toxic truth about sugar

Added sweeteners pose dangers to health that justify controlling them like alcohol, argue **Robert H. Lustig, Laura A. Schmidt** and **Claire D. Brindis.**

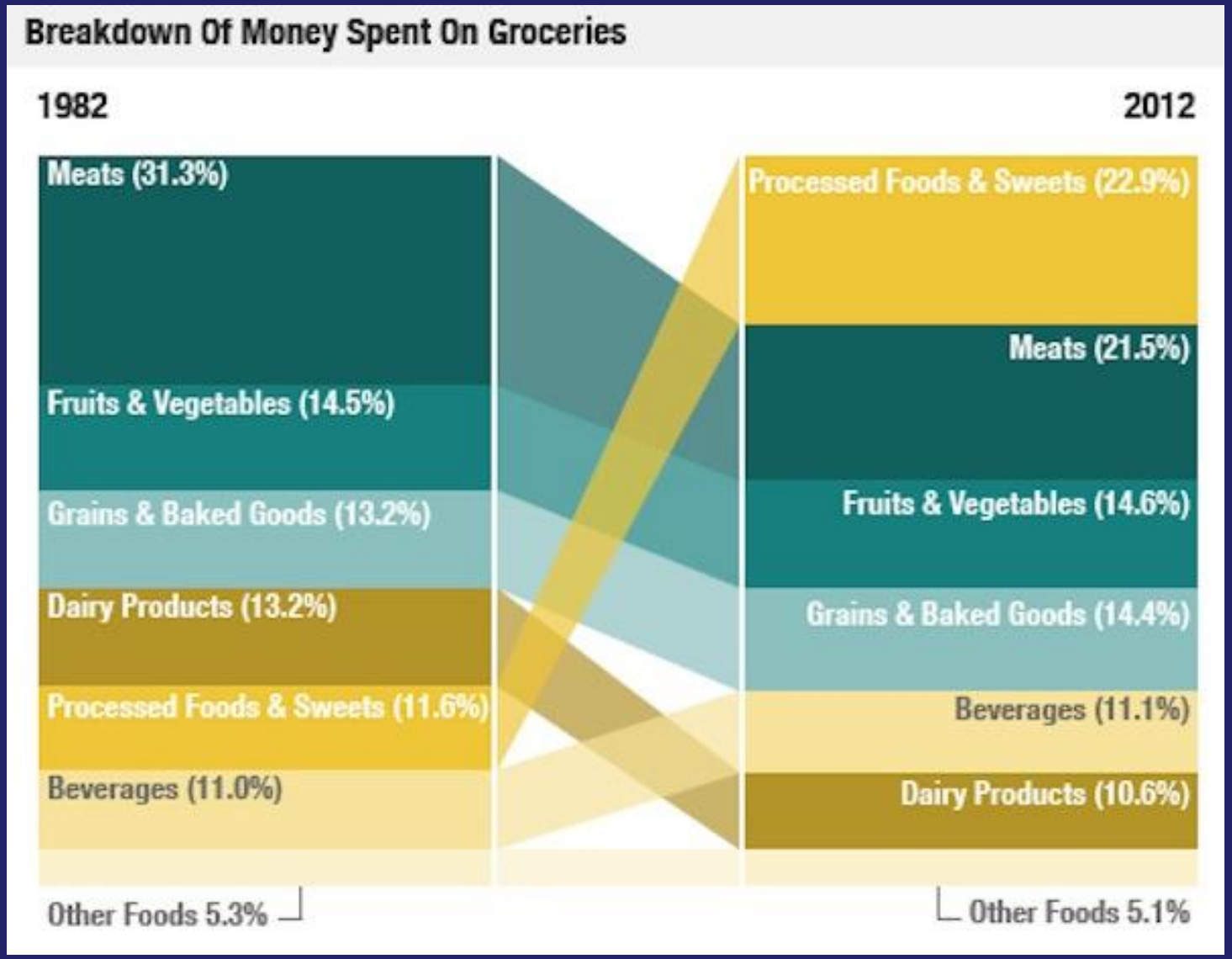
Addictive and hazardous to your health

Addictive and hazardous to your health

Summary — how does the science intersect with the law?

- It's not about obesity
- Food addiction is a misnomer
- Fat and salt increase the "salience" of food, but are not themselves addictive
- The only items in "junk" food that are addictive are sugar and caffeine; but they are really food additives
- Just because something has calories doesn't make it a food; it can be a "food additive" (e.g. ethanol, trans-fats)
- The only fix is through GRAS removal (e.g. trans-fats, nitrates)
- GRAS focuses on toxicity, not addiction; fructose is both
- Sugar is toxic and addictive in current doses, which were "never intended"

How our food dollars have been reallocated



Philpott, Mother Jones 2012 (from Bureau of Labor Statistics)

Of the 600,000 items in the American food supply,

80% have added sugar (sucrose, HFCS)

Ng et al. J Acad Nutr Diet 2012

Further reading

Fast Food, Central Nervous System Insulin Resistance, and Obesity

Elvira Isganaitis, Robert H. Lustig

Arterioscler Throm Vasc Biol 25:2451, 2005

Is fast food addictive?

Andrea K. Garber, Robert H. Lustig

Curr Drug Abuse Rev 4:146, 2011

The role of fructose in the pathogenesis of NAFLD and the metabolic syndrome

Jung Sub Lim, Michele Mietus-Snyder, Annie Valente, Jean-Marc Schwarz and Robert H. Lustig

Nat Rev Gastroenterol Hepatol 7:251, 2010

eat right. American Dietetic Association

RESEARCH

Review

Fructose: Metabolic, Hedonic, and Societal Parallels with Ethanol

ROBERT H. LUSTIG, MD

J Am Diet Assoc 110:1305, 2010

Further reading

Effects of Sugar-Sweetened Beverages on Children

Andrew A. Bremer, MD, PhD; and Robert H. Lustig, MD

Pediatric Annals 41:23, 2012

Toward a Unifying Hypothesis of Metabolic Syndrome

Andrew A. Bremer, M.D., Ph.D.[a], Michele Mietus-Snyder, M.D.[b], Robert H. Lustig, M.D.[c]*

Pediatrics 129:557, 2012

Further reading

Fructose: It's "Alcohol Without the Buzz"[1–3]

Robert H. Lustig*

Department of Pediatrics and the Philip R. Lee Institute for Health Policy Studies, University of California, San Francisco, CA

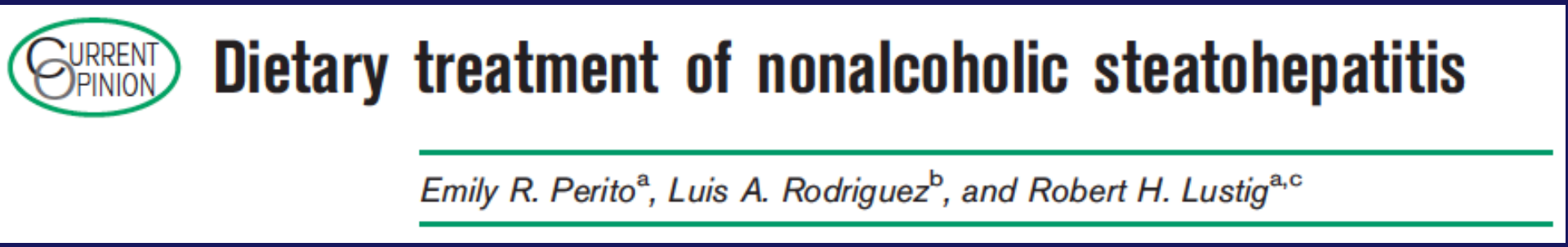
Advances in Nutrition 4:1, 2013

What is metabolic syndrome, and why are children getting it?

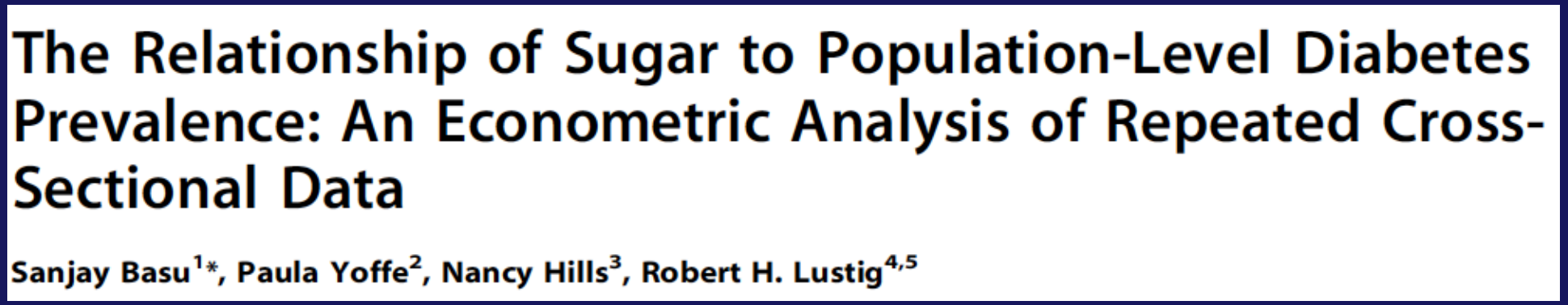
Ram Weiss,[1] Andrew A. Bremer,[2] and Robert H. Lustig[3,4]

Annals NY Academy of Sciences, 1, 2013

Further reading



Current Opinion Gastroenterology, 29:170, 2013



PLoS One 8:e57873, 2013

Further Reading

Original Article
PEDIATRIC OBESITY

Obesity

Isocaloric Fructose Restriction and Metabolic Improvement in Children with Obesity and Metabolic Syndrome

Robert H. Lustig[1], *Kathleen Mulligan*[2,3], *Susan M. Noworolski*[4], *Viva W. Tai*[2], *Michael J. Wen*[2], *Ayca Erkin-Cakmak*[1], *Alejandro Gugliucci*[3], *and Jean-Marc Schwarz*[5]

ELSEVIER

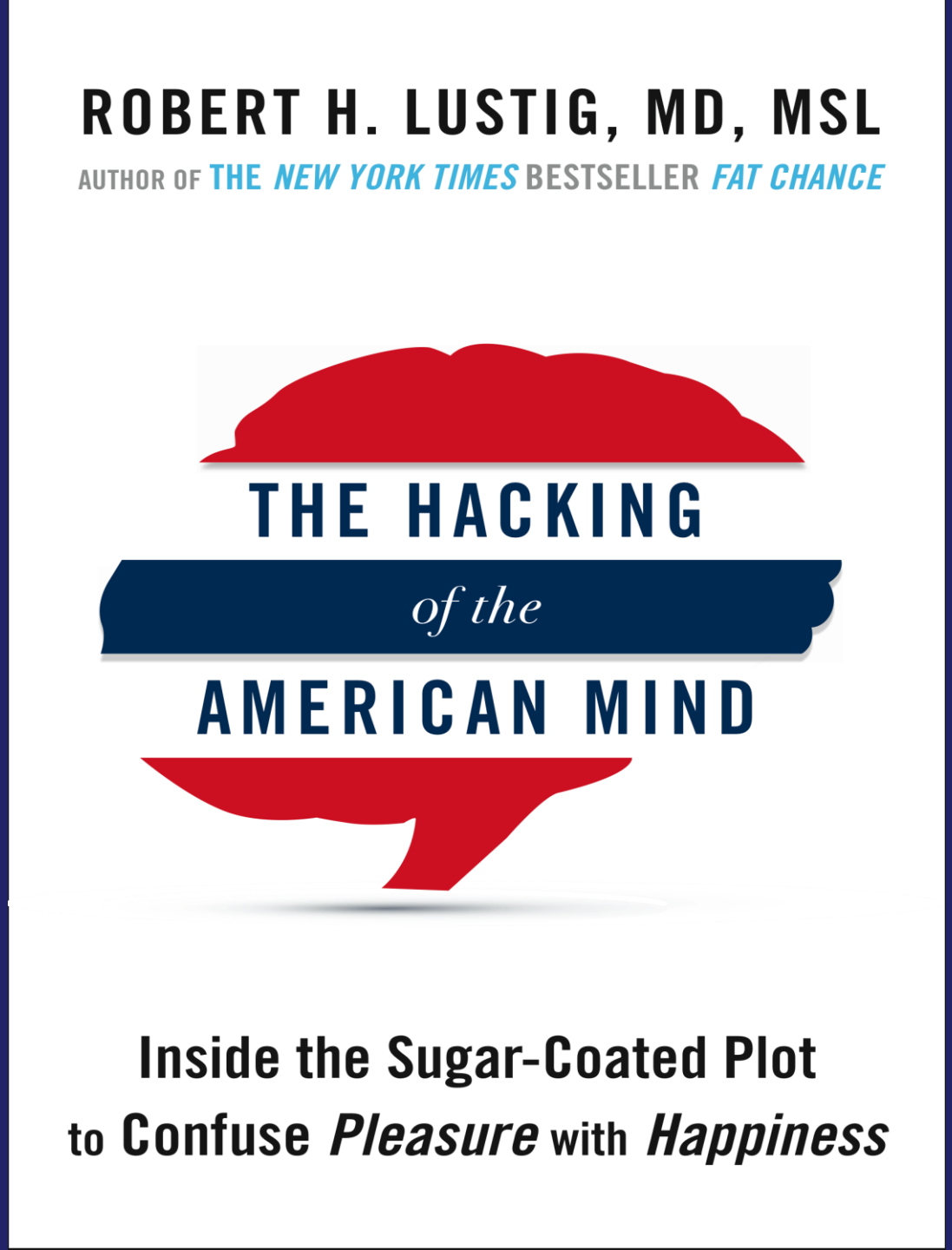
Contents lists available at ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

Short-term isocaloric fructose restriction lowers apoC-III levels and yields less atherogenic lipoprotein profiles in children with obesity and metabolic syndrome

Alejandro Gugliucci [a,*], Robert H. Lustig [b], Russell Caccavello [a], Ayca Erkin-Cakmak [b], Susan M. Noworolski [d], Viva W. Tai [c], Michael J. Wen [c], Kathleen Mulligan [a,c], Jean-Marc Schwarz [e]



A new book!

Release date
Sept 12

Avery Press

Penguin Random House

Collaborators

UCSF Weight Assessment for Teen and Child Health (WATCH)

Andrea Garber, Ph.D., R.D.
Patrika Tsai, M.D., M.P.H.
Stephanie Nguyen, M.D. M.A.S.
Kathryn Smith, M.D.
Emily Perito, M.D.
Luis Rodriguez, R.D.
Megan Murphy, R.D.
Maryann Christofas, R.D.

Touro University Dept. of Biochemistry

Jean-Marc Schwarz, Ph.D.

San Francisco General Hospital Depts. of Medicine and Radiology

Sanjay Basu, M.D., Ph.D.
Susan Noworolski, Ph.D.
Kathleen Mulligan, Ph.D.

UCSF Institute for Health Policy Studies

Laura Schmidt, Ph.D., M.S.W.
Cristin Kearns, D.D.S., M.B.A.
Claire Brindis, Dr.P.H.
Stanton Glantz, Ph.D.

Columbia University

Nicole Avena, Ph.D.