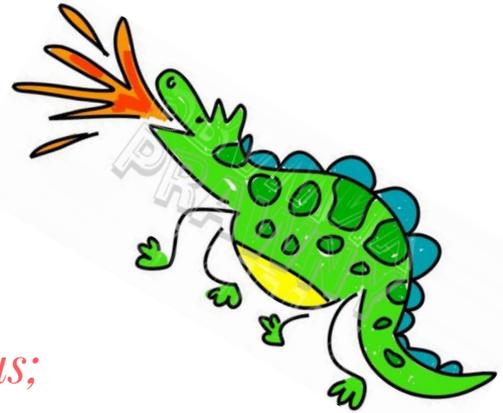
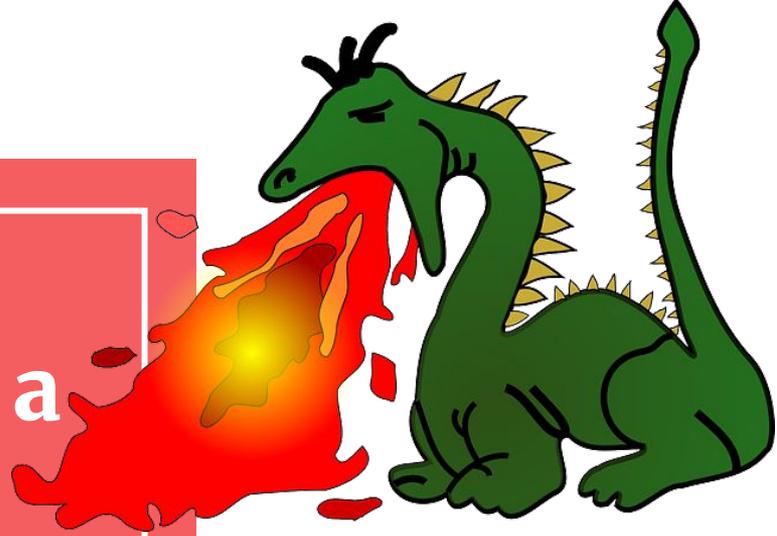


Is Obesity a Brain Disease?

Flaming Dinos



*Angela-saurus; Julia-dactyl; Mikaela-saurus;
Rachel-rex; tri-Sara-tops*

Introduction

- Obesity is often seen as an inability to control one's eating behavior and habits
- Review evidence that excessive nutrition or caloric intake can lead to:
 - Structural and functional changes in the brain
 - Decrease in metabolic control and cognitive deficits



Overnutrition is a Trap

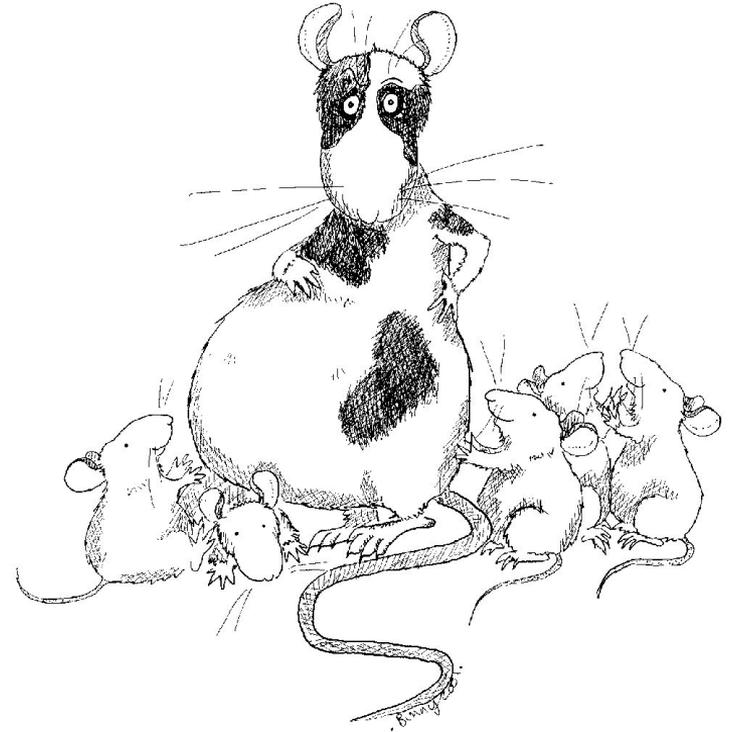
**IT'S
A
TRAP!**



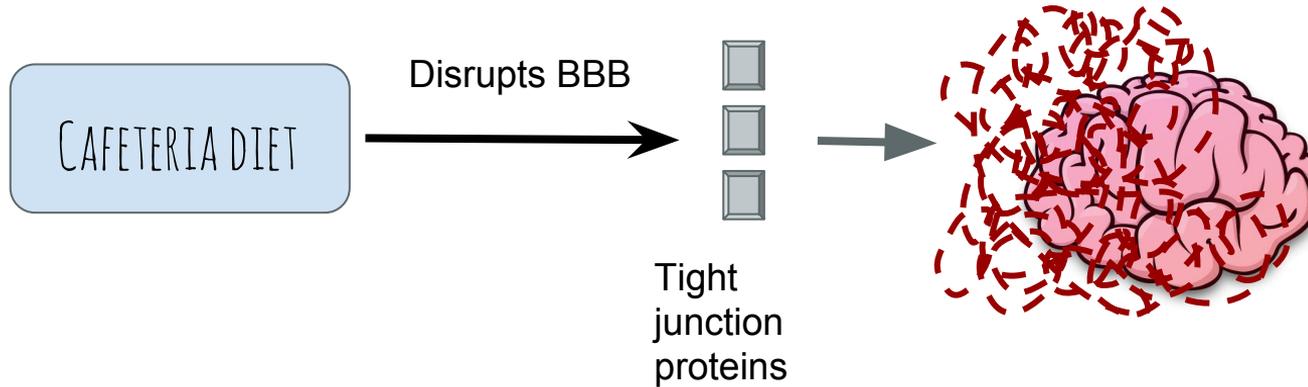
- Early exposure to fatty foods predisposes rats to favor high fat diet as adults
- SHR given choice of diet had increased body weight, leptin and insulin resistance, and higher blood pressure
- Calorie source and eating time equally as important as caloric value

Early Food Habits Programs Eating Control in Adult Life

- Juvenile exposure to fatty food reduced neural development and memory flexibility
- Maternal high fat diet led to increased offspring lipid peroxidation
- Newborns raised on high carb milk develop chronic insulinemia -> adult obesity
- Lean offspring nursed by obese mothers developed insulin-resistant phenotype

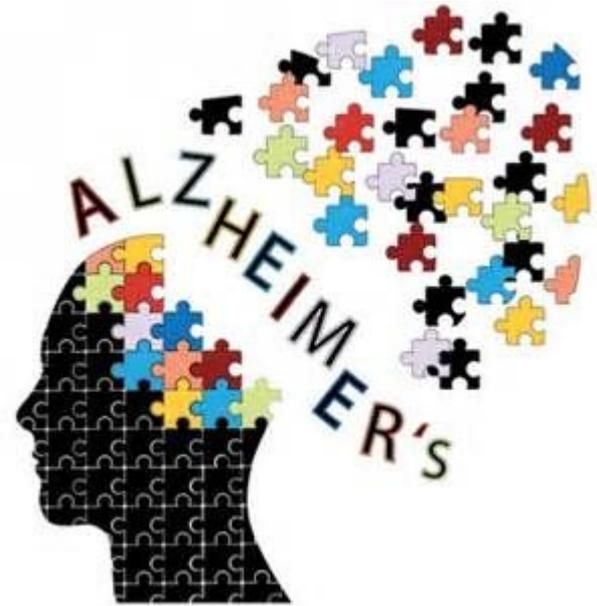
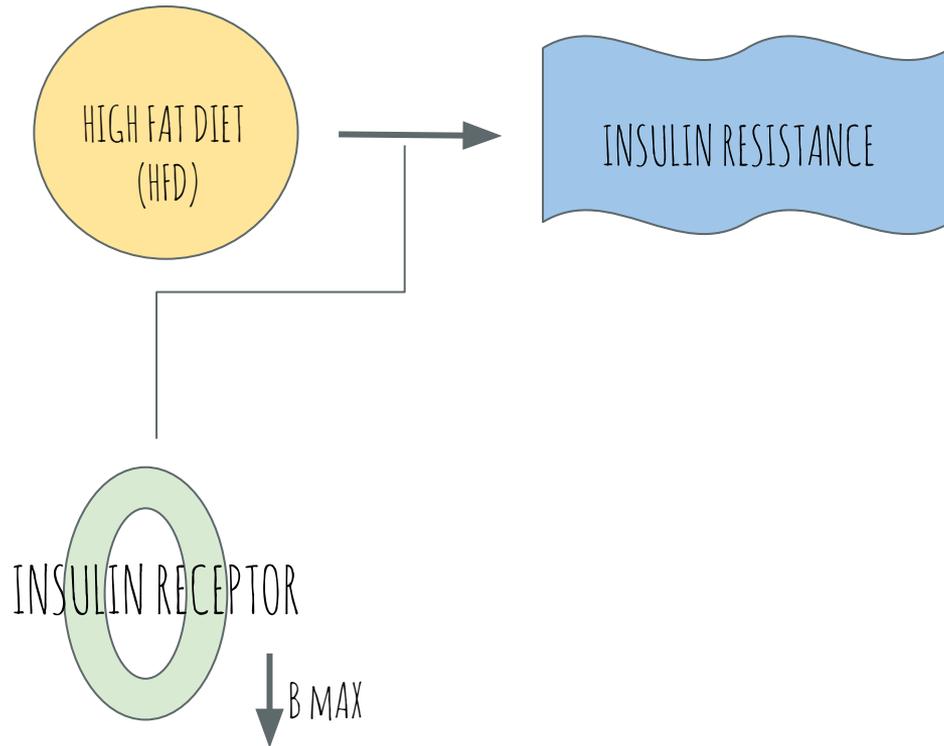


Excessive Nutrition Elicits Brain Disease



ISSUES WITH ENERGY HOMEOSTASIS, GENERAL FUNCTION AND STRUCTURAL IMPLICATIONS ENSUE FROM OBESITY RELATED INFLAMMATORY BRAIN CHANGES

Obesity Could Contribute to Alzheimer's



Who's to blame for obesity?



High Caloric Intake



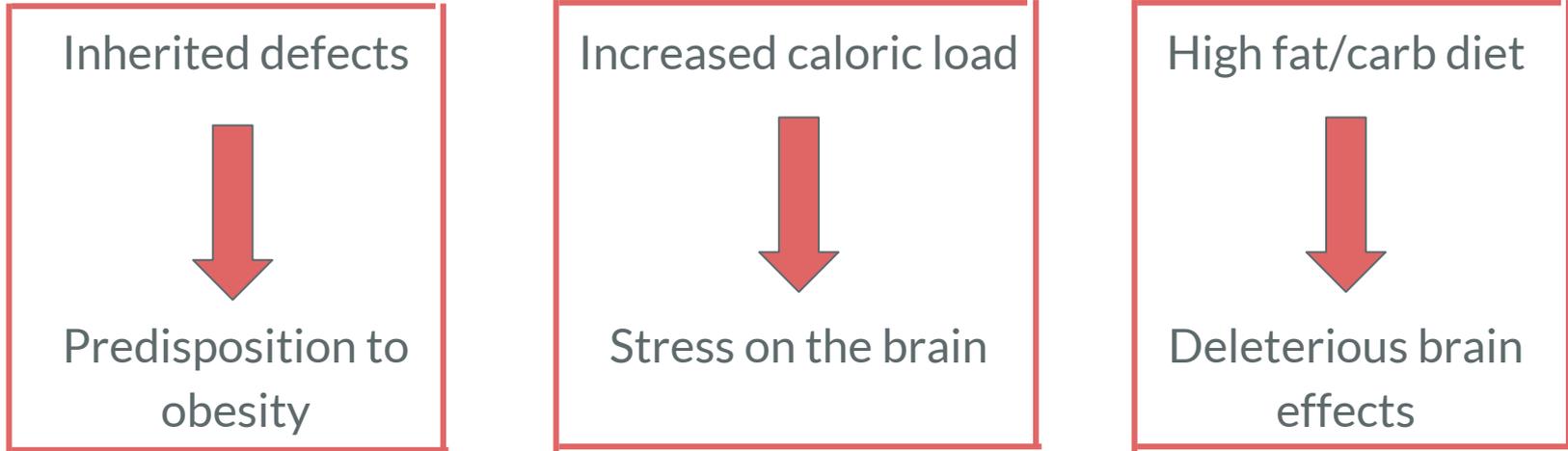
High Fat Diet



High Carb Diet

Answer: a little of everything:

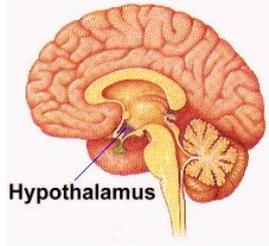
“Highly complex series of impairments” - Shefer and Marcus et al. (2012)



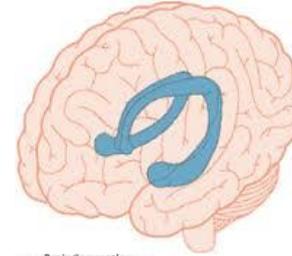
It is difficult to discern the individual effects of each variable in humans but various animal studies shed light on the effects of each individual factor

High Fat Diet Overview

Hypothalamus

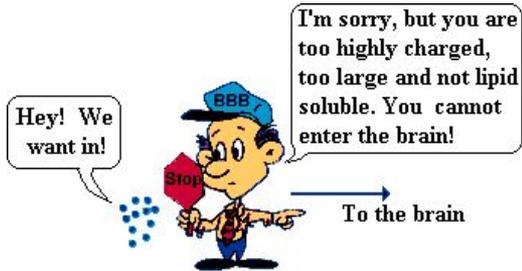


Hippocampus



www.BrainConnection.com
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Blood Brain Barrier



Always causes \uparrow Weight and
 \uparrow Body Fat



High Fat Diet

Hypothalamus

- Gliosis
- Increased Eating
 - ↓ response to insulin
 - ↓ anorexigenic
 - ↑ NPY
 - ↑ orexigenic
 - ↑ thermogenic = inflammation
- Inflammation
 - ↑ pro-inflammatory cytokines (TNF α , IL-1 β)
- Mitochondrial Dysfunction in POMC neurons
 - Associated with development of type 2 diabetes



Hippocampus

- ↓ BDNF
 - ↓ neurogenesis
- ↑ APP
- Activated microglia/astrocytes
 - Cleaning?
- ↑ lipid peroxidation
- “Deficient handling of increasing working memory load”

High Fat Diet (cont)

Reversal

- Hypothalamic inflammation can be reversed with ICV ω 3/ ω 9 administration
 - ↓ food intake/weight gain
- Exercise plasma ↑BDNF
- Caloric Restriction ↑ memory in older subjects (no change in BDNF)



Noteworthy

- ↓ BBB Proteins
 - ↓ BBB integrity
- ALTHOUGH ↓ in working memory, phenotype is dissimilar to Alzheimer's Disease
- 60% fat diet (NOT 40% fat diet) caused impaired cognition, ↑BDNF, ↑inflammation
- Monounsaturated fatty acids (MUFA) > insulin action, brain activity, locomotion than saturated fat diets (SFA)

High Fat Diet Summary

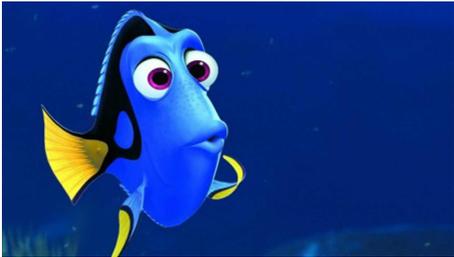
EAT MORE/Weight Gain



Inflammation



Decrease Memory



Decrease CNS Insulin Sensitivity



High Carb Diet

Hypothalamus

- Increased Eating
 - ↓ insulin/leptin receptors
 - ↓ anorexigenic
 - ↑ NPY
 - ↑ orexigenic
 - ↑ thermogenic = inflammation
 - ↓ CRH
 - ↓ anorexigenic



Throughout

- ↓ BBB Integrity
- ↓ Synaptic Plasticity
- ↓ insulin sensitivity in brain
- ↑ Weight
- ↑ body adiposity
 - For a mouse of the same weight
- Hyperinsulinemia

High Carb Diet Summary

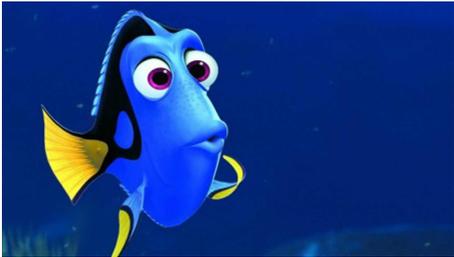
EAT MORE/Weight Gain



Weight Gain



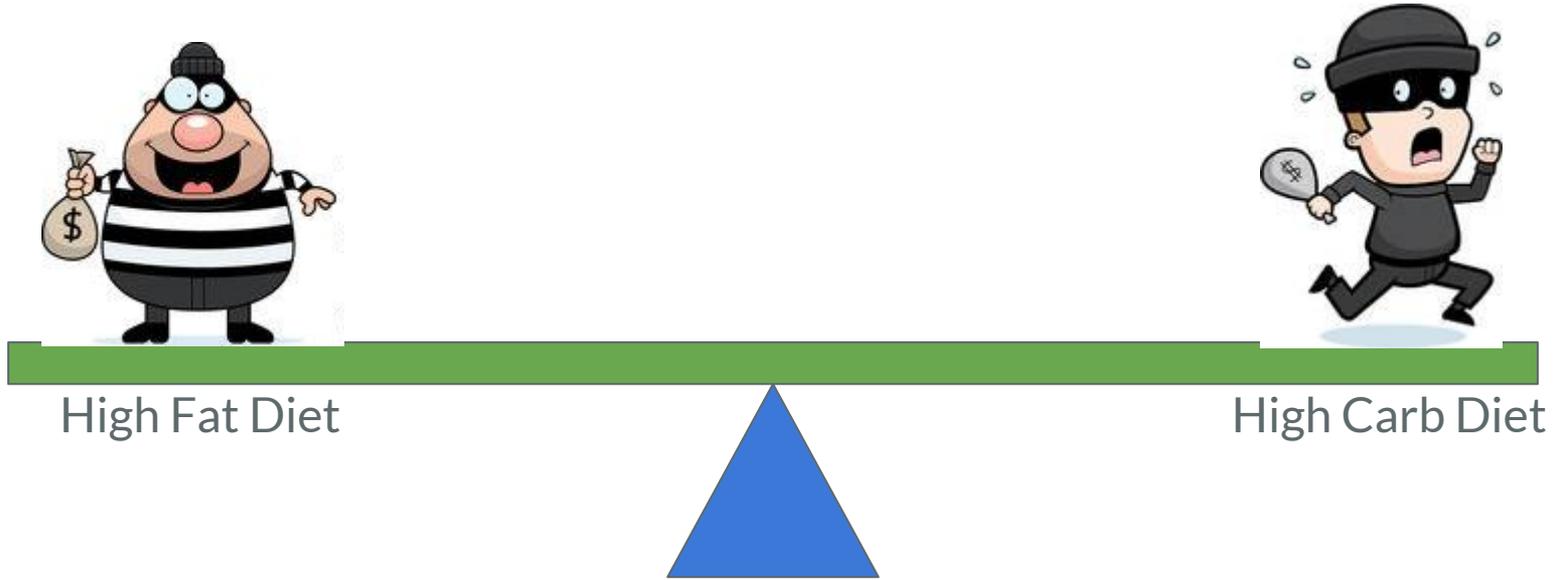
Decrease Memory



Decrease CNS Insulin Sensitivity



Who's To Blame??



When each was reduced independently = similar weightloss/working memory improvement

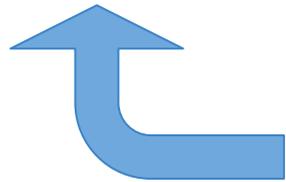
Neither improved processing speed

Brinkworth et al. (2009)

Differing fMRI between Obese and Lean

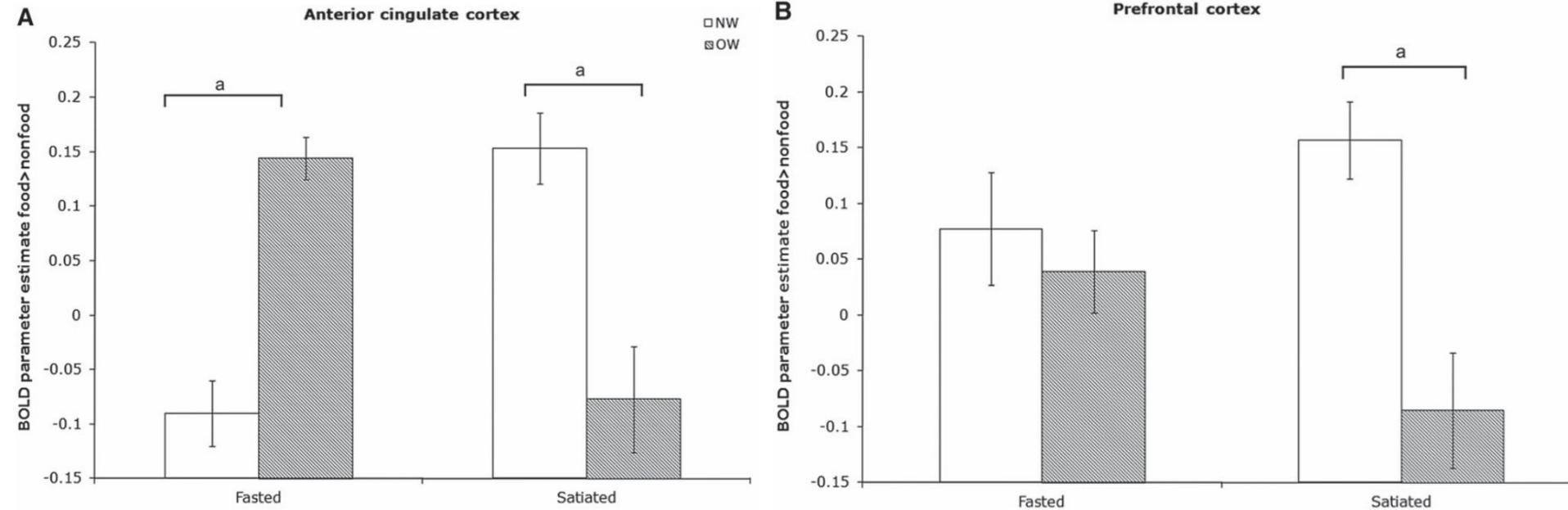
- Excess energy intake in obesity at least partly due to **nonhomeostatic eating**
- **Overweight/Obese Subjects (compared to Lean)**
 -  Brain activity in presence of food
 -  Food-reward related brain signaling (FRS) anticipating reward
 -  FRS post satiation
 -  Satiated inhibitory control in prefrontal cortex (PFC)

Increased responsiveness to food cues persists in formerly obese subjects and is associated with **weight gain.**

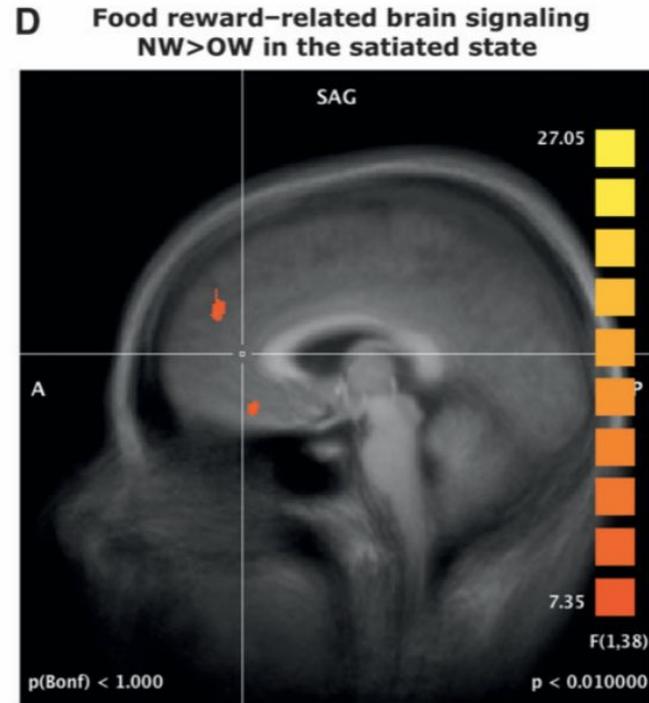
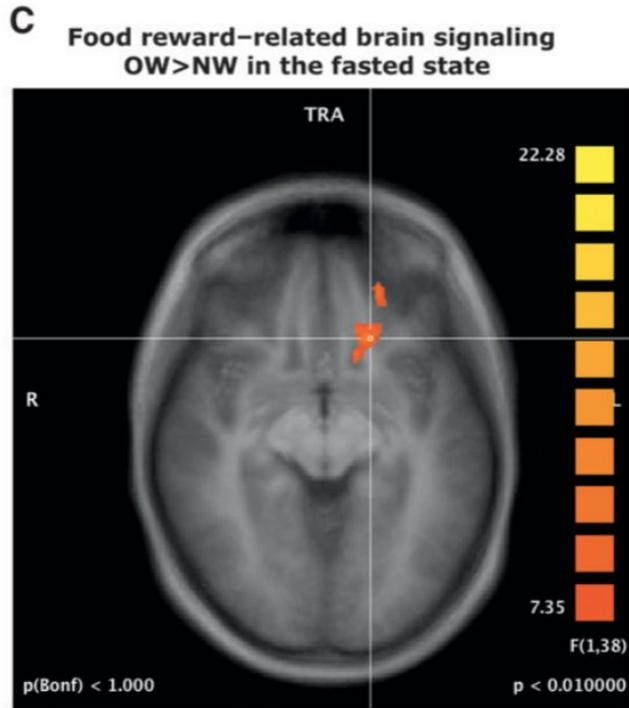


May represent a lack of a true biological need to provide **just adequate** caloric supply

Specific Food Reward-related Brain Signaling between Normal Weight (NW) and Overweight (OW) Subjects



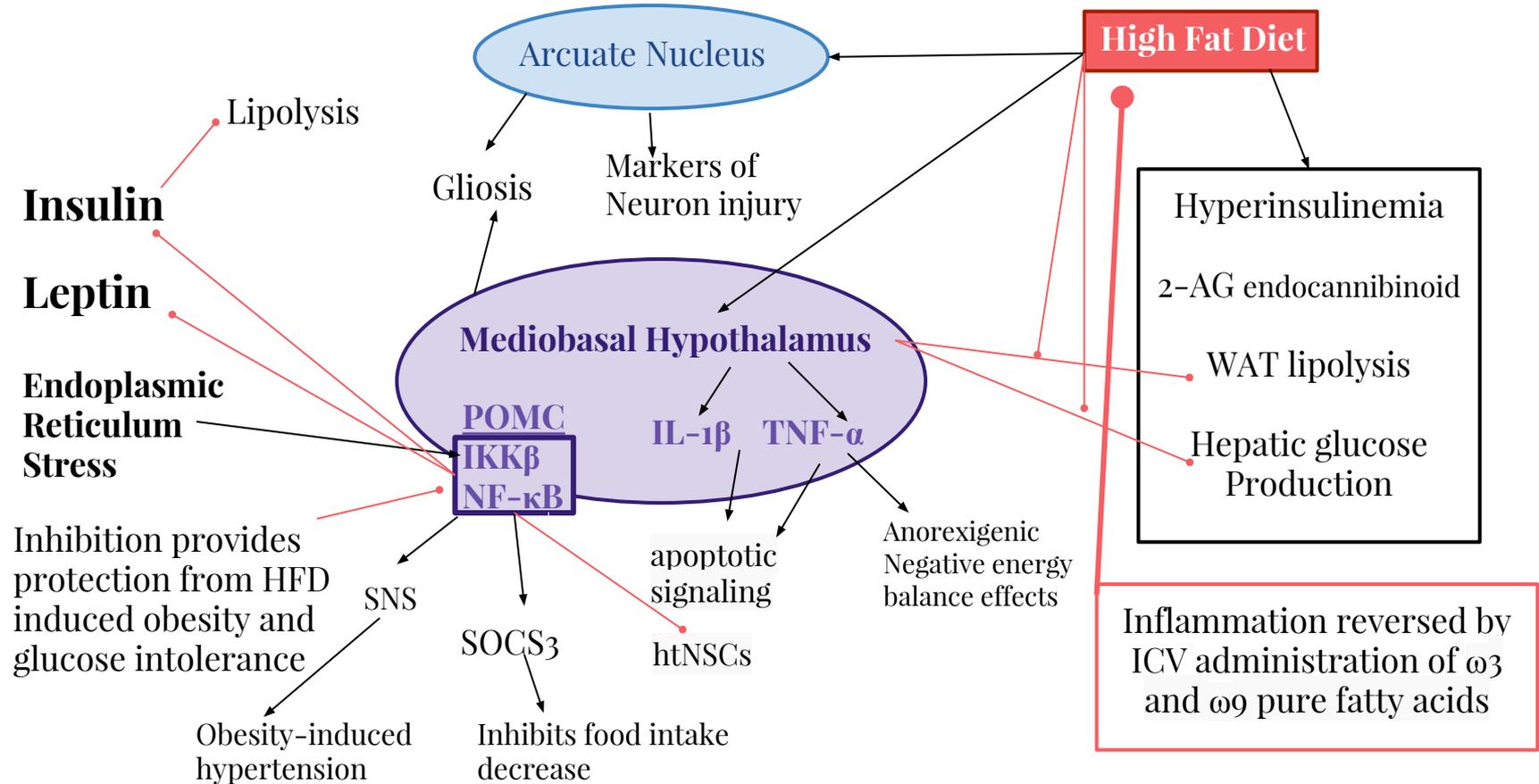
Same Experiment: but with the fMRI



But what about the brain itself?

- Weight gain may be associated with reduced sensitivity of reward circuitry
- With liquid meal (Ensure Plus):
 - Difference in activity between lean and obese in the **posterior cingulate** and **amygdala**
 - In obese subjects, activity increased in the **middle insula** and decreased in the **posterior hippocampus**
- With successful dieters:
 - Meal consumption activated the **dorsal prefrontal cortex**
 - Coordinated changes in **orbitofrontal cortex**
 - Enhanced activation of **primary and secondary visual cortices**
 - Enhanced visual attention to food cues
 - Greater engagement of **inhibitory control regions (frontal)** with food cues
 - Improved control of food intake

BEWARE of hypothalamic inflammation!



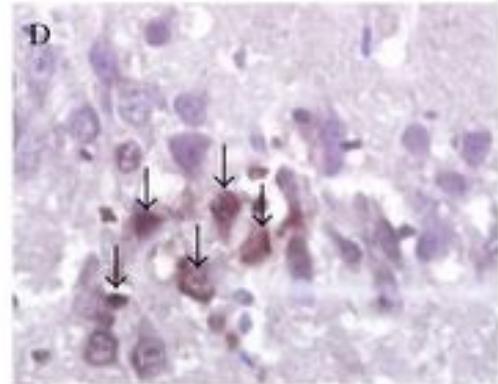
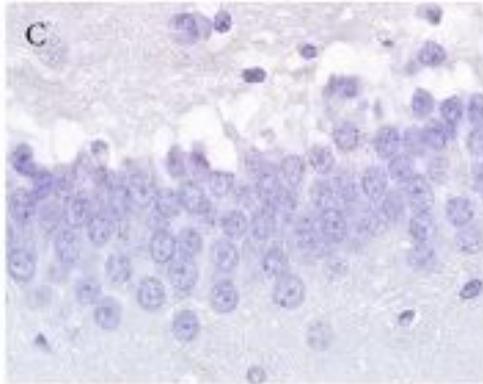
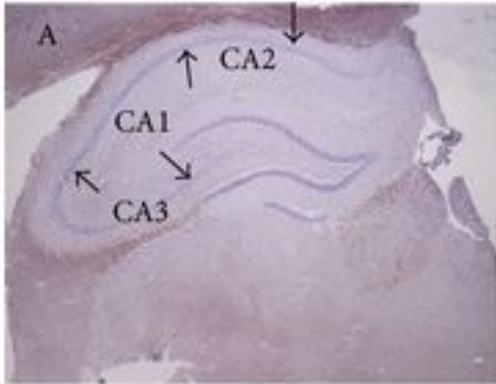
It even affects insulin release and action!

- Hypothalamic inflammation results not only in impaired central regulation of energy balance, but also:
 - disruption of normal insulin secretion
 - reduced peripheral insulin sensitivity
- Hypothalamic inflammation can be a negative modulator of pancreatic islet function
- May even correlate with pancreatic islet apoptosis
- It may negatively affect insulin signal transduction in the liver
- And also may worsen liver steatosis

BEWARE of hippocampal atrophy!

The hippocampus is vital for cognition...

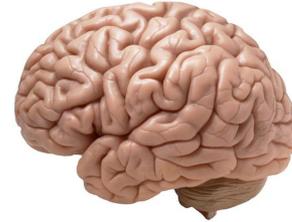
- Processes short to long term memory, learning, spatial navigation and emotions
- Preserved through continued neurogenesis in adult life



Structural Changes in the Brain

Due to Obesity

BMI



↑ BMI = ↓ brain volume and ↓ white matter integrity

(independent of age or other disease)

Grunstad et al. (2008), Ward et al. (2005)

Clinical Obesity = ↓ grey matter and ↑ frontal lobe white matter

Pannacciulli et al. (2006)

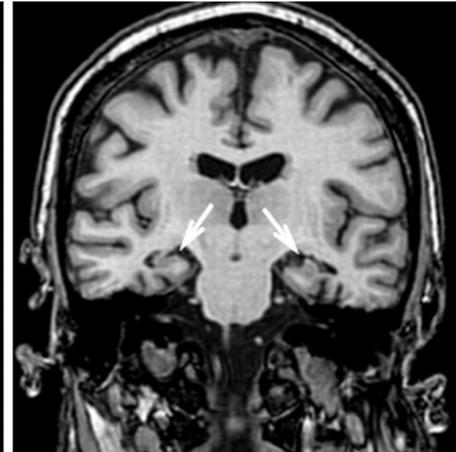
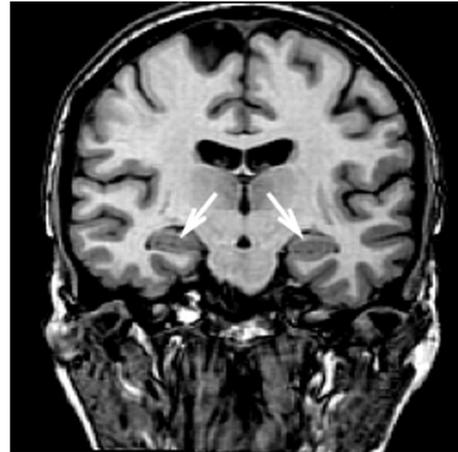
Effects of Obesity on the Hippocampus

- Though we know that diabetes and related conditions reduce hippocampal size, we don't know the role of hypertension hippocampal volume.
- SOME HINTS:
 - \uparrow TNF- α expression and \uparrow microglia means \uparrow lipid peroxidation (bad)
 - HFD can induce local pro-apoptotic signaling (\uparrow caspase-3, \uparrow gliosis in dentate gyrus)
- These things cause local inflammation and could lead to the loss of tissue in hippocampus.
 - \downarrow Hippocampal size in obesity \rightarrow accelerated cognitive impairment down the line.



Effects of Obesity on the Hippocampus

- A high midlife BMI is a marker for increased hippocampal atrophy in late life.
- An increase in one SD in the waist-to-hip ratio was reportedly linked to a 0.2 SD decrease in hippocampal volume (Jagust et al., 2005)
 - Does this adversely affect feeding behavior and further perpetuate obesity by uncontrolled feeding?
- Glucose too, has these effects!
 - In a longitudinal study of non-diabetic subjects, blood glucose was linked to hippocampal and amygdalar atrophy, explaining 6–10% in volume change



Does Diabetes cause Cognitive Decline?

- The very HFD causes \uparrow brain inflammation and \downarrow BDNF
- A wealth of studies link the obese state to cognitive disadvantages. These are supported by epidemiological cross-sectional and prospective studies but more so by improvement of cognitive measures following treatment of Metabolic Syndrome (MetS)
- Even healthy obese subjects have some deficits in learning, memory, and executive function (relative to nonobese individuals)
- Cognitive performance also declines with decreased physical activity/fitness.
- Obesity (+ MetS) may be a marker of future cognitive decline
- Weight loss may result in rapid improvement of some cognitive functions.

Effects of Cognitive Decline

- Early-life deficits include reduction in executive functioning and attention, decreased global functioning, or lesser IQ
 - This may make the obesity in the individual more persistent. Weak inhibitory control might lead to overeating.
- Both peripheral inflammation and central inflammatory processes may affect the brain in the obese state
 - inflammatory cytokine can be induced in brain cells, which then leads to neuronal apoptosis and impaired cognition.
- \uparrow CRP levels (due to MetS) lead to \uparrow inflammation

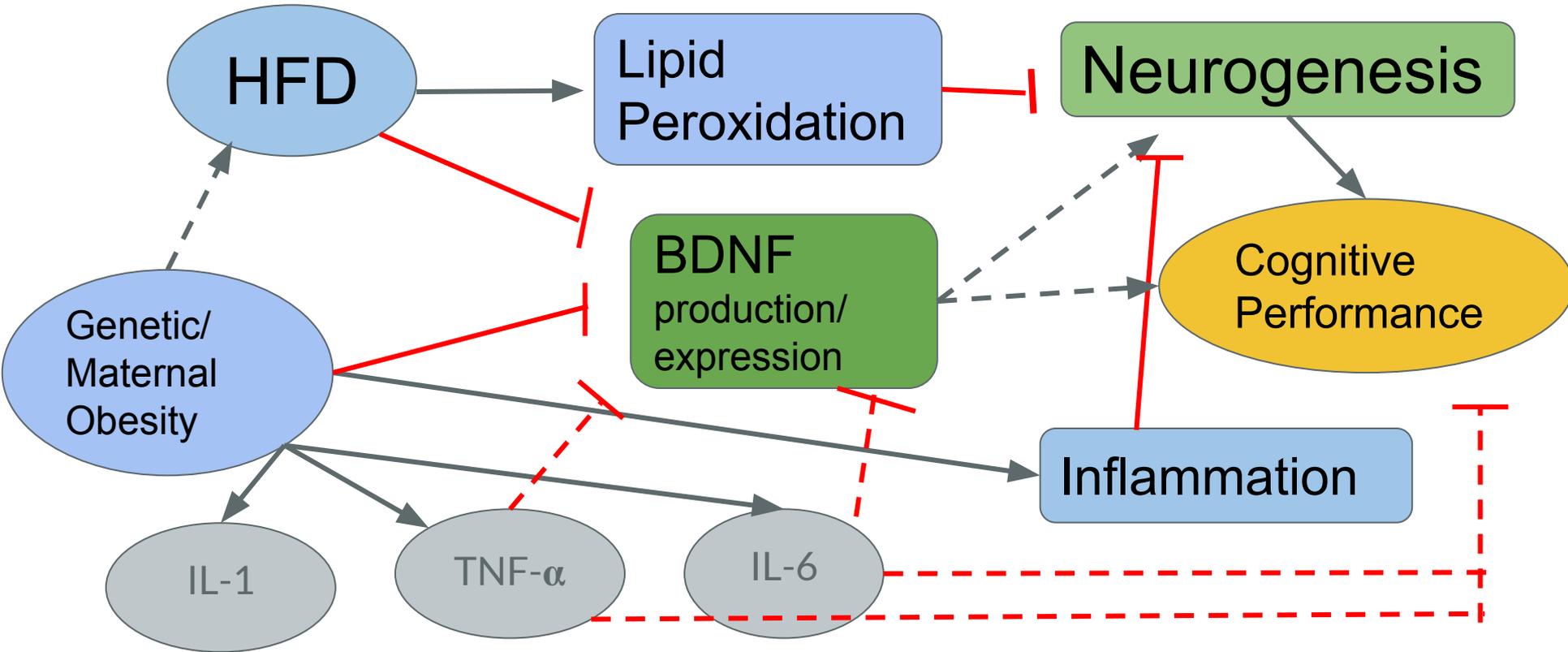


Hormonal Treatments for Cognitive Decline

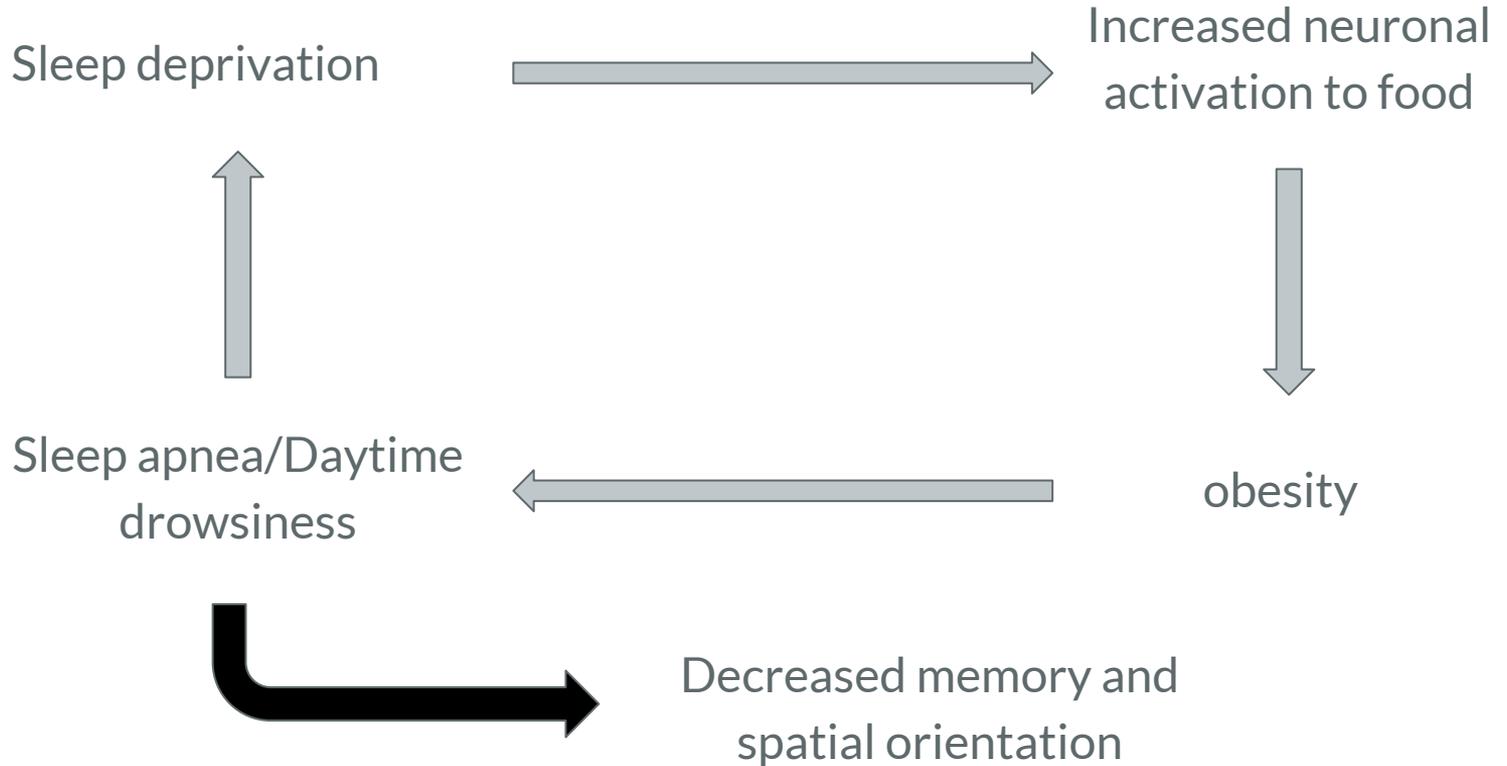
Brain leptin resistance seen in obesity might adversely affect naturally existing neuroprotective mechanisms

- GLP-1 normally ↑ food related insulin release → modulatory effects on both fat tissue homeostasis and learning capacity BUT these are blunted in obesity
- BDNF is a key regulator of neuronal development, survival, differentiation, that is functionally implicated in memory and cognitive ability and suppresses food intake
 - BDNF is activated via the proteins 4 (MCP-4) receptor pathway and leptin
 - Leads to weight loss in mice!
 - Hippocampal BDNF signaling restrains anxiety-like behavior patterns, and hippocampal BDNF mRNA expression and signal transduction are negatively regulated by proinflammatory cytokines

BDNF and the High Fat Diet



Sleep deprivation and obesity



Sleep deprivation in mice

Experiment: Circadian Disruption (Karatsoreos et al., 2011)

- Mice on 10 hr daylight/10 hr darkness cycle (Normal is 12 hr light/12hr dark)
- Disrupted mice:
 - Gained weight
 - Loss of dendritic length, decreased complexity of prelimbic PFC
 - Performed worse on Morris watermaze

Experiment: Clock gene KO mouse (Barclay et al., 2012)

- Clock gene transcribes CLOCK
 - regulates circadian rhythm, brain and muscle Arnt-like 1 (Baml-1)
- Adipocyte hypertrophy and obesity in mice

Sleep abnormalities and inflammation

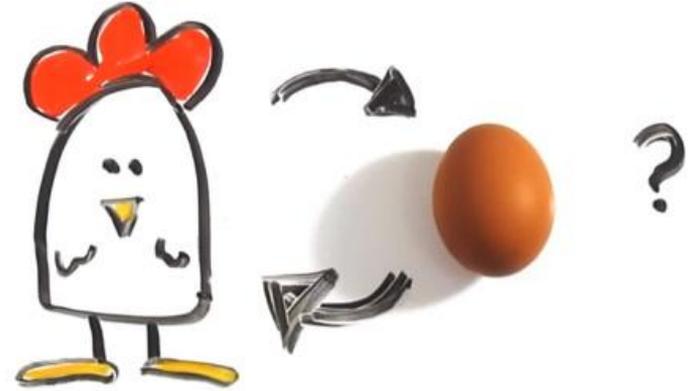
- Pro-inflammatory mechanisms caused by too little or too much sleep
- **Too much sleep:** CRP and IL-6 increase
 - CRP → inflammation response
 - IL-6 → mediates fever, inflammation response
- **Too little sleep:** TNF- α increase
 - TNF- α → regulation of immune cells
 - Induce fever and apoptosis
- Heart disease, cancer, Alzheimer's

Which came first?

Abnormal control in food related brain areas lead to obesity?

Or

Obesity leads to chronic brain damage?



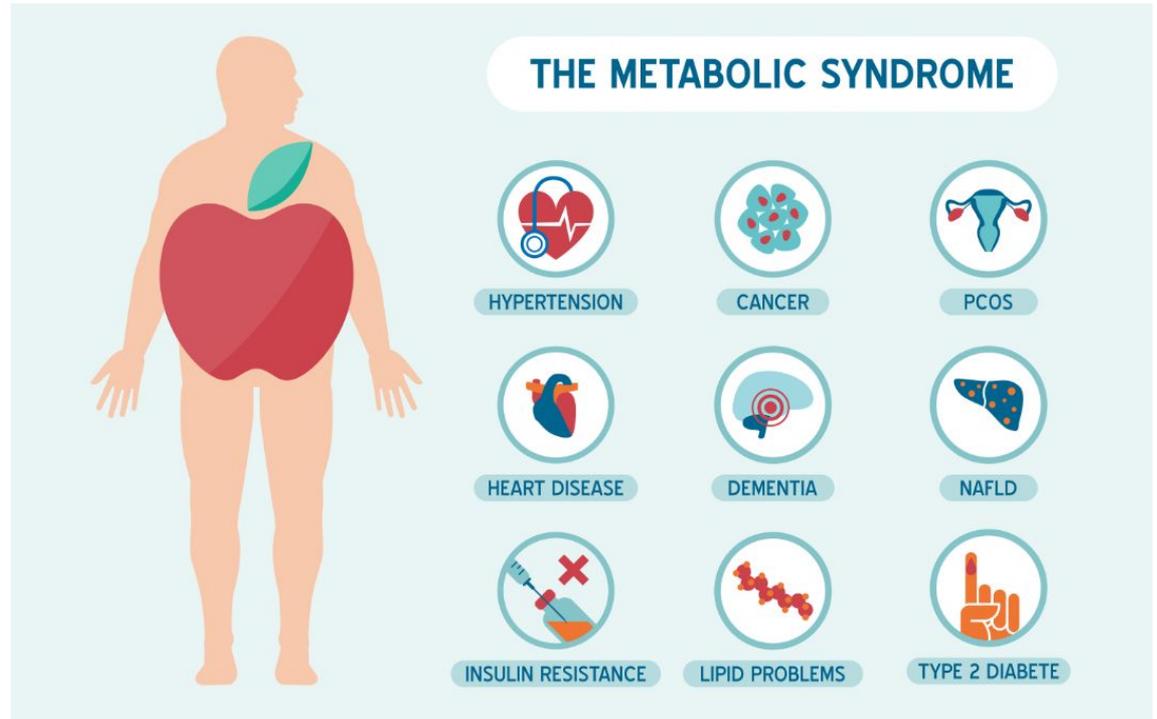
Overfeeding in early life

- Review from earlier:
 - High maternal BMI pre-pregnancy
 - Changes in hypothalamic activity
 - Increase in eating through adulthood → weight gain
- 24hr after mice on HFD leads to inflammatory response
- Evidence for impairment in feeding regulation before weight gain



Obesity first

- Develop several years to few decades after obesity
- Dysglycemia
 - Abnormal glucose levels
- Diabetes
 - Type II
- Hypertension
- MetS



Obesity and its confounds

- Obesity, hypertension, diabetes, and age overlap in neuroimaging
- Use children!
 - Obesity associated with decreased frontal/limbic gray matter regions

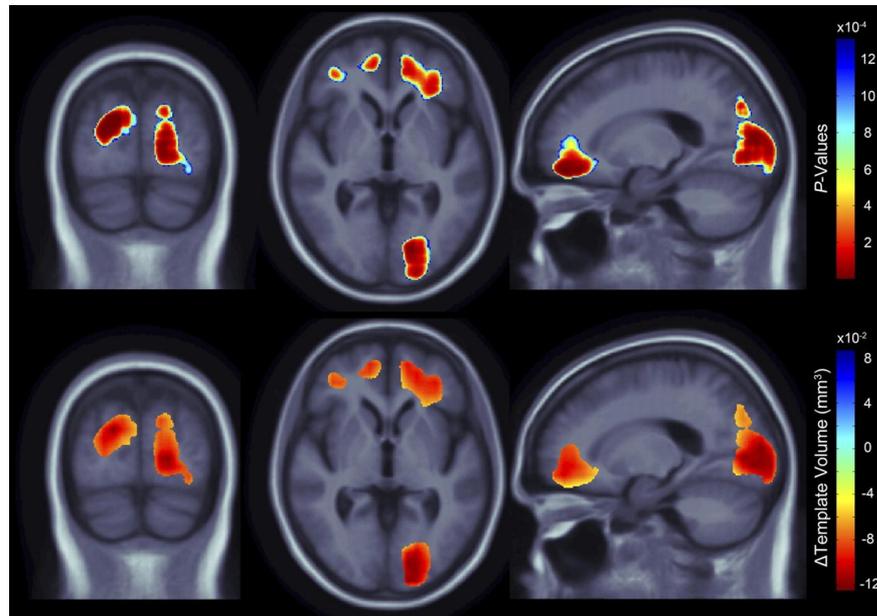
Table 4
Effects of obesity as compared to hypertension, diabetes and aging on human brain structural changes as detected by neuroimaging, particularly MRI studies.

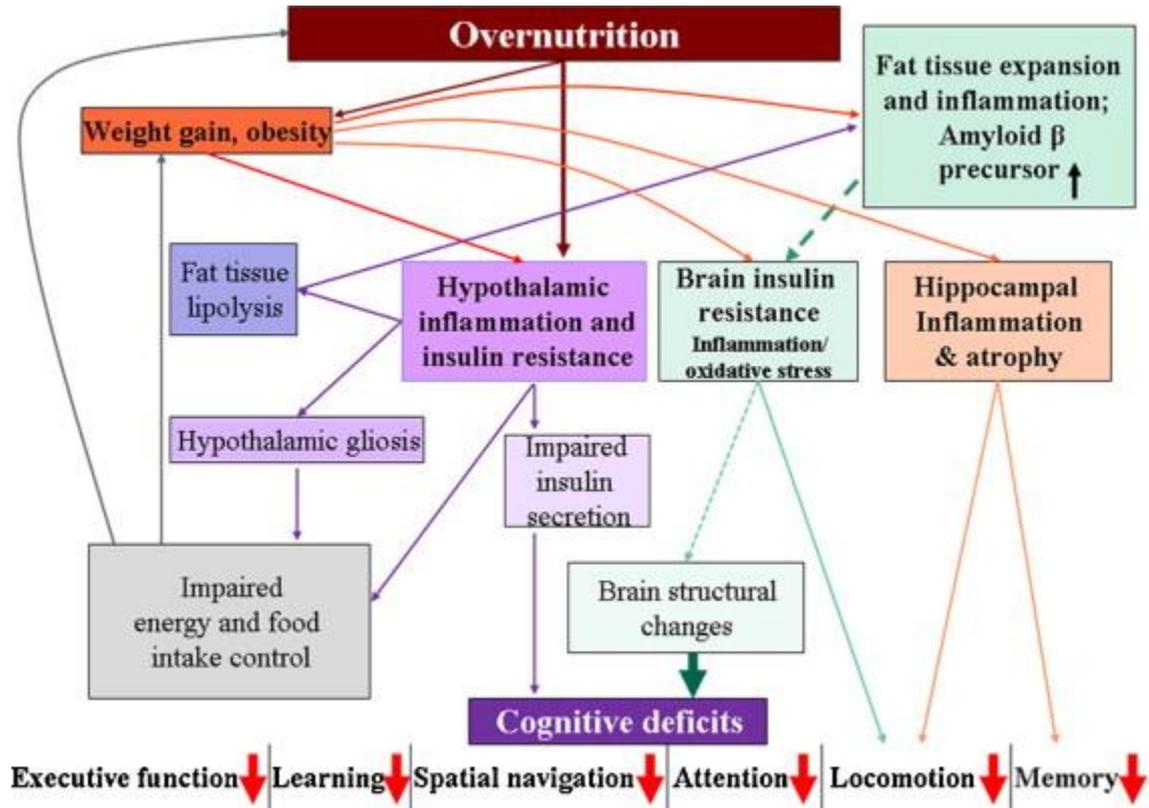
	Obesity	Hypertension	Diabetes	Aging
White matter intensities on MRI	+ in older subjects (Jagust et al., 2005) - in children and adolescents (Alosco et al., 2013)	++ (Valdes Hernandez et al., 2013)	++ (Reijmer et al., 2011; van Harten et al., 2007)	++
Reduced brain volume in children/adolescents-frontal and limbic cerebral gray matter regions	+ in obese children/adolescents (Alosco et al., 2013)	NR	+ in comparison with obese adolescents (Bruehl et al., 2011)	NA
Temporal lobe atrophy	++, but not linked to FTO risk allele (Ho et al., 2010)	- (Korf et al., 2007)	++ (Korf et al., 2007)	+ (Yao et al., 2012)
Frontal/prefrontal lobe atrophy	++ Even in adolescents (Alosco, 2013)	+ (Gold et al., 2005; Raz et al., 2002)	+ (Lee et al., 2013b)	+ (Mander et al., 2013)
Hippocampal atrophy	(+)(+) (Whitmer et al., 2008; Ho et al., 2011; Raji et al., 2009; Jagust et al., 2005)	- (Gold et al., 2005; Raz et al., 2003)	+ even with rising normal glucose (Cherbuin et al., 2012)	In proportion to total brain volume reduction with age (Knoops et al., 2012)

NR, not reported; NA, not applicable.

Fat mass and obesity gene (FTO)

- Rs9930333 variant as obesity risk allele (3 kg difference)
- Inverse relationship between brain volume and body fat
- Reduced frontal and occipital lobes volume
- Decline in verbal memory linked to FTO variant





Conclusion

- Excessive eating leads to early hypothalamic inflammation response and hippocampal atrophy
- Disrupt homeostasis of energy intake
- Disrupt insulin secretion and sensitivity
- Symptoms may perpetuate disease
- Brain disease and obesity are inseparable





Thank
you!

“In what aisle are the
‘won’t immediately kill you’ foods?”