Obesity, Physical Activity, and Dopamine

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Associate Professor
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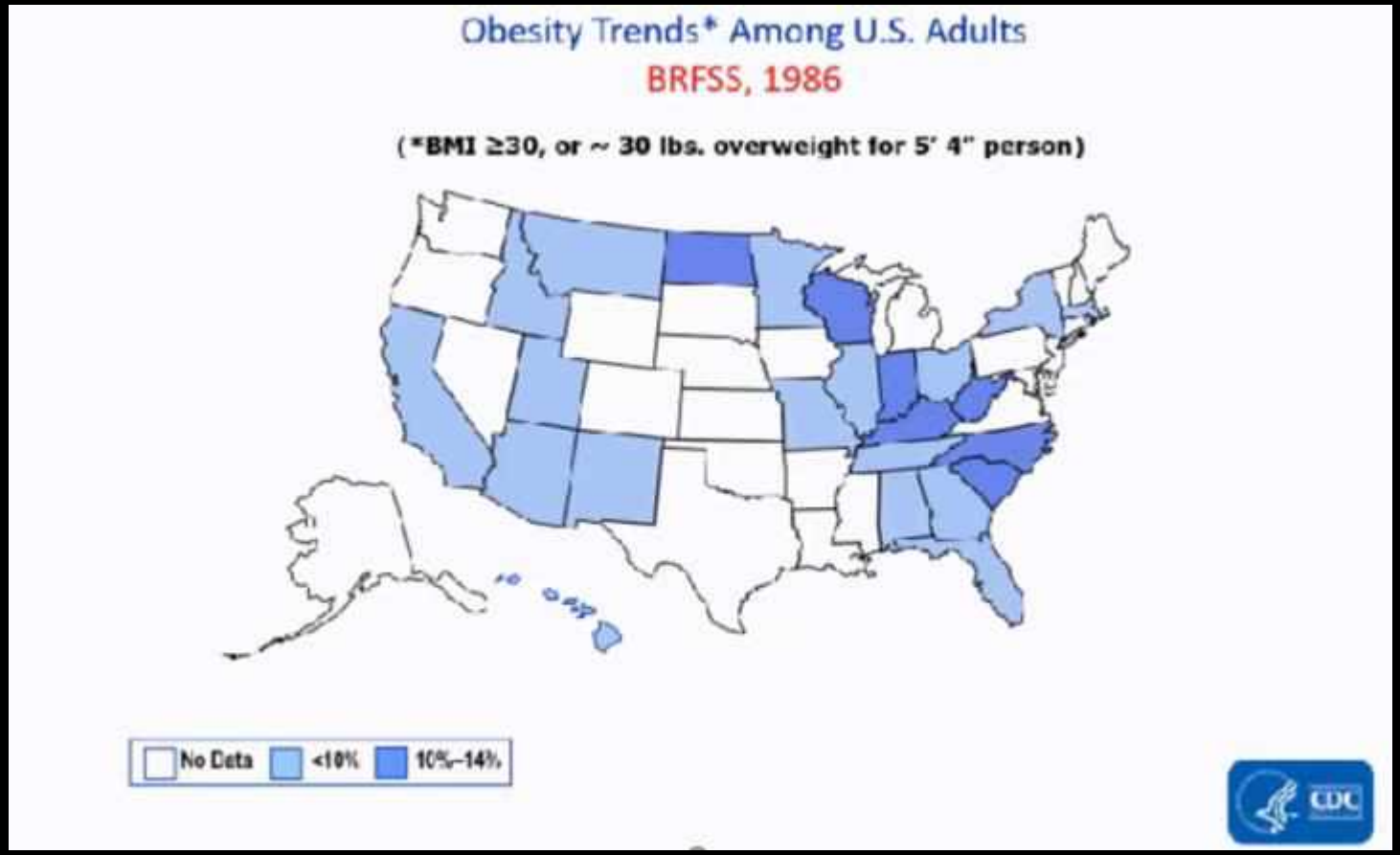
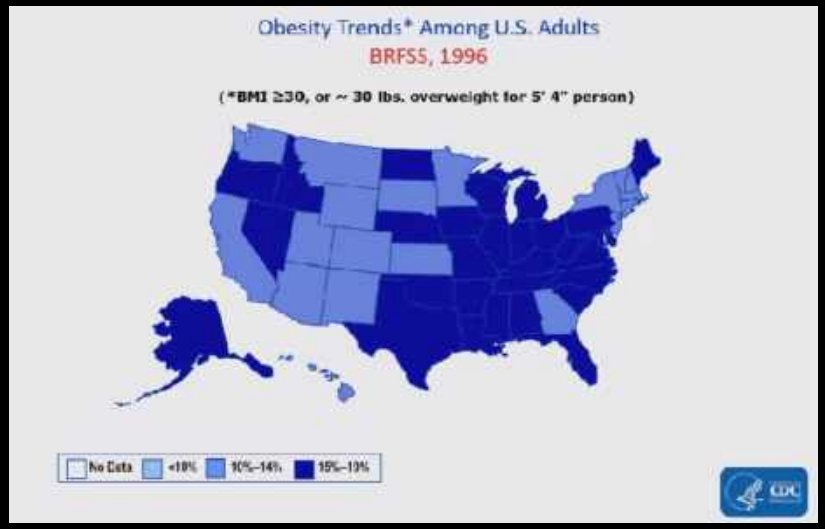
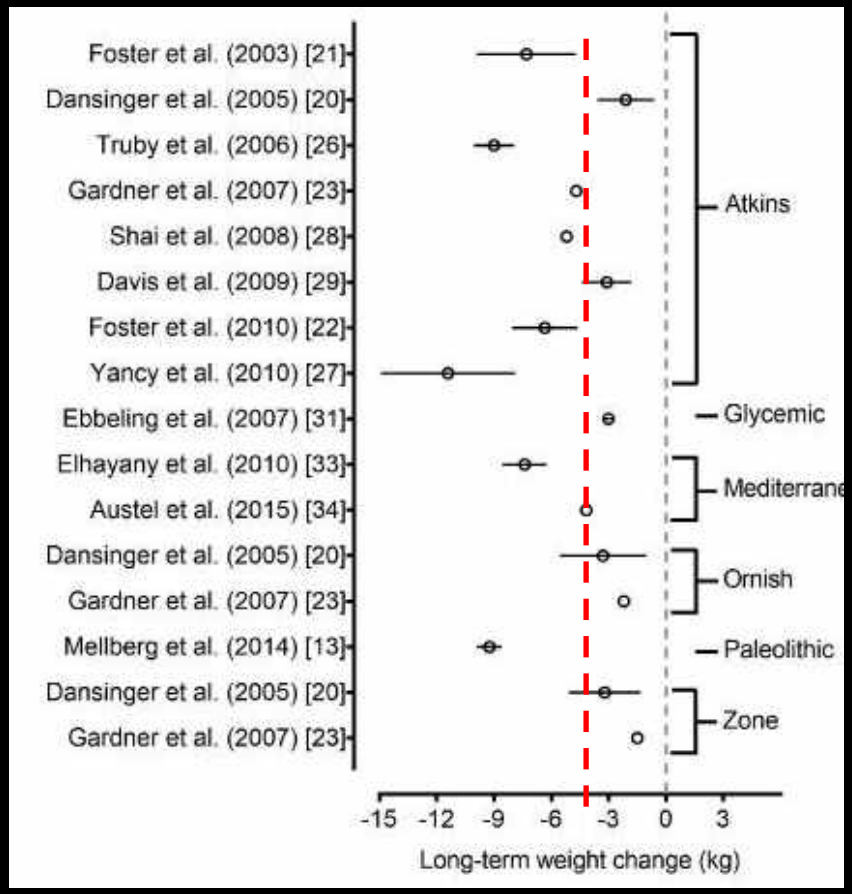
Over the last 30 years, obesity has emerged as a leading public health challenge



Over the last 30 years, obesity has emerged as a leading public health challenge

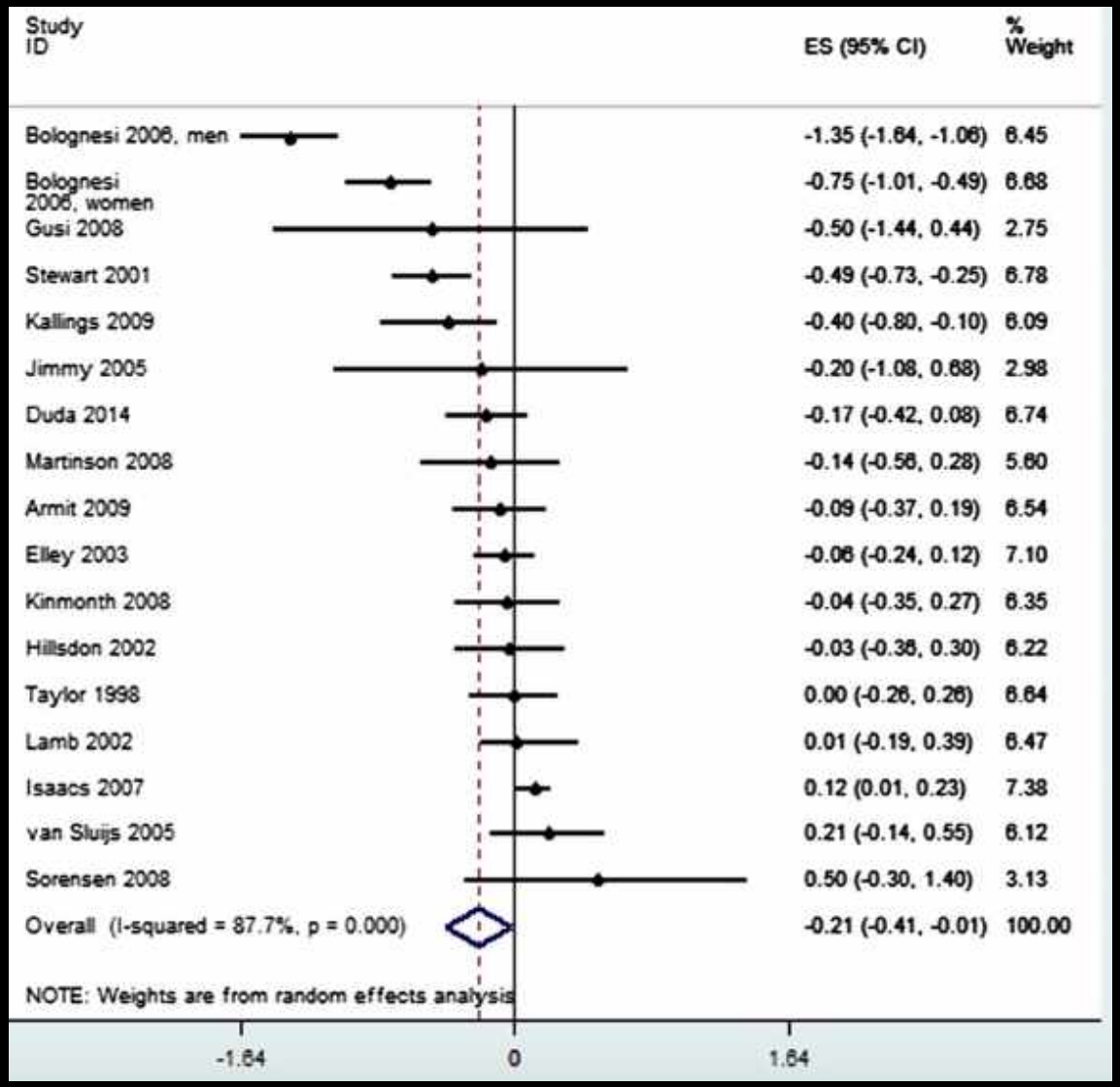


Changes in diet cause weight loss, but the effect sizes are generally small



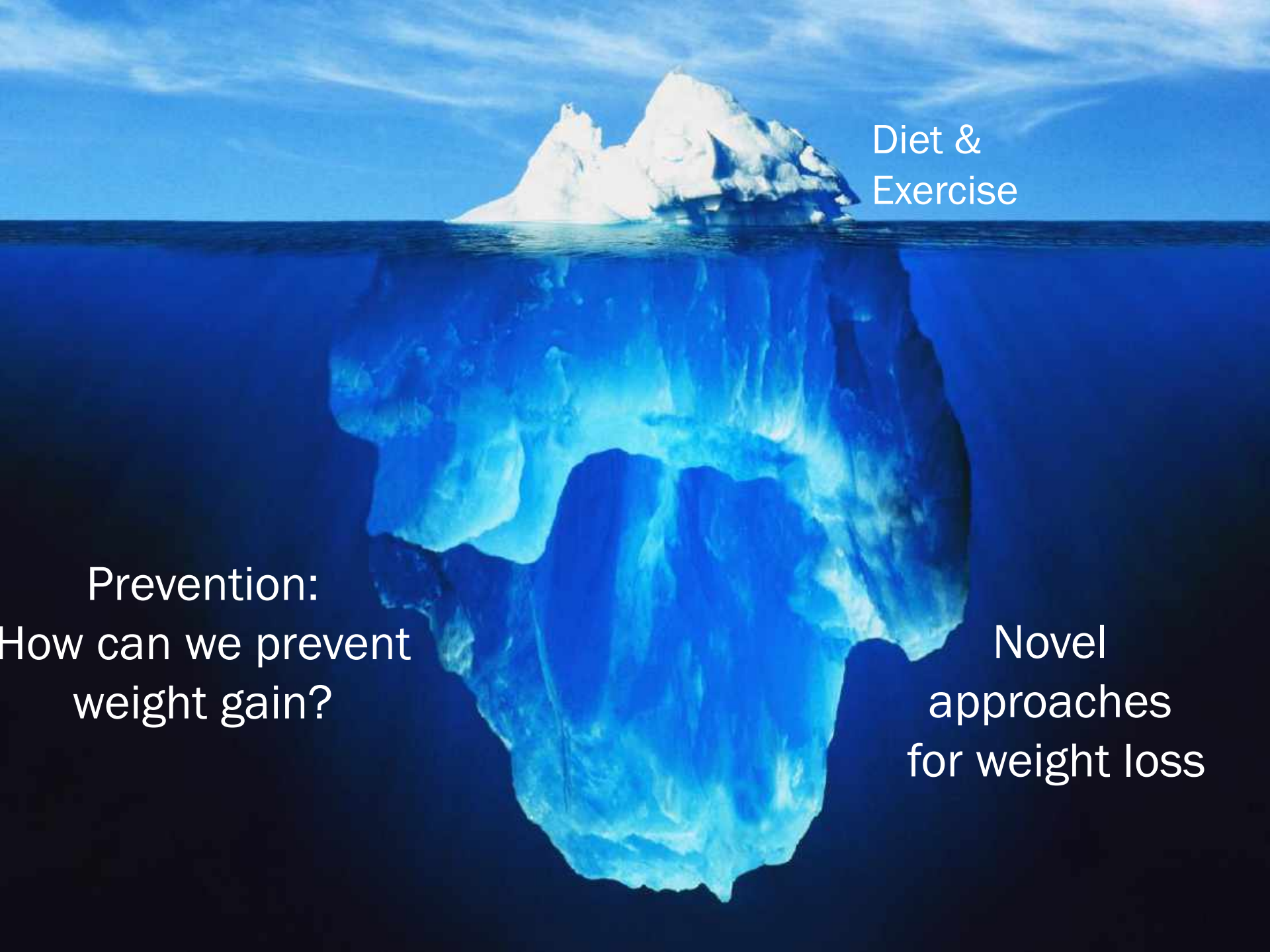
Anton, et al., Nutrients 2017, Aug; 9 (8) 822

Exercise also causes small effects on weight



BMI change

Goryakin, et al., Obes Rev. 2018 Apr;19(4):518-528


Diet &
Exercise
Prevention:
How can we prevent
weight gain?
Novel
approaches
for weight loss

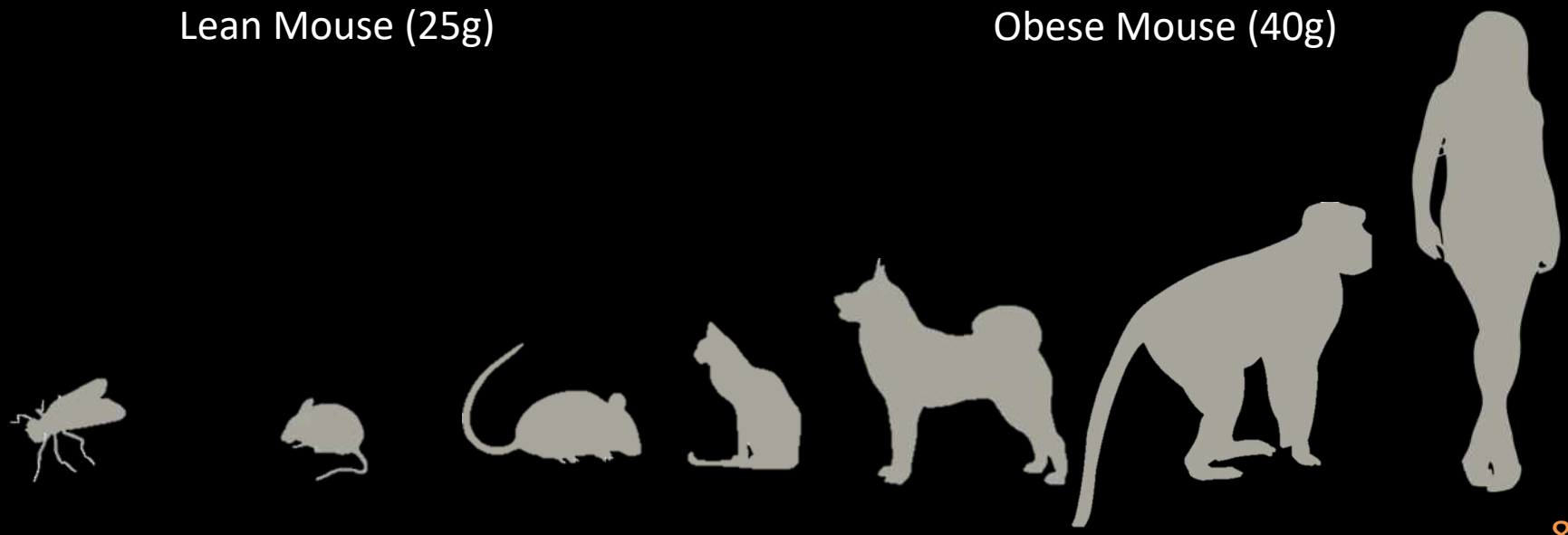
Outline

- What causes obesity (in mice)?
  - What is the role of inactivity?
  - What is the role of overeating?

Obesity is associated with physical inactivity

Lean Mouse (25g)

Obese Mouse (40g)



Hypothesis

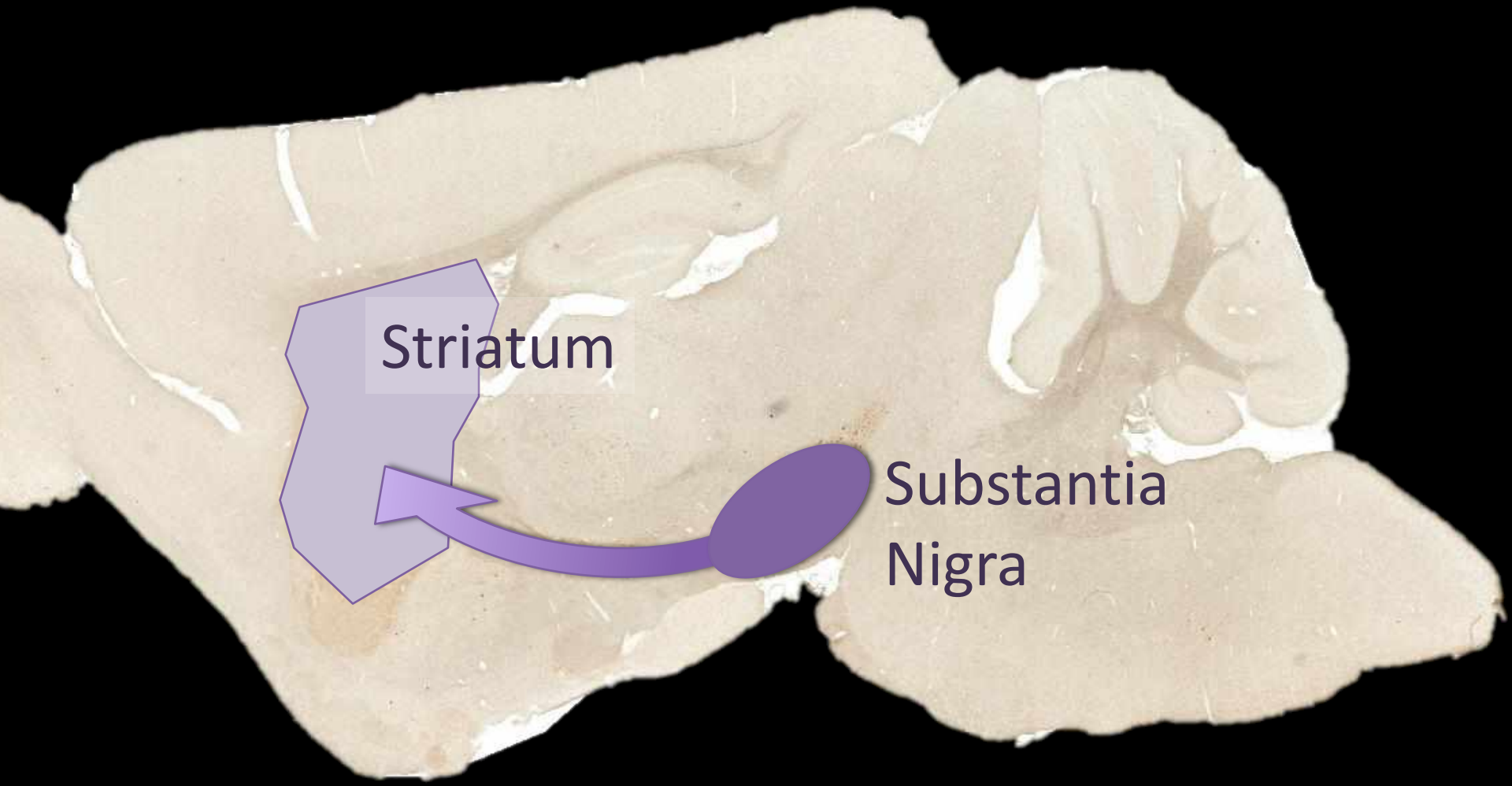
Impaired dopamine circuitry

Physical inactivity

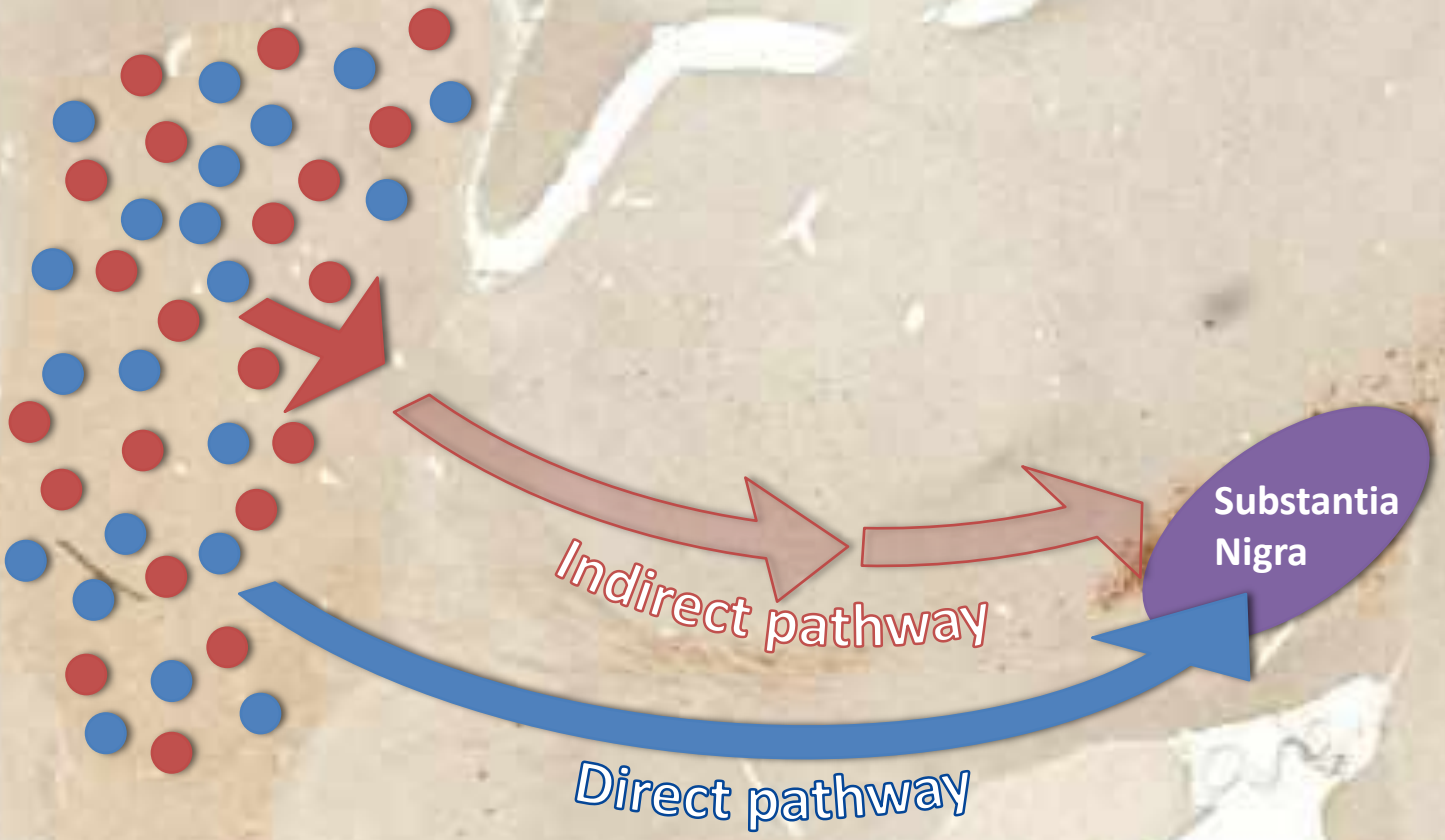
Weight gain

Kravitz AV, O'Neal TJ, Friend DM.
Front Hum Neurosci. 2016;10:514

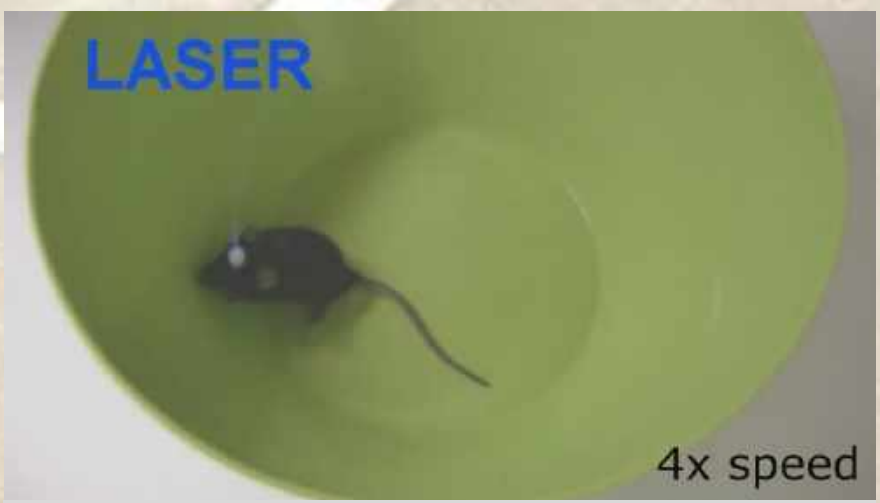
A brief overview of dopamine circuitry



A brief overview of dopamine circuitry



A brief overview of dopamine circuitry

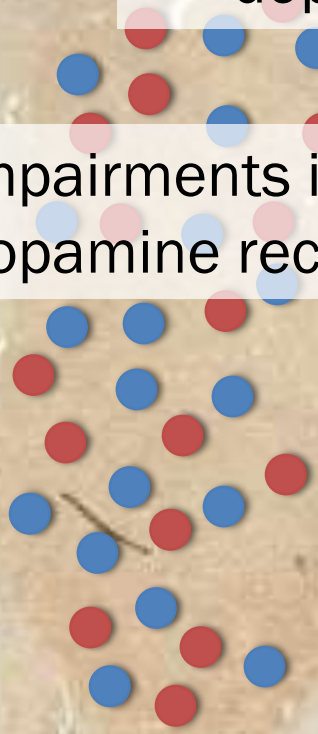


Kravitz et al., *Nature*, 2010

How does obesity affect this circuitry?

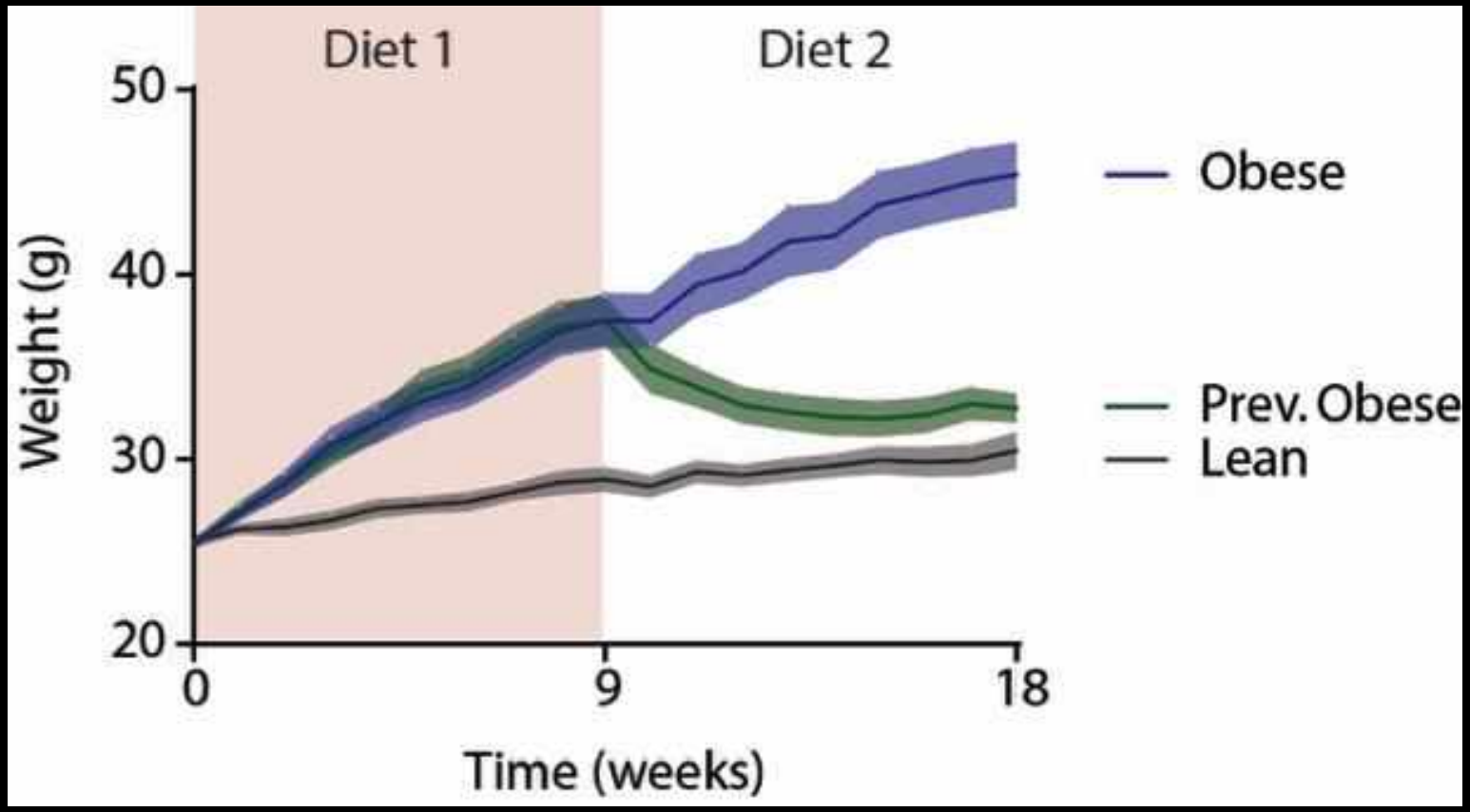
1. Reductions in dopamine release

2. Impairments in dopamine receptors



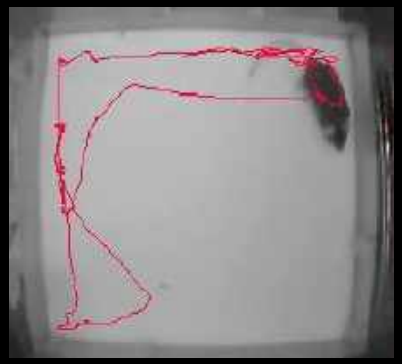
3. Alterations in dopamine synthesis

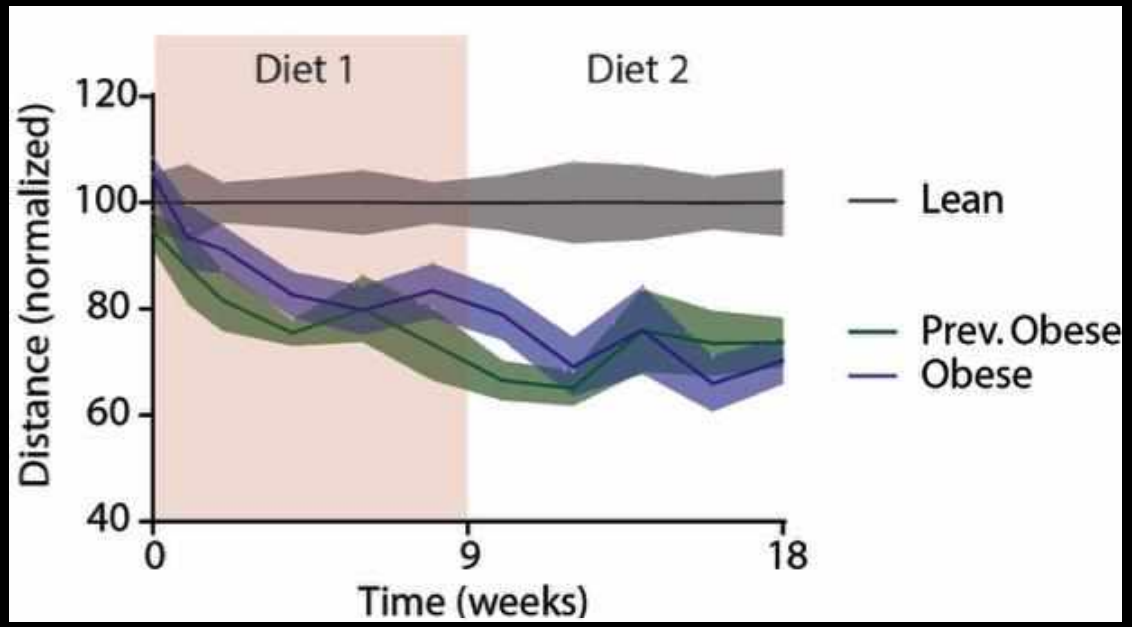
We exposed three groups of mice to different diets



Friend et al. *Cell Metabolism*. 2017 Feb 7;25(2):312-321.

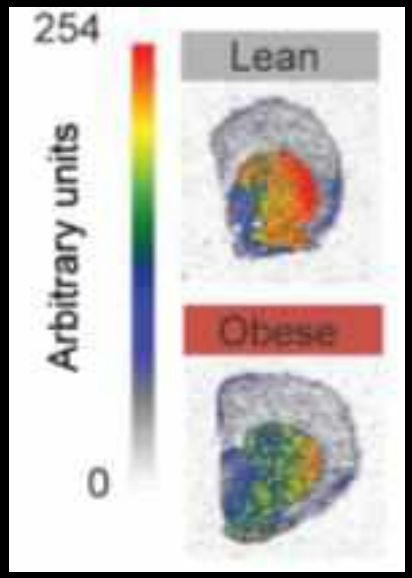
High fat diet depressed activity levels … and this didn't recover with weight loss

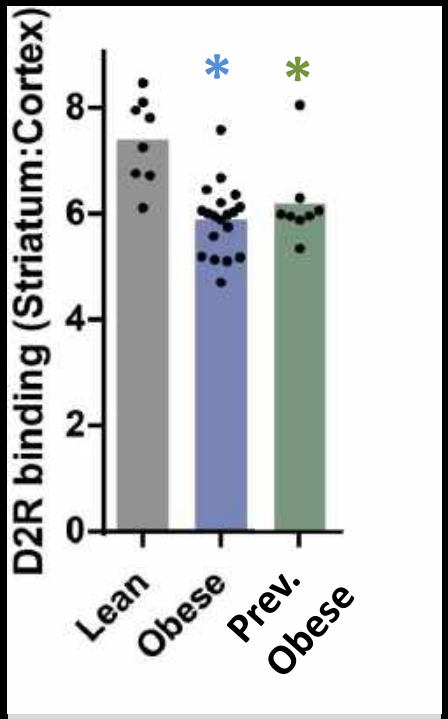




D2 receptor binding was significantly reduced in obese and previously obese mice

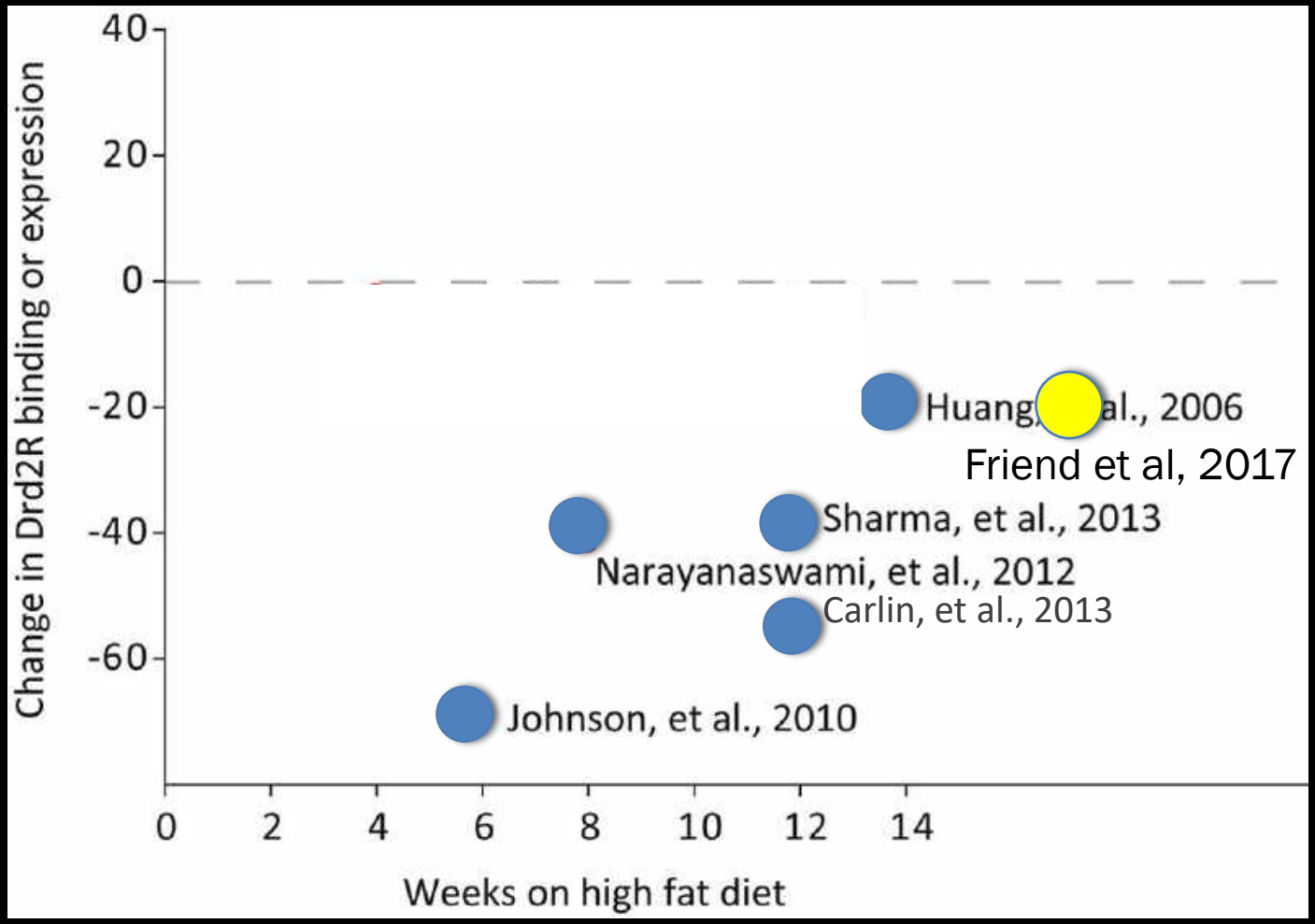
3H-spiperone binding



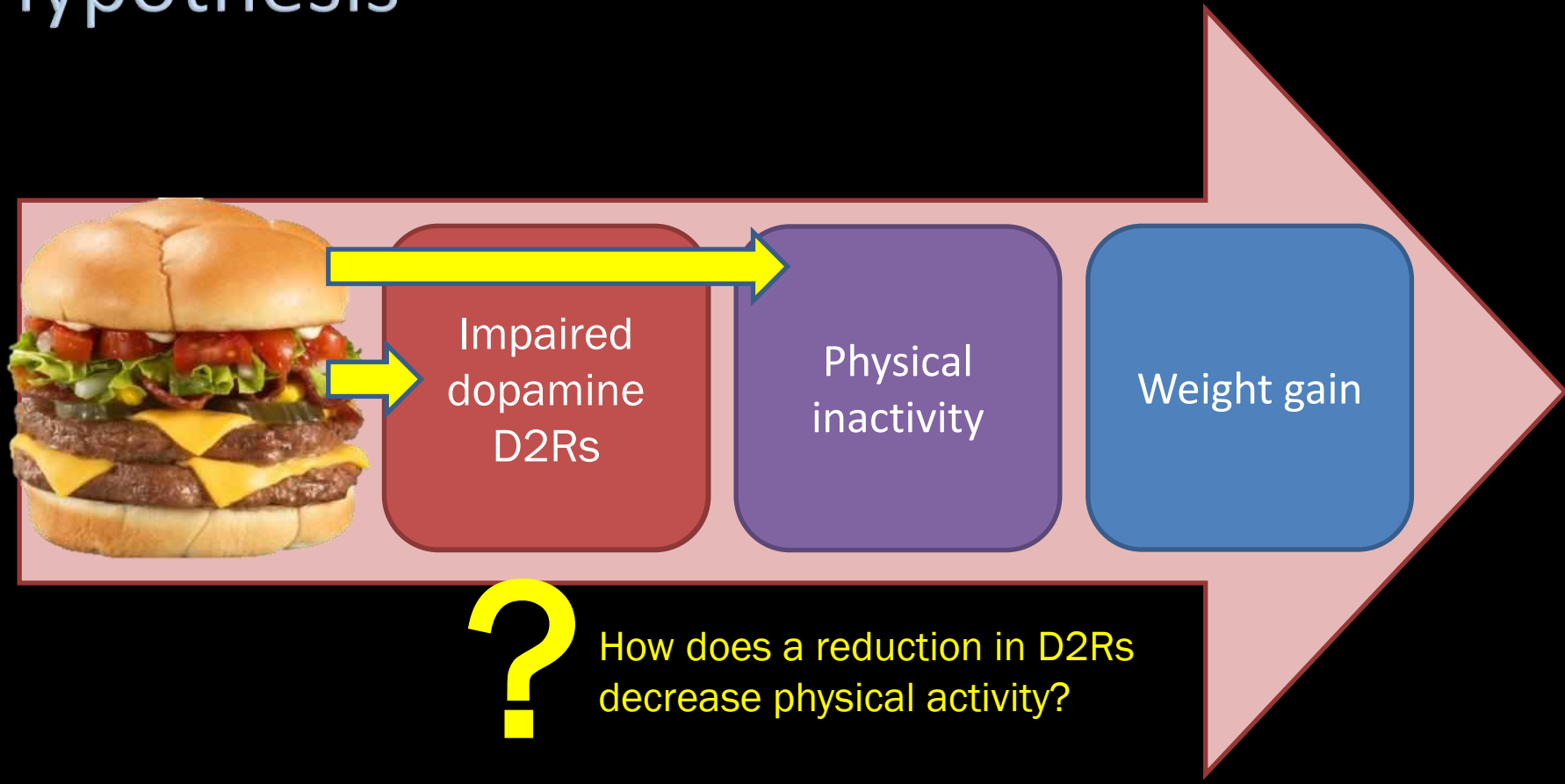


ANOVA: F(2,32) = 11.9
p<0.0001

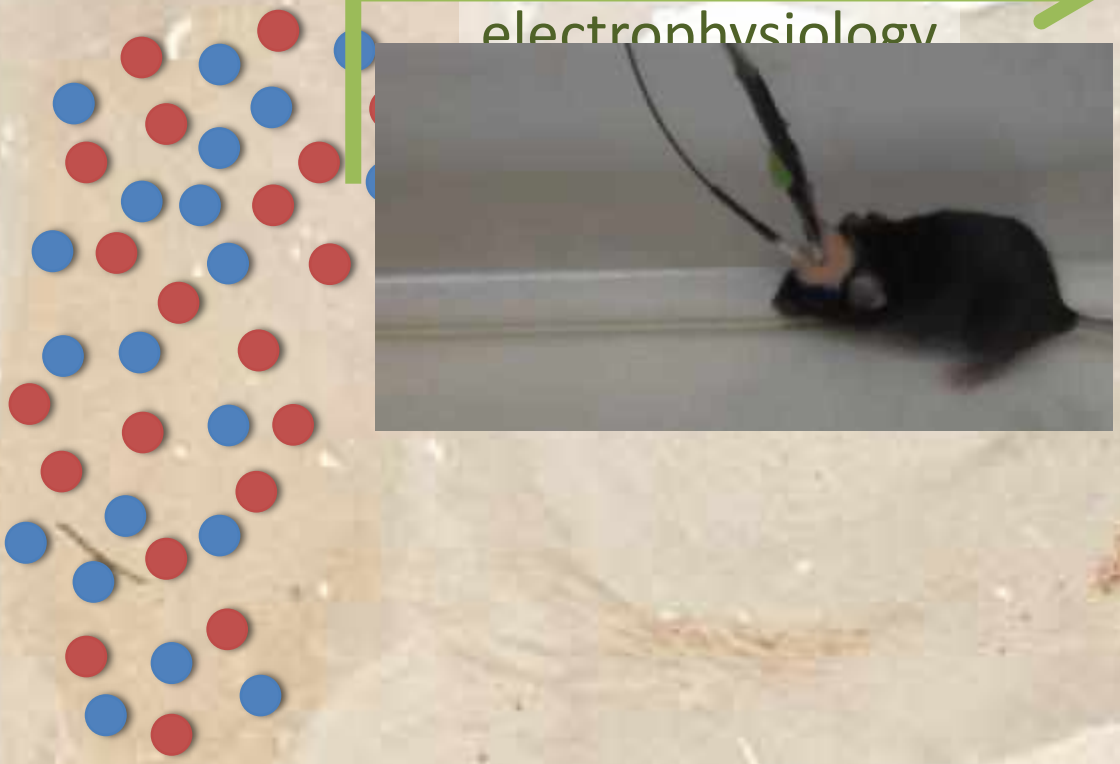
High fat diet impairs D2 receptors in rodents



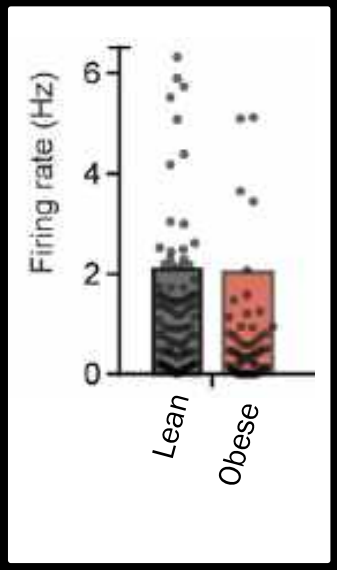
Hypothesis

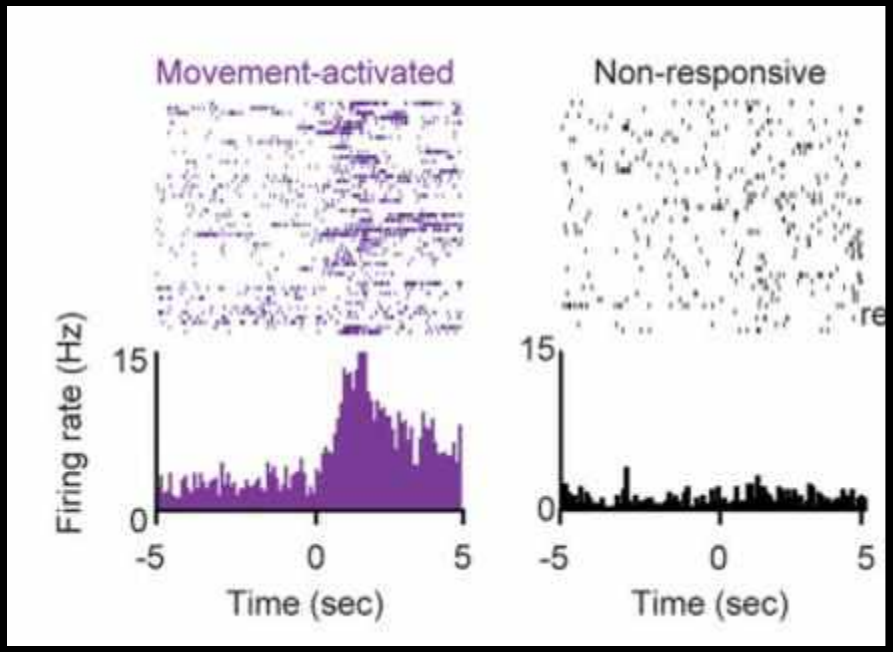

Impaired dopamine D2Rs
Physical inactivity
Weight gain
?
How does a reduction in D2Rs decrease physical activity?

We examined striatal neural activity in lean and obese mice

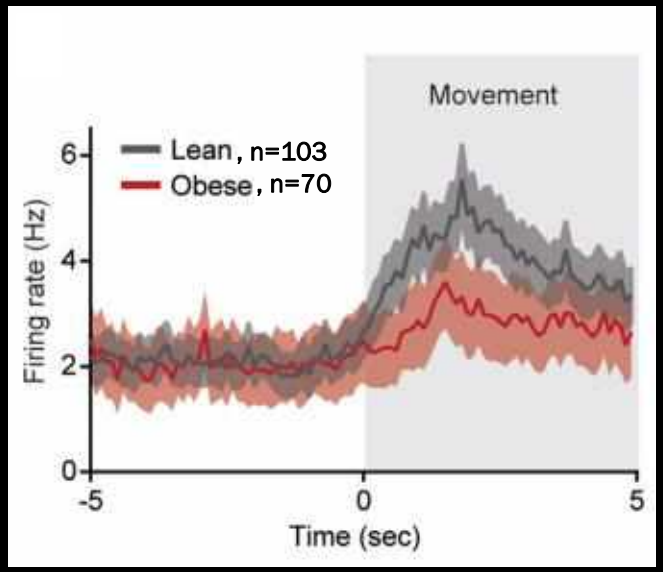


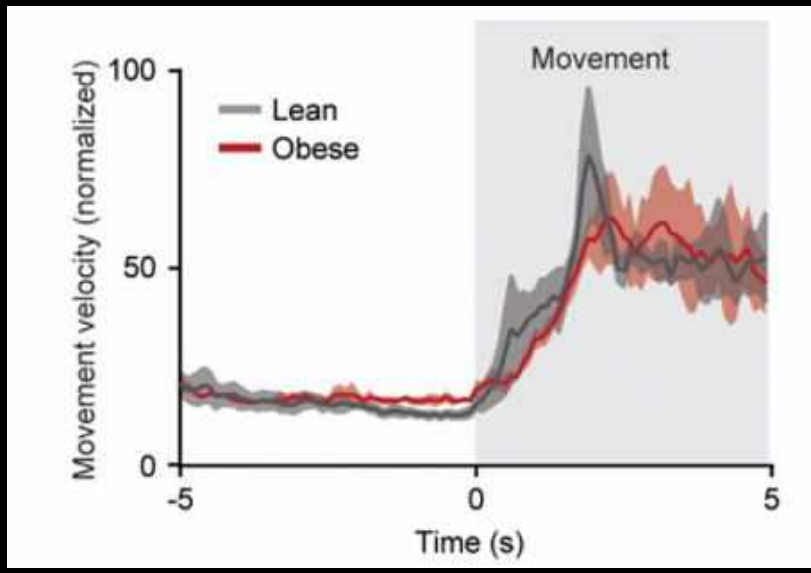
Average firing rates were not different between lean and obese mice



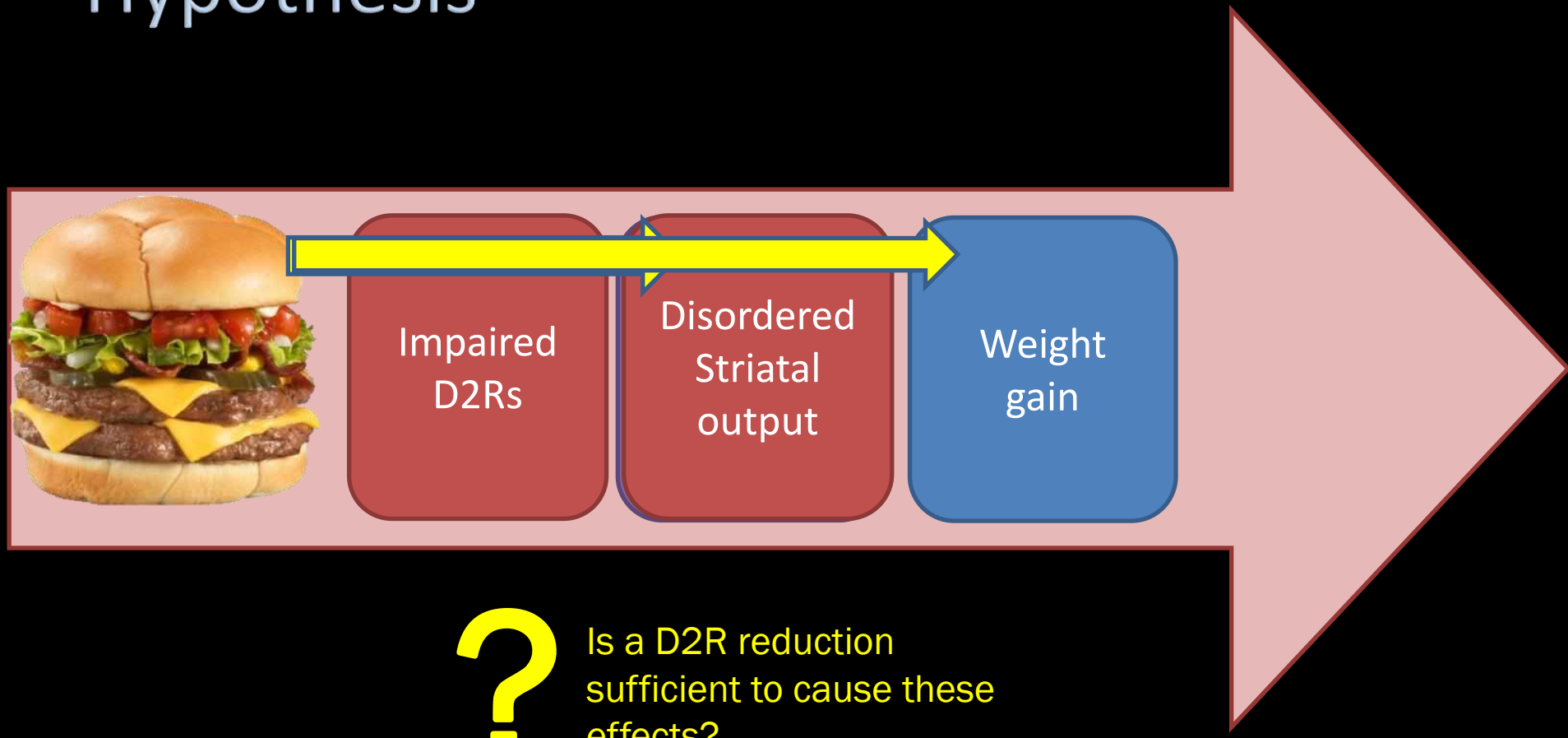


Movement related activity in the striatum was blunted in obese mice



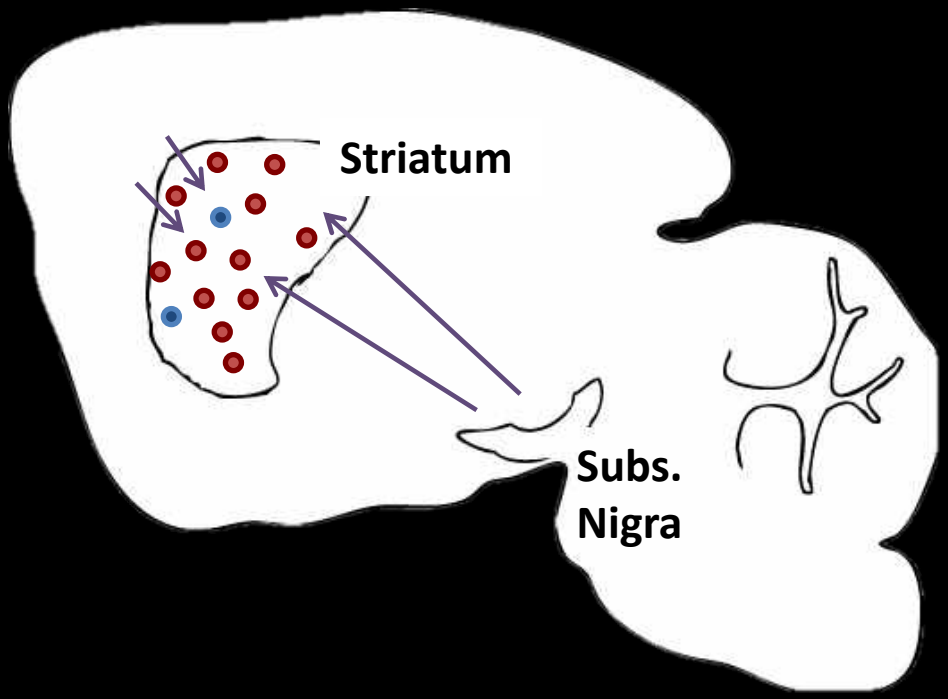


Hypothesis



? Is a D2R reduction sufficient to cause these effects?

D2 Receptors are Expressed by Multiple Cell Types in the Striatum



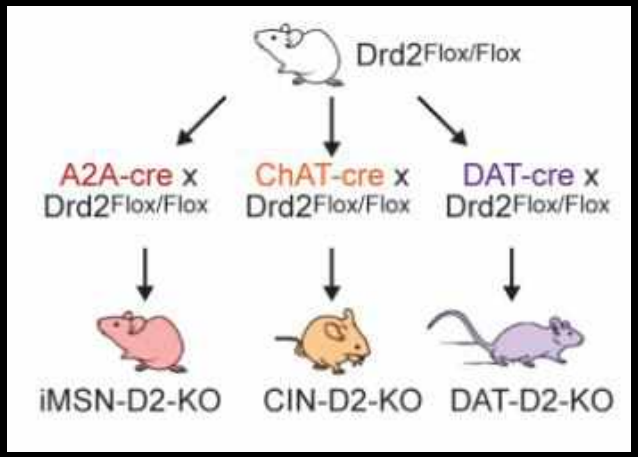
Indirect pathway neurons

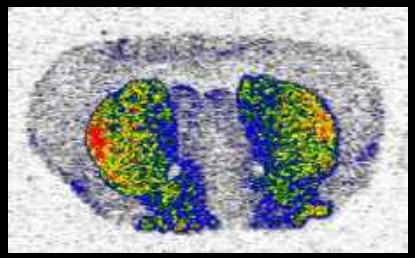
Cholinergic Interneurons

Dopaminergic Terminals

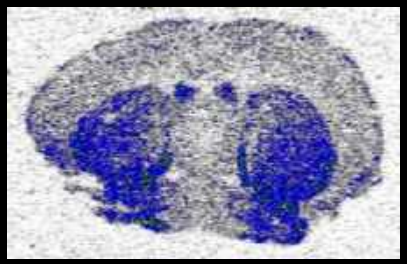
Cortical Terminals

We took a genetic approach to isolate the contribution of D2Rs in different cell types





Control

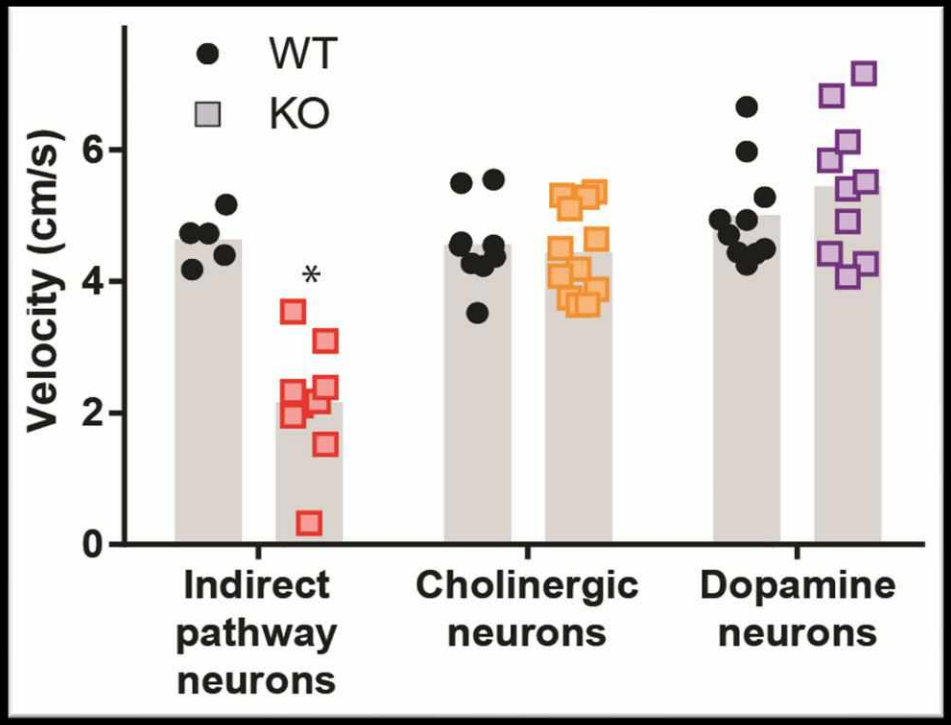


indirect-D2-KO

Collaborators:
Marcello Rubinstein, Julia Lemos, Veronica Alvarez

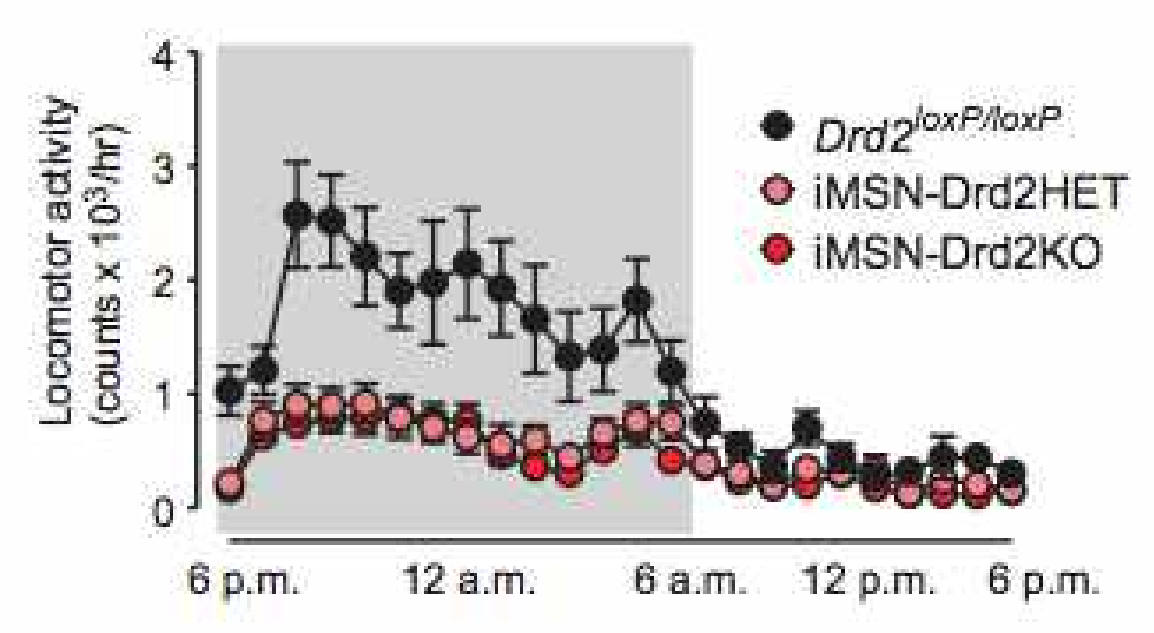
Removing D2Rs from iMSNs (but not other cell types) decreased physical activity

Kim LeBlanc and Tanisha London



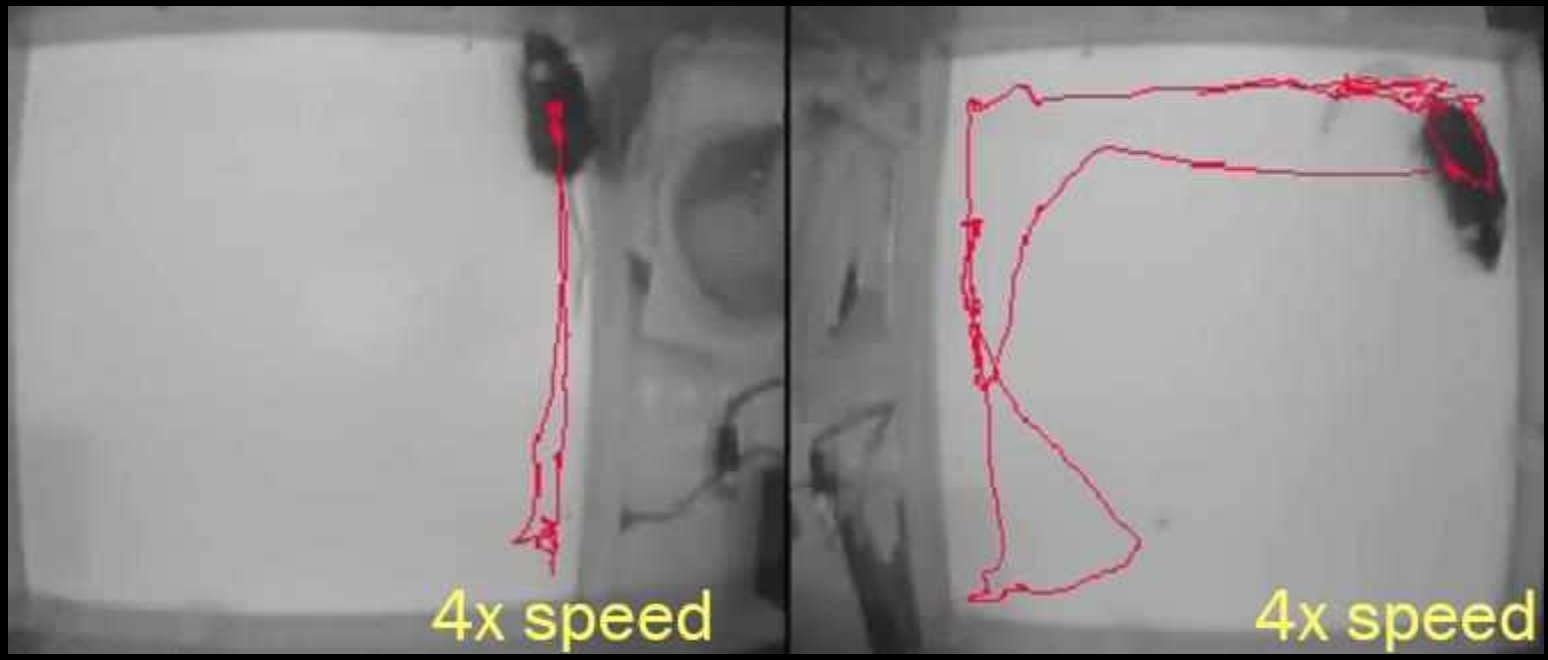
LeBlanc et al., 2018, Molecular Psychiatry

Partial knockdown of iMSN-D2Rs produces almost the full iMSN-D2-knockout phenotype



Lemos et al., 2016, Neuron

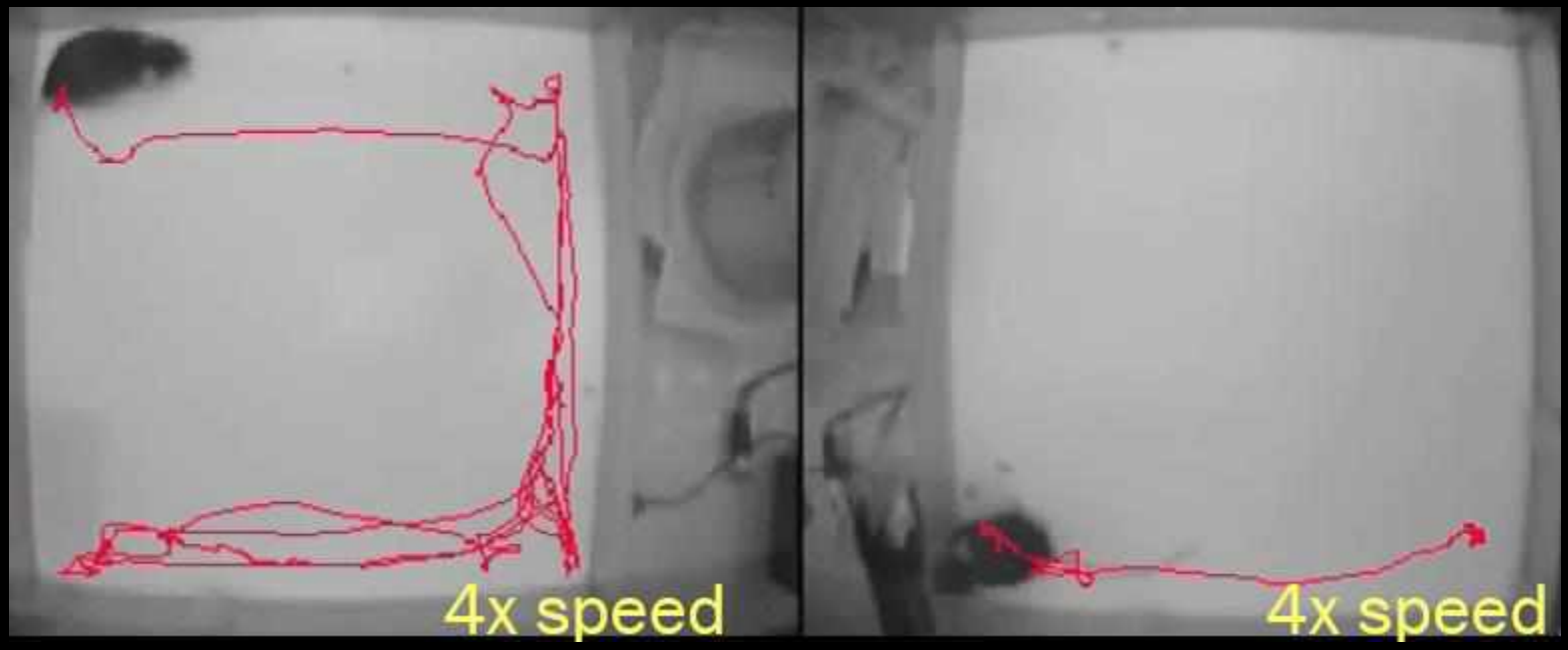
Obese mice have low activity levels



Obese

Lean

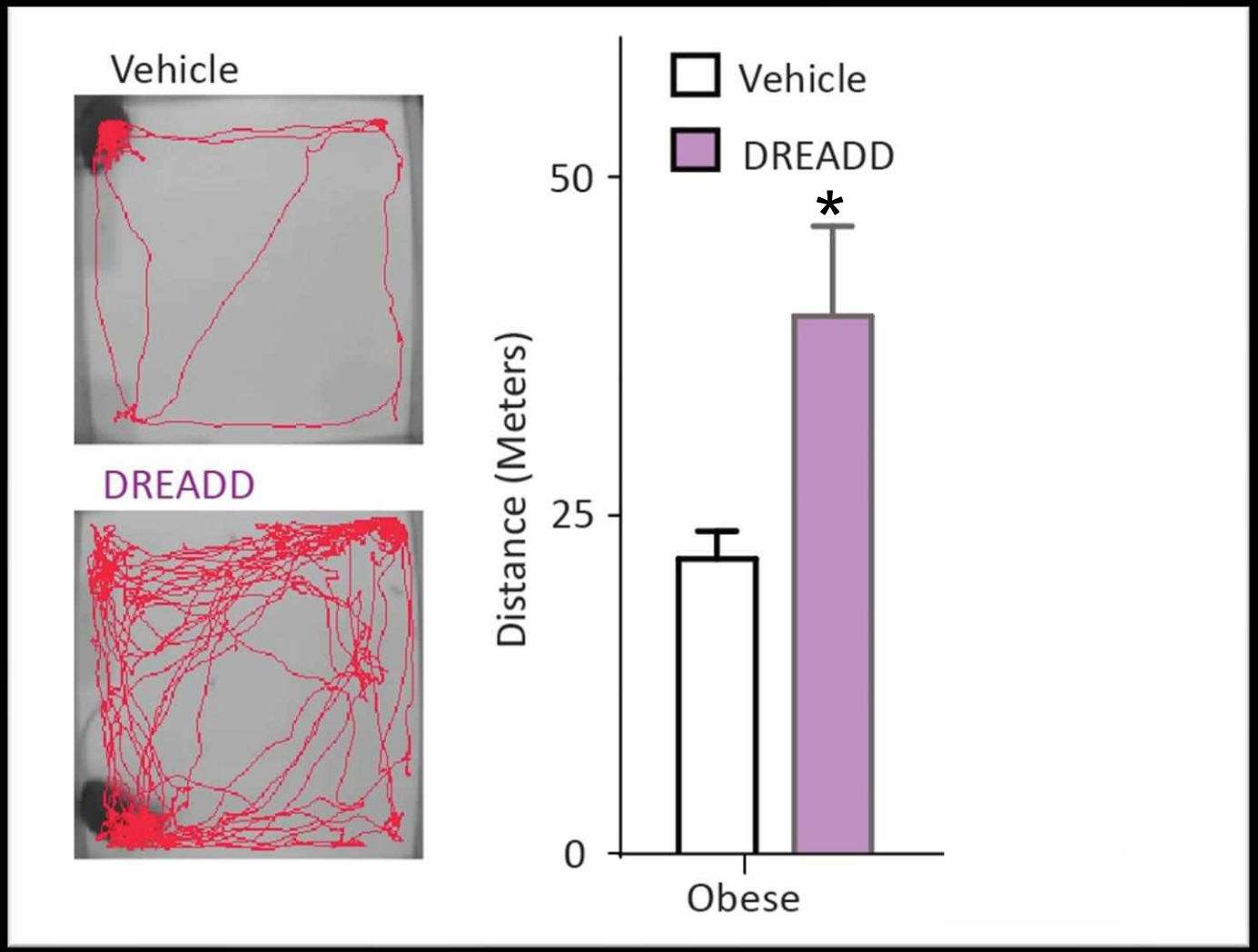
Inhibiting iMSNs restored movement in obese mice



Obese
With DREADD
activation

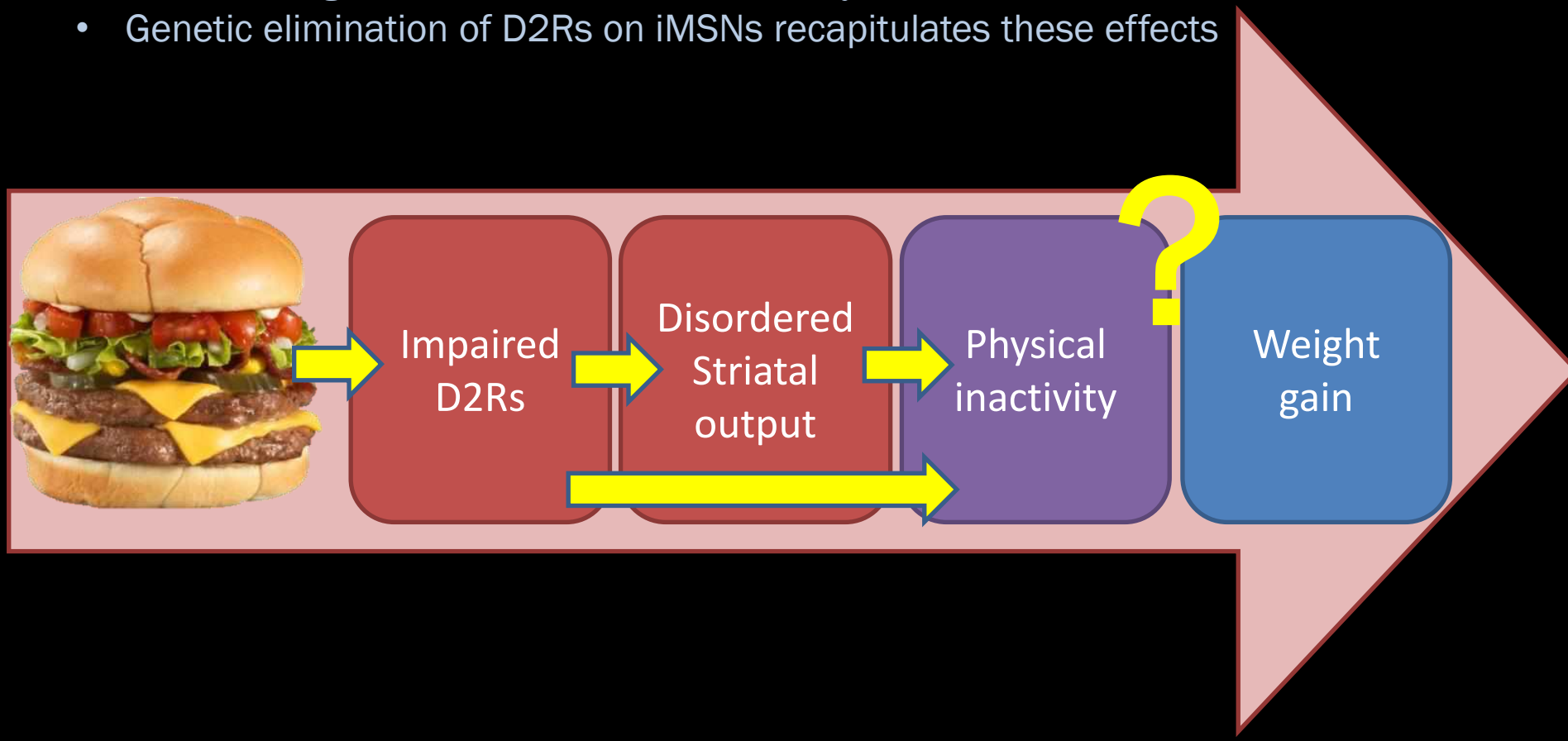
Lean
With DREADD
activation

Inhibiting iMSNs restored movement in obese mice



Interim summary (part 1)

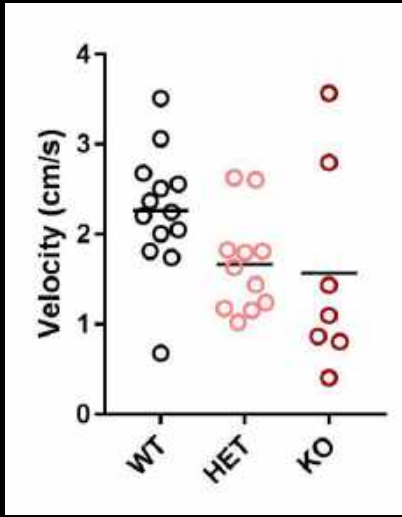
- High fat diet reduces striatal D2R binding, decreases activity levels, and disorganizes striatal neuronal activity
- Genetic elimination of D2Rs on iMSNs recapitulates these effects

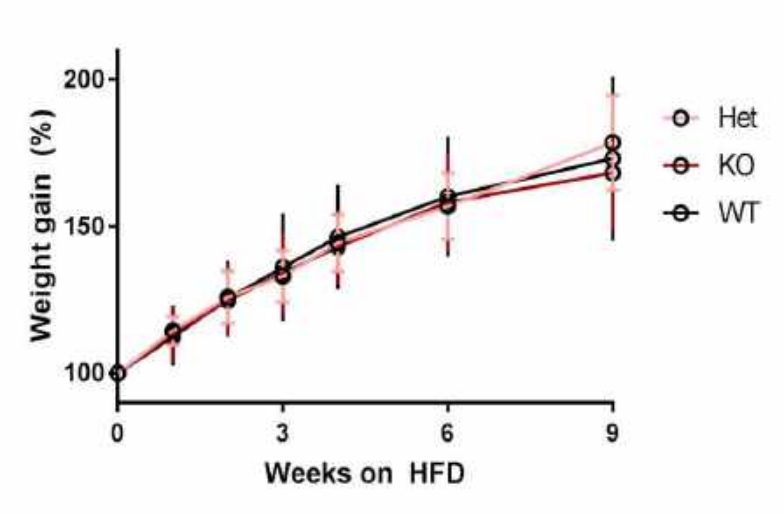


Outline

- What causes obesity (in mice)?
  - What is the role of inactivity?
  - What is the role of overeating?

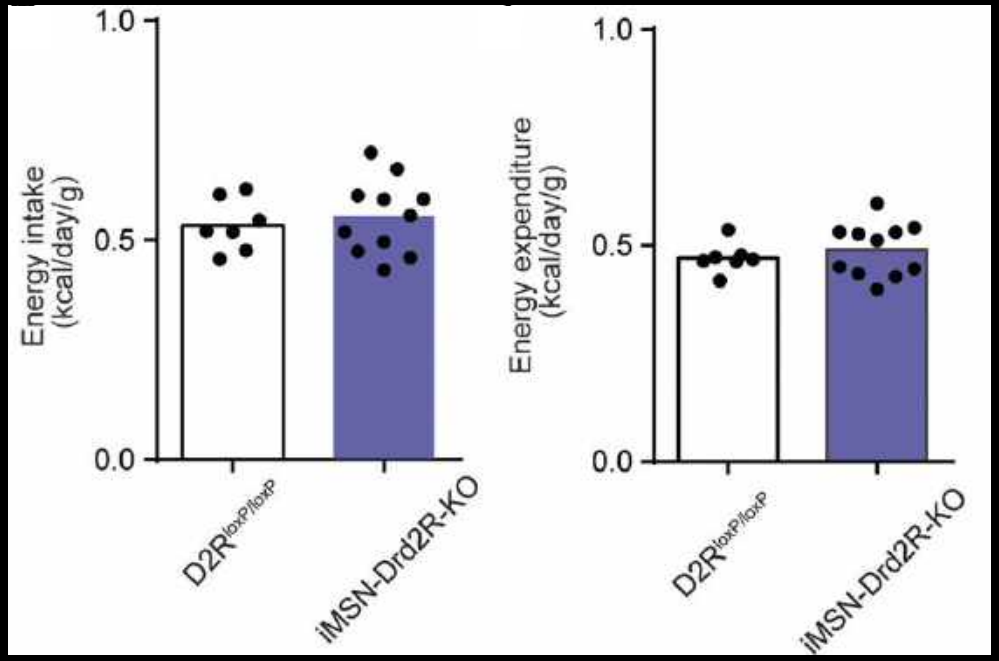
Is there a causal relationship between inactivity and obesity?





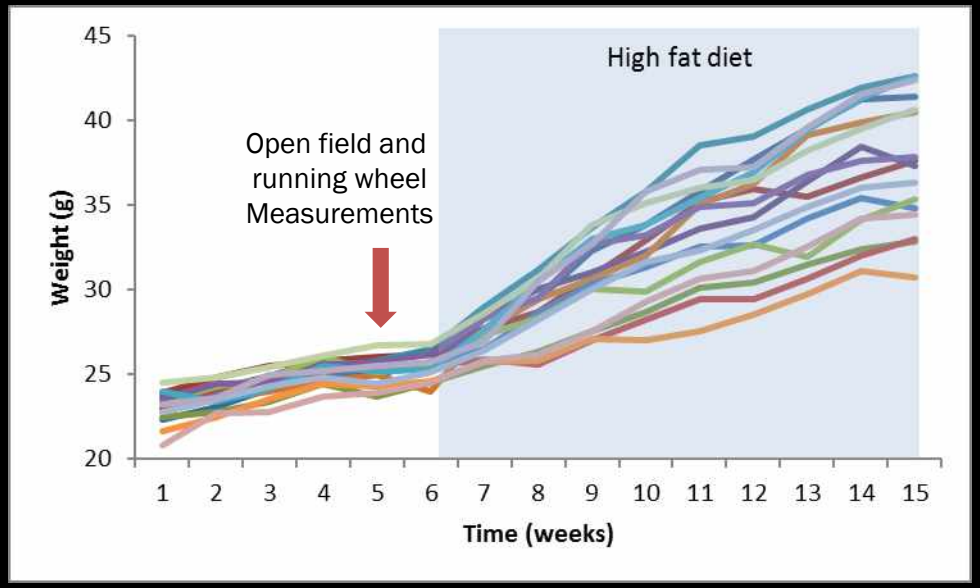
Friend et al. *Cell Metabolism*. 2017 Feb 7;25(2):312-321.

Removing D2Rs alters movement levels, but not caloric balance

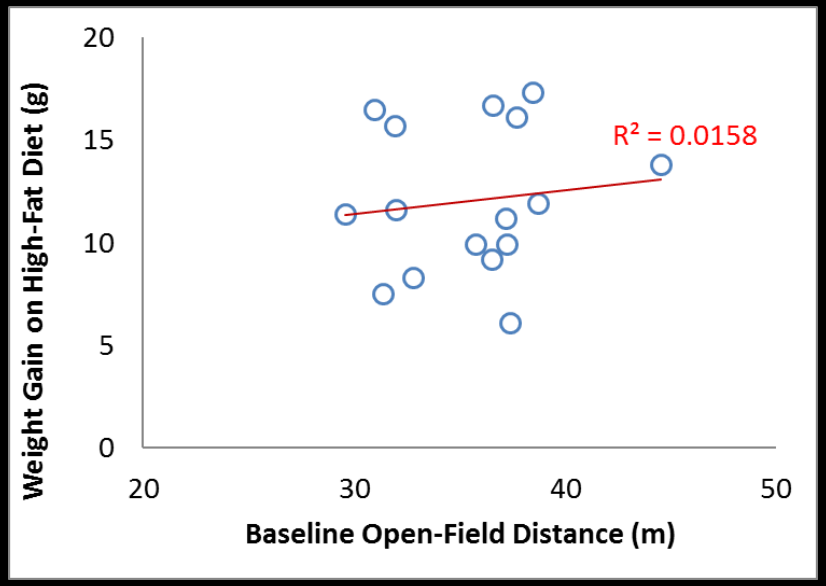


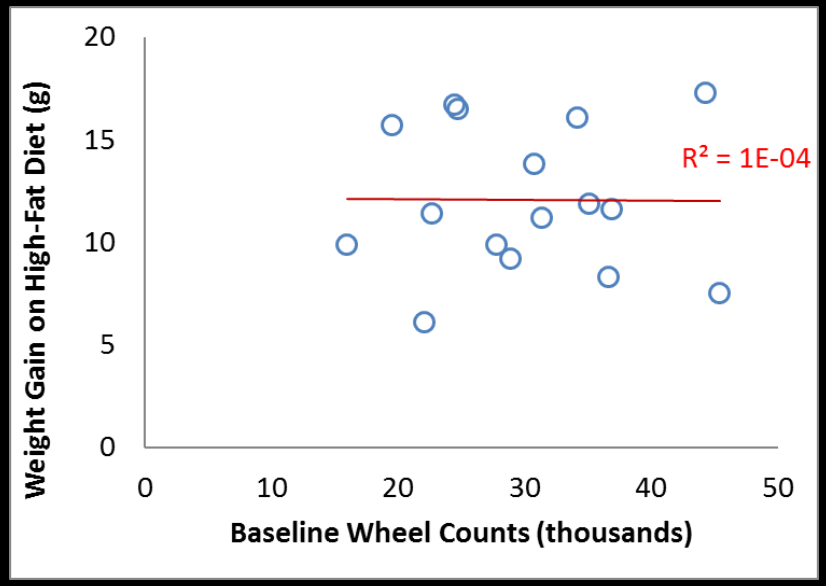
Friend et al. *Cell Metabolism*. 2017 Feb 7;25(2):312-321.

Does natural variance in activity levels correlate with weight gain in wildtype mice?

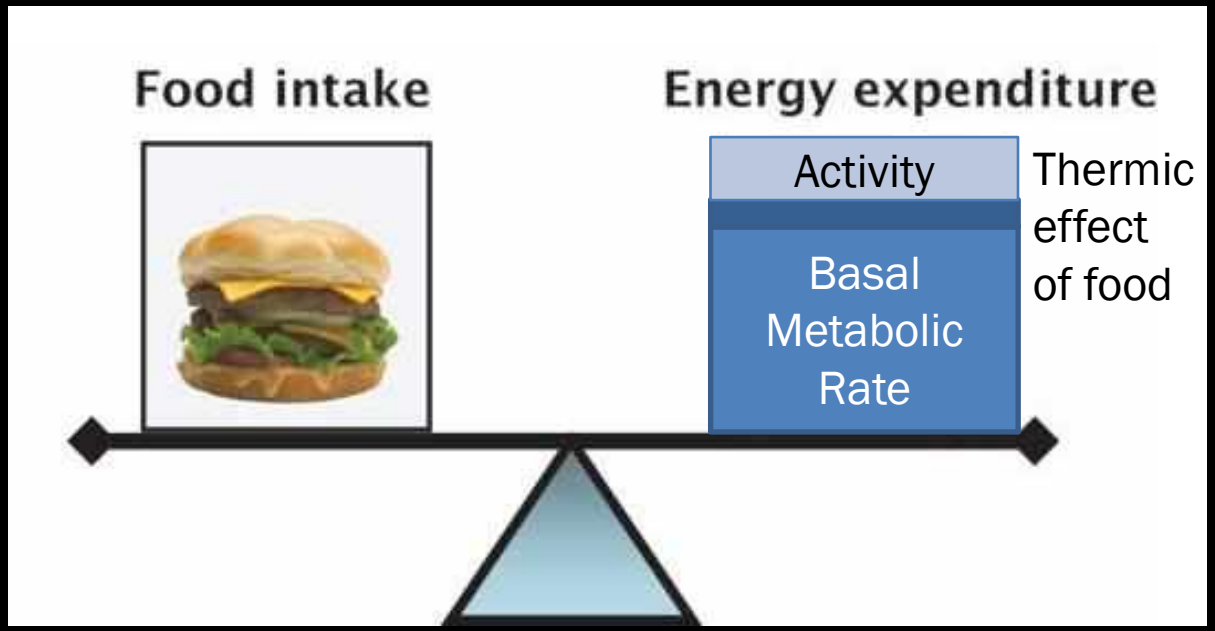


Natural variance in activity levels did not correlate with weight gain.

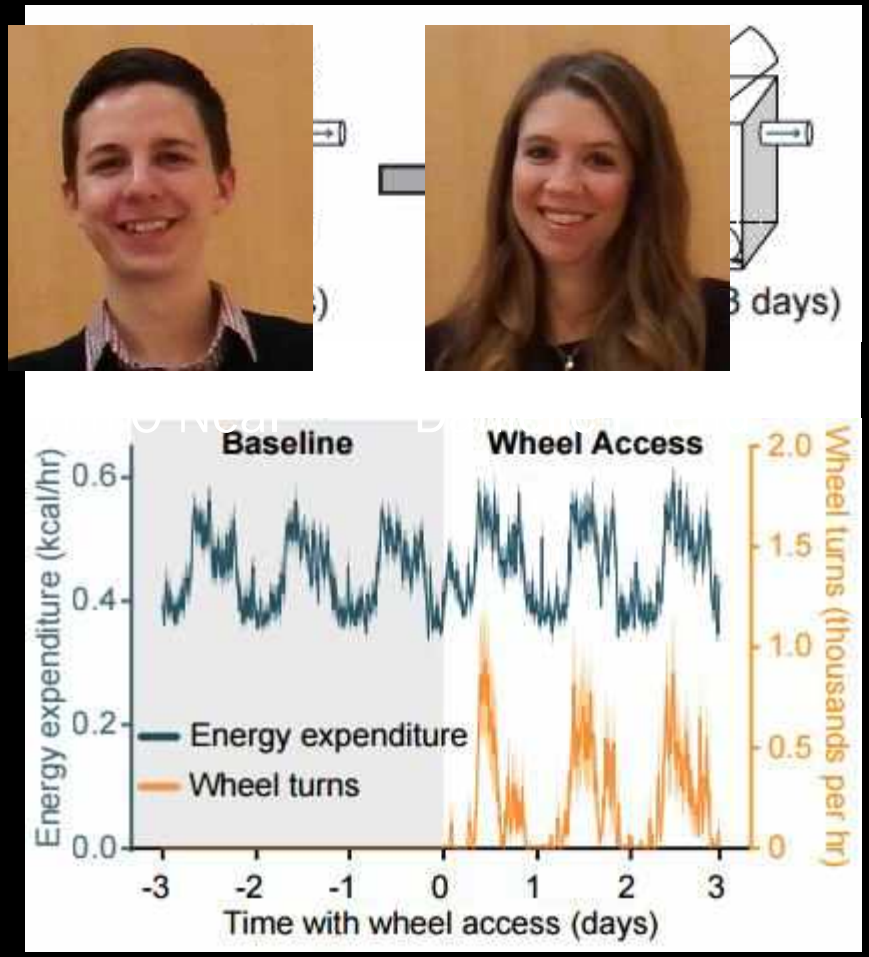


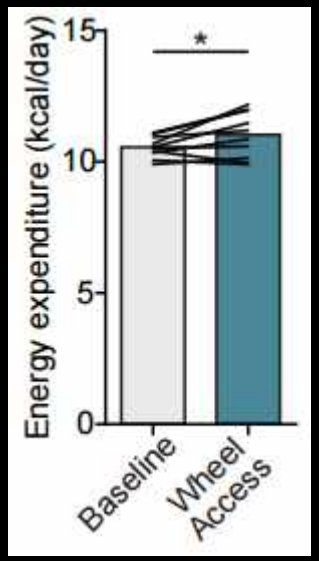


Why don’t inactive mice gain more weight?



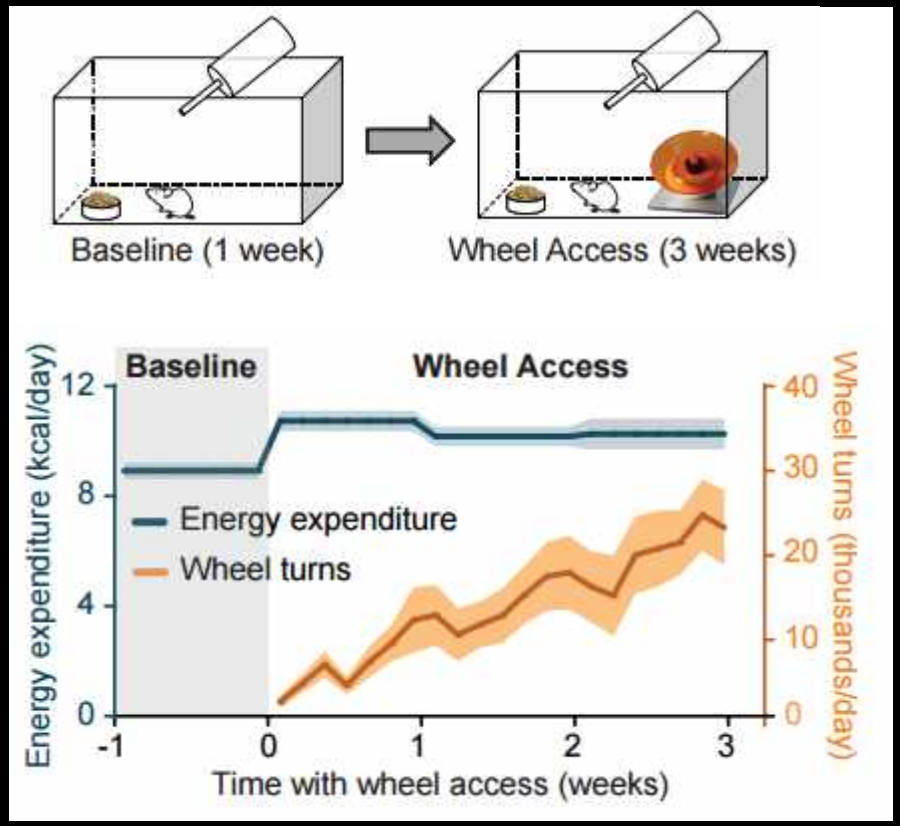
How does changing activity levels affect total daily energy expenditure?

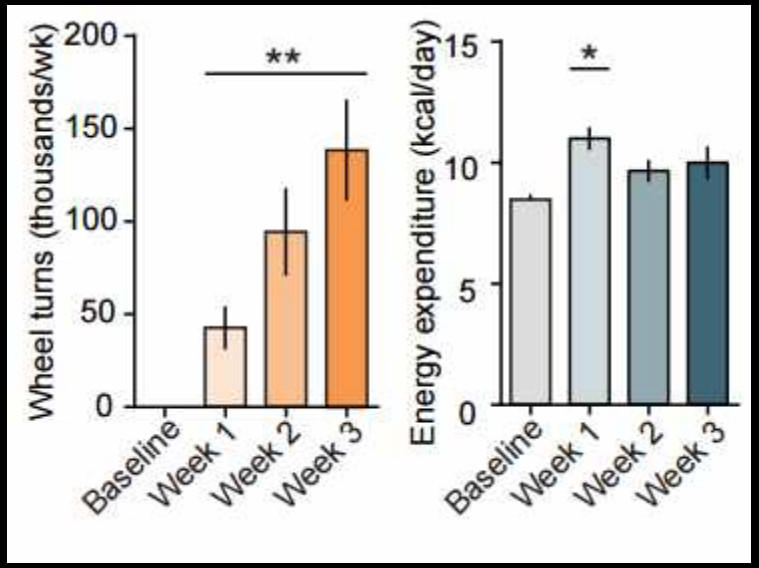




O'Neal TJ*, Friend DM*, Guo J, Hall KD, Kravitz AV. *Current Biology*. 2017 Feb 6;27(3):423-430.

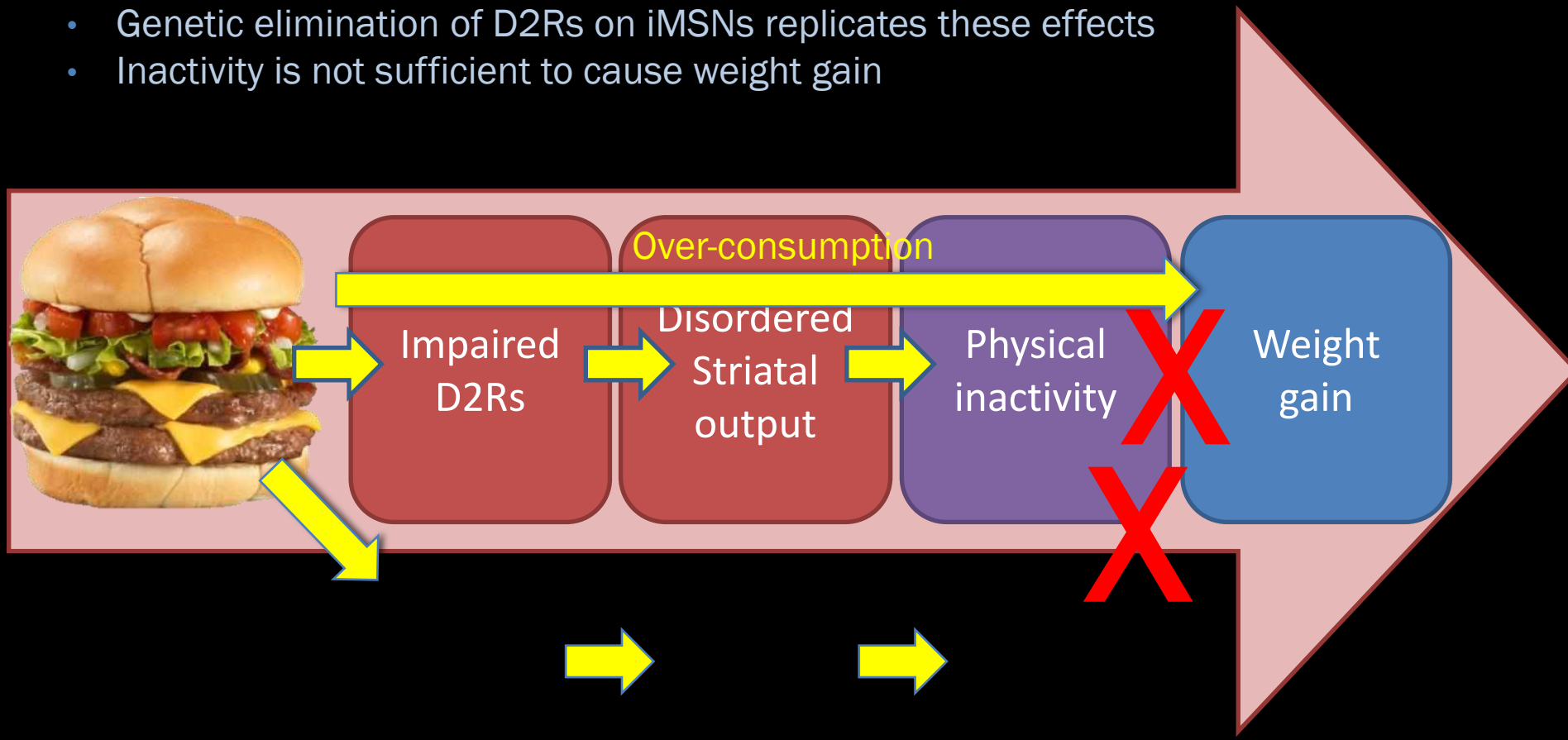
Would long term wheel access produce larger changes in daily energy expenditure?





Interim summary (part 2)

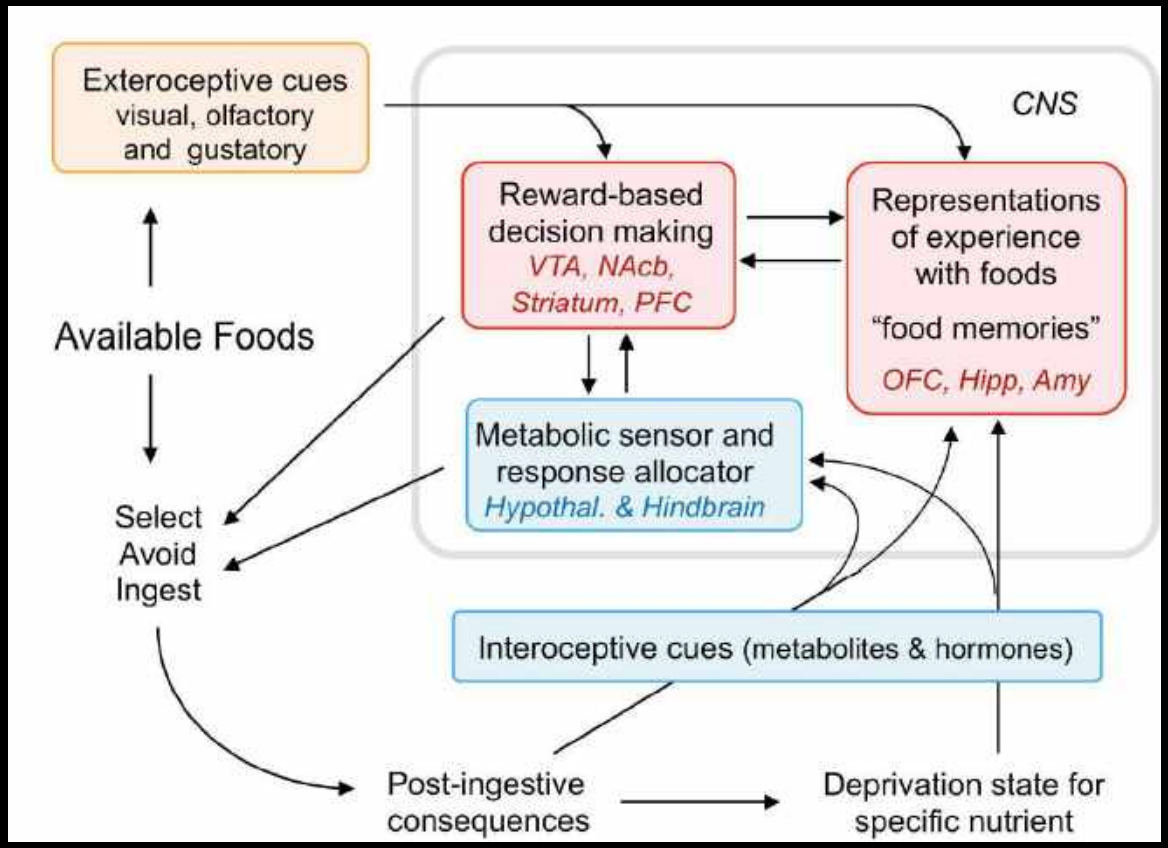
- High fat diet reduces striatal D2R binding, decreases activity levels, and disorganizes striatal neuronal activity
- Genetic elimination of D2Rs on iMSNs replicates these effects
- Inactivity is not sufficient to cause weight gain



Outline

- What causes obesity (in mice)?
  - What is the role of inactivity?
  - What is the role of overeating?

(at least) Two systems drive eating: Hedonic vs. homeostatic feeding



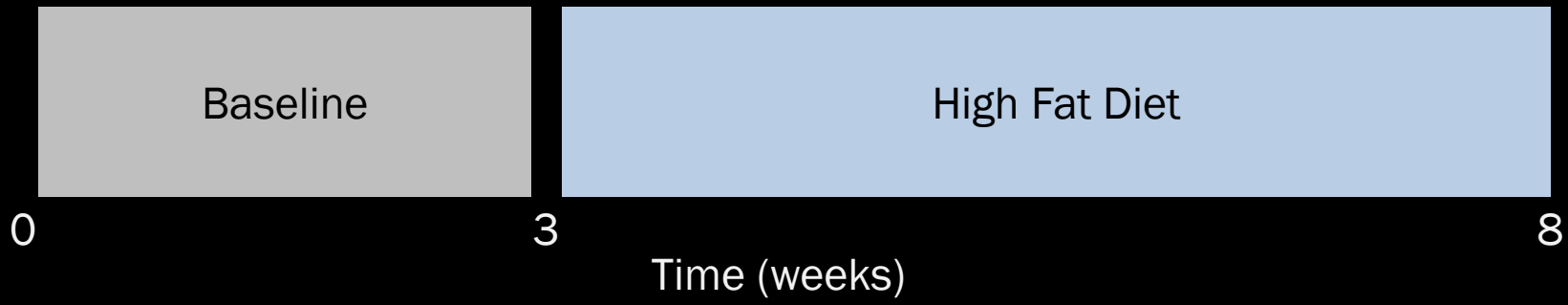
Berthoud, H.-R., Münzberg, H., & Morrison, C. D. (2017). *Blaming the Brain for Obesity: Integration of Hedonic and Homeostatic Mechanisms. Gastroenterology, 152(7), 1728–1738.*

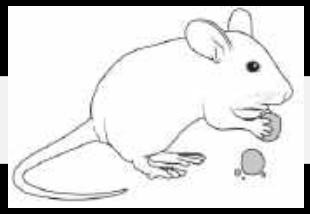
Can we quantify both hedonic and homeostatic drives to eat?

Total food intake = Metabolic need + Hedonic need

Hedonic need = Total food intake - Metabolic need

Experimental plan



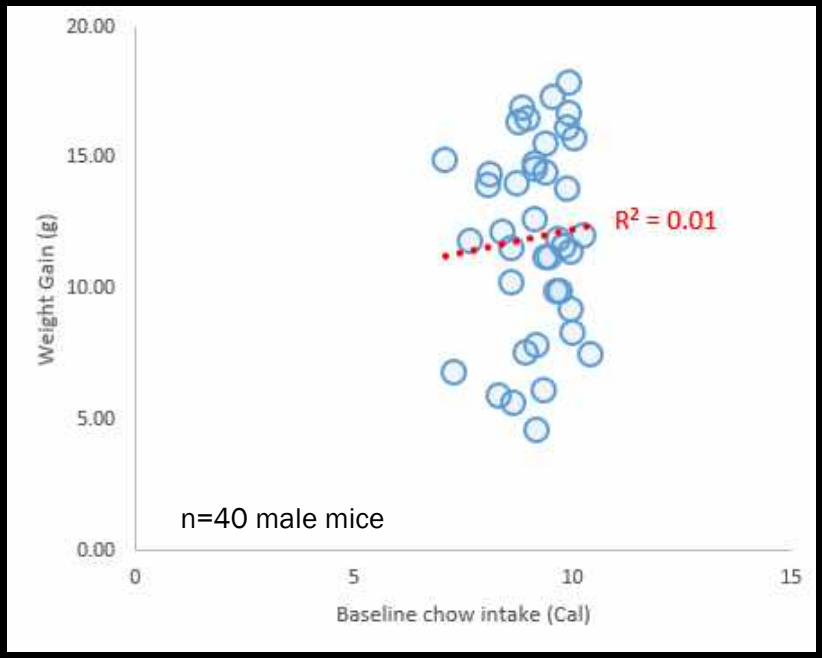


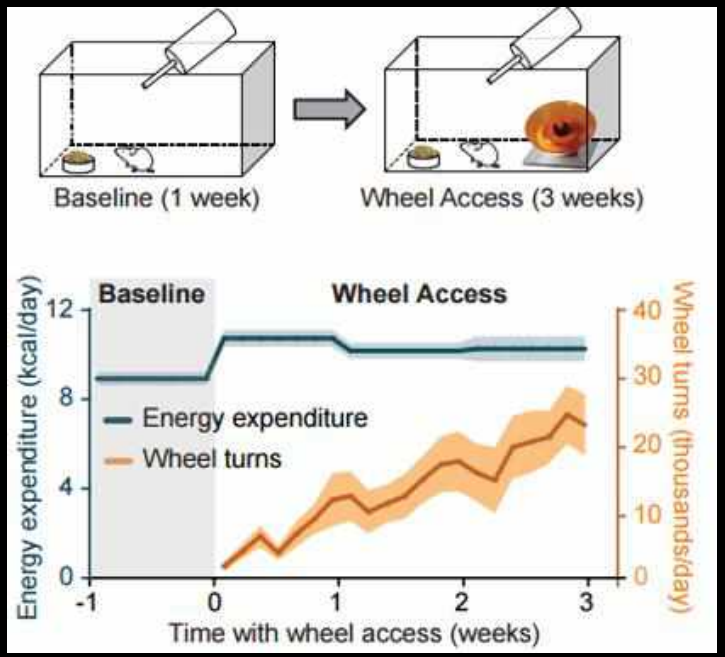
Weigh food every 3 days

Weigh mice every 7 days

The average metabolic need of a mouse is ~10Cal per day

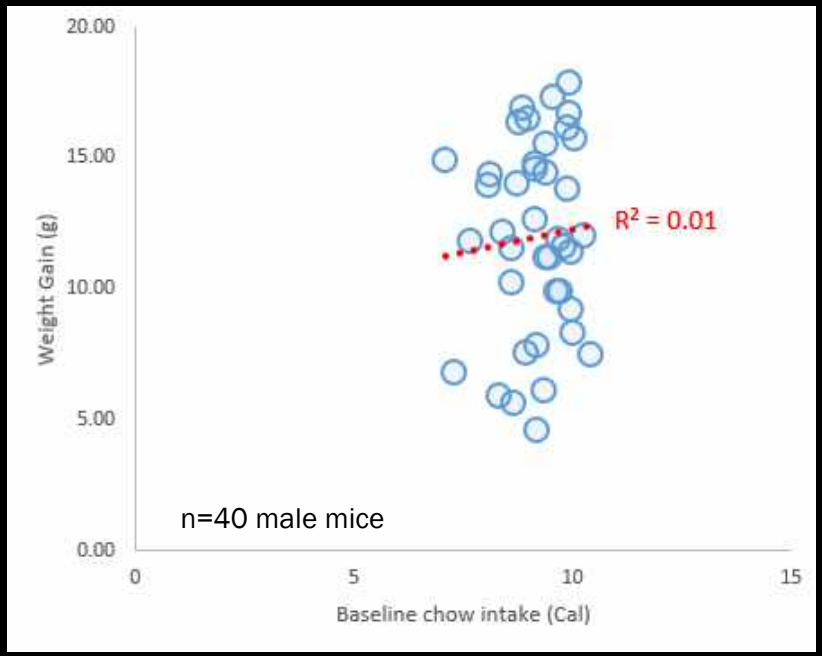
Total food intake = Metabolic need + Hedonic need

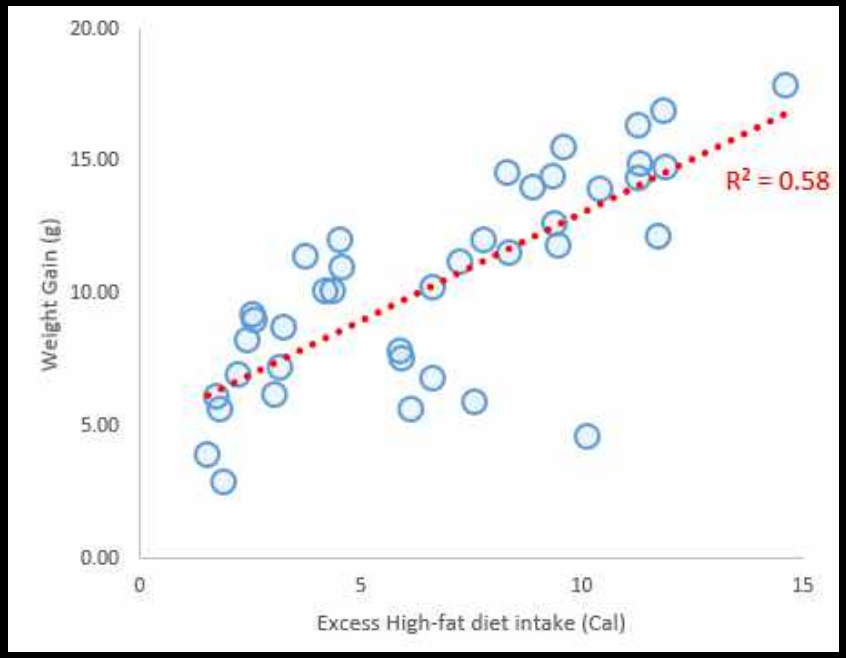




The average metabolic need of a mouse is ~10Cal per day

Hedonic need = *Total food intake - Metabolic need*



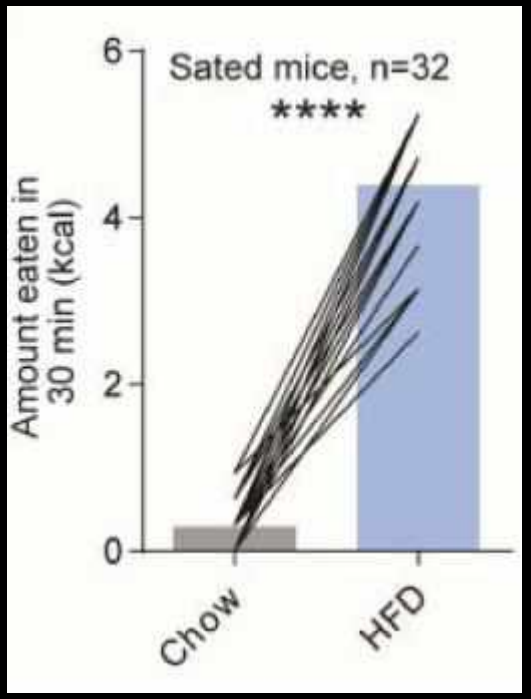


Outline

- What causes obesity (in mice)?
  - What is the role of inactivity?
  - What is the role of overeating?

Why do mice over-eat high fat diets? How high fat diet alters the regulation of daily caloric intake in mice

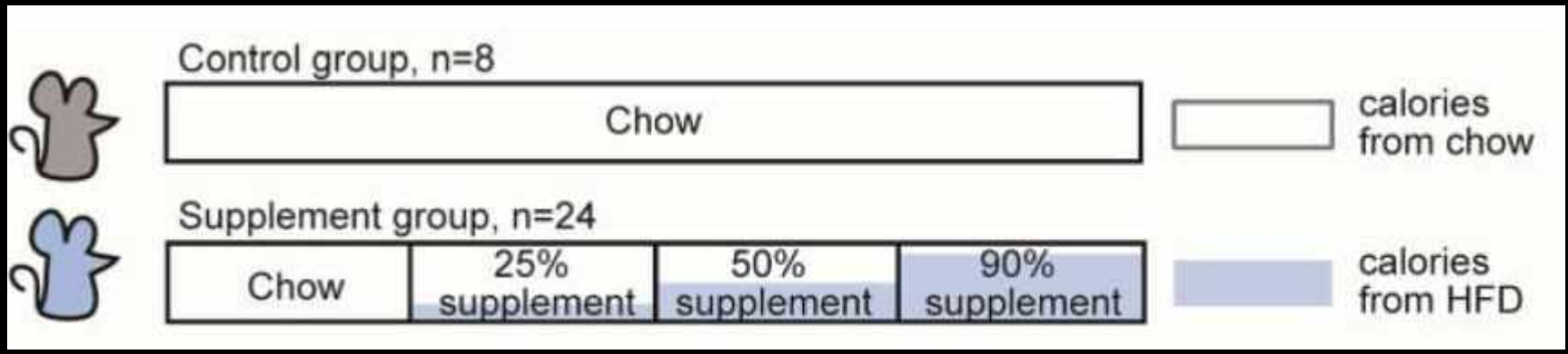
Julia A Licholai[1,4], Katrina P Nguyen[3,4], Wambura C Fobbs[1], Corbin J Schuster[1], Mohamed A Ali[1], and Alexxai V Kravitz[1,2]



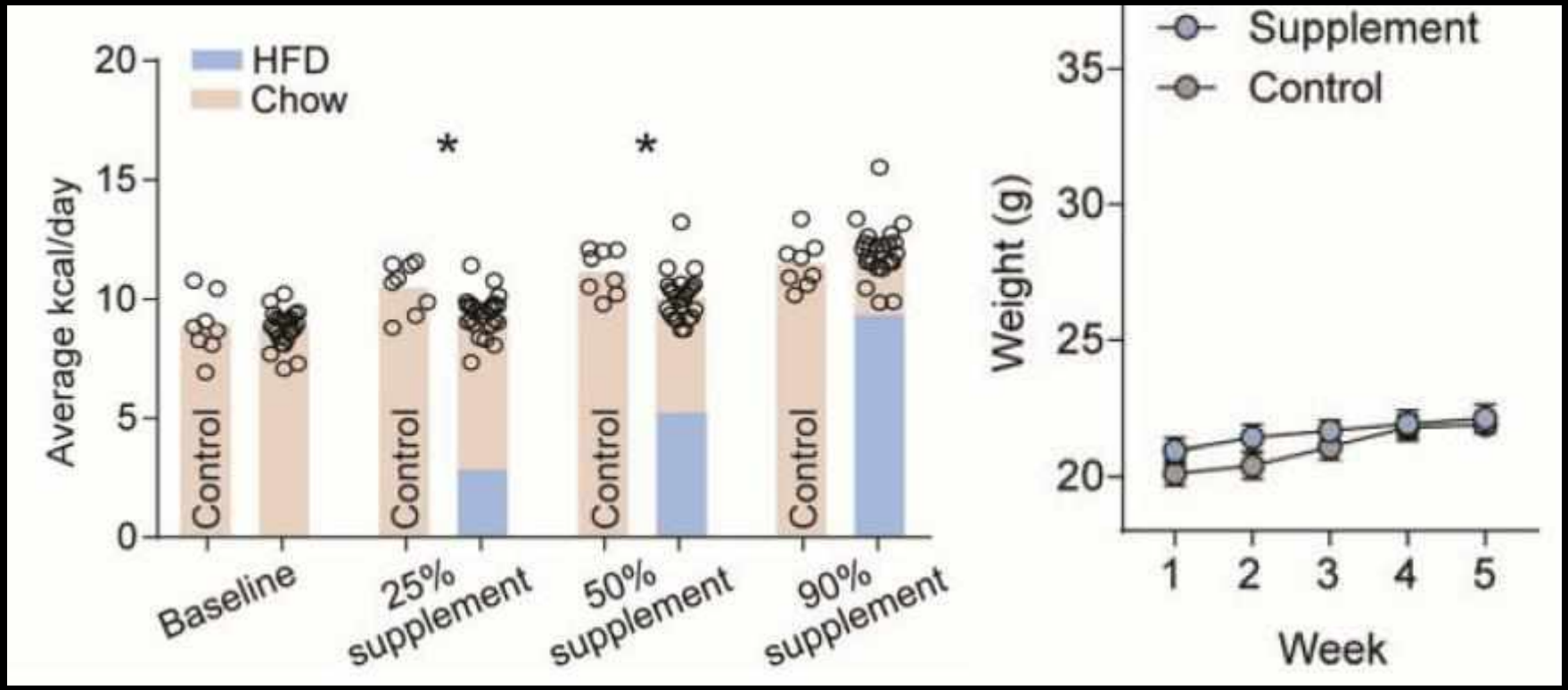
Conclusion #1: Mice will over-eat high-fat diet in the complete absence of hunger

Obesity (Silver Spring). 2018 Jun;26(6):1026-1033.

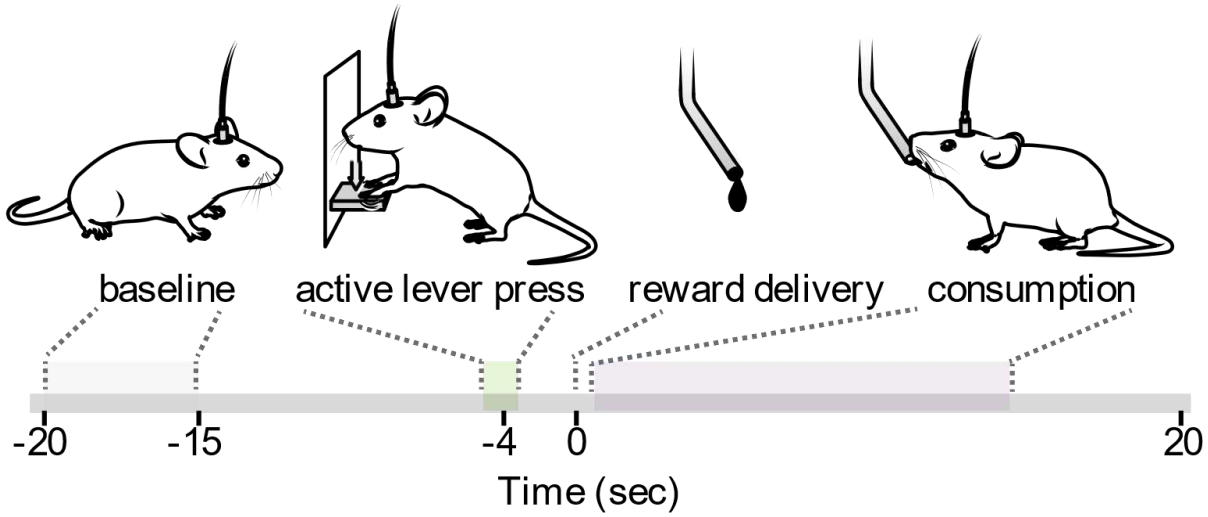
Does high-fat diet fail to activate satiety signals?

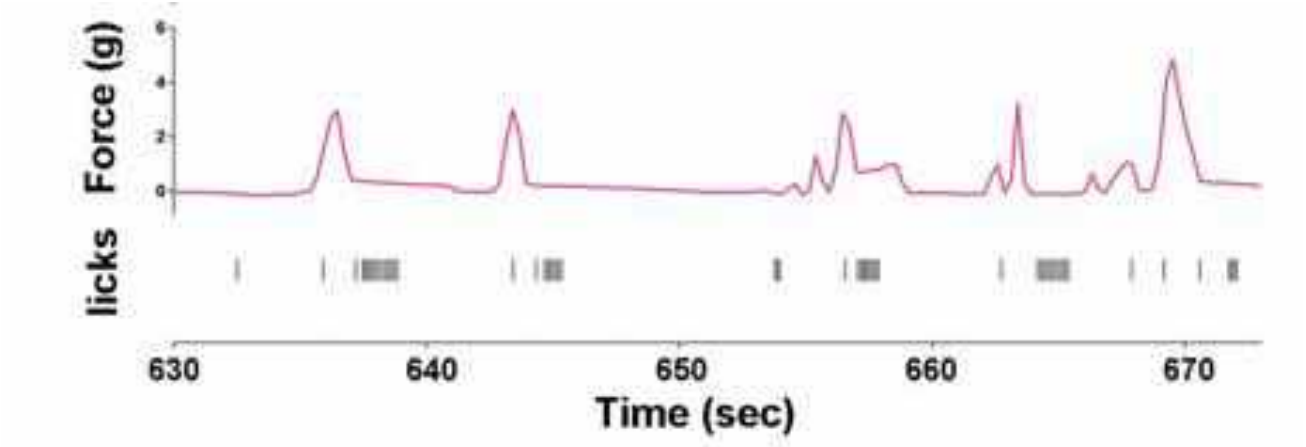


High-fat diet appropriately activates satiety signals

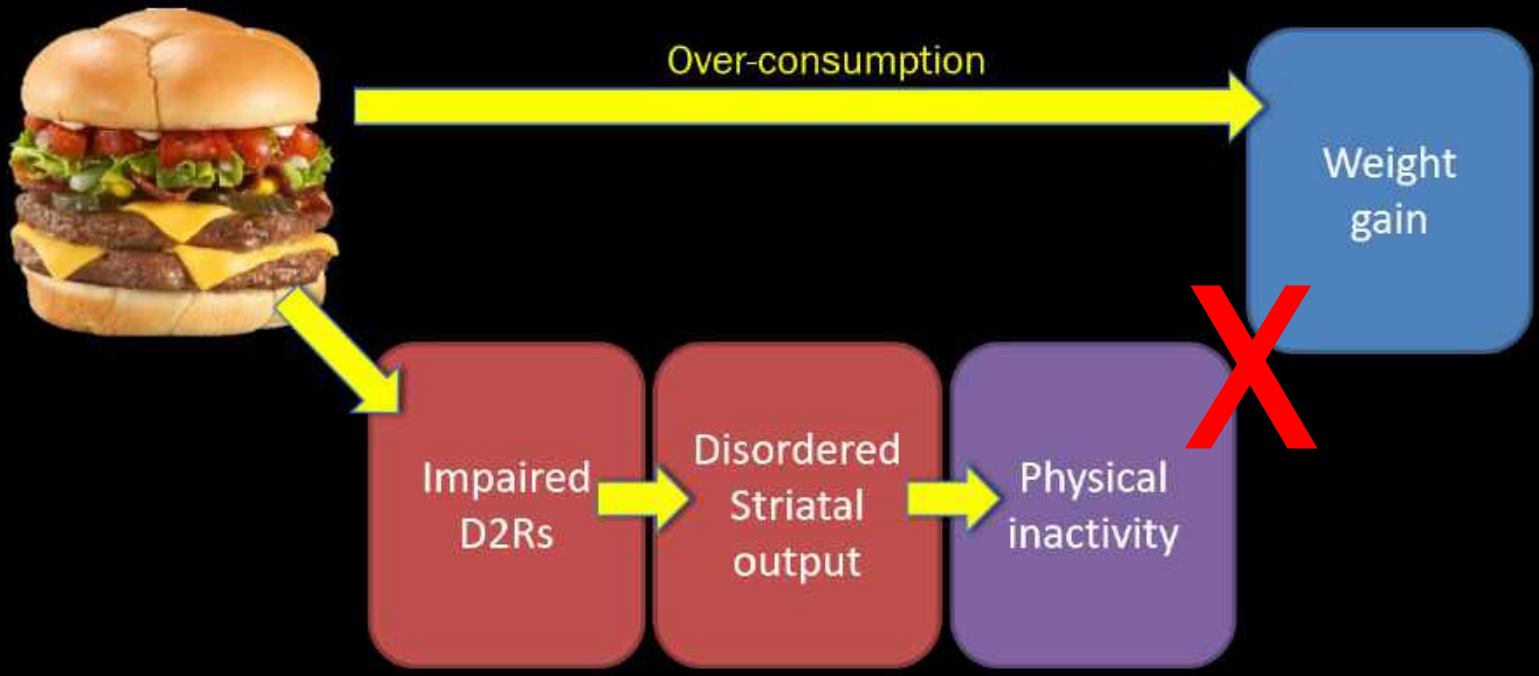


Bridget Matikainen-Ankney:
Operant task to assay effort for hedonic feeding





Conclusion


Over-consumption
Weight gain
Impaired D2Rs
Disordered Striatal output
Physical inactivity

Future directions

- Why do some mice eat more high fat diet than others?
- Can manipulations of brain circuitry prevent weight gain?
- Can manipulations of brain circuitry promote lasting weight loss?

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