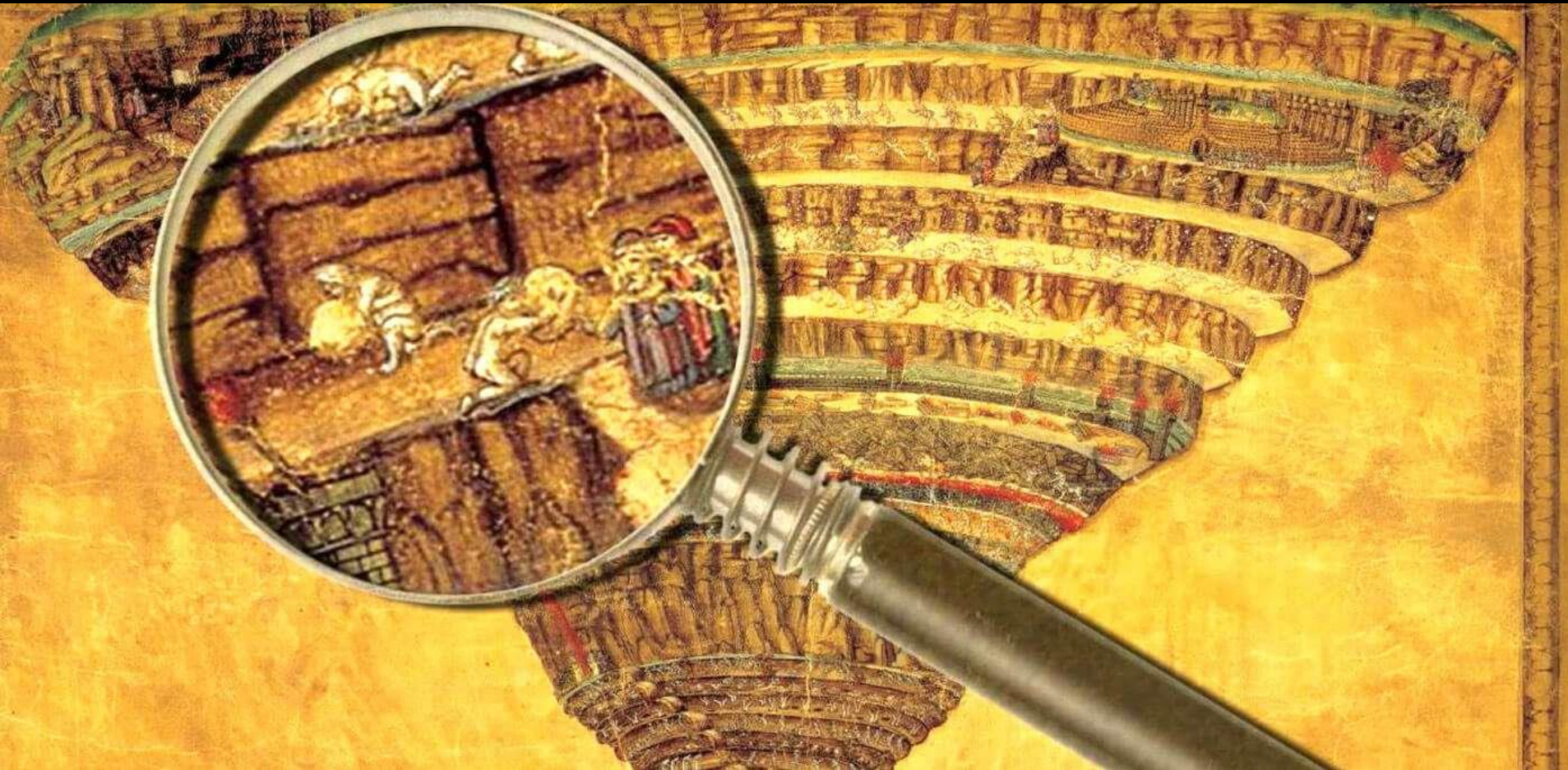


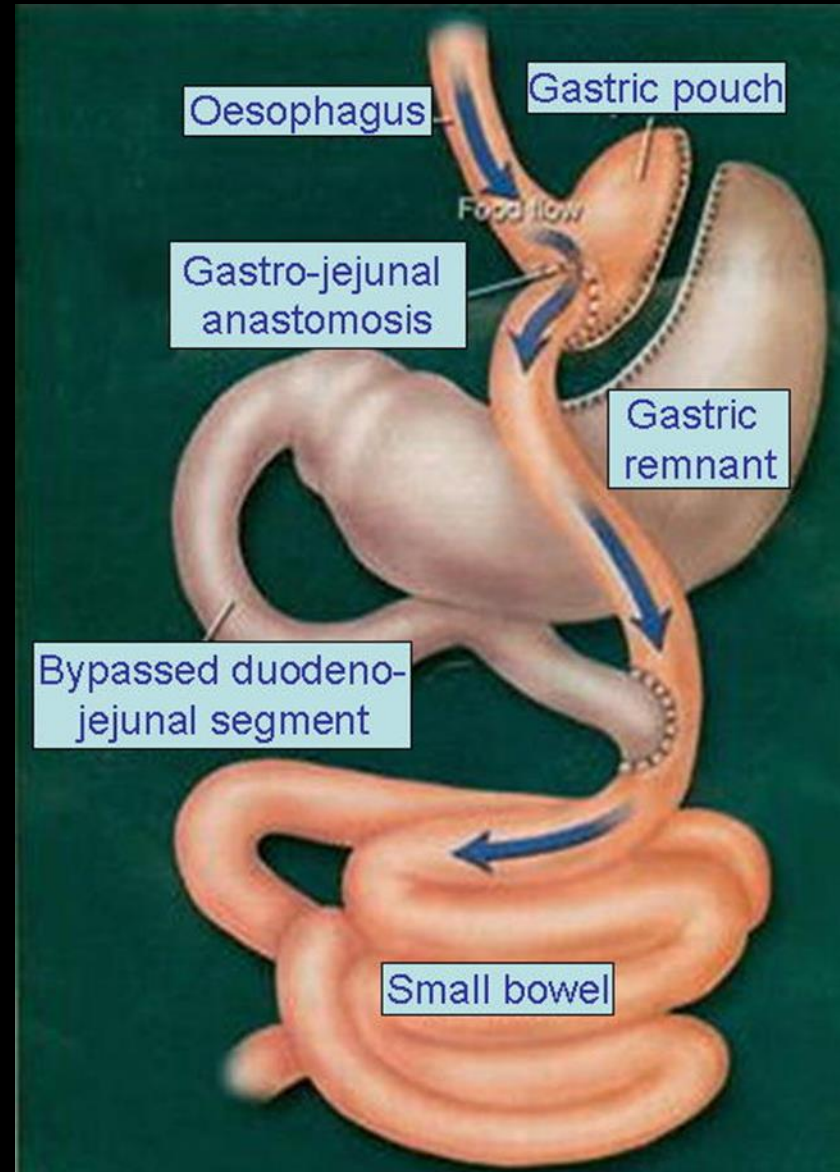
Physiological aspects on weight loss and weight loss maintenance

Carel le Roux University College Dublin,
Imperial College London



Conflict of interest

Consilient Health,
NovoNordisk,
Johnson & Johnson,
ONO pharmaceuticals,
Covidien,
Fractyl,
GI Dynamics,
Roche,
AstraZeneca
Lilly
Boehringer Ingelheim



What are the pathognomonic symptoms of obesity?

Eugenia Martinez Vallejo Nude

Eugenia Martinez Vallejo Nude

by Juan Carreño de Miranda



In 1680, she was brought to court to be admired as a monstrous manifestation of nature. She was six years old at the time, and already weighed 70 kg. She attended celebrations and gatherings in the palace in order to be seen by the royals and their guests.

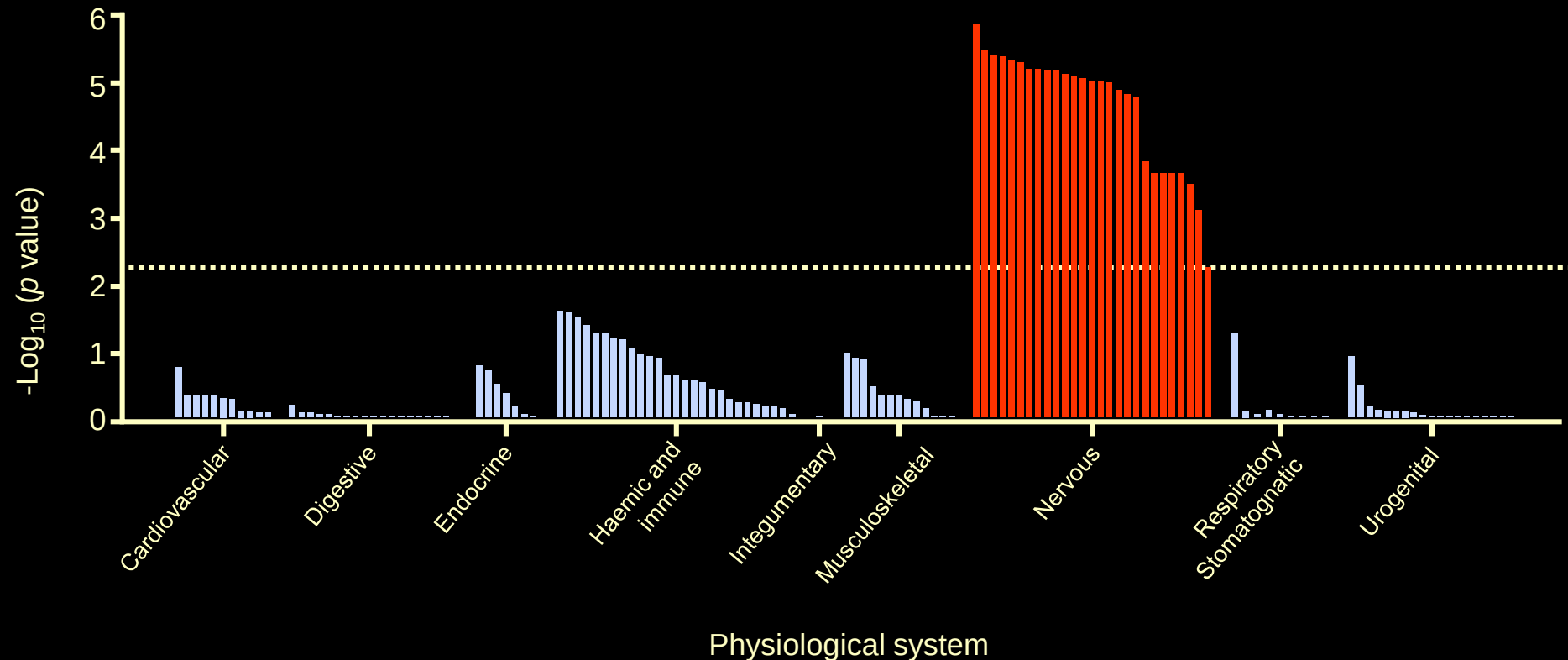


The Devil making her do it

Where are the neurons situated
that code for hunger and satiety?

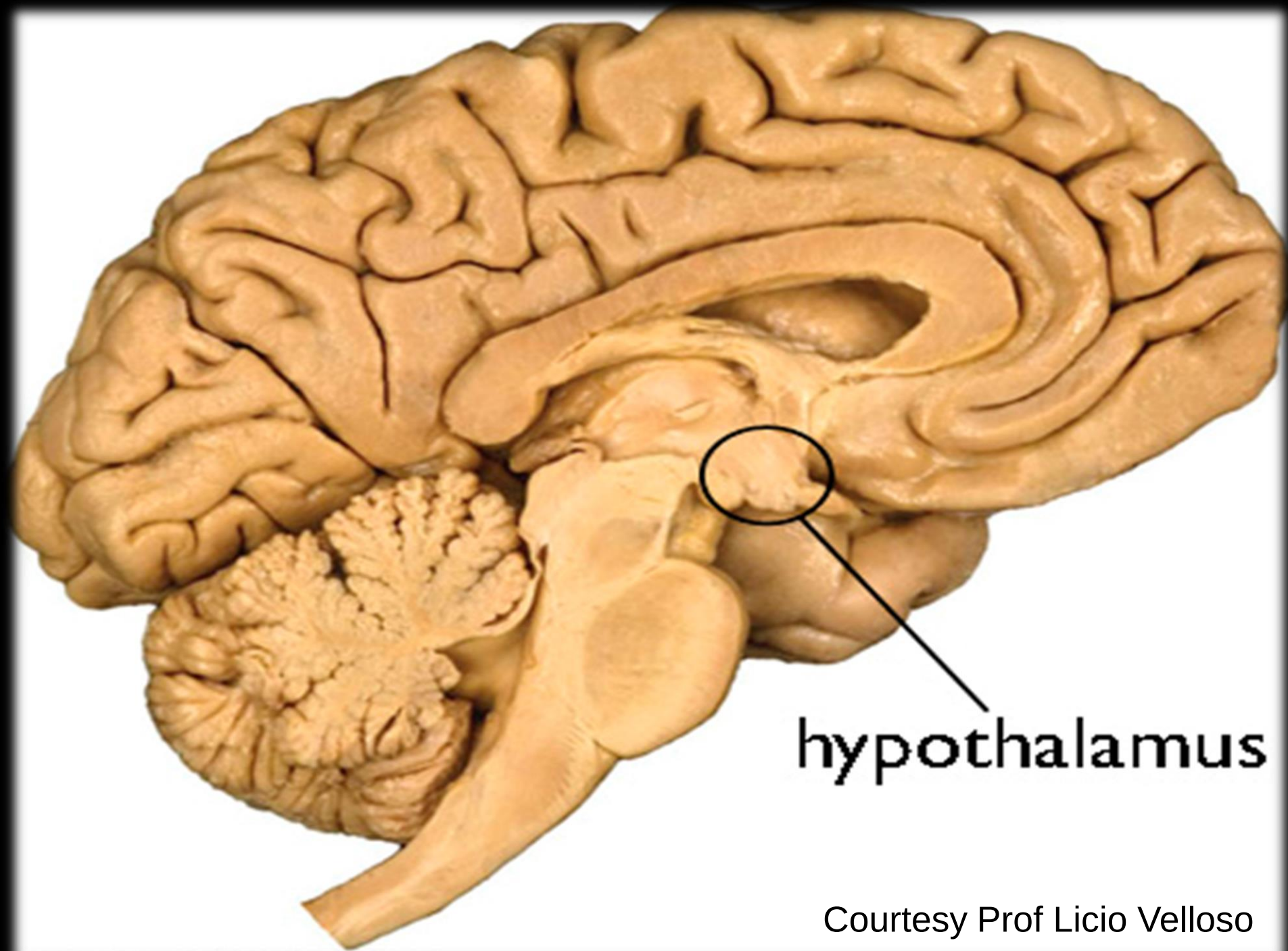
Obesity has genetic determinants: GWAS pathway analyses link CNS genes to obesity

Tissues sorted by physiological system – genes from CNS showed association (in red)



CNS, central nervous system; GWAS, Genome-Wide Association Study

Locke AE *et al.* *Nature* 2015;518:197–206

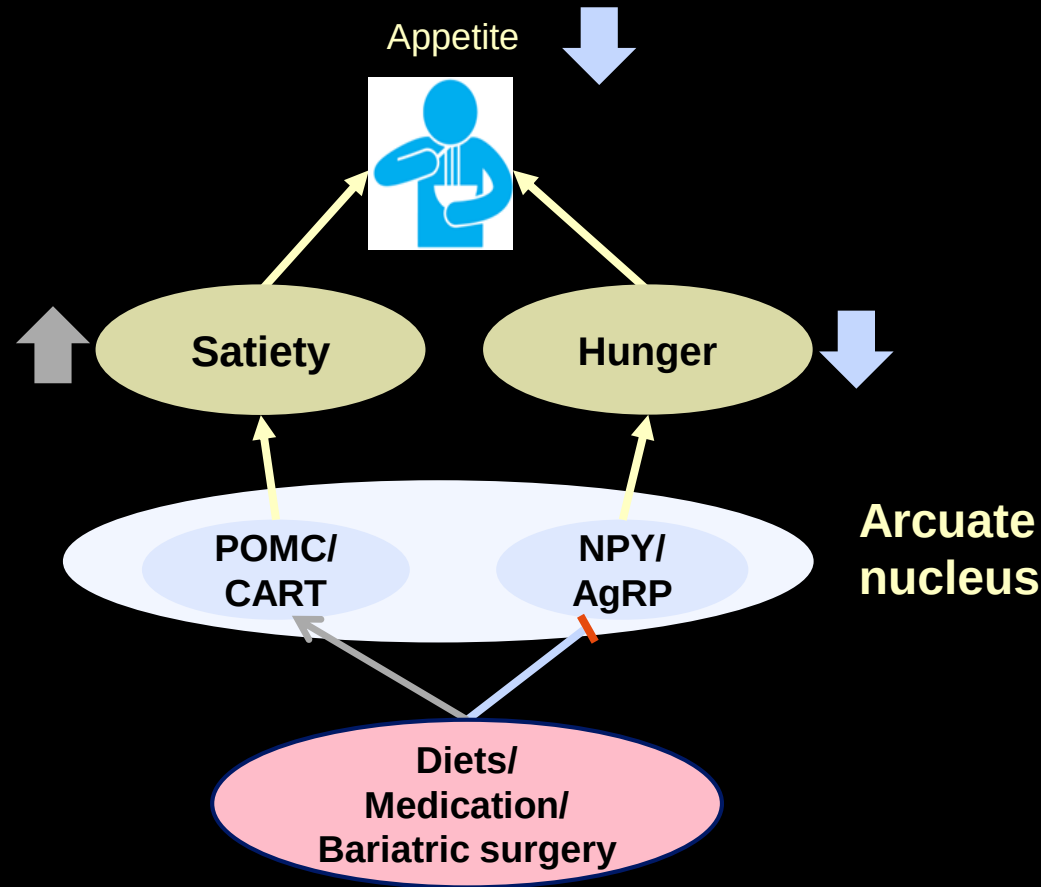


hypothalamus

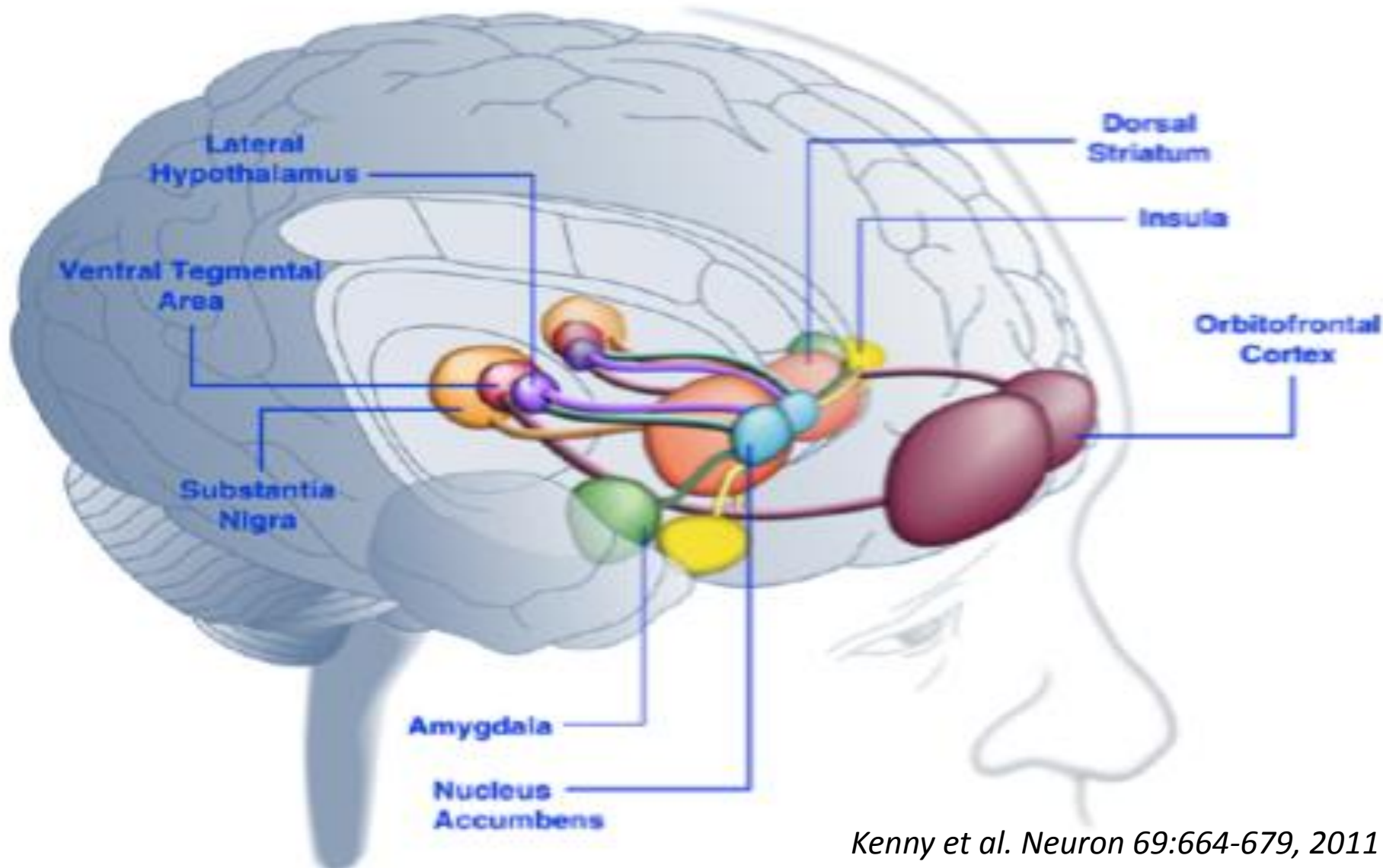
Courtesy Prof Licio Velloso

Successful weight loss treatments increase satiety and reduce hunger

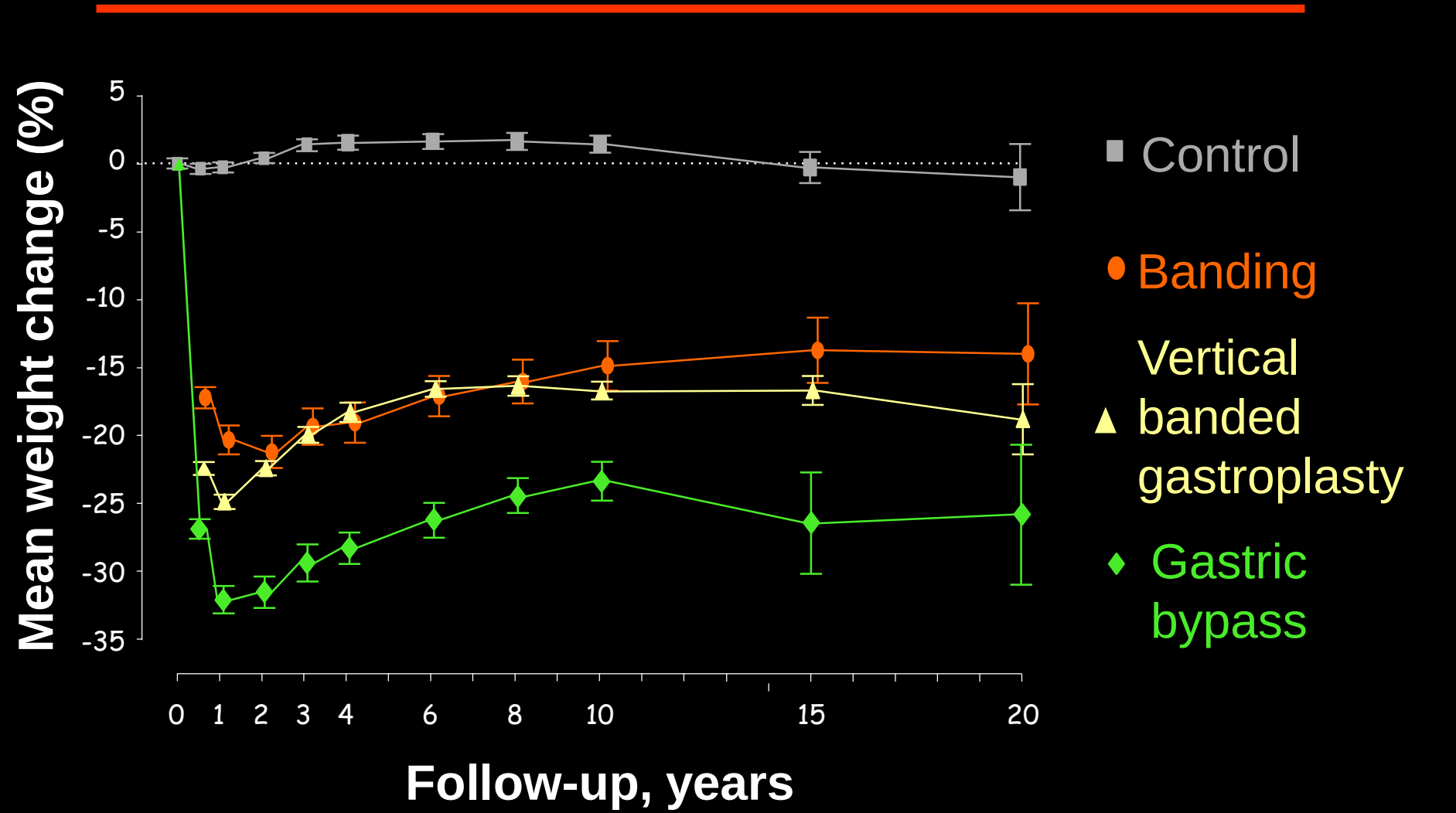
- Via neurons in the arcuate nucleus



Brain Regions Activated in Response to Palatable Food or Food-Associated Cues

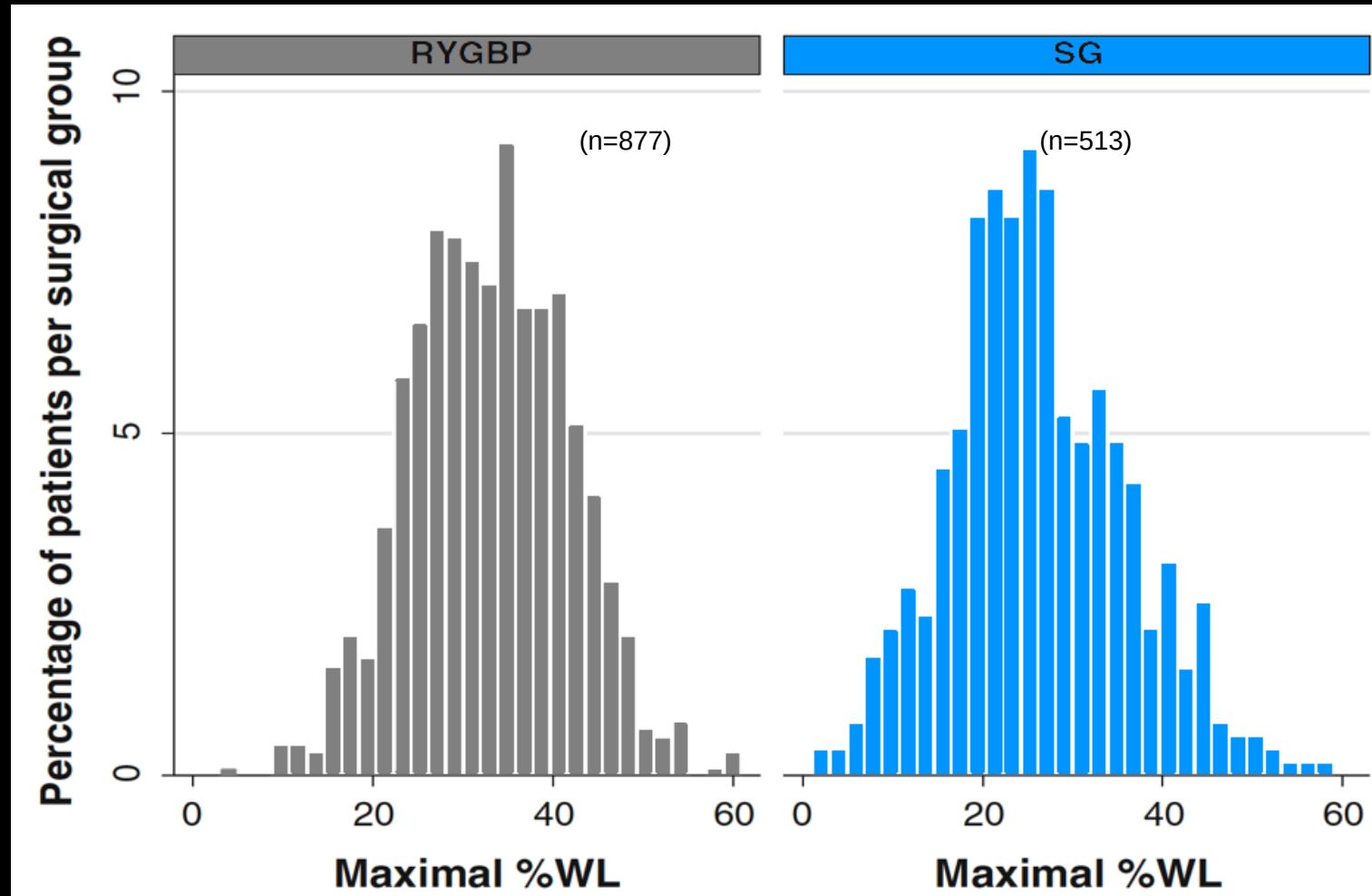


Body weight change: Swedish Obese Subjects study



Sjöström L, et al. JAMA 2012; 307:56–65.

Distribution of weight loss after bariatric surgery

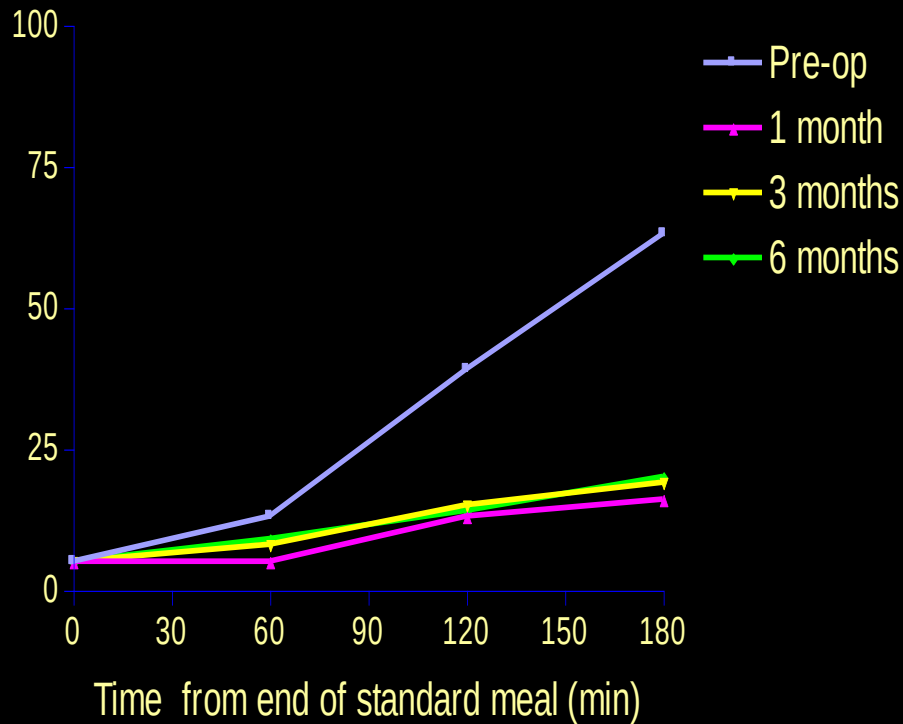


RYGBP, Roux-En Y gastric bypass; SG, sleeve gastrectomy.

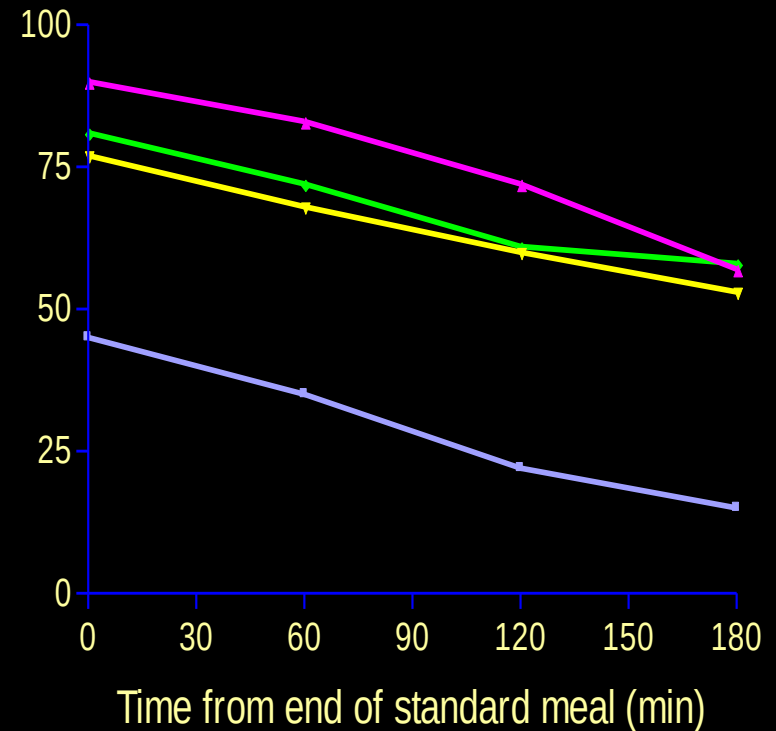
Manning et al. Surg Endosc 2015;29:1484–91.

Visual analogue scores

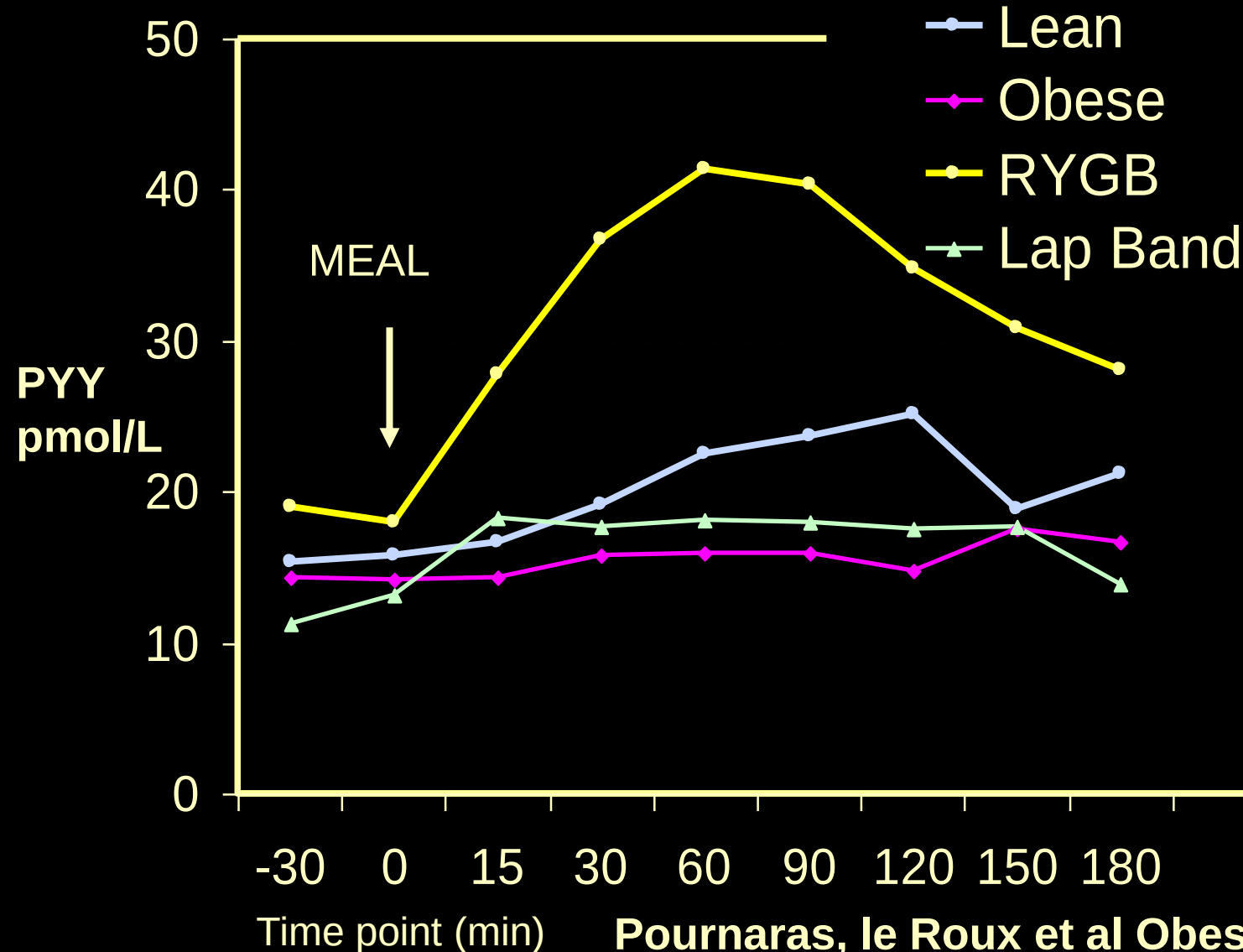
VAS - How hungry are you?



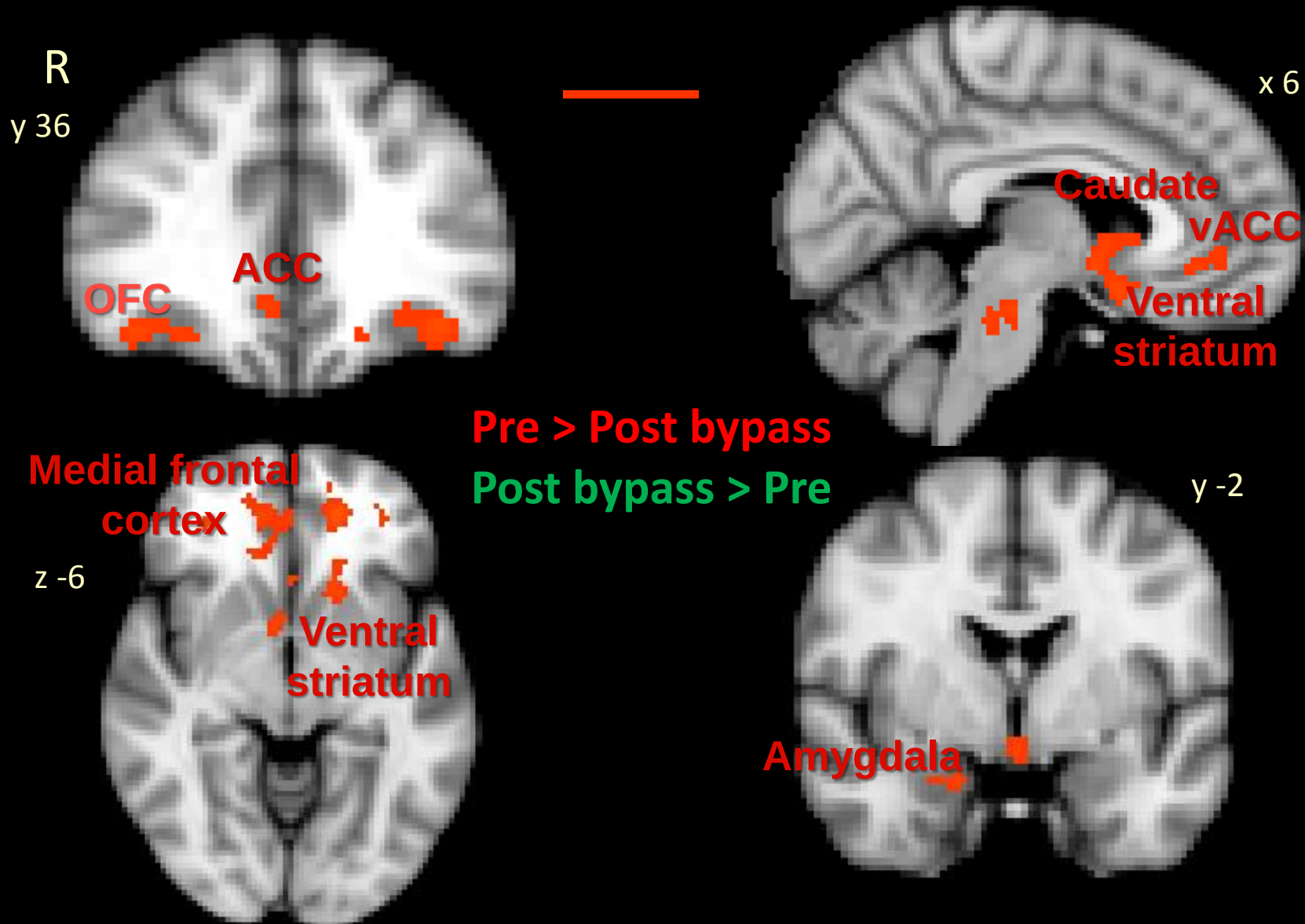
VAS - How full are you?



PYY response after bariatric surgery



↓ Activation to *High-Calorie Foods* after Gastric Bypass

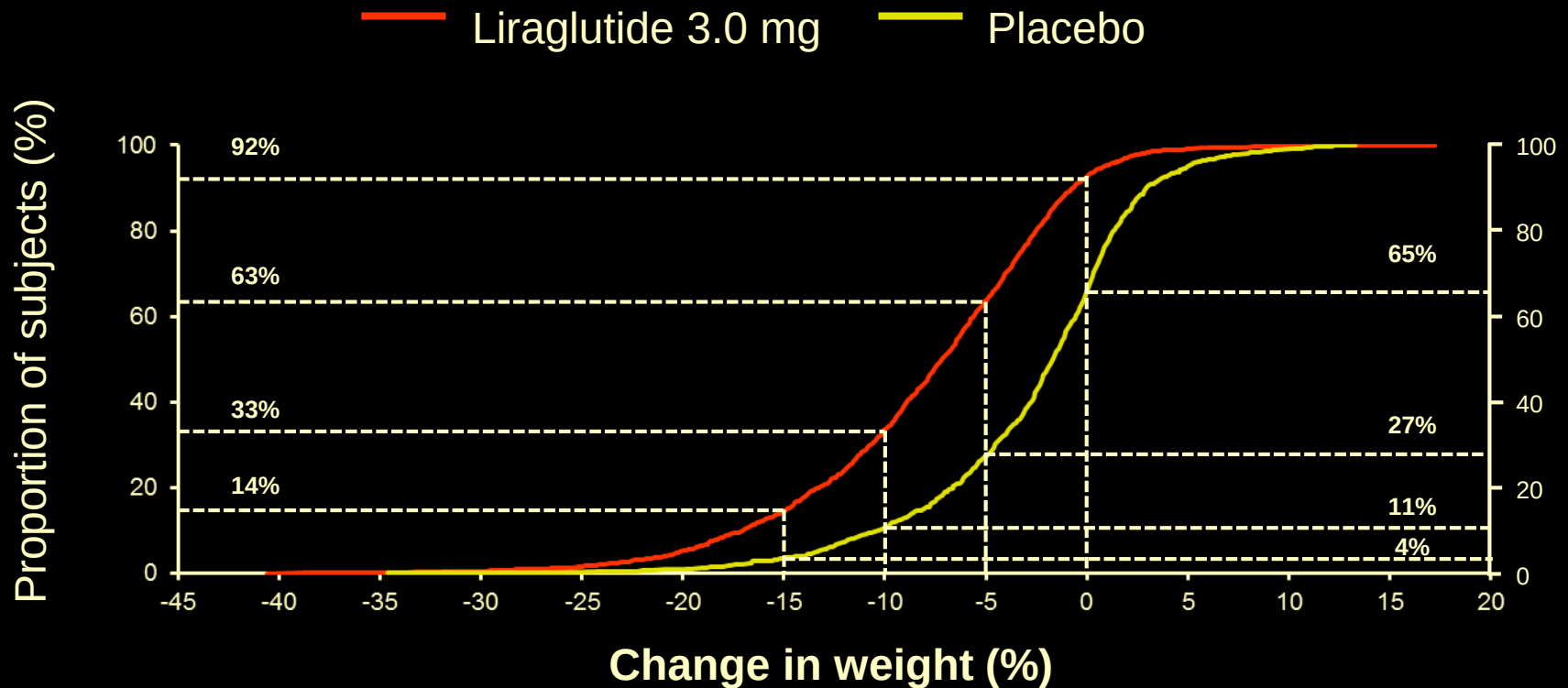


High-calorie food > Objects, n=19, cluster threshold $Z > 2.1$, $P < 0.05$

Scholtz, Miras, le Roux, Goldstone et al Gut 2013

Distribution of weight loss on liraglutide 3.0 mg

Week 0–56



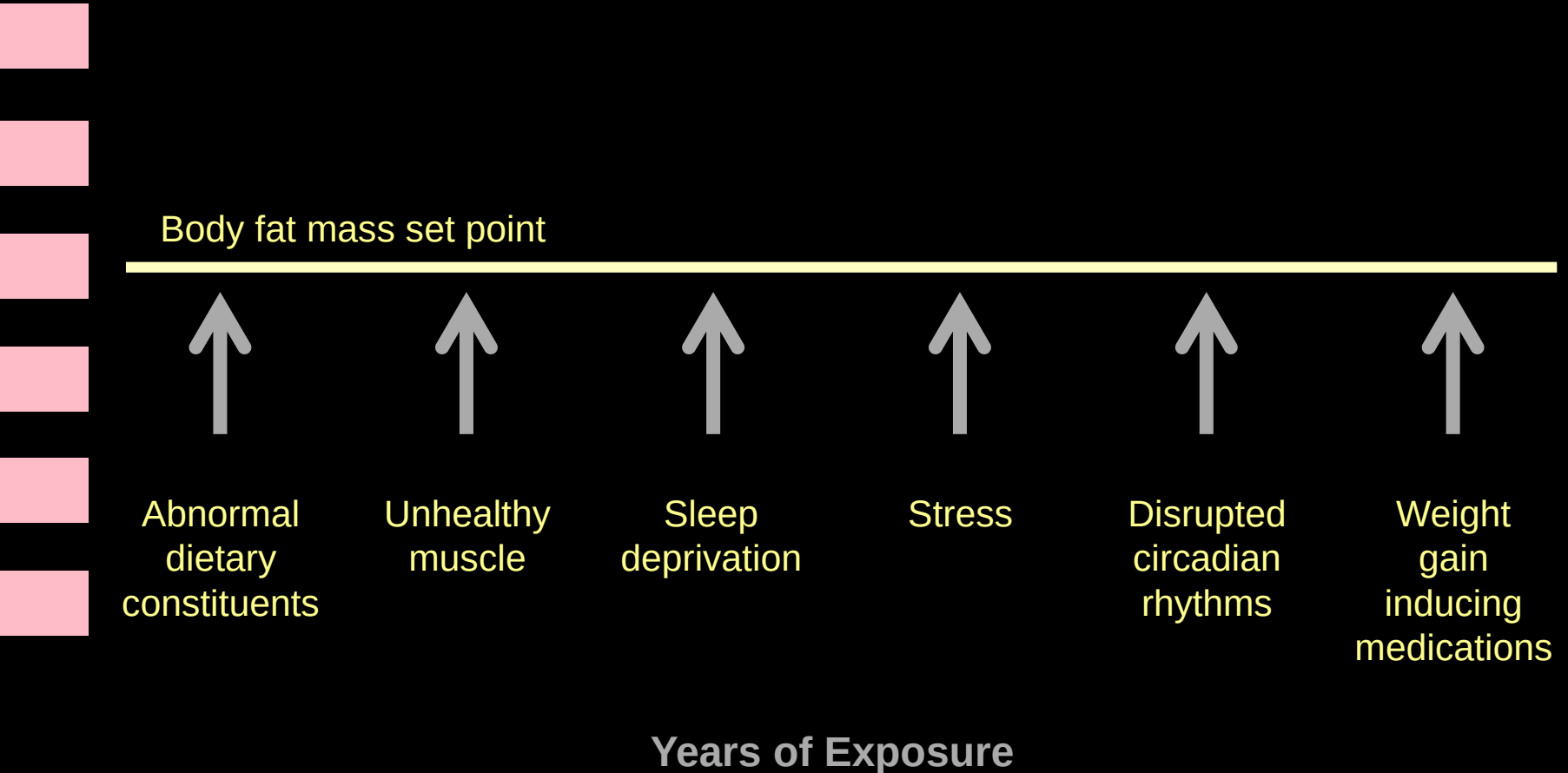
FAS, fasting visit data only, LOCF. Graphs are empirical cumulative distribution functions.
FAS, full analysis set; LOCF, last observation carried forward

The tools of the future?

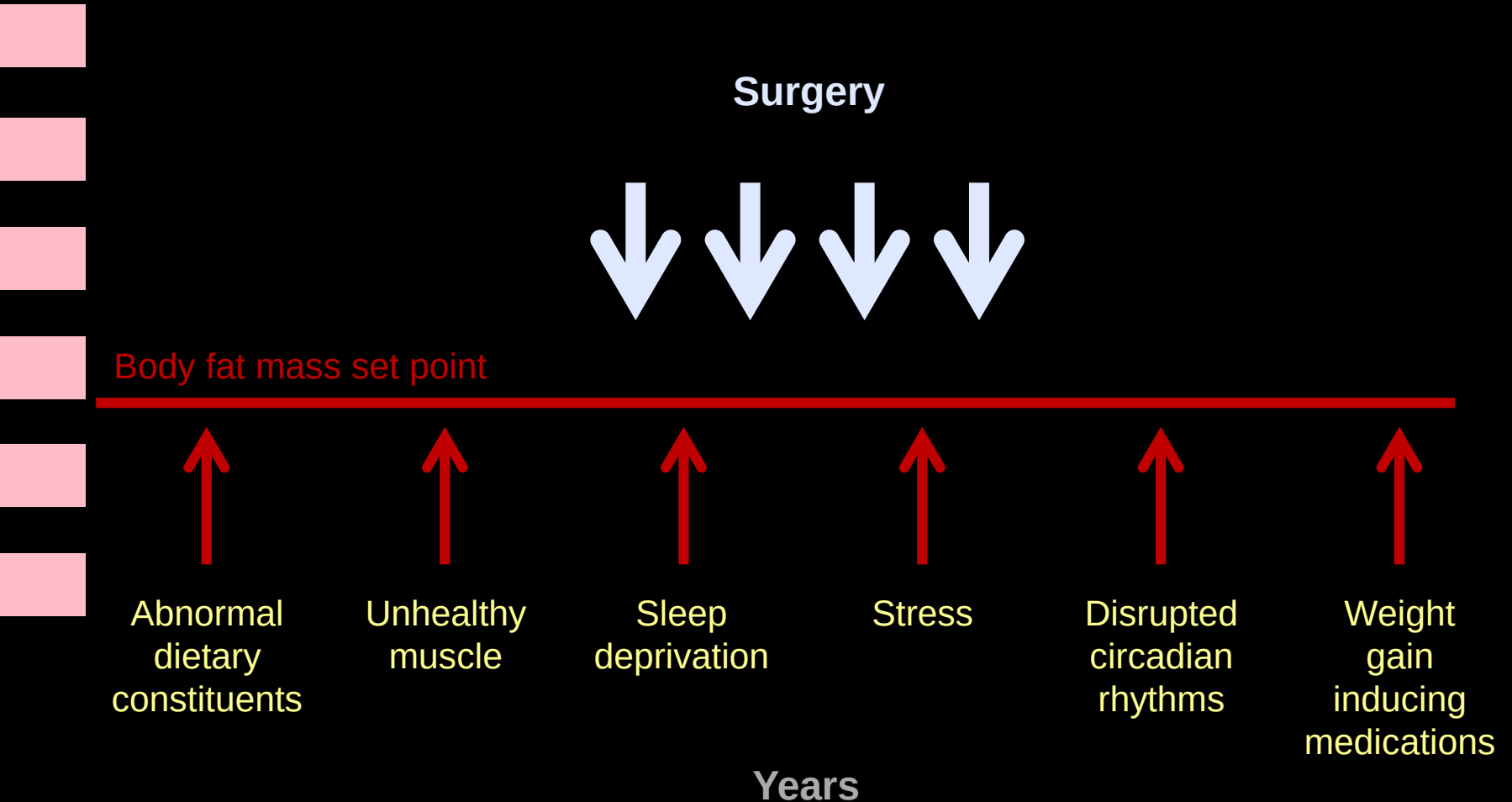
Early Stage	Phase 1	Phase 2a	Phase 2b	Phase 3	Regulatory/ approved
PYY Ligand J&J ¹ Genentech ² Novo Nordisk ³ Takeda ⁴	GLP-1/Glucagon dual agonist OPKO ⁹ J&J ¹⁰ BI/Zealand ⁹ Novo Nordisk ³	NPY5 antagonist Shionogi ¹⁴	SGLT1/2i Novartis ¹⁸	SGLT2/Phen Cana/phen ¹⁸	GLP-1R agonist Liraglutide ^{19,20}
MC4R Agonist Palatin ⁵	Amylin BI/Zealand ¹¹ Novo Nordisk ³	GLP-1R agonist Sanofi ¹⁵	GLP-1/Glucagon dual agonist AstraZeneca ¹⁸	MAOI Tosofensine ¹⁸	CNS Combos Phentermine/topiramate ²⁰ Naltrexone/bupropion ^{19,20}
MIC-1/GDF-15 Amgen ⁶	Amylin/Calcitonin dual agonist Lilly/Nordic ¹²	Ghrelin analogue Alizé ¹⁶	Amylin/Calcitonin dual agonist KeyBioscience ¹⁸	GLP-1R/GCG SAR425899 ⁹	5HT2cR agonist Lorcaserin ²⁰
NMUR2-agonist Takeda ⁷	GIP/GLP-1/Glucagon triple agonist Novo Nordisk ³	GOAT inhibitor Takeda ¹⁷	MetAP2 inhibitor Nordic ¹⁸	GLP-1R agonist Semaglutide ³	
GLP-1/GIP Zealand ⁸	Anti-FGFR1/KLB Genentech ¹³		Activin T2R mAb Novartis ¹⁸		

1. Shoblock JR et al. Psychopharmacology (Berl) 2010;208:265–77; 2. Loktev AV, Jackson PK. Cell Rep 2013;5:1316–29; 3. Novo Nordisk Pipeline: <https://www.novonordisk.com/rnd/rd-pipeline.html>; 4. Nishizawa N et al. ACS Med Chem Lett 2017;8:628–31; 5. Palatin MC4r agonist: <https://www.palatin.com/assets/Obesity-Diabetes-Jan2016-2.pdf>; 6. Xiong Y et al. Sci Transl Med 2017;9. pii:eaan8732; 7. Nishizawa N et al. Bioorg Med Chem Lett 2017;27:4626–9; 8. Nørregaard PK et al. Diabetes Obes Metab 2018;20:60–8; 9. Sánchez-Garrido MA et al. Diabetologia 2017;60:1851–61; 10. Kang J et al. Diabetologia 2015;58(Suppl 1):A#791; 11. Boehringer-Ingelheim/Zealand Amylin: <https://labiotech.eu/boehringer-ingelheim-zealand-diabetes/>; 12. Lilly/Nordic Amylin/Calcitonin: <https://investor.lilly.com/releasedetail.cfm?releaseid=1029518>; 13. Genentech FGFR1/KLB: <https://www.gene.com/medical-professionals/pipeline>; 14. Shionogi Pipeline: http://www.shionogi.co.jp/en/ir/pdf/pdf_09/development09.pdf; 15. Sanofi Pipeline: https://www.sanofi.com/-/media/Project/One-Sanofi-Web/Websites/Global/Sanofi-COM/Home/common/docs/science-and-innovation/Q3_2018_PostBoard_RnD_Mention-slide36-37-39.pdf?la=en&hash=03E2AC15C25A35FFD48D1185E30AACA4AC3789AC; 16. Allas S et al. PLoS One 2018;13:e0190849; 17. Kojima M et al. J Biochem 2016;160:189–94; 18. Clinicaltrials.gov; 19. FDA label: <https://www.fda.gov/>; 20. EMA SmPC: <http://www.ema.europa.eu/ema/>.

Obesity and Its Care: A Battle of Forces that Influence the Fat Mass Set Point

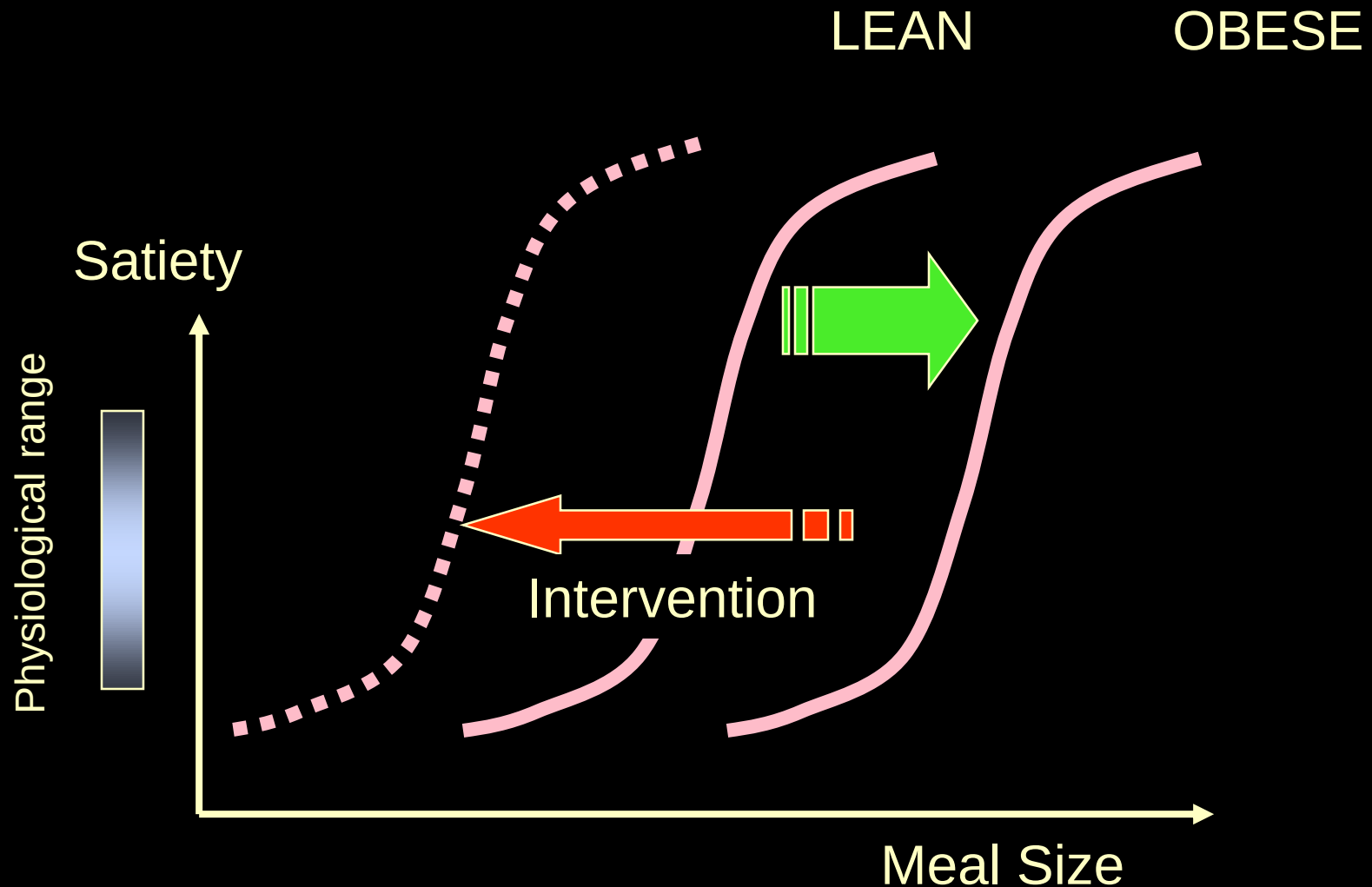


Obesity and Its Care: A Battle of Forces that Influence the Fat Mass Set Point

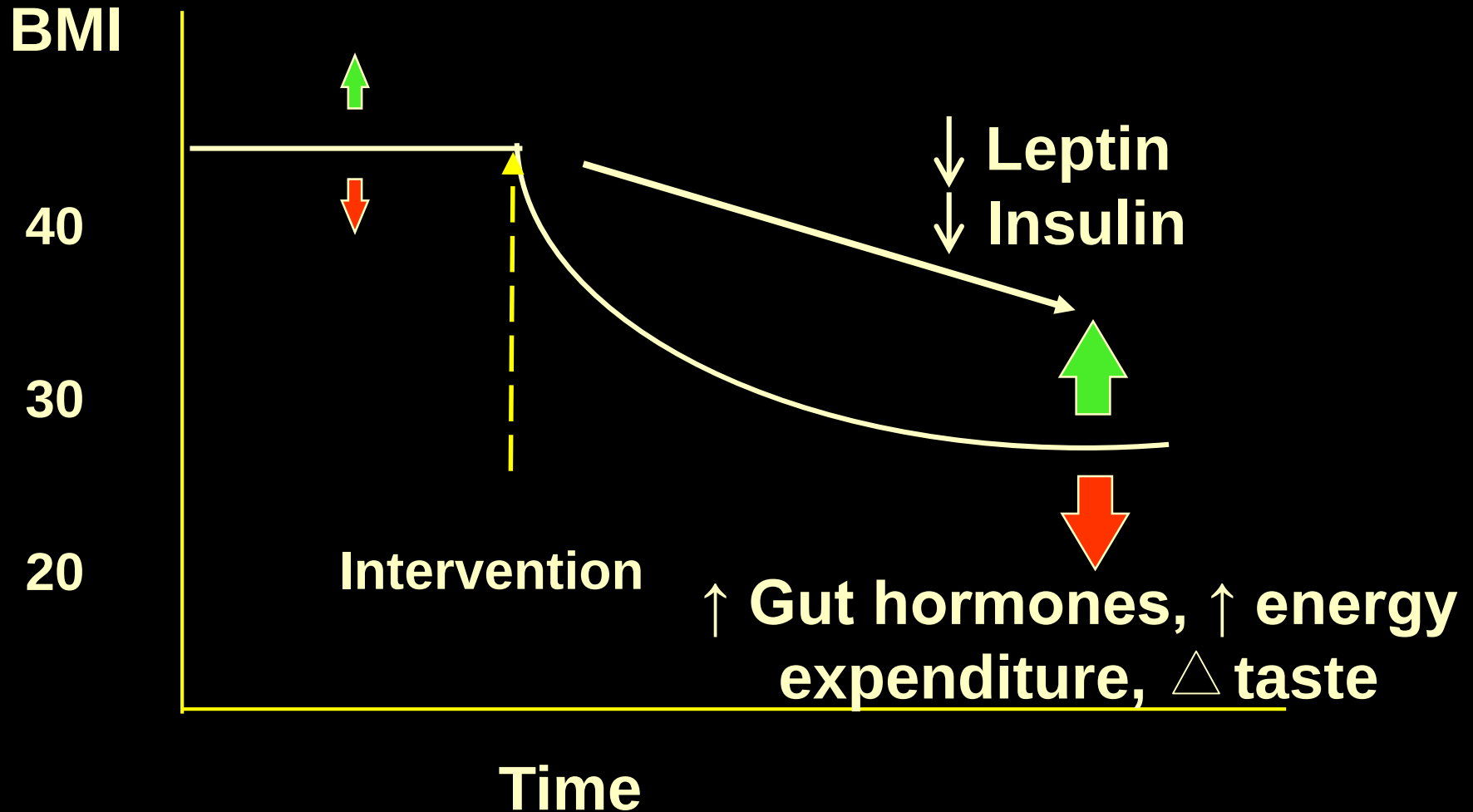


Dose response curve

Miras and le Roux. Cell Metabolism 2017



Hypothesis





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