

What drives us to eat?



brain mechanisms

Seoul National University
Hyung Jin Choi

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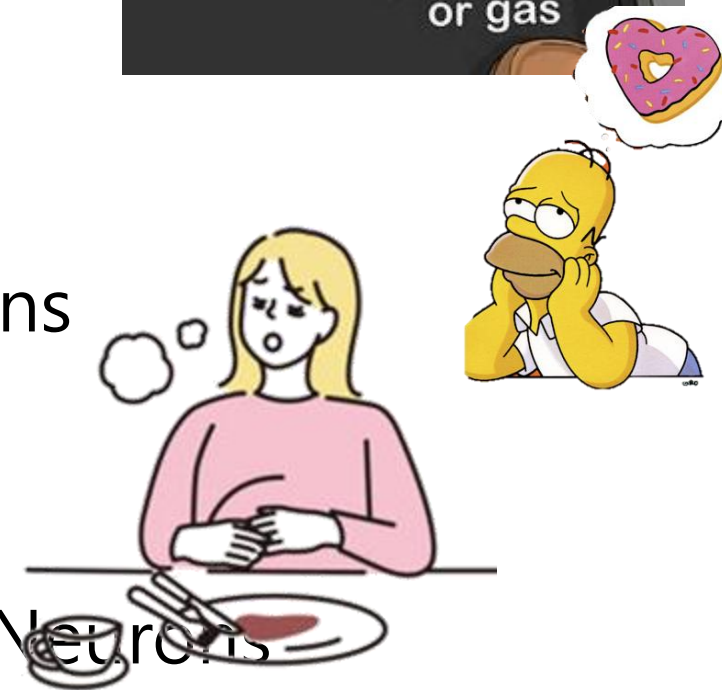
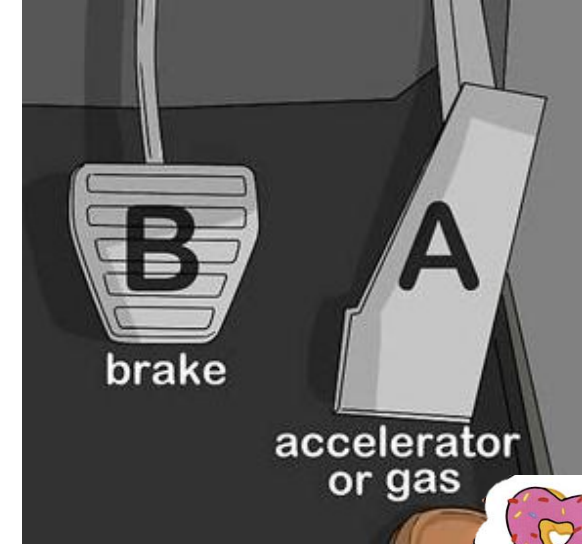
1. Overview- Targets for Metabolic Disease

2. Motivation (=Appetite)

Lateral Hypothalamus Leptin Receptor Neurons

3. Satiety

Dorsomedial Hypothalamus GLP-1 Receptor Neurons



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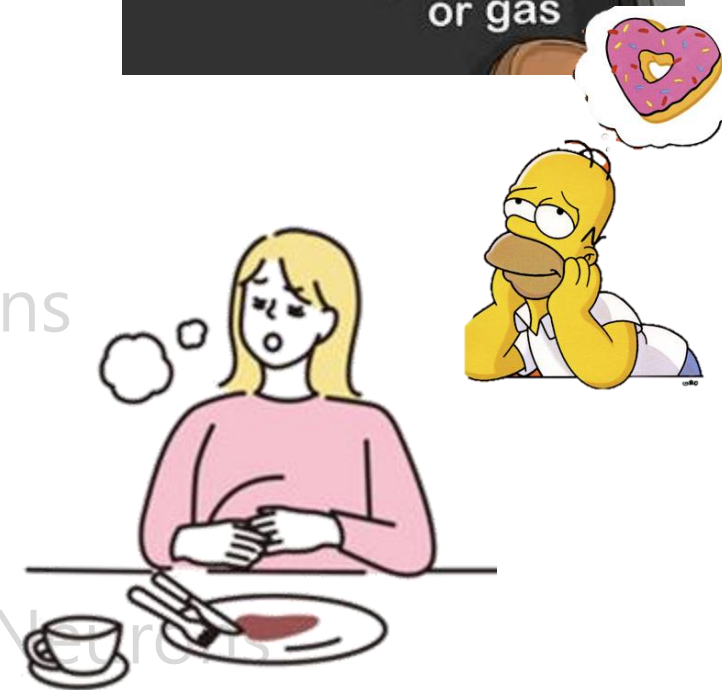
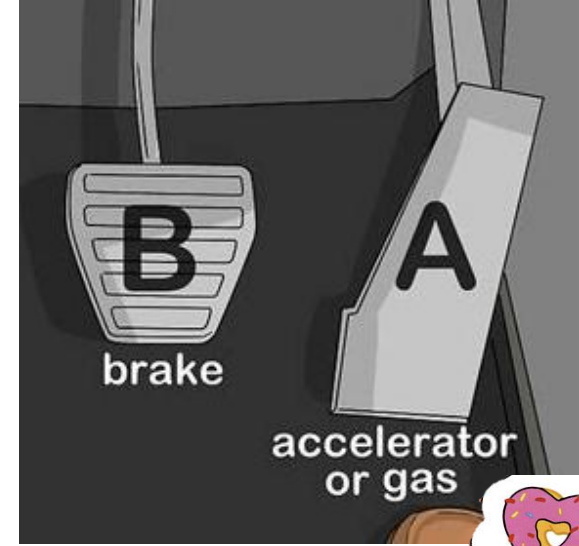
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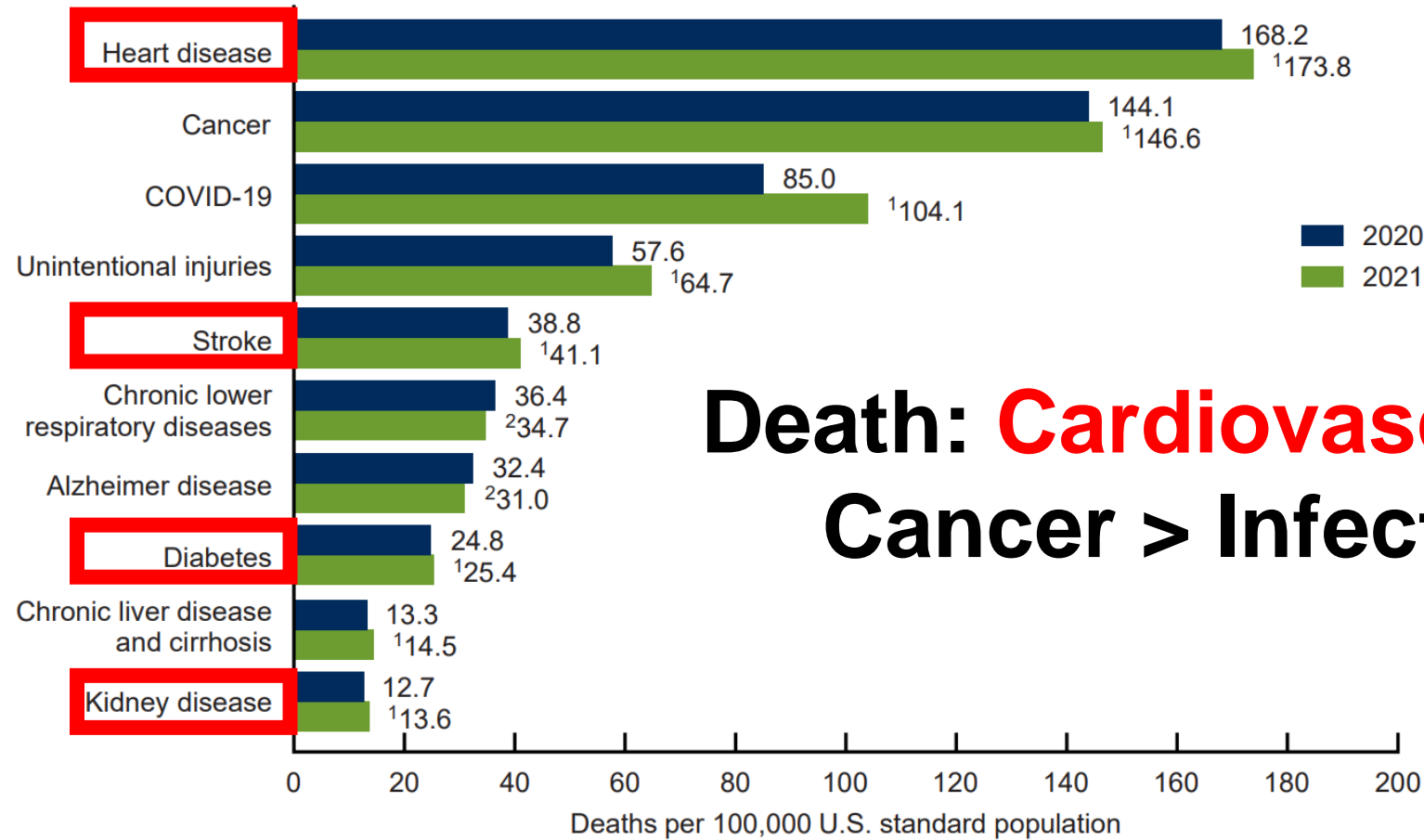
3. Satiety

Dorsomedial Hypothalamus GLP-1 Receptor Neurons



Modern Health Problem

Obesity, Metabolic Disease, Cardiovascular Death



Death: Cardiovascular > Cancer > Infection

Fundamental Cure

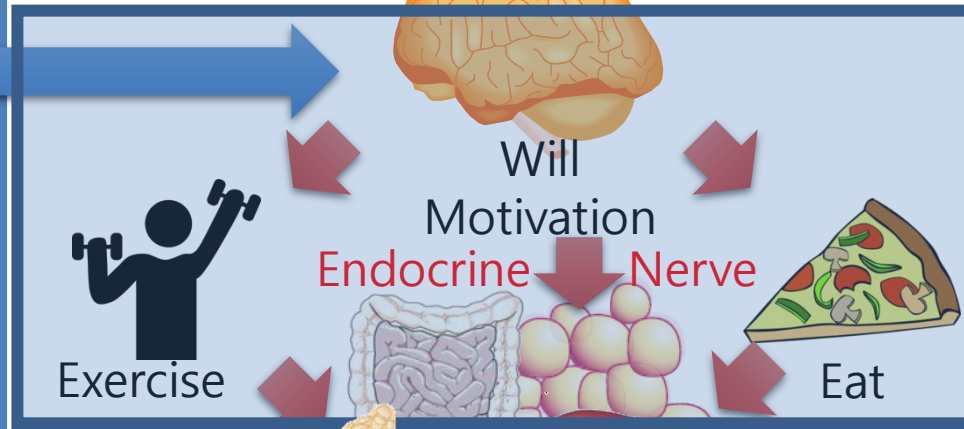


Psychotherapy



Nutritional Education

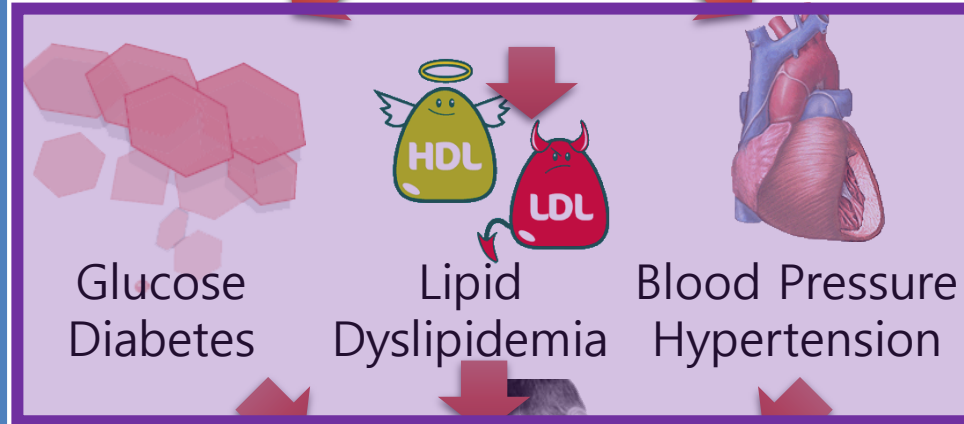
Eating Problem



Metabolic Diseases



Metabolism

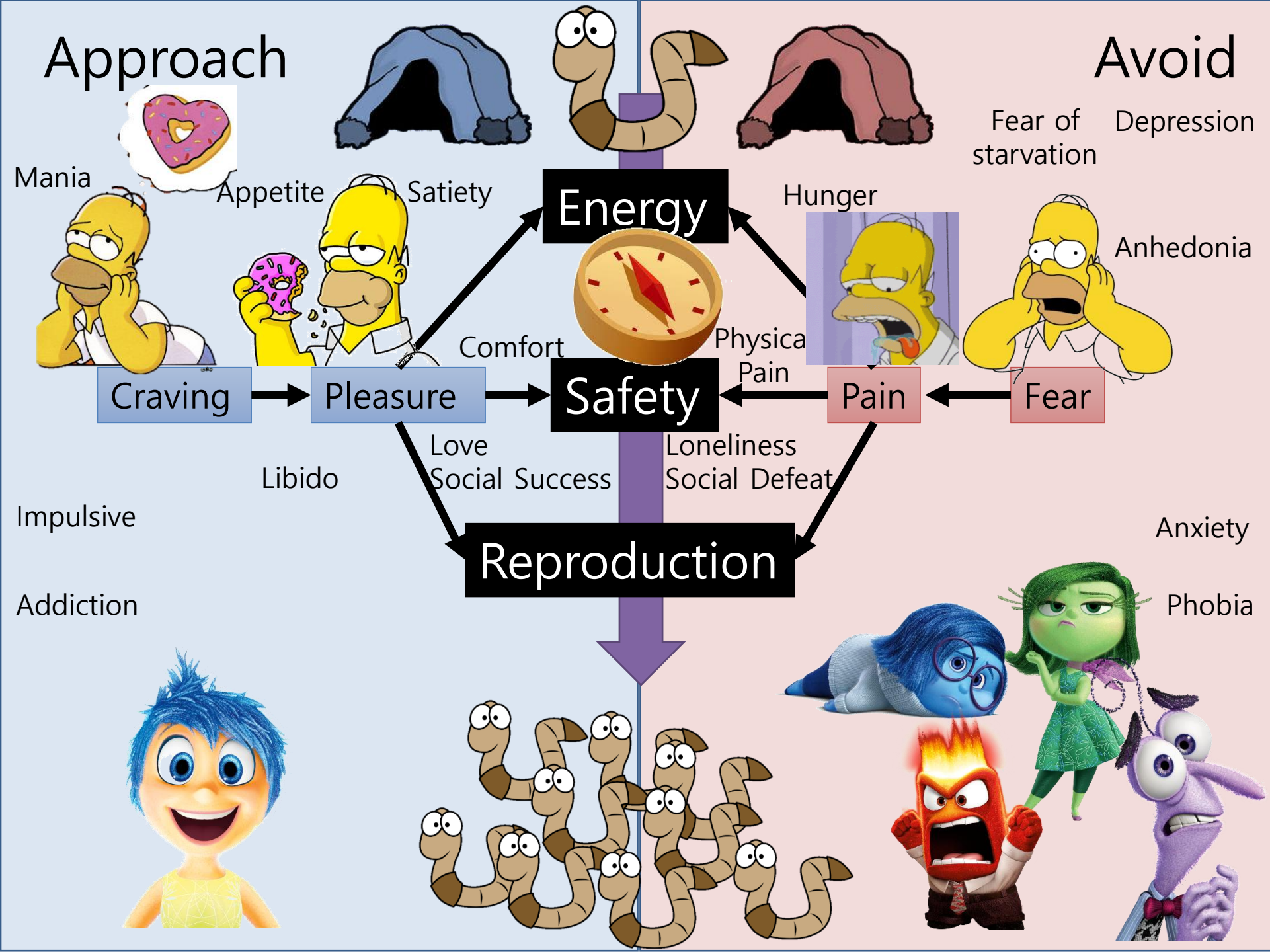


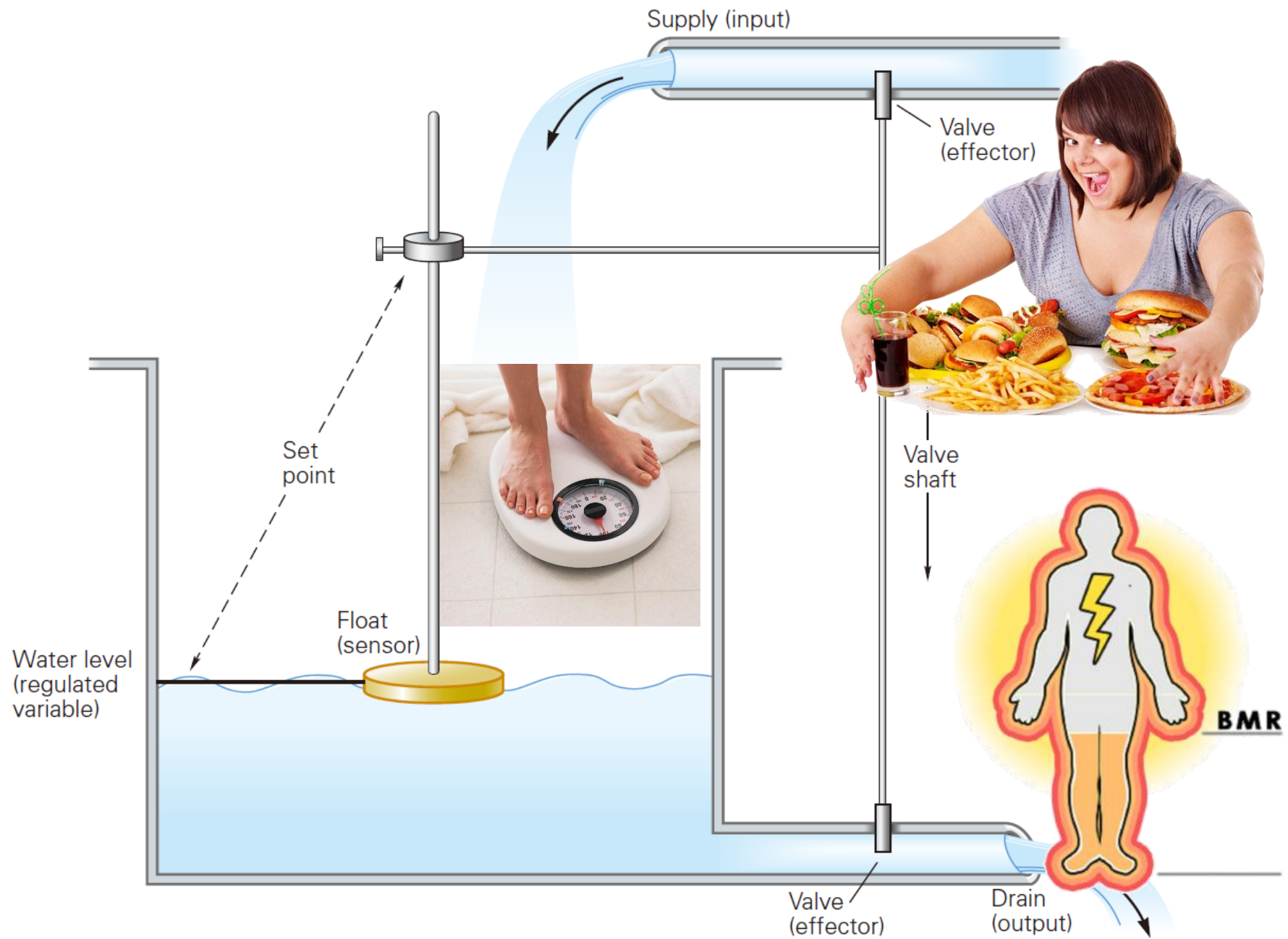
Complications



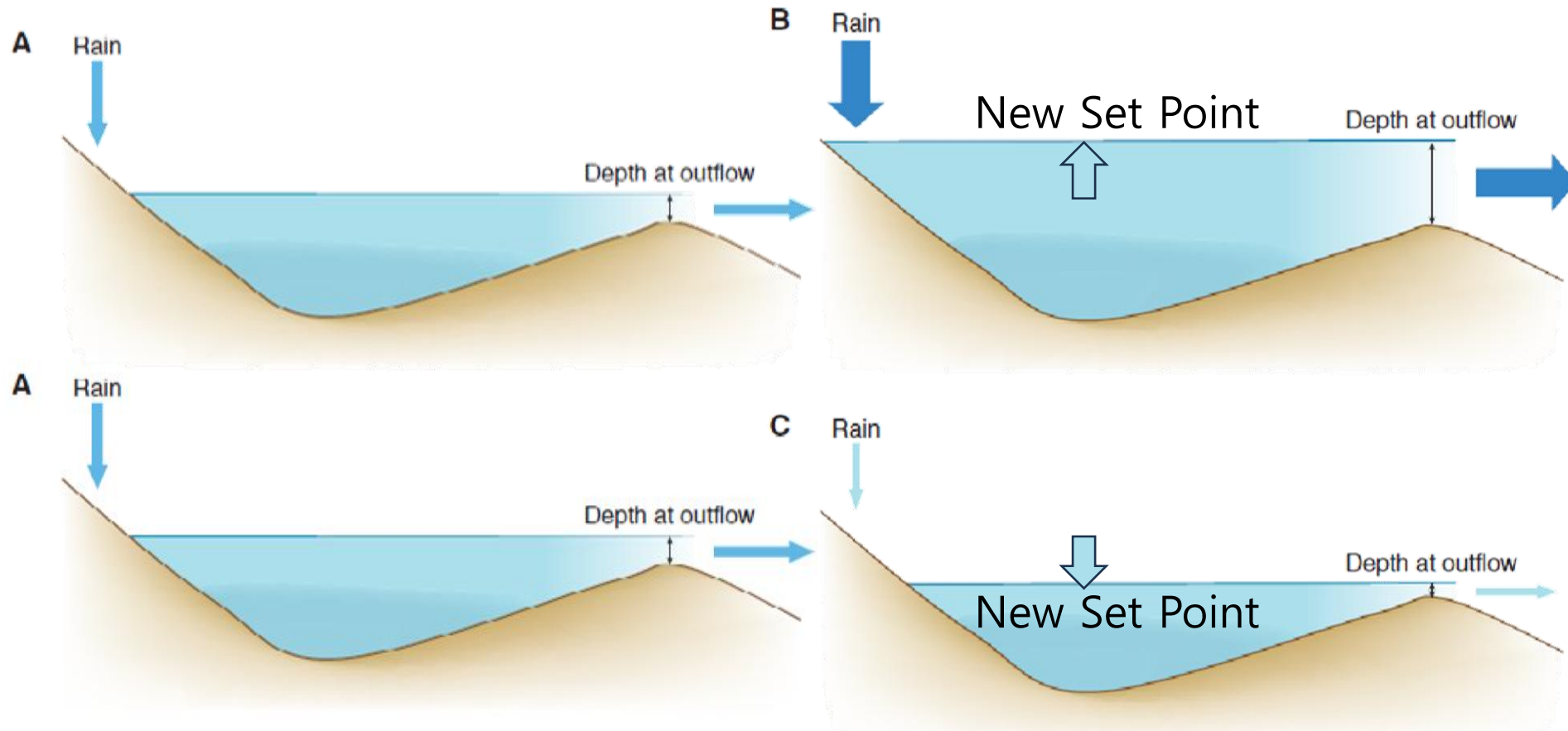
Fundamental Cause?

Rapid Rise of Metabolic and Cardiovascular Disease





Settling Point Model



Modern Obesity

Leptin Deficiency



weight = 40kg, age 3yrs
BEFORE LEPTIN



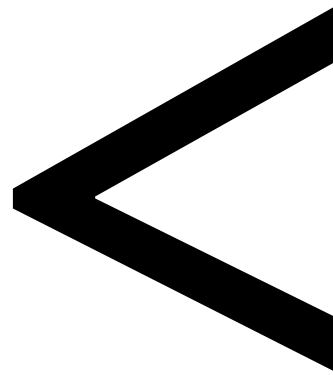
weight = 29kg, age 6yrs
AFTER LEPTIN



Prader
Willi

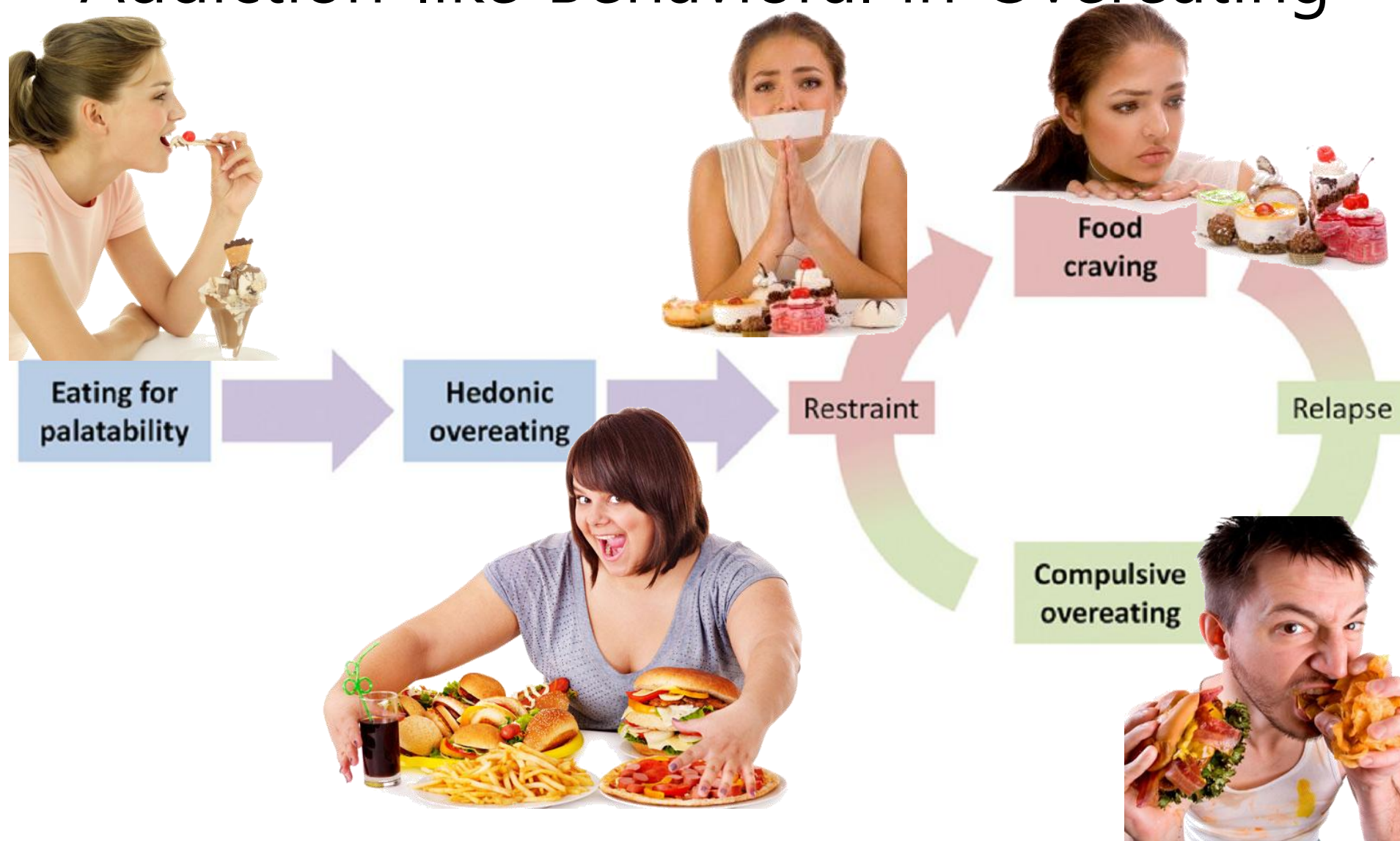


Genetic

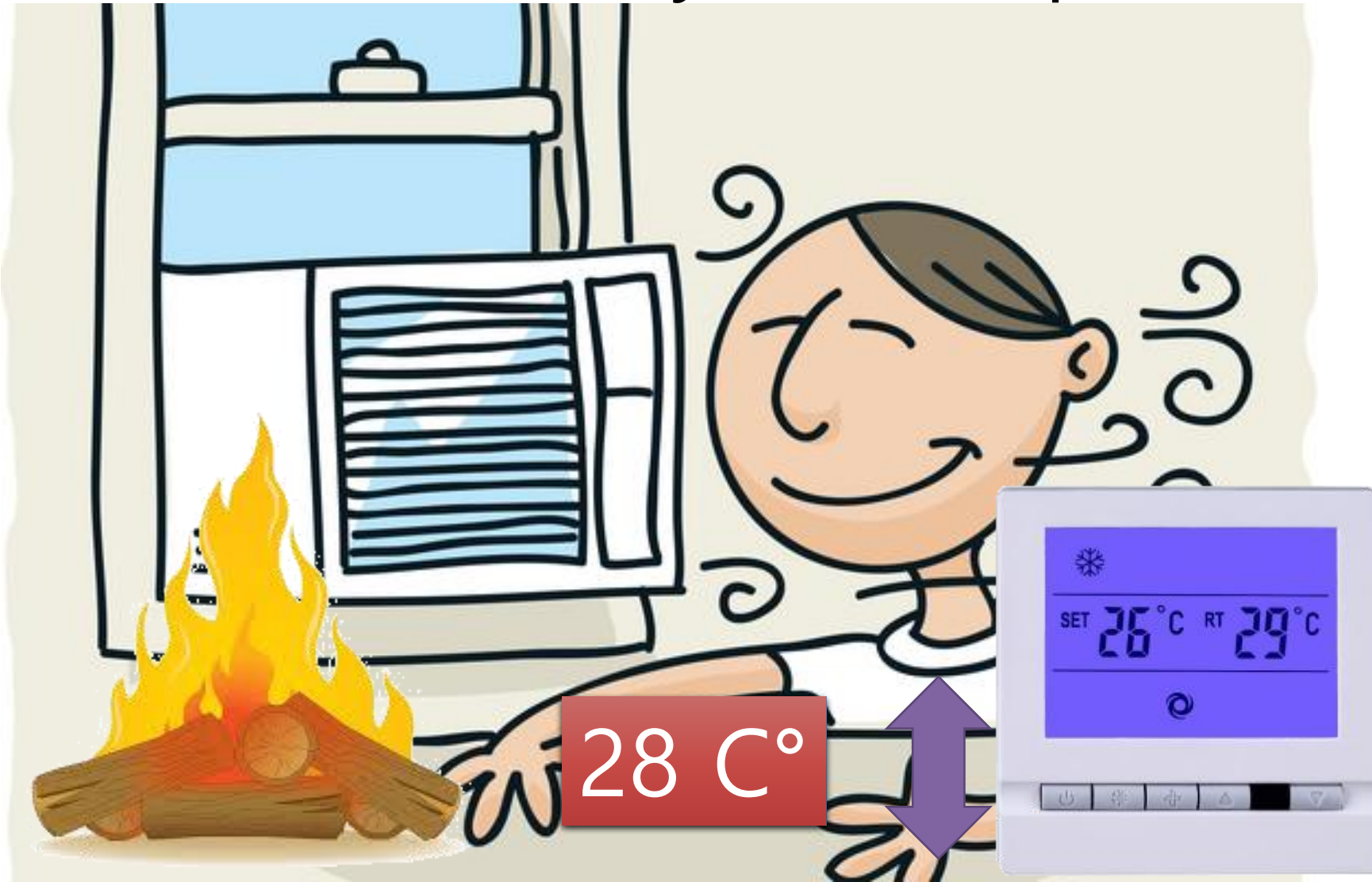


Environmental

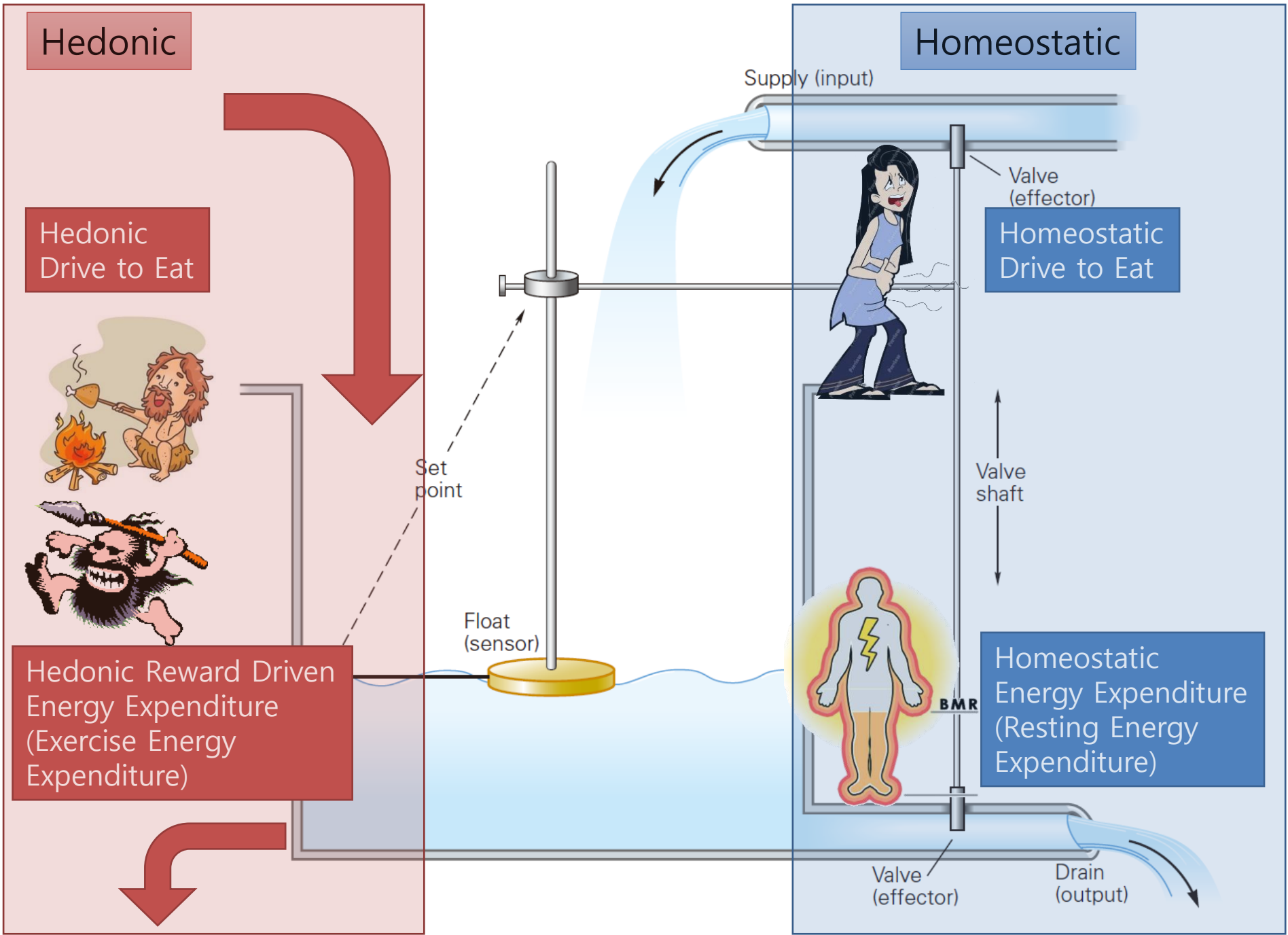
Addiction-like Behavioral in Overeating

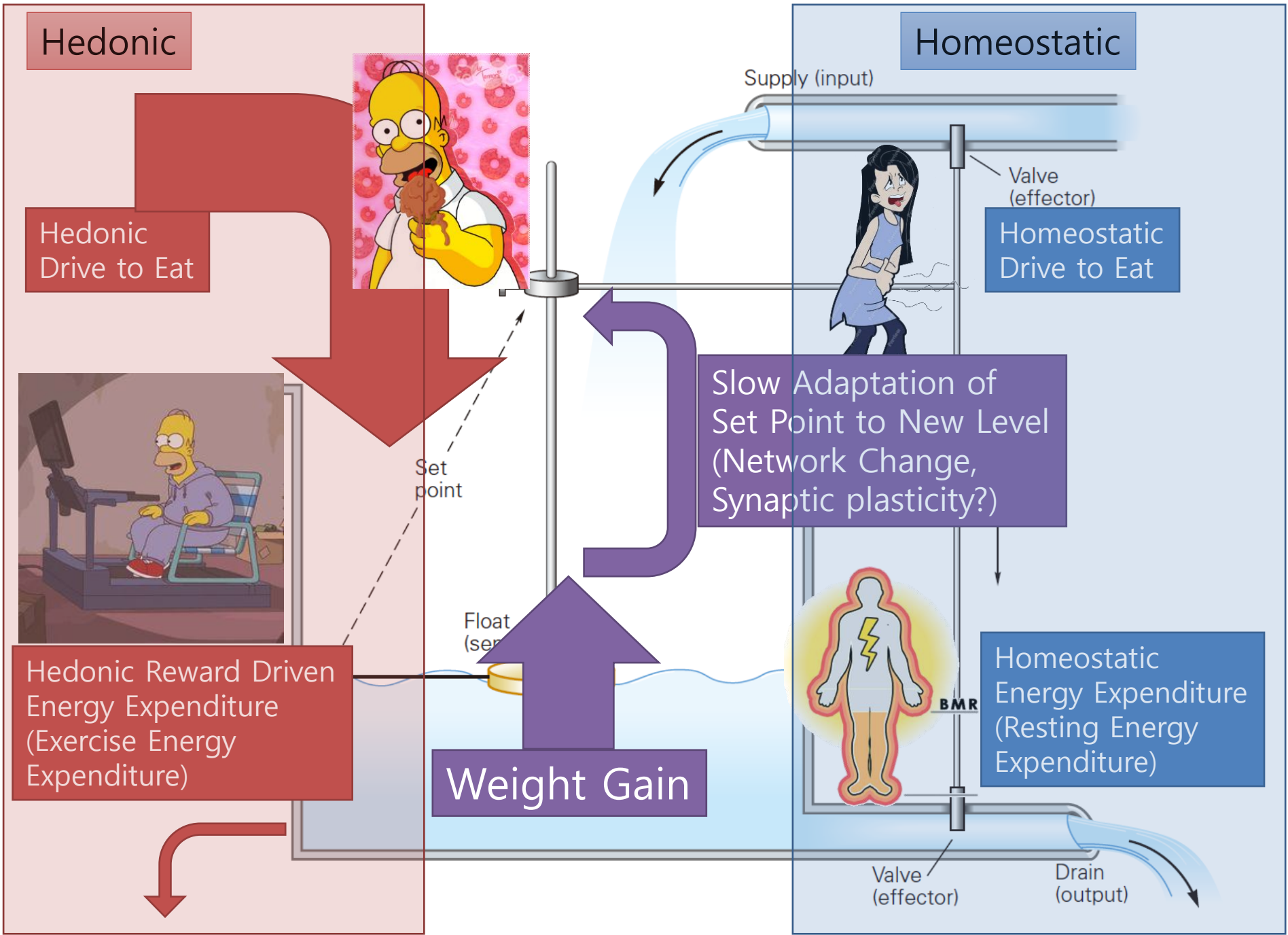


Air Conditioner vs. Fireplace Set Point → Dynamic Equilibrium

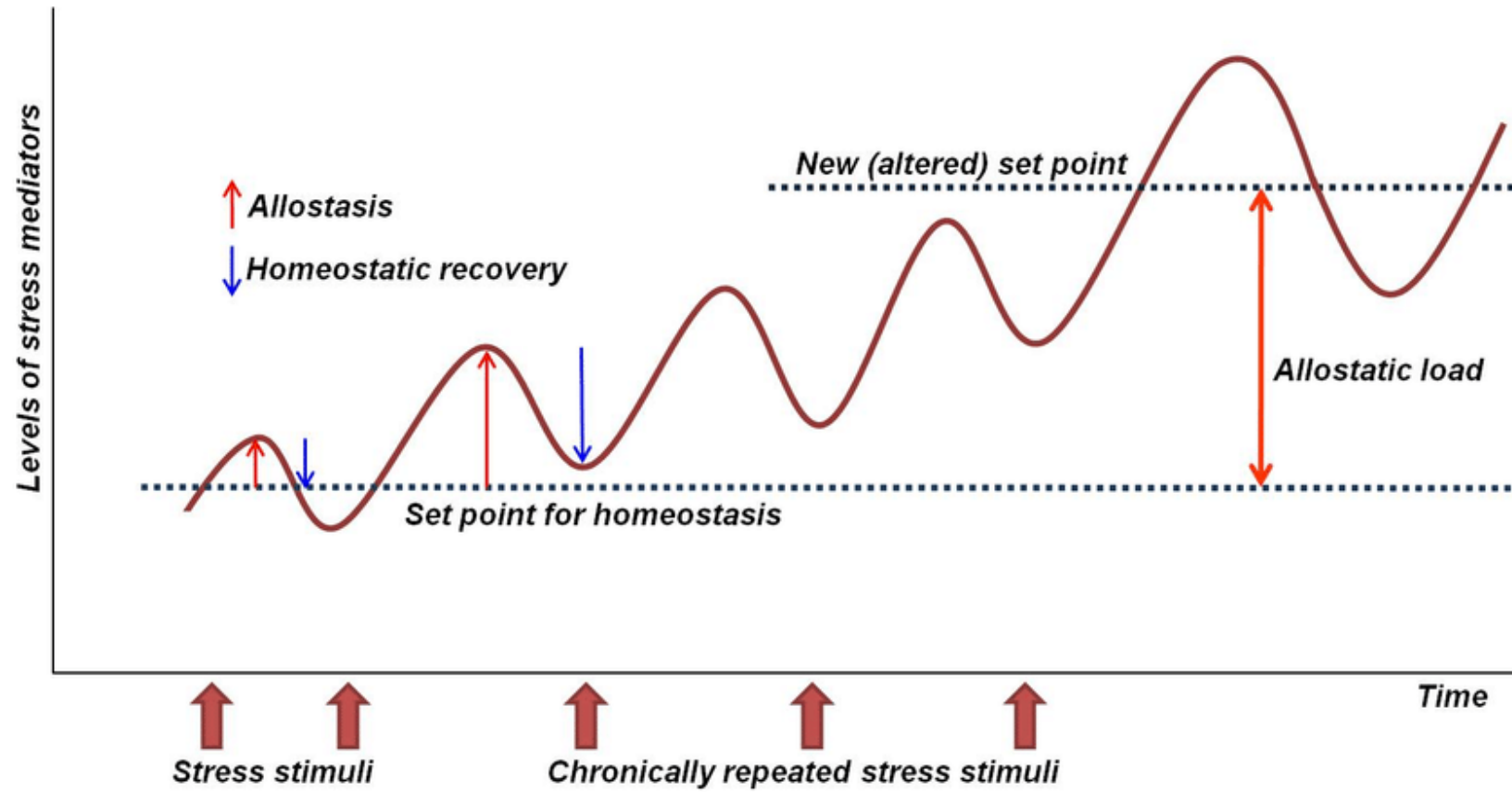


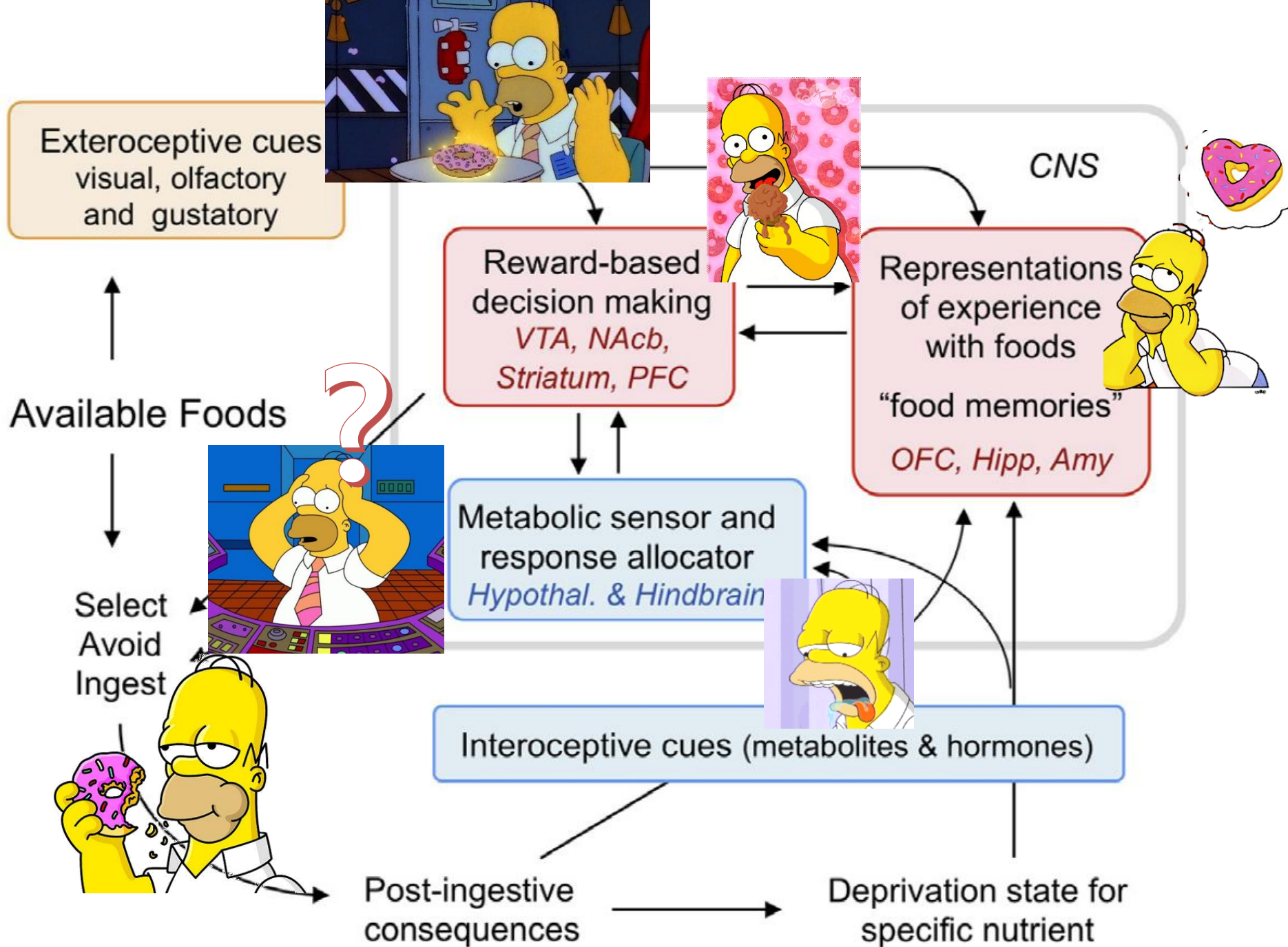




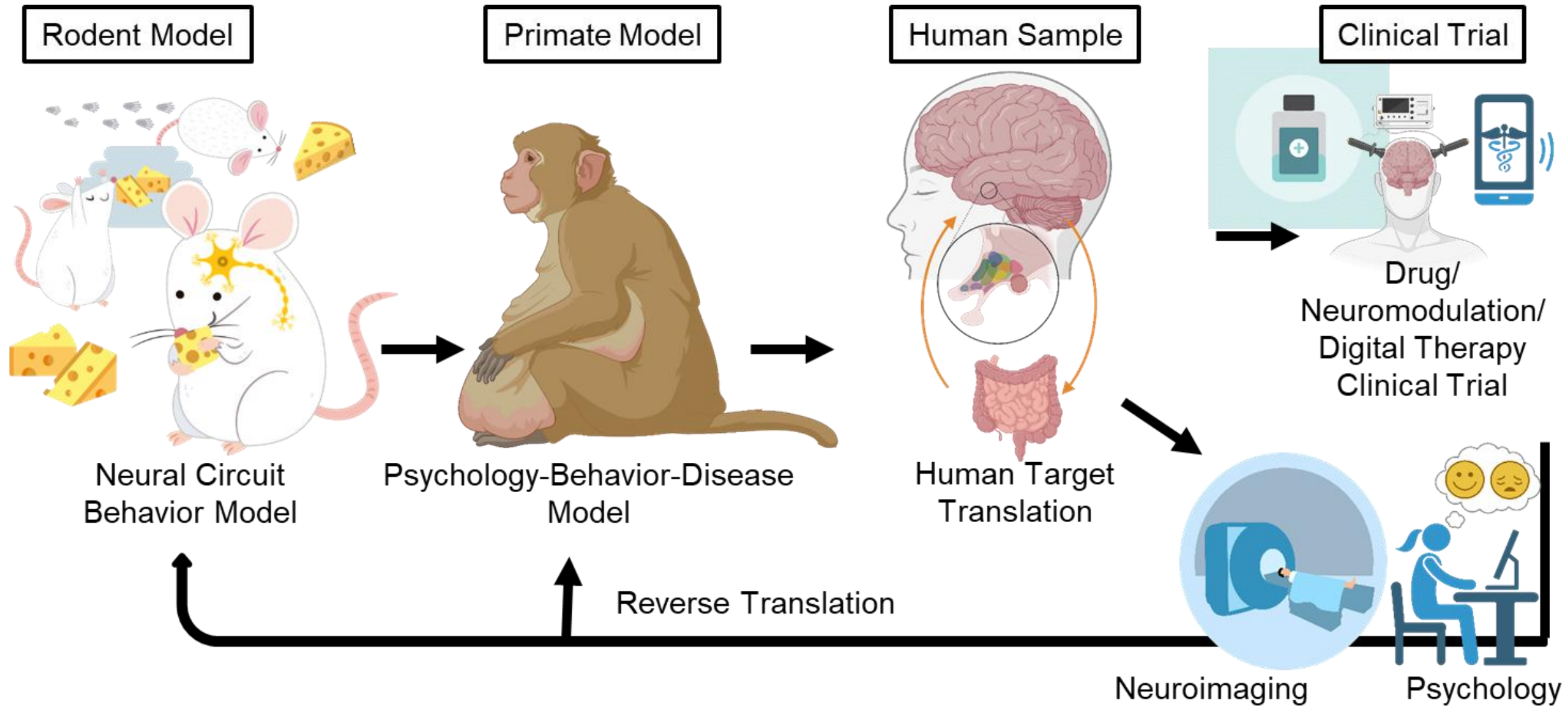


Stress, Allostasis, Allostatic Load





Neuron-Circuit-Psychology-Behavior-Disease Study



Environment

Cognition



Body - Sensory

Auditory

Visual

Olfactory

Touch

Taste

Hormone/Nutrient

Brain

Unconscious

Homeostasis Center
Need Calculation

Cue-driven
Craving
(Learned)

Circadian/
Time

Desire/Fear
Emotion

Impulsivity

Memory

Craving/
Wanting

Pleasure/
Liking

Valence

Conscious

Conflict
Drive

Initiation

Will

Decision

Decision

Decision

Satiation

Satiety

Body - Motor

Search

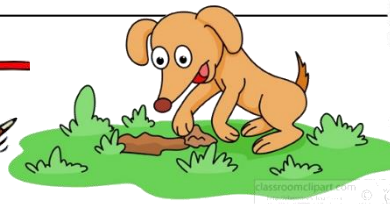
Approach

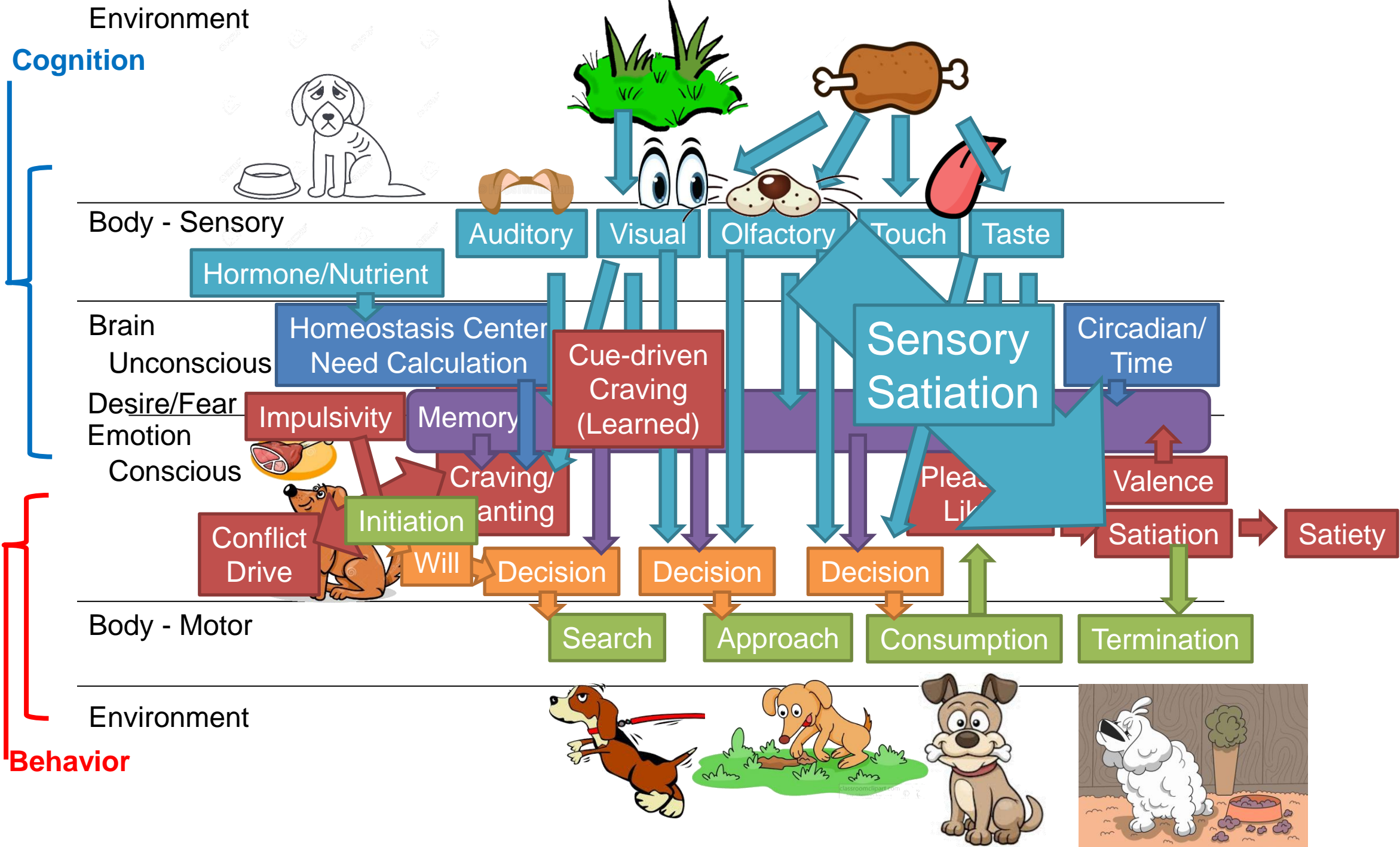
Consumption

Termination

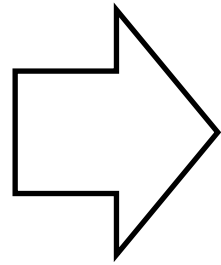
Environment

Behavior

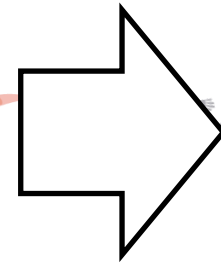




Cognition



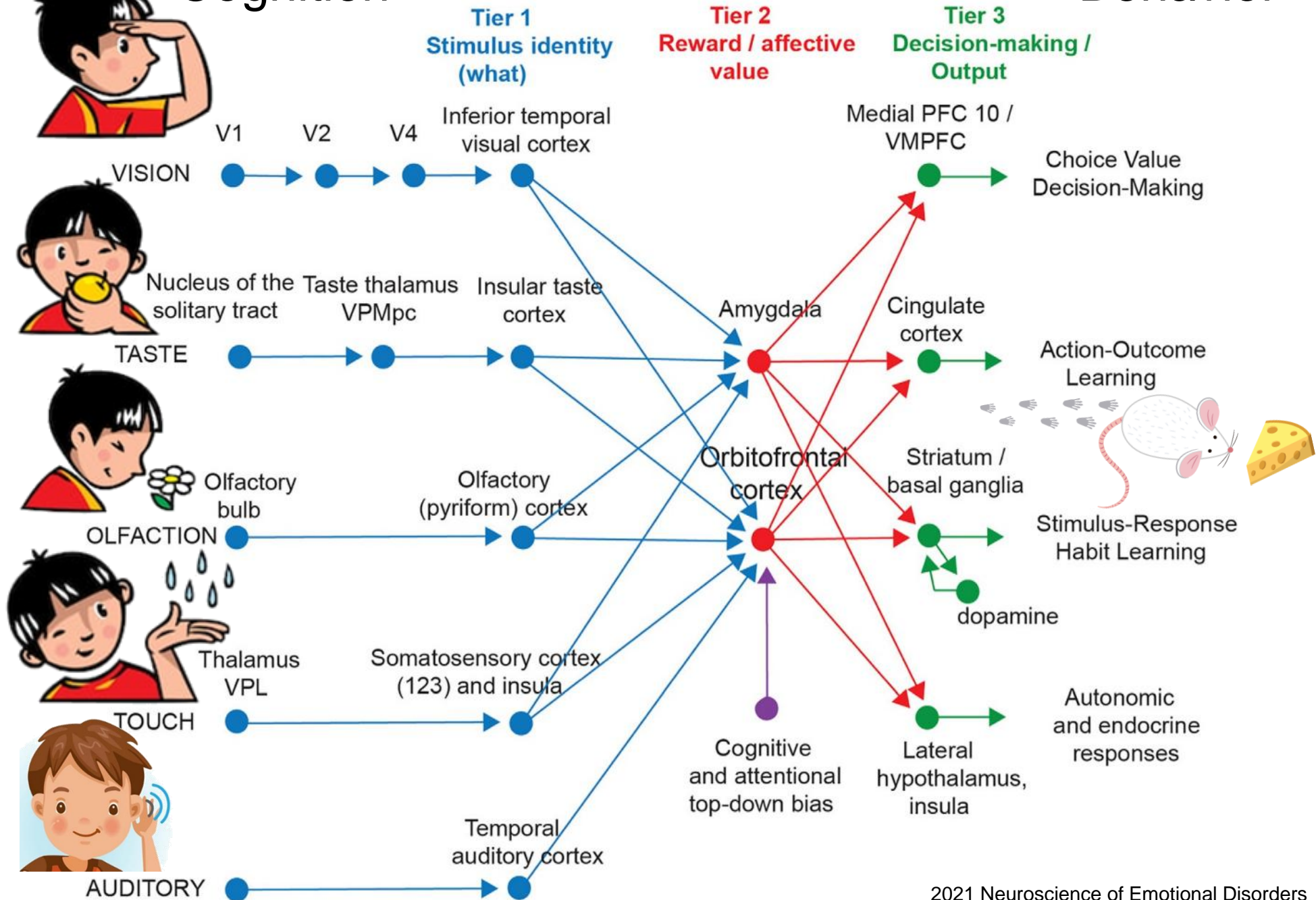
Neuron



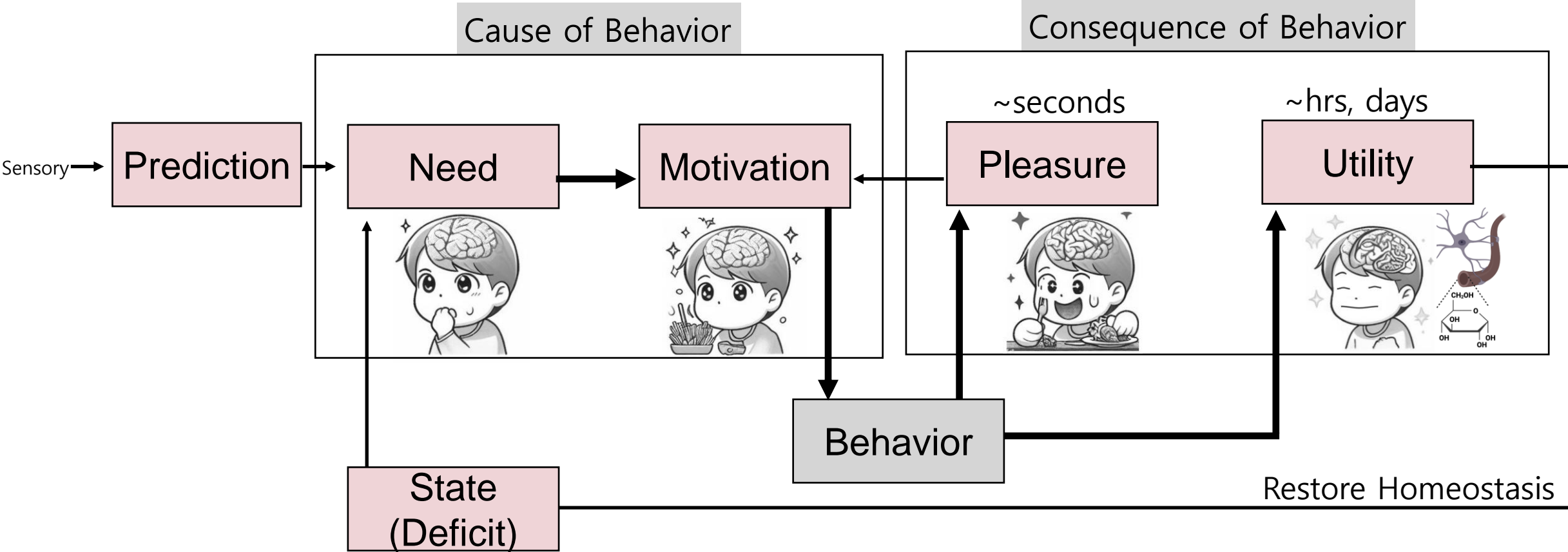
Behavior

Cognition

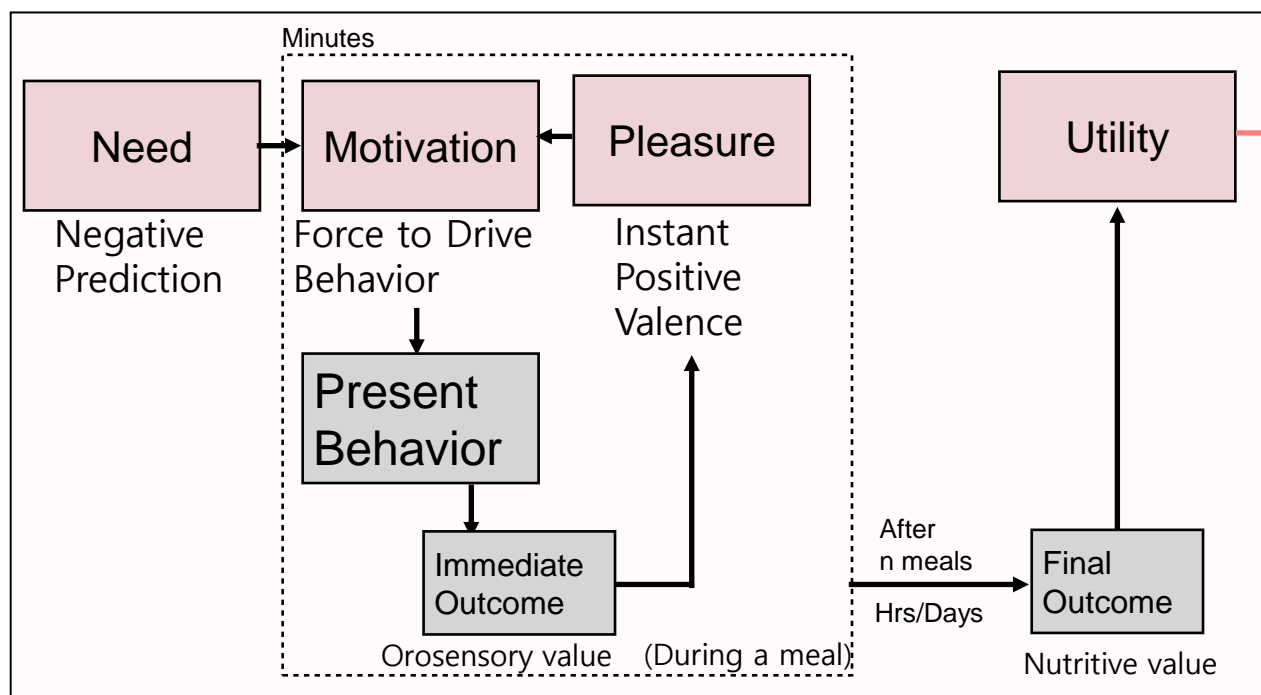
Behavior



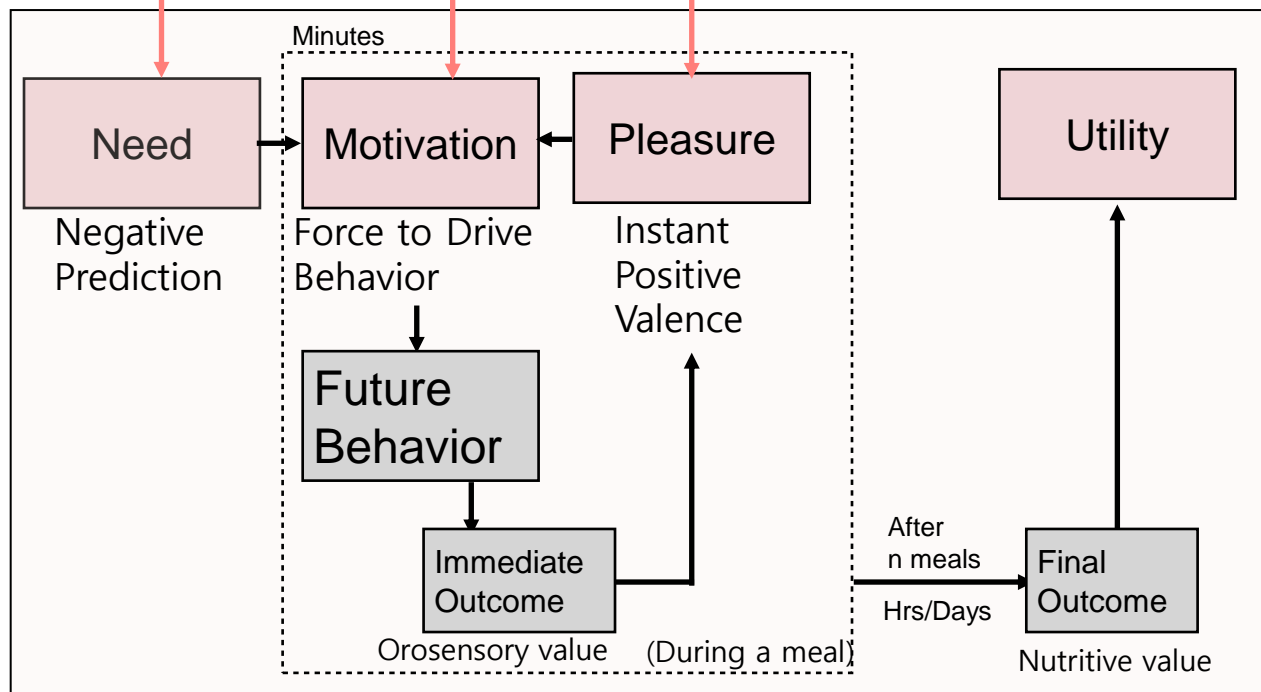
A Unified Theoretical Framework Underlying The Regulation of Motivated Behavior




Present



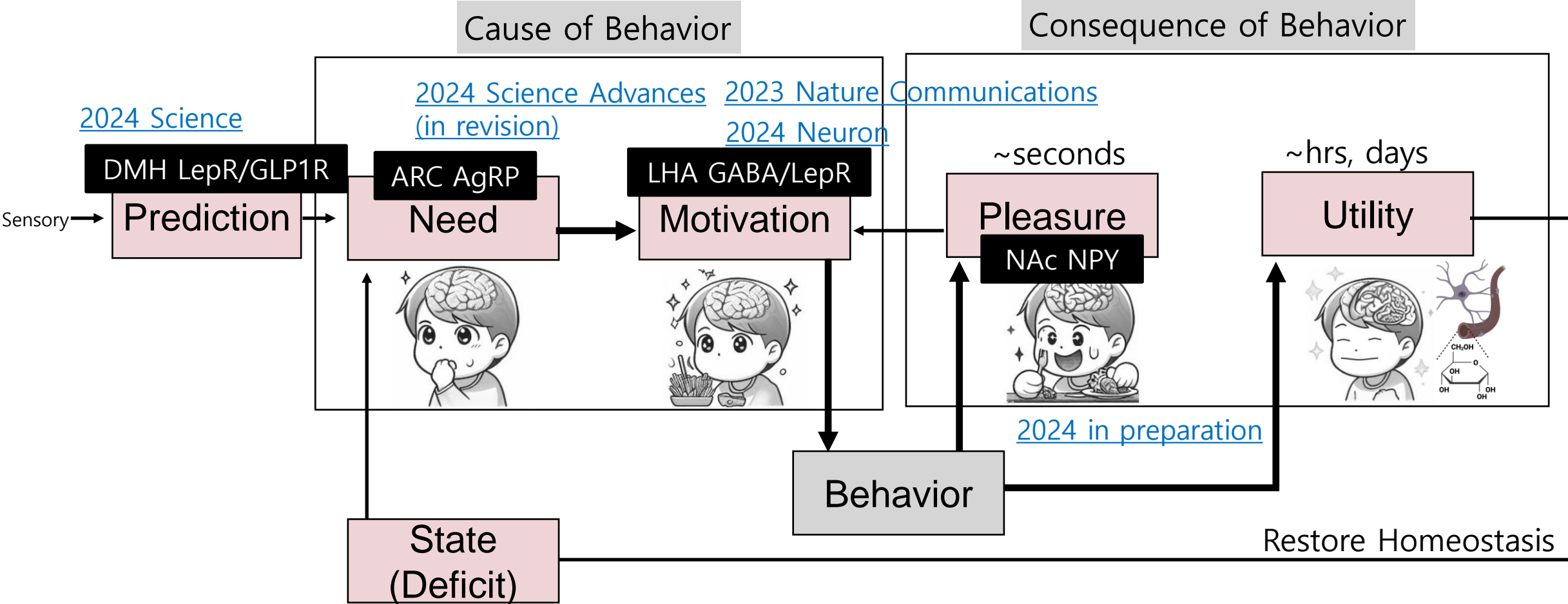
Future



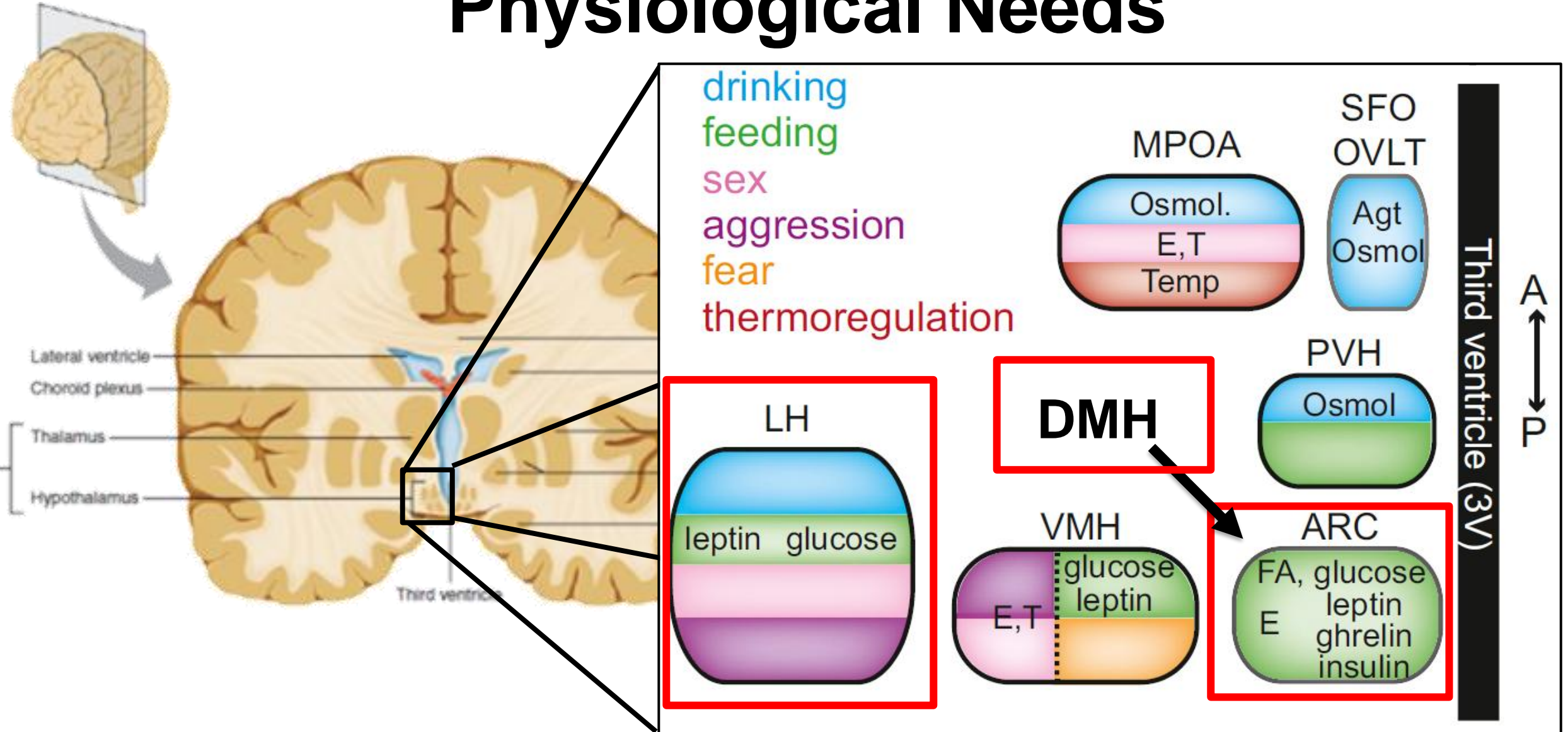


State Predicted State	<u>Motivation</u> Impulse, Intention	Instant Outcome	Final Outcome
<p>Surplus Excess</p> <p><u>Need</u> Deficiency Deficit Requirement</p>	<p>Wanting Craving Desire Urge Appealing Tempting</p> <p>Repulsive Revolting Hateful Fear Dread</p>	<p><u>Pleasure</u> Liking Plesant Palatable Tasty</p> <p>Unpleasant Aversive Unpalatable Disgust Pain</p>	<p><u>Utility</u> Benefit</p> <p>Harm</p>

A Unified Theoretical Framework Underlying The Regulation of Motivated Behavior

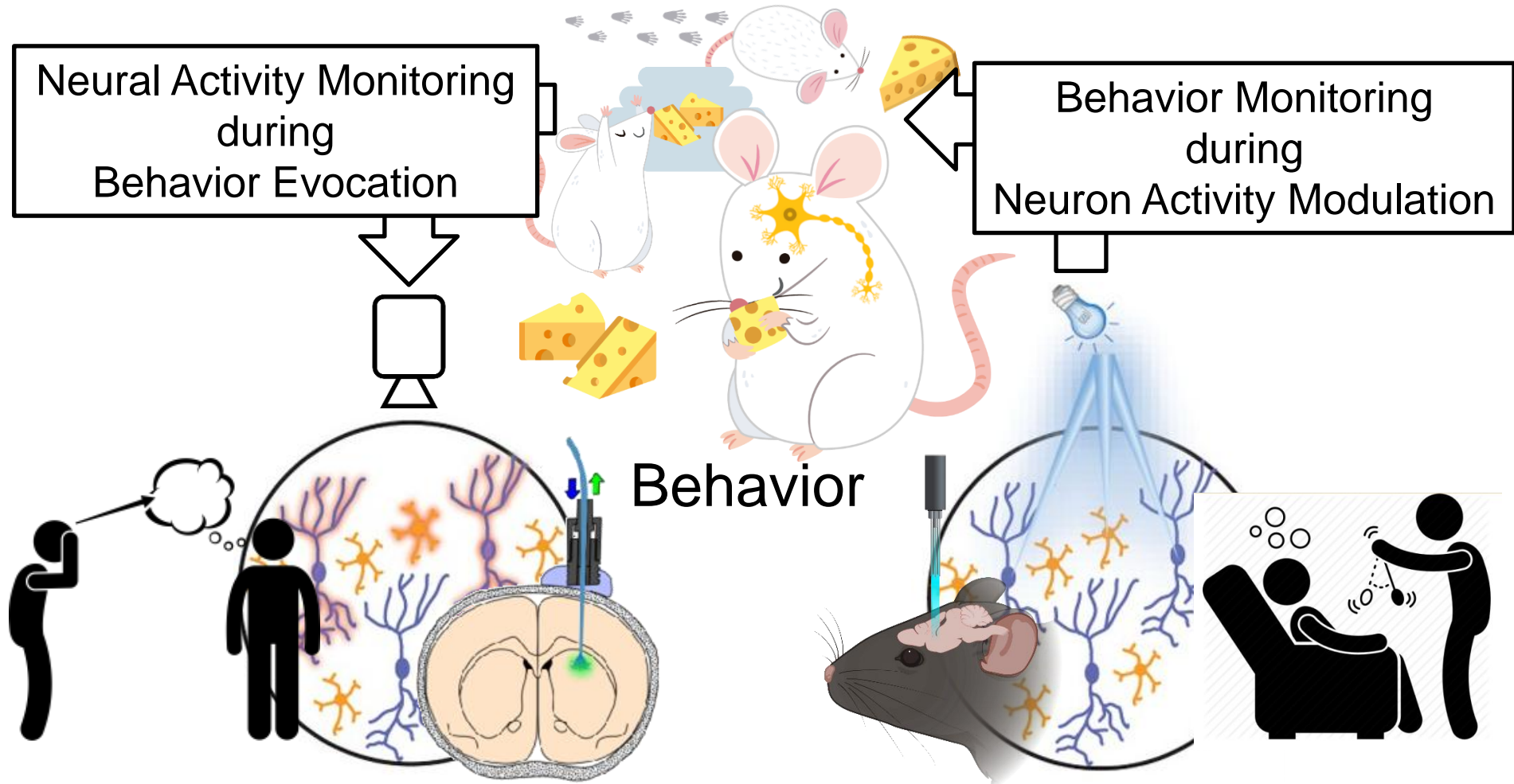


Hypothalamic Circuits for Physiological Needs



Neural Activity Monitoring
during
Behavior Evocation

Behavior Monitoring
during
Neuron Activity Modulation



Neural Activity Monitoring
(Mind Reading)

Neuron Activity Modulation
(Mind Writing
Hypnosis)

micro-endoscope, fiber photometry

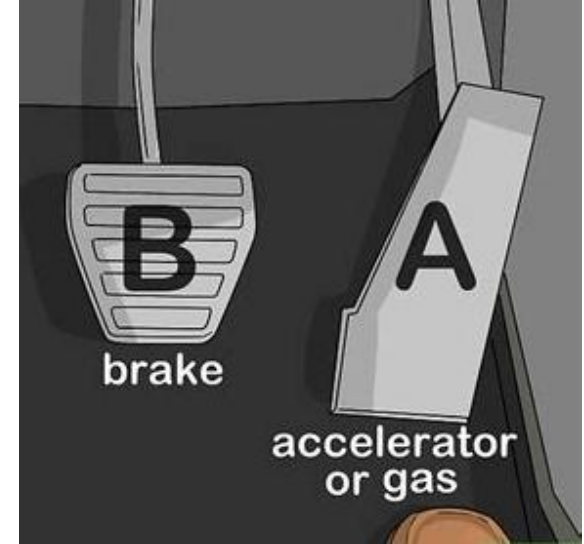
optogenetics

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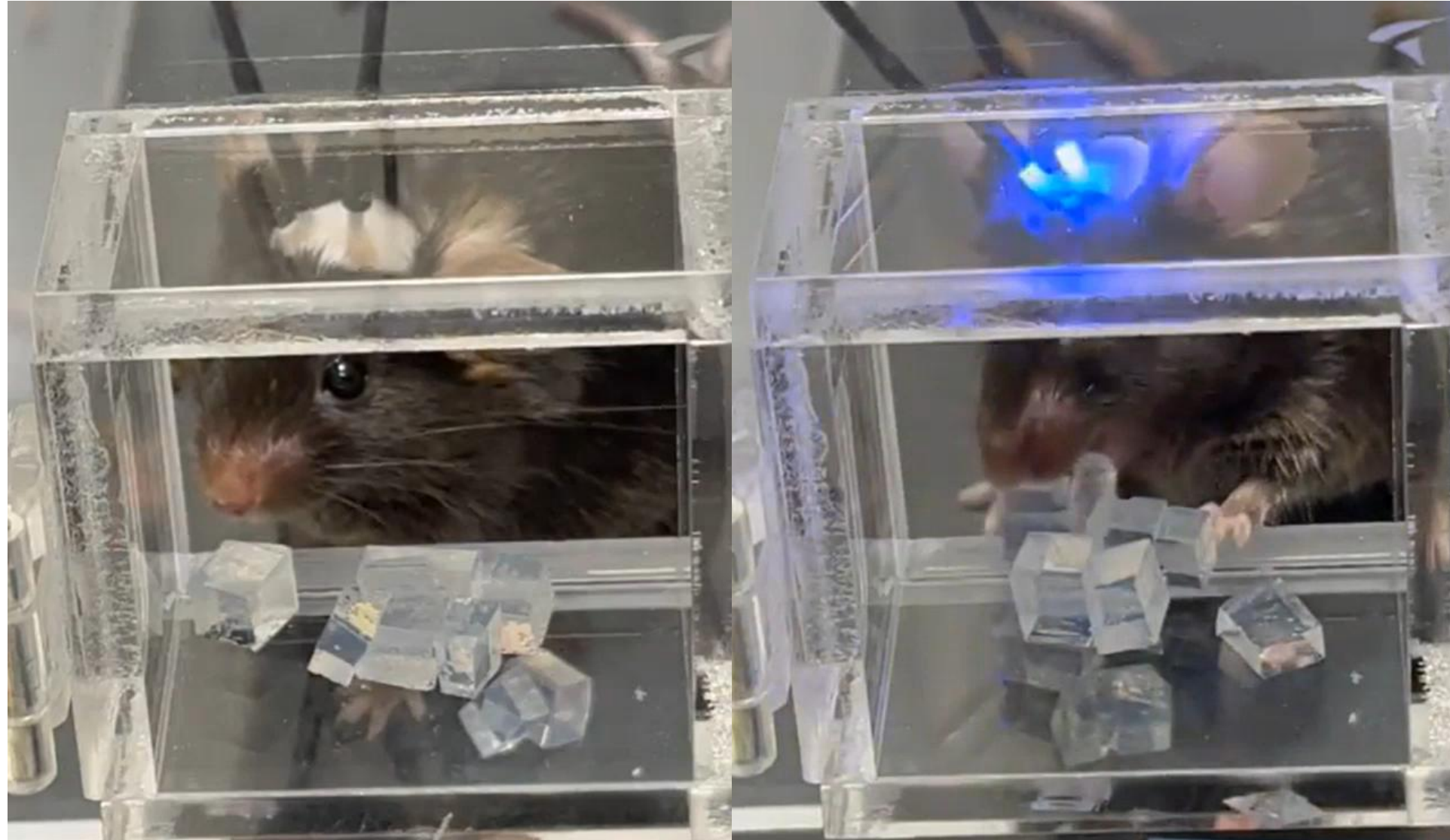
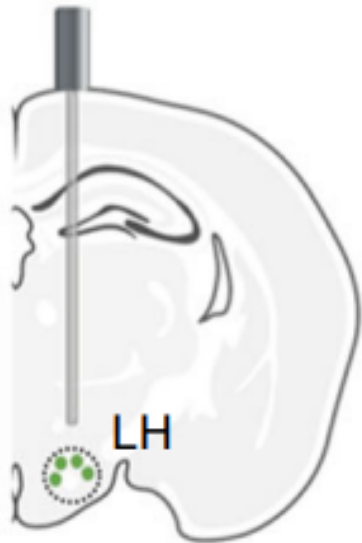
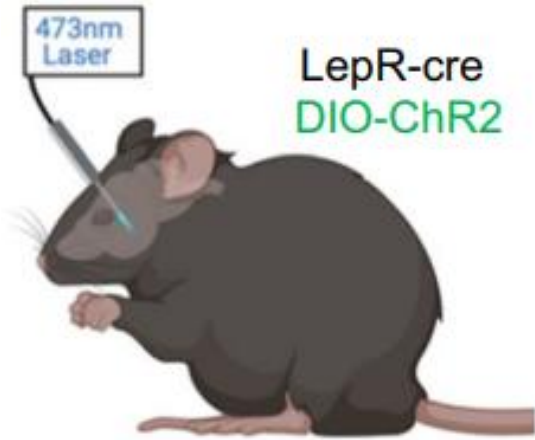
Motivation
LH LepR



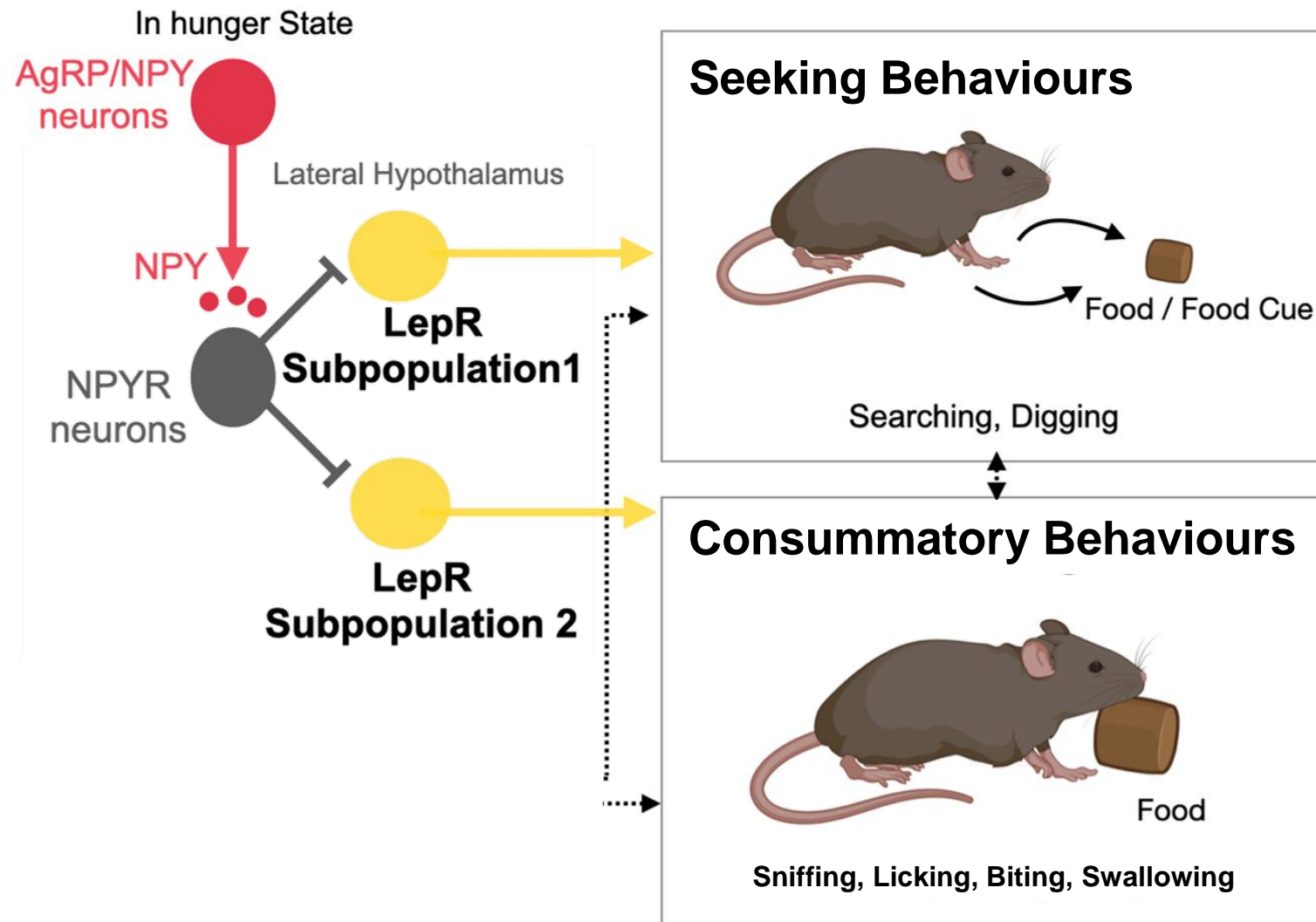
Two distinct populations of LH LepR neurons encode food-seeking and consummatory behaviours



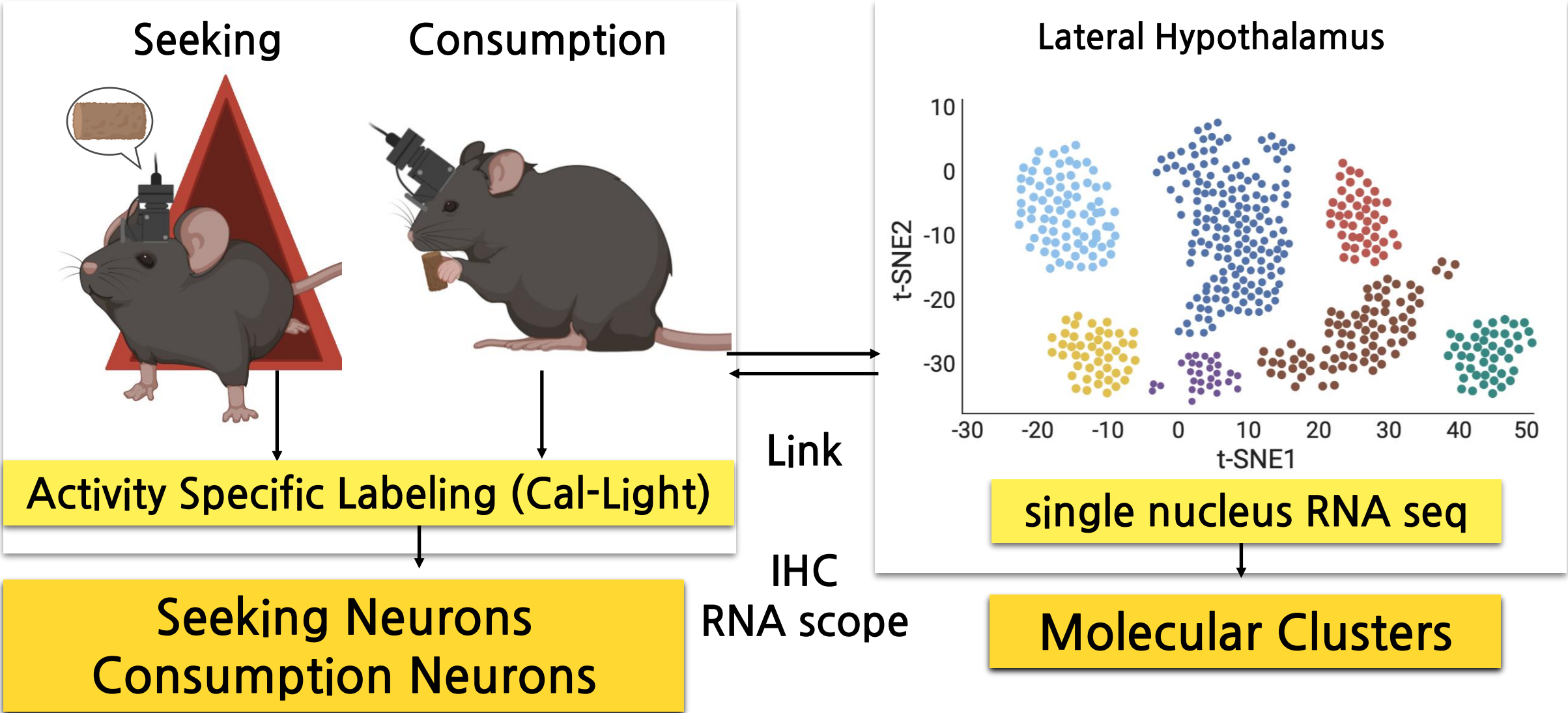
Activation of LH LepR neurons significantly increased consummatory behaviours



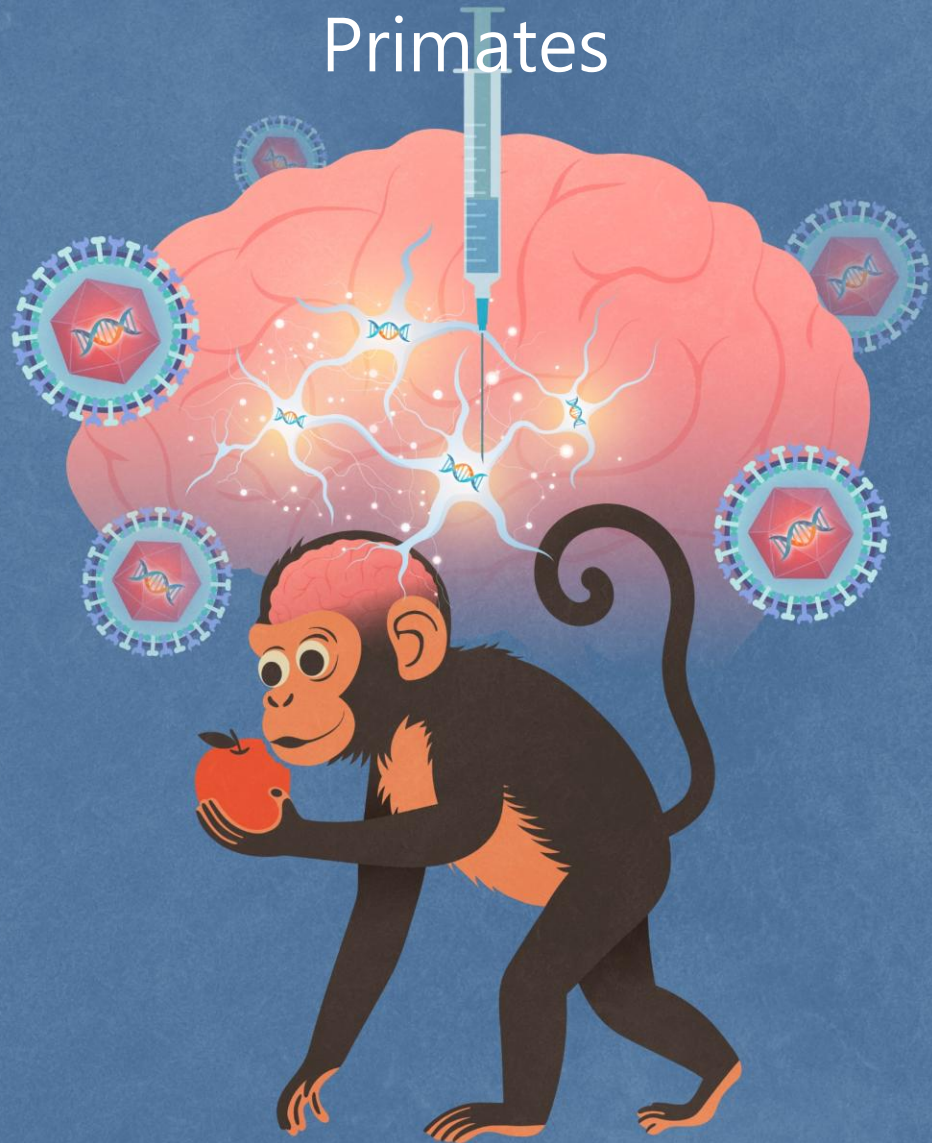
Leptin Receptor Neurons in Lateral Hypothalamus Regulates Hunger-gated Food-Seeking and Consumption Behaviours



Ongoing Studies

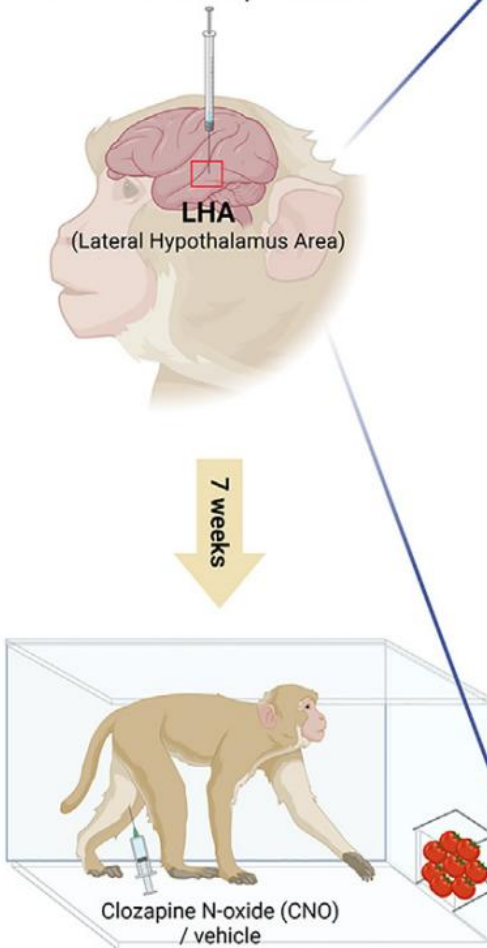


Lateral Hypothalamus GABAergic Neurons on Eating Behaviours in Non-human Primates

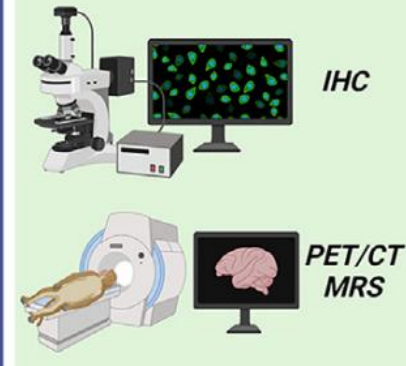


Chemogenetic activation virus

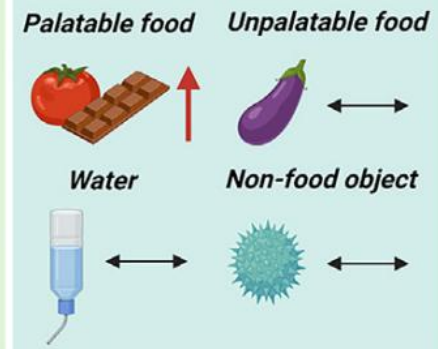
AAV9-hDlx-hM3Dq-dTomato



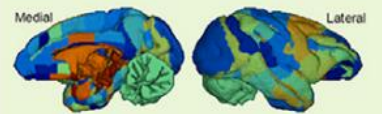
Functional / histological virus validation



Naturalistic goal-directed eating behavior



Rs-fMRI functional connectivity



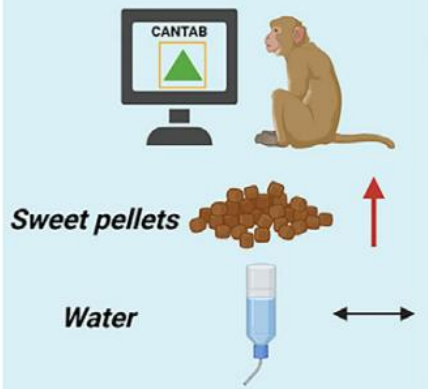
LHA seed-based FC

Increased FC LHA-frontal area

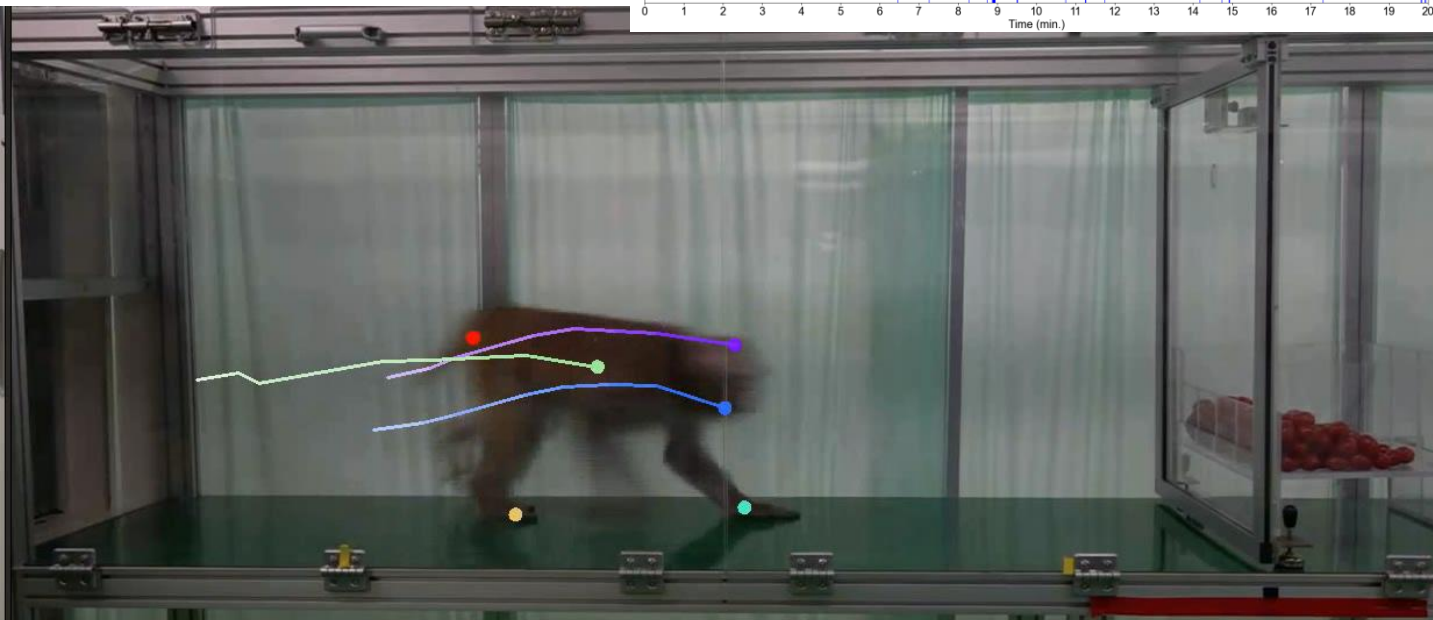
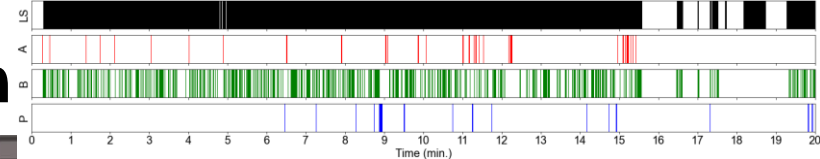
Whole-brain network FC

Decreased FC between frontal cortices

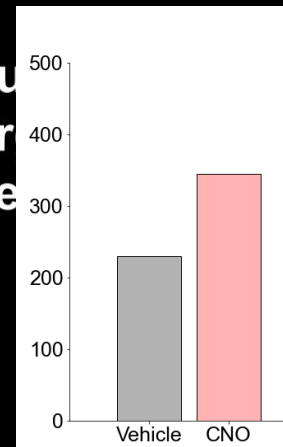
Goal-directed motivation



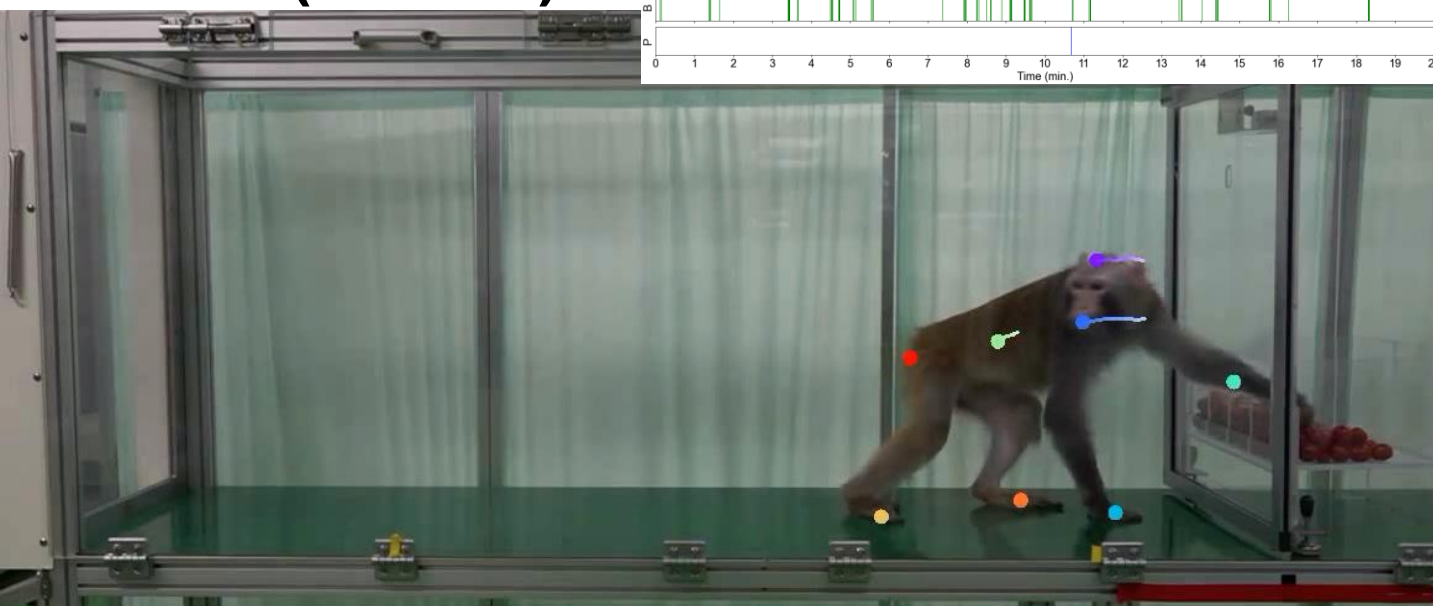
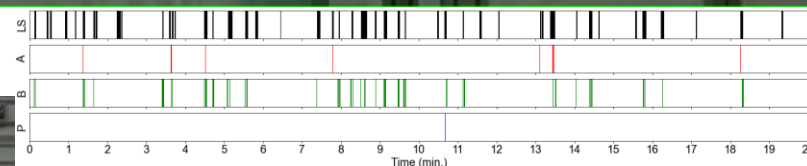
LH GABA activation



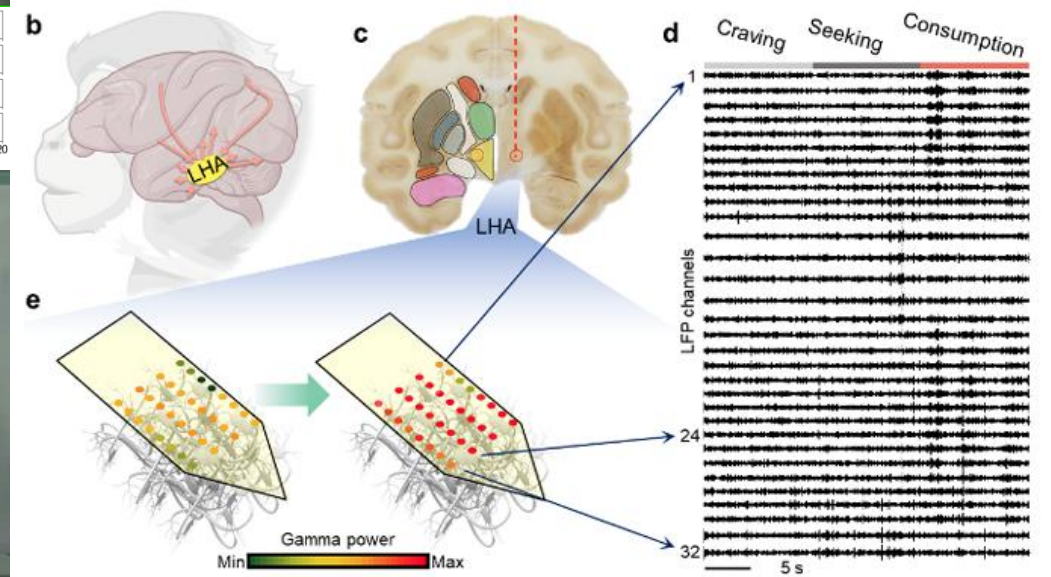
Motivated feeding behavior u
CANTAB after LHA GABAer
neuron activation of Monke
(CNO injection)



Vehicle (Control)



2024 Neuron



2024 Nature Biomedical Engineering (in press)

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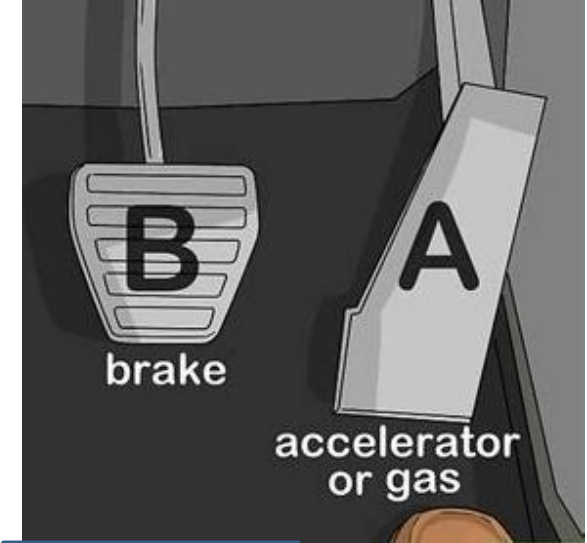
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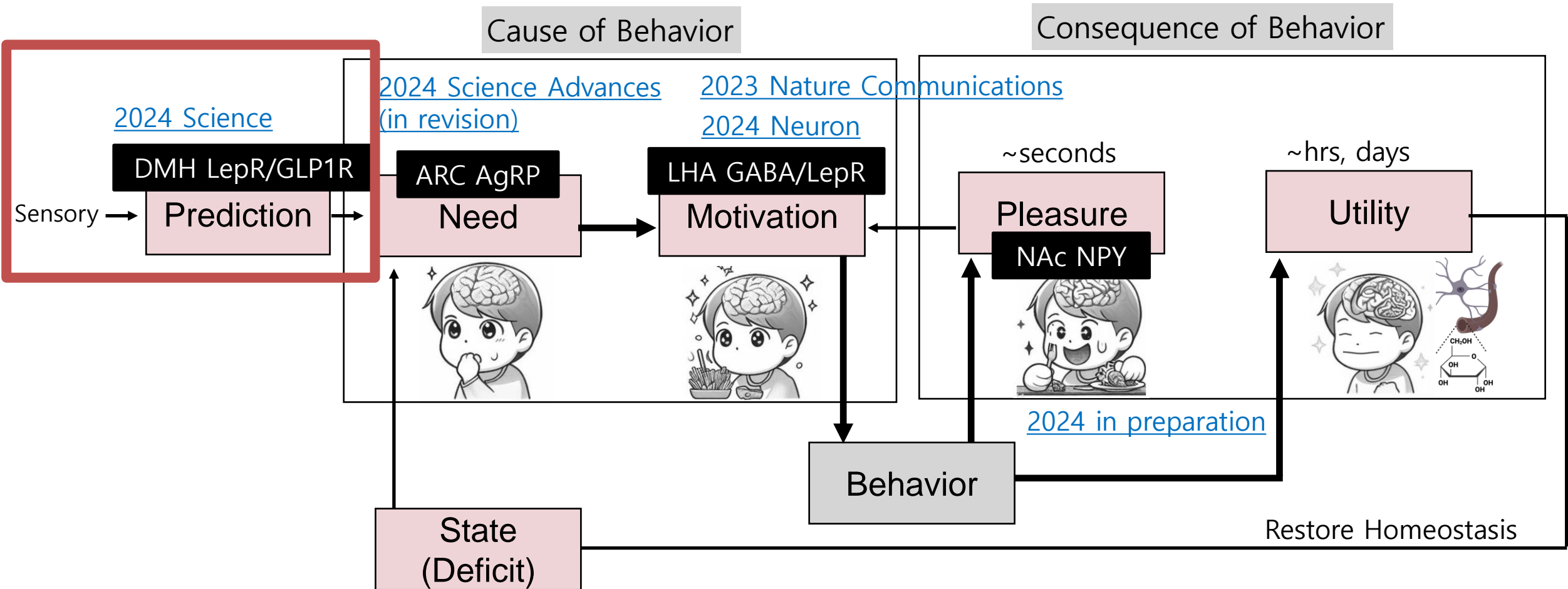


Satiety
DMH
GLP1R/LepR

Motivation
LH LepR



A Unified Theoretical Framework Underlying The Regulation of Motivated Behavior





Hunger



Seeking

Ghrelin



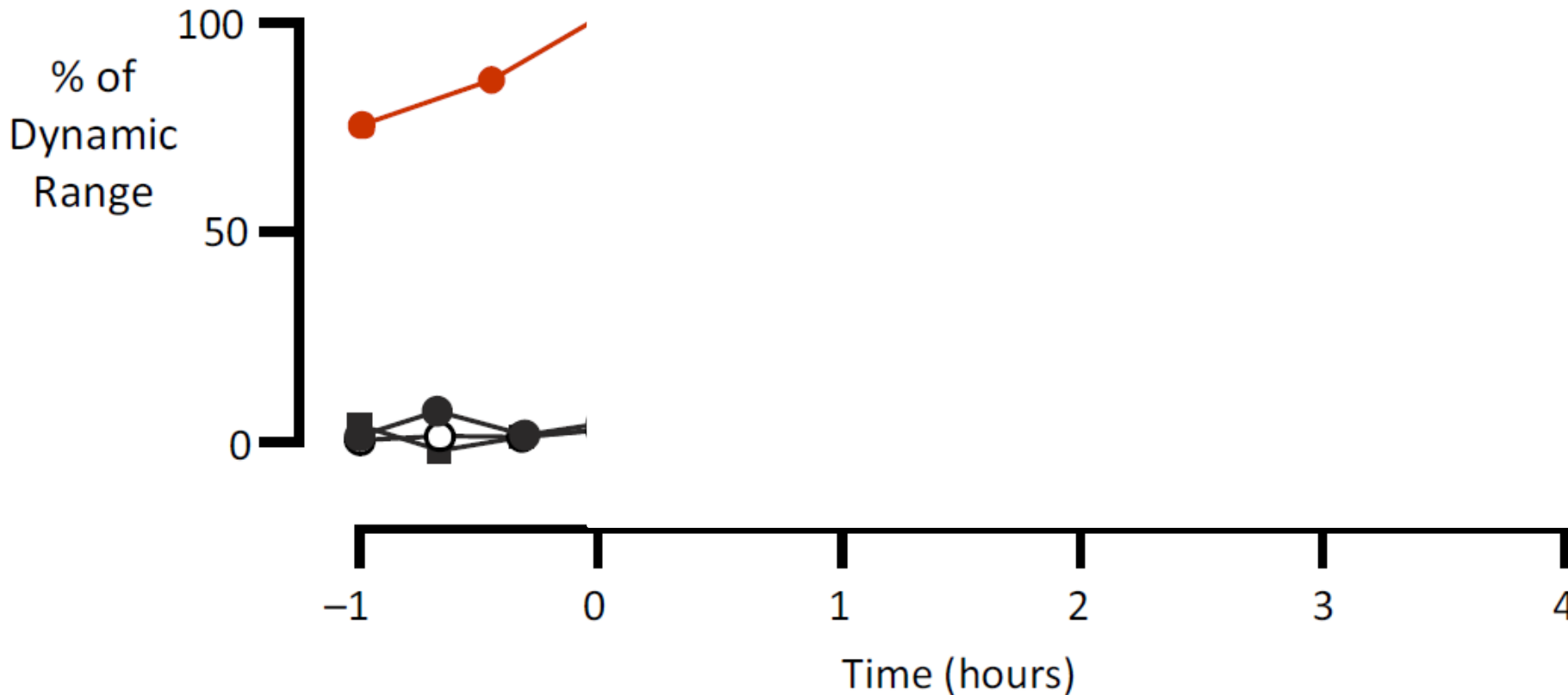
Initiation

Termination

Satiation



Obesity Drug
GLP-1 agonist
Satiation

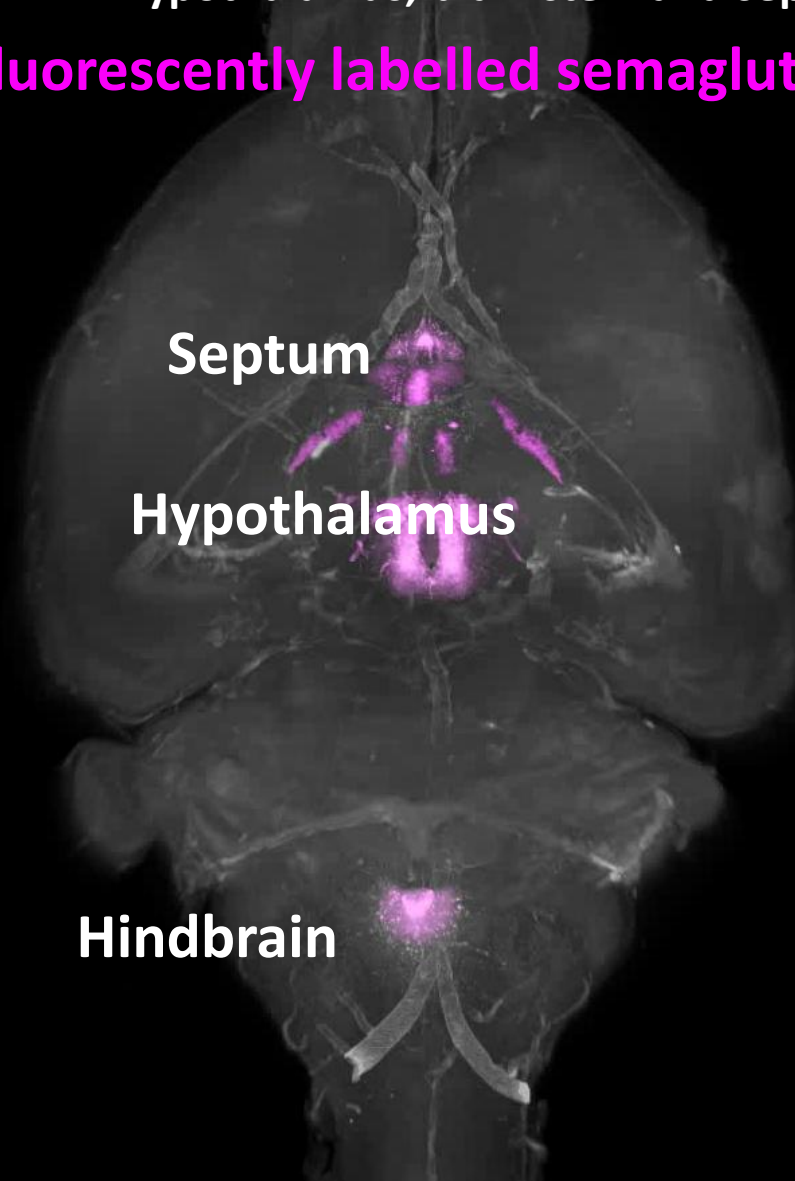


Several brain regions are activated by semaglutide

In rodents

Semaglutide distribution in the hypothalamus, brain stem and septum[†]

Fluorescently labelled semaglutide*



Septum

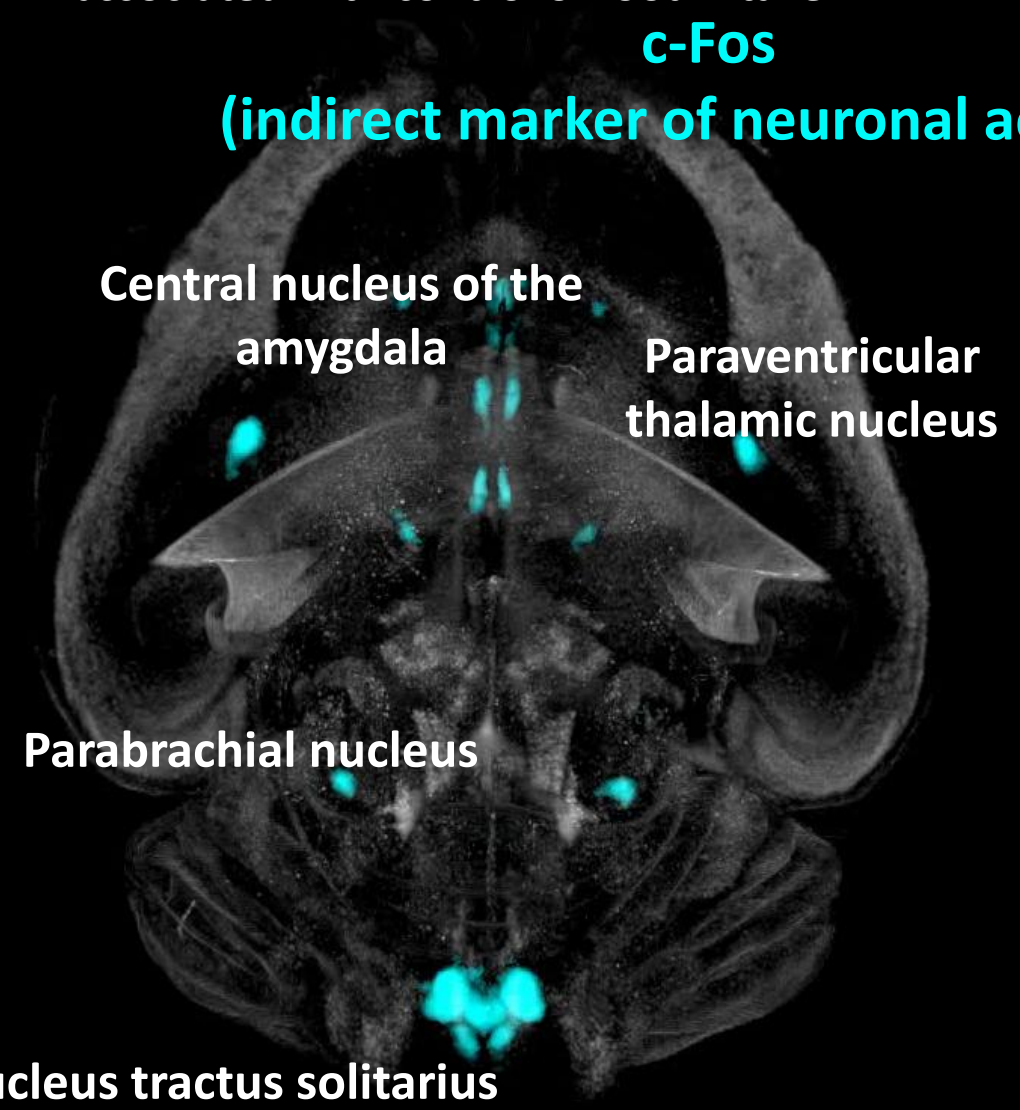
Hypothalamus

Hindbrain

Secondary activation in regions associated with control of food intake[‡]

c-Fos

(indirect marker of neuronal activity)



Central nucleus of the amygdala

Paraventricular thalamic nucleus

Parabrachial nucleus

Nucleus tractus solitarius

ing (10-30 nmol/kg). *SemaglutidecV7750. †Whole-brain c-Fos e.

Preingestive Sensory Satiation

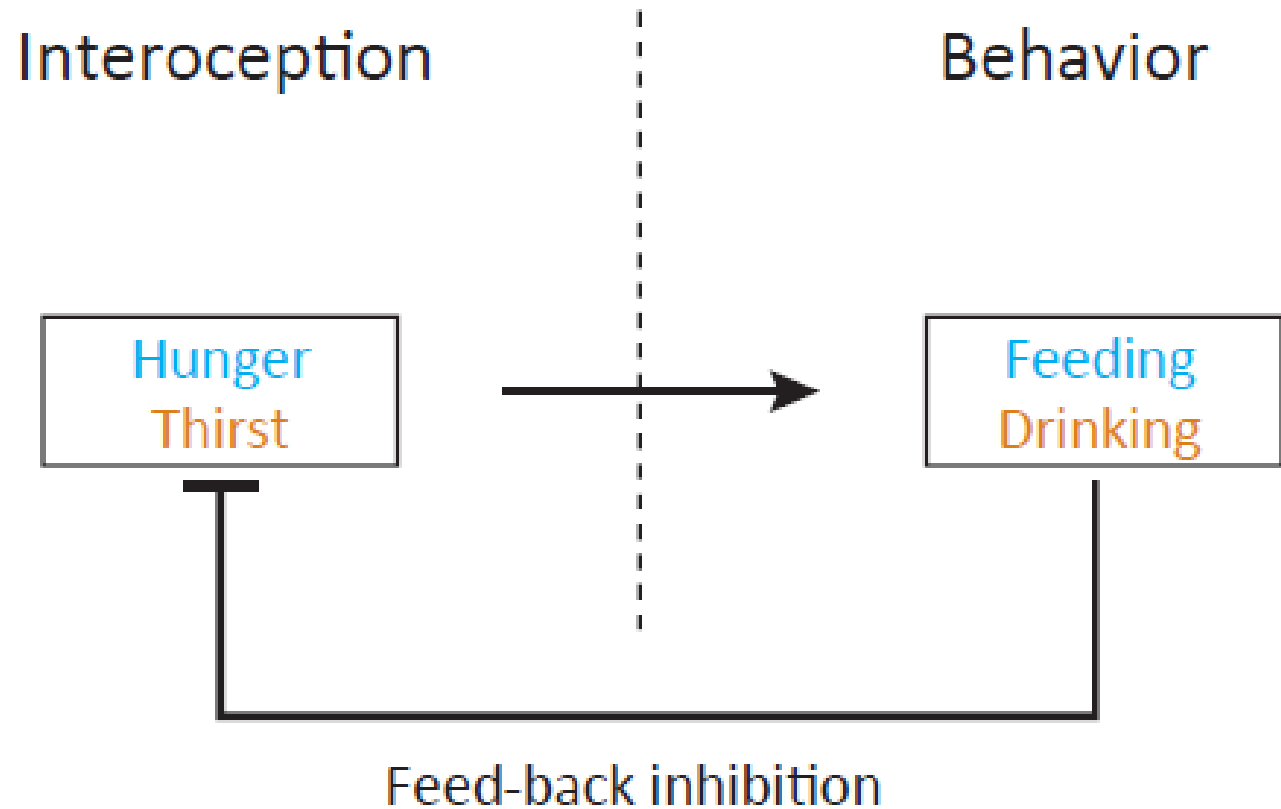
**Even just
looking at it
makes me
feel full**



Feed-forward and Feed-back regulation



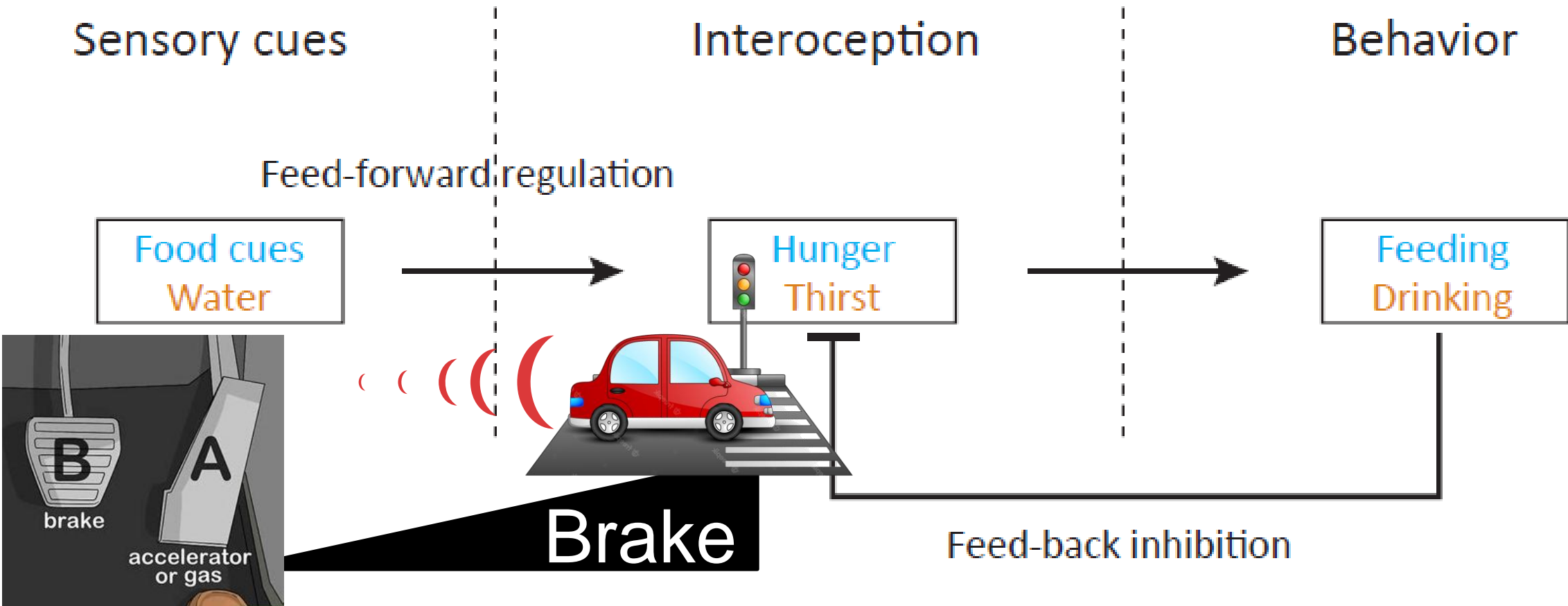
Yuki Oka



Feed-forward and Feed-back regulation



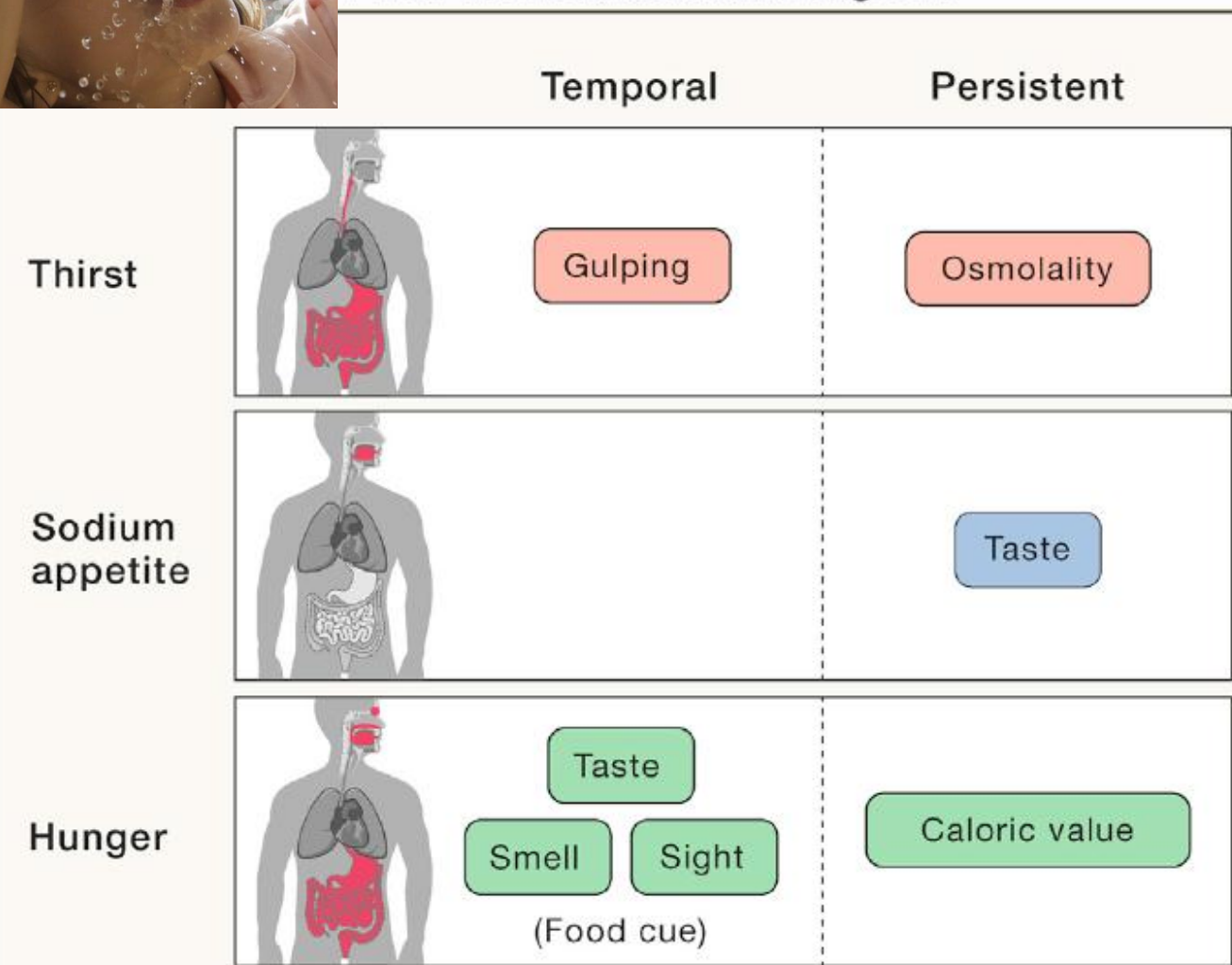
Yuki Oka



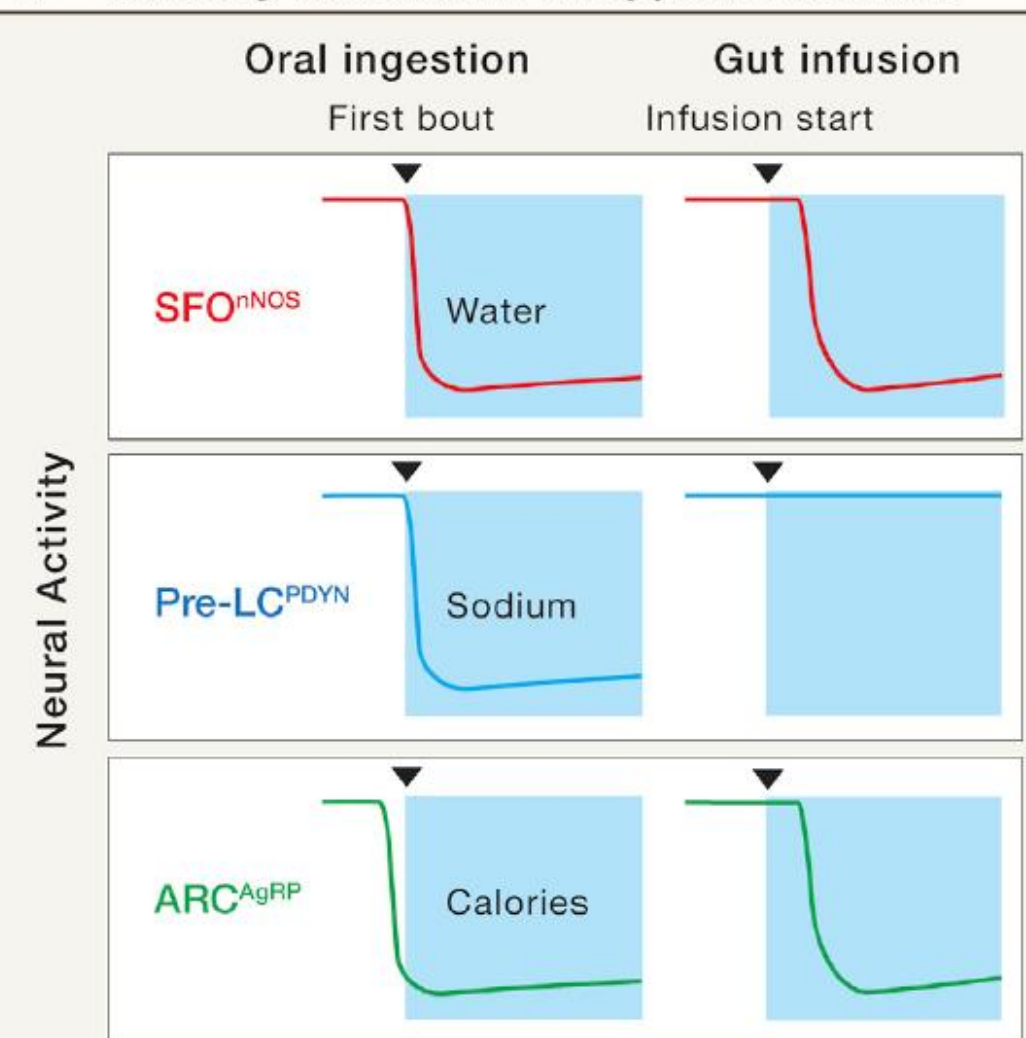


Yuki Oka

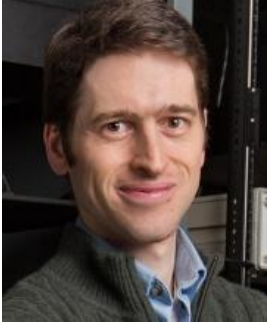
A Feed-forward satiation signals



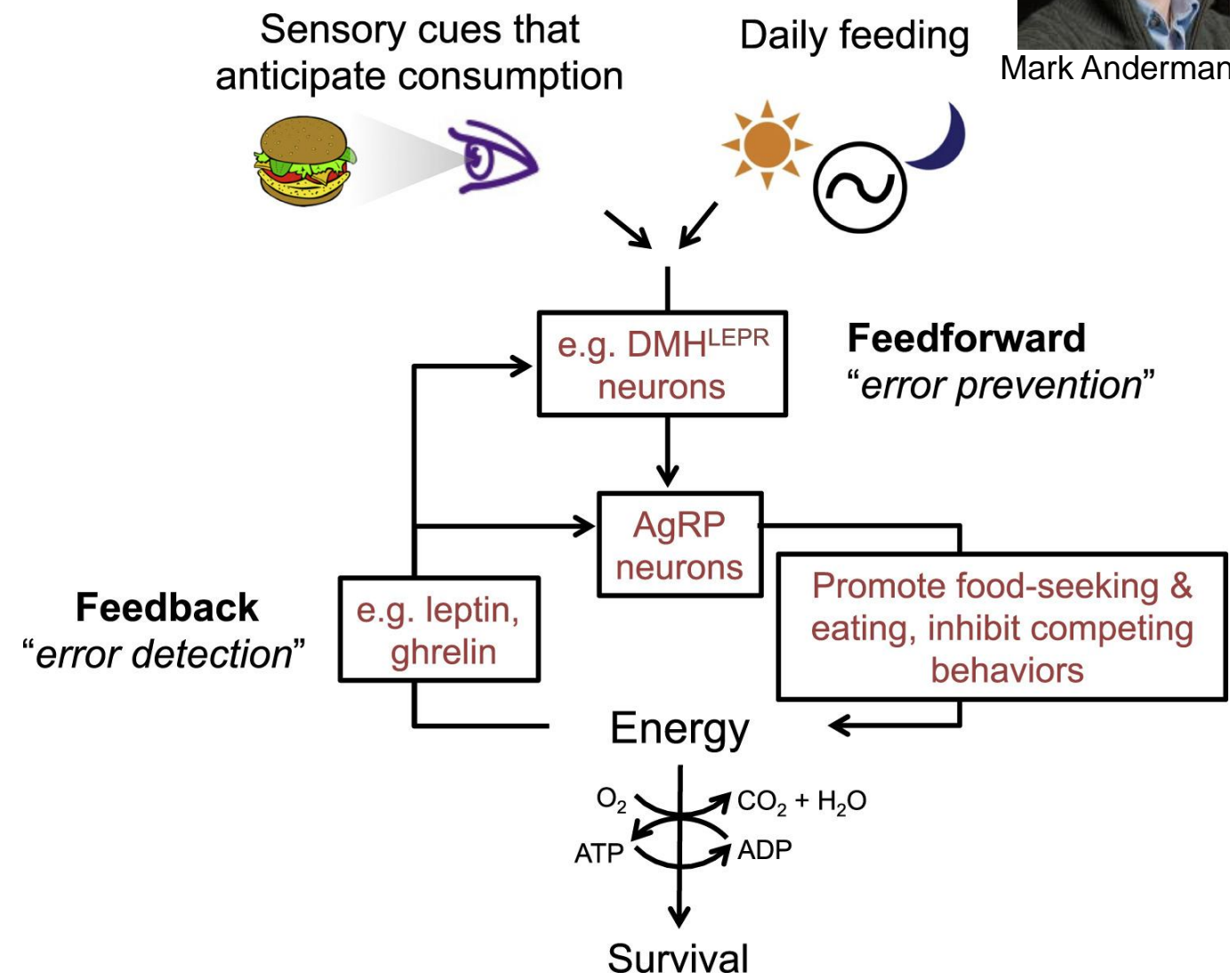
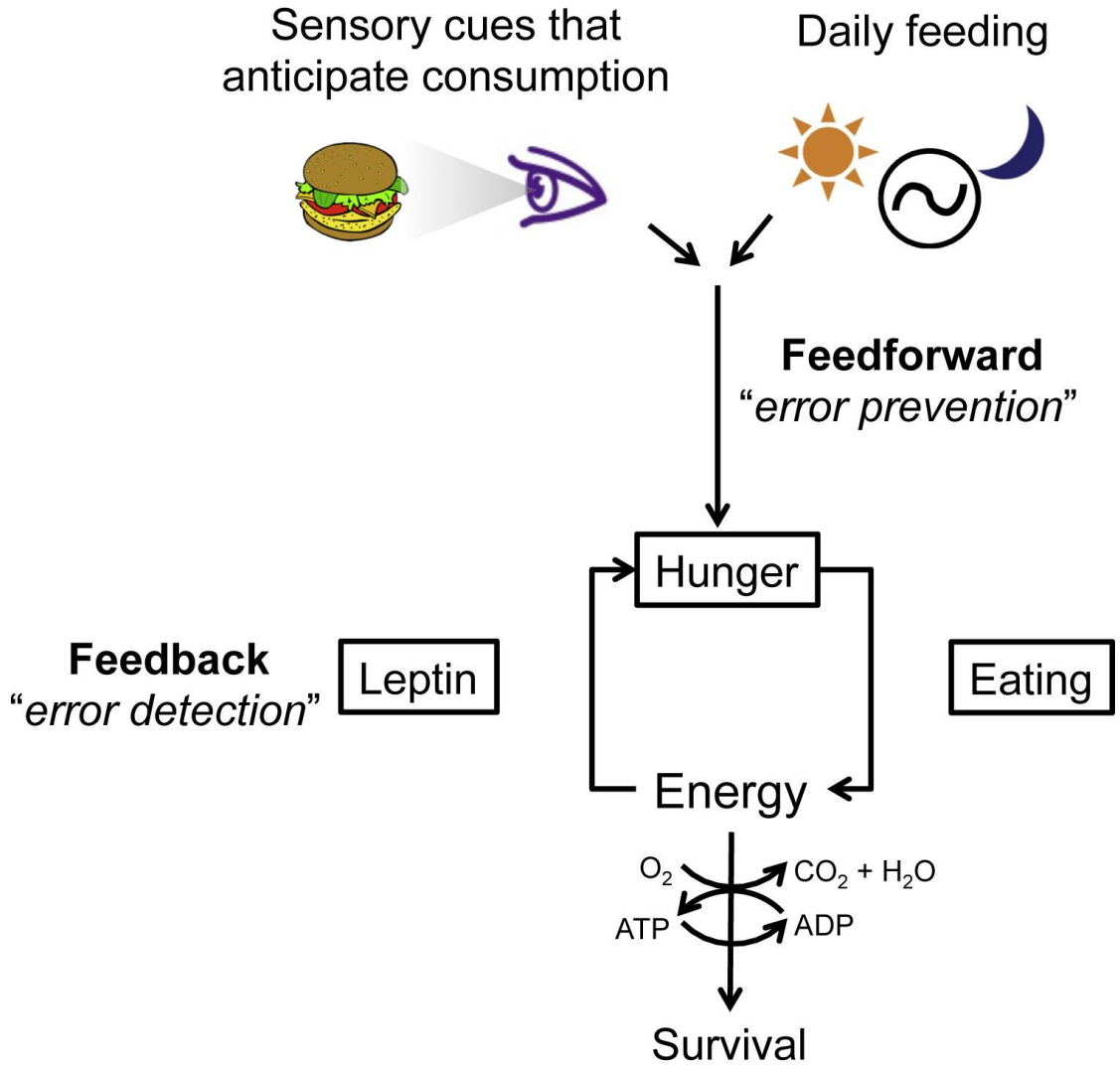
B Sensory modulation of appetite neurons



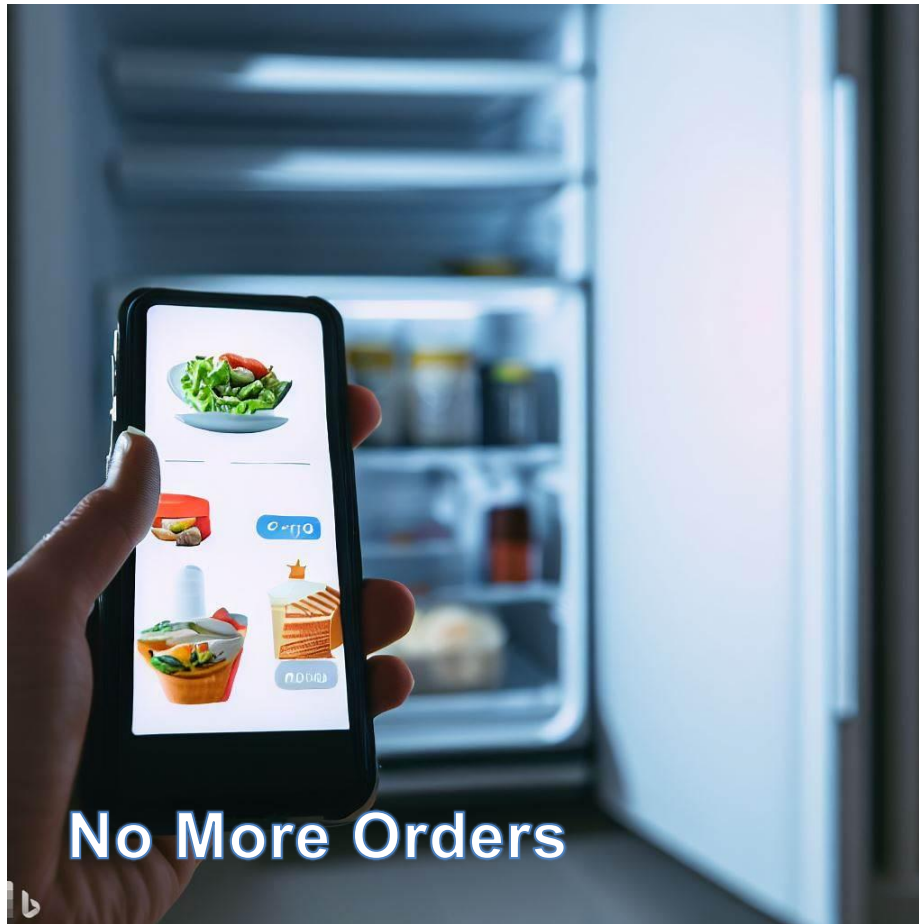
Feed-forward and Feed-back regulation



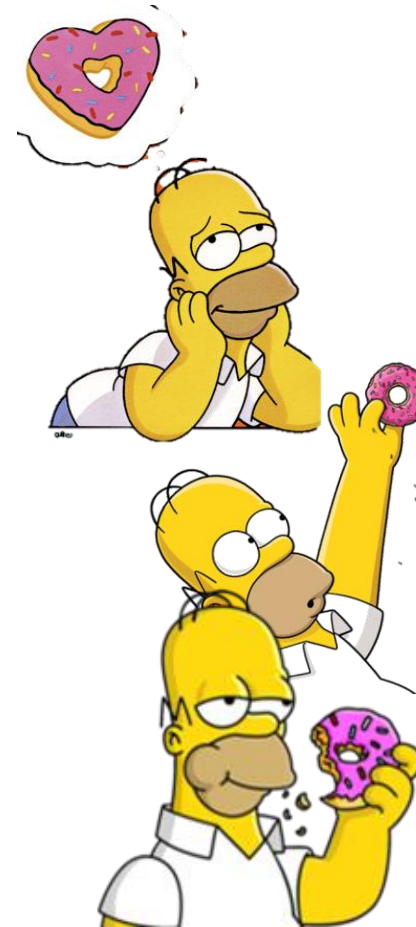
Mark Andermann



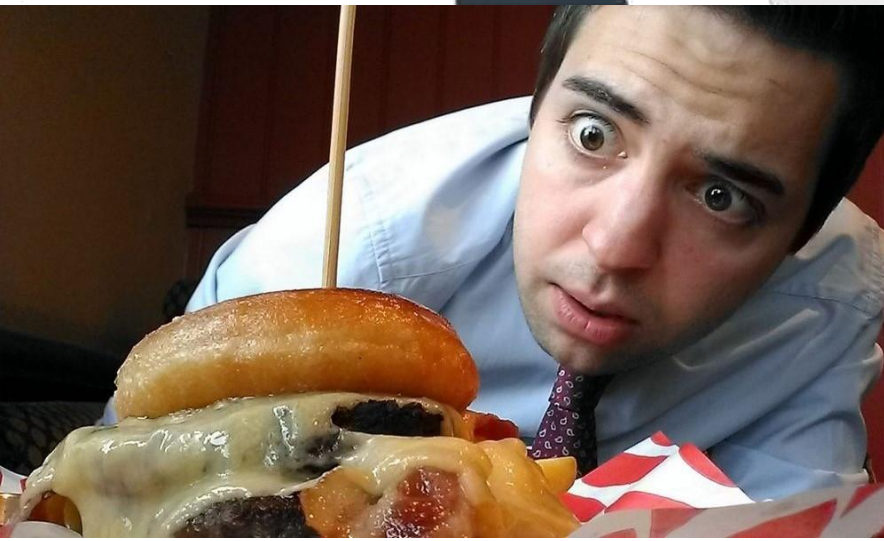
Need should be regulated by prediction



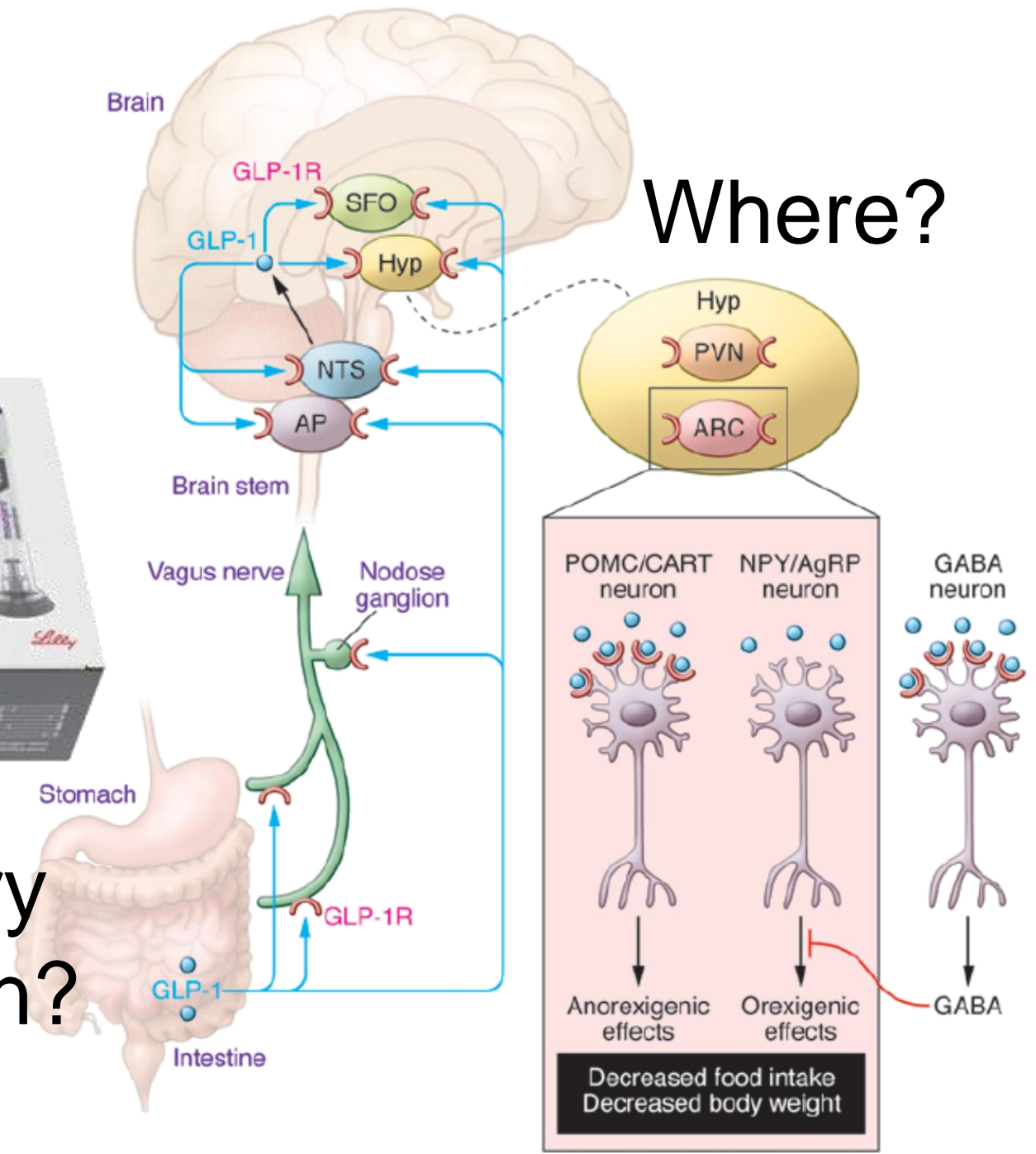
Current deficiency-based policy vs.
- Produce overshooting



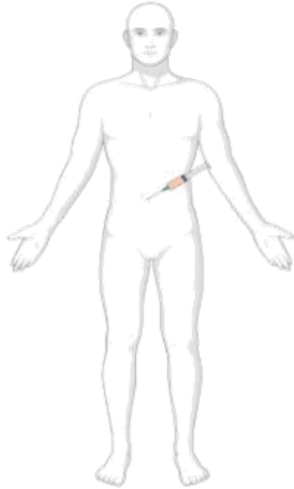
Predicted deficiency-based policy
- Avoid overshooting



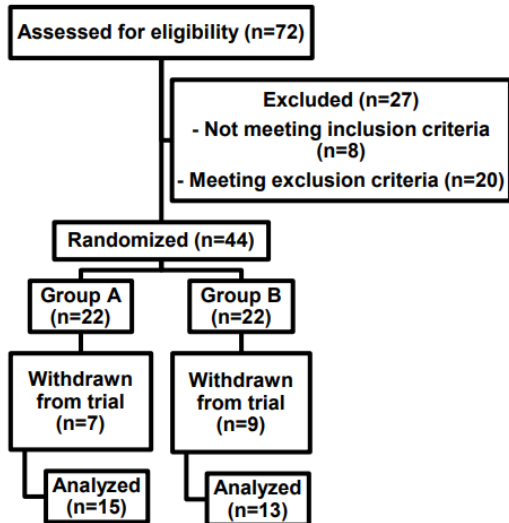
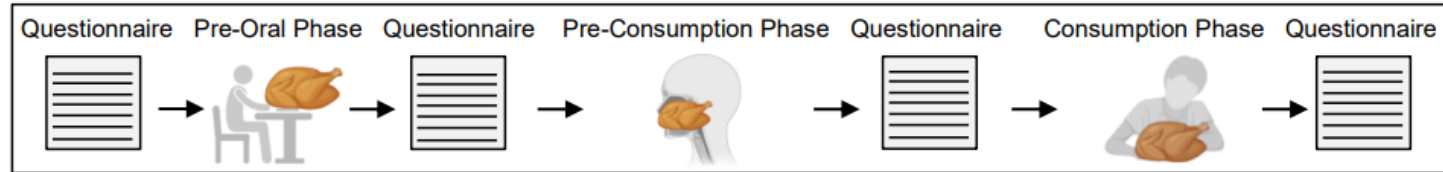
Sensory Satiation?

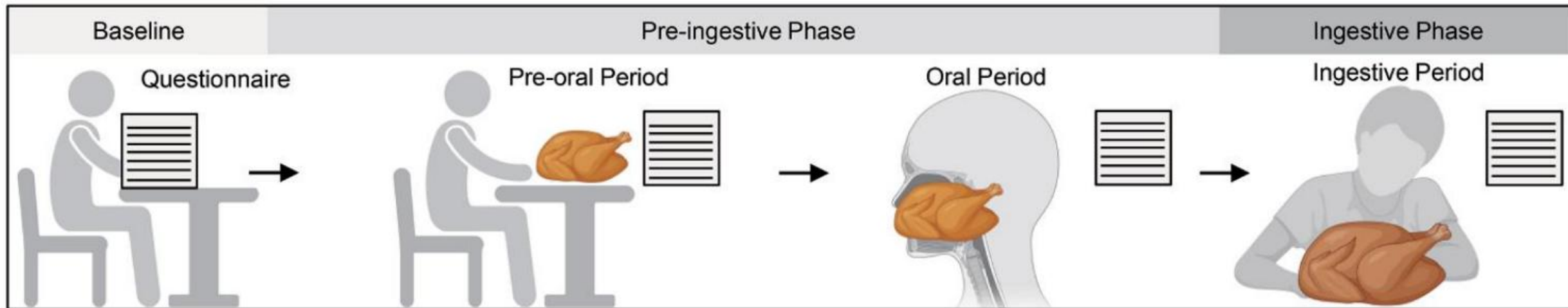


Effect of GLP-1 on Cognitive Satiation?

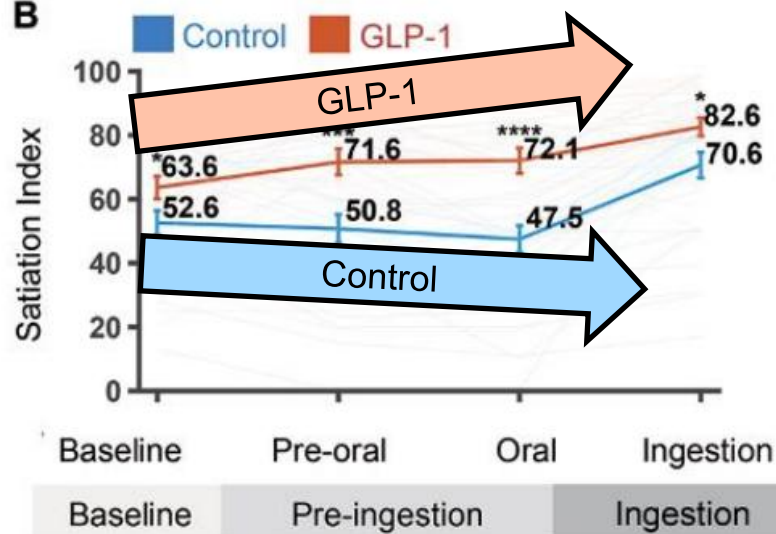
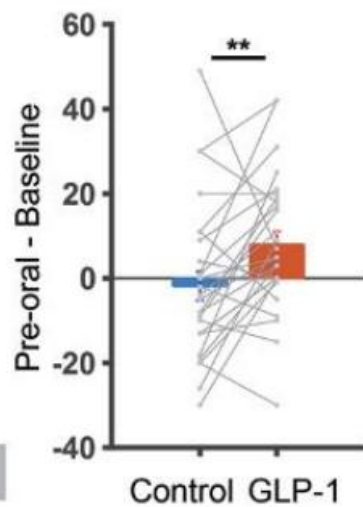
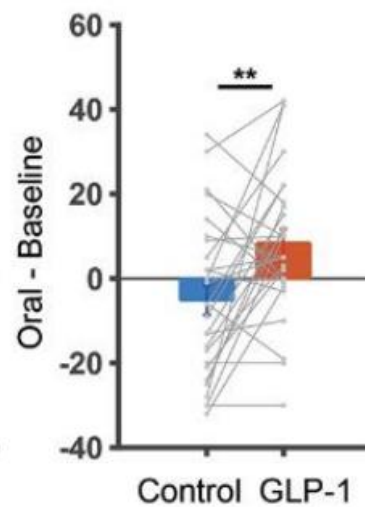
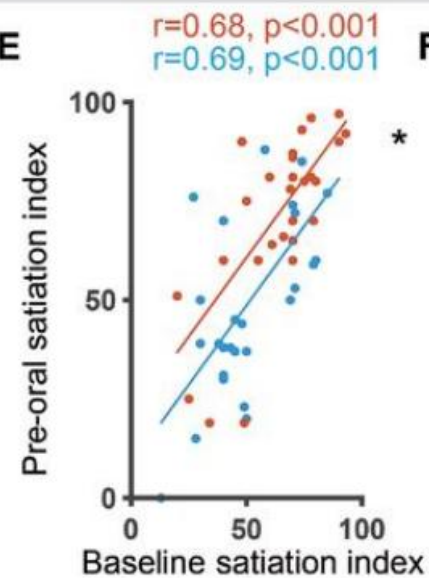
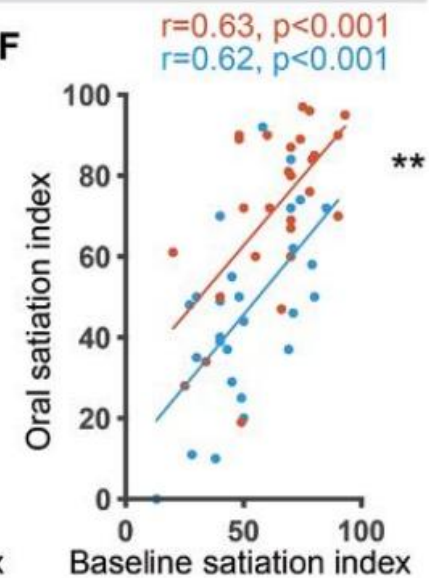


Task scheme

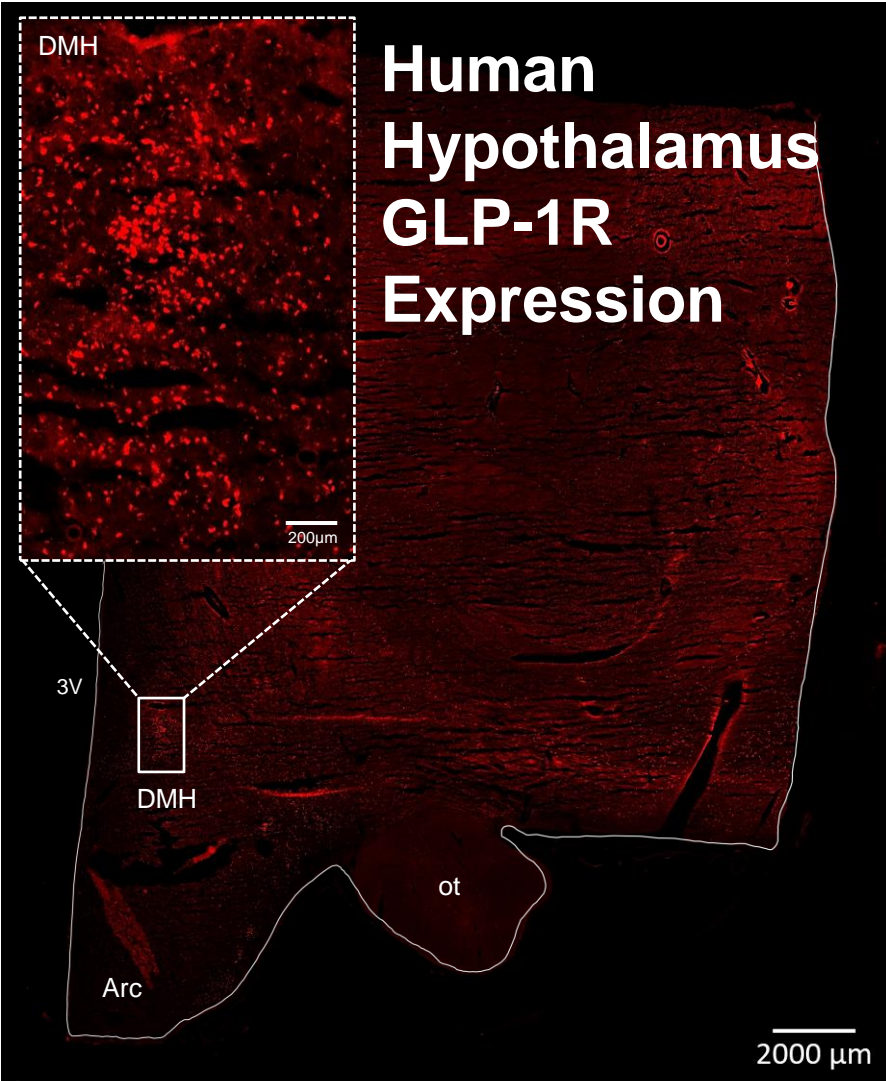


A

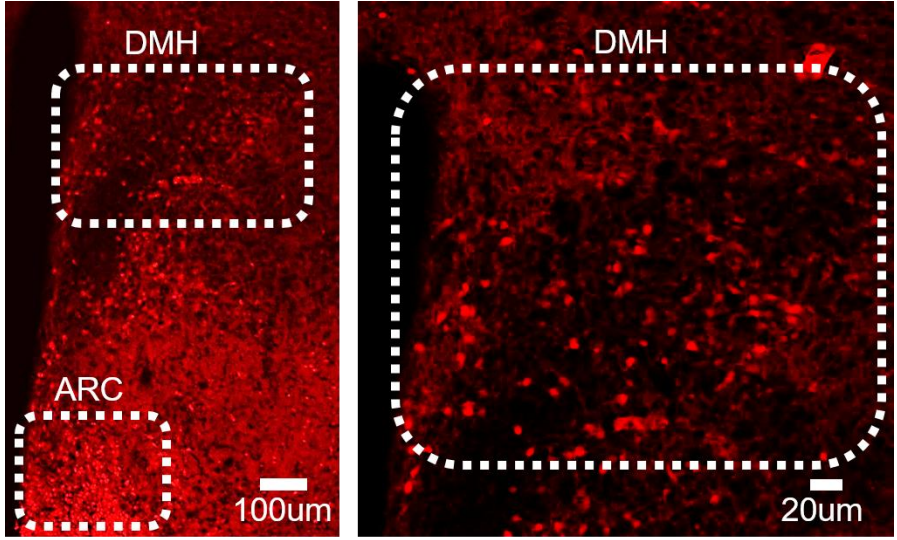
Satiety Index (Prospective food ingestion)

B**C****D****E****F**

DMH GLP-1R expression in Human and Mouse

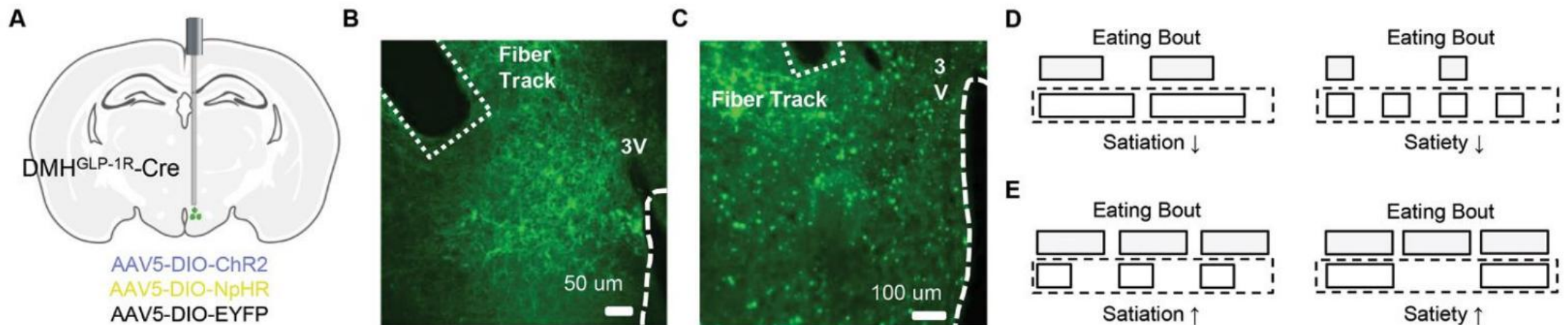


Mouse Hypothalamus GLP-1R Expression



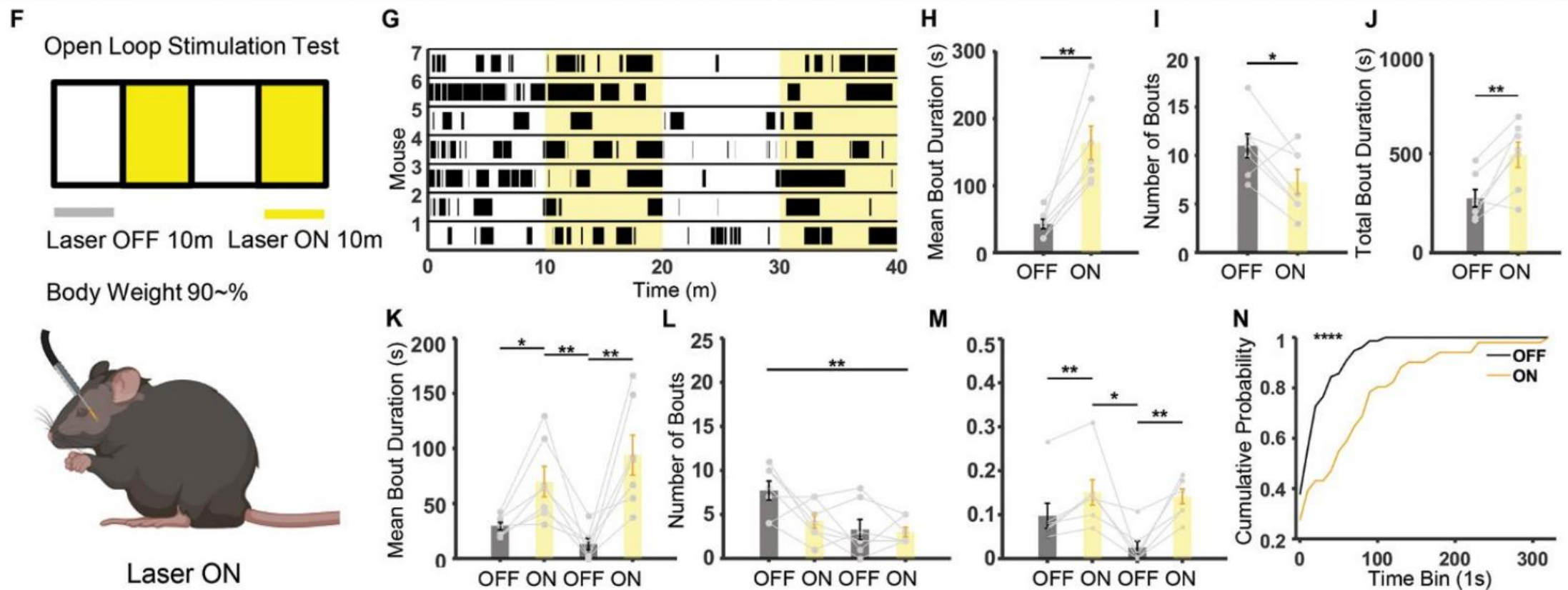
ot: optic tract
3V: 3rd ventricle
Arc: arcuate nucleus of hypothalamus
DMH: dorsomedial hypothalamic nucleus

Inhibition of DMH GLP-1R
Neurons Inhibit Satiety



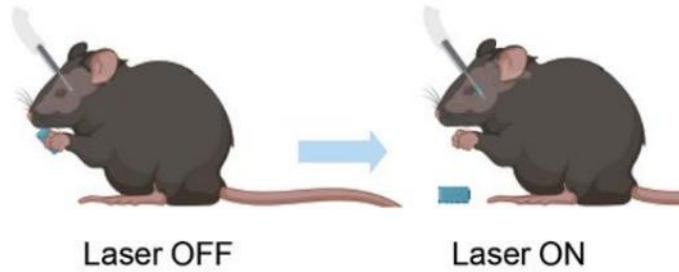
Optogenetic Inhibition of DMH^{GLP-1R} Neurons

NpHR

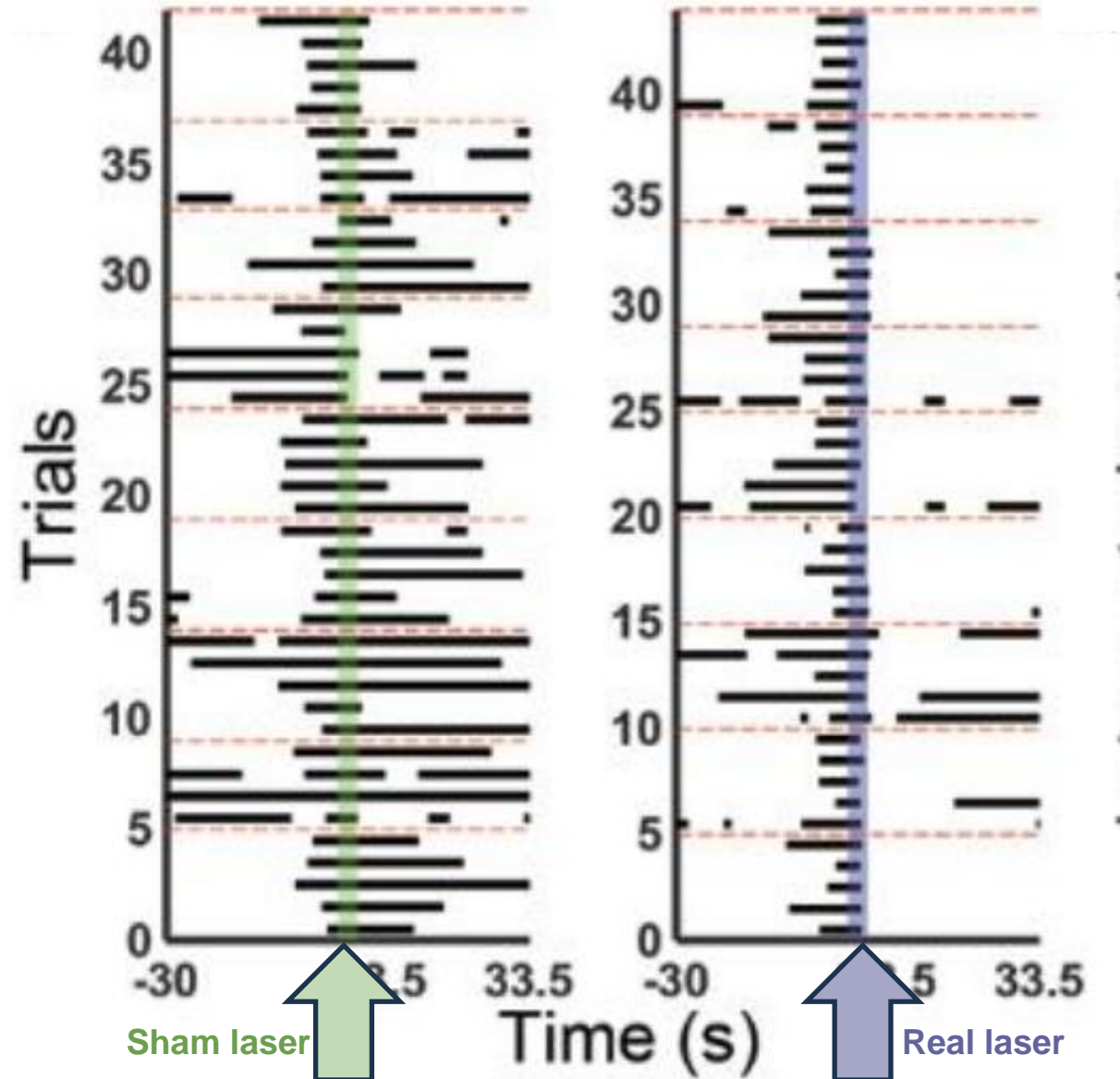


Activation of DMH GLP-1R
Neurons Evoke Satiating

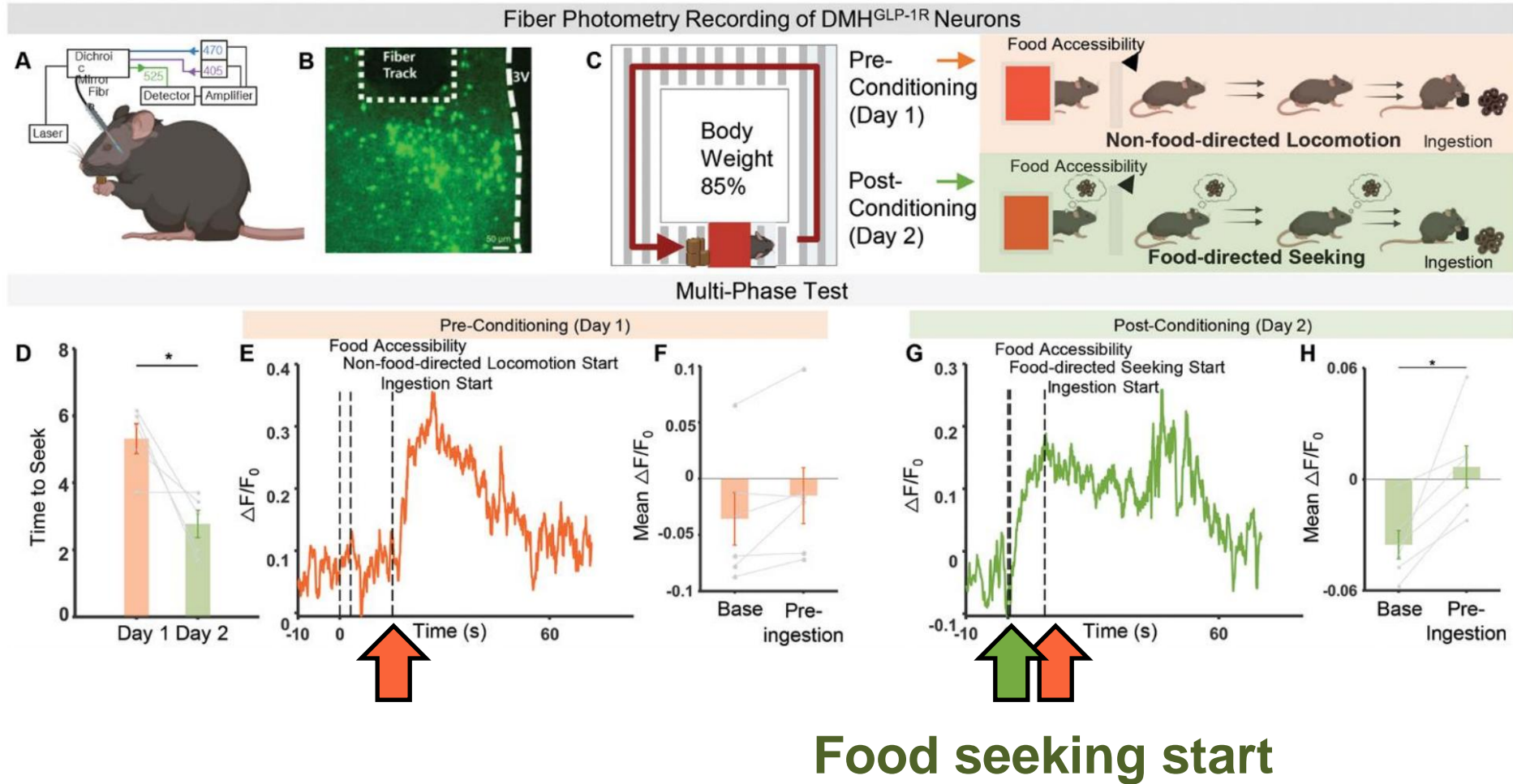
Termination of Eating by Activation of DMH GLP-1R Neurons during Eating



Activation During Eating **Immediate Termination of Eating**

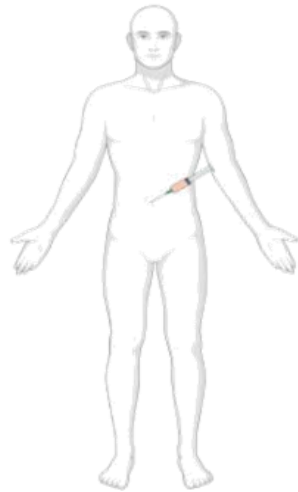


DMH GLP-1R Neurons are Activated by Anticipation of Eating

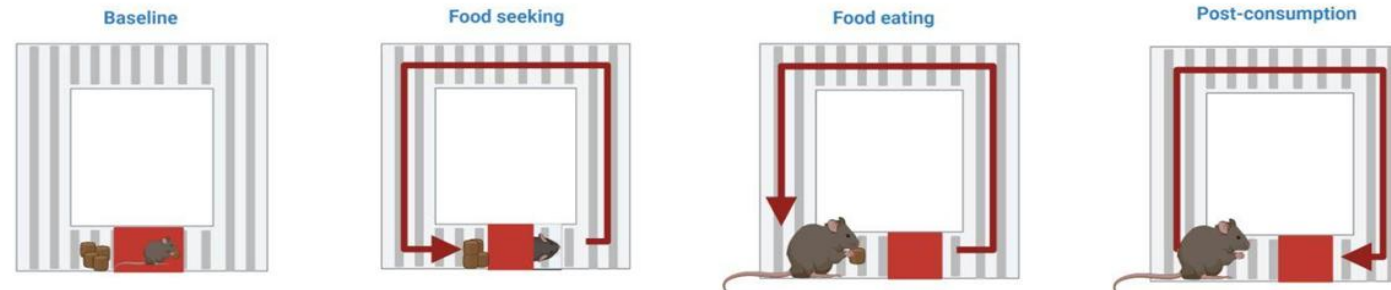
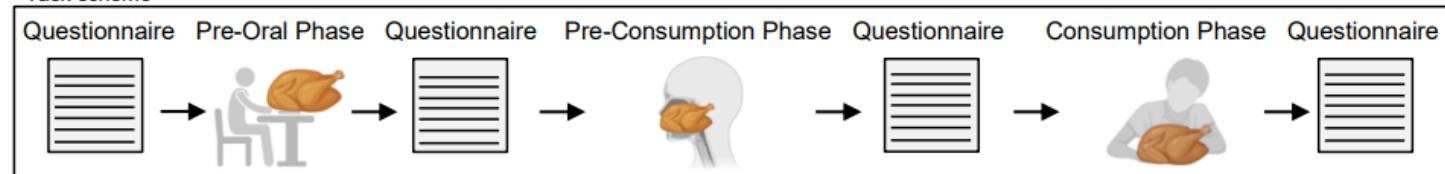


Two Distinct Population of
DMH GLP-1R Neurons Respond to
Different Phase of Eating

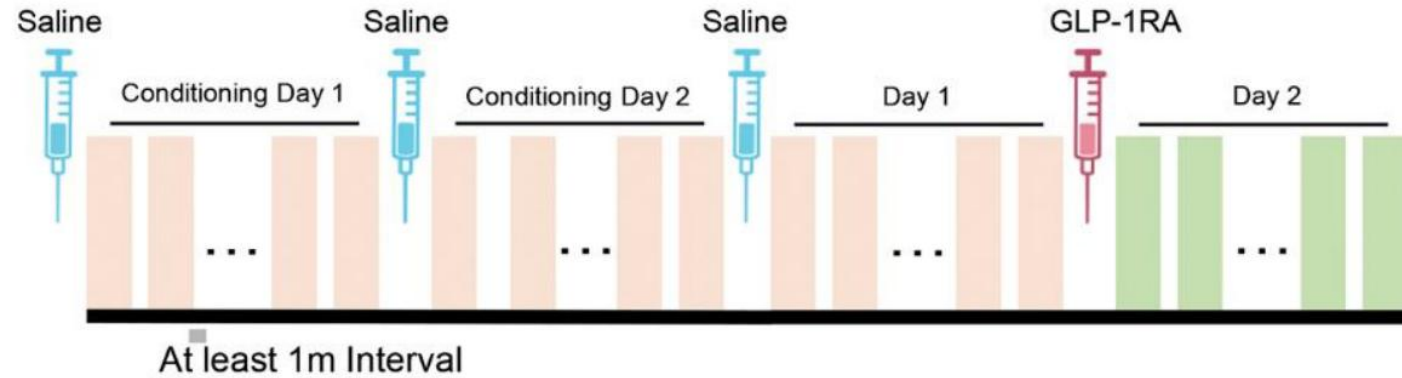
Effect of GLP-1 Drug on DMH GLP-1R Response



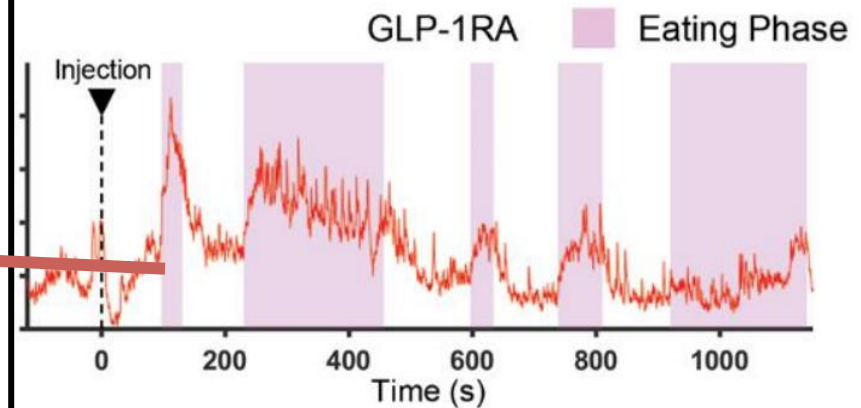
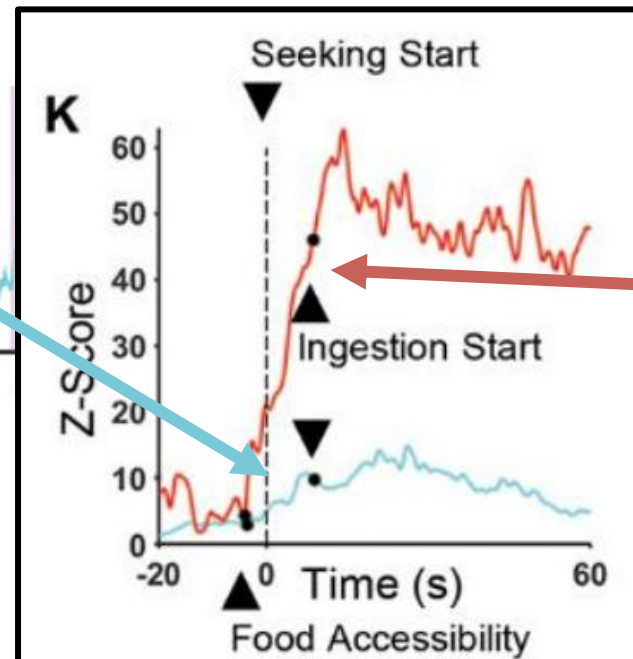
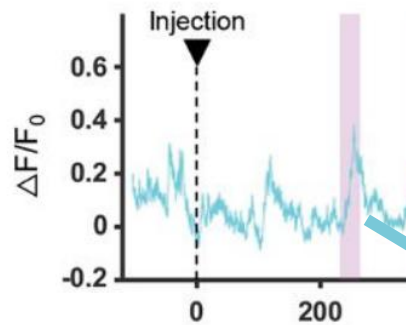
Task scheme

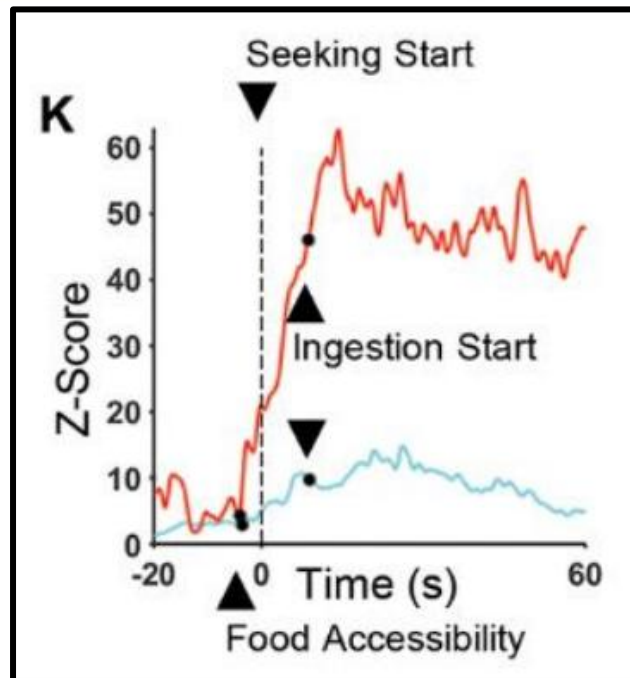
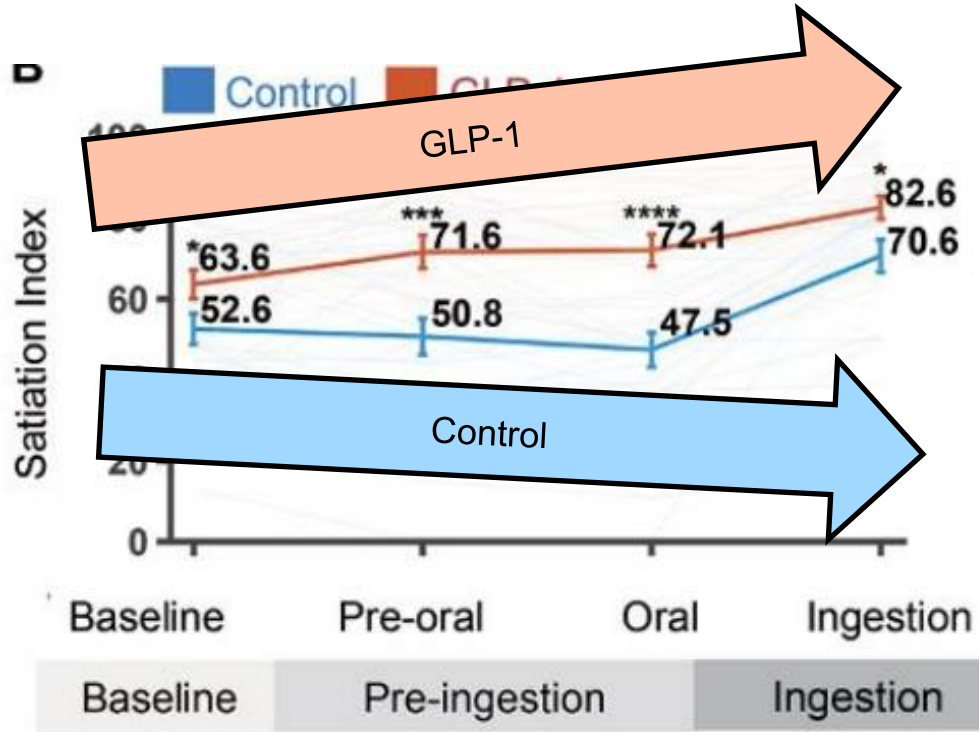


GLP-1R Agonist Injection Activates DMH GLP-1R Neurons



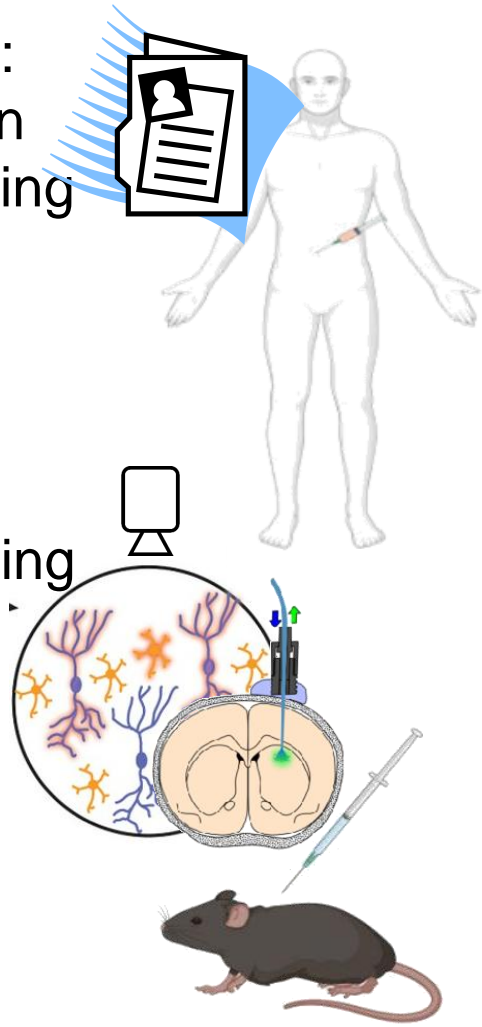
C





Human:
Emotion
Recording

Mouse:
Neural
Recording

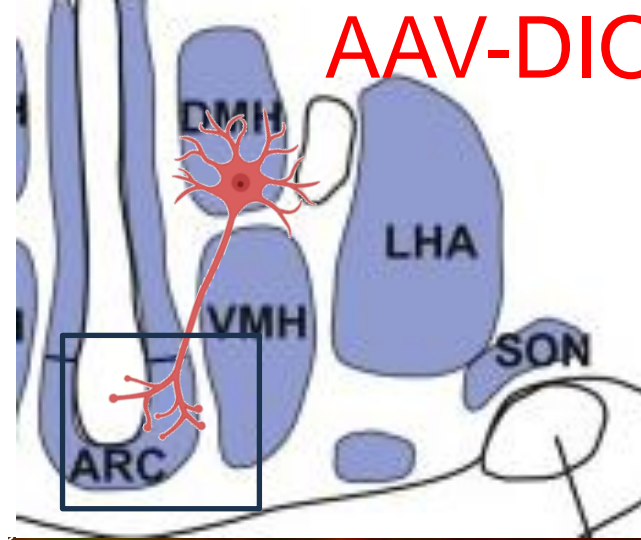


3D Mapping of DMH GLP-1R Neuron Outputs

3D Mapping of DMH^{GLP-1R} Neuron Outputs

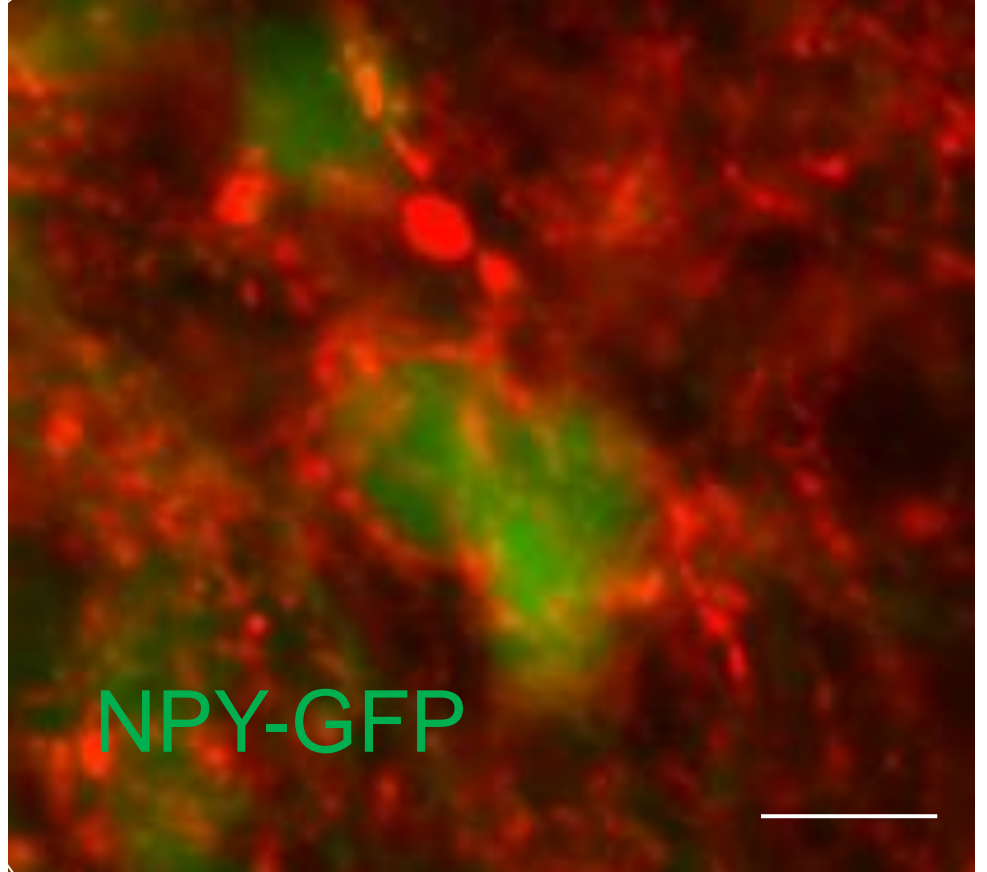
DMH^{GLP-1R} → ARC^{NPY/AgRP}

3V

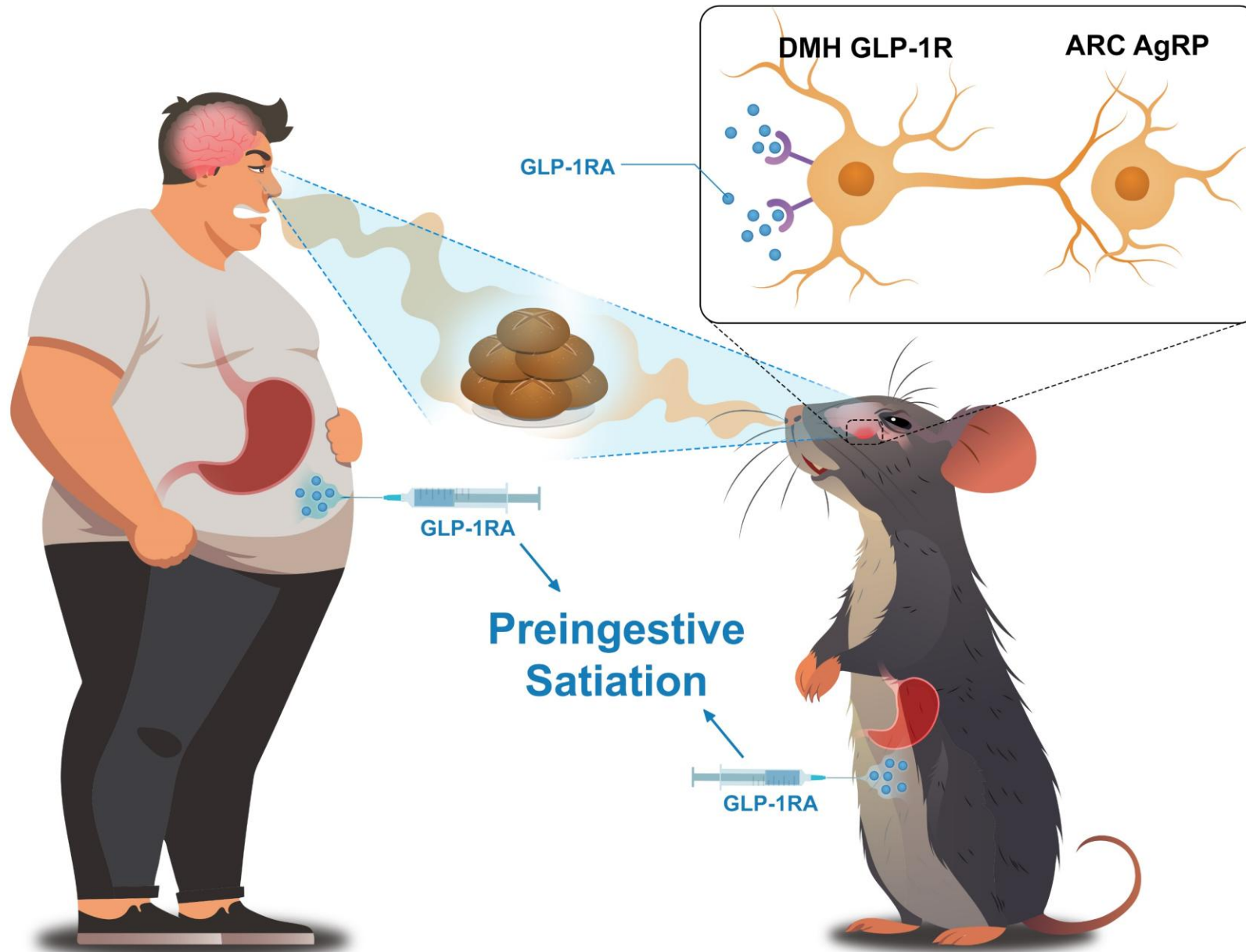


AAV-DIO-mCherry

Eunsang Hwang,
Kevin W. Williams,
UT Southwestern



NPY-GFP

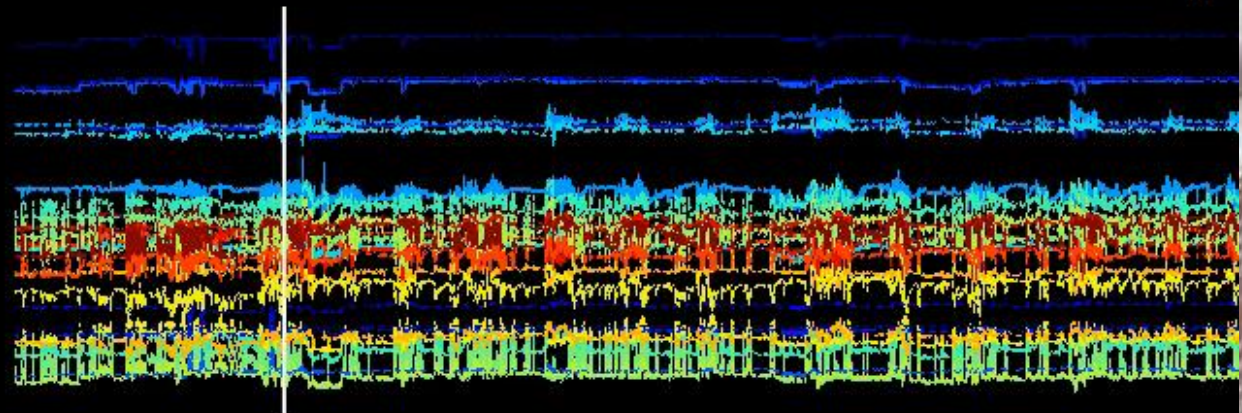




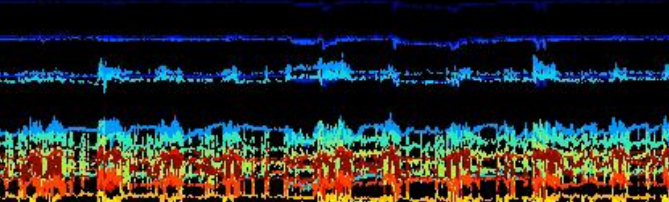
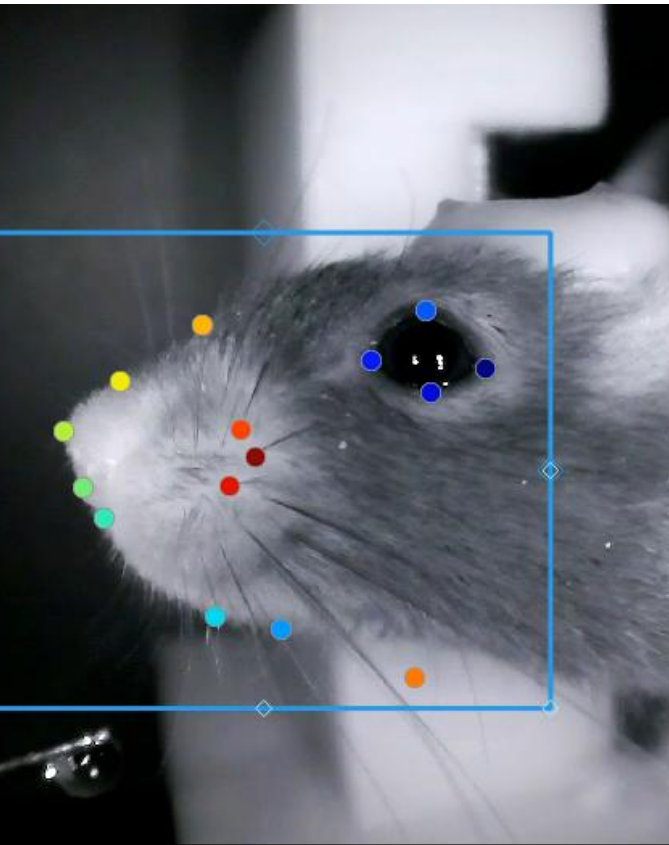
Yu-Been Kim

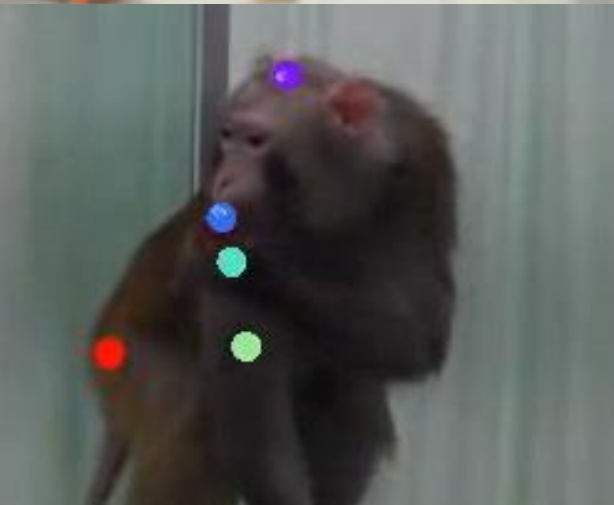


Keypo



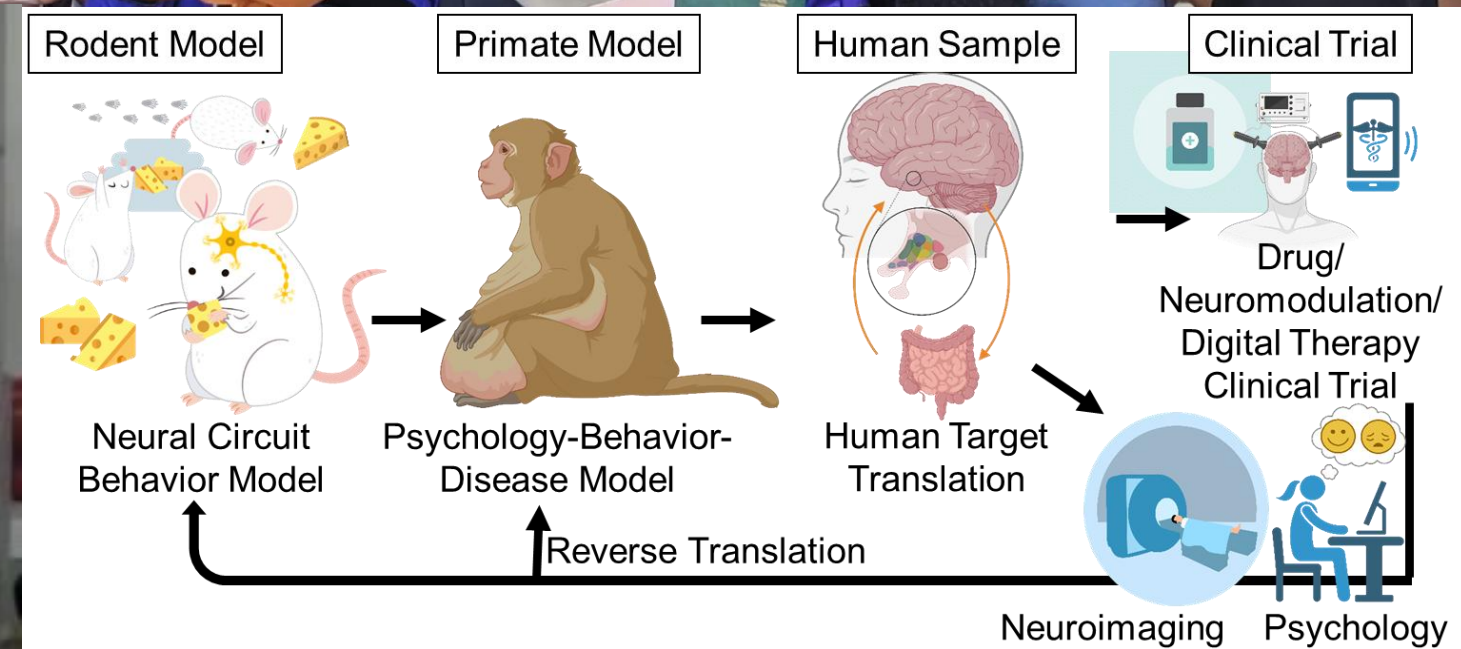
Translational Neuroscience Research for Eating Emotions





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Translational Appetite Research - Inviting Postdocs & Students

SNU Laboratory of Neurophysiology: Sang Jeong Kim Sungkyunkwan Univ.: HyungGoo R Kim
 UT Southwestern Medical Center, Kevin W. Williams Yonsei Univ.: Kiwoo Kim
 KAIST: Jong-Woo Sohn KRIBB National Primate Research Center: Youngjeon Lee
 SNU Hospital: Jung Hee Kim, Yong Hwy Kim