Neural circuits that control feeding

Avi Adhikari
Associate Professor, Department of Psychology,
Wenzel and Jeffrey Term Endowed Chair in Behavioral Neuroscience
University of California, Los Angeles
avi@psych.ucla.edu

Usual talk structure

-Based on prior data we predict these 13 very specific experimental outcomes

-All predictions were observed

Conclusion

-We are so good at predicting!

This talk's structure

-Based on prior data we made some predictions

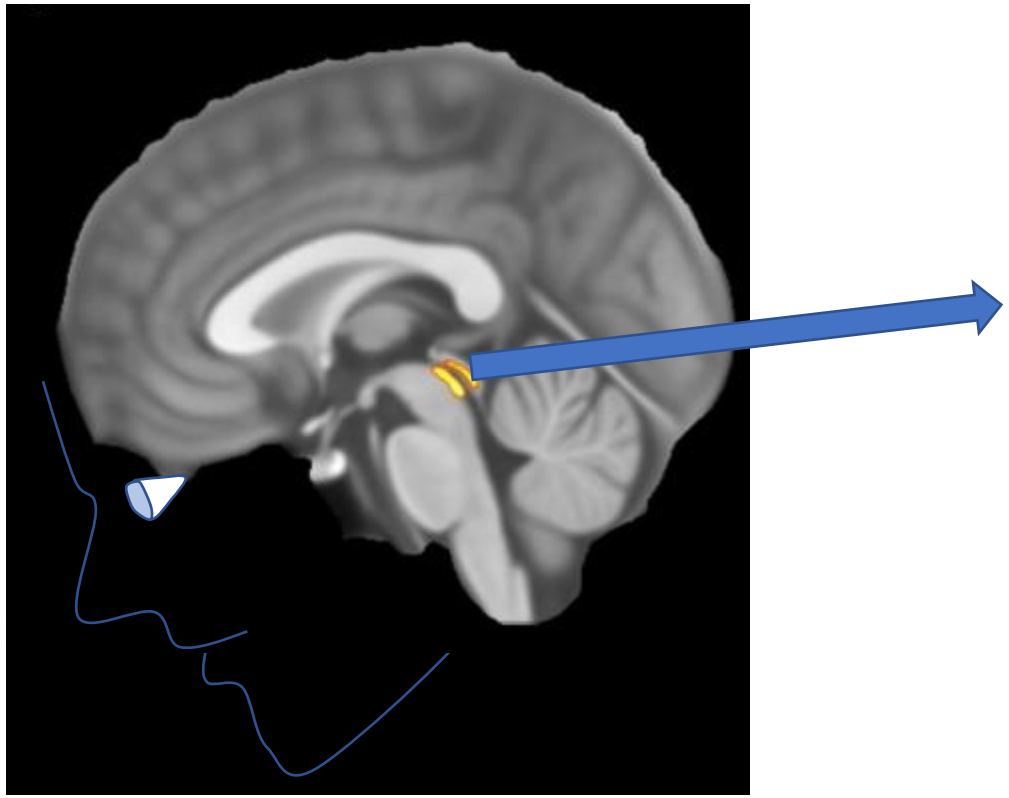
-No predictions were observed

-Unexpected results were seen

Conclusion

-We are bad at predicting, but unexpected results lead to new discoveries!

Activation of the brainstem periaqueductal gray (PAG) induces panic in humans



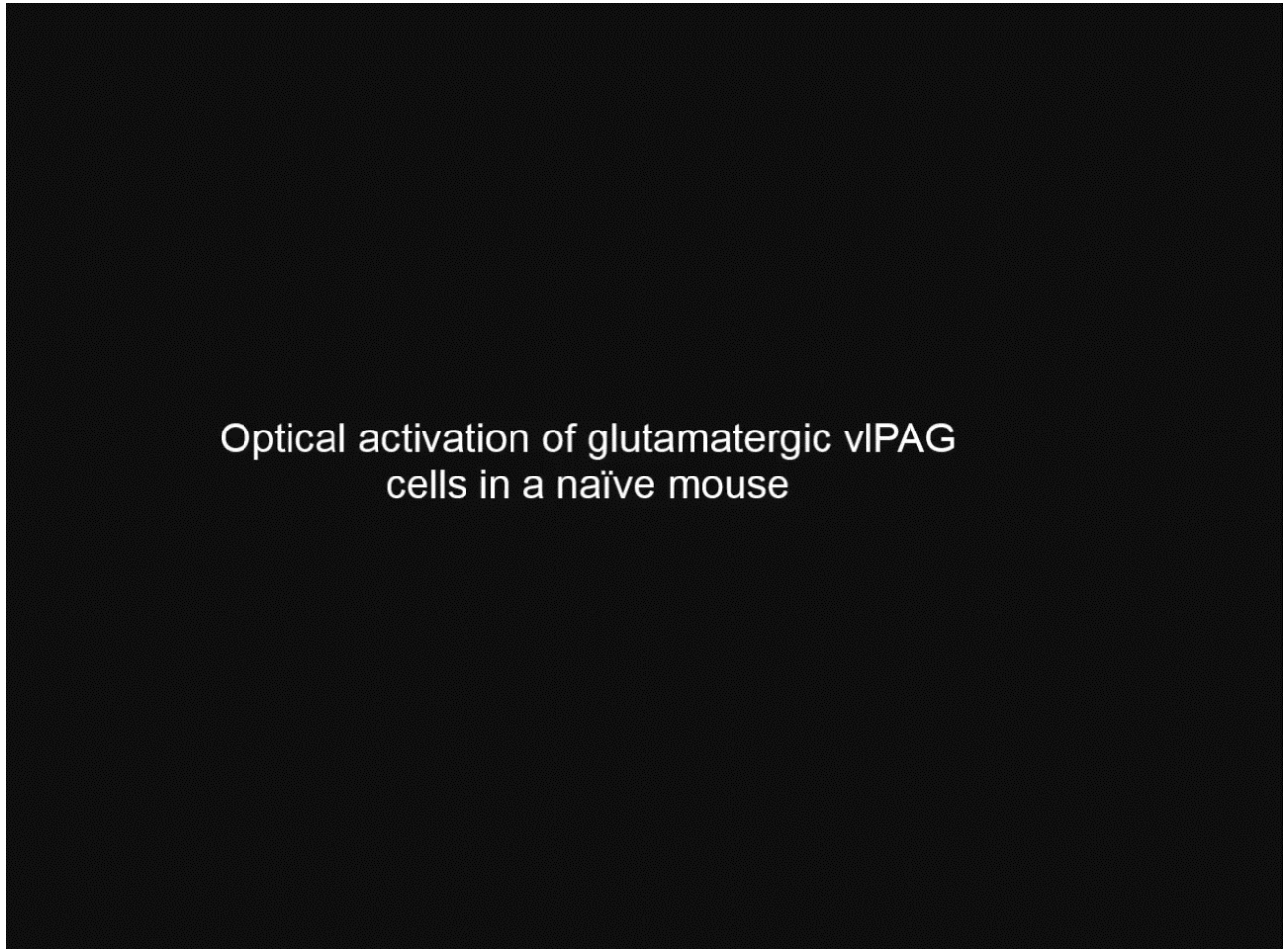
Electrical stimulation of the periaqueductal gray (PAG) region in the brain of patients causes panic. Subjects report feelings of being terrified, frightened and impending death!

Nashold, *J Neurosurgery*, 1969

Artificial activation of excitatory periaqueductal gray (PAG) neurons causes fear in mice (freezing)

Excitatory neurons (“gas pedal”) → Increase brain region’s electrical activity

Inhibitory neurons (“break pedal”) → Decrease brain region’s electrical activity



Tovote, *Nature* 2016

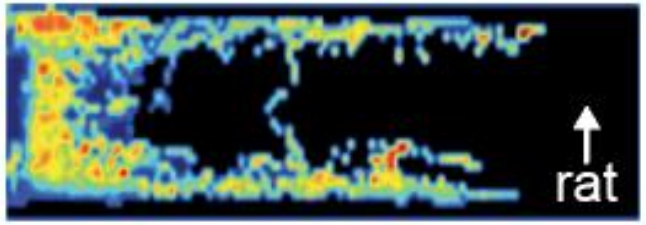
Prior work

Activation of the periaqueductal gray (PAG) → Induces fear and panic attacks

Our hypothesis

Activation of inhibitory neurons (“break pedals”) in the periaqueductal gray (PAG vgat neurons) → Inhibits fear?

Do inhibitory PAG vgat cells respond to a live predator?

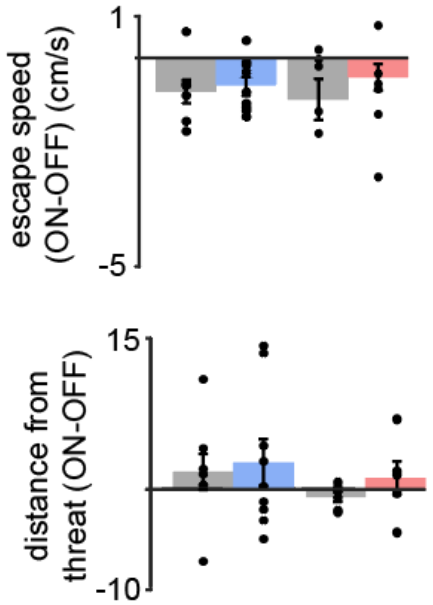


PAG vgat neural activity

Min. Max.

Inhibitory PAG vgat cells are not naturally more activated in mice near a predator

Does altering the activity of PAG vgat neurons change fear behaviors?

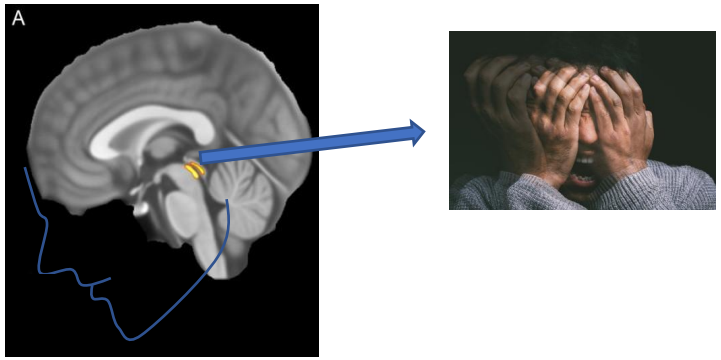


PAG vgat control

PAG vgat inhibition

PAG vgat excitation

Periaqueductal gray (PAG)



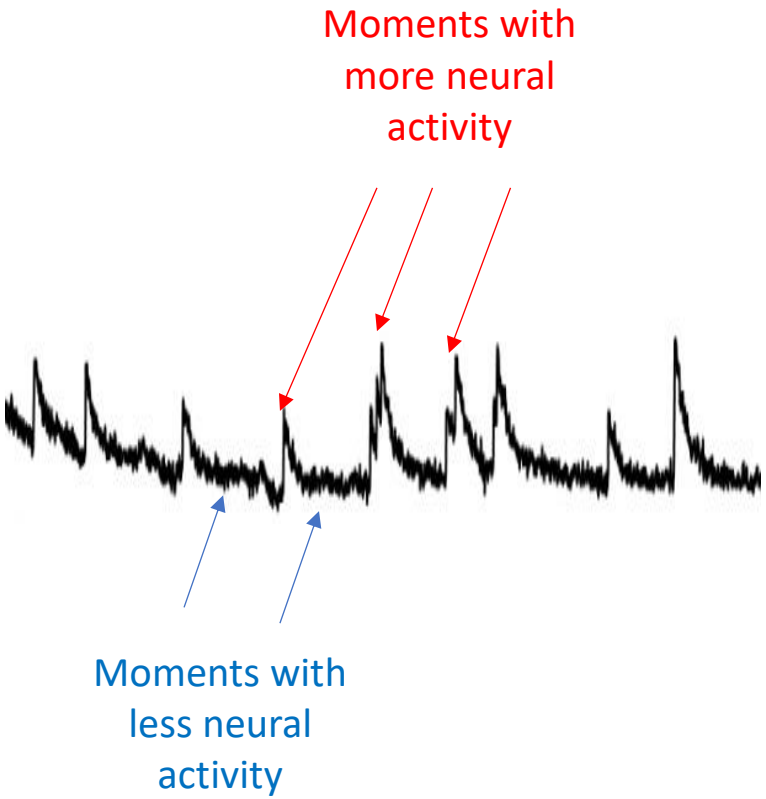
Inhibition or excitation of inhibitory PAG vgat neurons in mice does not alter fear

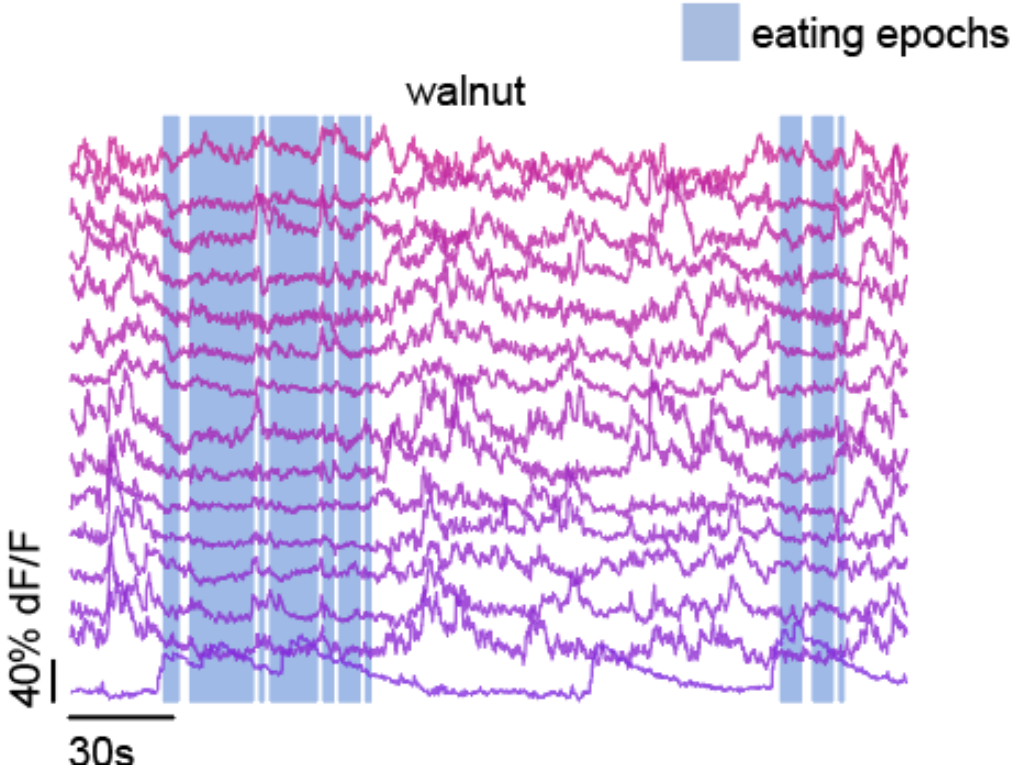
Excitation of PAG vgat cells induces more consumption of caloric foods in non-hungry mice

chow

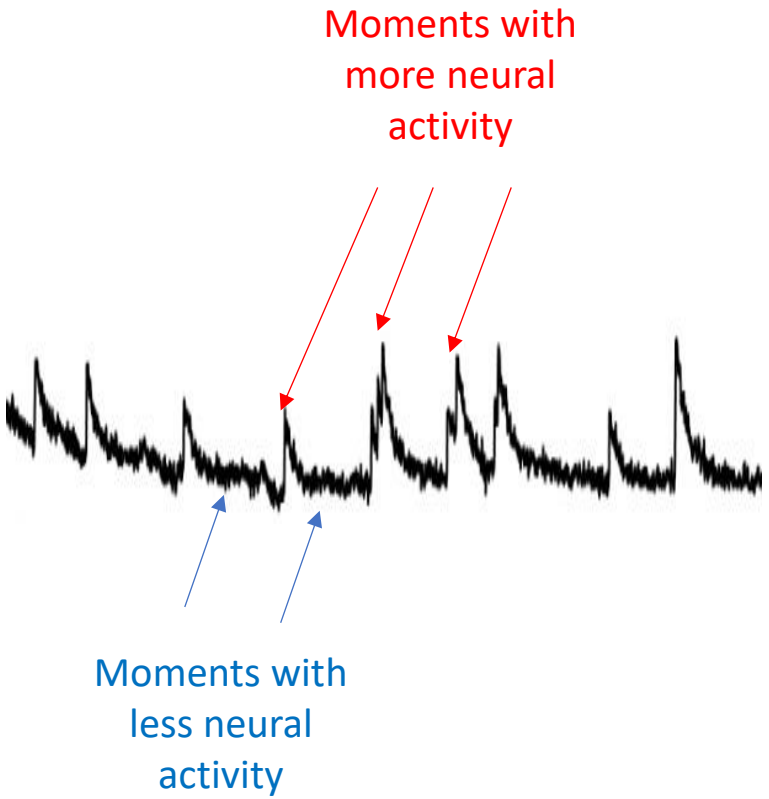
chocolate

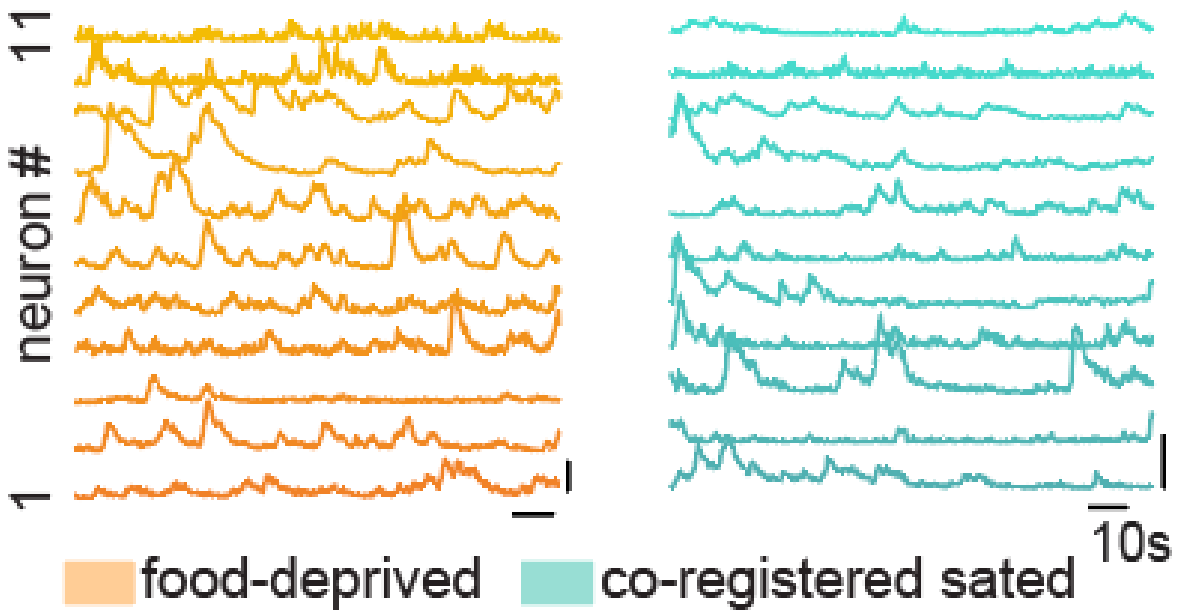
PAG inhibitory vgat neurons are more active while food seeking and less active during eating



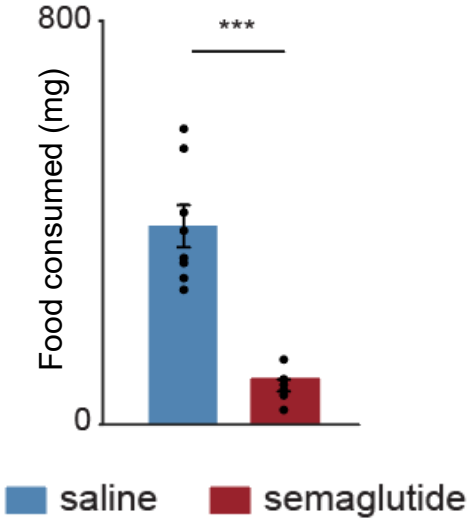


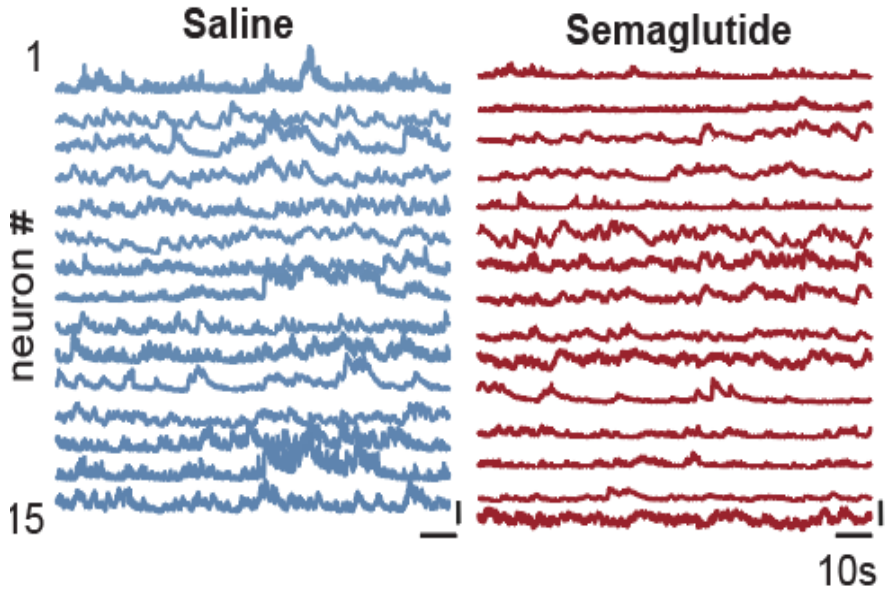
Inhibitory PAG vgat cells are more active during hunger





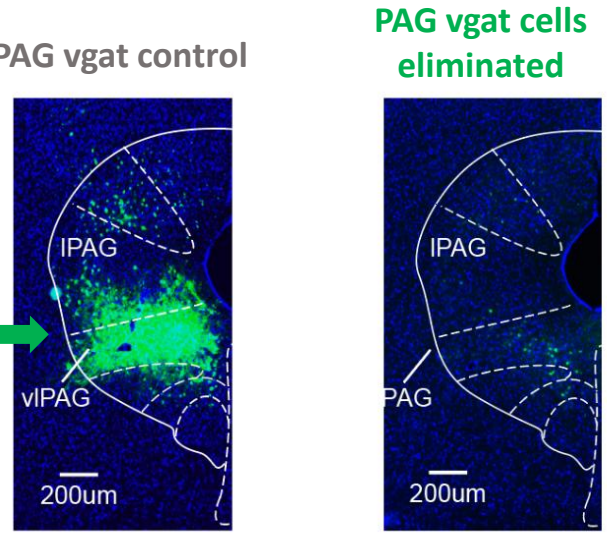
PAG vgat cells are inhibited by Ozempic (semaglutide)

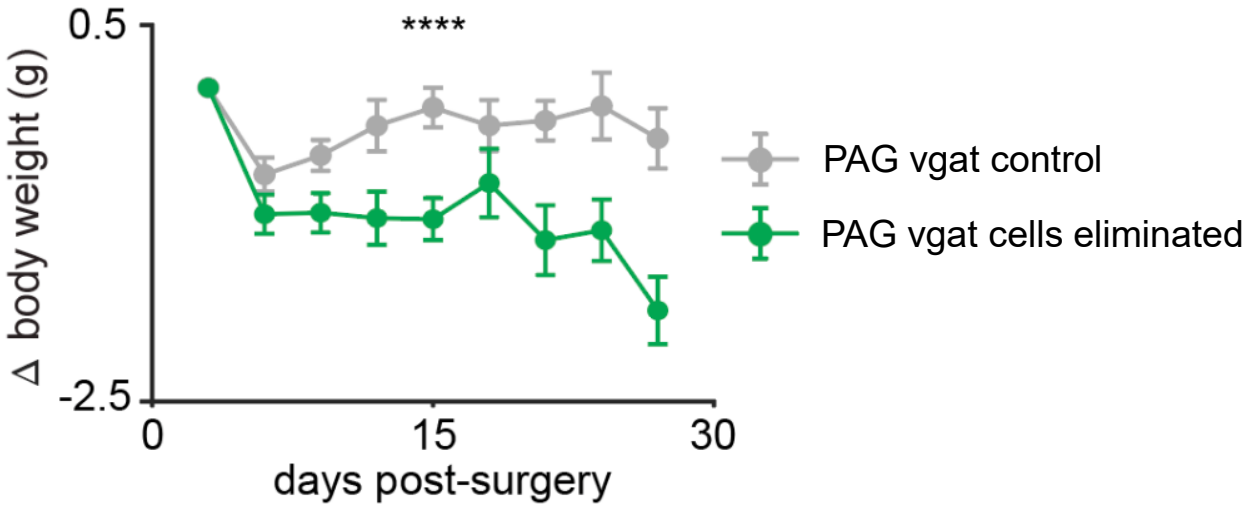




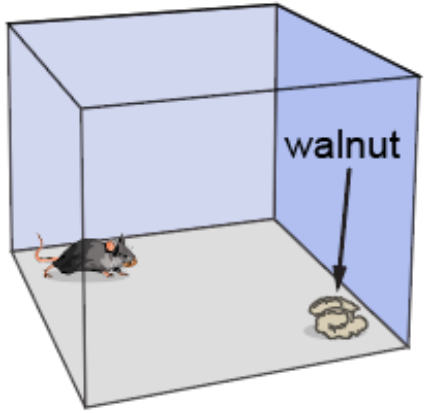
Eliminating PAG vgat cells decreases body weight

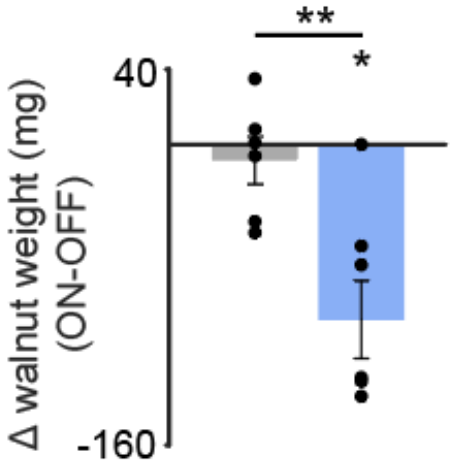
PAG vgat cells are shown in green





Artificial PAG vgat neuron inhibition decreases eating in hungry mice





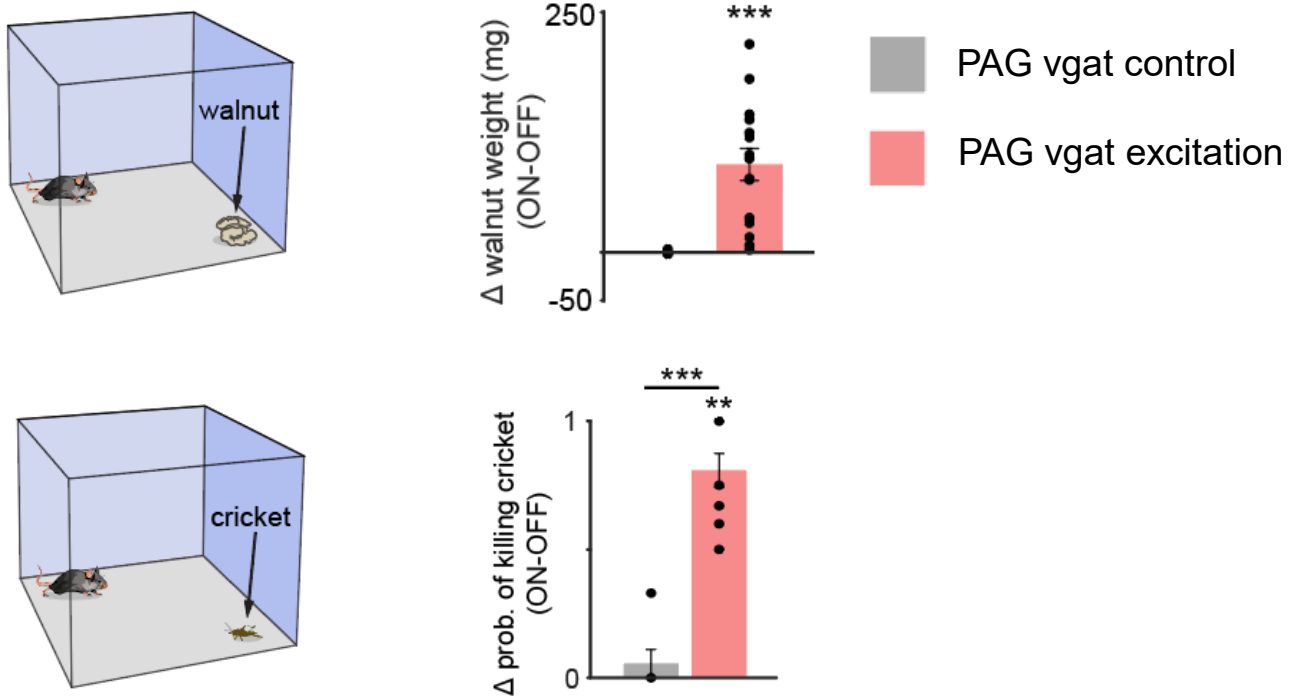
PAG vgat control

PAG vgat inhibition

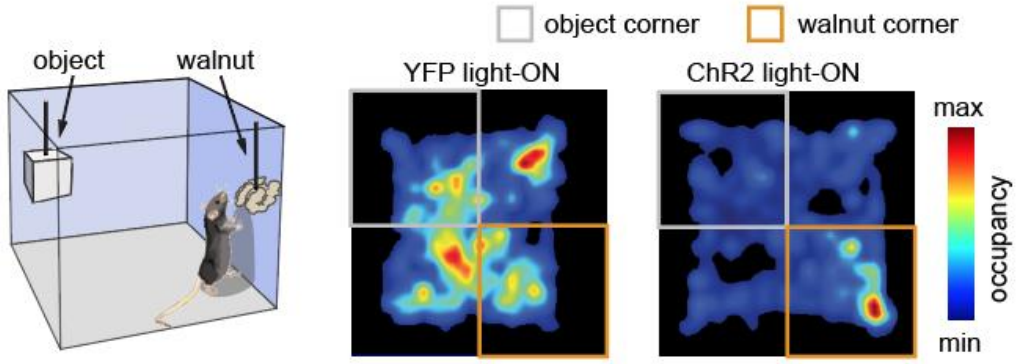
Activation of PAG vgat cells induces hunting

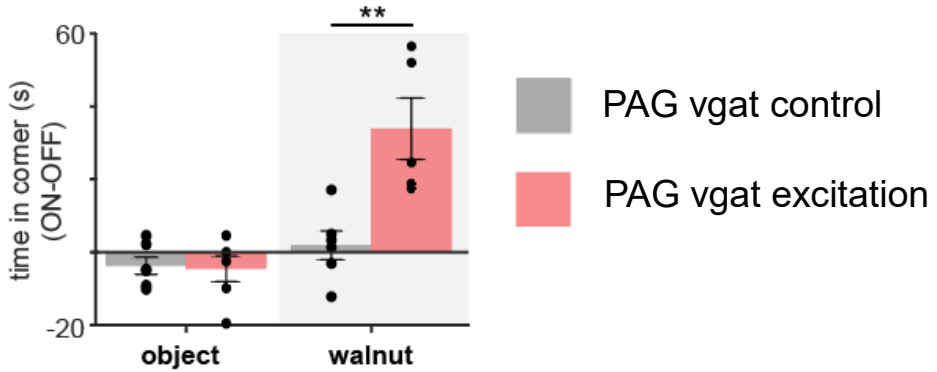
Reis et al., Nature Communications 2024

PAG vgat activation increases eating in non-hungry mice

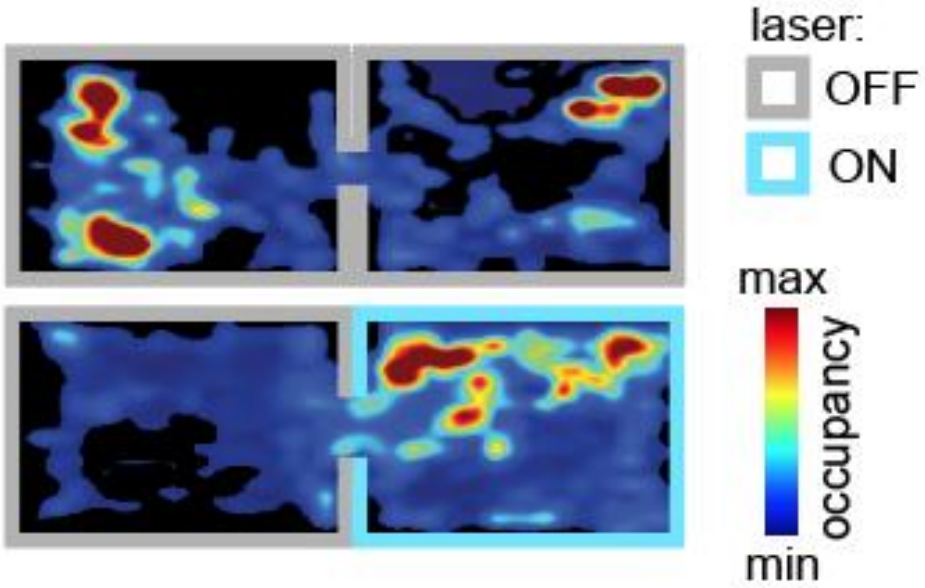


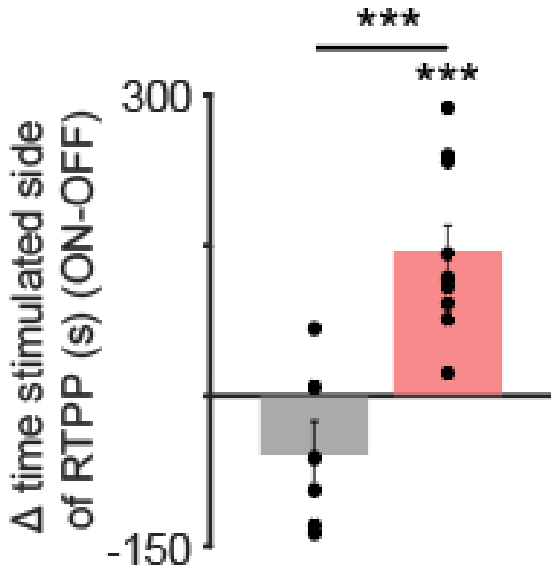
PAG vgat excitation increases approach to food but not objects





PAG vgat excitation induces positive motivation



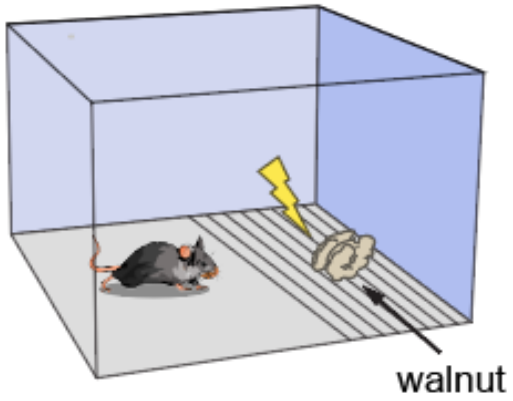


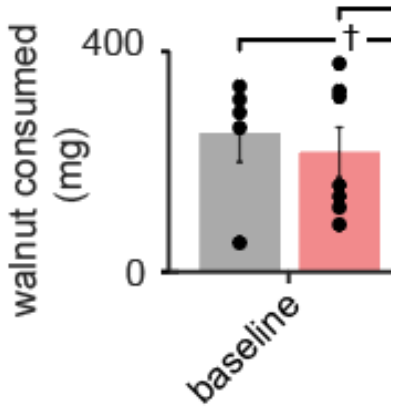
PAG vgat control

PAG vgat excitation

Since mice “like” or “seek” activation of PAG vgat cells, these neurons are not creating unpleasant hunger when activated

PAG vgat excitation induces compulsive food seeking (foraging despite a negative consequence)

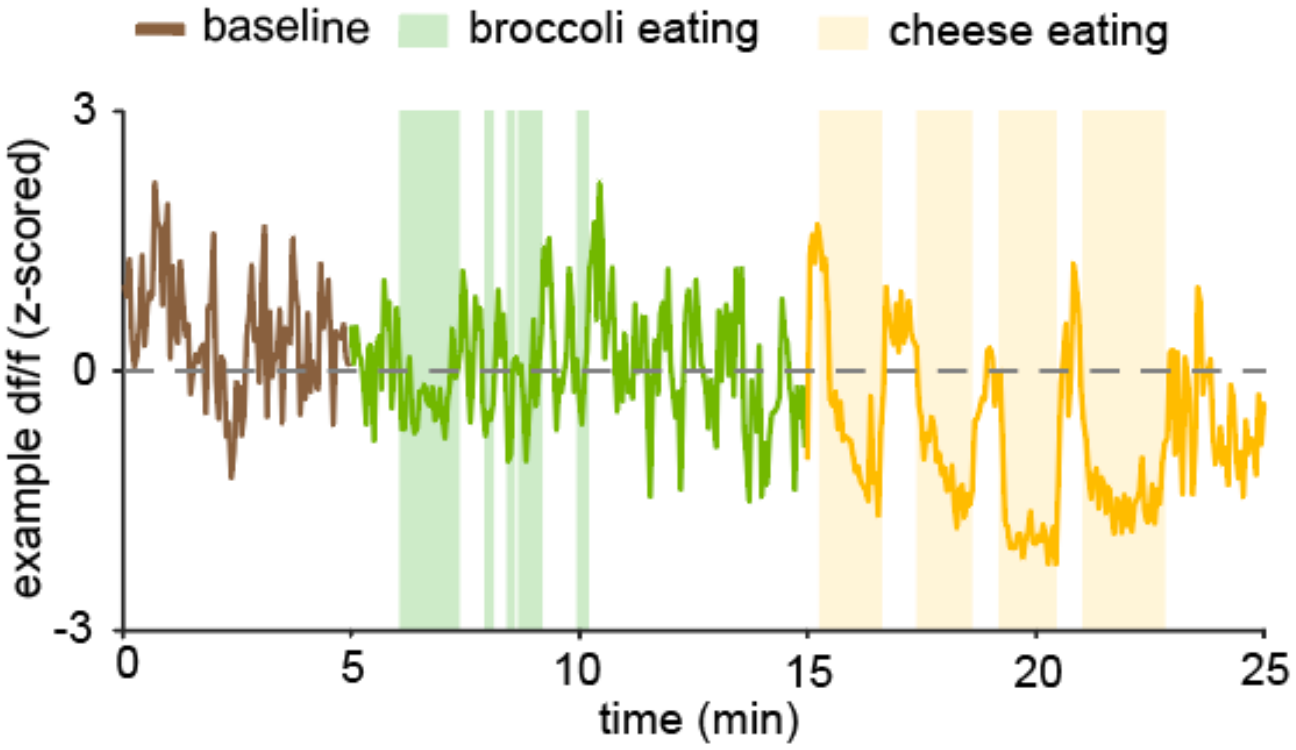




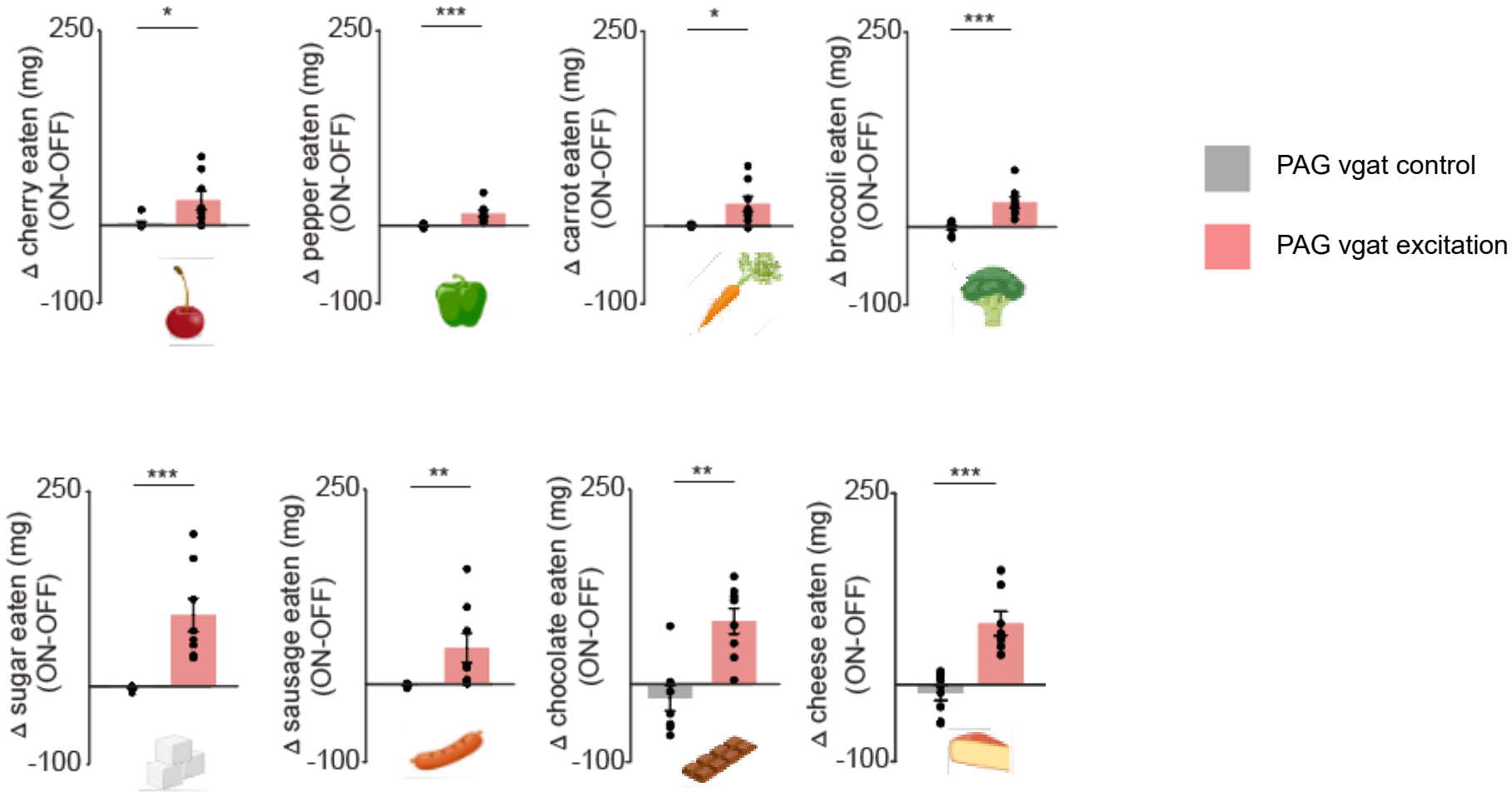
PAG vgat control

PAG vgat excitation

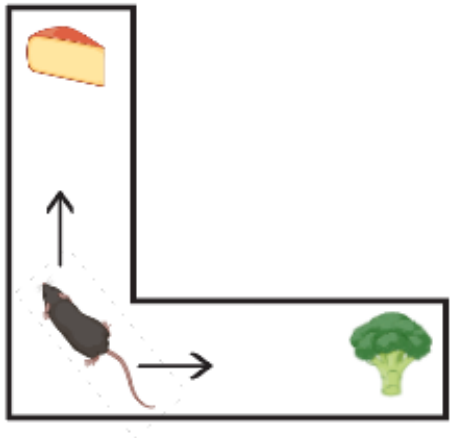
PAG vgat cells show increased neural activity modulation during consumption of caloric foods

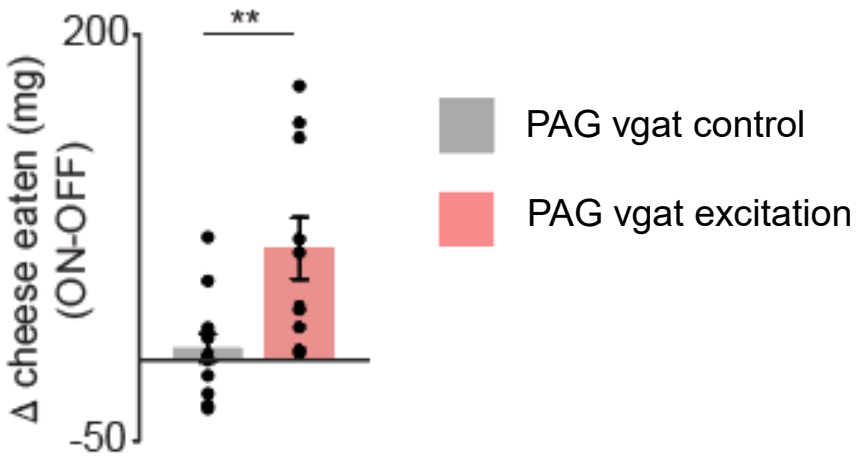


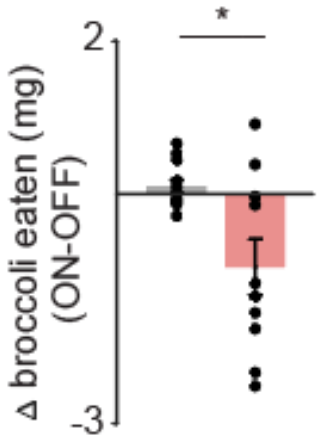
Excitation of PAG vgat cells in non-hungry mice induces more consumption of caloric foods compared to vegetables

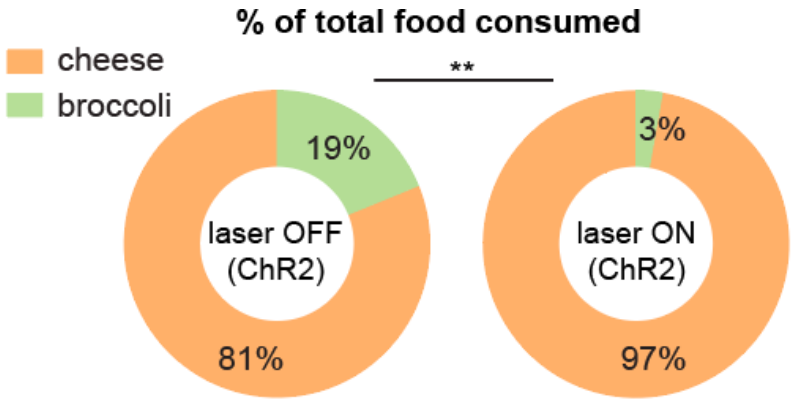


Excitation of PAG vgat cells shifts eating choices towards caloric foods





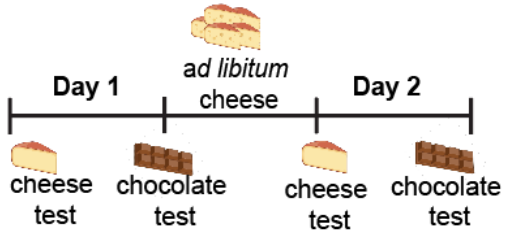


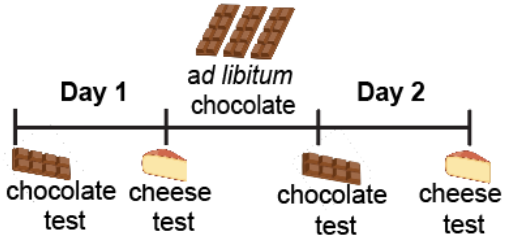


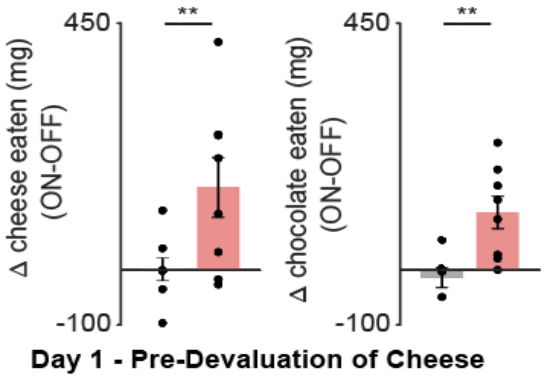
PAG vgat activation does not induce consumption of de-valued foods

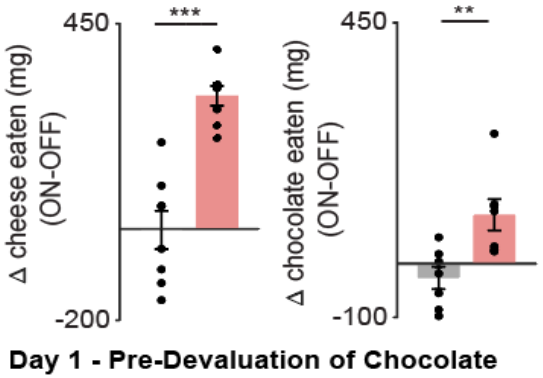
PAG vgat control

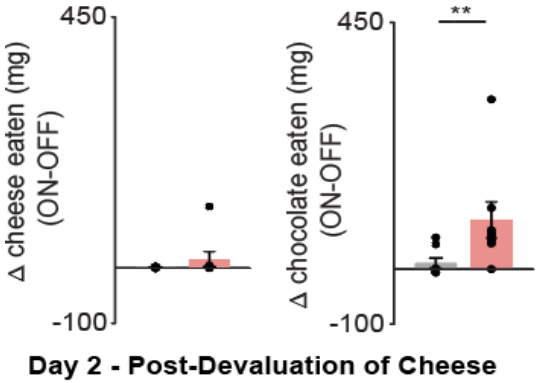
PAG vgat excitation

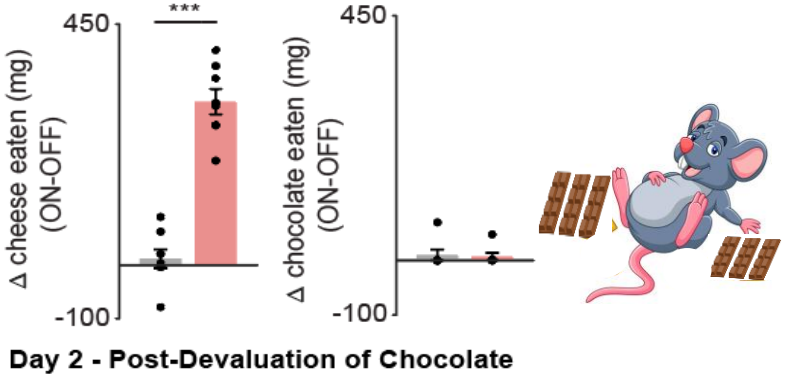




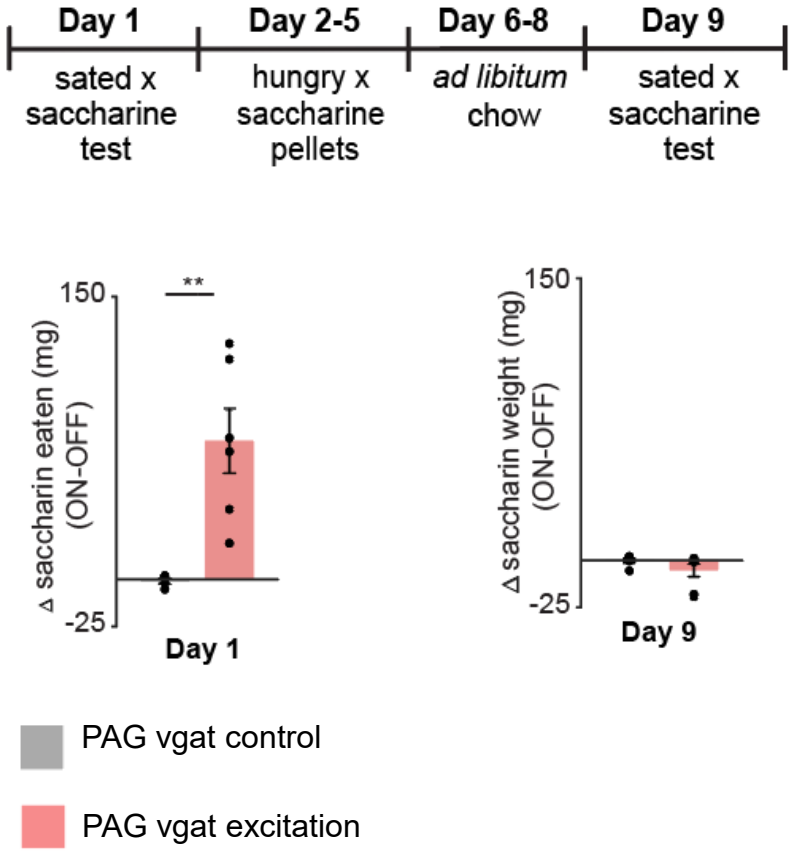




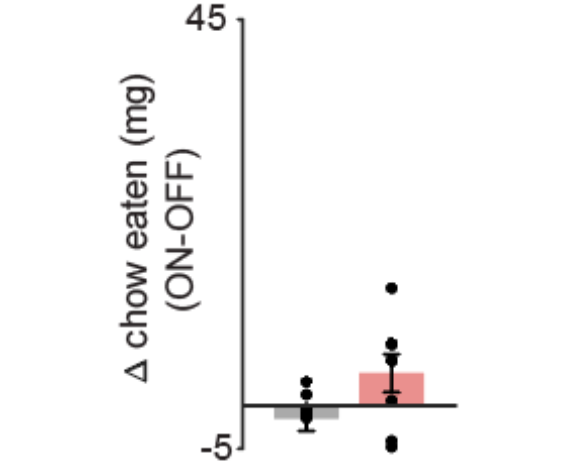




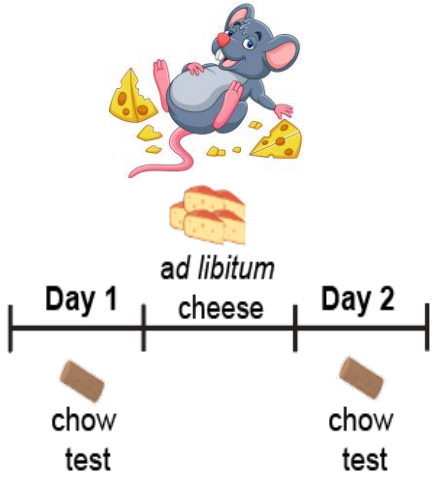
PAG vgat activation increases consumption of saccharine only before mice learn that saccharine does not decrease hunger

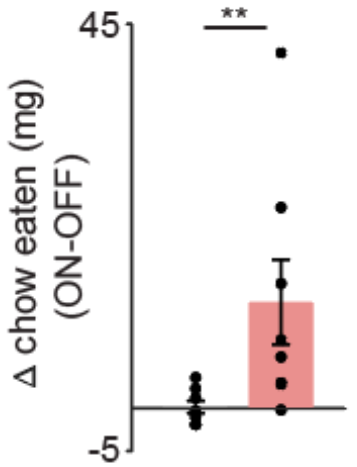


PAG vgat cells activation causes chow eating in sated mice only after chow deprivation



Day 1 - Pre-Revaluation of Chow



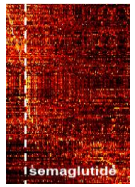


Day 2 - Post-Revaluation of Chow

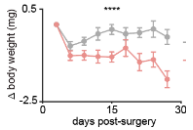
PAG vgat control

PAG vgat excitation

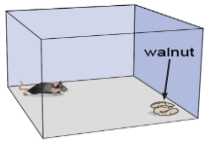
Conclusions



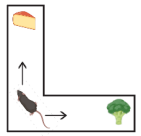
These neurons are more active during hunger, and is suppressed by Ozempic



Elimination of PAG vgat cells induces weight loss



PAG vgat activation causes eating in non-hungry mice and inhibiting these cells decreases eating in hungry mice



ad libitum
cheese

PAG vgat activation shifts dietary preferences towards caloric foods

Activating these cells induces consumption of foods according to their current value

Potential consequences

PAG vgat neurons may contribute to Ozempic-mediated weight loss

Activation of these cells may be used to treat anorexia

Inhibition of these cells may be used to treat binge eating disorder

Excessive activation of these cells may promote overeating of caloric foods that are being craved

Humans also have PAG vgat neurons, so these results may be applicable to people as well!

Acknowledgements

Nitish Patel
Anita Liu
Fernando Reis
Huan Zhao
Blake Miranda
Enya Walker
Hillary Leeds
Milena Mnatsakanyan
Sabrina Liao

Stephanie Correa and E. van Veen labs (UCLA)
Garrett Blair (New York U)

Parents Sadhan and Ratna and wife Emily

No financial disclosures

Acknowledgements

National Institute of Mental Health

BRAIN & BEHAVIOR RESEARCH FOUNDATION
Awarding NARSAD Grants
(NARSAD x 4!)

Karl Deisseroth

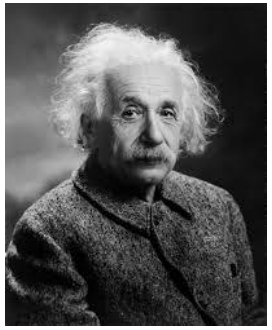
Joshua Gordon

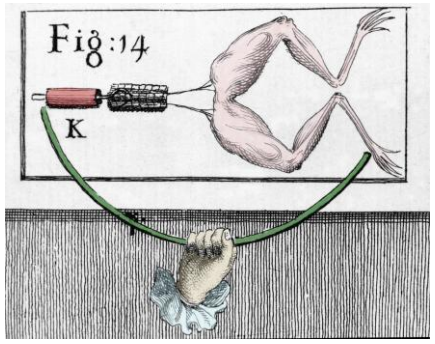
Hellman Fellows Fund

NSF

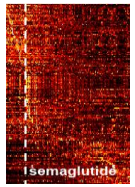
NIH National Institute of Diabetes and Digestive and Kidney Diseases

Discoveries often lead to very unexpected applications

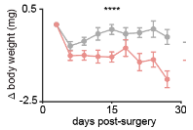




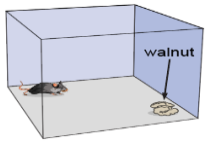
Questions?



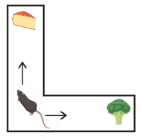
These neurons are more active during hunger, and is suppressed by Ozempic



Elimination of PAG vgat cells induces weight loss



PAG vgat activation causes eating in non-hungry mice and inhibiting these cells decreases eating in hungry mice



ad libitum
cheese

PAG vgat activation shifts dietary preferences towards caloric foods

Activating these cells induces consumption of foods according to their current value

PAG vgat neurons may contribute to Ozempic-mediated weight loss

Activation of these cells may be used to treat anorexia

Inhibition of these cells may be used to treat binge eating disorder

Excessive activation of these cells may promote overeating of caloric foods that are being craved

Humans also have PAG vgat neurons, so these results may be applicable to people as well!