Semaglutide Alters Global Network Connectivity and Reward Processing in Awake Rats

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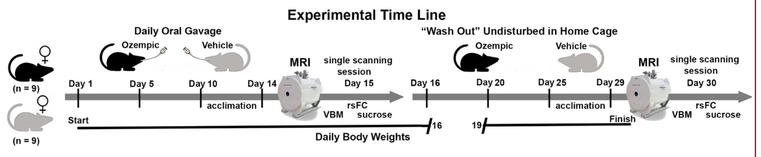
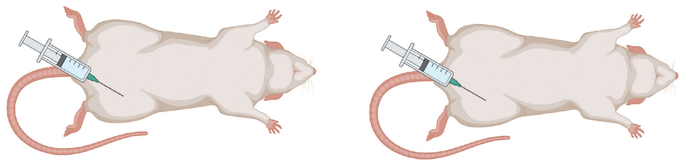
Introduction

Glucagon-like peptide-1 (GLP-1) receptor agonists reduce food craving and hedonic intake beyond metabolic effects. However, the neural mechanisms underlying GLP-1-mediated changes in sensory processing remain poorly understood. We investigated how semaglutide influences reward processing and neural activity using gustatory stimulus-based BOLD fMRI, voxel-based morphometry (VBM), and resting state functional connectivity (rsFC).

Experimental Design



Ozempic Administration

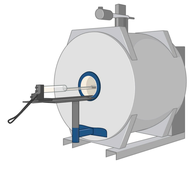


Vehicle **Semaglutide (Ozempic)**

Day 1 and Day 15

- Female Sprague Dawley rats were divided into two groups receiving either semaglutide (n=9) or vehicle (n=9) treatment through daily intraperitoneal injections
- Weights were collected daily as well
- A 10-day titration phase was conducted, increasing doses from 5 to 50µg/kg
- Following titration, rats were maintained at 50µg/kg until day 15.

7T Magnetic Resonance Imaging (MRI)



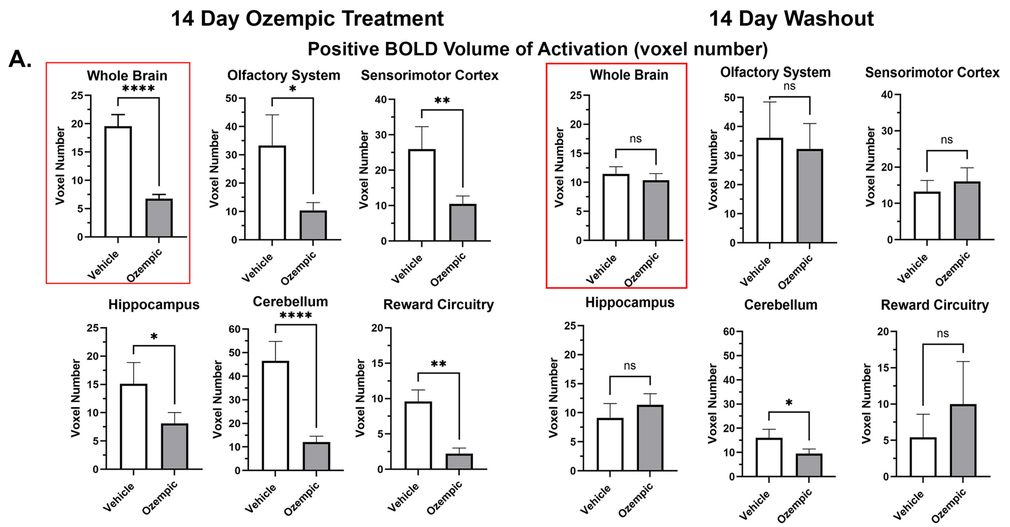
Sucrose Bite Bar Administration

Day 16 and Day 30

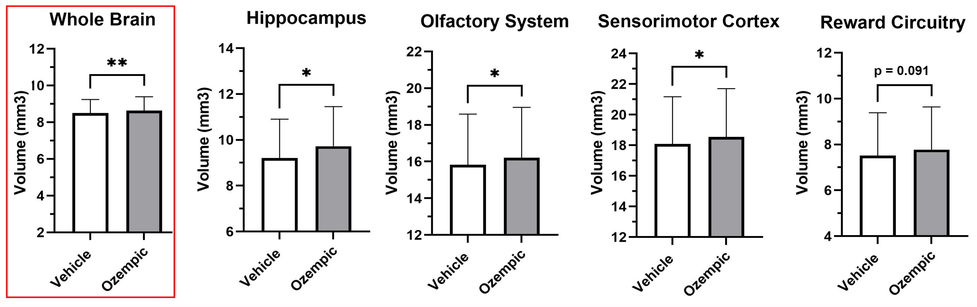
- Voxel-based morphology (VBM), gustatory stimulus based BOLD fMRI, and resting-state functional connectivity (rsFC) were done on a 7T Bruker Biospec 70/20
- 0.1mL of sucrose was administrated through the bite bar at a 30% concentration

Imaging

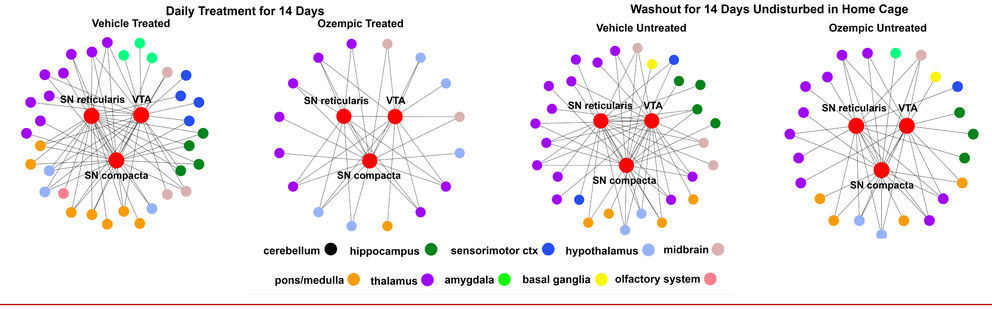
Stimulus-based BOLD fMRI



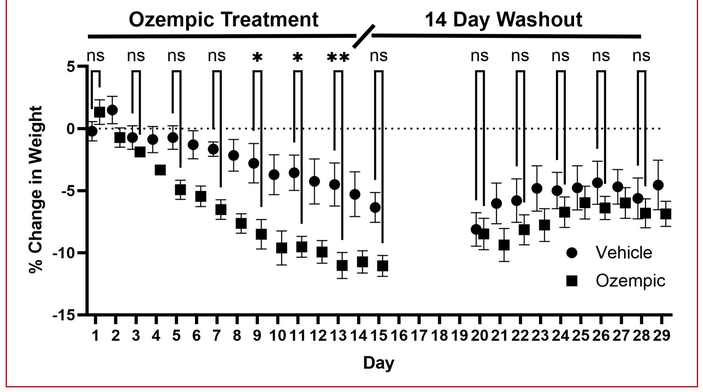
Voxel-based Morphometry: Daily Treatment for 14 Days



Functional Connectivity to Midbrain Dopaminergic Nuclei



Body Weights



Discussion

Chronic semaglutide treatment broadly suppressed food craving, reducing BOLD activation across reward circuitry, cerebellum, sensorimotor cortex, and hippocampus. The negative BOLD response in reward circuitry suggests active inhibition of mesolimbic engagement with food stimuli, consistent with GLP-1 agonists lowering the hedonic value of food. Functional connectivity between midbrain dopaminergic nuclei and downstream targets was also reduced, indicating disrupted coordination within feeding-related reward circuits.

After a 14-day washout, most rats partially regained body weight, suggesting some effects are reversible. However, neither body weight nor dopaminergic connectivity fully normalized, indicating incomplete recovery within this period. Overall, these findings suggest semaglutide suppresses neural systems involved in motivational salience to food, with some effects persisting after drug discontinuation.

Conclusion

Future directions include examining molecular relationships using lipidomics. Overall, this research has important clinical relevance, highlighting how semaglutide not only alters feeding behaviors but also affects neurobiological mechanisms that may contribute to broader metabolic and behavioral outcomes.

Acknowledgements

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