Semaglutide Alters Reward Circuit Activation and Connectivity with Partial but Incomplete Normalization After Washout

***T. CHUKWUEMEKA**[1], B. AXE[1], S. GALLO[1], T. MUSKU[1], R. J. ORTIZ[4], A. MAHESWARI[1], N. CAVALLARO[1], P. P. KULKARNI[2], C. F. FERRIS[3]

[1]Northeastern University, Boston, MA; [2]Psychology; [3]Dept Psychology, Boston, MA; [4]Northern Illinois Univ., Northern Illinois Univ., DeKalb, IL

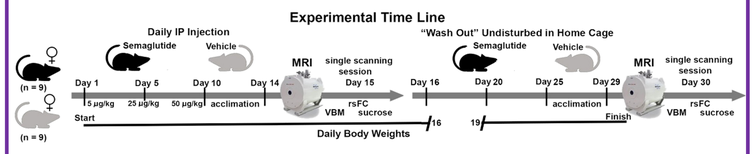
Northeastern University
John Martinson Honors Program

Center for Translational Neuro-Imaging

Introduction

Glucagon-like peptide-1 (GLP-1) receptor agonists are widely used for type 2 diabetes and body weight management, yet the neural mechanisms underlying their effects on reward processing, appetite regulation, and metabolism remain poorly understood. Our study investigates 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



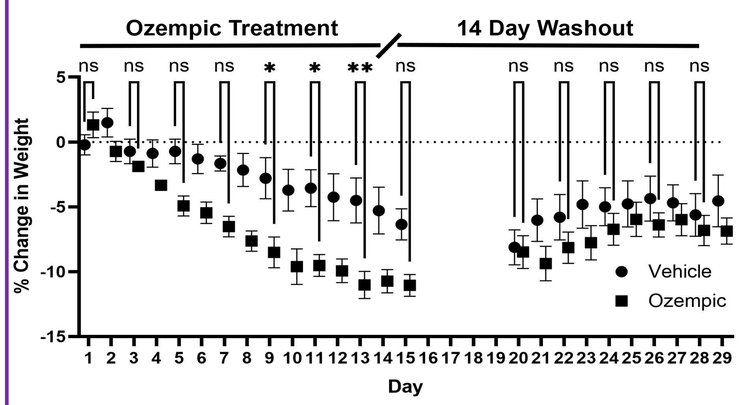
Day 1 through Day 14

- Female Sprague Dawley rats were divided into two groups: Semaglutide (N=9) or Vehicle (N=9) receiving treatment through daily intraperitoneal injections
- Weights were collected daily
- A 10-day titration phase was conducted, increasing doses from 5 to 50µg/kg
- Following titration, rats were maintained at 50µg/kg until day 14

Day 15 and Day 30

- Imaging performed after the end of treatment (Day 15) and at the end of 14-day drug free washout period (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
- Plasma samples collected on Day 14 (end of treatment) and Day 30 (end of washout) for lipidome profiling

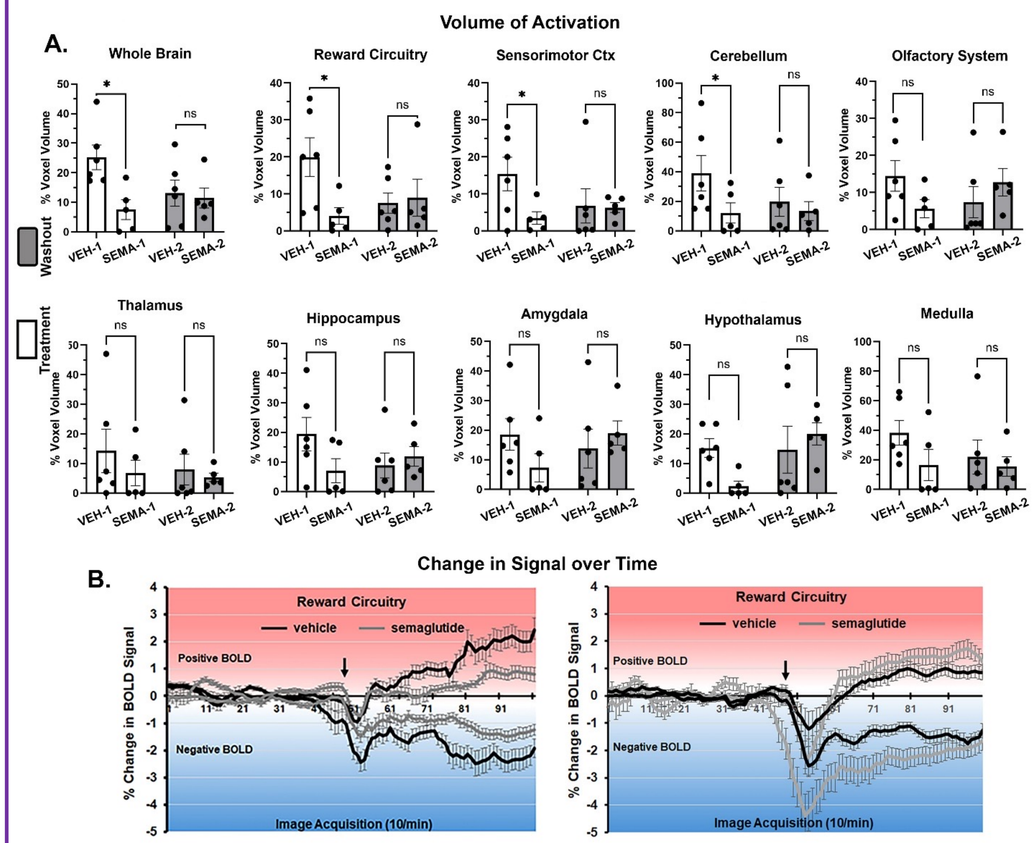
Body weight



Two-way ANOVA with Sidak's multiple comparisons test

Treatment x day interaction ($F_{(24,300)}$ = 1.506, p = 0.063), significance in treatment effect ($F_{(1,300)}$ = 88.91, p <0.0001); Sidak comparison test showed reduced body weight (day 8 to 14); No significant between groups after washout period

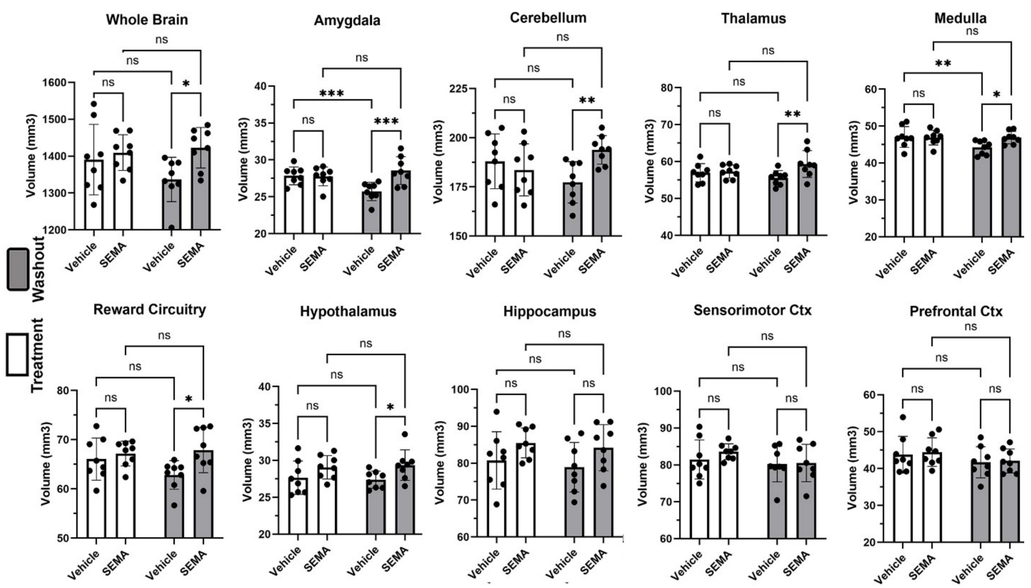
Gustatory Stimulus-based BOLD fMRI



Two-way mixed-model ANOVA (Drug × Scan), repeated-measures two-way ANOVA, and independent-samples t-tests

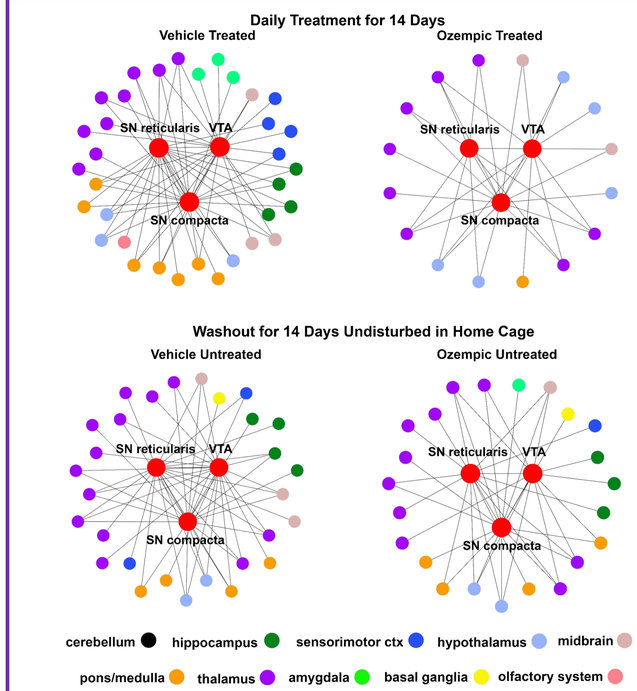
P<0.05, ****p<0.0001

Voxel Based Morphometry



Two-way mixed ANOVA with Sidak's multiple comparisons test; ***P<0.05, ****p<0.0001***

Functional Connectivity to Midbrain Dopaminergic Nuclei



Discussion

In awake female rats, 14 days of semaglutide reduced body weight and suppressed the brain's response to sucrose across reward circuitry, sensorimotor cortex, and cerebellum, suggesting a blunted response to an innately rewarding taste. Connectivity around the midbrain dopaminergic nuclei was reorganized rather than simply reduced, with VTA coupling increasing with the ventral striatum and hypothalamus and decreasing with the dorsal striatum and insular cortex.

Following washout, body weight recovered, the dopaminergic reorganization largely reversed, and positive BOLD differences disappeared, though a trend toward suppressed negative BOLD in reward circuitry remained. Plasma lipids showed a similar split. Taurocholic acid, a bile acid, dropped during treatment and fully recovered, paralleling the reversible neural effects. In contrast, docosahexaenoic acid, a major structural fatty acid of neuronal membranes, and N-arachidonoyl glycine stayed reduced, indicating a lipid signature that lasts beyond treatment.

Overall, these exploratory findings suggest semaglutide alters reward processing in a partly reversible way, which may help explain weight regain. Without a pair-fed control, drug effects cannot be separated from reduced intake.

Acknowledgements

Ekam Imaging: Project funding & RF electronics for awake imaging

EKAM
THE IMAGE OF DRUG DISCOVERY