The Neurobiology of GLP-1: from Physiology to Clinical Applications

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UHN Toronto General Toronto Western Princess Margaret Toronto Rehab

Glucagon-Like Peptide-1 Effects

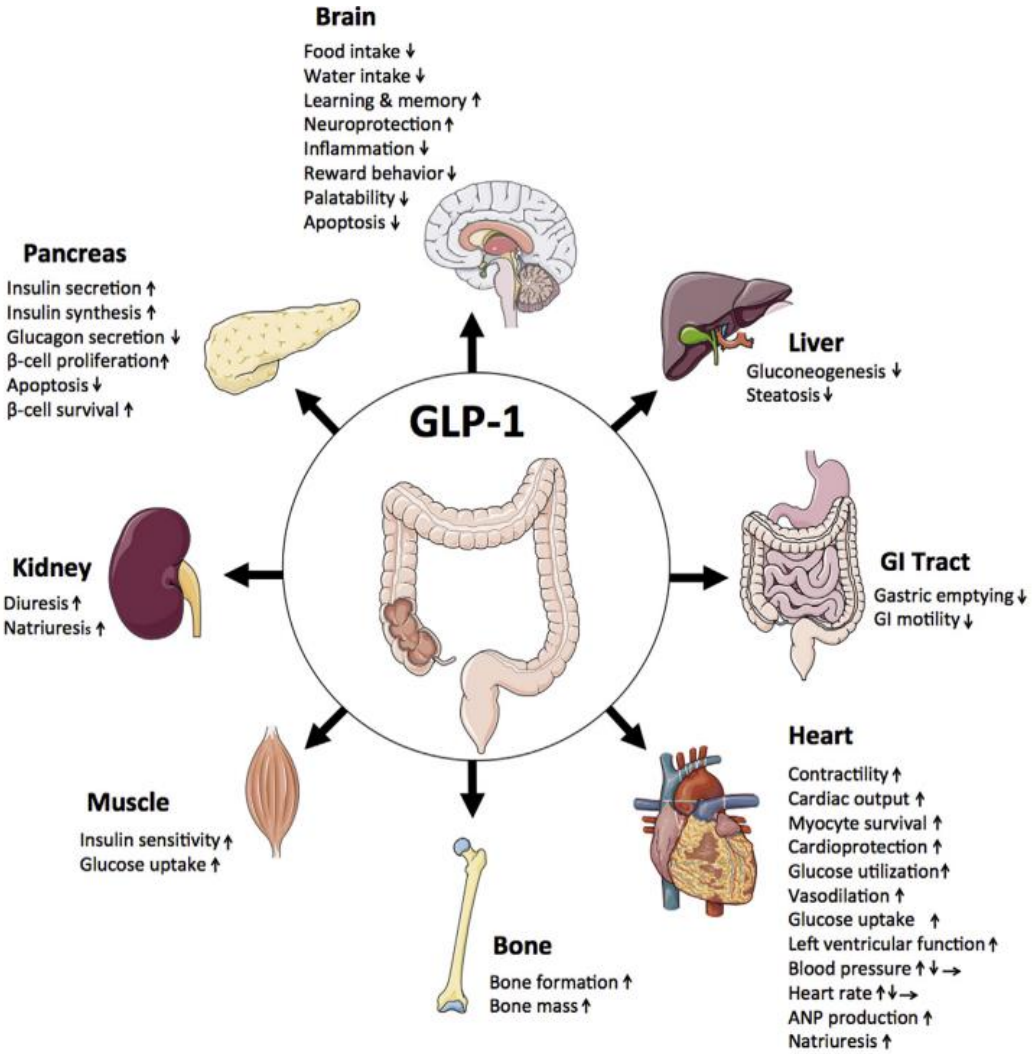


Figure 7: Schematic on the metabolic effects of GLP-1.

Muller et al. Mol Metab. 2019 Dec:30:72-130

GLP-1 in the Periphery

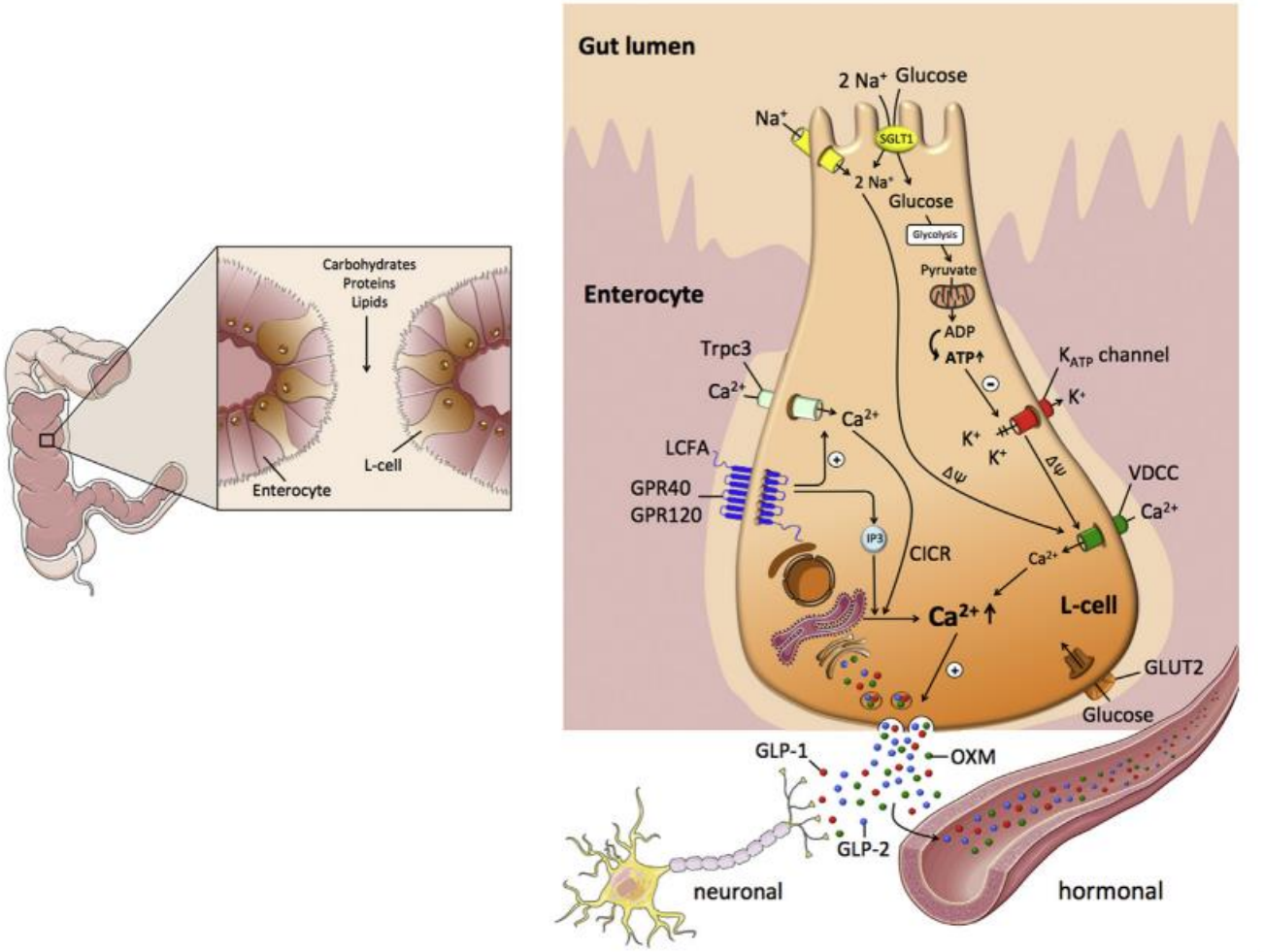


Figure 3: Schematic on the nutrient-induced stimulation of GLP-1 secretion in the L-cell.

Muller et al. Mol Metab. 2019 Dec:30:72-130

GLP-1 in the Periphery

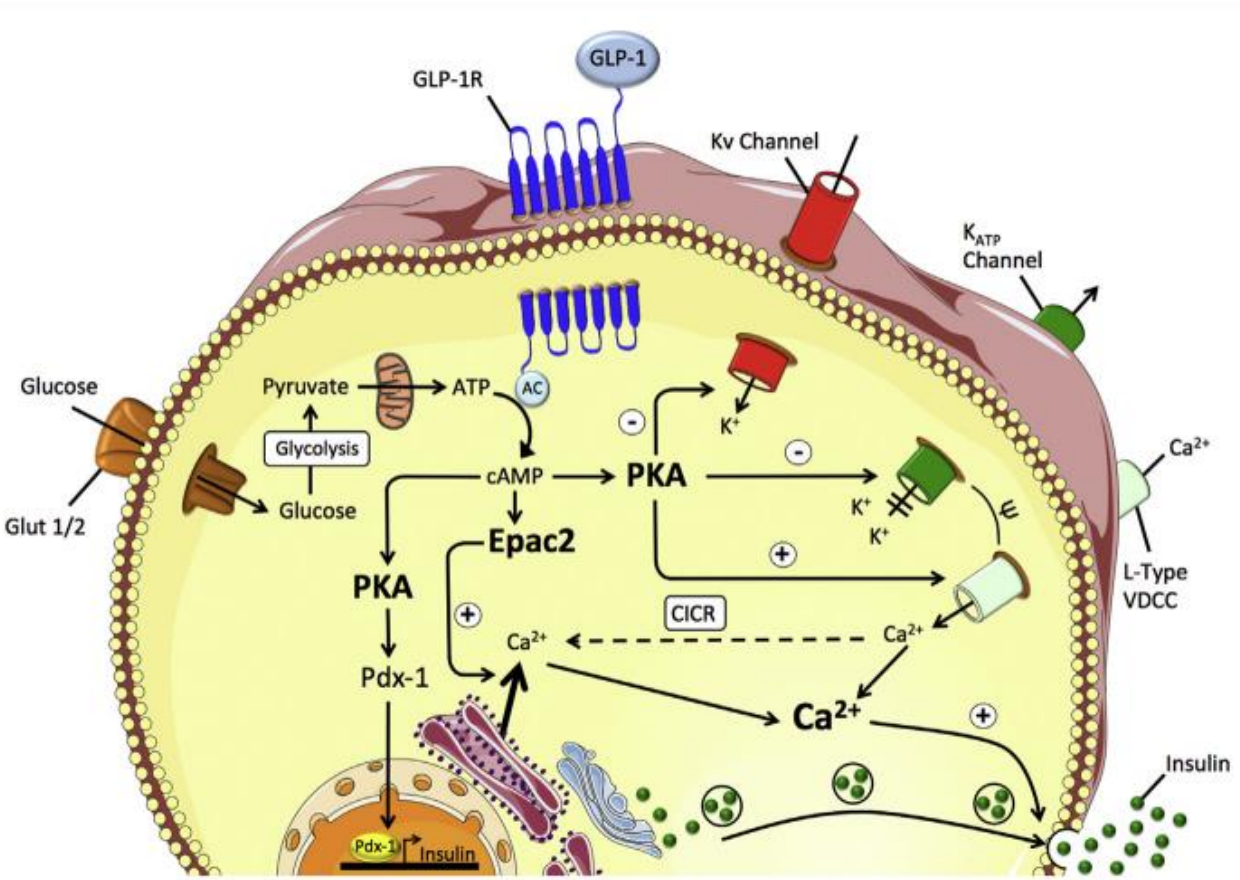
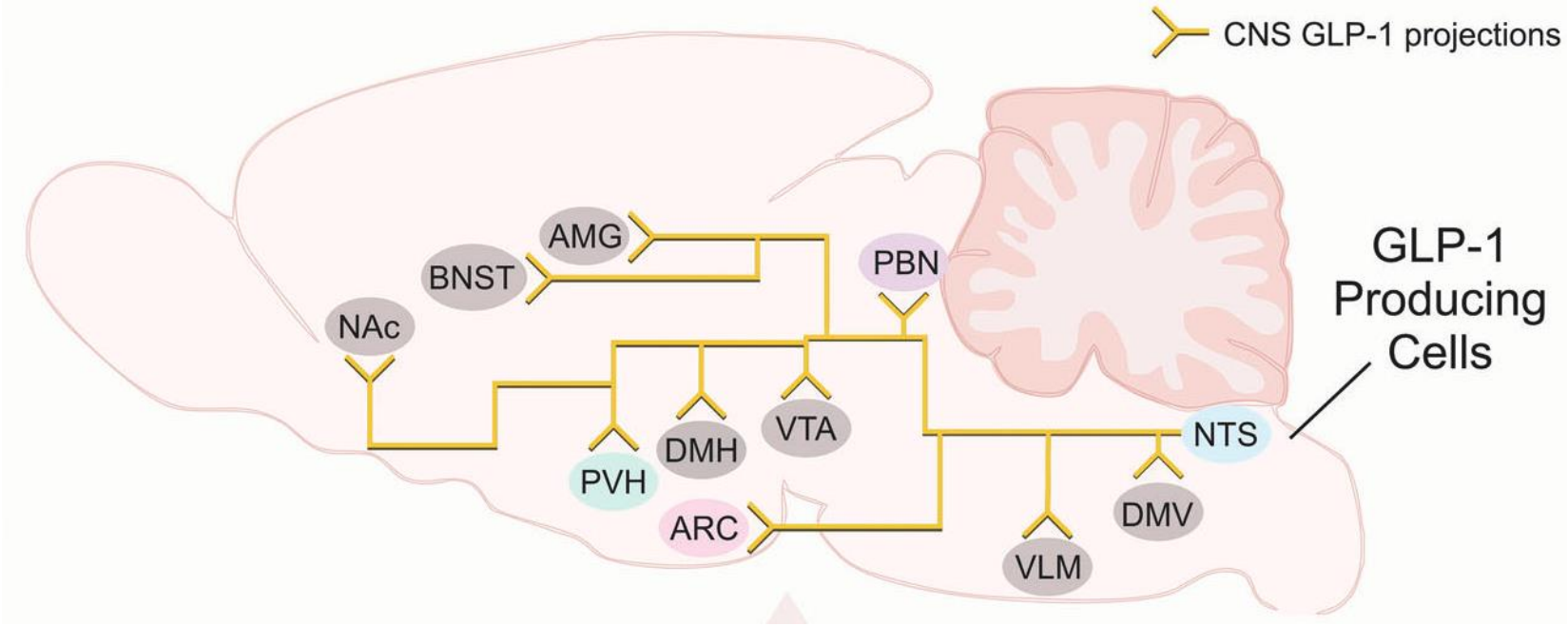


Figure 5: Schematic on GLP-1 mediated insulin secretion in the β-cell

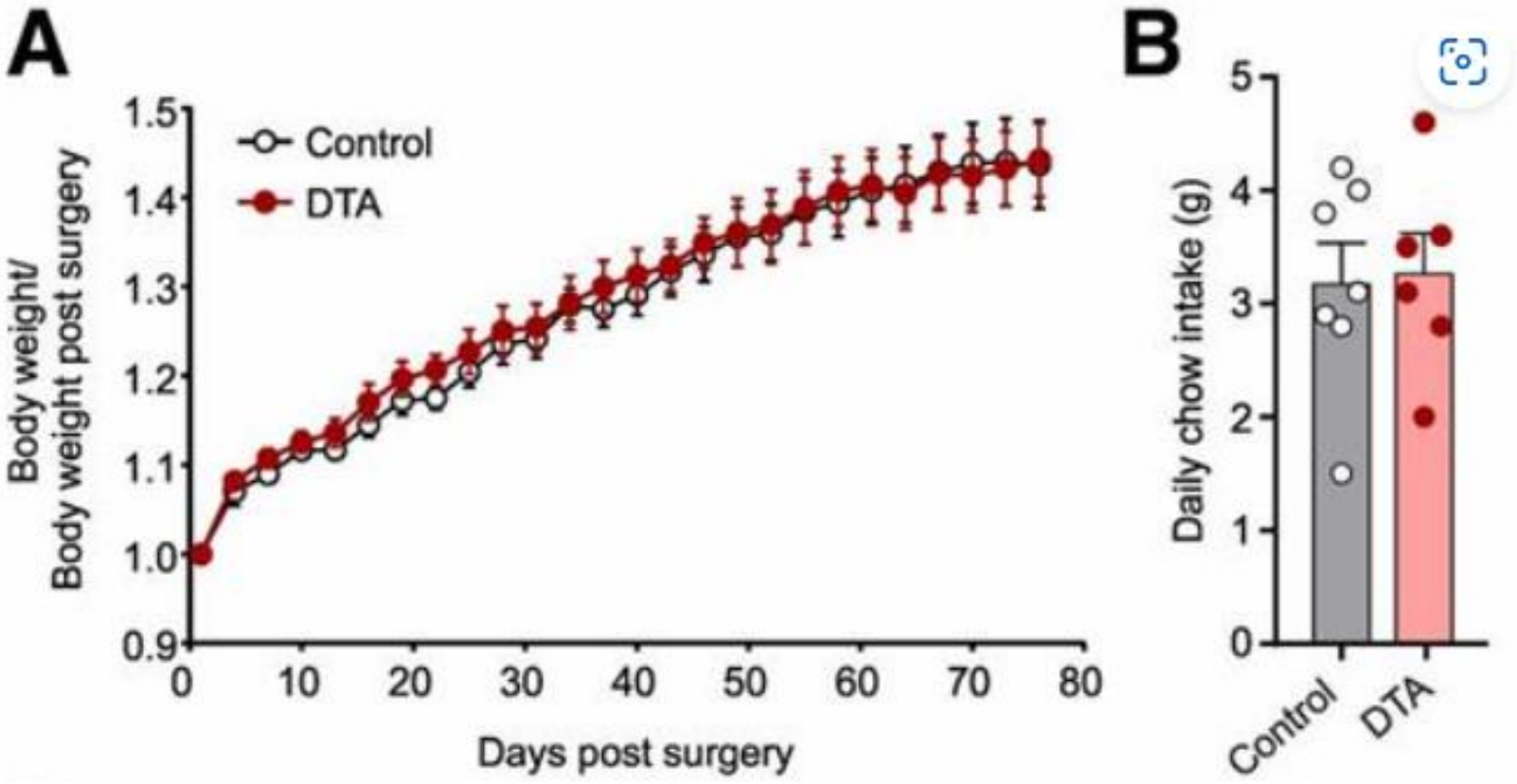
Muller et al. Mol Metab. 2019 Dec:30:72-130

GLP-1 in the Brain



Kabahizi A, et al. Br J Pharmacol. 2022.

GLP-1 in the Brain

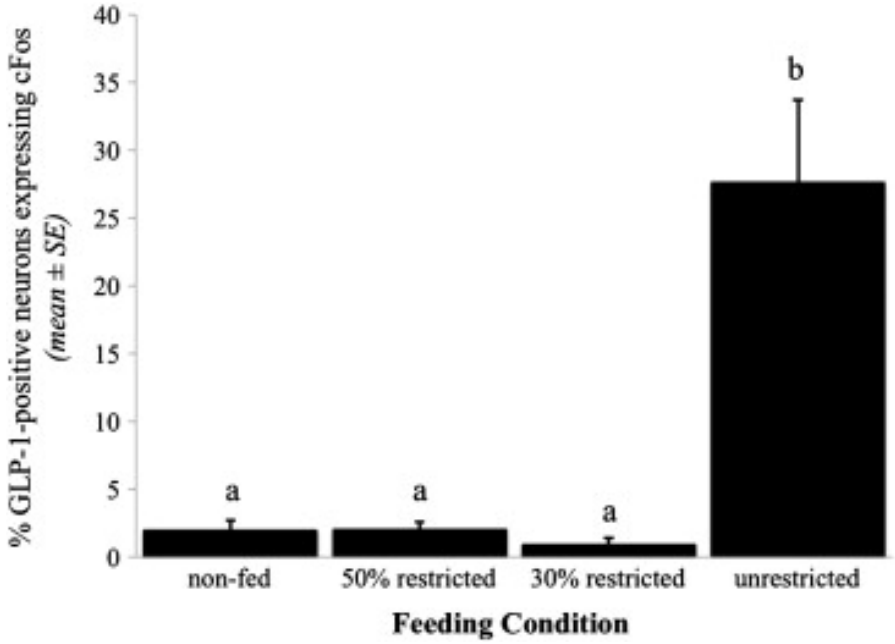


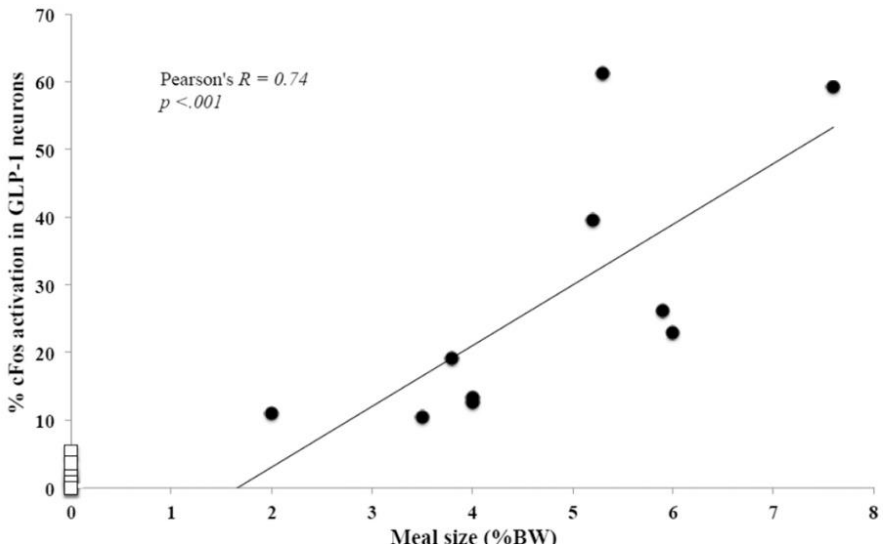
Ablation of NTS PPG neurons has no impact on body weight, food intake, or glucose tolerance.

Body weight change (*A*) and daily chow intake (*B*)

Holt et al. Diabetes. 2019 Jan;68(1):21-33.

GLP-1 in the Brain





Kreisler, et al. Physiol Behav. 2014 Sep:136:47-54.

GLP-1 and Dopamine Signaling

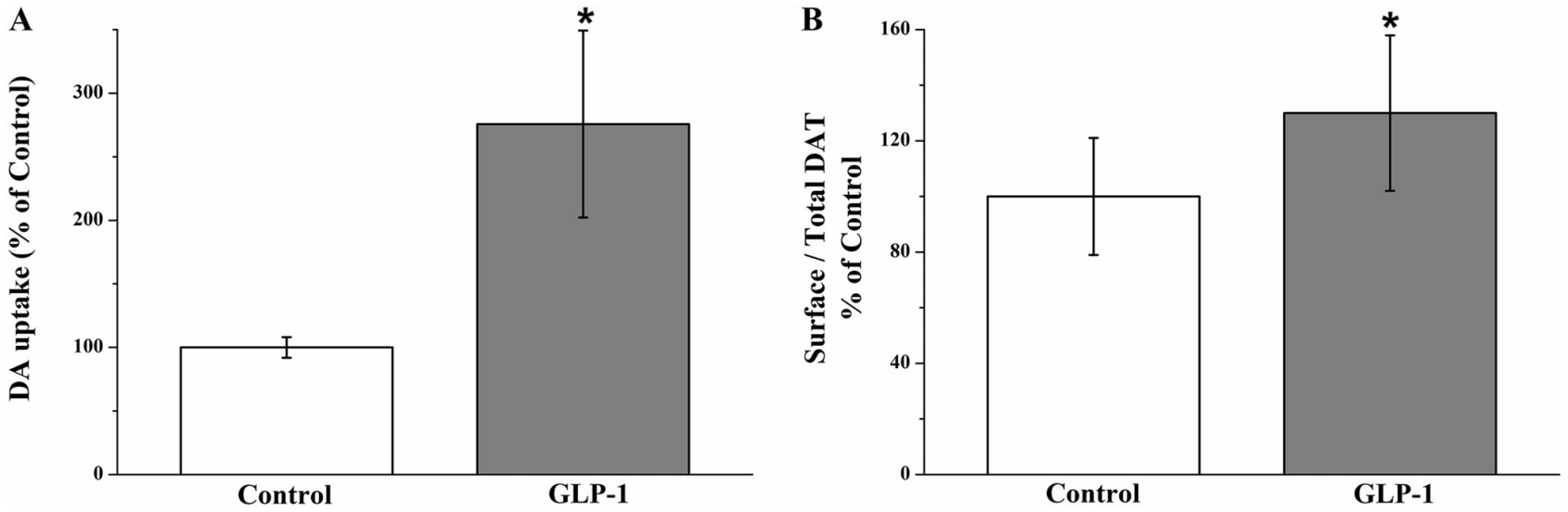
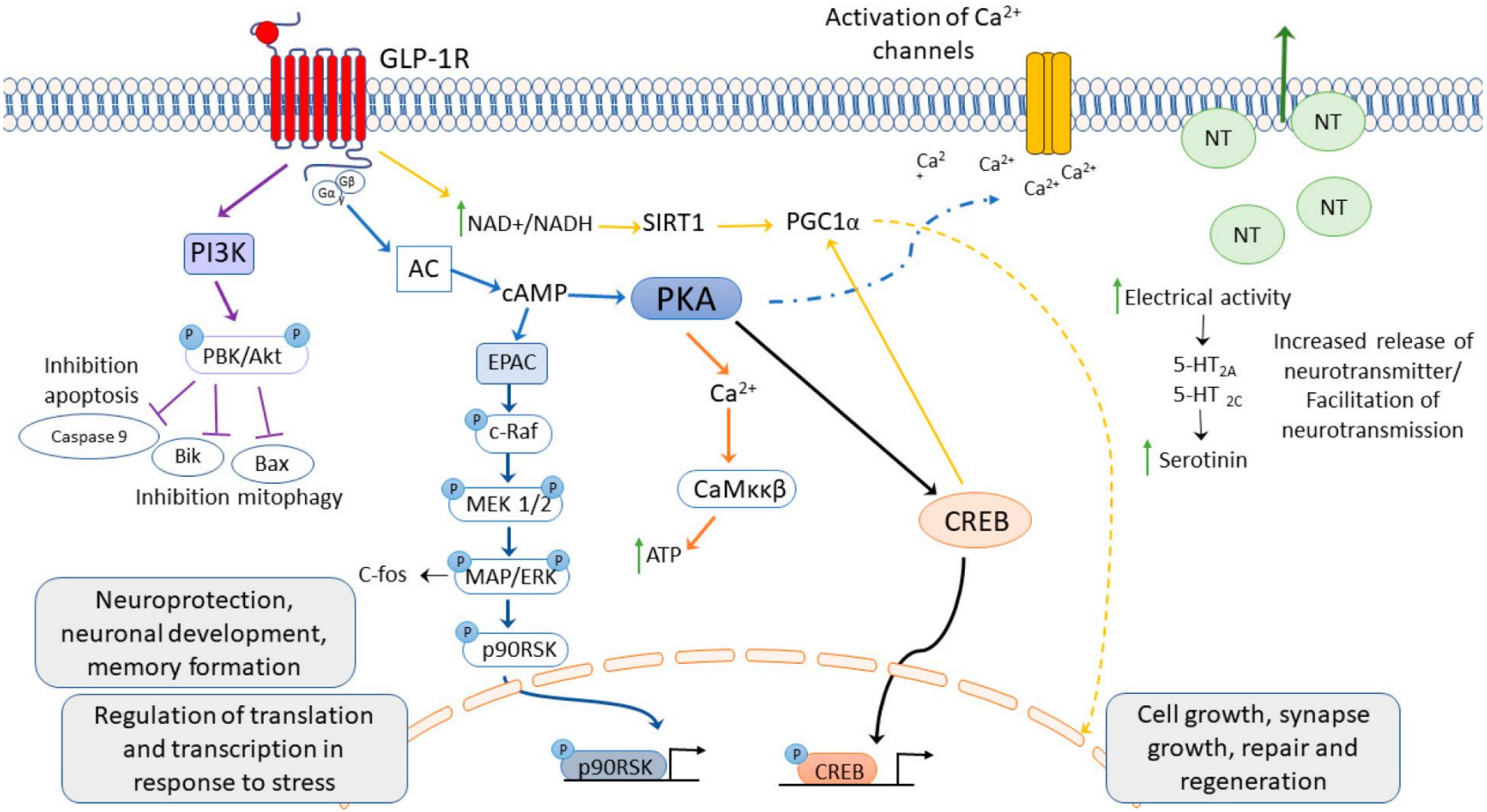


Fig. 1. Experiment 1: increased DA uptake (A) and DAT expression (B) after treatment with GLP-1 (7–36)-amide.
A, DA uptake into striatal synaptosomes as % of aCSF control in striatal slices incubated with aCSF (Control) or 100 nM GLP-1 (7–36)-amide (n = 20 slices - one-way ANOVA followed by Bonferroni-Holm post-hoc test). B, ratio of surface to total DAT protein as % of aCSF control in striatal slices incubated with aCSF (control) or 100 nM GLP-1 (7–36)-amide (n = 7 slices - one tailed paired *t*-test).*p < 0.05 vs. aCSF control.

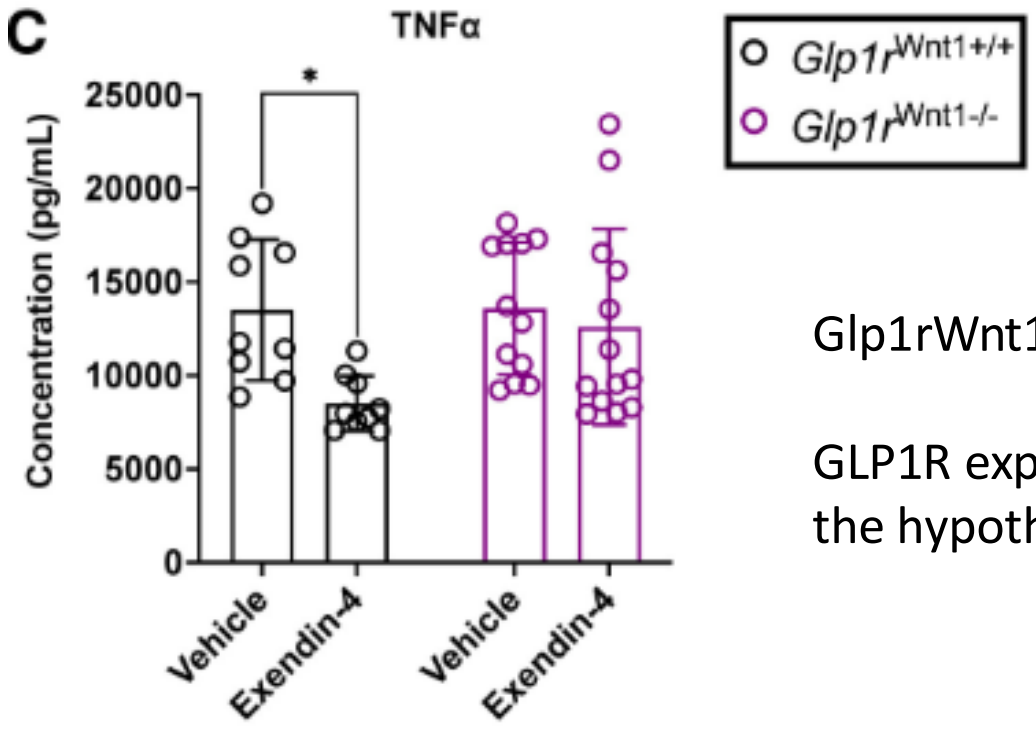
Jensen et al. Neurochem Int. 2020 Sep:138:104772.

GLP-1 and Neuroplasticity



Diz-Chaves et al. Int J Mol Sci. 2022 Aug 24;23(17):9583.

Central GLP-1 and Inflammation



Glp1rWnt1−/− mice:

GLP1R expression reduced in both the hypothalamus and brainstem

Wong et al. Cell Metab 2024; 36(1): 130-43 e5.

GLP-1 Receptor Agonists

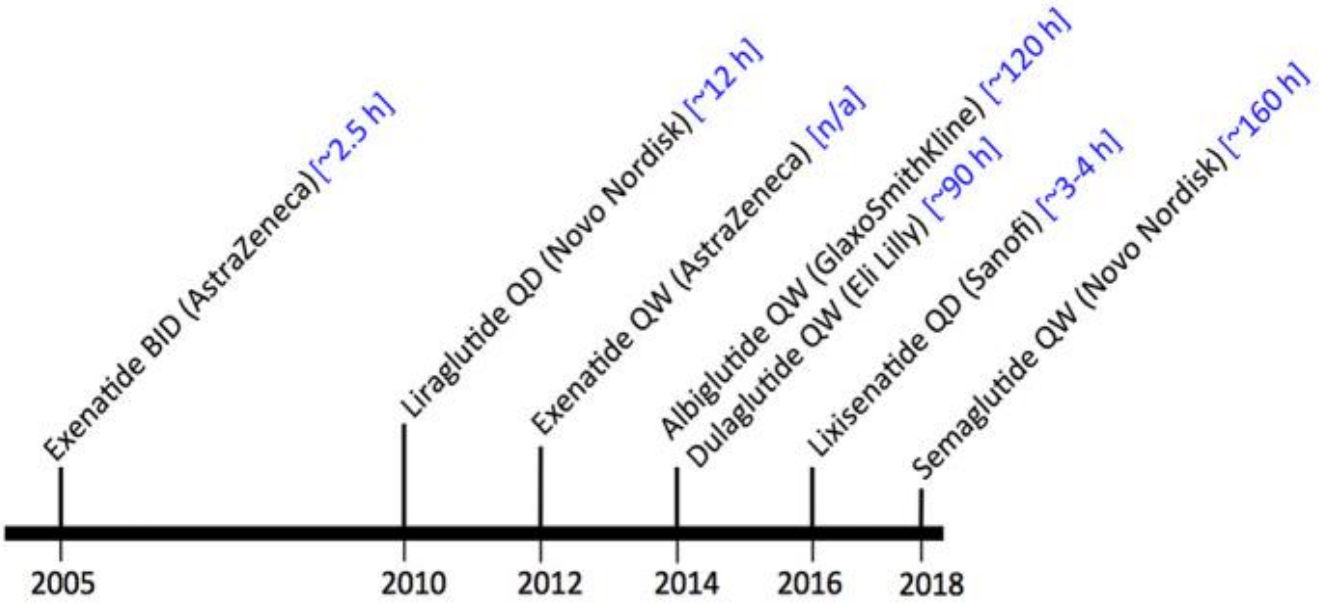
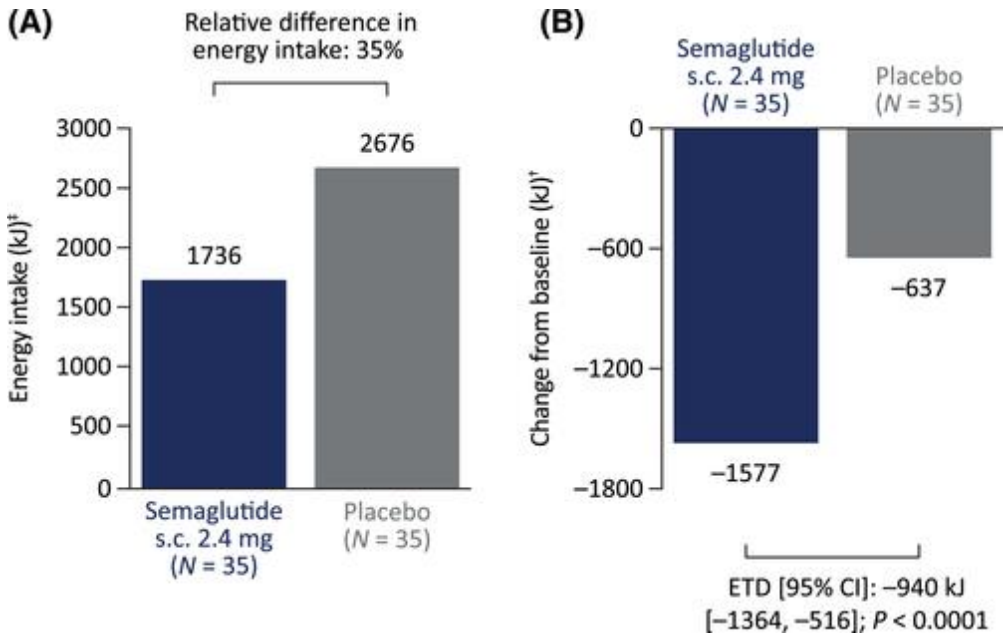
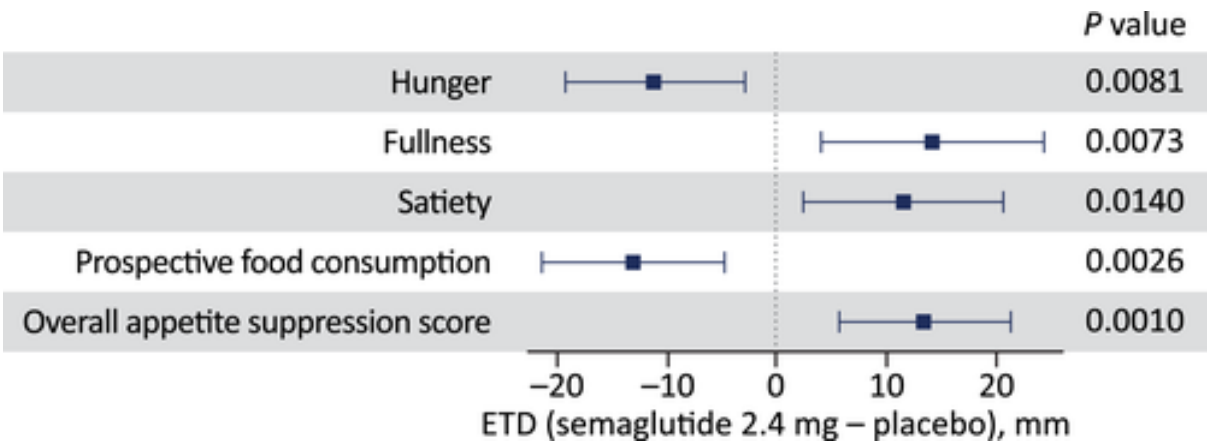


Figure 8: Timeline of GLP-1R agonists approved by the FDA for the treatment of diabetes.

Muller et al. Mol Metab. 2019 Dec:30:72-130

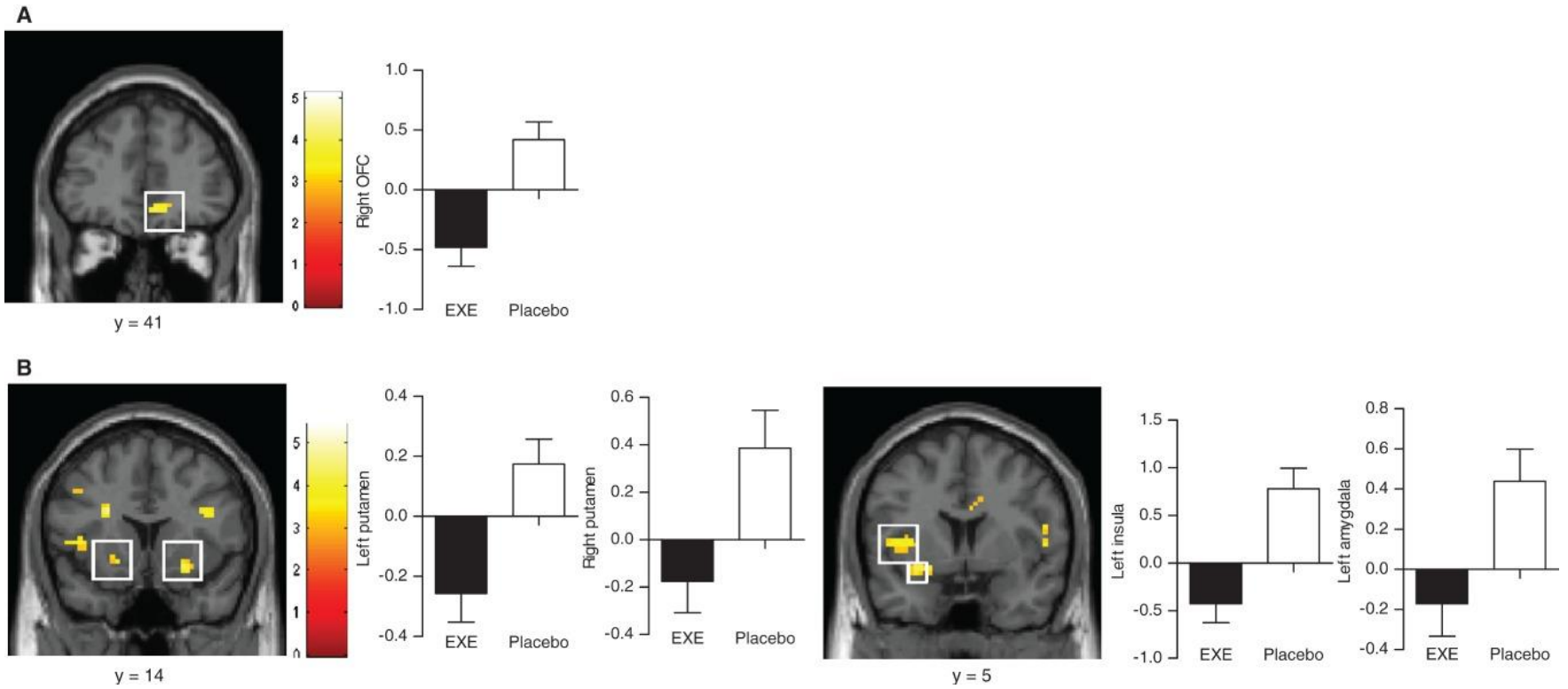
Behavioral Effects of GLP-1RAs





Friedrichsen et al. Diabetes Obes Metab. 2021 Mar;23(3):754-762.

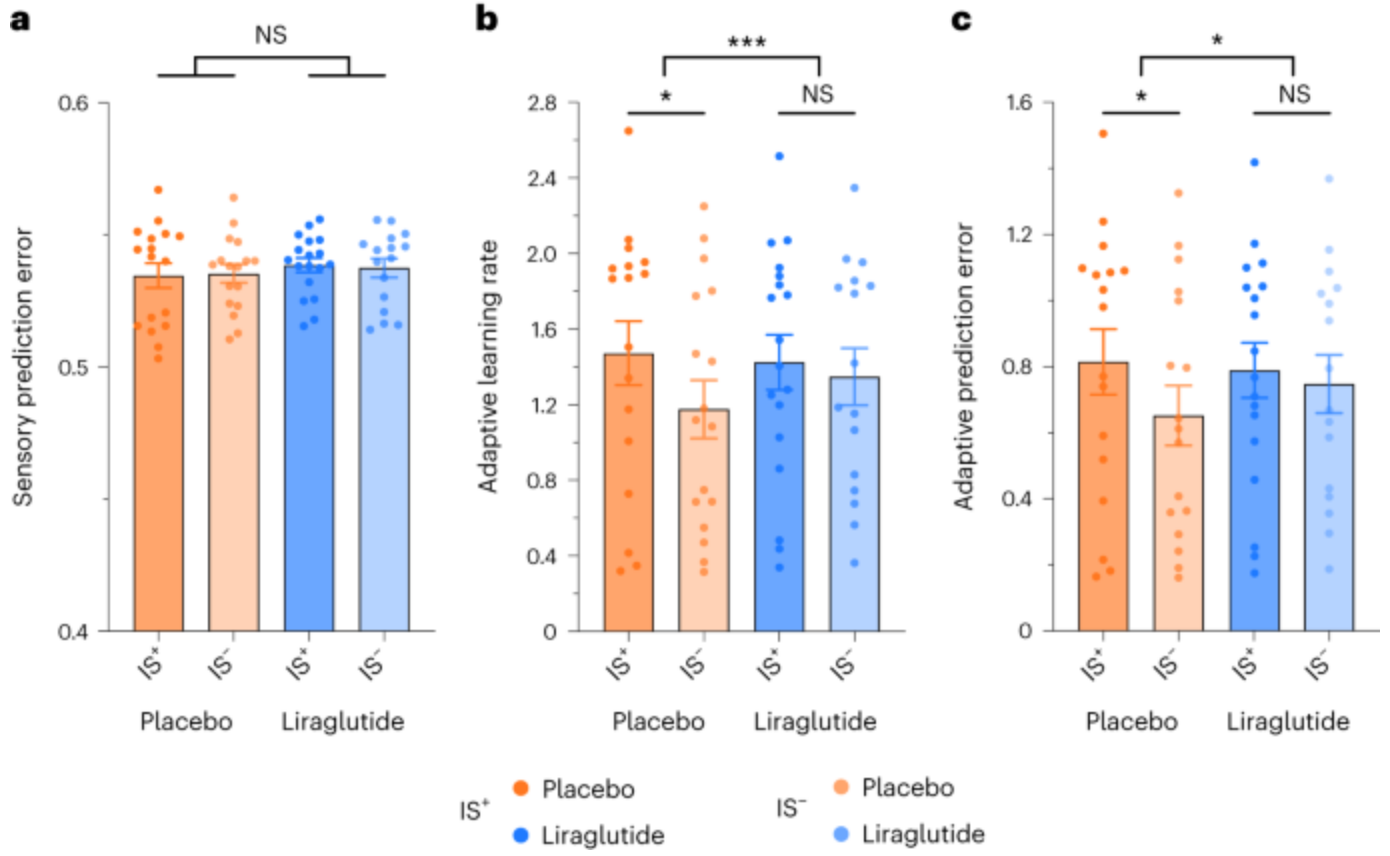
Neural Effects of GLP-1RAs



Effects of glucagon-like peptide-1 (GLP-1) receptor activation on brain responses to anticipatory food reward.

van Bloemendaal et al. Diabetes Obes Metab. 2015 Sep;17(9):878-86.

Behavioral Effects of GLP-1RAs

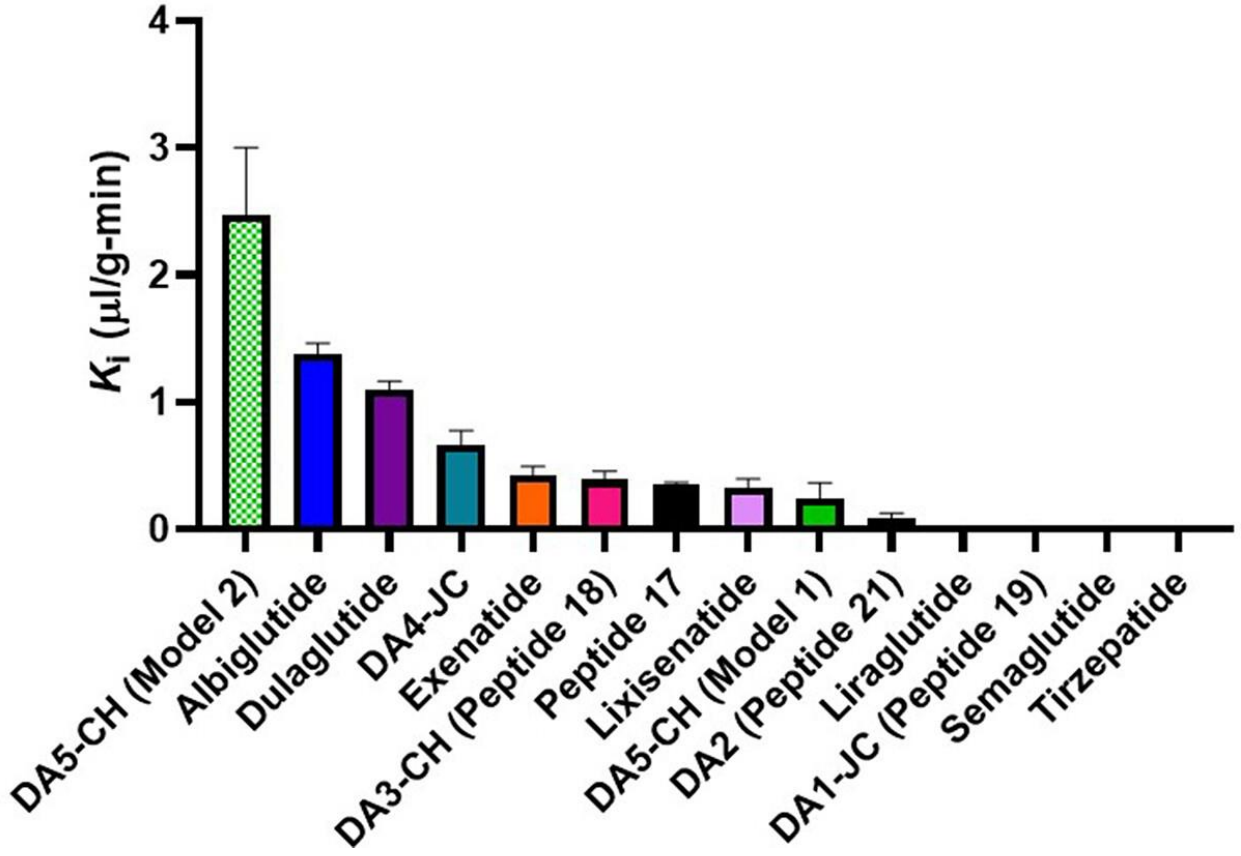


Liraglutide normalizes the adaptive learning rate (b) and adaptive prediction error (c) in individuals with impaired insulin sensitivity

Hanssen et al. Nat Metab 2023; 5(8): 1352-63.

Brain uptake of GLP-1RAs

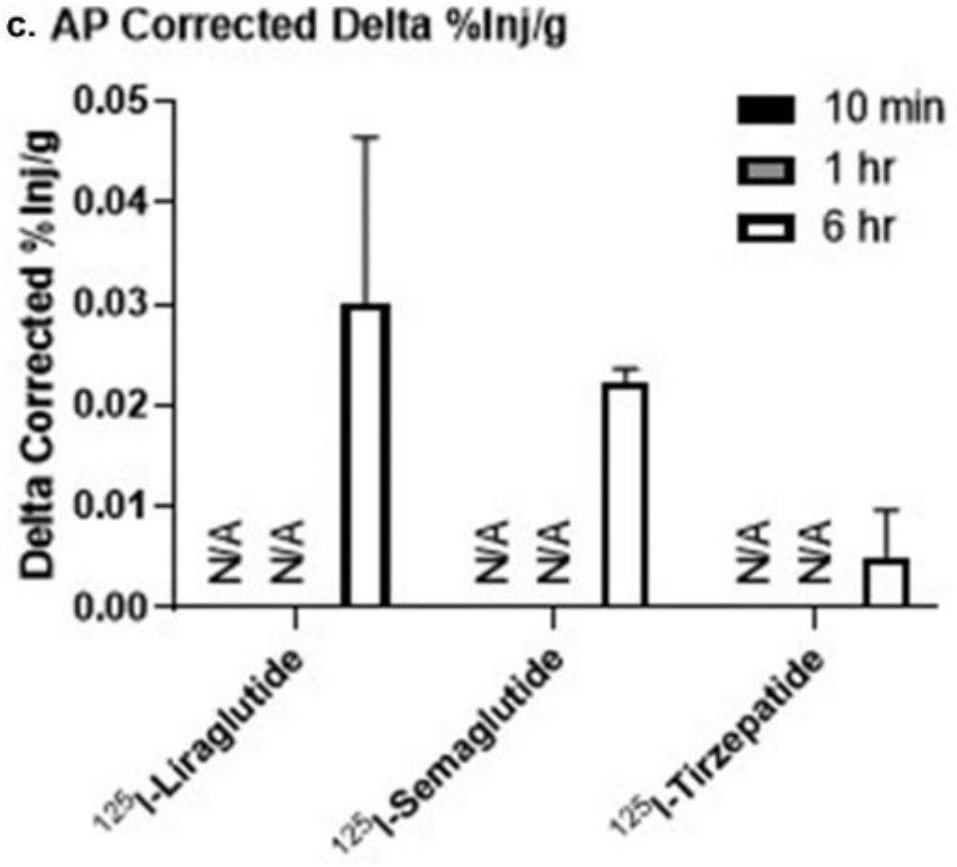
Rate of transport into whole brain within one hour



Rhea et al. Tissue Barriers. 2024 Oct;12(4):2292461.

Brain uptake of GLP-1RAs

Brain/serum (B/S) ratios at each time point



Rhea et al. Tissue Barriers. 2024 Oct;12(4):2292461.

Central and Peripheral GLP-1R Activation

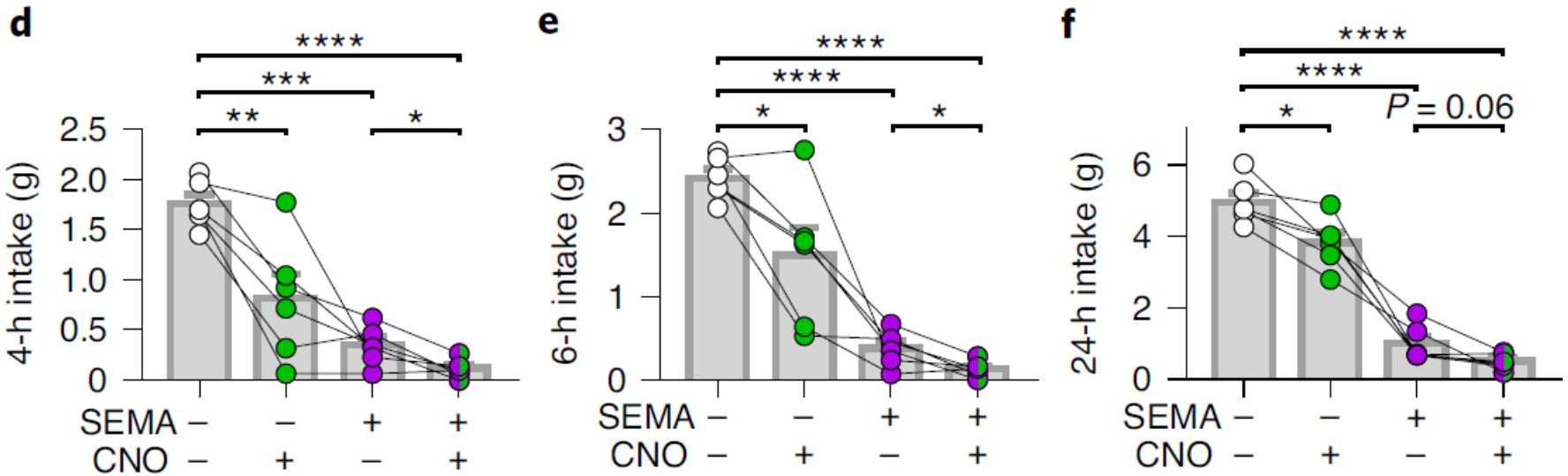


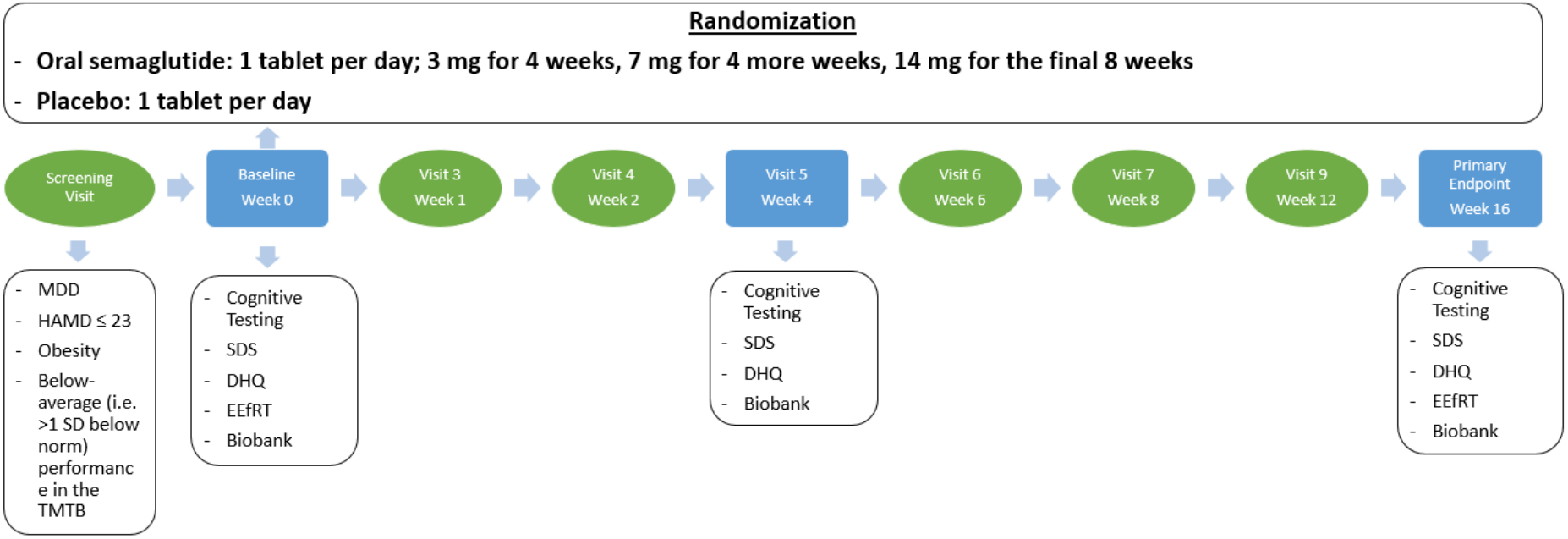
Fig. 8 | PPG^{NTS} neuron activation augments semaglutide-induced eating suppression. a,

CNO: Chemogenetic activation of PPG-NTS neurons with hM3Dq

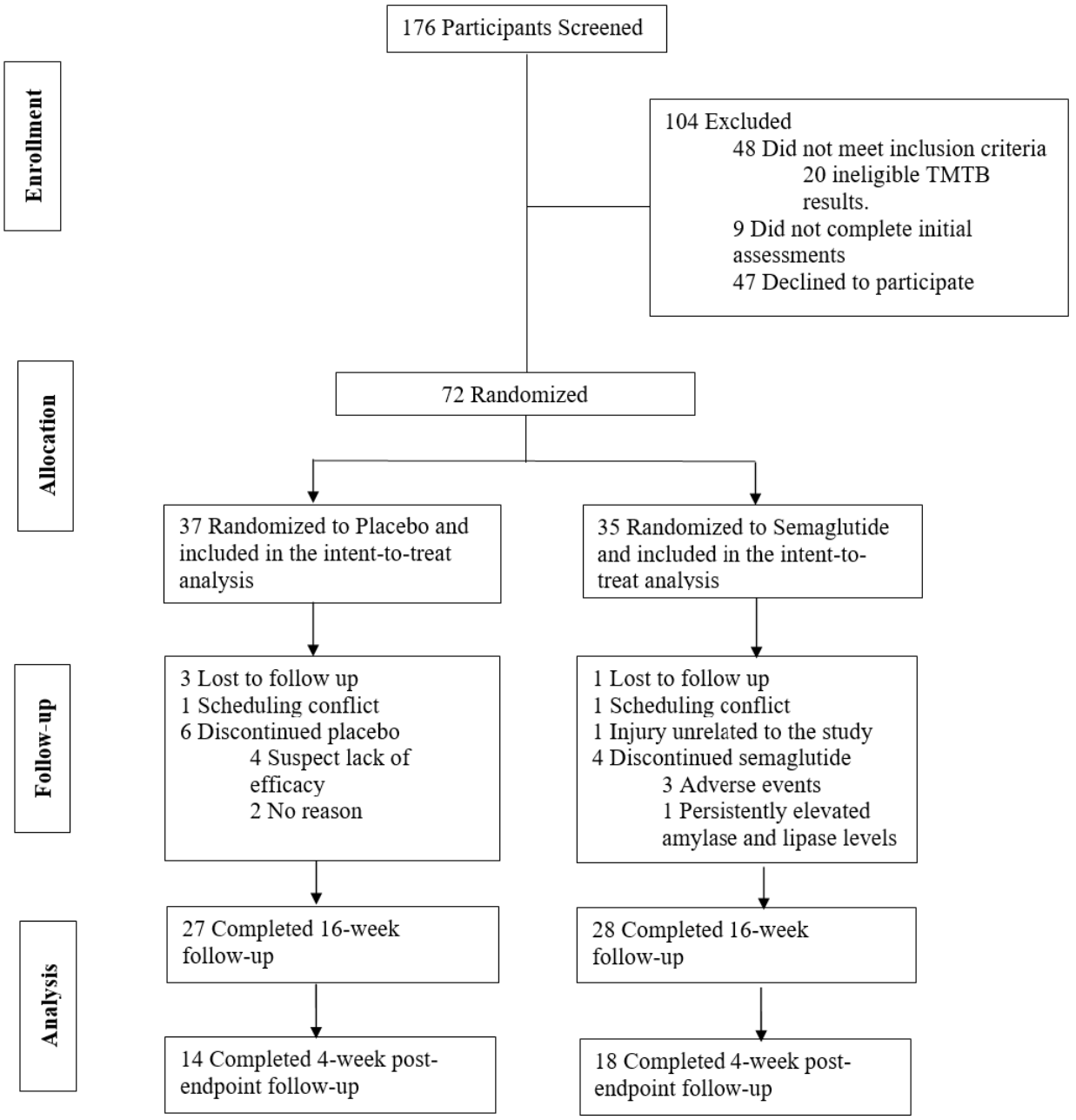
Rhea et al. Tissue Barriers. 2024 Oct;12(4):2292461.

Semaglutide for Cognitive Dysfunction in MDD

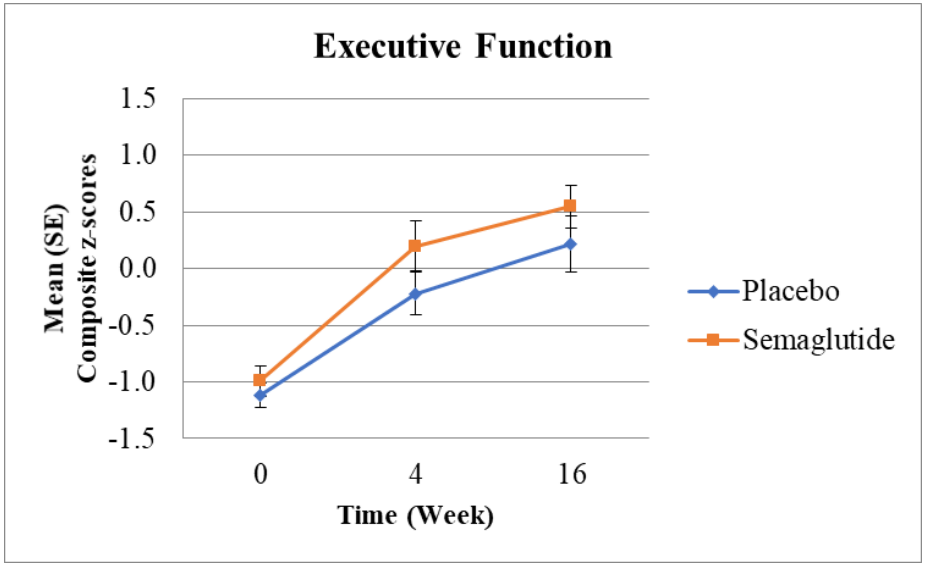
Adjunctive Semaglutide for the Treatment of Cognitive Dysfunction in Major Depressive Disorder: a Randomized, Double-Blind, Placebo-Controlled Study (NCT04466345)

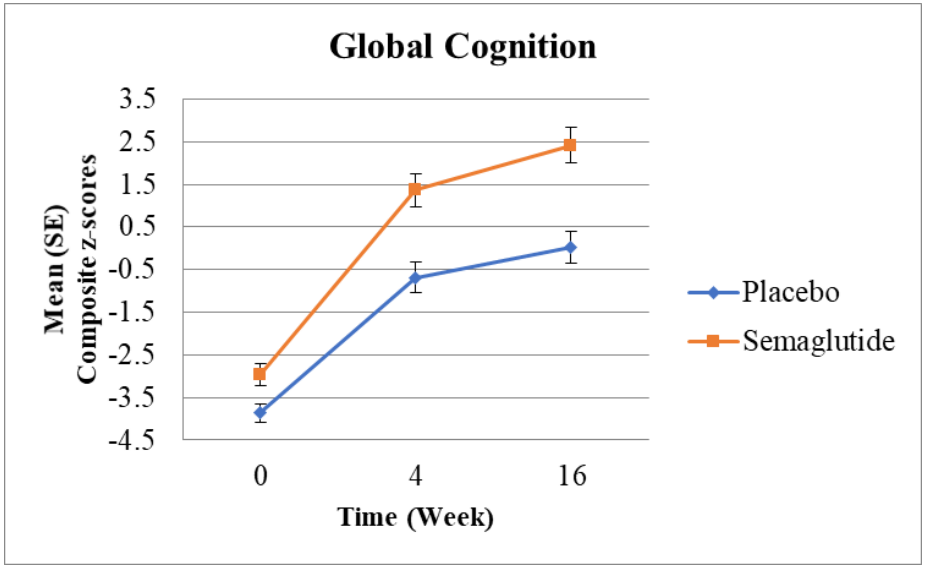


PSI FOUNDATION


Enrollment
176 Participants Screened
104 Excluded
48 Did not meet inclusion criteria
20 ineligible TMTB results.
9 Did not complete initial assessments
47 Declined to participate
Allocation
72 Randomized
37 Randomized to Placebo and included in the intent-to-treat analysis
35 Randomized to Semaglutide and included in the intent-to-treat analysis
Follow-up
3 Lost to follow up
1 Scheduling conflict
6 Discontinued placebo
4 Suspect lack of efficacy
2 No reason
1 Lost to follow up
1 Scheduling conflict
1 Injury unrelated to the study
4 Discontinued semaglutide
3 Adverse events
1 Persistently elevated amylase and lipase levels
Analysis
27 Completed 16-week follow-up
28 Completed 16-week follow-up
14 Completed 4-week post-endpoint follow-up
18 Completed 4-week post-endpoint follow-up

Semaglutide for Cognitive Dysfunction in MDD





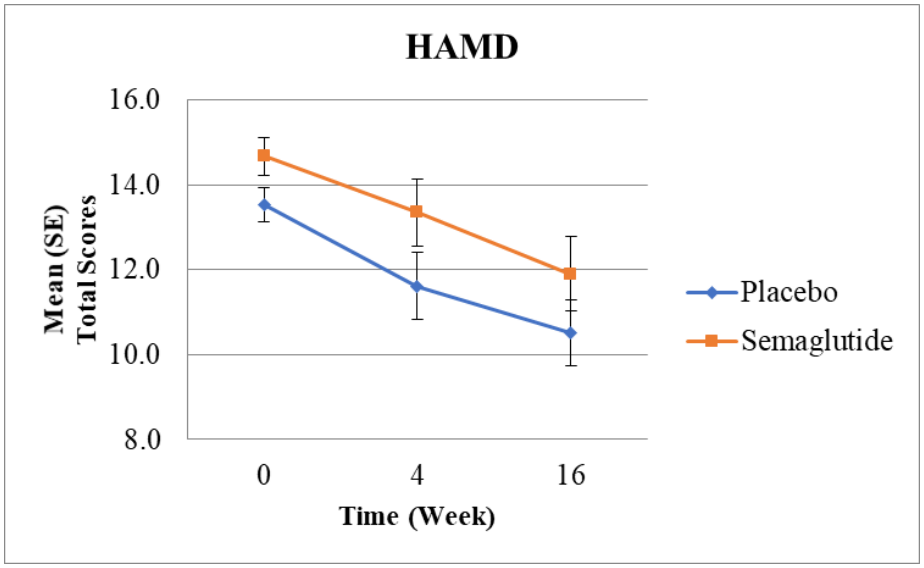
Endpoint Adjusted z score differences [semaglutide - placebo]

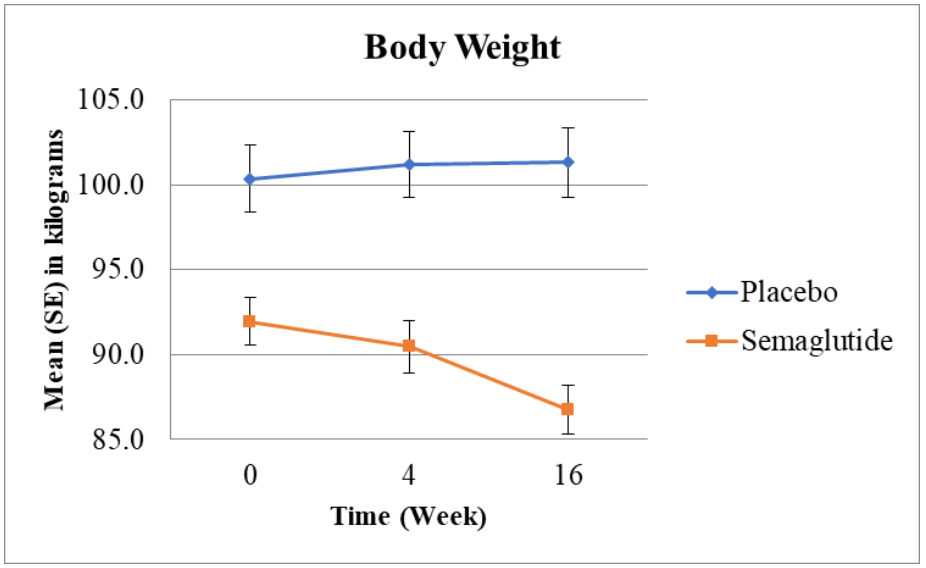
0.32, 95% CI, -0.92 to 1.58, p = 0.60

2.39, 95% CI, 0.19 to 4.60, p = 0.03

Badulescu et al. Under Review

Semaglutide for Cognitive Dysfunction in MDD



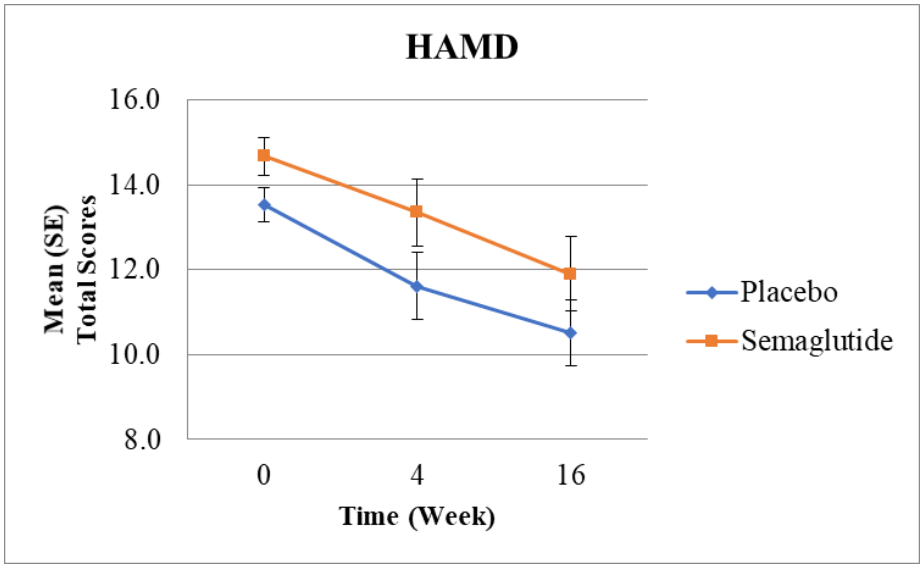


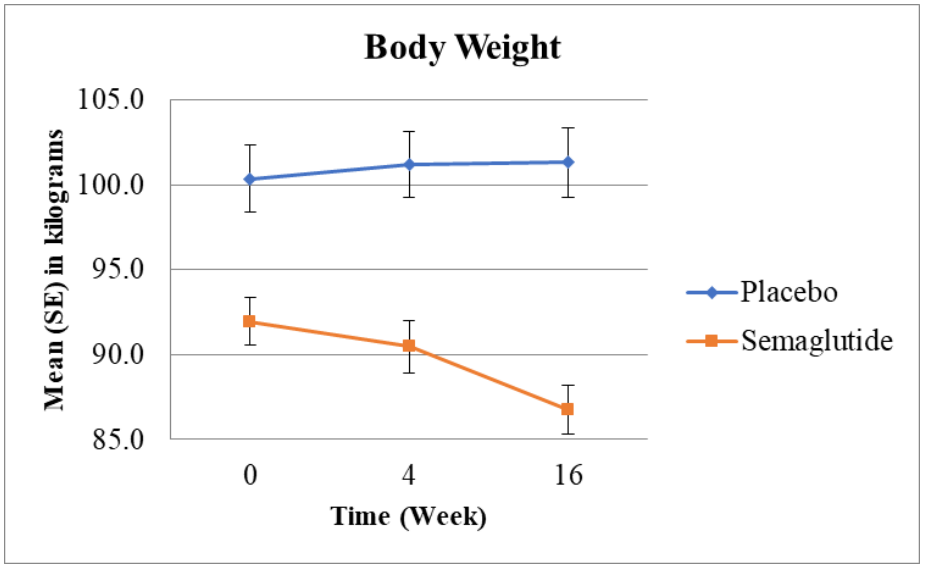
p = 0.319

Mean difference at endpoint
-6.03, (95% CI, -8.76 to -3.29), p < 0.001

Badulescu et al. Under Review

Semaglutide for Cognitive Dysfunction in MDD





p = 0.319

Mean difference at endpoint
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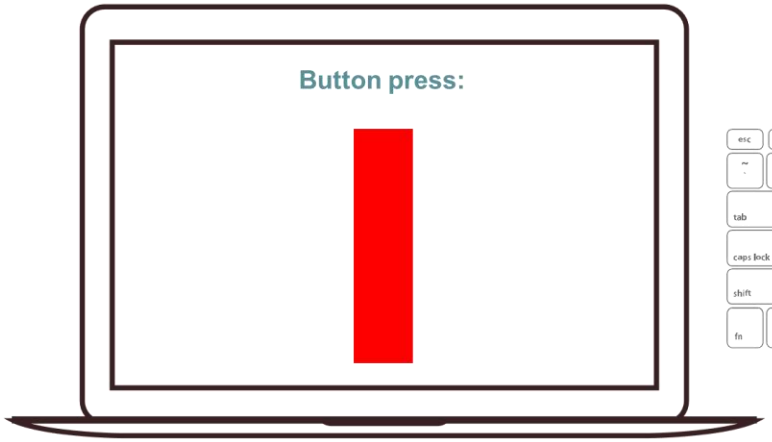
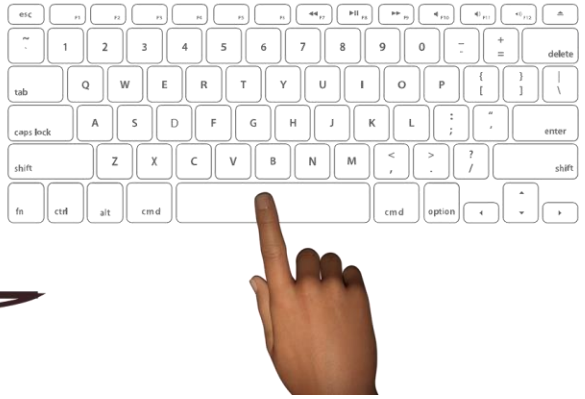
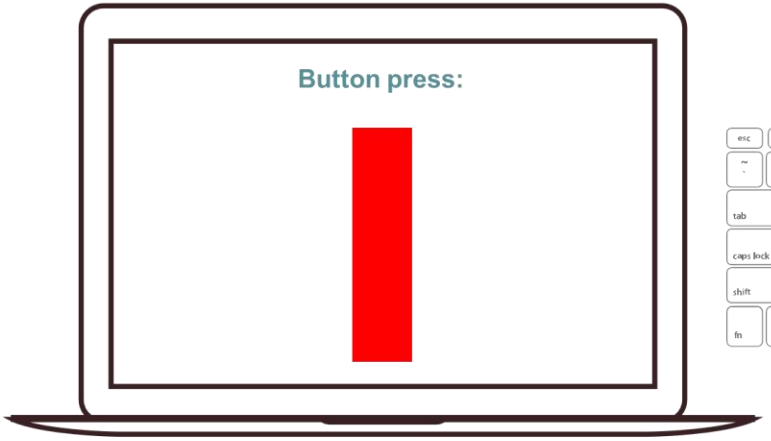
Badulescu et al. Under Review

Effort-Expenditure for Rewards Task

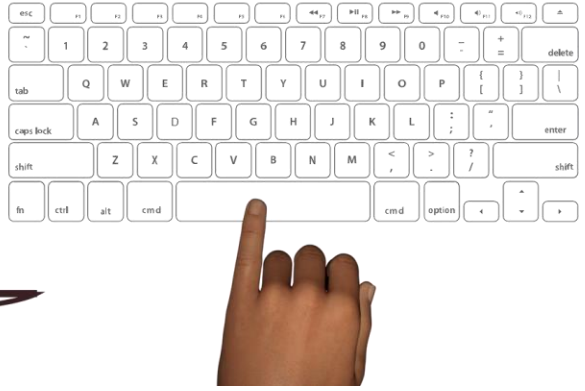


Easy task:
30 button presses in 7 seconds



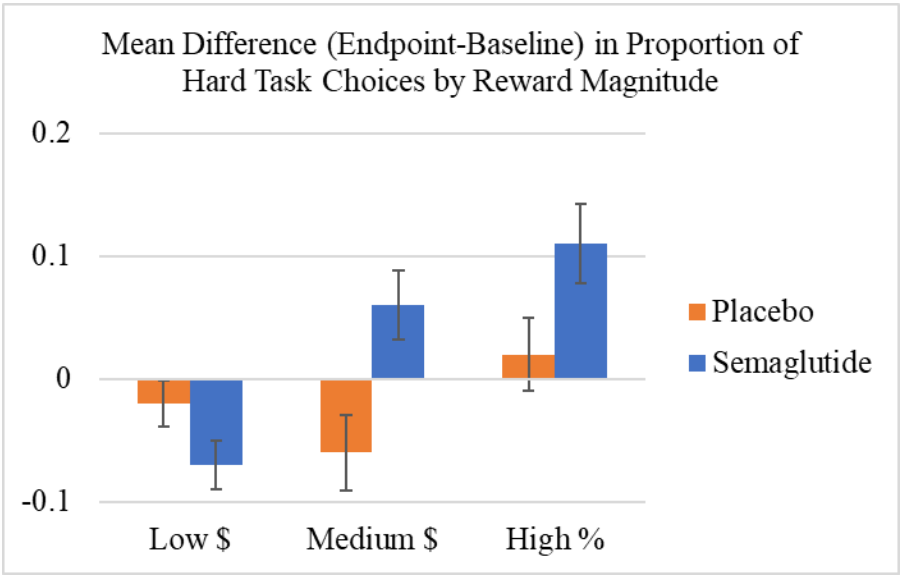


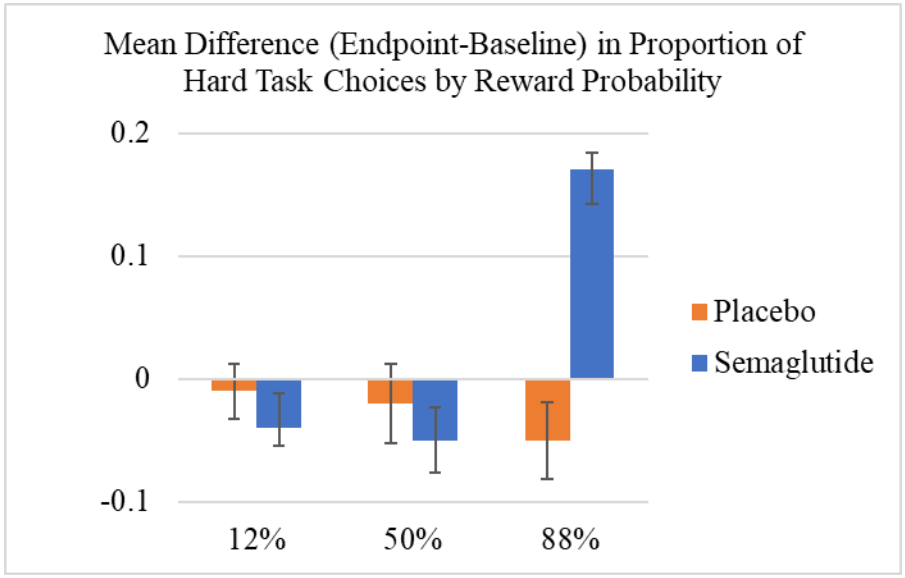
Hard task:
100 button presses in 21 seconds



Treadway et al. PLoS One. 2009 Aug 12;4(8):e6598

Semaglutide for Reward Dysfunction in MDD





Treatment x visit x expected value interactions ($\chi 2 = 12.024$, $p = 0.017$).

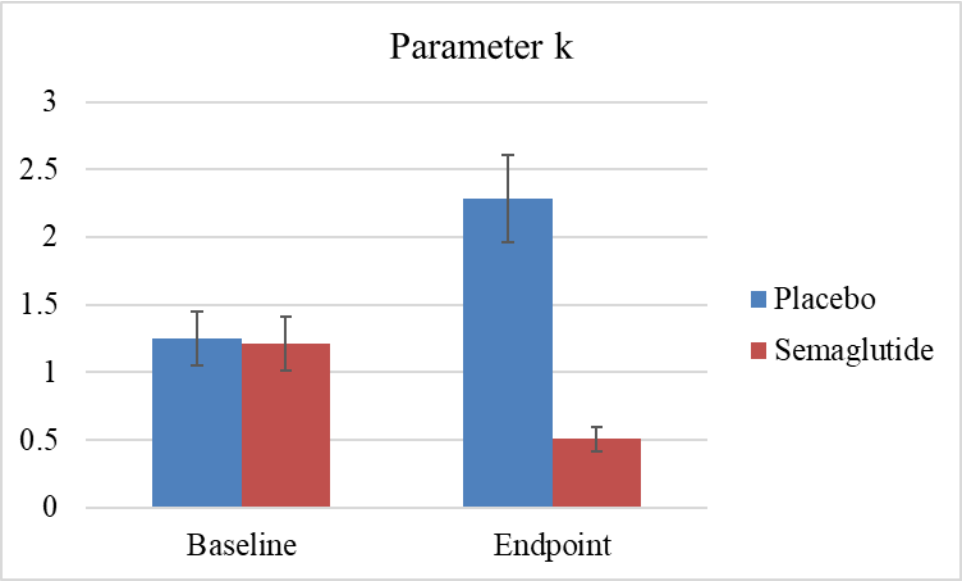
Gill et al. Unpublished data

Computational Modeling

Subjective Value (SV) Model

$SV = R*P^h - k*E$

R = Reward Magnitude
P = Reward Probability
E = Effort level
h = Sensitivity to probability
k = Sensitivity to effort



β = -1.737, p = 0.026
Adjusted for age, sex and HAMD scores

Semaglutide significantly decreased the sensitivity to effort (i.e. lower effort aversion)

Gill et al. Unpublished data

Acknowledgements

- Roger McIntyre
- Joshua Rosenblat
- Cristian-Daniel LLach
- Sebastian Badulescu
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- Lee Phan
- Ryan Brudner
- Joshua Di Vincenzo
- Hiya Shah

CIHR IRSC Canadian Institutes of Health Research / Instituts de recherche en santé du Canada

BASZUCKI BRAIN RESEARCH FUND

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