Biological processes underlying a cognitive-anatomical signature of intervention strategies in mice

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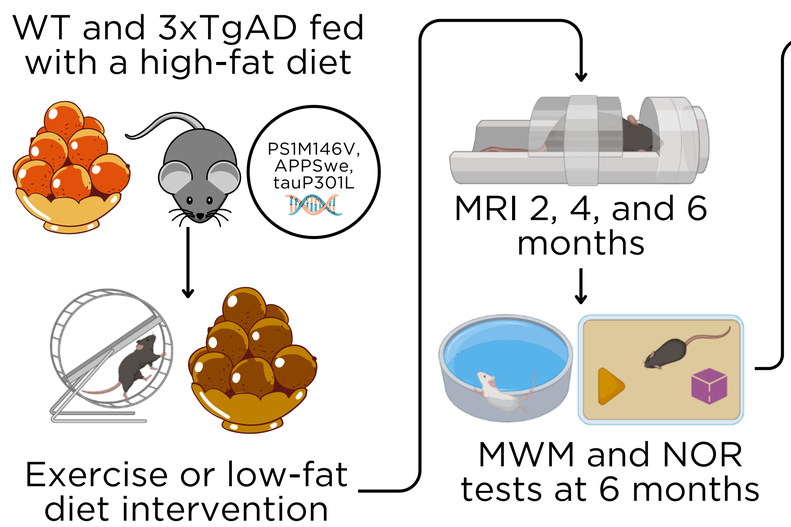
Introduction

We studied how diet and exercise impact brain structure and behavior in wild-type mice (WT) and a mouse model of Alzheimer's disease (3xTgAD mice) fed with a high-fat diet. To analyze the relationship between changes in the brain and the behavior performance of the mice, we employed partial least squares analysis that revealed a behavioral-anatomical signature of the intervention's effect. To uncover the possible biological processes underlying this signature, we correlated it with gene expression data.

Experiment design

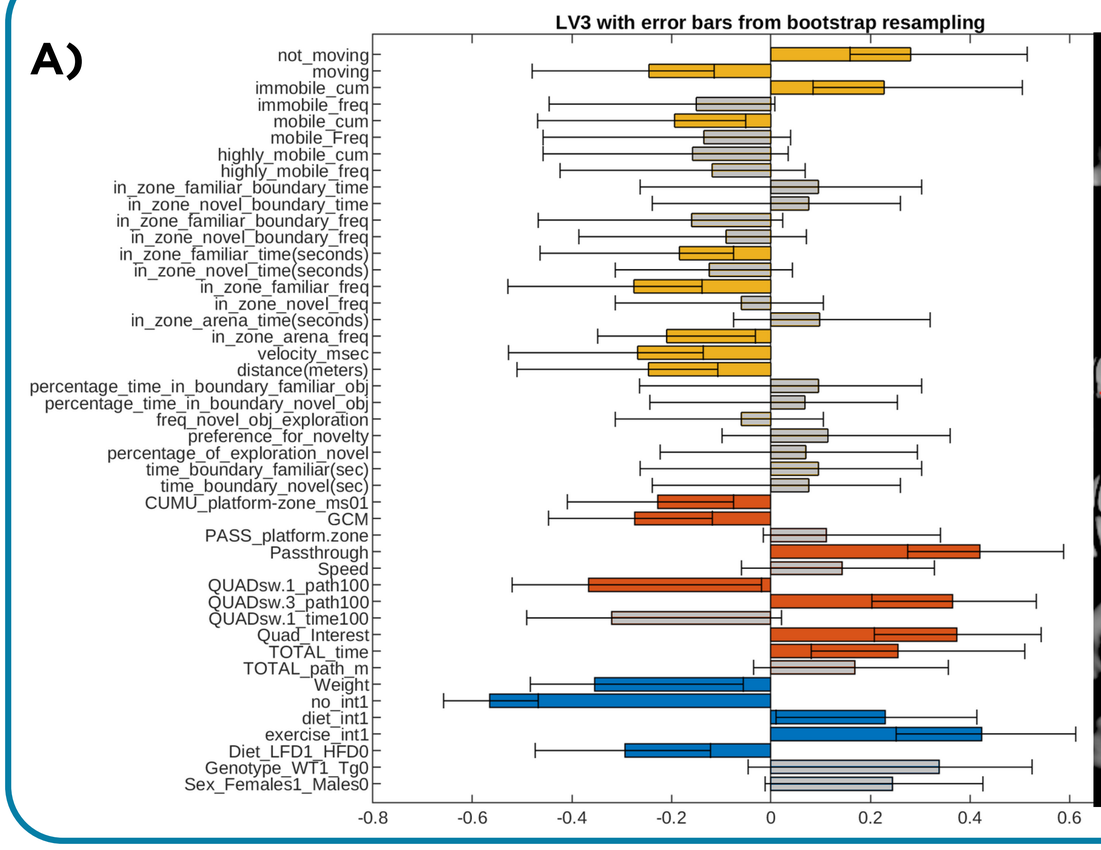
Mice fed with a high-fat diet were intervened with exercise or a low-fat diet. T1 weighted MRI scans were collected at three time-points. The Morris Water Maze (MWM) and Novel Object Recognition (NOR) tests were performed after interventions.

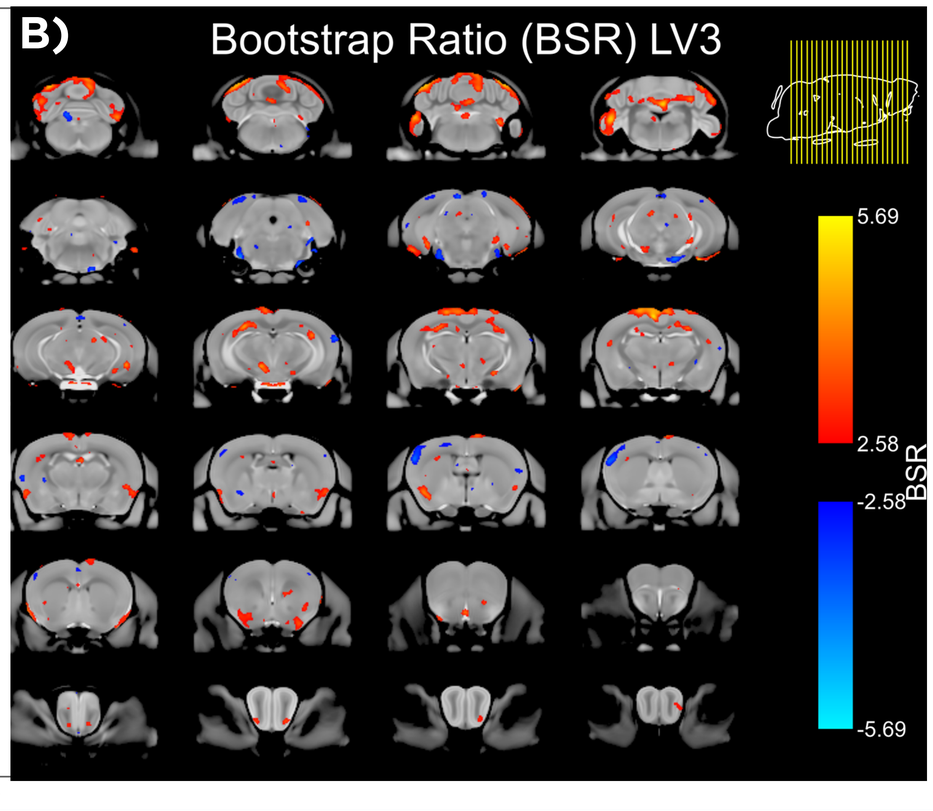


Number of mice remaining by the end of the experiment:

Group	Intervention	N
LFD-NI-WT	None	15 (6M,9F)
HFD-NI-WT	None	15 (9M, 6F)
HFD-D-WT	Diet	17 (10M, 7F)
HFD-EX-WT	Exercise	18 (12M, 6F)
LFD-NI-Tg	None	16 (6M, 10F)
HFD-NI-Tg	None	16 (10M, 6F)
HFD-D-Tg	Diet	15 (5M, 10F)
HFD-EX-Tg	Exercise	16 (9M, 7F)

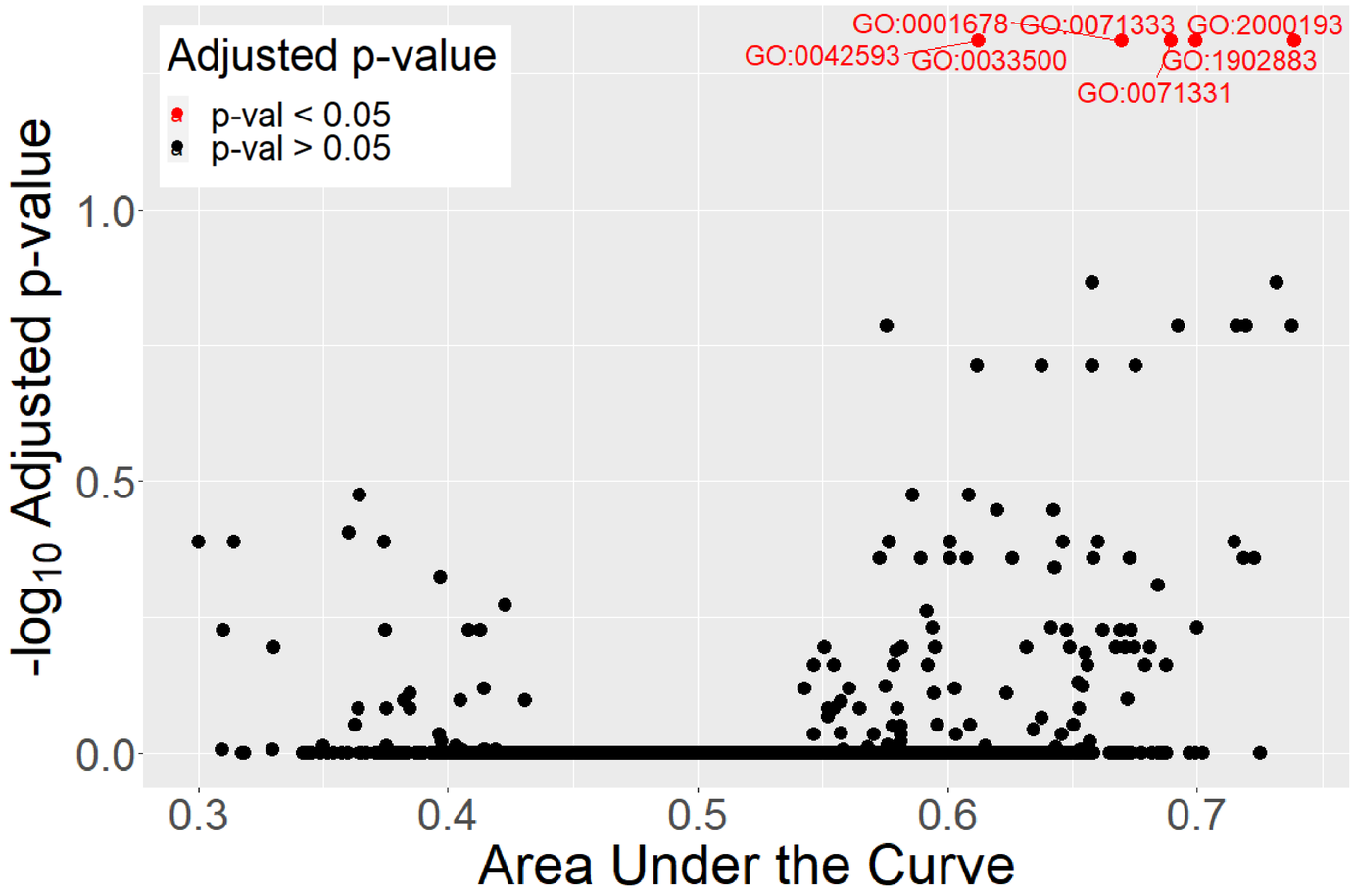
Partial Least Square Analysis (PLS)





Voxel-wise Jacobians and behavior were correlated and the correlation matrix was subjected to singular value decomposition (SVD), obtaining significant latent variables (LV) made of a brain pattern and behavioral loadings that maximally covary. LV3 was selected for further investigation because its brain pattern was uniquely correlated with intervention strategies and wasn't correlated with sex or genotype. LV3 explained 12.46% of the covariance. **A)** Behavior weights from the NOR (in yellow), MWM (in orange), and demographics (in blue). SVD estimated the weights. Confidence intervals were estimated by bootstrapping. **B)** Brain loading bootstrap ratios (BSR; 99% confidence interval) on the population average. PLS was useful in extracting a brain pattern that positively correlates with the intervention strategies, mainly characterize for the increase in volume of different brain regions.

Spatial Gene Enrichment Analysis (SGEA)



The brain pattern from LV3 was correlated with gene expression data from the Allen Brain Institute. Genes were then ranked by their Spearman correlation, and SGEA was done using the tmod package/0.46.2 in R/4.1.3. Given the ranked list of genes, Mann-Whitney tests were used to compute U-statistics/Area Under the Curve (AUC) values and p-values for each gene module. P-values were recomputed by comparing the AUC of each module against randomized AUC null distributions and corrected with false discovery rate.

significant GO terms:
1902883: Negative regulation of response to oxidative stress
0042593: Glucose homeostasis
0033500: Carbohydrate homeostasis
0001678: Cellular glucose homeostasis
0071331: Cellular response to hexose stimulus
0071333: Cellular response to glucose stimulus
2000193: Positive regulation of fatty acid transport

Conclusions

PLS analysis demonstrated a favorable impact of interventions on the brain anatomy of mice, which was associated with positive behavioral outcomes. Additionally, the SGEA identified gene modules related to glucose and carbohydrate homeostasis, indicating that the beneficial effects of the interventions might be attributed to the regulation of genes involved in maintaining energy balance.