The effects of obesity and a potential rescue through diet & exercise in 3Tg-AD mice

Chloe Anastassiadis[1], Mila Urosevic[1], Colleen Rollins[1,2], Daniel Gallino[1], Vincent Kong[1], Gülebru Ayranci[1], Gabriel A. Devenyi[1,3], Jürgen Germann[1], M. Mallar Chakravarty[1,3,4]

[1] Cerebral Imaging Centre, Douglas Mental Health University Institute, Verdun, Canada. [2] Brain Mapping Unit, Cambridge University, Cambridge, UK. [3] Deparment of Psychiatry, McGill University, Montreal, Canada. [4] Department of Biomedical Engineering, McGill University.

Introduction

Research suggests that up to ~35% of dementias, most of which are caused by Alzheimer's disease (AD), are attributable to modifiable risk factors such as obesity and lack of exercise (1).

Research goals To assess the impact of high-fat diet (HFD)-induced obesity on neuroanatomy and memory in a mouse model of Alzheimer's disease (AD), and a potential rescue through lifestyle changes, namely diet and exercise intervention.

Hypotheses HFD will induce a different neuroanatomical trajectory and more severe memory impairment than control diet (CD). Return to a CD and/or increased exercise will bring them closer to baseline.

Design

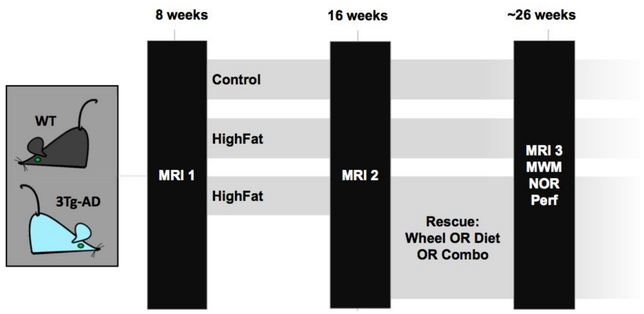

Figure 1 (above). **Study design.** Magnetic Resonance Imaging (MRI) scans were obtained at 3 timepoints. Memory function was examined through the Morris Water Maze (MWM) and Novel Object Recognition (NOR) tests. Brains were collected though perfusion. Interventions were 1) CD (10% cal from fat); 2) HFD (63% cal from fat); and 3) rescue, with a) access to a wheel, b) return to CD (diet), and c) both (combo). Triple transgenic (3Tg-AD) mice, which develop the amyloid and tau pathology specific to AD and memory loss, and their background strain (WT) (B6J.129S) (2) were used.

Intervention	CD	HFD	Wheel	Diet	Combo
Genotype (# males)					
3Tg-AD	14 (9)	14 (7)	11 (6)	8 (5)	7 (4)
WT	16 (8)	15 (6)	11 (5)	14 (7)	15 (8)

Table 1. Number of mice per intervention per genotype for the MRI results. For preliminary analyses 2 datasets (one still in collection) have been pooled, hence the unequal n's. For behaviour, groups are all of fairly equal size (n ~ 8-10).

Methods

MRI Following a $MnCl_2$ injection (62.5 mg/kg based on baseline weight), 3D T1-w images (2 averages (TR=20 ms, TE=4.5ms, matrix size: 180x160x190, voxel size: 100µm^3, flip angle=20°; Bruker 23mm volumetric transmit/receive quadrature coil)) were acquired on a 7T Bruker Biospec.

Deformation-based morphometry

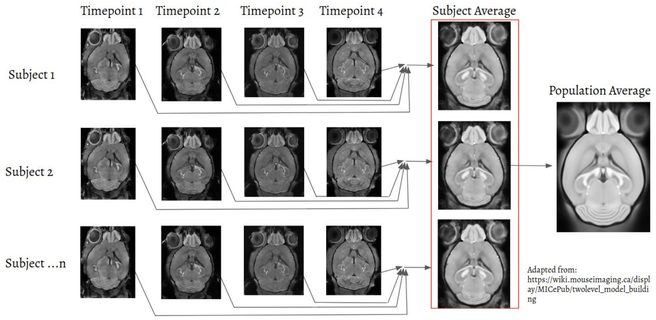

Figure 2 (above). Obtention of a population average using the 2-level model building tool Pydpiper (3), following strict QC and linear registration. *Courtesy of Elisa Guma.*

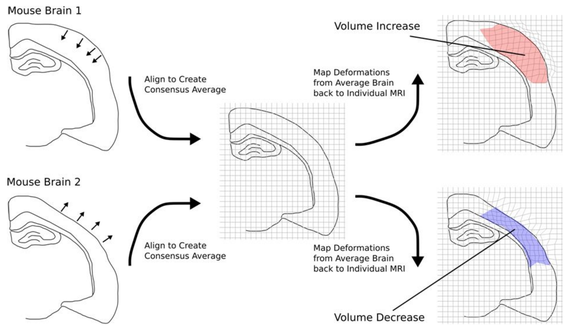

Figure 3 (above). Obtention of the absolute Jacobian determinants, which represent whole brain and local volume differences compared to the population average.*Courtesy of Jason Lerch.*

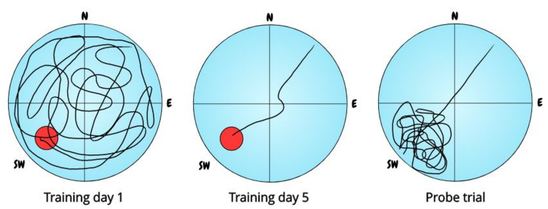

Figure 4 (above). The MWM was used to assess spatial, long-term memory.

Immunohistochemistry The brains were collected via intracardiac perfusion, stored in PFA 4% then PBS-sodium azide, deep frozen and cut.

Results

Weight
A 3-way repeated measures ANOVA showed a significant main effect of intervention ($p<0.001$) and week ($p<0.001$) but not genotype.

MWM
HFD vs CD: CD mice performed better than HFD mice.
HFD vs rescue: There was a beneficial effect of rescues, driven by the wheel group, and WT improved the most.

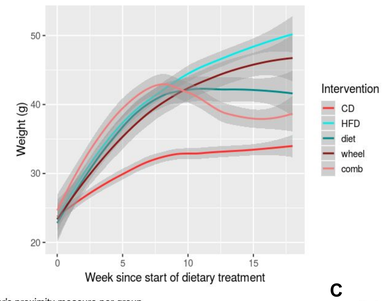

Figure 5. Changes in weight per intervention between HFD start (week 0) and MRI 3 (week 18). Rescue starts at week 8.

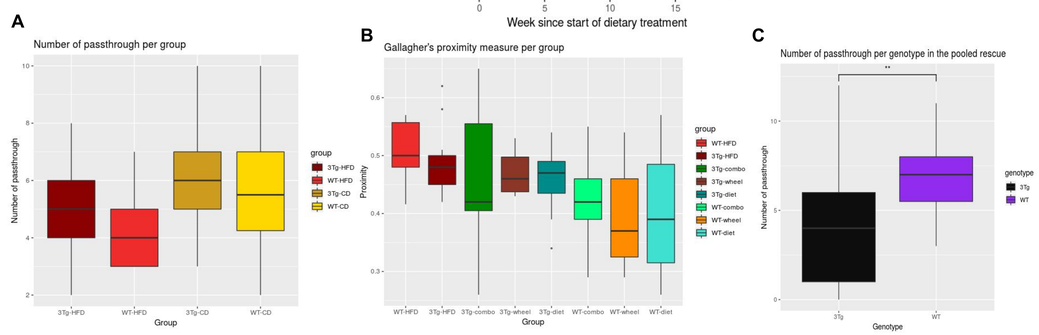

Figure 6 (above) A. Number of passthrough per group. CD mice passed through the platform previous location significantly more ($p<0.03$) and tended to be closer to it ($p<0.08$) than HFD mice, independently of genotype. **B.** Gallagher's proximity measure per group. There was a significant effect of intervention on proximity ($p<0.04$) driven by the differences between wheel and HFD mice ($p<0.05$ with Tukey's test), & rescue mice overall swam closer to the platform location (lower Gallagher measure of proximity). **C**. Number of passthrough per genotype in the pooled rescue. WT mice benefited the most from the rescue, with more passthrough than the 3Tg ($p<0.003$).

MRI A linear mixed effect models was used to assess differences between interventions and genotypes in neuroanatomical trajectory (Jacobian determinant). Overall the differences were related to intervention more than genotype.
HFD vs CD: There were significant differences (most at FDR 5%) in the slope of volumetric change between different interventions, including in the hippocampal formation. Most regions showed increased volume in HFD (possibly a compensatory mechanism as seen in mouse models of AD (4)), sometimes followed by a steep decrease.
HFD vs rescue: The most interesting results were significant differences (most at FDR 5%) in the slope of change between rescue conditions and HFD (hippocampal formation & cerebellum; and cingulate & orbital cortex for the groups with a wheel), with in most cases less or no decline following the beginning of rescue, especially in the wheel and combined rescue groups.

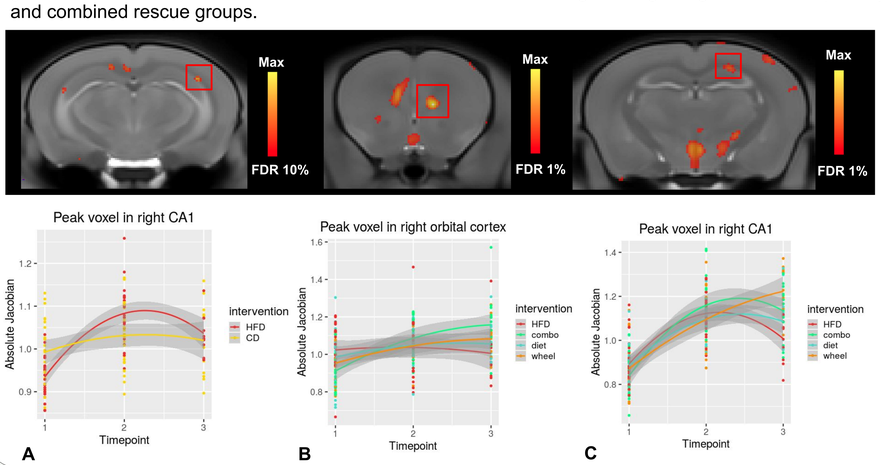

Figure 7 (left)
A. Visualization of significant differences across all genotypes between HFD and CD in the right CA1 (above), and of the peak voxel (below).
B. Visualization of significant differences between the combined rescue and HFD in the right orbital cortex.
C. Same as B, in the right CA1.

Conclusion and limitations

- Only sensitive measures picked up group differences in MWM, suggesting the presence of light memory impairments only.
  - HFD mice performed worse than both CD and rescue groups
  - 3Tg-mice on any rescue showed less improvement than WT did, suggesting beyond certain levels of brain pathology recovery through lifestyle changes is limited.
- MRI analyses showed that CD and HFD mice, as well as HFD and rescue mice, differed in the neuroanatomical trajectory of important memory structures. There seems to be mitigation of HFD-induced decline in volume in such regions. Interpretation of MRI results is limited due to the stage of data acquisition, and immunohistochemistry will be performed later to complement MRI results.
- A limitation is the lack of monitoring for social interactions and wheel use.

References

1) Livingston et al. **2017.** Dementia prevention, intervention, and care. *The Lancet 390,* 10113
2) Kong et al. **2018.** Early-in-life neuroanatomical and behavioural trajectories in a triple transgenic mouse model of AD *Brain Struct Func.*223(2).
3) Friedel et al. **2013.** Pydpiper: a flexible toolkit for constructing novel registration pipelines. *Front. Neuroinform* 8, 67.
4) Noristani et al. **2011.** Increased hippocampal CA1 density of serotonergic terminals in a triple transgenic mouse model of AD: an ultrastructural study. *Cell Death Dis* 2(9): e210.