Investigating the impact of midlife obesity on Alzheimer's disease pathology

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Introduction

Midlife obesity is a significant risk factor for Alzheimer's disease (AD)[1]. Studies have supported that obesity in midlife accelerates AD-related pathology and memory impairment in mouse models of AD[2]. To elucidate the relationship between midlife obesity and AD-related neuropathophysiology, we evaluated the impact of midlife obesity on the brain morphology of the triple transgenic mouse model of AD (3xTg; harbouring mutations leading to both amyloid and tau accumulation) using longitudinally acquired magnetic resonance imaging (MRI).

The objective of the project is to determine the effect of midlife obesity on AD neuropathology and behaviour in the 3xTg mouse model of AD.

Methods

3xTg mice and non-transgenic (non-Tg) control mice (129S/C57BL6) underwent T1-weighted MRI at 2 months of age and were subsequently placed on either a high-fat diet (HFD) or a low-fat, ingredient-equivalent control diet (CD). Animals underwent a second MRI at 4 months (midlife) and a third at 6 months. Animals then performed the novel object recognition (NOR) task for assessment of short-term nonassociative memory.

Deformation-based morphometry was used to measure trajectories of voxel-wise volumetric change in all subjects and were expressed as the Jacobian determinant of the deformation field mapping each mouse to the average of the group[3]. A quadratic mixed effects model was used to examine the interaction of group and time point (covaried for sex) on the Jacobian determinants. Correction for multiple comparisons was done using FDR.

Age	Procedure	Group			
		3xTg HFD	3xTg CD	B6129s HFD	B6129s CD
8 weeks	MRI	10	10	9	9
16 weeks	MRI	10	10	9	9
24 weeks	MRI	10	10	9	9
25 weeks	NOR	10	10	8	9

Table 1. Number of animals per group for each experimental procedure.

Results

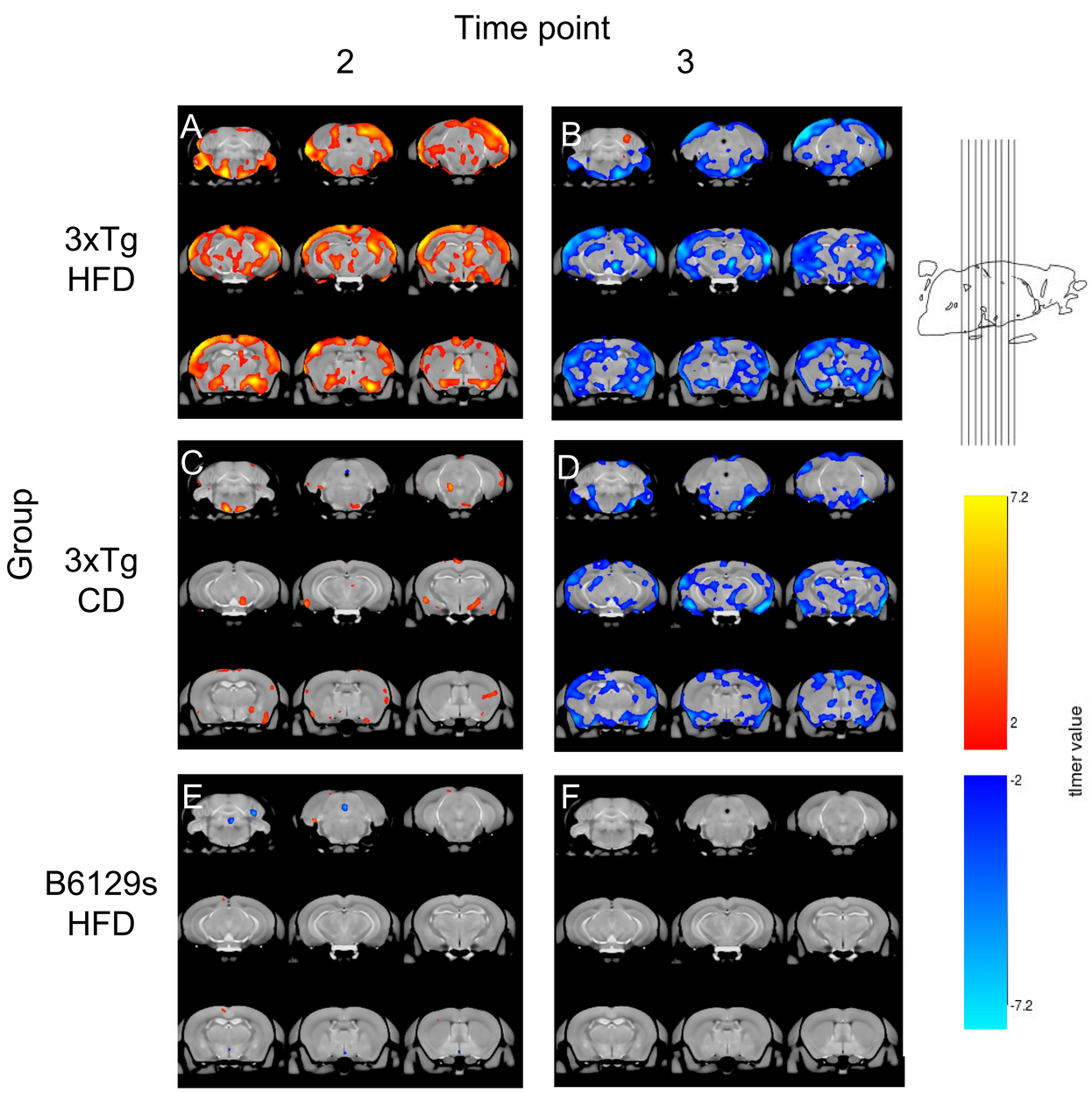
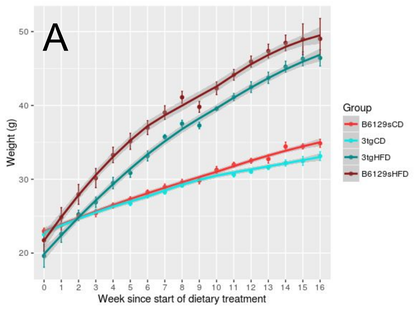


Figure 1. Voxel-wise difference in local volume for the interaction of group and scanning time point using a quadratic model. A significant interaction (t=2.38) between the 3xTg-HFD group and time point 2 (A) indicates that there was an increase in local volume in the 3xTg-HFD group at the second time point (4 months) in comparison to the B6129s-CD group. A significant interaction (t=2.30) between the 3xTg-HFD group and time point 3 (B) indicates that there was a decrease in local volume in the 3xTg-HFD group at the third time point (6 months) in comparison to the B6129s-CD group. A similar pattern was observed for the 3xTg-CD group, wherein there was a significant interaction (t=3.38) between group and time point 2 (C) and group and time point 3 (t=2.50) (D), indicating an initial increase and subsequent decrease in local volume in the 3xTg-CD group in comparison to the B6129s-CD group. For the B6129s-HFD group, there was a significant interaction (t=3.81) between group and time point 2 (E), but no significant interaction between group and time point 3 (F). FDR<5% for all.



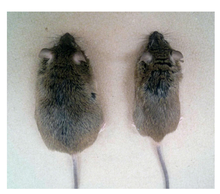


Figure 2. (A) Body weight of 3xTg-AD and non-Tg control mice in response to dietary treatment. All mice were maintained on either a control diet or high fat diet from 8 weeks of age (Week 0) and were weighed weekly for the remainder of the experiment. The effect of group and week on body weight was examined with a linear mixed effects model (covaried for sex). A significant interaction between group and week was observed at all weeks following Week 2 ($p<0.05$). **(B)** 3xTg-AD mice at midlife (4 months) on the HFD (left) and CD (right).

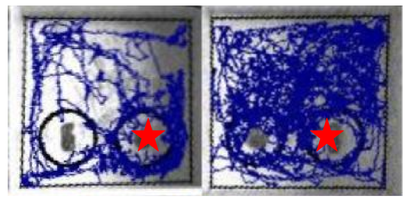


Figure 3. Exploration trace in the novel object recognition task for a non-Tg control mouse on a CD (left) and a 3xTg-AD mouse on a HFD (right). The novel object is indicated with a red star.

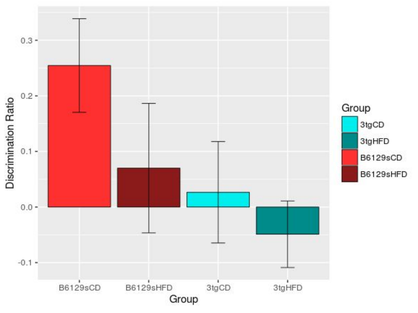


Figure 4. Novel object recognition task. At 25 weeks of age, memory was evaluated in all animals with the NOR task. The effect of genotype and diet on discrimination ratio was examined with a 2-way ANOVA. Impaired memory was observed for 3xTg-AD mice ($F(1,1) = 4.98$, $p<0.05$) in comparison to non-Tg control mice, as assessed by a reduced discrimination ratio. There was no significant effect of diet or genotype by diet on discrimination ratio.

Conclusions

A group by time point interaction was significant for voxel-wise changes in local brain volume in 3xTg-AD and non-Tg control mice. NOR testing revealed memory impairments associated with genotype, but not high-fat feeding. Our results suggest that high-fat feeding interacts with AD pathology in the 3xTg-AD mouse model to initially increase local brain volume by midlife, but subsequently decrease local brain volume by late life, suggesting a potentially synergistic relationship between midlife obesity and risk for AD.

Bibliography

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Brain Canada Foundation
with financial support from Health Canada