Long-term treadmill exercise delays onset of cognitive decline in APPSWE/PS-1ΔE9 mice; assessment of potential underlying mechanisms

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Exercise promotes hippocampal neurogenesis and cognitive performance and alleviates Alzheimer's Disease (AD)- type pathology in several mouse models of AD. We determined whether regular treadmill exercise could delay the onset of cognitive decline in the APP_{SWE}/PS-1ΔE9 AD model and investigated any underlying changes in neurogenesis, neuroinflammation and Aβ burden (protein associated with Alzheimer's).

Methods:

- Three-month old WT (wild Type) and APP_{SWE}/PS-1ΔE9 (Alzheimer's model) mice were allocated to sedentary or exercise groups.
- Exercise mice ran on a treadmill three times per week for six months.
- Recognition and spatial memory was assessed by object recognition and location tasks at three, five, seven and nine months.
- At eight months, half of the mice in each experimental group received daily injections of BrdU (detects neurogenesis) (50 mg/kg; i.p.) for seven days.
- Following the last session of cognitive testing at nine months, mice were sacrificed and samples stored for tissue analysis.

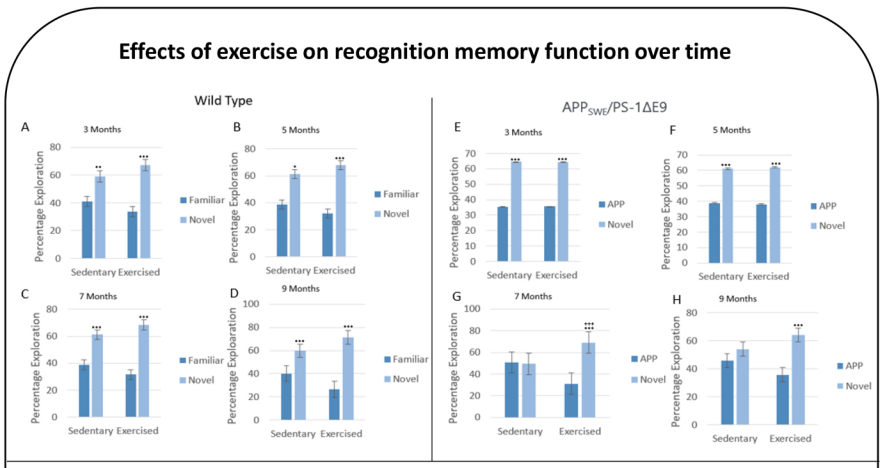

Figure 1: Effects of exercise on recognition memory in wild type (A-D) and APP_{SWE}/PS-1ΔE9 mice (E-H) assessed by novel object recognition task at three (A,E), five (B,F), seven (C, G) and nine (D,H) months old. Data are expressed as means ± SEM. ** p<0.01, *** p<0.001 vs familiar object, +++ vs novel object. Data are analysed by one-way ANOVA and Bonferroni's post hoc test.

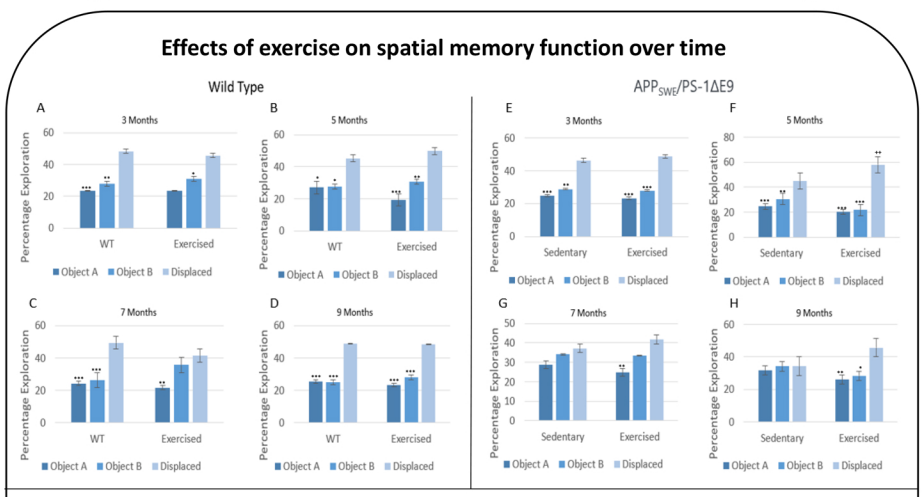

Figure 2: Effects of exercise on spatial memory in wild type (A-D) and APP_{SWE}/PS-1ΔE9 (E-H) mice assessed by object displacement task at three (A,E), five (B,F), seven (C, G) and nine (D,H) months old. Data are expressed as means ± SEM. * p<0.05, **P<<0.01, *** p<0.001 vs displaced object, ++ p<0.01 vs displaced object in sedentary group. Data are analysed by one-way ANOVA with Bonferroni's post hoc test.

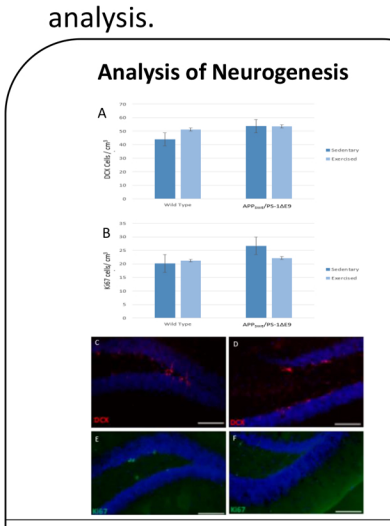

Figure 3: Quantification of new-born neurons (DCX) (A) and proliferating cells (Ki67) (B) in 9 month old Wild Type and APP_{SWE}/PS-1ΔE9 mice in sedentary and exercised conditions. Representative images of DCX cells (red) and Ki67 cells (green) in the dentate gyrus of APP_{SWE}/PS-1ΔE9 mice sedentary (C,E) and exercised (D,F). Scale bar represents 100 µm. Sections are counterstained with DAPI (blue). Data are expressed as means ± SEM. Data are analysed by two way ANOVA with Bonferroni's post hoc test.

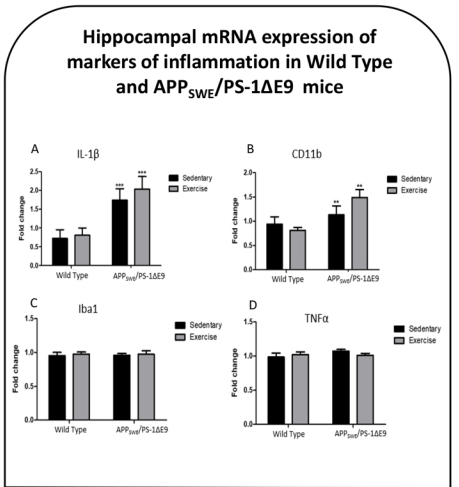

Figure 4: qPCR analysis of hippocampal tissue from nine month old WT and APP_{SWE}/PS-1ΔE9 mice: Fold change in gene expression of IL-1β (A), CD11b (B), Iba1 (C) and TNFα (D). Data are expressed as means ± SEM. ** p<0.01, *** p<0.001 vs WT equivalents. Data are analysed by two way ANOVA with Bonferroni's post hoc test

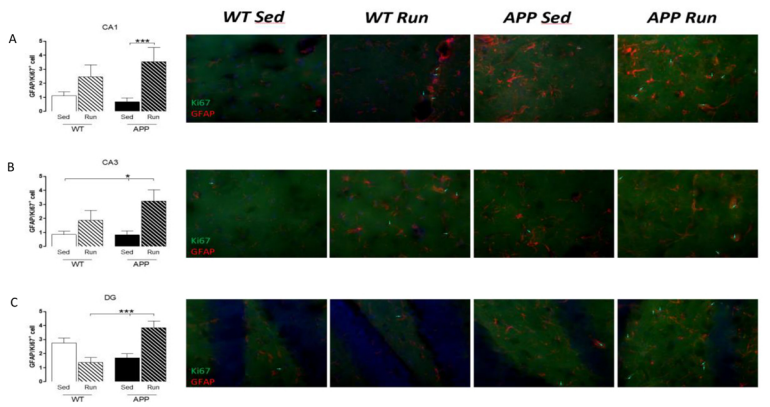

Figure 5: Immunofluorescence staining of GFAP and Ki67 in hippocampal samples of nine month old WT and APP_{SWE}/PS-1ΔE9 mice. Ratio of GFAP/Ki67 in CA1 (A), CA3 (B) and DG (C) of the hippocampus. Data are expressed as means ± SEM. Data are analysed by two-way ANOVA, Tukey posthoc: *p<0.05; ***p,0.005. A similar analysis was carried out using Iba1 as a marker of microglia, but no significant changes were observed between the groups (data not shown)

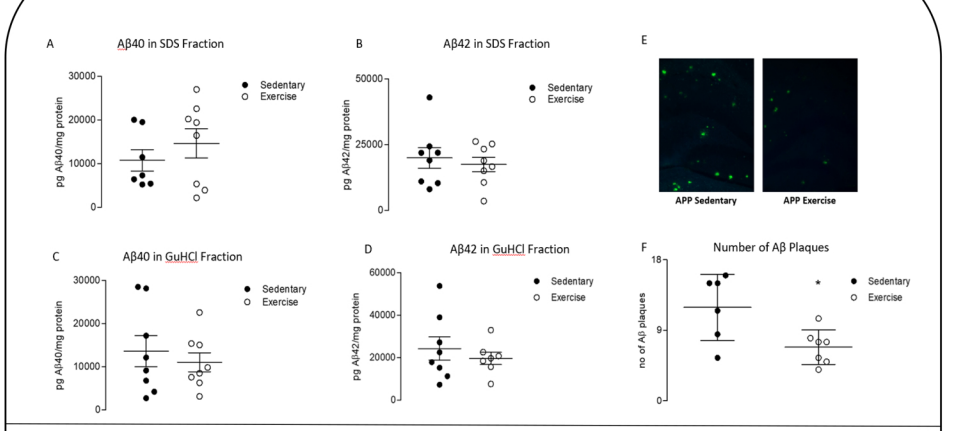

Figure 6: Aβ burden in exercised and sedentary mice assessed by meso analysis in SDS fractions (A-B) and GuHCl fractions (C-D). Data are analysed by unpaired t-test: * p < 0.05.

Conclusions:

- WT and APP_{SWE}/PS-1ΔE9 mice displayed identical cognitive performance at three and five months old.
- Progressive decline was seen in sedentary APP_{SWE}/PS-1ΔE9 mice at seven and nine months, while their exercising counterparts displayed normal recognition and spatial memory.
- No significant difference was observed between groups in markers of neurogenesis DCX and Ki67
- A genotype-related increase was seen in the markers of inflammation IL-1β and CD11b
- Aβ protein concentration did not change significantly in the exercised cohorts, but the number of Aβ plaques decreased significantly.
- Immunofluorescence staining showed a significant increase in GFAP (astrocyte (neuron support cell with some immune functions) marker) in the exercised cohorts
- The observed decrease in Aβ plaques and increase in GFAP could be explained by astrocytic phagocytosis (engulfment) of Aβ plaques, with delayed Aβ protein degradation. Further experiments are required to test this hypothesis.

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