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## Development of new models and analysis methods/seeding and spreading of proteinopathies

# Heterogeneity of Alzheimer's disease: Insight from a novel mouse model of amyloid and tau lesions based on the inoculation of human brain preparations

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### Abstract

**Background:** A major challenge in clinical research is to better understand the heterogeneity of AD. Indeed, AD is heterogeneous regarding its origin, neuropathology and clinical expressions. While classical sporadic forms of AD (cAD) evolve over approximately 10 years, the “rapidly progressive form of AD” (rAD) is a non-genetic aggressive form associated with a rapid clinical decline that evolves over approximately 2 years (Schmidt et al., Arch Neurol. 2011). Several studies have shown that the experimental inoculation of brain samples with A $\beta$ - and/or tau pathology into transgenic (tg) mouse models overexpressing mutant human APP or tau promotes either A $\beta$  or tau aggregation in the brain of the recipient animal (Gary et al., Acta Neuropathol Com. 2019). The phenotype of the inoculated brains is moreover reproduced in the recipient host (Watts et al., PNAS. 2014). The aim of this work was to study the impact of the inoculations of rAD versus cAD-human brain preparations in tg mice mouse models of  $\beta$ -amyloidosis to explore the mechanisms associated to AD heterogeneity.

**Method:** Brain samples were characterized pathologically and biochemically. The rAD, cAD, and ctrl (non-Alzheimer) samples were inoculated in the CA1 region of 2-month-old APP/PS1dE9 mice (n = 15-20/group). At 8 months post-inoculation, an object recognition task (V-maze) was conducted to assess memory performance. A $\beta$  deposits (4G8 antibody), tau inclusions (AT8 antibody) and synaptic density were then quantified by immunohistochemistry in the hippocampus.

**Result:** Mice inoculated with either rAD or cAD brain preparations developed a similar increase of A $\beta$  plaques and tau deposits as compared to ctrl-inoculated mice. However, only the aggressive form of AD (rAD) led to significant cognitive alterations (Figure 1) and synaptic loss (Figure 2) after 8 months.

**Conclusion:** APP/PS1dE9 mice inoculated with AD brain preparations are new models to study both amyloid and tau lesions occurrence. Our results suggest that, independently from the amyloid plaque load or the severity of tau intraneuronal pathology, synaptic health variability may contribute to the heterogeneity of AD-like phenotype.

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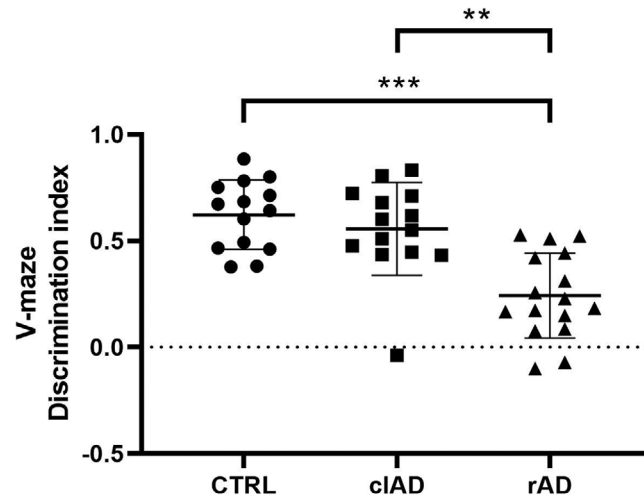


FIGURE 1

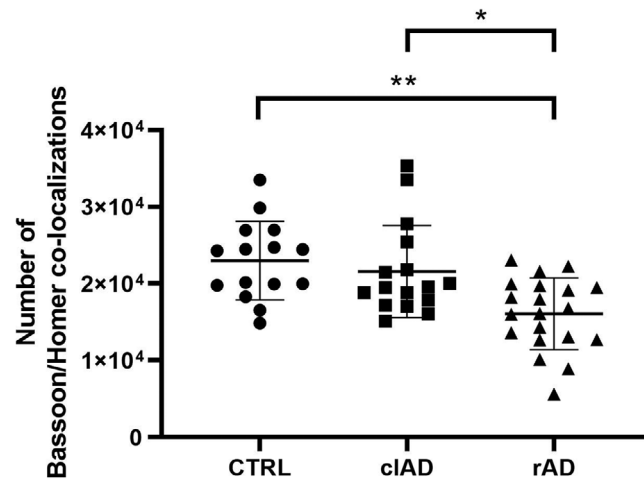


FIGURE 2