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Sex-effect in the treatment response to low-dose radiation therapy for Alzheimer's disease.

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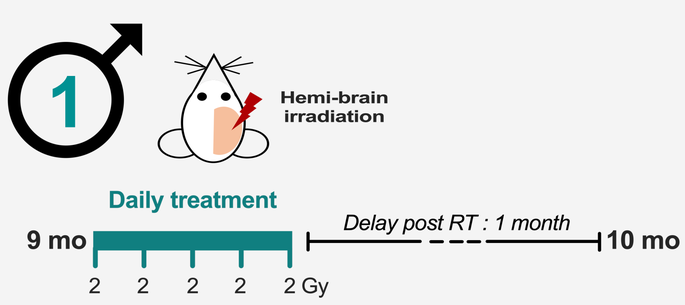
BACKGROUND

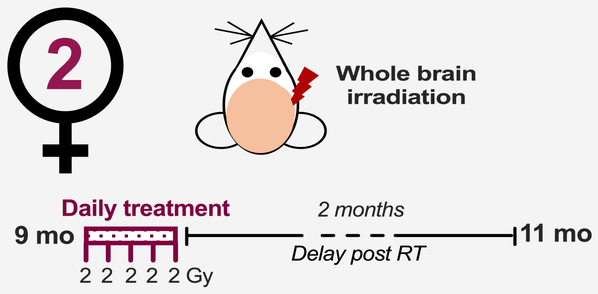
Numerous treatments against AD have been developed to target amyloid, tau or neuroinflammation, without a clear success, highlighting the necessity to develop new therapeutic strategies[1]. **Radiation therapy (RT**), one of the mainstay cancer treatments, has been recently studied in AD. It has been postulated that this treatment, applied at **low doses (LD)**, could achieve two important effects for AD: a **decrease of amyloid load and neuroinflammation**[2]. Only 6 studies evaluated its impact in the brain of AD mouse models, using different regimens or delay post RT[3-8]. However, the radiation doses, the delay post treatment, the models and the stage of treatment differ between studies, making difficult to define the effect and the mechanisms of actions of LD-RT in AD.

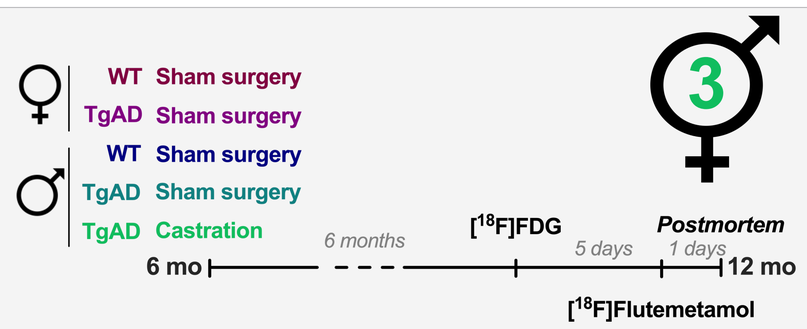
AIMS

1) The main objective of this study is to assess the **clinical relevance of a reference regimen** (2 Gy in 5 fractions delivered daily) in an AD rat model applied at a pre-symptomatic stage in males and females.
2) Better understand the **sex effect** observed in the treatment response.

METHODS



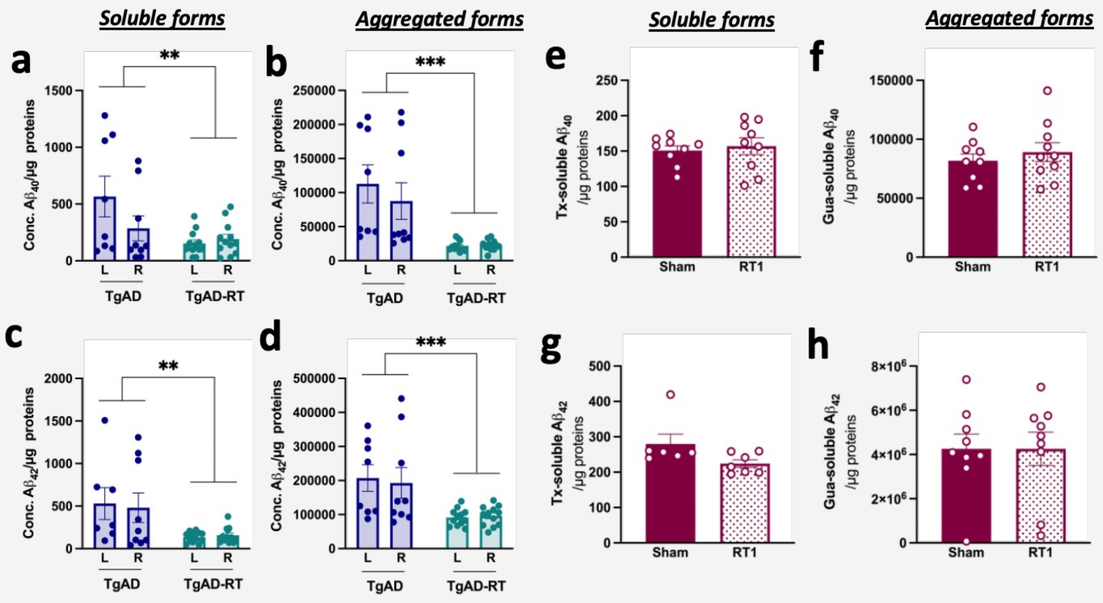




TgF344-AD (TgAD) rats, harboring the hAPPswe and hPS1dE9 transgenes, were treated with 10Gy in 5 fractions of 2Gy delivered daily.
Males and **females** were treated separately at 9-months-old. One or 2 months later, the effect of LD-RT was evaluated postmortem.
In a third cohort, TgAD males were **castrated** at 6-month-old and analyzed with sham-operated males and females (TgAD and WT) at 12-months-old by PET imaging ([18F]FDG and [18F]Flutemetamol to quantify brain metabolism and amyloid plaques respectively). *Postmortem* anaylses are ongoing.

FIGURE 1

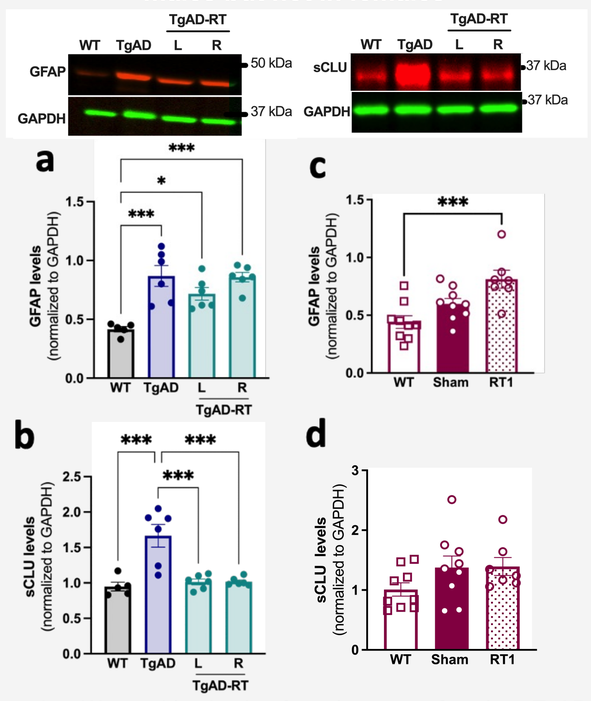
LD-RT significantly reduces amyloid load in young males but not in females



Concentrations of different amyloid peptides were measured by ELISA in the hippocampus and normalized to the total protein levels. A decrease of soluble amyloid peptides in a Triton (Tx) buffer (known to be the most toxic forms; **a, c**) and more aggregeted forms soluble in a Guanidine (Gua) buffer (**b, d**) was observed in males but not in females (**e-h**).

FIGURE 2

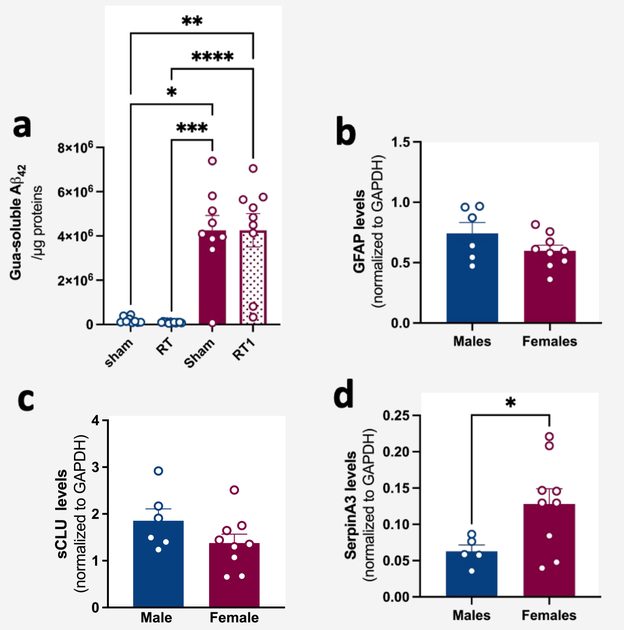
LD-RT significantly reduces neuroinflammation in young males but not in females



Representative Westernblot in the frontal cortex of males. TgAD rats already presented an astrocytic inflammation at a pre-symptomatic stages as shown by the increase of GFAP (**a, c**) and sCLUSTERIN (sCLU; **b, d**) levels in TgAD rats compared to WT. A decrease of some markers was measured in males (**a, b**) but not in females (**c, d**) after treatment.

FIGURE 3

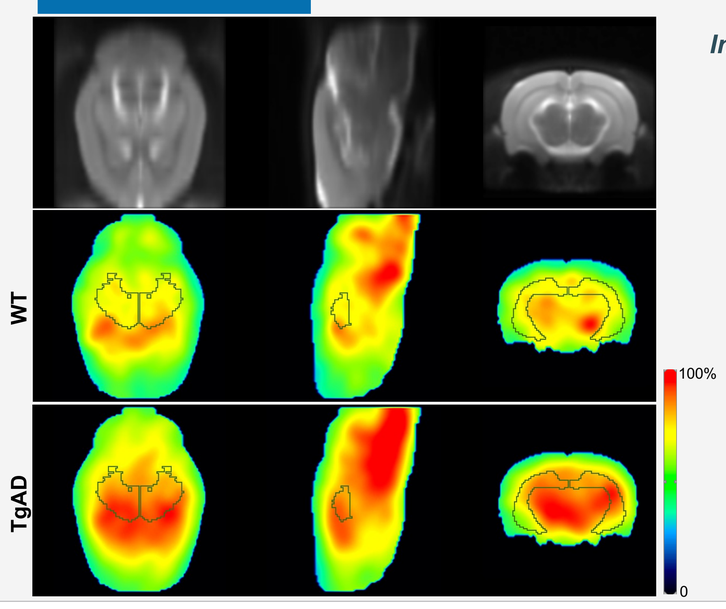
Females present a more advanced pathology than males



Females showed clearly higher levels of aggregated forms of amyloid peptides measured by ELISA than males (**a**). No difference was observed between both sexes for GFAP **(b)** or CLU (**c**) levels but females expressed more the SerpinA3 protein, suggesting also an higher neuroinflammation in females (**d**) .

FIGURE 4

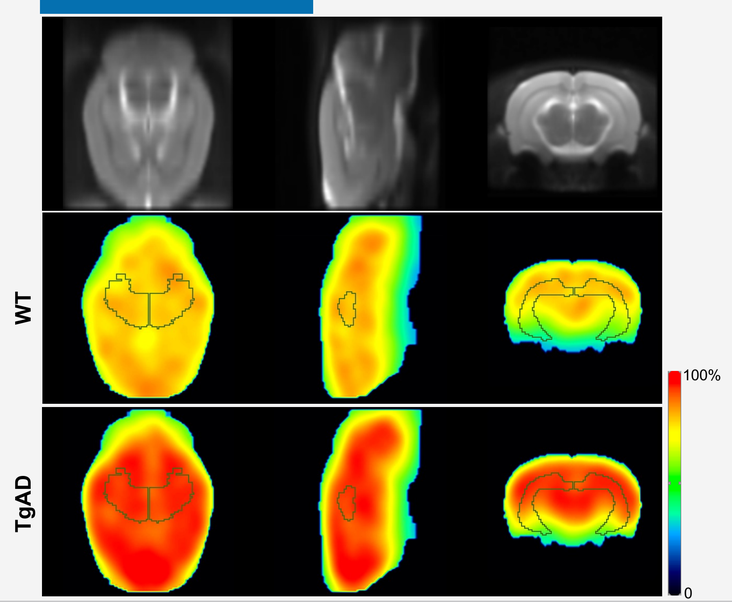
In vivo quantification of amyloid plaques by PET imaging



Average of SUV images of male WT rats (n=2) and male TgAD rats (n=5). Rats were injected with **[18F]Flutemetamol** (Vizamyl) in the tail vein and scanned 30 minutes by PET/CT imaging 30 minutes post injection. Images were realigned to the CT scan and coregistered to Schwartz MRI template using pmod. The analyses are ongoing.

FIGURE 5

In vivo quantification of brain metabolism by PET imaging



Average of SUV images of male WT rats (n=5) and male TgAD rats (n=9). A food deprivation was realized the day before imaging. Rats were injected with **[18F]Fluoro-2-deoxyglucose** (FDG) in the tail vein and scanned 20 minutes by PET/CT imaging 40 minutes post injection. Animals were awake during the uptake period. Images were realigned to the CT scan and coregistered to Schwartz MRI template using pmod. The analyses are ongoing.

CONCLUSION

- Low-dose radiation therapy significantly reduced different markers of the AD pathology (amyloid plaques and neuroinflammation) at a pre-clinical stage in males. Interestingly, the same treatment did not impact the pathology in females.
- Females TgAD rats present a more advanced pathology than males.
- We are currently evaluating the effect of sex hormones in the pathogenesis of AD: amyloid, metabolism and brain atrophy in a multimodal imaging study. The difference between both sexes and the effect of testosterone depletion on different amyloid forms, amyloid phagocytosis and neuroinflammation will be evaluated *postmortem.*

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