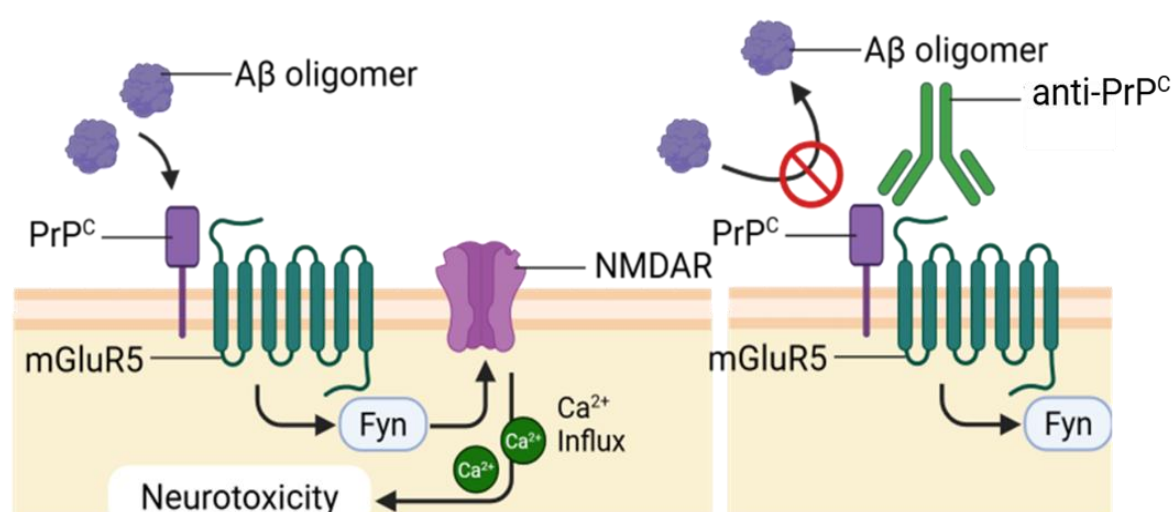


INTRODUCTION

Alzheimer's disease (AD) is the most prevalent cause of dementia in the elderly. It is often associated with neuropsychiatric symptoms (NPS). AD immunotherapies utilize antibodies to inhibit the function of pathology-associated molecules such as amyloid- β (A β) and tau. Our group, along with others, has recently demonstrated the efficacy of immunotherapies targeting the cellular prion protein (PrP^C), a cell-surface receptor mediating the toxicity of A β and tau oligomers. Chronic anti-PrP^C treatments in middle-aged AD models have been shown to improve cognition. However, whether anti-PrP^C has an ameliorating effect on cognitive decline, as well as NPS such as anxiety, is unclear. To address this, we tested a novel monoclonal anti-PrP^C (TW1) developed in our laboratory that targets the PrP 94-108 epitope, which overlaps with the A β -binding region of PrP^C.



KEY WORDS

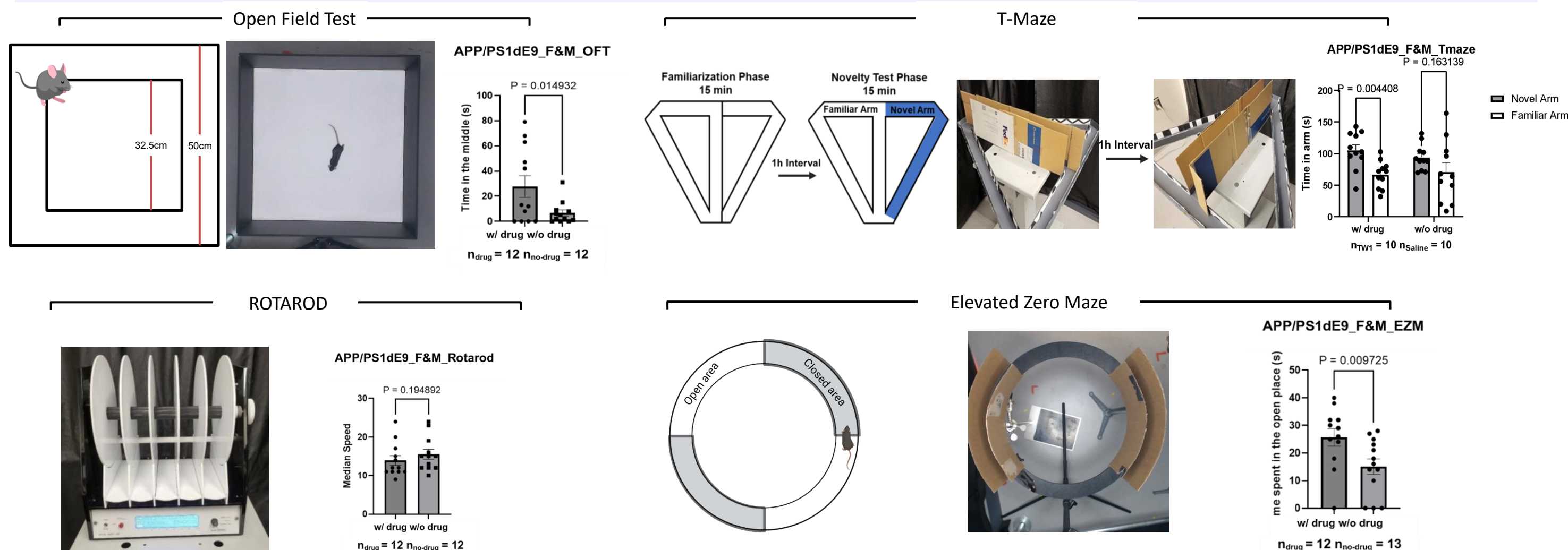
Alzheimer's disease; Anti-PrP^C immunotherapy; Anxiety; Fiber photometry

METHODS

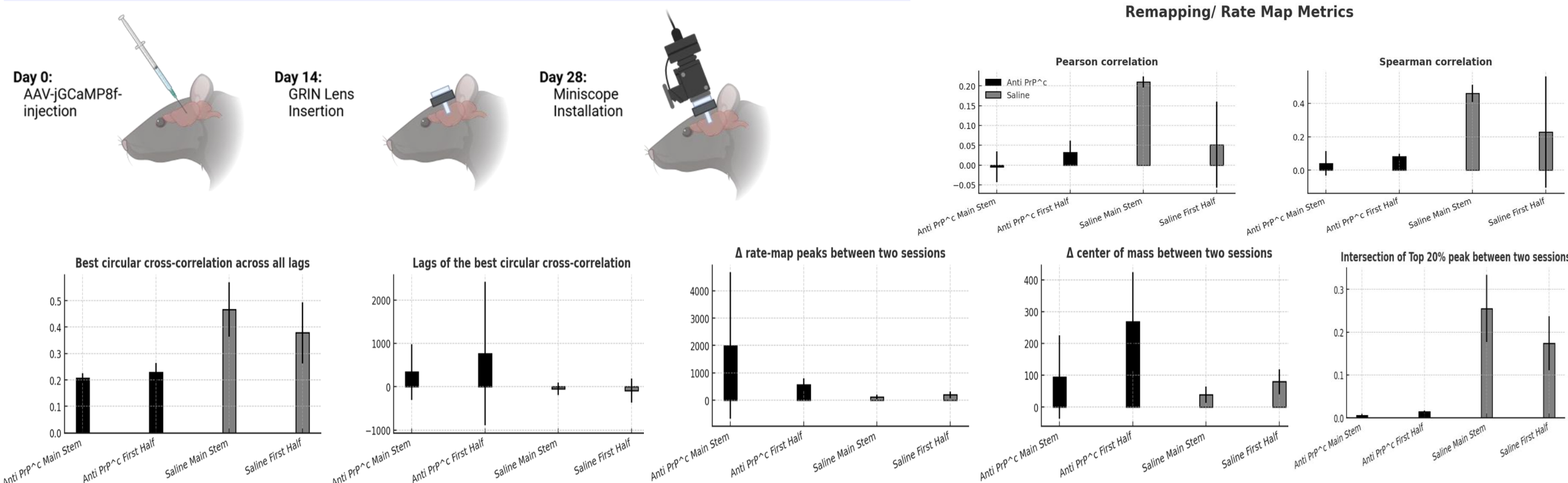
Both middle-aged (12-16 months) and old (18-24 months) APP/PS1dE9 mice were intraperitoneally injected with anti-PrP^C, while control mice received only saline. Behavioral tests including ROTAROD (locomotor), T-maze, anxiety in open field and elevated zero maze (EZM) tests. For in vivo calcium imaging, adeno-associated virus expressing GCaMP8f was injected into hippocampal CA1, above which a GRIN lens was implanted. Four weeks later real-time calcium transients of single CA1 neurons were recorded during spatial navigation tasks.

RESULTS

Behavioral Tests



In vivo Fibre Photometry



CONCLUSIONS

These results suggest that acute anti-PrP^C immunotherapy restores synaptic plasticity, rescues cognitive deficits, and alleviates anxiety in advanced-stage AD models characterized by extensive A β pathology. These findings support targeting PrP^C as a therapeutic strategy for mitigating both cognitive and neuropsychiatric symptoms in late-stage AD.

ACKNOWLEDGEMENTS