

Introduction

- Due to the burden posed by dementia and its comorbidities, and the current lack of viable treatment options, we need to shift towards targeting shared disease mechanisms.
- Drug repurposing offers a rapid, highly translatable pathway.
- Dementia and atherosclerosis are extremely common comorbidities in elderly populations and contribute to each others development through shared mechanisms such as chronic inflammation.
- Modulation of chronic inflammation may be a viable treatment option to reduce symptom severity and delay disease onset.
- Interleukin-1 (IL-1) is a cytokine integral to the induction of chronic inflammation and is associated with both dementia and cardiovascular disease (CVD).
- Anakinra is a pre-approved IL-1 antagonist for rheumatoid arthritis that has previously demonstrated clinical utility and safety in humans.

Aim

- This study will analyse the utility of anakinra in a comorbid mouse model of mixed dementia and atherosclerosis, analysing its effects on cognition, neurovascular function, post-mortem inflammation and neuropathology.

Hypotheses

- IL-1 inhibition will improve cognitive and neurovascular function in comorbid disease mice
- IL-1 inhibition will reduce expression of markers of inflammation and pathology when analysed postmortem.

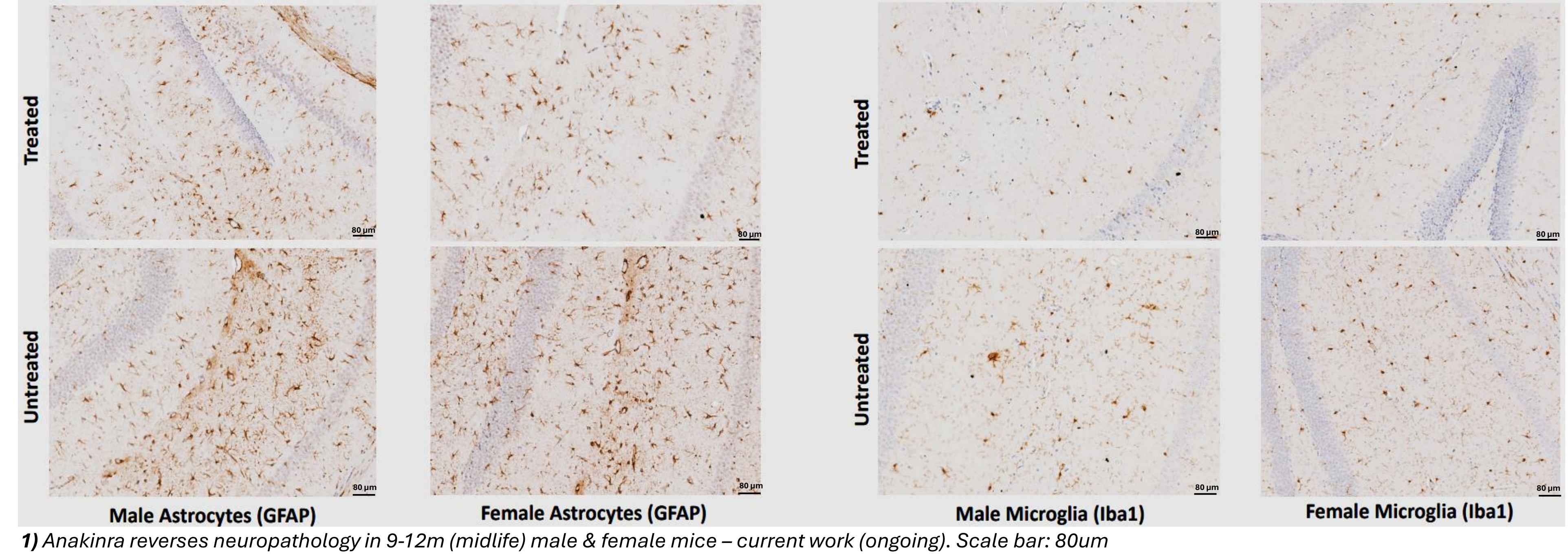
Methods

- Disease induction:** Intravenous AAV-PCSK9 viral vector and high-fat diet (Western diet) for atherosclerosis induction in C57BL6 or APP/PS1 mice
- Behavioural tests:** 1. **Barnes Maze:** Visuospatial memory 2. **Novel Object Recognition:** Object recognition and short-term memory (3-minute delay)
- Anakinra/placebo Treatment:** 100mg/kg in sterile PBS administered via daily s/c injection for a minimum of 60 days.
- Thinned cranial window surgery:** Over right somatosensory cortex to reveal middle cerebral artery
- Imaging:** 2D-Optical imaging spectroscopy assessing haemodynamic changes in response to whisker stimulation (NVC). Simultaneous locomotion tracking is conducted
- Postmortem analyses:** Immunohistochemical analysis of microglial and astrocytic phenotype, oil-red-O imaging of the aortic arch, lipid counts of plasma, A β 42 ELISA, genomics

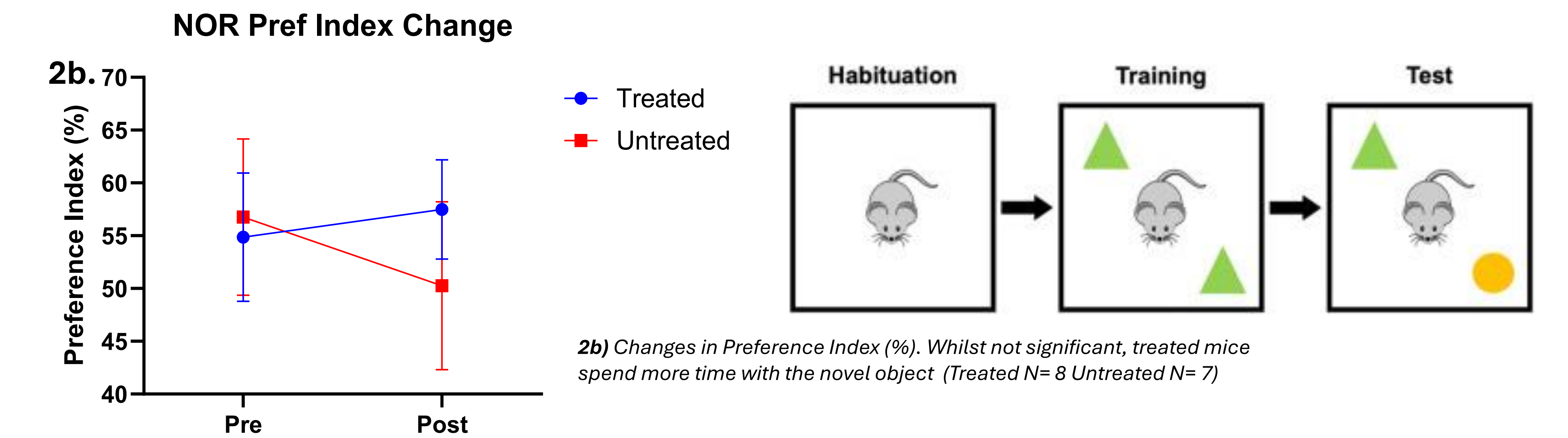
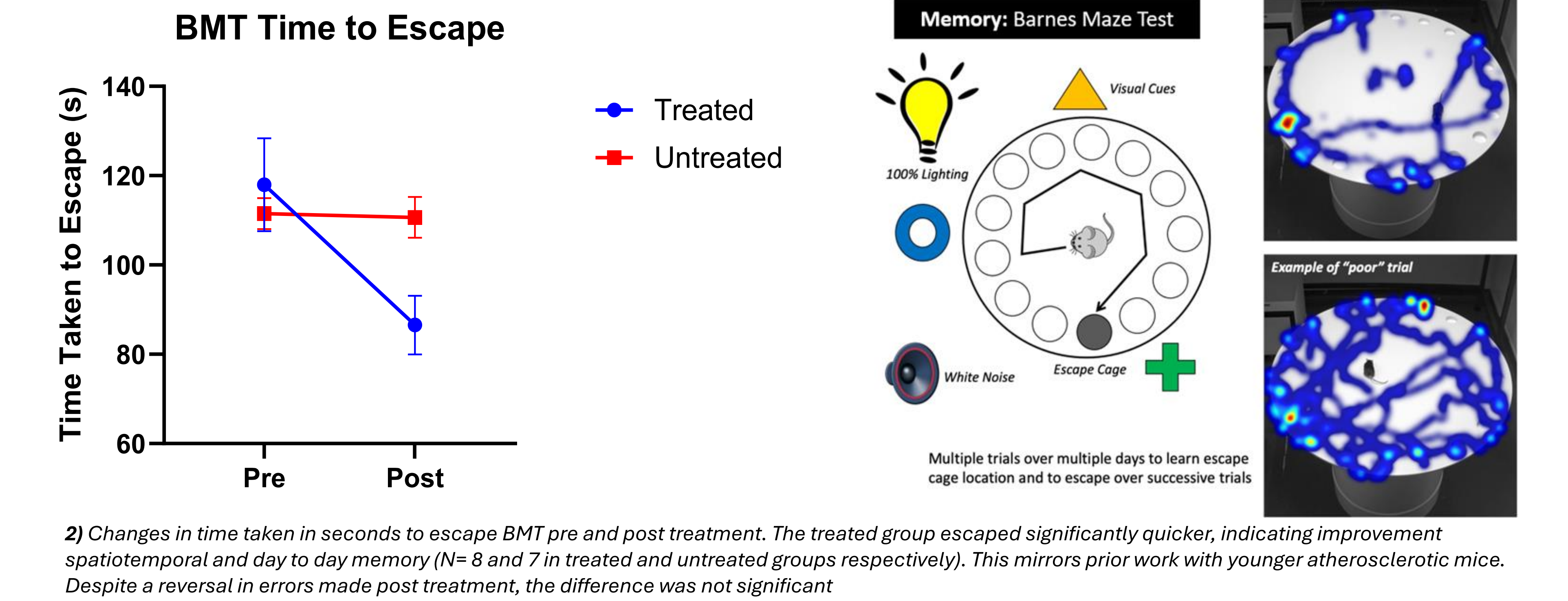
Translational Outcomes and Initial Findings

- This project has the potential to have a significant translational impact, reducing both disease progression, symptom severity, improving quality of life, and rapidly reducing disease burden for patients, their families, and healthcare infrastructure
- Anakinra appears to show a beneficial effect on cognition in late-life atherosclerotic mice, most notably in the Barnes maze test, replicating prior research in younger mice.
- Awake imaging and histological analysis is ongoing!

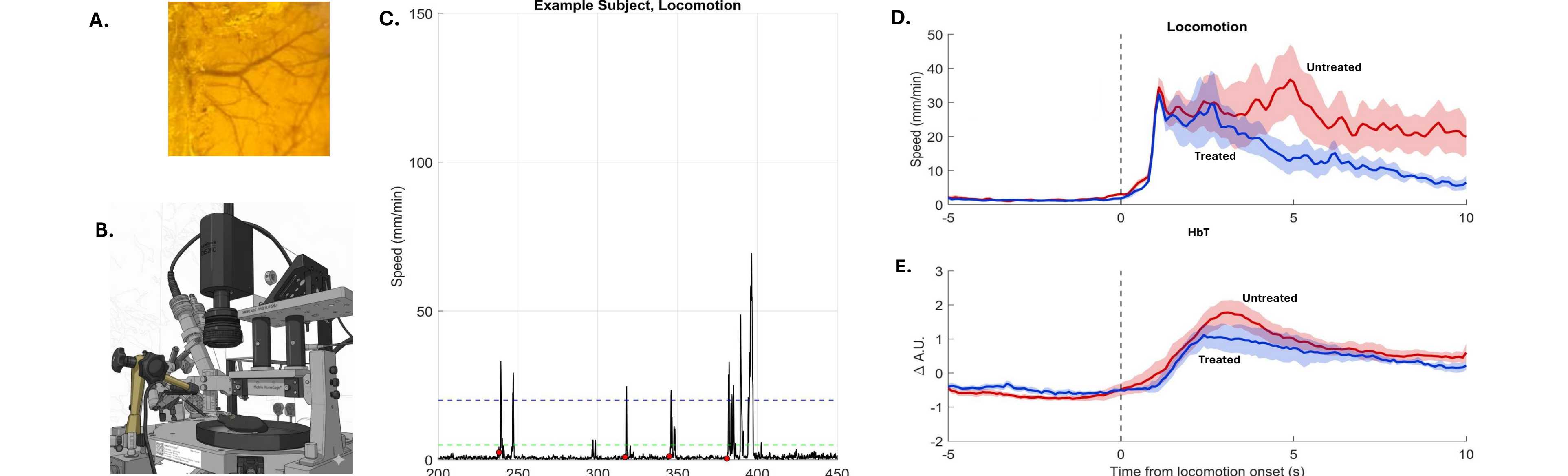
1. Neuropathological Changes in Treated and Untreated Mouse Hippocampus



2. Behavioural changes in Treated and Untreated Mice



3. Preliminary 2D:OIS Locomotion and HbT Differences in Treated and Untreated Mice



3) **A.** Example thinned window over MCA. **B.** Labeotech apparatus. **C.** Example subject locomotion from spontaneous session. **D.** Average of locomotion in treated and untreated mice **E.** Average of HbT in treated and untreated mice. Contrary to the hypothesis, treated mice displayed a smaller change in blood volume post-locomotion (Treated N= 4 Untreated N= 6)