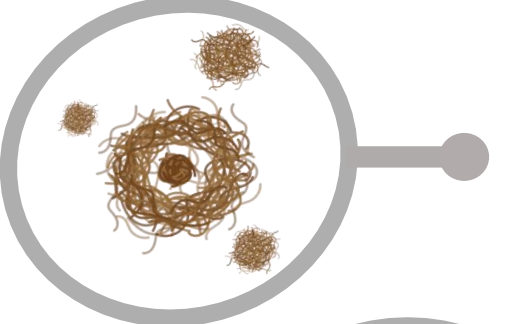


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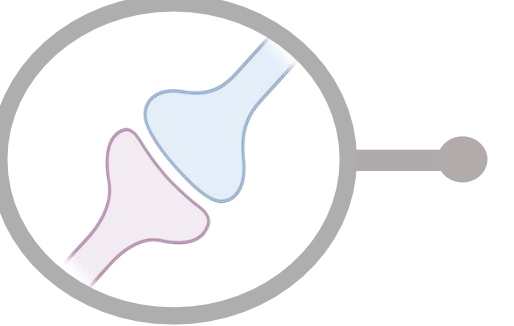
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1. Background

- Therapeutic IV treatment with **lecanemab** has been shown to modestly **slow cognitive decline** in human sporadic Alzheimer’s Disease (AD) ¹.
- Lecanemab effectively **clears plaques from the brain** through a poorly understood mechanism ¹.
- **However...**



Plaque load alone is a poor correlate of cognitive decline ^{2, 3}.



Synapse loss is the strongest correlate of declining cognition ^{3, 4, 5}.

○ Synapse loss is **exacerbated** in the halo surrounding dense core neuritic plaques and is associated with toxic **Aβ oligomers** ^{6, 7, 8}.

2. Hypothesis

Lecanemab can bind and clear toxic Aβ oligomers from “at risk” synapses in the dense core plaque halo, potentially acting to temper synapse loss and cognitive decline.

3. Experimental Methods

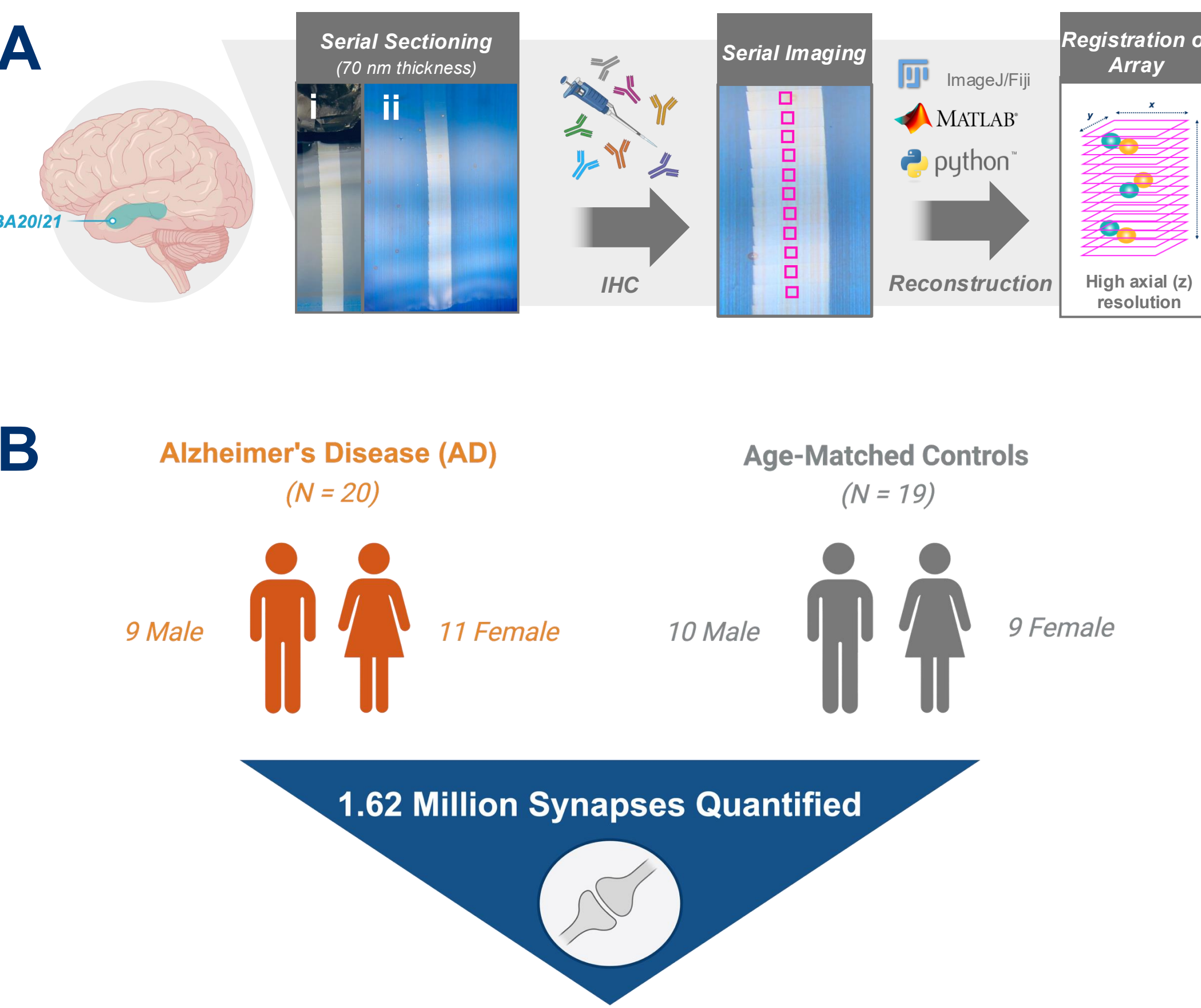
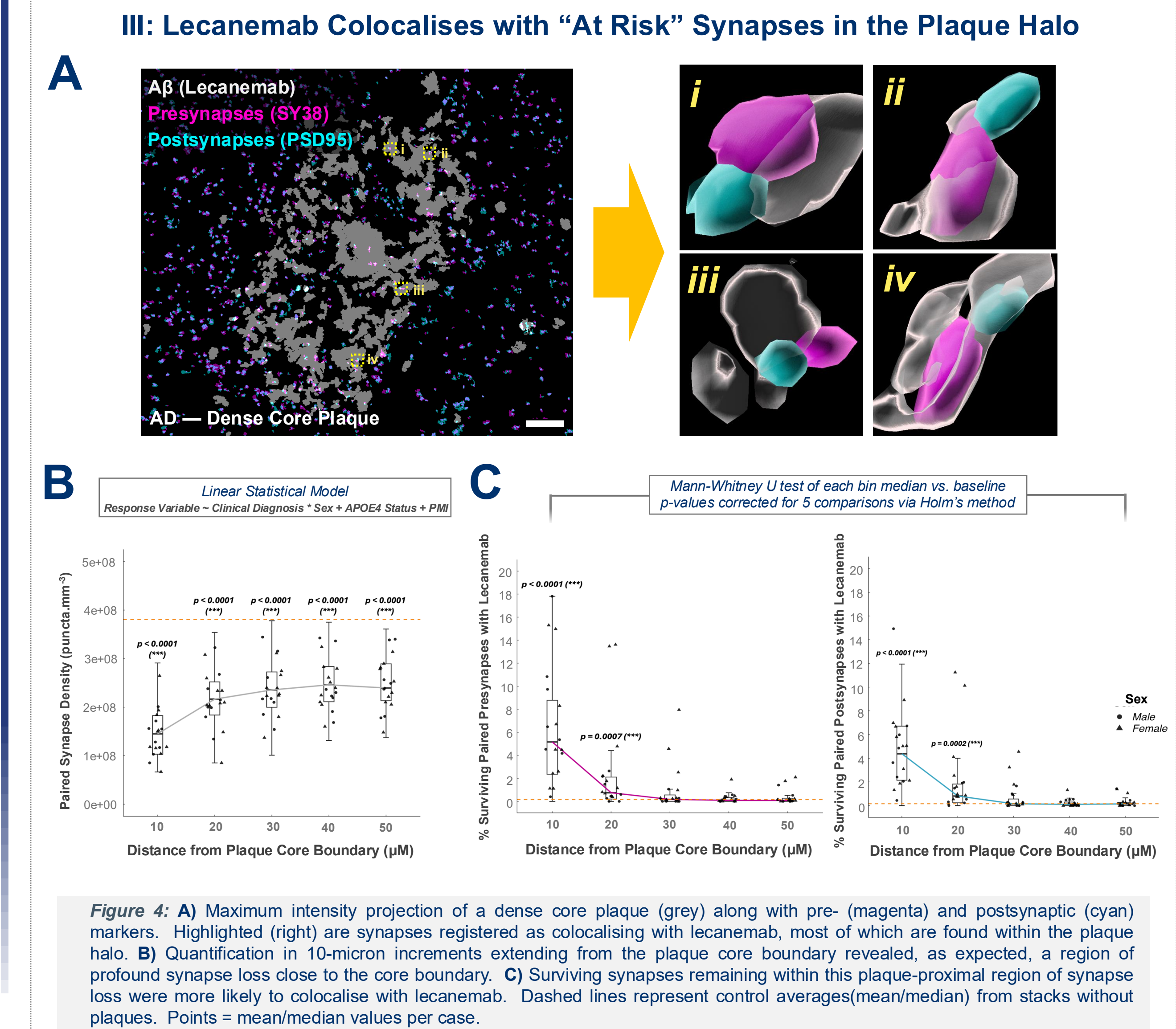
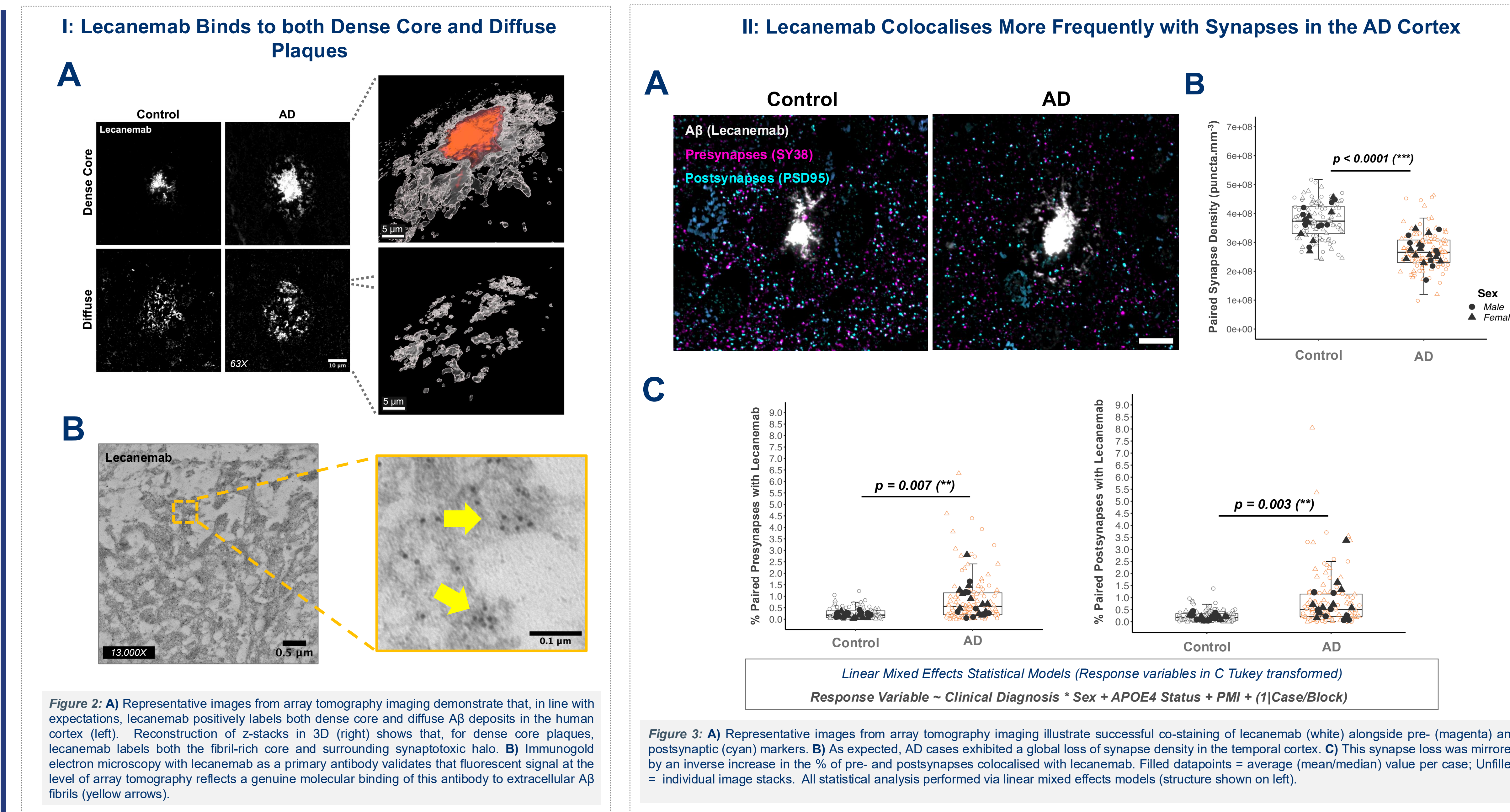


Figure 1: A) Tissue from the temporal cortex (BA20/21) was embedded in acrylic resin and sectioned into ribbons of contiguous sections, each of sub-synaptic (70nm) thickness. Ribbons were immunostained using lecanemab as a primary antibody, alongside pre- and postsynaptic markers (SY38 and PSD95) and serial images acquired from each section. Serial images were computationally stacked and registered into 3D volumes allowing for single-synapse analysis. **B)** In total, 20 AD cases and 19 age-matched controls were included for analysis, amounting to approximately 1.62 million synapses profiled as part of this study.

4. Results



5. Conclusions

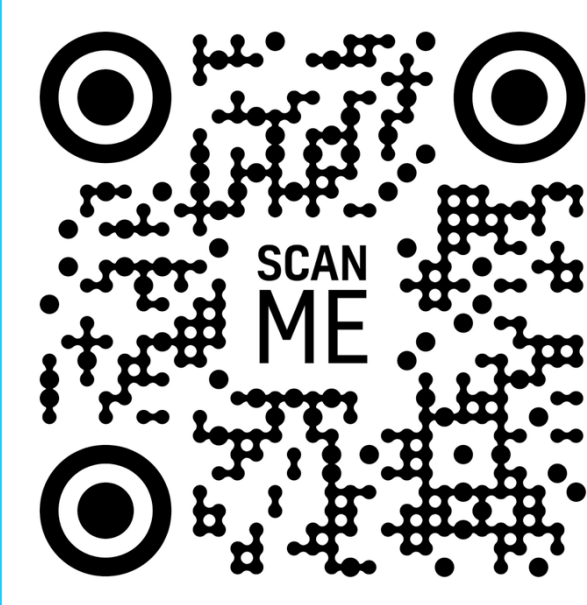
- 1 **Quantifiable lecanemab antibody signal is observed at synapses in the human cortex.**
- 2 **Colocalisation increases in AD; especially with synapses at risk of loss in the oligomer-rich dense core plaque halo.**
- 3 **Clearance of synaptic Aβ by lecanemab, likely via microglial mechanisms ^{9, 10}, could perhaps protect from synapse loss.**

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