Analyzing the Effects of Synaptic Pruning and Neuronal Death in Alzheimer's Disease on Memory Recall Accuracy in a CA1 Hippocampal Model

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Introduction

- **Alzheimer's Disease (AD)** is a neurodegenerative disease characterized by significant progressive memory loss
  - Advanced by synaptic pruning and neuron death
- **Synaptic pruning** is a natural process that occurs during adolescence to trim unnecessary synapses
  - In AD, it excessively removes important neuronal connections
- **Neuron death** happens due to the disruption of cellular processes
- The **CA1 region** is a subfield in the hippocampus crucial for memory and learning
  - Regulates the strengths of synaptic connections
  - Made up of pyramidal neurons and interneurons
- **Our goal** is to compare the effects of synaptic pruning and neuron death on cognitive function, ultimately paving the way for further targeted drug development

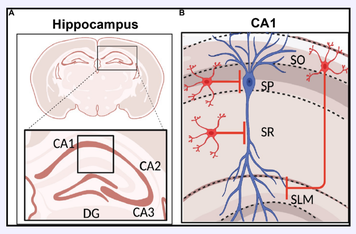

Fig 1. The CA1 hippocampal region of the brain[6]

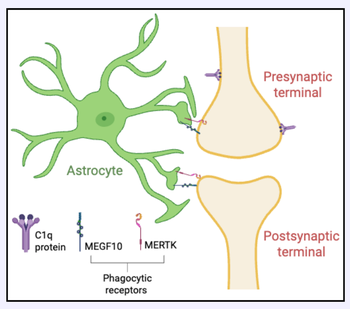

Fig 2. Illustration of the process of synaptic pruning

Methods

The **Cutsuridis Model**[1] replicates the CA1 subregion of the hippocampus

- Model components
  - 100 CA1 pyramidal neurons that receive inputs from CA3 pyramidal neurons,
  - Inhibitory interneurons: 2 basket (B) cells, 1 axo-axonal (AA) cell, 1 bistratified (BS) cell, and 1 Oriens Lacunosum-moleculare (OLM) cell
  - Entorhinal cortex (EC), burst cells, and medial septum as inputs
  - Five patterns stored in model as "memories"

The **experiment** was conducted in five trials for each simulation

- **Simulation 1: Neuron cell death**
  - Neuronal data collected after every year
    - Average recall over all five patterns graphed against years since MCI onset
    - Data of year zero collected as the control
  - 4% neuron loss (4 pyramidal neurons lost) per year in CA1 for 22 years, totaling 88%[2]
- **Simulation 2: Synaptic pruning**
  - Neuronal data collected after every year
    - Average recall over all five patterns graphed against years since MCI onset
    - Data of year zero collected as the control
  - Mild Cognitive Impairment (duration of 7 years) has a mean synaptic loss of 18%, while Mild Alzheimer's (duration of 2 years) has a mean synaptic decline of 55%[5]
  - In our model, for the first 7 years, 2.57% of total initial synapses are lost; the next 2 years, 18.5% of total initial synapses are lost

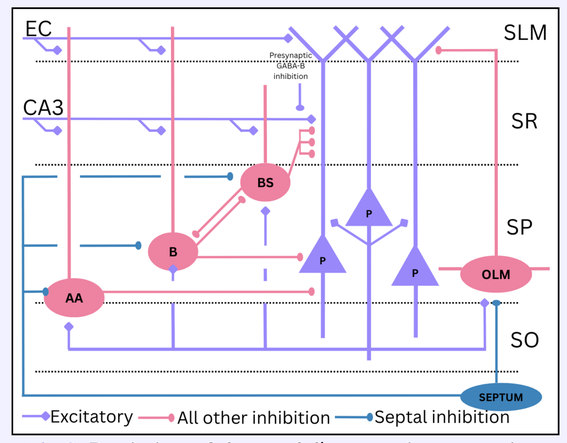

Fig 3. Depiction of the model's synaptic connections and components[1]

Results

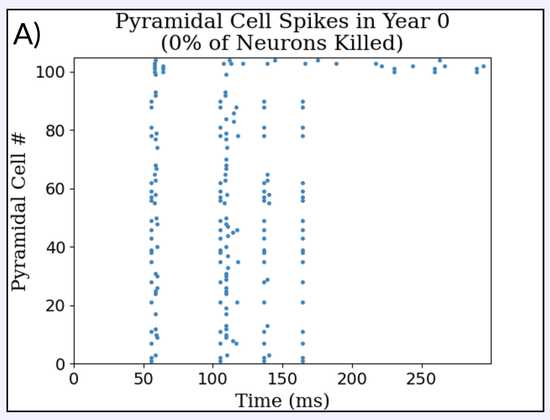

Fig 4. Raster plots of A) year 0 and B) year 22 of pyramidal cell spikes in the neuron death simulation

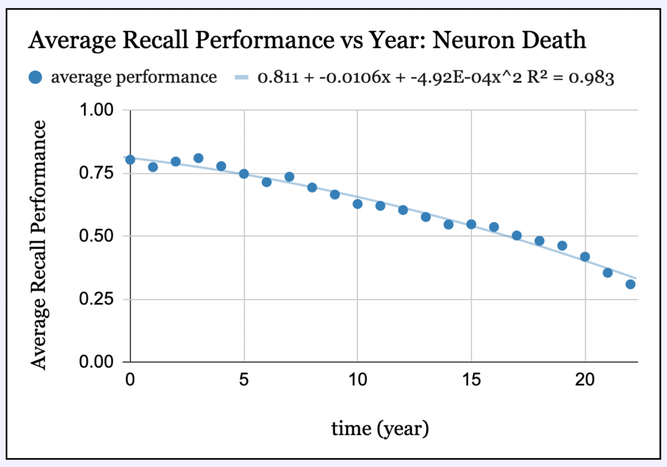

Fig 5. Graph of the average recall data and line of best fit during the 22-year-long neuron death simulation

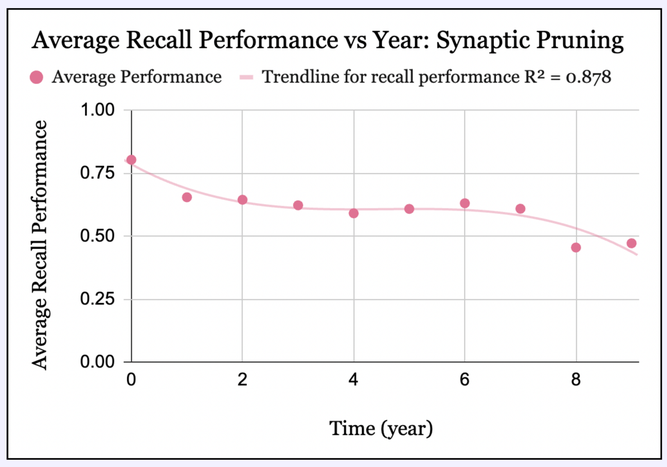

Fig 6. Graph of the average recall data and cubic of best fit during the 9-year-long synaptic pruning simulation

Analysis:

- **Neuron Death**
  - Over 22 years, recall follows a steady downward linear trend
  - Less spikes by the end of simulation due to having less pyramidal cells overall
- **Synaptic Pruning**
  - Over 9 years, recall follows a cubic trend, where recall declines then stays steady until year 8, when more synapses are suddenly pruned
  - More spikes in year 9 than year 0 due to the loss of synapses between inhibitory interneurons and pyramidal cells, causing pyramidal cells to fire more

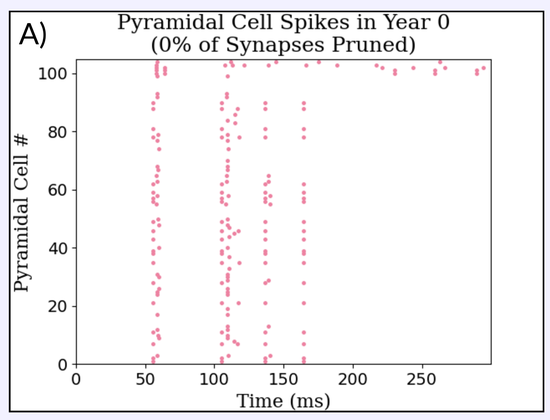

Fig 7. Raster plots of A) year 0 and B) year 9 of pyramidal cell spikes in the synaptic pruning simulation

Discussion

Significance:

- Our model provides a visualization of the complex processes affecting memory in AD
- Synaptic pruning causes more dramatic declines earlier
- Neuron death takes longer to fully impact recall performance
- Synaptic pruning graph correlates with cognitive decline patterns found in previous research[4]
- Implications for explaining differences in disease progressions among different patients[3]

Further Research:

- Investigate the importance of different types of neurons in memory recall
  - Different types of neurons
  - Different types of synaptic connections
- Further expansion to larger models, then biological models

Limitations:

- **Process Asssumptions:**
  - Synaptic pruning and neuronal death occur independently of each other
  - The processes continue with a consistent trend
  - The ratio of synapses pruned and neurons removed
- **Model Limitations**
  - Simplified learning rules: postsynaptic neuron just needed a depolarized dendritic membrane potential to increase strength
  - Cholinergic cells not present
  - Only the GABAergic effects of septum considered
- **Research Limitations:**
  - Unable to find more data on synaptic pruning through severe Alzheimer's, so unclear if trend will continue
  - Assumed linear decline of synapses within a stage

References

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