ALZHEIMER'S RISK FACTOR APOE4'S EFFECT ON SODIUM CONDUCTANCE AND NEURON FIRING

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1 INTRODUCTION

Apolipoprotein E (APOE) is a regulatory molecule of cholesterol and lipids in the peripheral and central nervous systems; it exists as 3 isoforms, APOE2, APOE3 and APOE4 (Phillips, 2014). APOE3 is the most common isoform, with APOE4 being the second – existing in **10-15% of the population**. This isoform has been linked to a **2-3x increased risk** of developing Alzheimer's Disease (AD) in heterozygous carriers, and a **12x increased risk** in homozygous carriers, with the age of disease onset reducing in a gene dose-dependent manner up to 9 years per allele copy. (Michaelson, 2014).

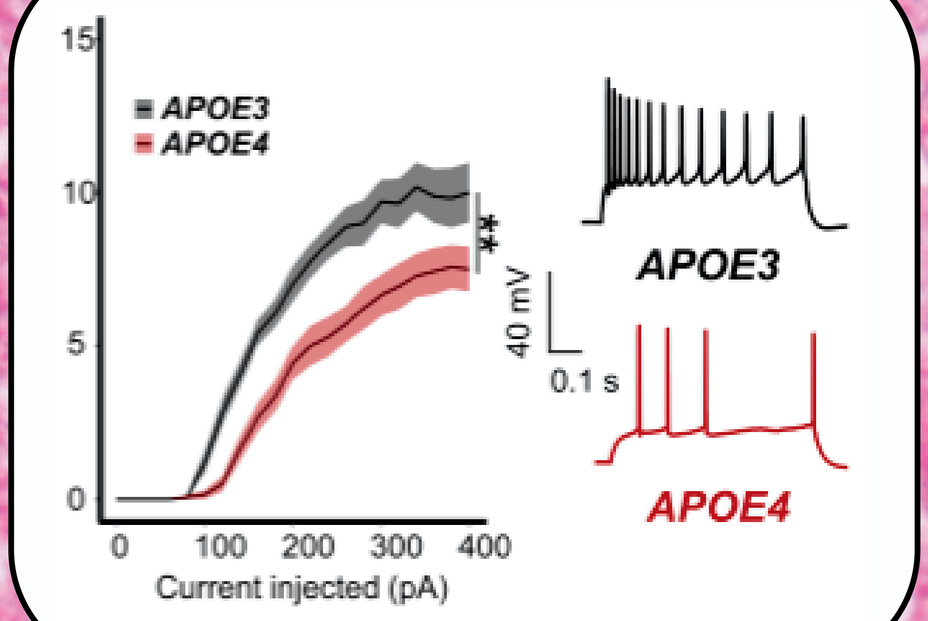


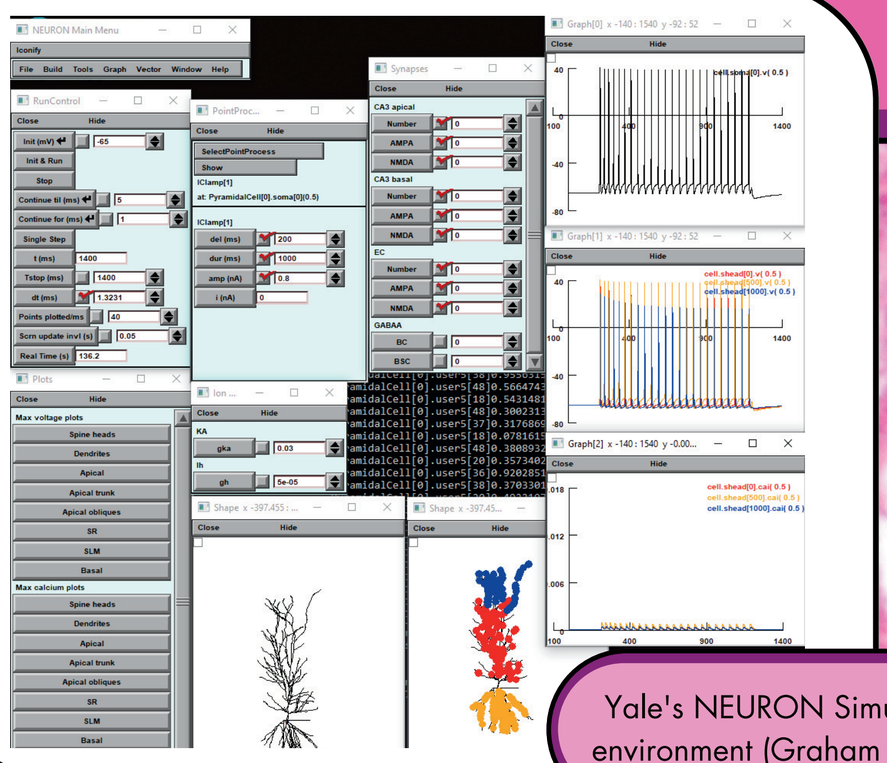
Figure 1: *Spike frequency seen in APOE3 wildtype mice against APOE4 mice (O.G. Steele - unpublished thesis)*

2 AIMS

The interactions by which APOE4 influences the development of AD are still unknown, with sparse literature covering the effect of the gene on principal neurons and their intrinsic excitability. It has been shown that **AD patients exhibit impaired membrane excitability** (Fang et al., 2021), with findings by Penn lab suggesting that APOE4 may cause this decreased action potential (AP) firing rate in CA1 pyramidal neurons. This implies an **association between the allele and reduced voltage-gated sodium conductance**. Some candidate mechanisms for this process have been proposed, such as altered cholesterol and lipid transport, which some studies have shown can reduce NMDAR-mediated currents (Korinek et al., 2020). To further investigate this link without the influence of external factors, computational neuron modelling was used to characterise the effect of decreased sodium conductance on the AP firing rate on both CA3 and CA1 model neurons.

3 METHODS

- Utilised Yale's NEURON simulation environment
- Using the python API and model files, altered the parameters of two model neurons (Migliore et al (1995) and Graham et al (2014)) to match in-vitro protocol conditions
- Ran simulated volt-step experiments using a current clamp process
- Tested different values of Na conductance at each voltage step
- Exported data via csv files for cubic interpolation
- Analysed through a statistics and graphing program supplied by Penn lab



Yale's NEURON Simulation environment (Graham Model)

4 RESULTS

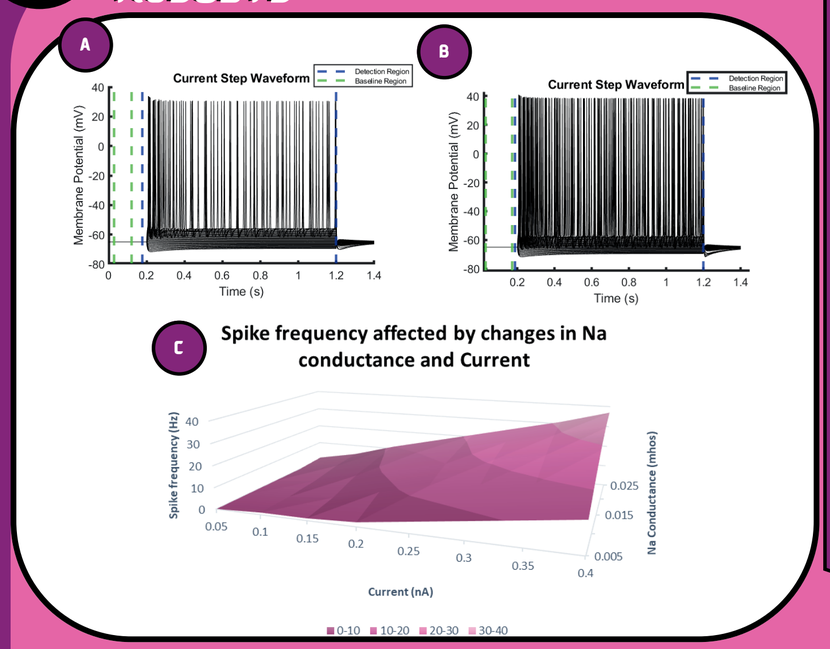


Figure 2:
A) low Spike frequency in low Na conduction voltage steps

B) high spike frequency in high Na conduction voltage steps

C) Area graph demonstrating direct variation of firing rate and Na conductance

These experiments supported the previous findings, indicating a decrease in Na conductance results in decreased firing rate relative to each voltage step in CA3 and CA1 model neurons. This mirrors the APOE4 mice exhibiting decreased firing rate relative to the wildtype APOE3 mice.

5 CONCLUSIONS AND WIDER SIGNIFICANCE

- The data shows that simulating APOE genotype-associated changes in Na conductance was **sufficient to explain the observed changes in AP firing rate**
- This forms a stronger link between APOE4 and attenuation of sodium conductance

It has been noted that both the use of ketamine and memantine (a widely used drug to slow Alzheimer's symptom progression) reverse this change, **further conjecturally linking the suppressed AP firing rate to the progression of AD**. More experiments must be conducted to shed light on the mechanism by which APOE4 affects the firing rate of CA1 and CA3 neurons, and by extension, contributes to the progression of AD symptoms.

6 REFERENCES AND ACKNOWLEDGEMENTS

- Fang, X., Jiang, S., Wang, J., Bai, Y., Kim, C. S., Blake, D., Weintraub, N. L., Lei, Y., & Lu, X. Y. (2021). Chronic unpredictable stress induces depression-related behaviors by suppressing AgRP neuron activity. Molecular Psychiatry, 26(6), 2299–2315. https://doi.org/10.1038/s41380-020-01004-x
- Korinek, M., Gonzalez-Gonzalez, I. M., Smejkalova, T., Hajdukovic, D., Skrenkova, K., Krusek, J., Horak, M., & Vyklicky, L. (2020). Cholesterol modulates presynaptic and postsynaptic properties of excitatory synaptic transmission. Scientific Reports, 10(1). https://doi.org/10.1038/s41598-020-69454-5
- Michaelson, D. M. (2014). APOE ε4: The most prevalent yet understudied risk factor for Alzheimer's disease. In Alzheimer's and Dementia (Vol. 10, Issue 6, pp. 861–868). Elsevier Inc. https://doi.org/10.1016/j.jalz.2014.06.015
- Phillips, M. C. (2014). Apolipoprotein e isoforms and lipoprotein metabolism. In IUBMB Life (Vol. 66, Issue 9, pp. 616–623). Blackwell Publishing Ltd. https://doi.org/10.1002/iub.1314

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