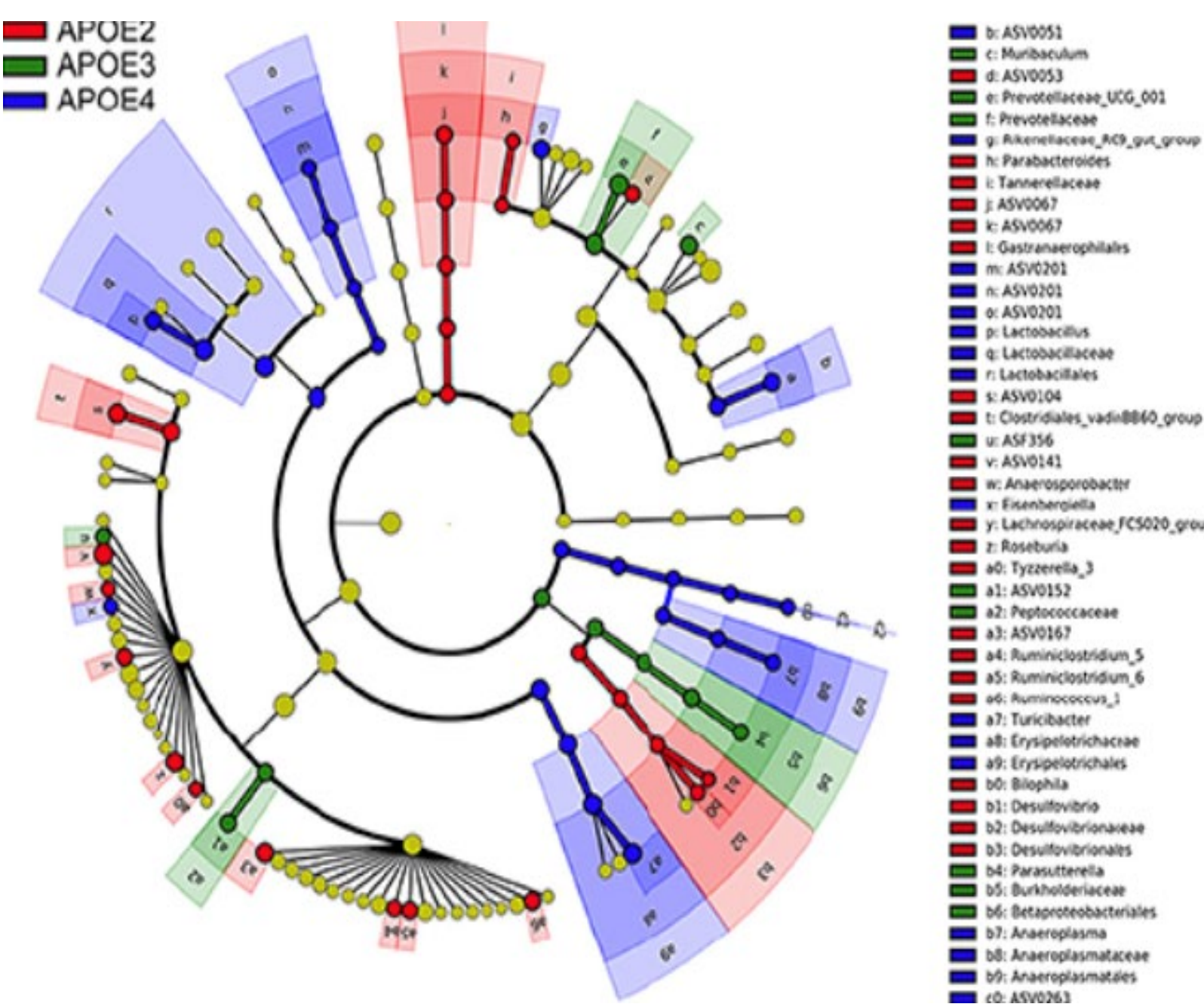


# Fecal Microbiota Transfer (FMT) From ApoE4 Targeted Replacement Mice Fails to Rescue Post-TBI Cognitive Impairment

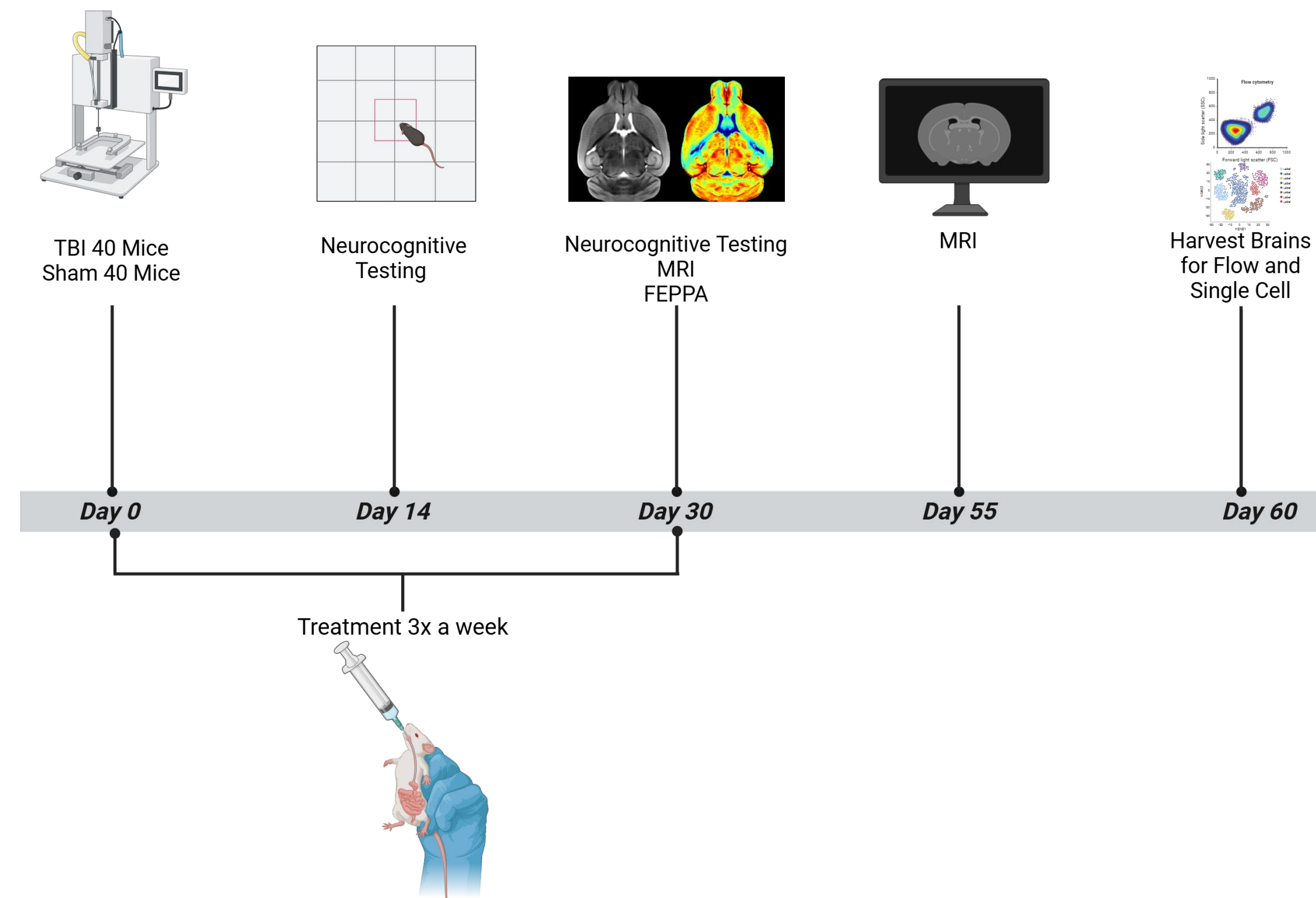
## Introduction

Apolipoprotein E (ApoE) is a lipid-transport protein and the major human ApoE isoforms are encoded by distinct alleles (2, 3, and 4). Compared with ApoE 2 and 3, ApoE4 increases the risk of neurodegenerative disease. In fact, ApoE4 is the strongest genetic risk factor for sporadic Alzheimer's disease (AD), and ApoE4 allelic variants are also known to have worse outcomes after TBI. On the other hand, the ApoE2 allele has been identified as neuroprotective (Huynh et al., 2017)<sup>1</sup>. Additionally, ApoE variants have genotype-dependent differences in their gut microbiome (Fig1;Parikh et al., 2020)<sup>2</sup>. Given the known influence of the gut microbiome on neurologic function, whether these baseline differences in gut microbial structure between ApoE allelic variants contributes to the differential outcomes after TBI has yet to be studied.

### ApoE Allelic Differences in Gut Microbial Community Structure



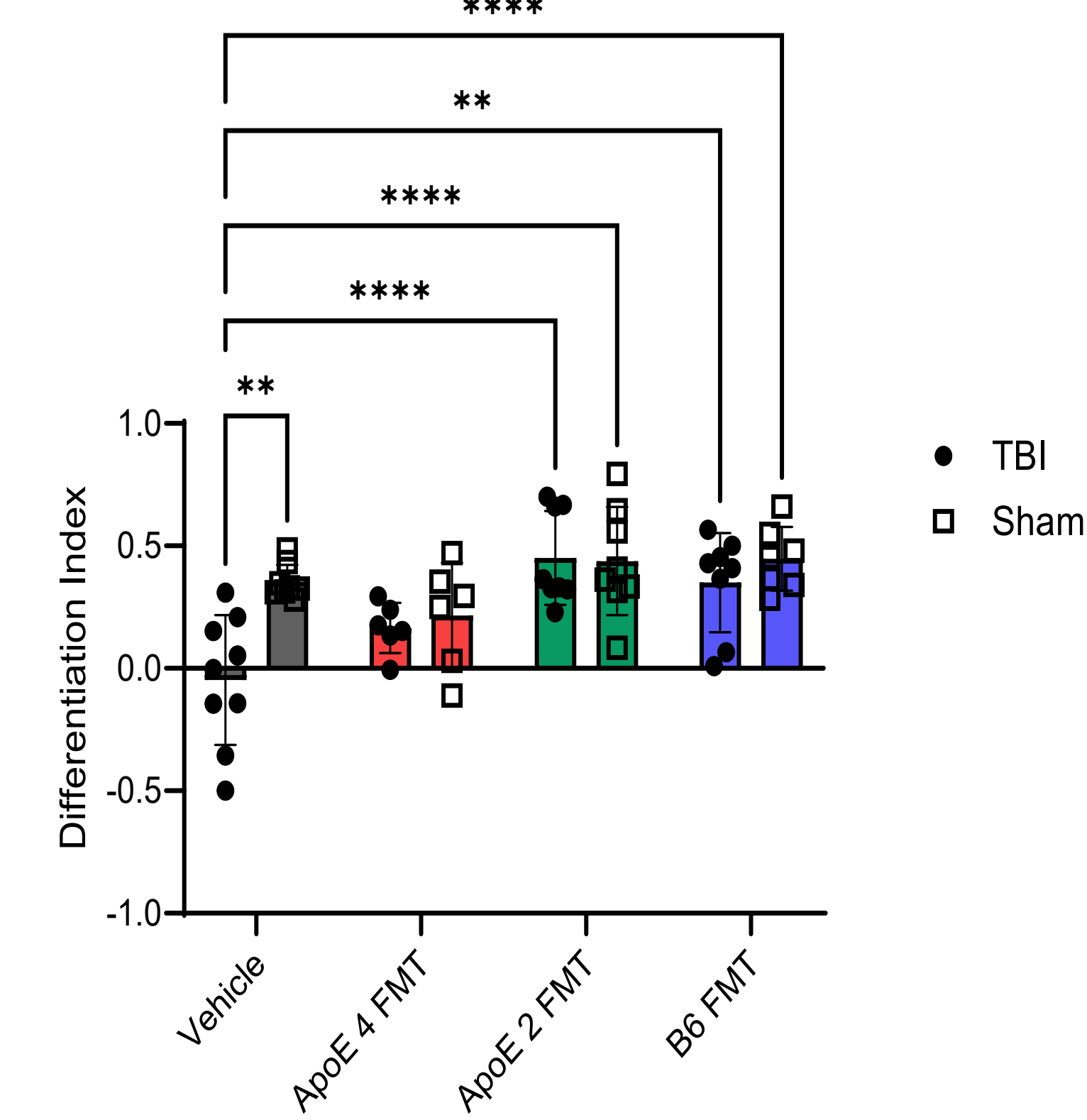
## Experimental Design



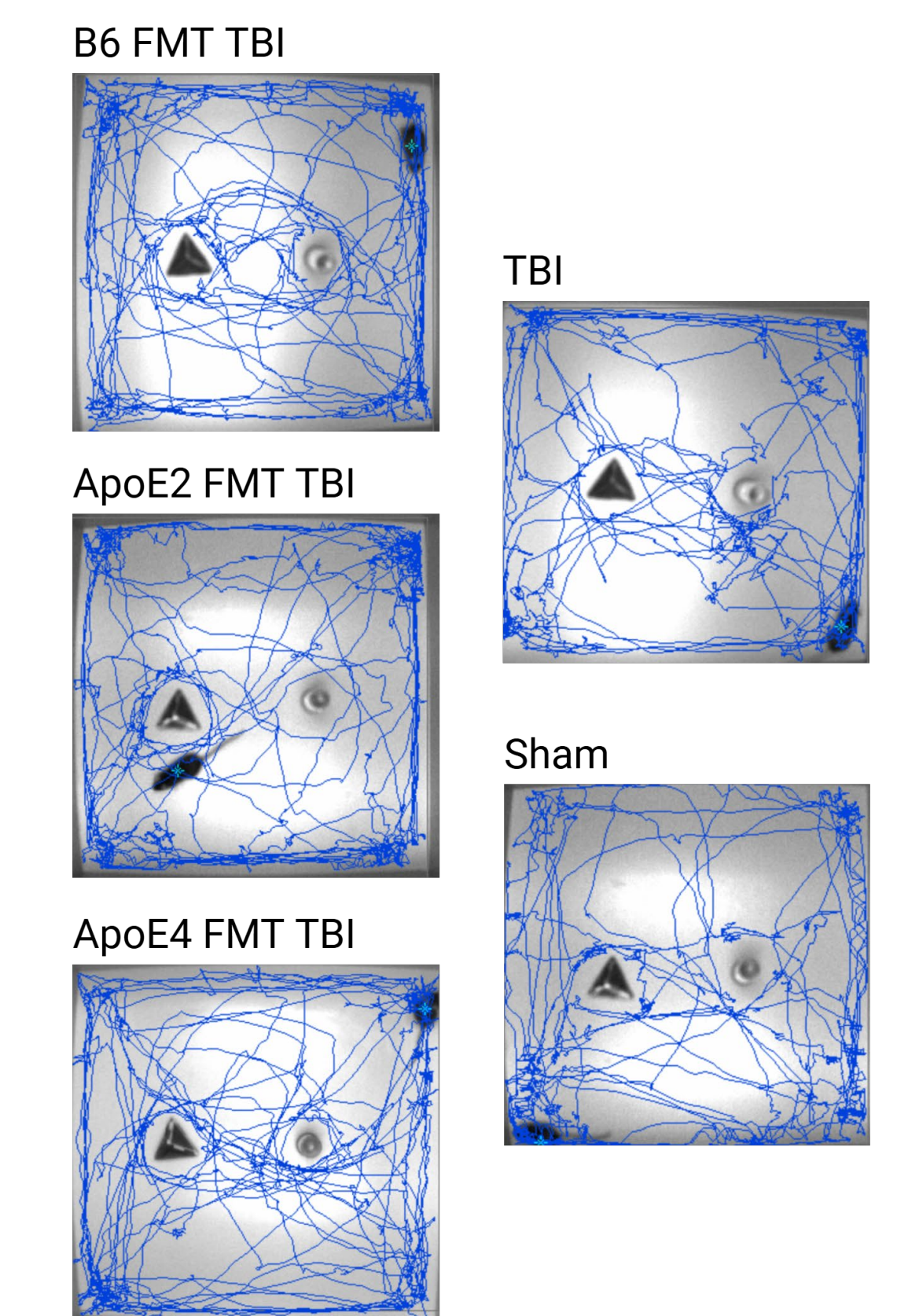
Mice were given a traumatic brain injury or a sham injury. They were then treated with FMT 3 times per week for 30 days. Neurocognitive testing was completed and brains were harvested on day 60 for further analysis.

## Neurocognitive Behavior

### Novel Object Recognition



### Novel Object Recognition Tracings



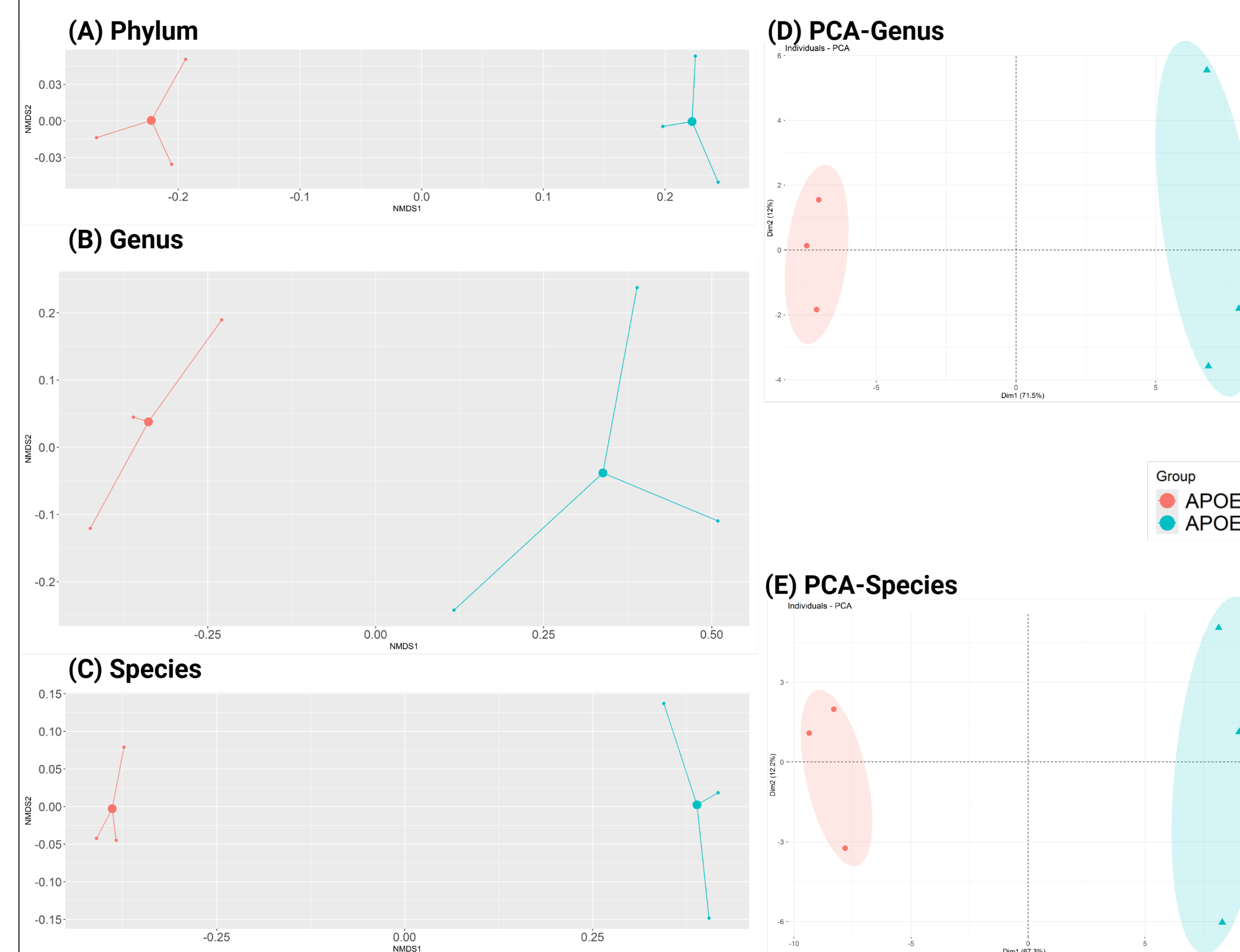
Mice receiving APOE2 FMT after TBI showed significant preservation of memory as compared to mice receiving APOE4 FMT. In fact, mice receiving APOE4 FMT showed no difference to vehicle alone in memory-based deficits.

Mice receiving APOE2 FMT after TBI had improved memory-based neurocognition as compared to mice receiving APOE4 FMT post injury.

## Hypothesis

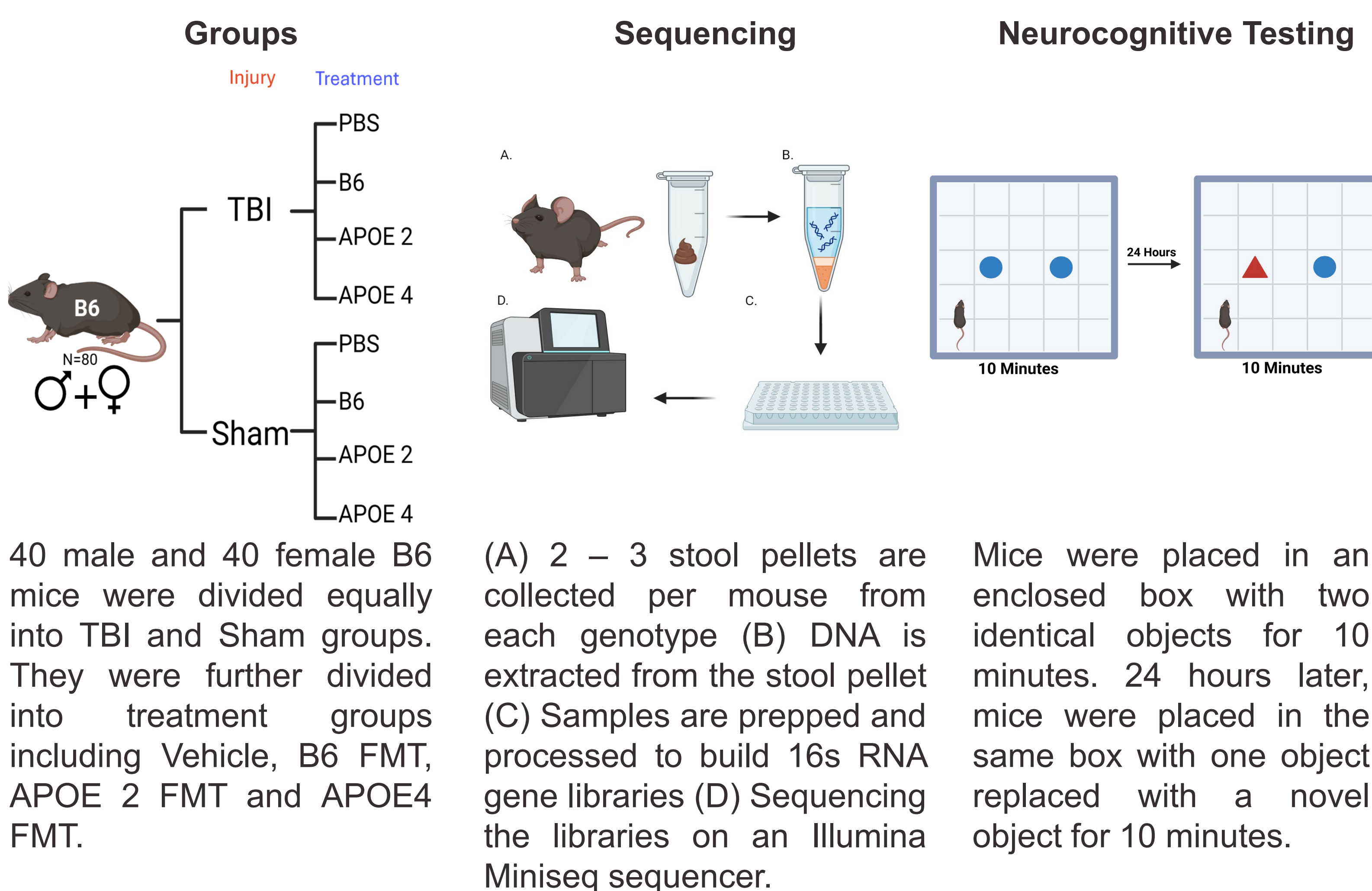
**We hypothesized that fecal microbiota transplantation (FMT) from ApoE2 donor mice would attenuate neurocognitive decline following traumatic brain injury (TBI), whereas FMT from ApoE4 donors would exacerbate neurocognitive impairment.**

## ApoE2 and ApoE4 Microbiomes Differ



(A) The distance between APOE2 and APOE4 groups on cNMDS plots demonstrate significant differences at the phyla level. (B) Similar to phyla, this shows the difference in composition of genus between groups. (C) This exhibits the disparity between species compositions among the two groups. (D) The placement of each individual sample on PCA plots shows intra-group similarities as well as differences between APOE2 and APOE4 at the genus level. (E) This exhibits the similarities and differences at the species level.

## Methods



## Conclusions

- ApoE4 genotype-dependent differences in the gut microbial community structure fail to provide neuroprotection after FMT in TBI mice.
- These data suggest an additional mechanisms underlying the neurocognitive outcome differences between the ApoE allelic variants.
- Ongoing studies will investigate taxa-specific correlates to transcriptional changes within the brain between the ApoE allelic variants to identify novel therapeutic avenues such as probiotics, dietary intervention, and targeted antibiotics.

## References

- Huynh TV, Davis AA, Ulrich JD, Holtzman DM. Apolipoprotein E and Alzheimer's disease: the influence of apolipoprotein E on amyloid-beta and other amyloidogenic proteins. *J Lipid Res.*
- Parikh JJ, Estes JL, Zajac DJ, Malik M, Maldonado Weng J, Tai LM, Chipata GE, LaDu MJ, Green SJ, Estes S. Murine Gut Microbiome Association With APOE Alleles. *Front Immunol.* 2020;11:200. Epub 2020/03/03. doi: 10.3389/fimmu.2020.00200. PubMed PMID: 32117315; PMCID: PMC7034241.

## Acknowledgements

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