

Sickle Cell Trait Contributes to APOE ε4/TREM2 Driven Microvascular Injury, Neuroinflammation, And Cognitive Decline

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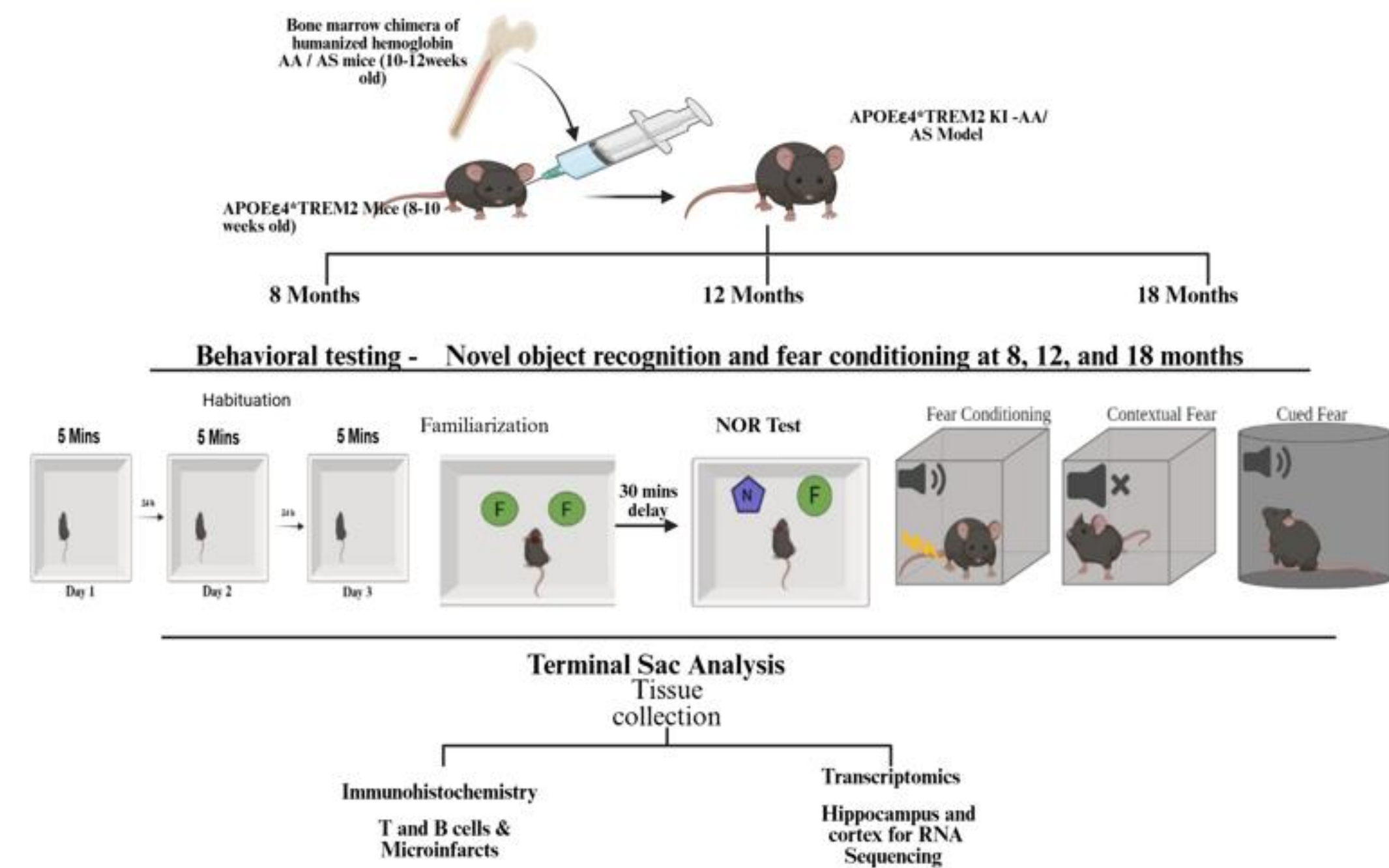
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Background

Alzheimer's disease (AD) has been shown to disproportionately affect individuals of African ancestry. Microvascular injury and dysregulated neuroimmune markers are major contributors to cognitive decline. Genetic risk factors such as apolipoprotein E ε4 (APOE ε4) and triggering receptor on myeloid cells 2 (TREM2 (R47H)) variant, which influence cortical microinfarct burden, and neuroinflammation, further increase susceptibility to AD with aging. We recently showed that African Americans with sickle cell trait (AS) and the APOE ε4 allele were more likely to have cognitive impairment and a faster rate of cognitive decline; however, the mechanism is unknown. Here, we hypothesized that SCT would interact with late-onset AD genetic risk variants, including APOEε4*TREM2, to accelerate cognitive decline through mechanisms involving increased neuroinflammation and microinfarcts injury.

Methods and Experimental Timeline



Results

1. APOEε4*TREM2-AS mice had significantly more evidence of cognitive impairment with aging.

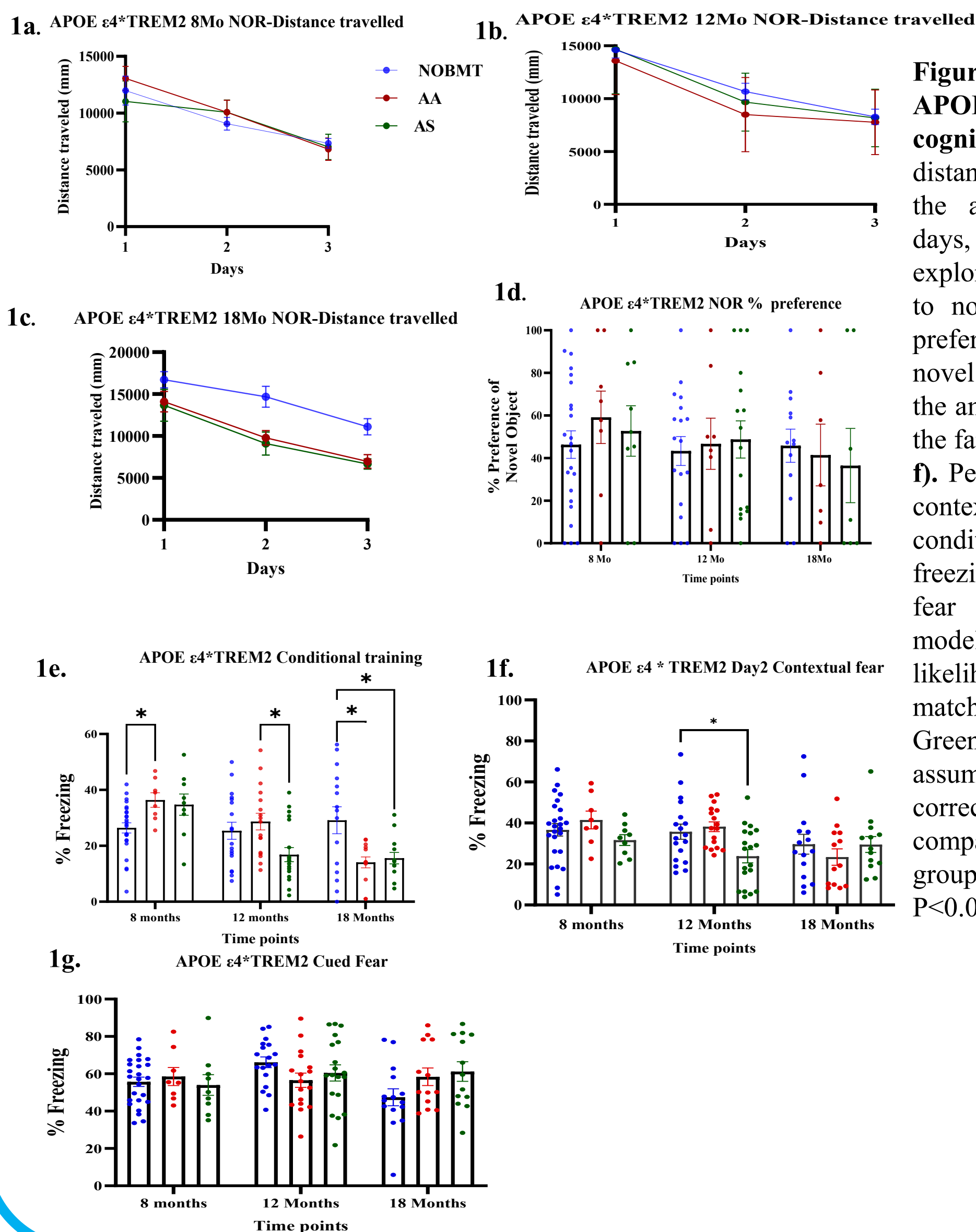


Figure 1. Interaction of SCT with APOEε4*TREM2 worsens cognitive function. (a-c) The distance travelled was calculated as the average over 3 habituation days, with 300 seconds of exploration/day. (d) % preference to novel object recognition. The preference and discrimination for novel objects were determined by the amount of time spent exploring the familiar versus novel object. (e-f). Percent of time freezing due to contextual fear following fear conditioning. (g). Percent of time freezing due to cued fear following fear conditioning. Mixed-effects model, restricted maximum likelihood (REML), factors matched by time point, Geisser-Greenhouse correction without assumed sphericity, Tukey correction for multiple comparisons. N=14-16 mice per group * P<0.05. ** P<0.01. *** P<0.001.

2. Presence of SCT increased the density of B- and T-cell infiltrates in the hippocampus of APOEε4*TREM2 mice with aging.

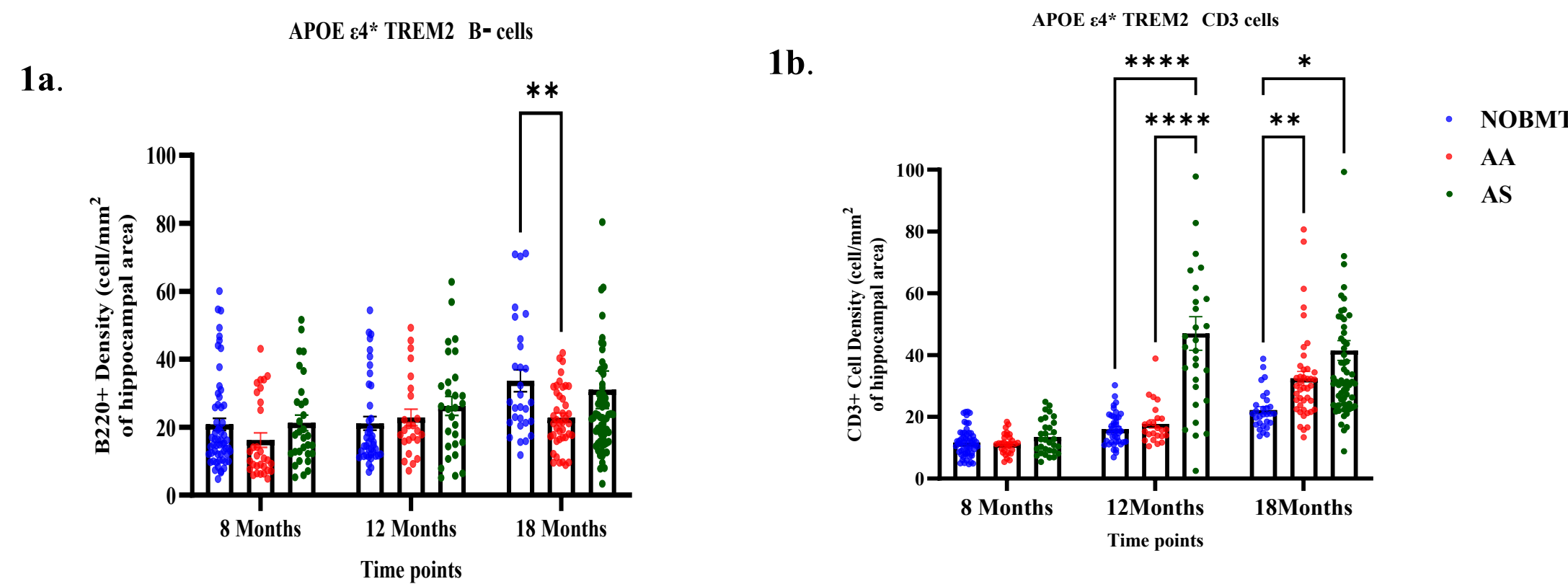


Figure 2. Presence of SCT amplifies the age-associated increase in hippocampal B- and T-cell density. a. B220⁺ (B-cells) density in the hippocampus of APOEε4*TREM2 mice at 8, 12, and 18 months. b. CD3⁺ T-cells infiltration in the hippocampus of APOEε4*TREM2 mice across 8, 12, and 18 months. At 18 months, the density of CD3⁺ T-cells increased significantly, with the highest levels observed in the AS (SCT) group compared to AA and NoBMT. N=3-4 mice/group. * P<0.05. ** P<0.01. *** P<0.001. **** P<0.0001.

3. Microinfarct burden is elevated in APOEε4*TREM2-AS mice with increasing age. A potential contributor to the cognitive deficit observed in these mice compared to controls.

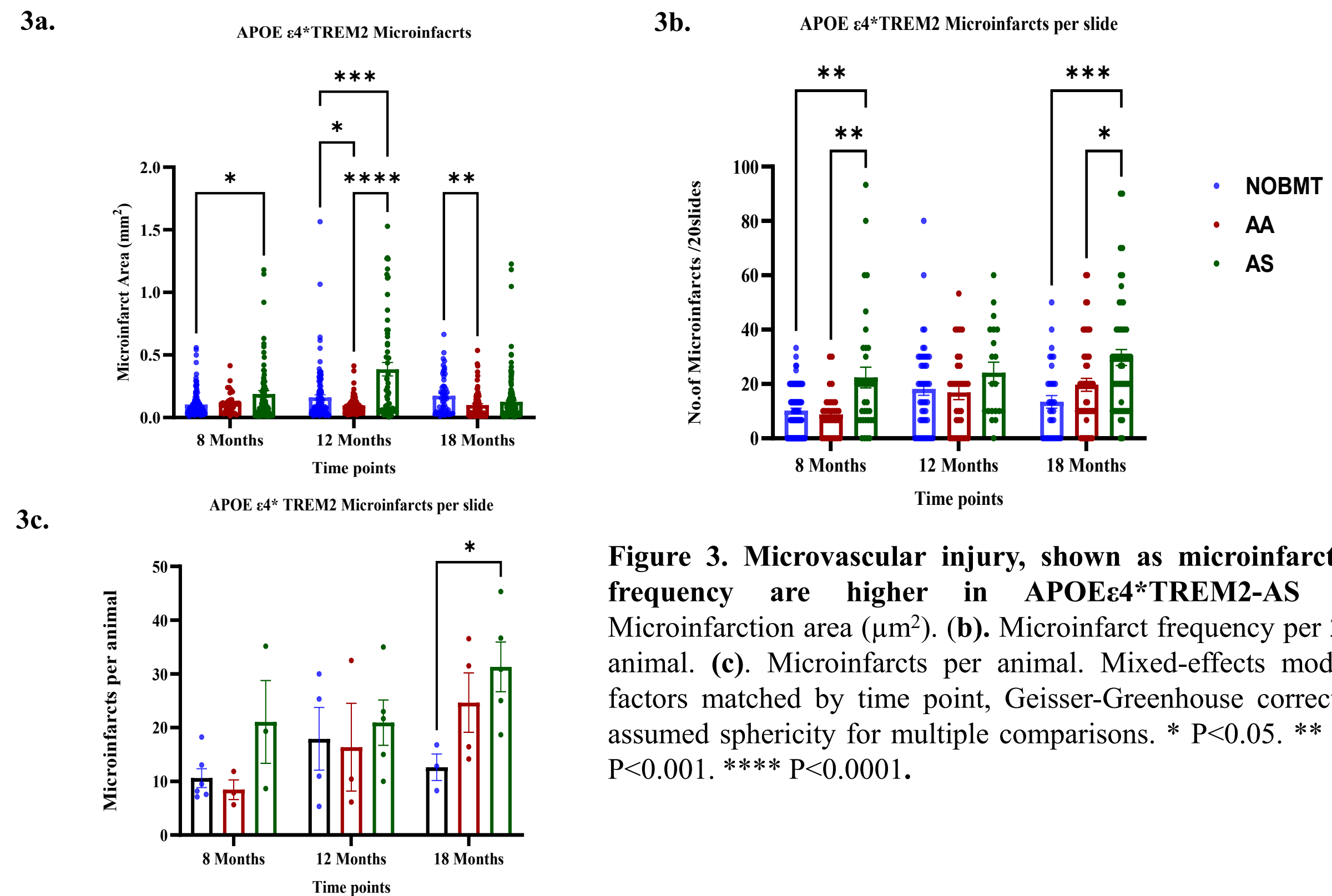


Figure 3. Microvascular injury, shown as microinfarcts area and frequency are higher in APOEε4*TREM2-AS mice. (a). Microinfarction area (μm²). (b). Microinfarct frequency per 20 slices per animal. (c). Microinfarcts per animal. Mixed-effects model (REML), factors matched by time point, Geisser-Greenhouse correction without assumed sphericity for multiple comparisons. * P<0.05. ** P<0.01. *** P<0.001. **** P<0.0001.

4. Transcriptomics -GO-BP Enrichment Summary

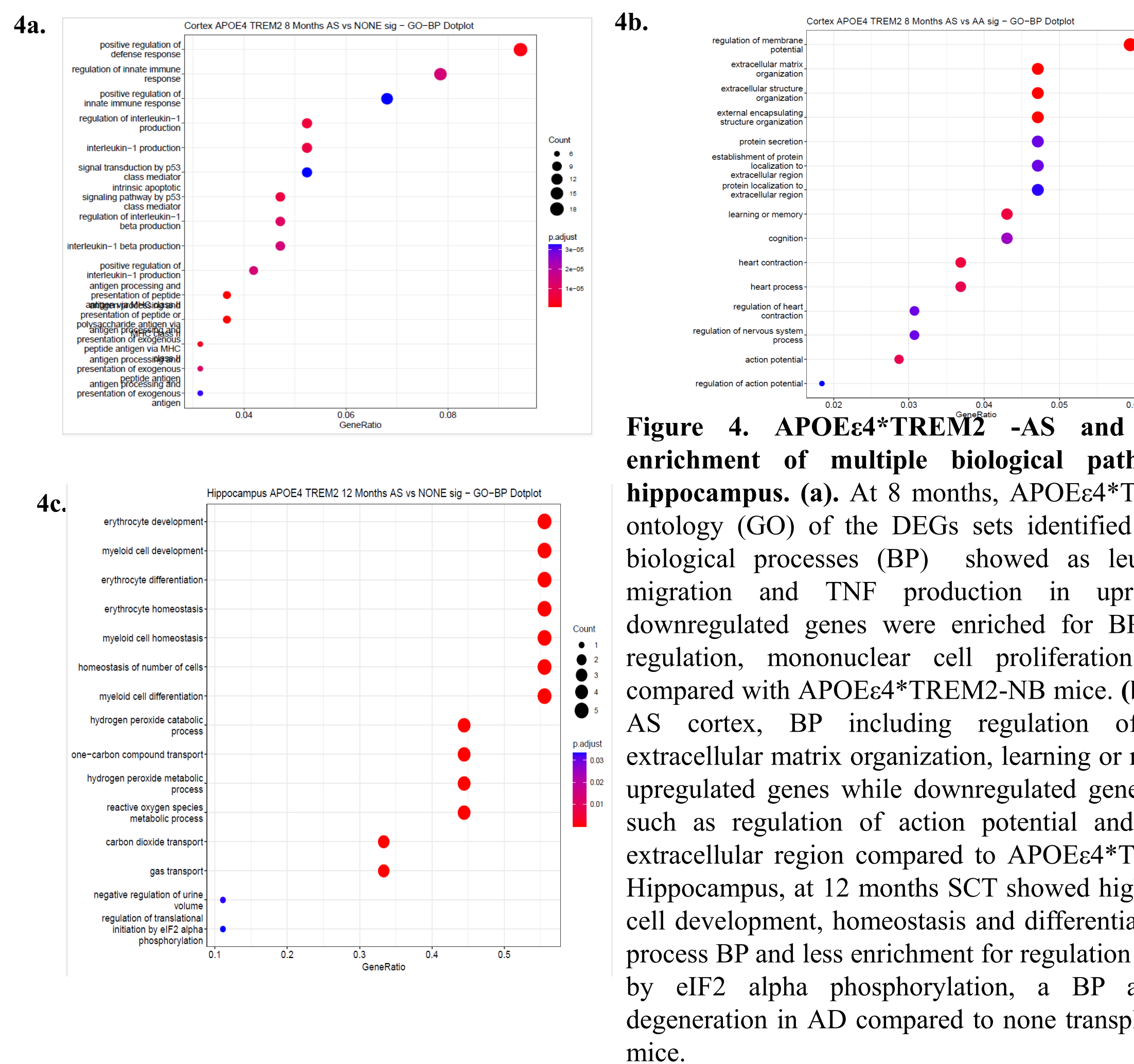


Figure 4. APOEε4*TREM2-AS and APOEε4*TREM2-AA enrichment of multiple biological pathways in cortex and hippocampus. (a). At 8 months, APOEε4*TREM2-AA cortex gene ontology (GO) of the DEGs sets identified enrichment of multiple biological processes (BPs) showed as leukocyte proliferation & migration and TNF production in upregulated genes, while downregulated genes were enriched for BP such as inflammatory regulation, mononuclear cell proliferation and IL-6 production compared with APOEε4*TREM2-NB mice. (b). In APOEε4*TREM2-AS cortex, BP including regulation of membrane potential, extracellular matrix organization, learning or memory and cognition in upregulated genes while downregulated genes were enriched for BP such as regulation of action potential and protein localization to extracellular region compared to APOEε4*TREM2-AA mice. (c). In Hippocampus, at 12 months SCT showed high enrichment of myeloid cell development, homeostasis and differentiation and ROS metabolic process BP and less enrichment for regulation of translational initiation by eIF2 alpha phosphorylation, a BP associated with neuron degeneration in AD compared to none transplanted APOEε4*TREM2 mice.

Summary

- ✓ The interaction of APOEε4*TREM2 and SCT leads to earlier onset or more severe progressive impairments in hippocampal- and amygdala-dependent learning and memory with increasing age.
- ✓ APOEε4*TREM2-AS mice showed age-dependent elevation in hippocampal B- and T-cell infiltration in the hippocampus compared to healthy control (APOEε4*TREM2-AA) mice, which became more pronounced at 18 months, suggesting that SCT interacts with APOEε4*TREM2 by amplifying neuroinflammation and immune dysregulation during aging.
- ✓ Microinfarct burden increased with age in APOEε4*TREM2-AS mice compared to healthy APOEε4*TREM2-AA controls, indicating accelerated microvascular injury in the APOEε4*TREM2 background.
- ✓ APOEε4*TREM2-SCT interaction produced distinct gene-regulation patterns in the cortex and hippocampus. In the cortex, synaptic and neuronal-regulatory pathways were enriched at 8 months, while myeloid-cell and oxidative-stress pathways were enriched at 12 months. In contrast, the hippocampus showed enrichment of inflammatory and metabolic pathways.
- ✓ Together, these findings indicate that SCT in an APOEε4*TREM2 background exacerbates age-related microinfarct injury, increases adaptive immune-cell infiltration and contributes to worsening neuroinflammation and cognitive vulnerability. Future studies will delineate individual contributions of APOEε4 and TREM2 to these SCT-driven effects.

References

- Alzheimer's Association. 2022 Alzheimer's disease facts and figures. *Alzheimers Dement.* 2022;18:18-79
- Inequalities in dementia incidence between six racial and ethnic groups over 14 years. Mayeda ER, Glymour MM, Quesenberry CP and Whitmer RA. *Alzheimers Dement.* 2016;12:216-24.
- Rates of dementia in three ethnorracial groups Gurland BJ, Wilder DE, Lantigua R, Stern Y, Chen J, Killeffer EHP and Mayeux R.. *International Journal of Geriatric Psychiatry.* 1999;14:481-493.
- Association of sickle cell trait with measures of cognitive function and dementia in African Americans. Chen N, Caruso C, Alonso A, Derebail VK, Kshirsagar AV, Sharrett AR, Key NS, Gottesman RF, Grove ML, Bressler J, Boerwinkle E, Windham BG, Mosley TH, Jr. and Hyacinth HI. *eNeurologicalSci.* 2019;16:100201

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