

Characterization of the Brain Vasculature in hA β KI and hA β KI.hAPOE4

Mouse Models of Alzheimer's Disease

Mya Nguyen¹, Timothy Simon¹, Amandine Jullienne¹, Annie Le¹, Ishan Kurup¹, Greer Cisneros¹, UCI MODEL-AD², Andre Obenaus^{1,2}

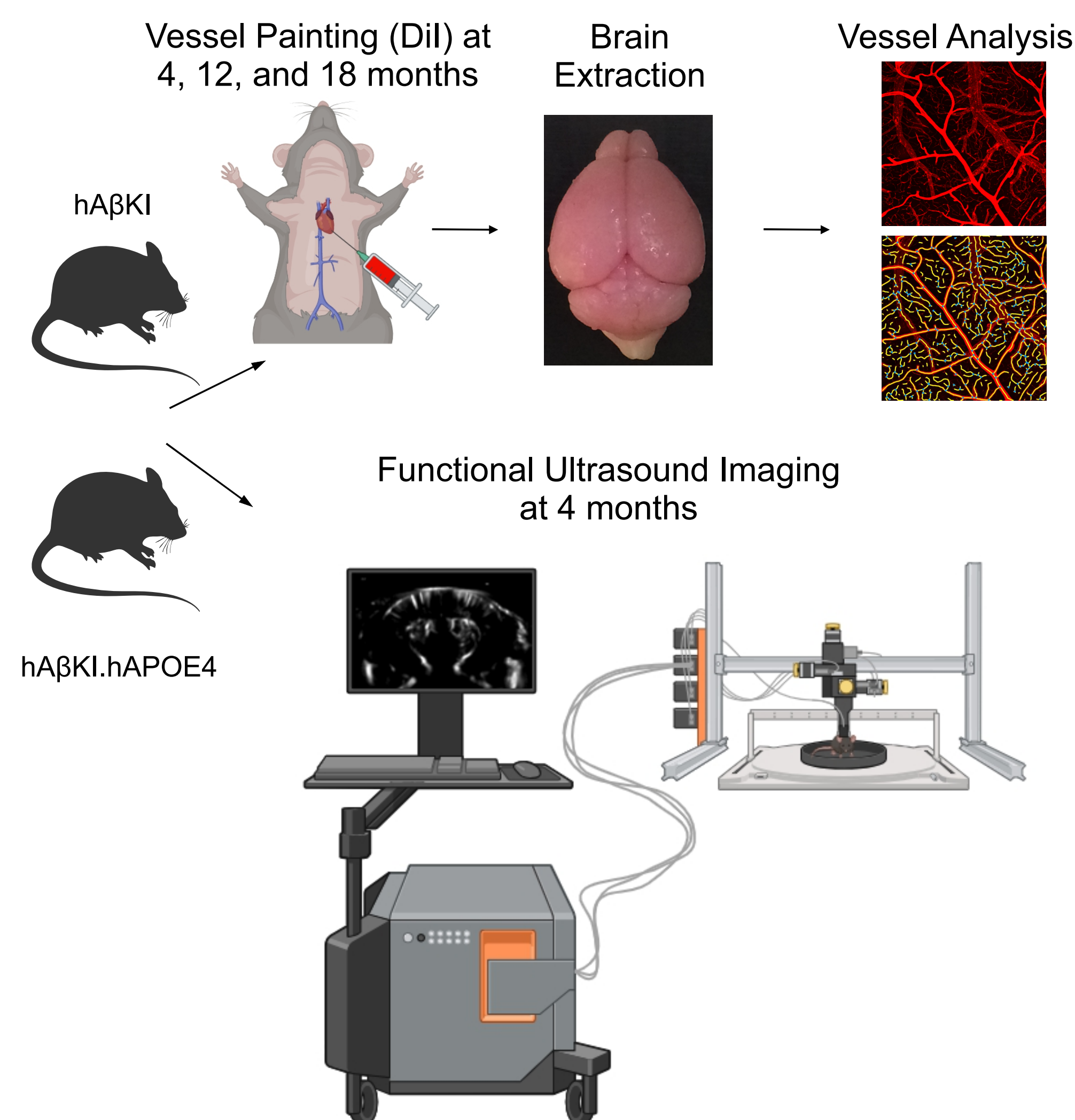
1 – University of California Riverside, School of Medicine, Riverside, CA, USA;

2 – University of California Irvine, School of Biological Sciences, Irvine, CA, USA.

Introduction

The MODEL-AD consortium develops clinically relevant Alzheimer's Disease (AD) models to align with human AD. Two such models are the human amyloid- β (A β) knock-in (hA β KI) mouse and the hA β KI mouse carrying the human APOE4 allele (hA β KI.hAPOE4), a major genetic risk factor for AD. Cerebrovascular dysfunction in AD has been reported, however, the contribution of the hAPOE4 allele to vascular deficits has not been well characterized. Here, we compared the angioarchitecture of hA β KI and hA β KI.hAPOE4 mouse models to characterize the temporal evolution of their vasculature.

Methods



Vessel painting was performed on hA β KI and hA β KI.hAPOE4 mice to label the vasculature at 4, 12, and 18 months of age. Mice were transcardially perfused with Dil to stain cerebral vessels. Brains were then extracted and imaged by wide field epi-fluorescence. Axial cerebrovasculature was analyzed using Angiotool software.

A separate cohort of hA β KI and hA β KI.hAPOE4 mice underwent functional ultrasound imaging (fUSI) at 4 months of age to assess vascular morphology and neurovascular responses to whisker stimulation.

Contact

Andre Obenaus, Ph.D (PI): Andre.Obenaus@medsch.ucr.edu

Mya Nguyen: mnguy478@ucr.edu

Results-4 mo Vessel Painting

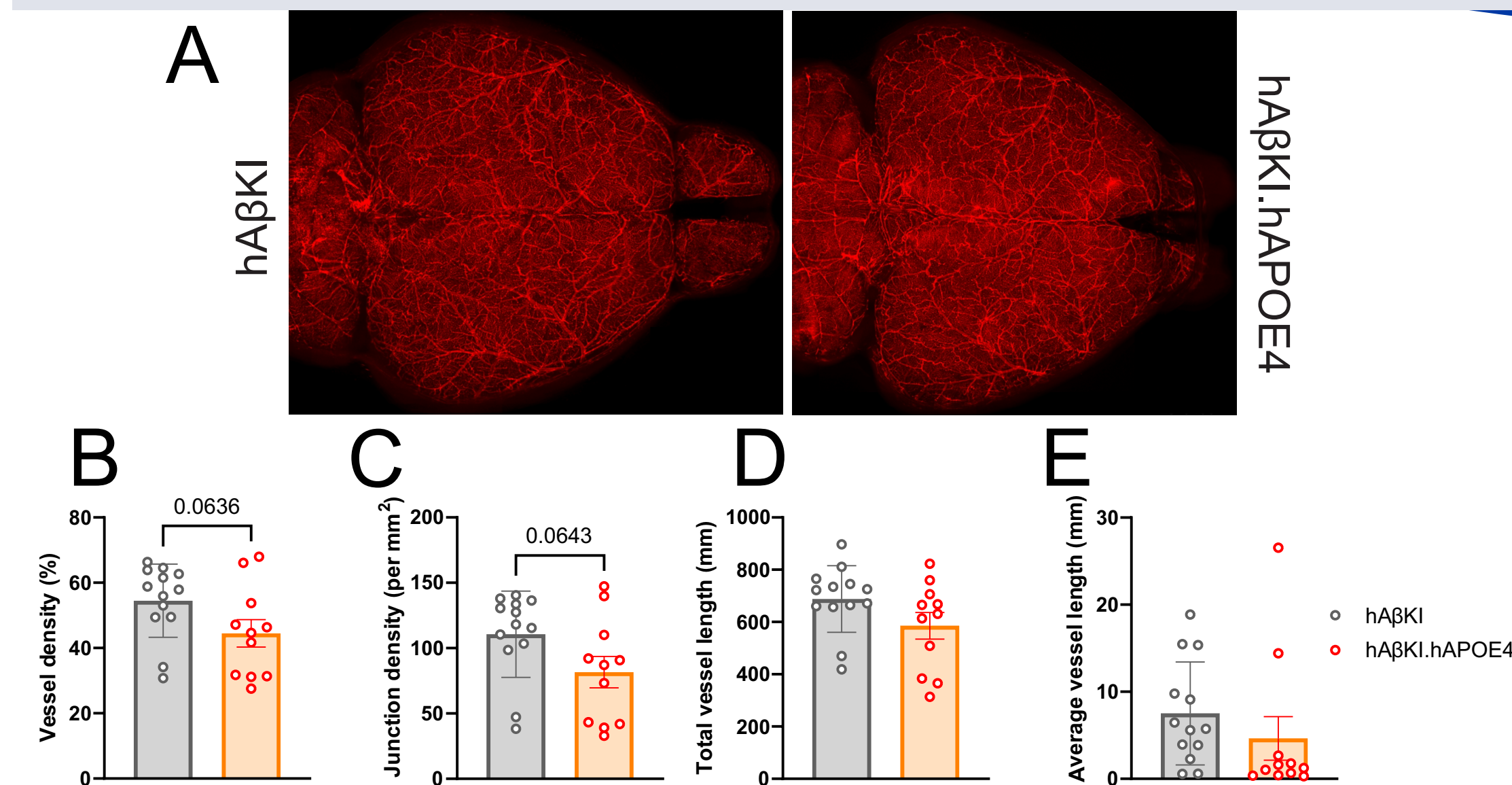


Fig 1. (A) Representative images of cortical vessels on the axial surface of hA β KI and hA β KI.hAPOE4 mice at 4 months of age. (B) hA β KI.hAPOE4 mice had a trending decrease in vessel density compared to hA β KI mice. (C) There was a trending decrease in junction density in hA β KI.hAPOE4 compared to hA β KI mice. (D, E) No significant differences were observed in the total or average vessel lengths.

Results-12 mo Vessel Painting

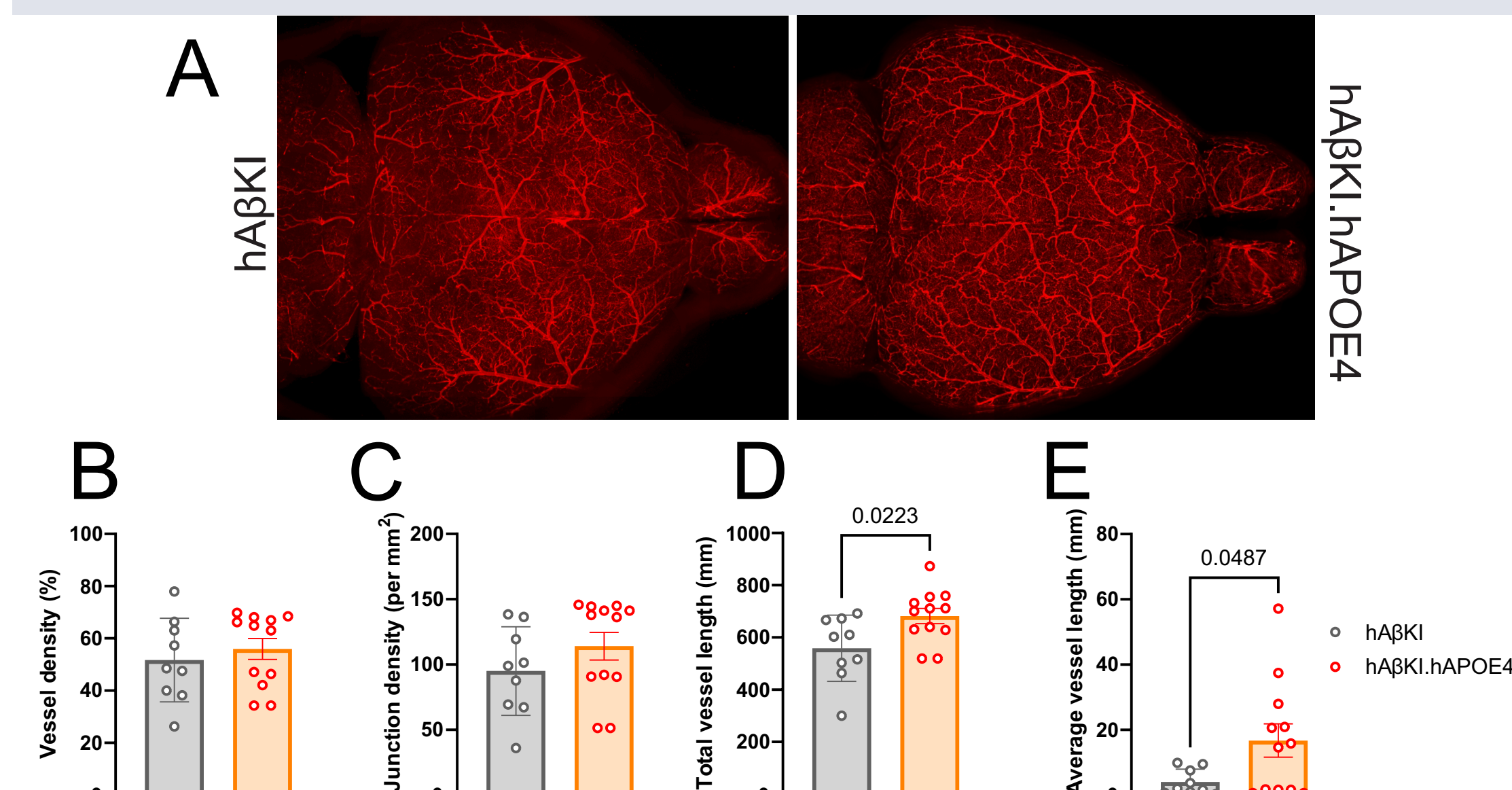


Fig 2. (A) Representative images of cortical vessels on the axial surface of hA β KI and hA β KI.hAPOE4 mice at 12 months of age. (B, C) There were no significant differences in vessel or junction density. (D) At 12 months, hA β KI.hAPOE4 mice had increased total vessel length compared to hA β KI mice. (E) Average vessel length was increased in hA β KI.hAPOE4 mice compared to hA β KI mice.

Results-18 mo Vessel Painting

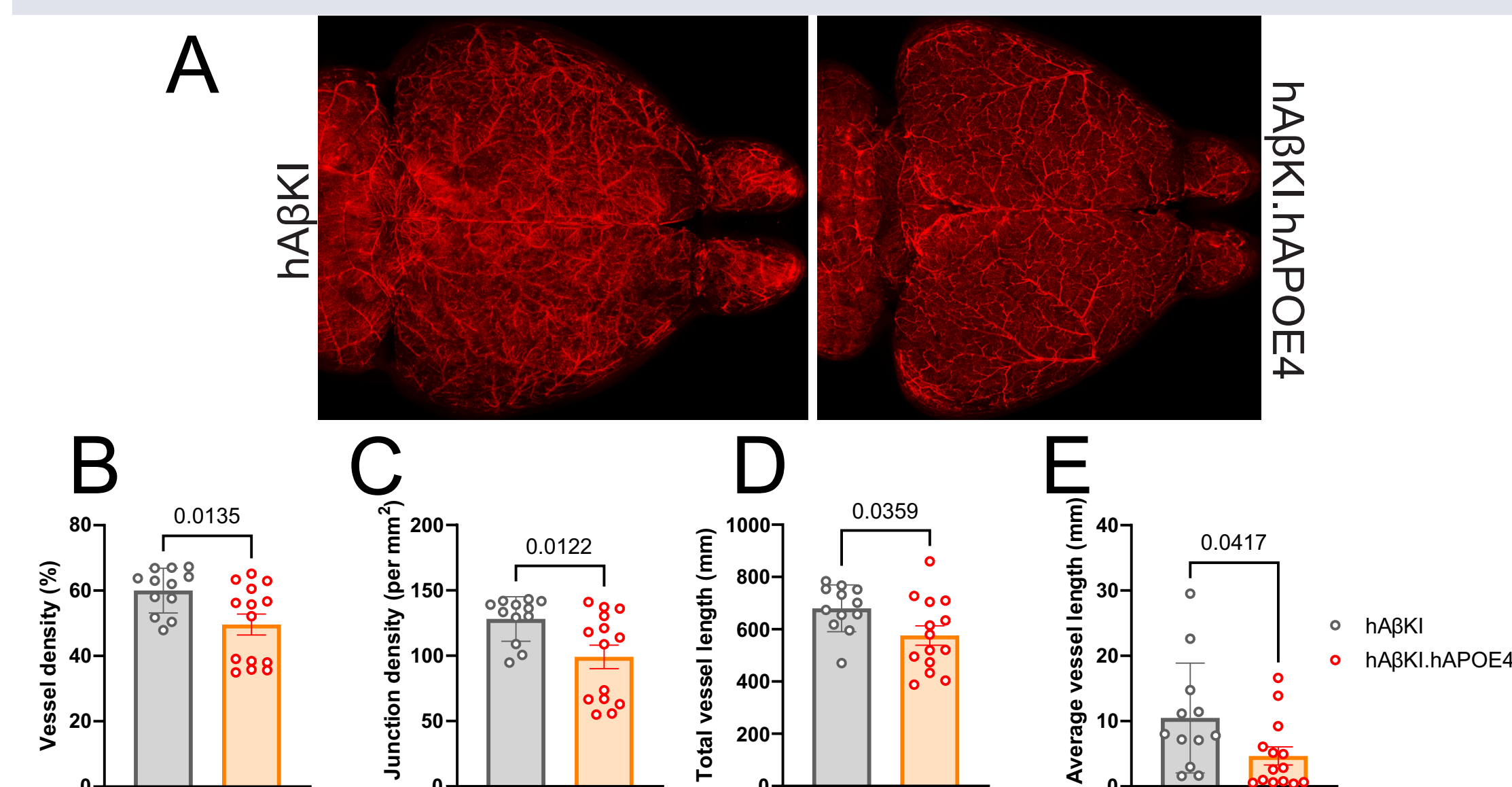


Fig 3. (A) Representative images of cortical vessels on the axial surface of hA β KI and hA β KI.hAPOE4 mice at 18 months of age. (B) At 18 months, there was a significant decrease in vessel density in hA β KI.hAPOE4 compared to hA β KI mice. (C) Junction density was also decreased in hA β KI.hAPOE4 mice compared to hA β KI mice. (D) Total vessel length was significantly decreased in hA β KI.hAPOE4 mice compared to hA β KI mice. (E) There was a significant decrease in average vessel length in hA β KI.hAPOE4 compared to hA β KI mice.

Results-4 mo Functional Ultrasound Imaging

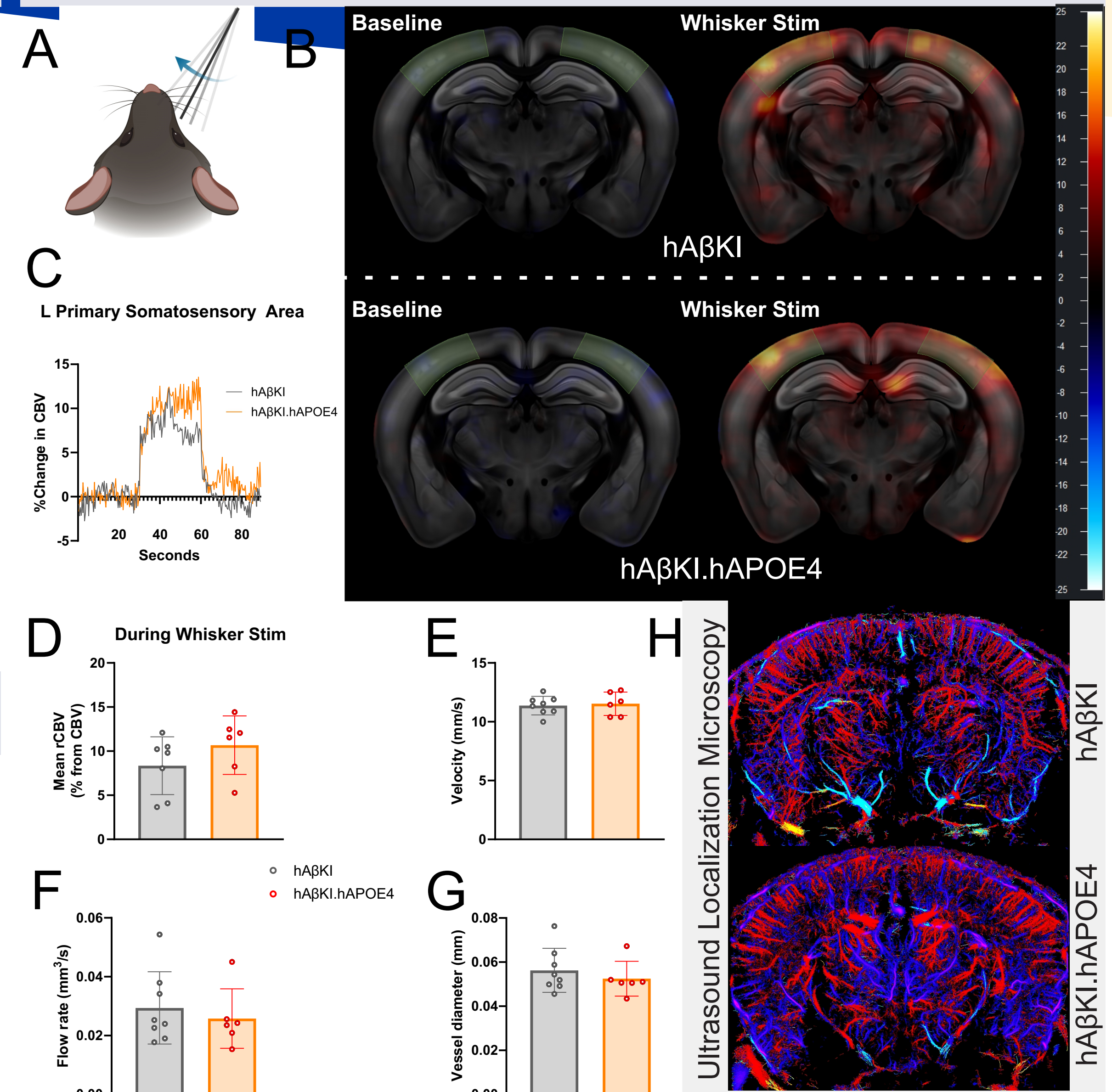


Fig 4. (A) Schematic of whisker stimulation on an anesthetized mouse at 4 months of age. (B) Representative images of relative cerebral blood volume (rCBV) maps during baseline and whisker stimulation in hA β KI and hA β KI.hAPOE4 mice. (C) Representative traces of averaged CBV relative to the baseline during 6 X 30-seconds whisker stimulation intervals and 30-seconds off intervals. (D) There were no significant differences in rCBV between hA β KI and hA β KI.hAPOE4 mice. (E, F, G) Velocity, flow rate, and vessel diameter derived from microbubble tracking using ultrasound localization microscopy (ULM) revealed no differences of the cerebral vasculature. (H) Representative ULM maps of hA β KI and hA β KI.hAPOE4 mice at 4 months of age.

Conclusions

- hA β KI.hAPOE4 compared to hA β KI mice exhibited blunted cerebrovascular development with increasing age (4 to 18mo).
- At 12 months of age, there was a recovery of total and average vessel length (potentially due to compensatory mechanisms).
- At 18 months, the hA β KI.hAPOE4 mice continued to report decreased cerebrovascular density relative to hA β KI mice.
- Addition of the hAPOE4 risk allele may blunt the development of the cerebrovasculature and may impact cerebral hemodynamics.
- Functional ultrasound imaging (fUSI) at 4 months of age showed no differences in blood flow and or in neurovascular coupling.
- Additional fUSI studies at 12 and 18 months of age are needed to clarify the role of hAPOE4 in vascular function.

Acknowledgements



Funding: NIH NINDS RO1NS135556 (Obenaus) and 1U54AG05434 (MODEL-AD)

National Institutes of Health