3D whole-brain imaging of parenchymal/vascular amyloid plaque architecture during disease progression in a transgenic mouse model of Alzheimer's disease

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Background & Aim

Alzheimer's disease (AD) is histologically defined by accumulation of Abeta (Aβ) plaques in the brain. Age and gender are important factors in AD pathology. To develop more effective interventions, preclinical studies should therefore consider these factors in the evaluation of drug candidates. Using quantitative 3D light sheet fluorescence microscopy (LSFM), we mapped age-dependent changes in plaque architecture in female and male transgenic AD mice.

Methods

Intact brains from 15, 30 and 42-week-old female and male APP/PS1 transgenic (ARTE10, n=5-6 per group) and 30-week-old male wildtype (C57BL/6, n=6) mice were co-stained for amyloid plaques (anti-human Aβ) and vasculature (anti-mouse CD31, podocalyxin), optically cleared and scanned on a LSFM. Deep-learning assisted image analysis was applied for whole-brain segmentation, mapping and quantification of plaques (counts, volume fraction) in more than 400 individual regions using a custom mouse brain atlas.

Conclusion

+ We mapped and quantified Aβ plaque accumulation throughout the intact brain of female and male ARTE10 mice at different ages
+ ARTE10 mice demonstrate substantial vascular-associated plaque deposition, a histological hallmark of cerebral amyloid angiopathy (CAA)
+ In both sexes, parenchymal plaques were detected at 15-weeks of age while vascular-associated plaques were most consistently observed at 30 and 42 weeks of age
+ Amyloidosis progressed at a faster rate and was overall more severe in female ARTE10 mice
+ Greater sex differences were observed for plaque count compared to plaque volume fraction
+ 3D LSFM imaging enables brain-wide assessment of plaque-clearing efficacy of Aβ targeted therapeutics

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1 Quantitative 3D whole-brain imaging pipeline

A

Sex	Genotype	Age (weeks)	N
Male	Wild-type	30	6
Male	ARTE10	15	6
Male	ARTE10	30	5
Male	ARTE10	42	6
Female	ARTE10	15	6
Female	ARTE10	30	6
Female	ARTE10	42	6

B

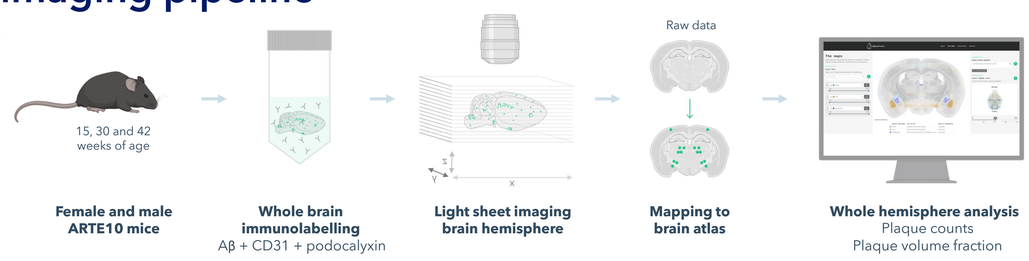

Figure 1. Study groups and quantitative 3D light sheet fluorescence microscopy imaging workflow. (A) Study groups. **(B)** A deep learning-enabled automated whole-brain imaging pipeline was applied to evaluate whole-brain distribution of Aβ plaques in transgenic ARTE10 mice. Whole-brain triple-staining was performed to visualize localization of amyloid-beta (Aβ) plaques associated with the vasculature (CD31, podocalyxin).

2 3D whole-brain imaging of parenchymal and vascular plaque architecture in ARTE10 mice

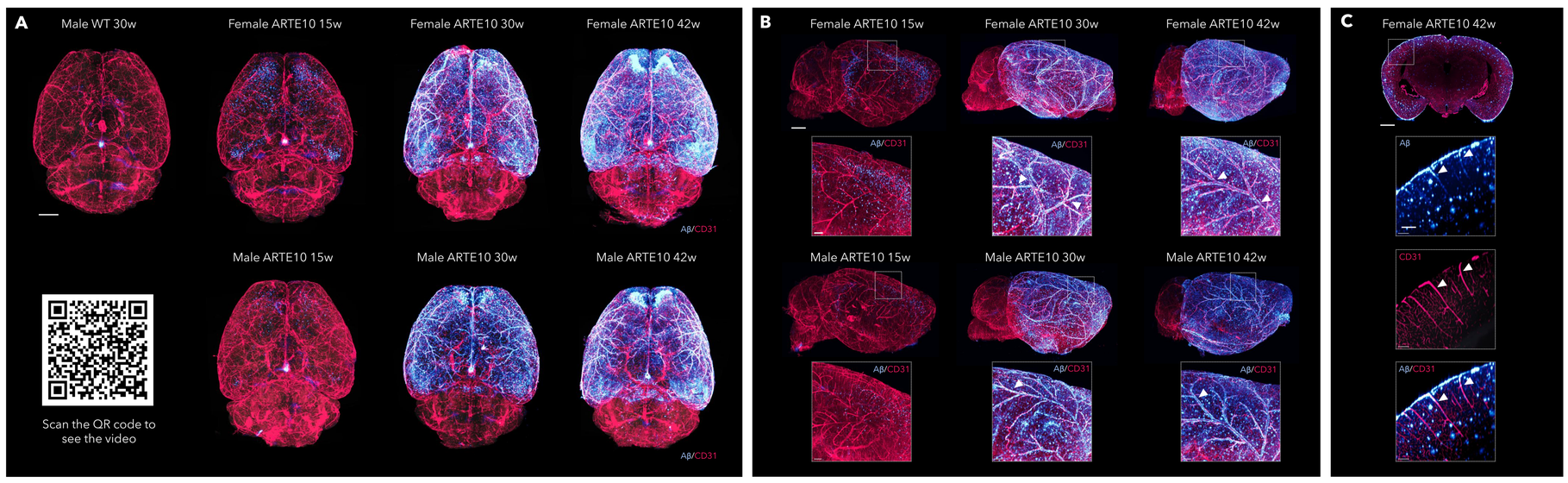

Figure 2. Representative raw data images. Whole-brain samples were triple-stained for Aβ (blue, plaques), CD31 and podocalyxin (magenta, vasculature) in female and male ARTE10 mice at different ages. **(A)** Dorsal view. Male wild-type (WT, 30 weeks-old) mice served as healthy controls (scale bar, 1000 µm). QR code links to representative 3D whole-brain video of female ARTE10 mouse at 42 weeks of age. **(B)** Sagittal view (scale bar, 1000 µm). Magnified cortical area shows age- and sex-dependent parenchymal and vascular plaque accumulation. Arrows indicate vascular-associated plaque deposits (scale bar, 500 µm). **(C)** Coronal view. Arrowheads indicating plaques located along cortical penetrating arterioles (scale bars, 1000 µm (top panel); 400 µm (lower panels)).

3 Age and sex-dependent differences in whole-brain Aβ plaque architecture in ARTE10 mice

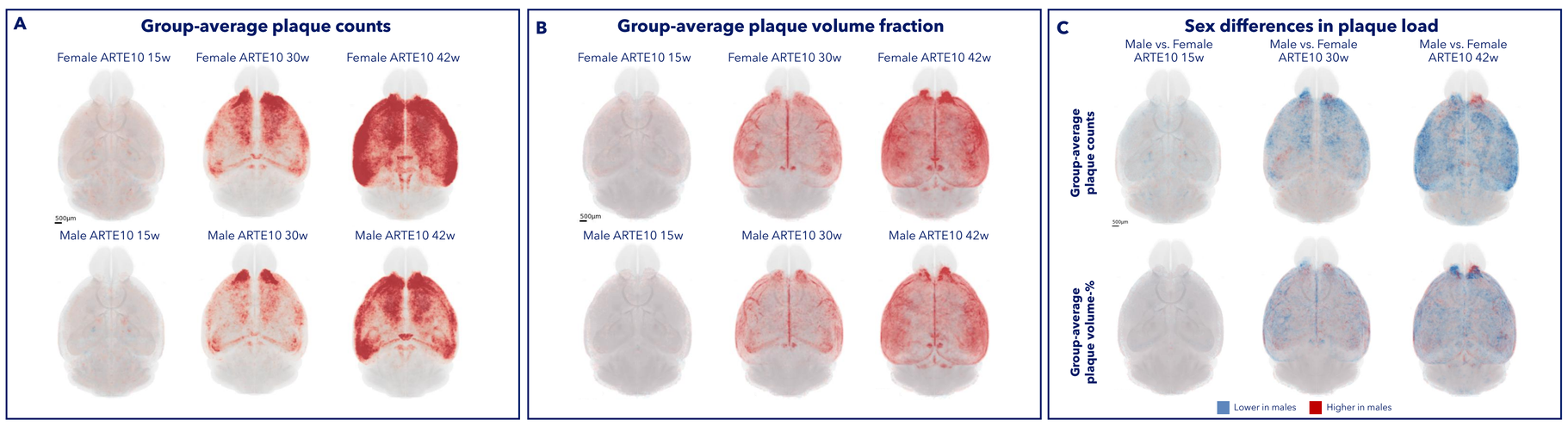

Figure 3. Overview of age-and sex-dependent differences in Aβ plaque load in ARTE10 mice. **(A)** Group-average plaque counts compared to WT controls (dorsal view). Brain regions with increased plaque load is indicated in red color. **(B)** Group-average plaque volume fraction. Plaque volume fraction is expressed as volume of plaques in % of total brain area volume. Brain regions with increased plaque load is indicated in red color. **(C)** Comparison of plaque counts (upper panels) and volume-% (lower panels) in male vs. female ARTE10 mice across ages. Brain regions with lower (blue color) or higher (red color) plaque load in male ARTE10 mice vs. female ARTE10 mice are indicated.

4 Brain-wide quantification of plaque load in female and male ARTE10 mice

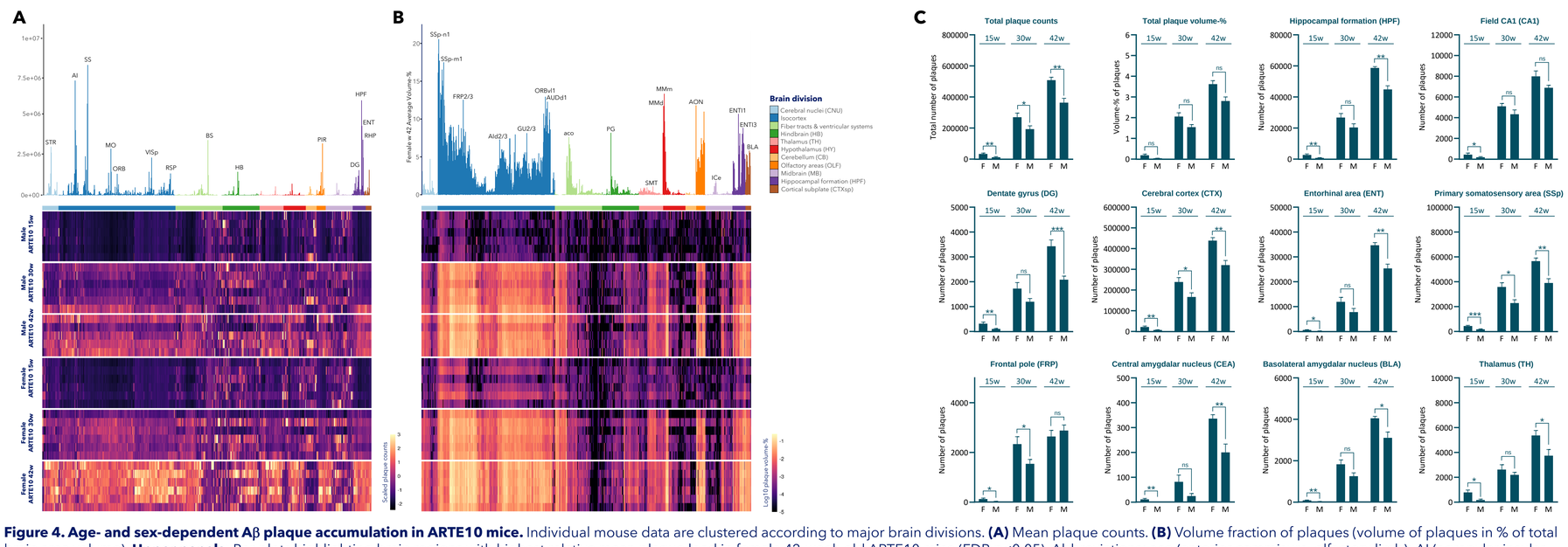

Figure 4. Age- and sex-dependent Aβ plaque accumulation in ARTE10 mice. Individual mouse data are clustered according to major brain divisions. **(A)** Mean plaque counts. **(B)** Volume fraction of plaques (volume of plaques in % of total brain area volume). **Upper panels:** Bar plots highlighting brain regions with highest relative mean plaque load in female 42-week-old ARTE10 mice (FDR p<0.05). Abbreviations: aco (anterior commisure, olfactory limb); AI (agranular insular area); AON (anterior olfactory nucleus); AUD (auditory areas); BLA (basolateral amygdalar nucleus); BS (brain stem); DG (dentate gyrus); ENT (entorhinal areas); FRP (frontal pole layers); GU (gustatory areas); HB (hindbrain); HPF (hippocampal formation); ICd (inferior colliculus, external nucleus); MM (mammillary body); MO (somatomotor areas); OLF (olfactory areas); ORB (orbital area); PG (pontine gray); PIR (piriform area); RHP (retrohippocampal region); RSP (retrosplenial areas); SMT (submedial nucleus of the thalamus); SS (somatosensory areas); STR (striatum); VIS (visual areas). **Lower panels:** Heatmap on brain regional plaque load in individual mice. **(C)** Plaque load in selected brain regions of female (F) and male (M) ARTE10 mice. *p<0.05, **p<0.01, **p<0.001 (Dunnett's test negative binomial generalized linear model).