High-throughput quantitative whole-brain 3D imaging of congophilic amyloid plaque load 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 β-amyloid plaques in the brain. In addition to parenchymal plaque deposition, AD is also accompanied by vascular pathology, notably congophilic amyloid angiopathy (CAA), where amyloid plaques are deposited in the brain vasculature which may contribute to the pathogenesis of AD. To assess drug effects on parenchymal and cerebrovascular amyloid pathology in these models, high-resolution plaque detection and quantification methods are required. To this end, we developed a light sheet fluorescence microscopy (LSFM) pipeline coupled with deep-learning image analysis, enabling automated whole-brain 3D mapping and quantification of congophilic amyloid plaques in a transgenic mouse model of AD.

METHODS

Brains from 12-month-old APP/PS1 transgenic (ARTE10, n=7) and age-matched wild-type control (C57BL/6, n=5) mice were stained with Congo red dye, cleared and scanned on a LSFM. A deep-learning image analysis algorithm was developed for automated segmentation and anatomical mapping of whole-brain vasculature and parenchymal amyloid plaques. Congophilic plaques were quantified in 1,372 brain regions using a custom mouse brain atlas.

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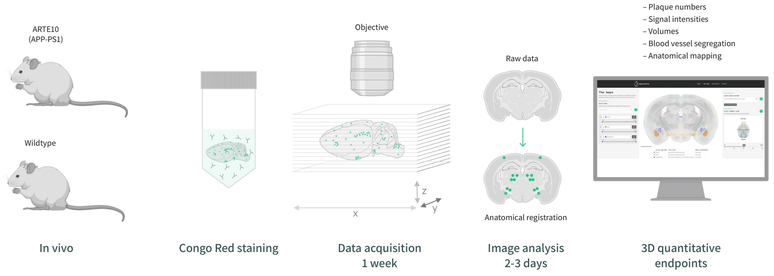
1 High-throughput whole-brain 3D imaging pipeline



2 Whole-brain 3D imaging of congophilic amyloid plaques

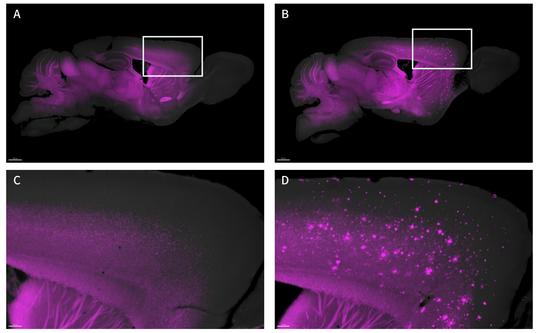


Figure 2. Whole-brain imaging of congophilic amyloid plaque deposition. (A,B) Parasagittal digital micrographs of Congo red-stained whole-brain of age-matched wild-type **(A)**, and ARTE10 **(B)** mouse. Scale bars = 700 µm. **(C,D)** Further magnification of boxed area in panels A and B. Scale bar, 150 µm.

3 Deep-learning based segregation of blood vessel and plaques

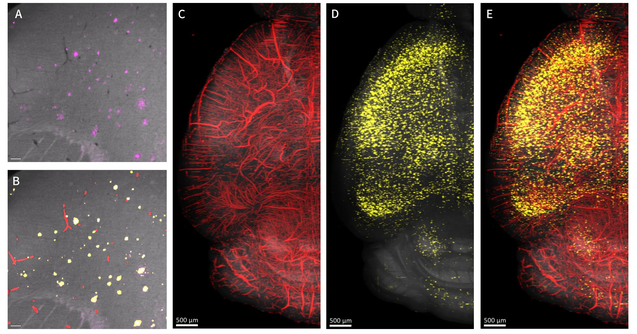


Figure 3. Deep-learning computational segregation of blood vessels and amyloid plaques in ARTE10 mice. (A,B) 2D panel of a Congo red-stained ARTE10 mouse brain before **(A)** and after **(B)** deep learning-based annotation of blood vessels and amyloid plaques. Congo red fluorescence (magenta), autofluorescence (grey), blood vessel (red), congophilic amyloid plaques (yellow), scale bar, 100 µm. **(C-E)** 3D reconstructions of brain vasculature (red) **(C)**, congophilic amyloid plaques (yellow) **(D)** and overlay **(E)**. Scale bar, 500 µm.

4 Segregation of brain parenchymal and cerebrovascular amyloid plaques

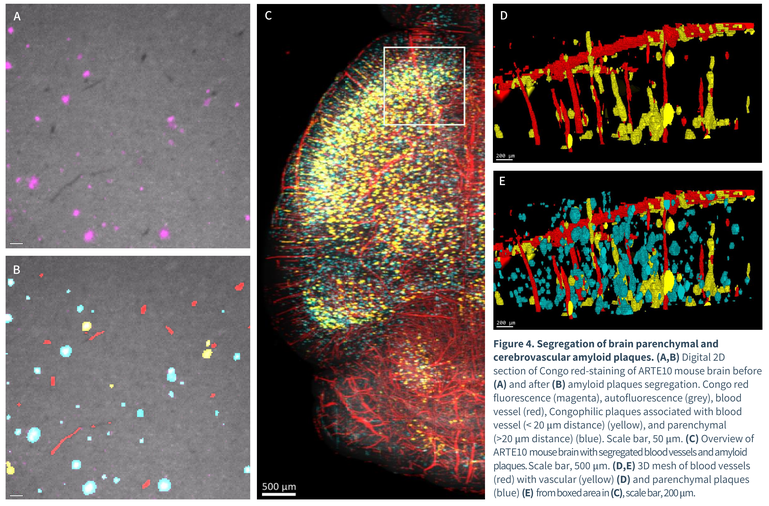


Figure 4. Segregation of brain parenchymal and cerebrovascular amyloid plaques. (A,B) Digital 2D section of Congo red-staining of ARTE10 mouse brain before **(A)** and after **(B)** amyloid plaques segregation. Congo red fluorescence (magenta), autofluorescence (grey), blood vessel (red), Congophilic plaques associated with blood vessel (< 20 µm distance) (yellow), and parenchymal (>20 µm distance) (blue). Scale bar, 50 µm. **(C)** Overview of ARTE10 mouse brain with segregated blood vessels and amyloid plaques. Scale bar, 500 µm. **(D,E)** 3D mesh of blood vessels (red) with vascular (yellow) **(D)** and parenchymal plaques (blue) **(E)** from boxed area in **(C)**, scale bar, 200 µm.

5 Brain parenchymal and vascular amyloid plaque profile in ARTE10 mice

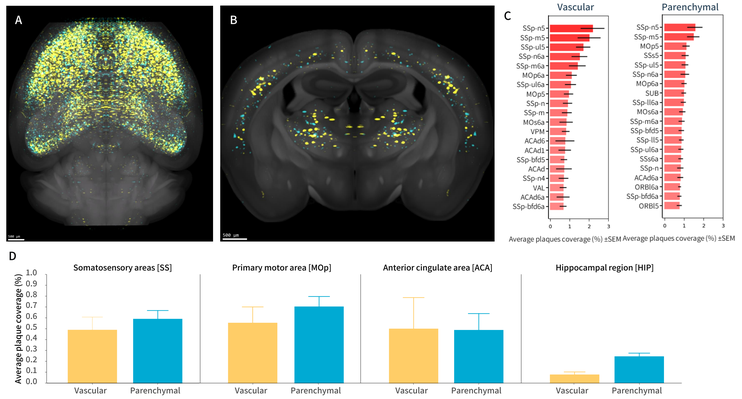


Fig. 5. Whole-brain parenchymal and cerebrovascular Aβ plaques distribution profile in ARTE10 mice. (A,B) Average distribution profile of brain parenchymal (blue) and vascular (yellow) amyloid plaques in ARTE10 mice (n=7). 3D overview **(A)** and coronal 2D cross-section (100 µm thick) at the mid-brain level **(B)**, scale bar, 500 µm. **(C)** Top-20 brain regions with highest brain vascular and parenchymal amyloid plaque density (proportional (%) area, mean of n = 7 + SEM). *Abbreviations:* ACA: Anterior cingulate area, MOp: Primary motor area, MOs: Secondary motor area, ORB: Orbital area, SSp: Primary somatosensory area, SS: Supplemental somatosensory area, SUB: Subiculum, VAL: Ventral anterior-lateral complex of the thalamus, VPM: Ventral posteromedial nucleus of the thalamus, l: lateral part, d:dorsal part, bfd: barrel field, ll: lower limb, m: mouth, n: nose, ul: upper limb, 1: layer 1, 5: layer 5, 4: layer 4, 6a: layer 6a,**(D)** Brain amyloid plaque density in the cortical somatosensory area (SS), primary motor area (MOp), anterior cingulate area (ACA), and hippocampal region (HIP).

CONCLUSION

- We have developed a high-throughput 3D imaging deep learning pipeline for brain-wide analysis of congophilic amyloid plaque load in mouse models of Alzheimer's disease.
- The work flow includes mapping and quantification of parenchymal and cerebrovascular amyloid plaque distribution.
- Our pipeline is highly applicable for profiling anti-amyloid therapies in mouse models of Alzheimer's disease.

Scan the QR code to see a 3D movie of whole-brain congophilic amyloid β plaque distribution in an ARTE10 mouse brain

Explore **www.neuropedia.dk**, Gubra's open access resource of interactive mouse whole-brain histology maps

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