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Cellular morphometric analysis: from microscopic scale to whole mouse brains

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Context

Neurodegenerative diseases occur when neurons in the brain and spinal cord begin to deteriorate.

In certain cases such as Alzheimer's disease, cell morphology and function are disturbed (Fig. 1) and **pathological aggregates** form in the brain. Characterizing the relationship between these anomalies is important to understand the mechanisms involved in this pathology.

Quantifying the morphological changes is crucial and **Whole-slide imaging (WSI)** offers the unique opportunity to **analyze whole brain sections at the cellular level** using various histological markers. However, this technique generates terabytes of data which can be difficult to analyze.

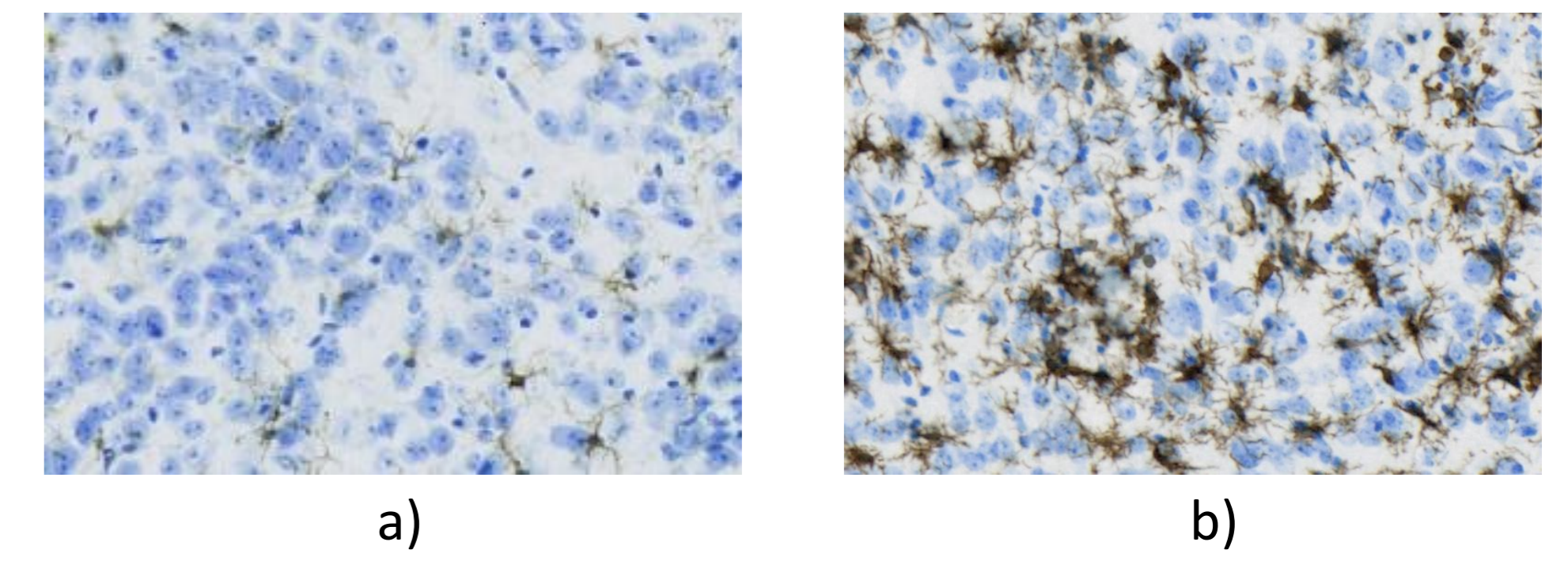


Figure 1: a) microglial cells (brown) in a normal mouse
b) activated microglial cells in a mouse model of Alzheimer's disease

Materials

- We worked on an **APP/PS1 mouse model** of Alzheimer's disease.
- A mouse brain was cut into 20- μm -thick sections, yielding a total of about 400 sections.
- Sections were stained with **Iba-1 antibody to mark microglial cells** and scanned using an AxioScan.Z1 (Zeiss) at a resolution of **0.44 μm (x10)** (Fig. 3a).

Methods

- Each section (Fig. 3a) was **segmented to detect microglial cells** by a machine learning classifier¹ (Fig. 3b).
- The microglial cells were labelled** (Fig. 3c) and corresponding **Voronoi partitions were calculated** to estimate their spatial influence i.e. each point was attributed to the closest cell (Fig. 3d).
- Based on the original RGB image, labelled image and Voronoi image, **parameters of interest** (Fig. 2) were calculated for each microglial cell and **stored in the form of a table** (Fig. 3e).
- According to this parametric information, we spatially summarized information (Fig. 3f-g) by generating **quantitative heat maps** (Fig. 3h-n) at a lower resolution (**112 μm**) for each parameter of interest.

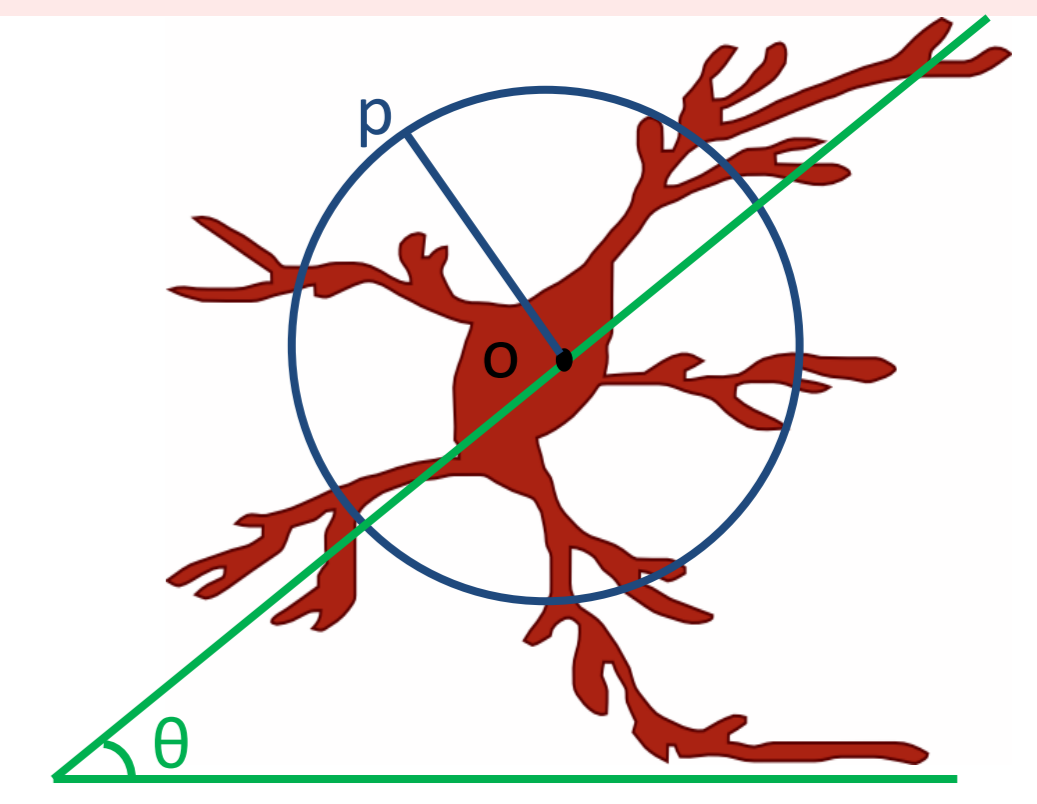
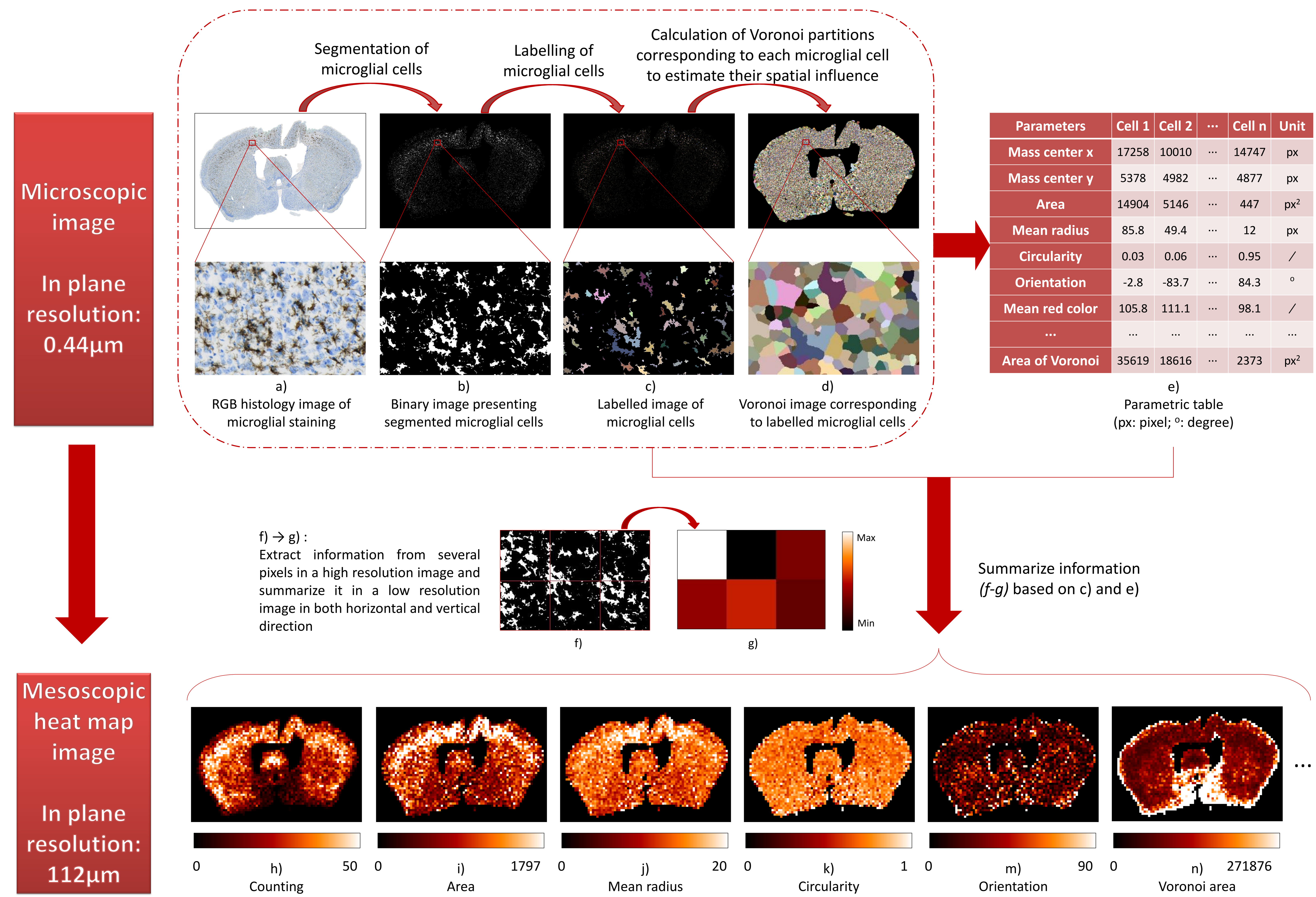


Figure 2: Parameters of interest. o: mass center, op : mean radius, Orientation (θ): angle between the direction of maximal Feret diameter and horizontal axis

Results

Figure 3: General flow chart, method proposed to integrate mesoscopic quantitative information from high-resolution histology images



Discussion and perspectives

- This original approach enables:
 - to extract and summarize pertinent information from high-resolution qualitative images,
 - to dramatically reduce (ratio = 65536) the amount of information to be processed.
- Analysis has been extended to other staining of interest (Fig. 4 cells: Nissl staining, amyloid plaques: 6E10 staining) and from brain sections to the entire reconstructed brains in 3D using our in-house software BrainVISA (<http://brainvisa.info>).
- 3D Voxel-wise statistical studies will be realized to investigate cellular structural alterations without *a priori* between groups as already performed on autoradiography data^[2].
- The possibility to correlate 3D whole-brain parametric maps with *in vivo* imaging modalities (MRI, fMRI, PET, *in vivo* microscopy, etc.) will improve the understanding of the relationship between brain structure and function in disease.

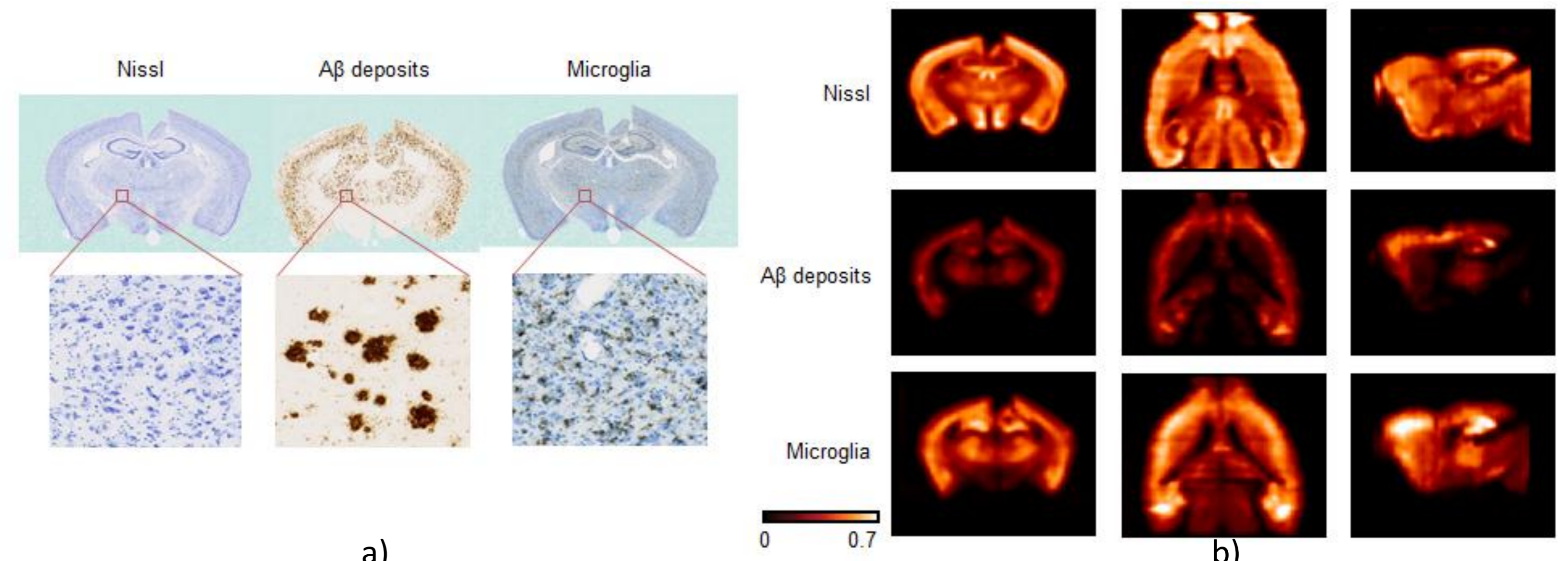


Figure 4: a) Supplementary staining tested, b) 3D density maps obtained in whole mouse brains