107° CONGRESSO NAZIONALE
della SOCIETÀ ITALIANA DI FISICA

X-ray Phase Contrast Tomography for Pre-clinical Studies of Neurodegenerative Diseases

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CNR NANOTEC INSTITUTE OF NANOTECHNOLOGY

TOMA Lab TOmography for Medical Applications

Neurodegenerative diseases

Neurodegeneration is a process by which a progressive loss of neuronal structure and functions occurs in many central nervous system (CNS) pathologies.
Generally associated with neuroinflammation.
Neurodegenerative diseases are presently incurable and current therapies have minimal or no significant effect in reversing the CNS damage.

Alzheimer's disease (AD) is the most common form of dementia and is characterized by a progressive loss of cognitive abilities.

Amyotrophic Lateral Sclerosis (ALS) is characterized by a progressive loss of control of major muscle activities.

Multiple Sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system, inducing neurological deficits and long-term irreversible disability.

Animal models and pre-clinical studies

Reasearch relies on **pre-clinical studies** on appropriate animal models:

to **investigate the pathological mechanisms** of the disease and

to **develop and monitoring therapeutic strategies.**

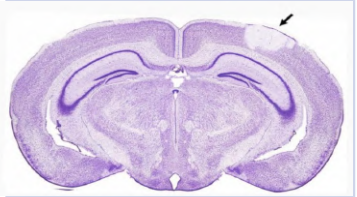
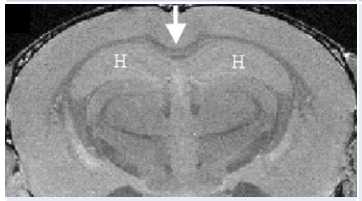
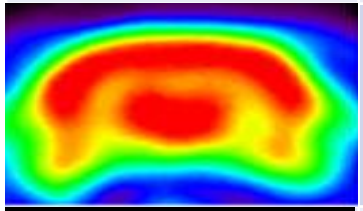
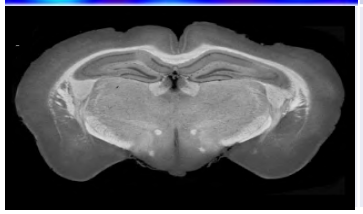
Animal models advantages:

- Rapid development of the disease and shorter life cycle
- Access to early stages of the disease
- Immunological surveillance
- Lower costs
- Control over experimental conditions

MOUSE MODELS:

- *AD → APP/PS1*
- *ALS → SOD1*
- *MS → Experimental Autoimmune Encephalomyelitis*

Biomedical imaging techniques

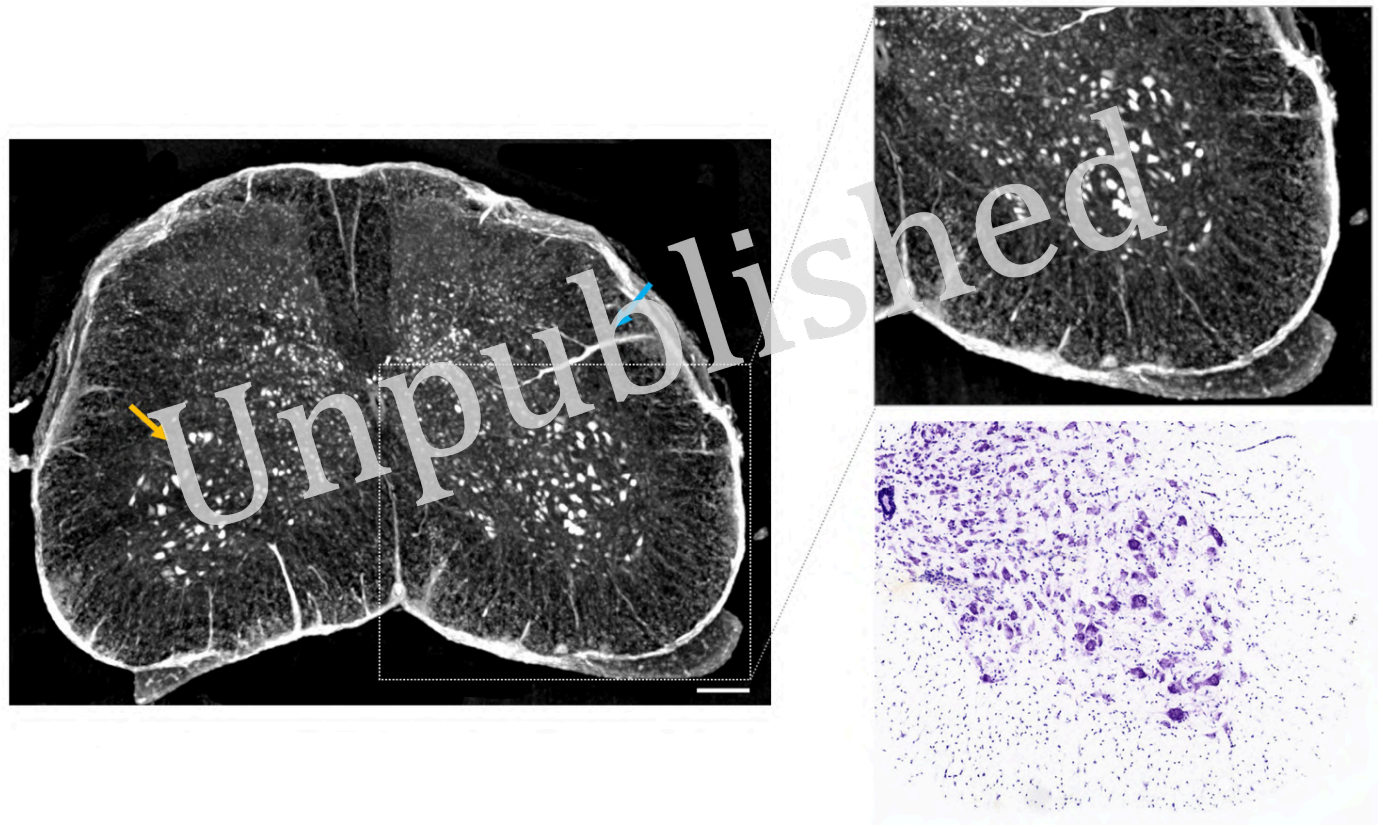
TECHNIQUE	2D/3D	HIGH CONTRAST	SPECIFICITY	HIGH SPATIAL RESOLUTION
	2D	✓	✓	✓
	3D	✓	✗	✗
	3D	✓	✓	✗
	3D	✗	✗	✓

X-ray Phase Contrast Tomography

X-Ray Phase Contrast Tomography (XPCT) is rising importance in pre-clinical investigation of neurodegenerative diseases. It is a 3D, direct, highly resolved, sensitive and noninvasive imaging technique.

XPCT provides complementary or additional information compared to 2D or other 3D techniques.

Histology-like resolution



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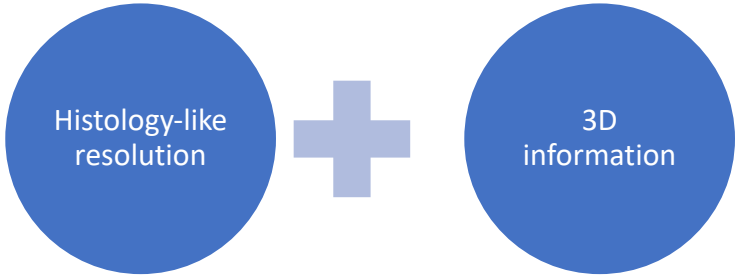
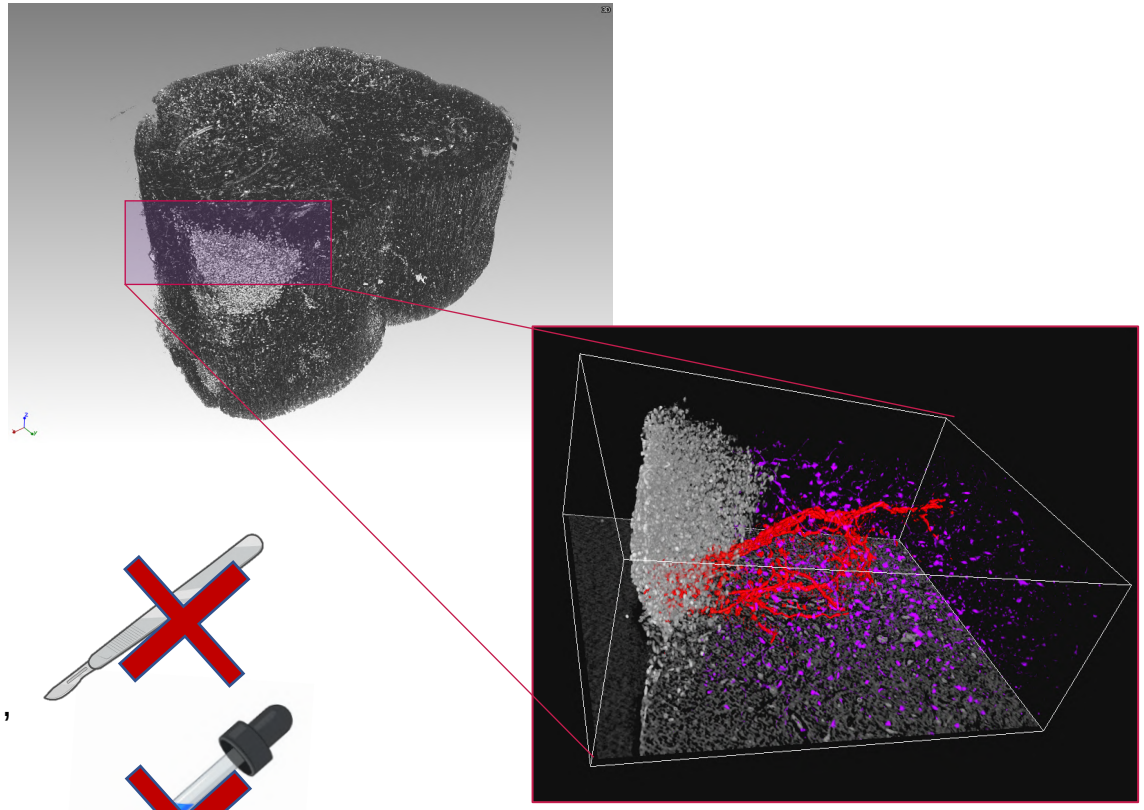




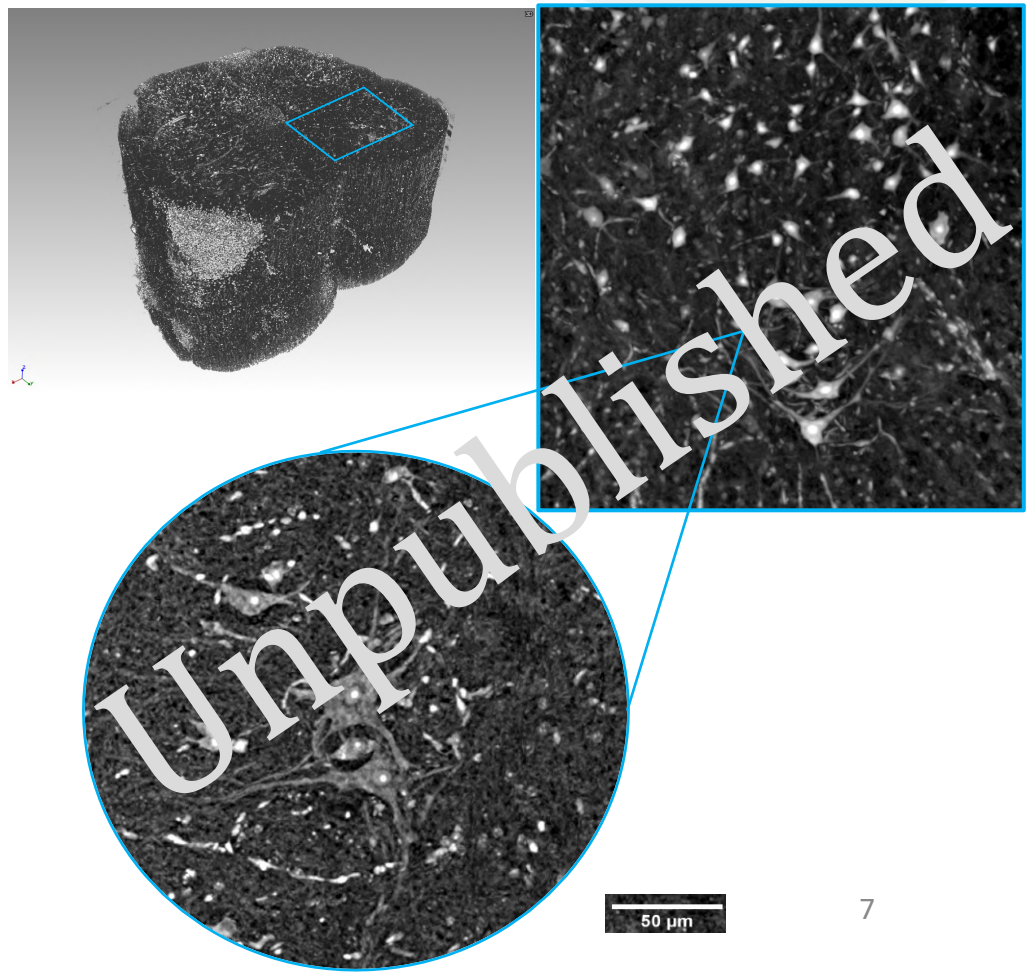
- No aggressive preparation, no staining

Palermo et al, Front. Neurosci. (2021)

X-ray Phase Contrast Tomography

XPCT X-Ray Phase Contrast Tomography (XPCT) is rising importance in pre-clinical investigation of neurodegenerative diseases. It is a 3D, direct, highly resolved, sensitive and noninvasive imaging technique.

Histology-like resolution + 3D information + Multiscale



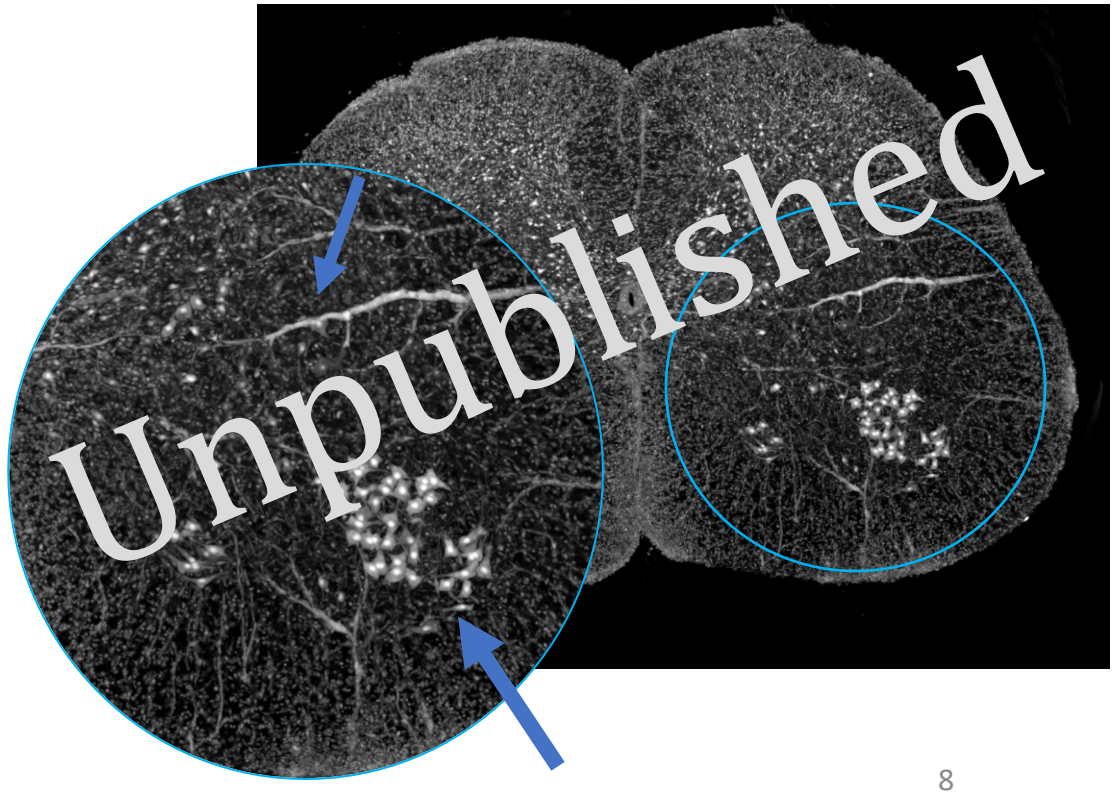
- From the organ as a whole down to the single cell
- Investigate disease-related alterations in the context of and in relation to their surrounding environment

X-ray Phase Contrast Tomography

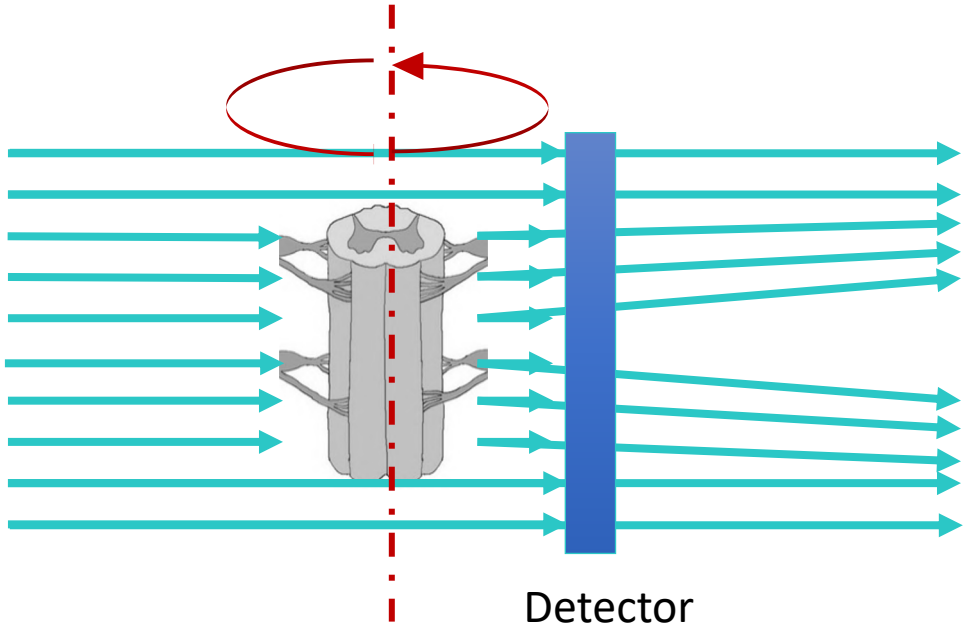
XPCT X-Ray Phase Contrast Tomography (XPCT) is rising importance in pre-clinical investigation of neurodegenerative diseases. It is a 3D, direct, highly resolved, sensitive and noninvasive imaging technique.

Histology-like resolution + 3D information + Multiscale + Simultaneous visualization

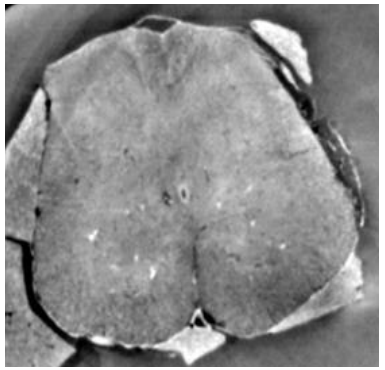
- Strict interplay between vascular and neuronal networks in the progression of neurodegenerative process of many CNS diseases



Propagation-based XPCT in a nutshell

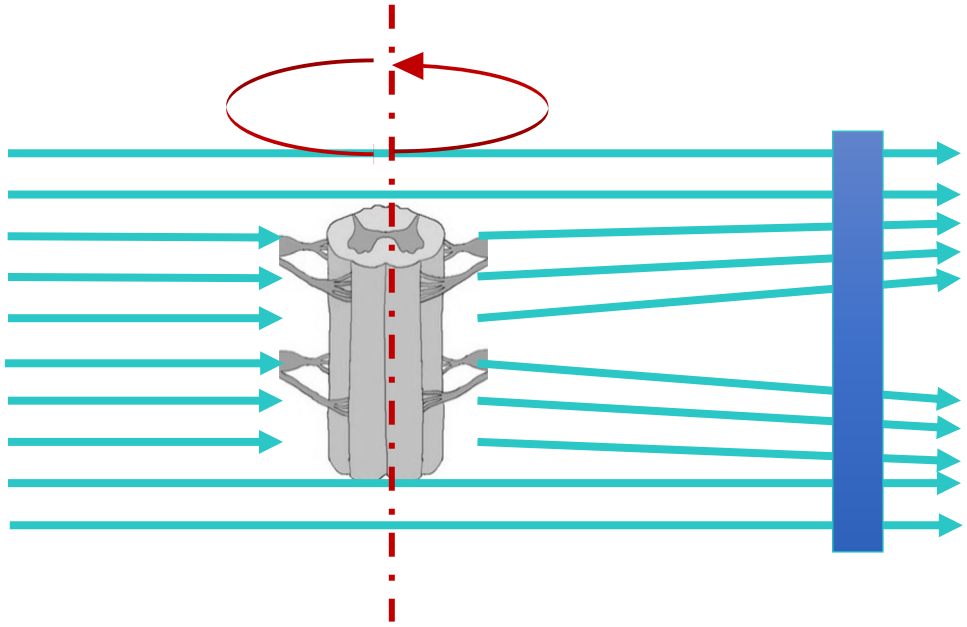


Propagation-based phase contrast tomo

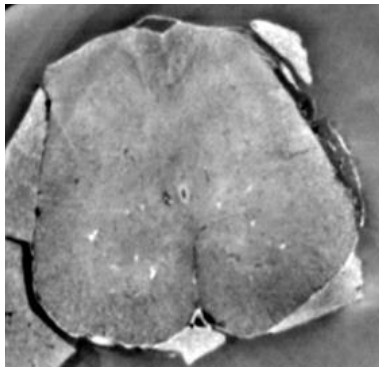


No good contrast for soft tissues (low values of absorption coefficient)!

Propagation-based XPCT in a nutshell

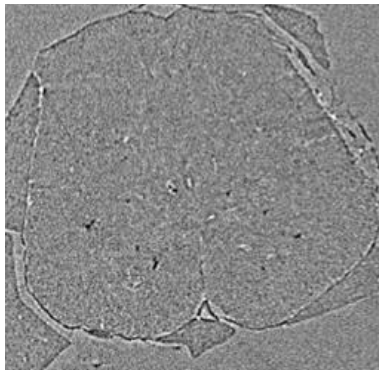


Propagation-based phase contrast tomo



VS

Absorption contrast



Synchrotron light

High spatial resolution
High spatial coherence
High phase-contrast signal

AD Model: APP/PS1dE9 mouse

AD Model: APP/PS1dE9 mouse

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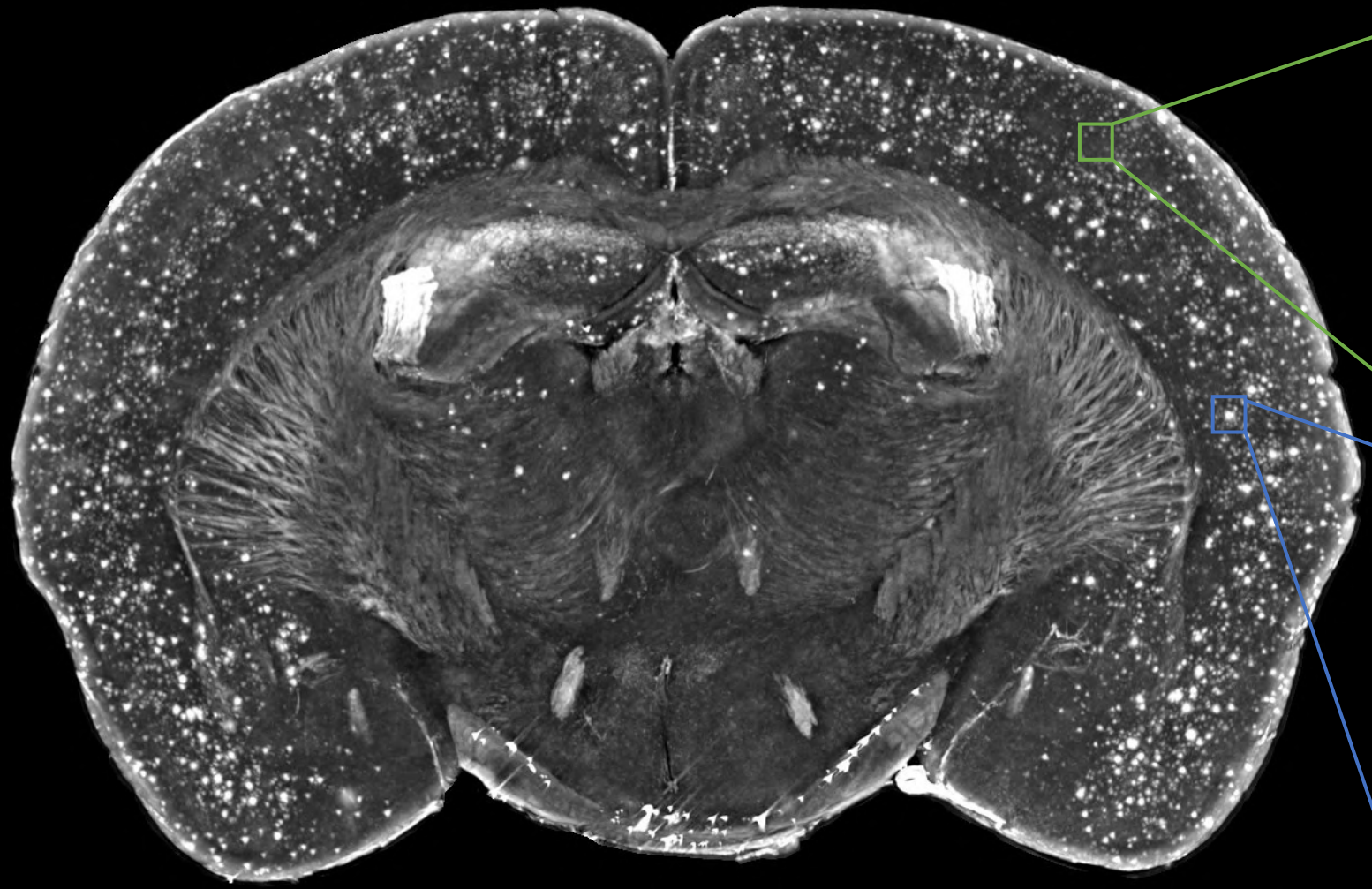
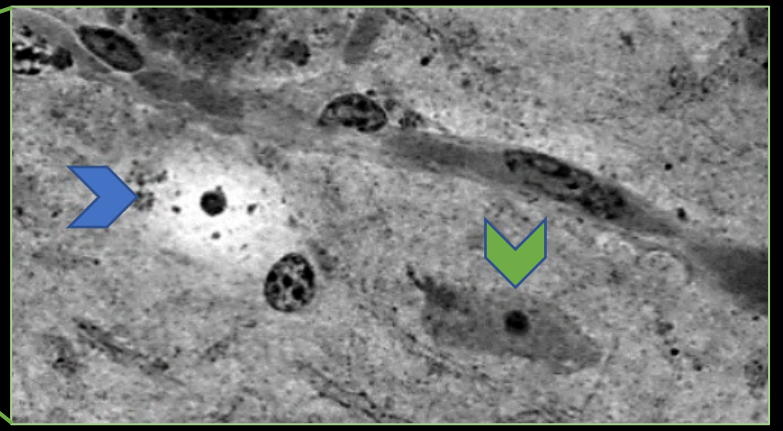
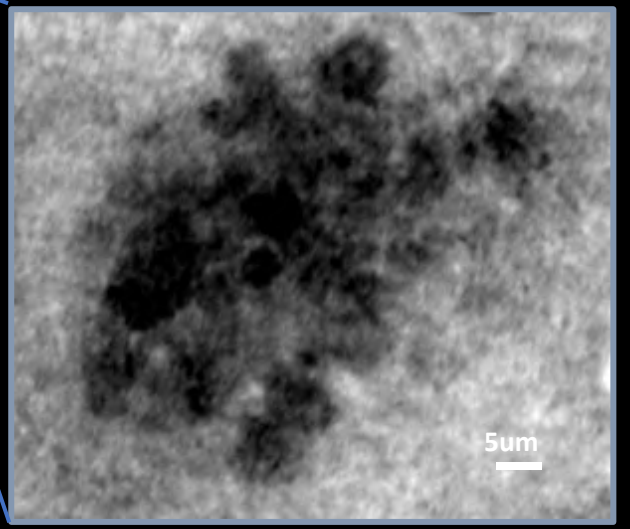
Nano-XPCT



Neurons



Ab plaque



Palermo et al, Front. Neurosci. (2021)

AD Model: APP/PS1dE9 mouse

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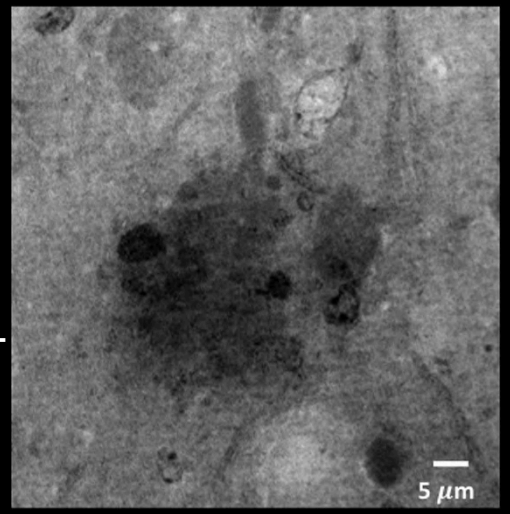
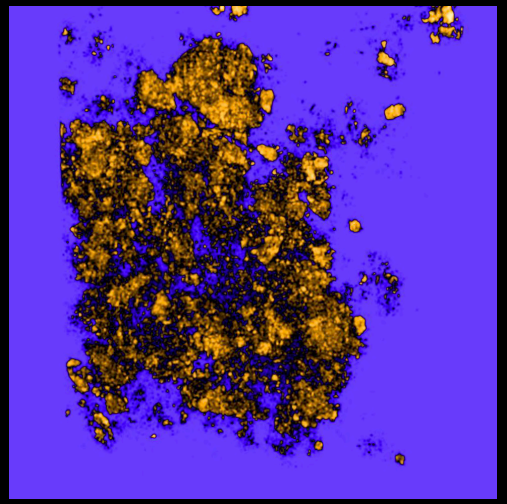
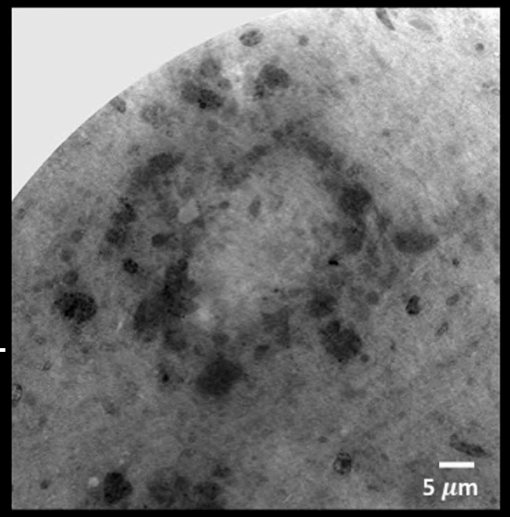
Nano-XPCT

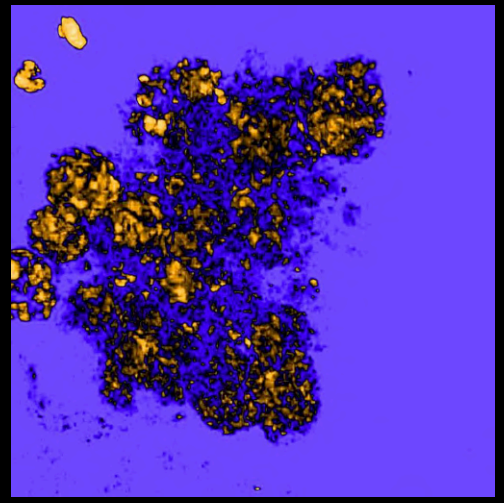
Plaque with core



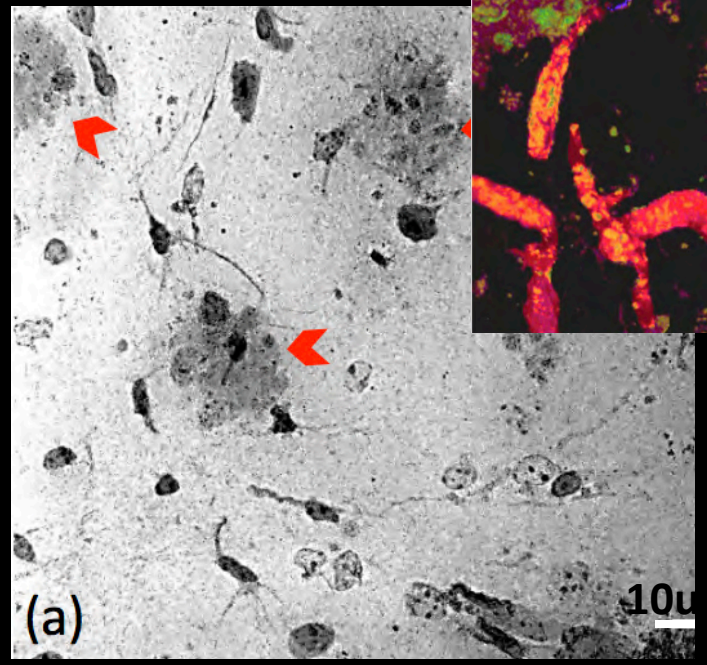


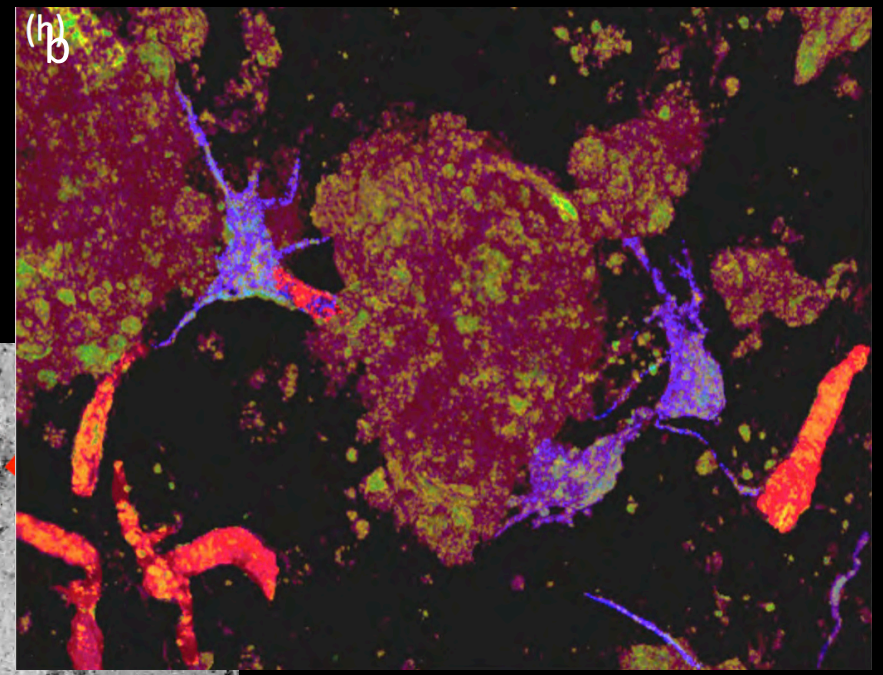
Plaque without core





- Ab plaques characterization
- Cellular environment



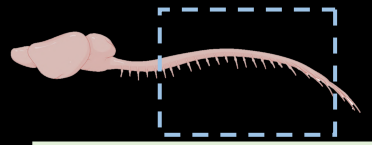


Massimi et al, Neuroimage (2019)

Palermo et al, Front. Neurosci. (2021)

ALS Model: SOD1 mouse

ALS Model: SOD1 mouse



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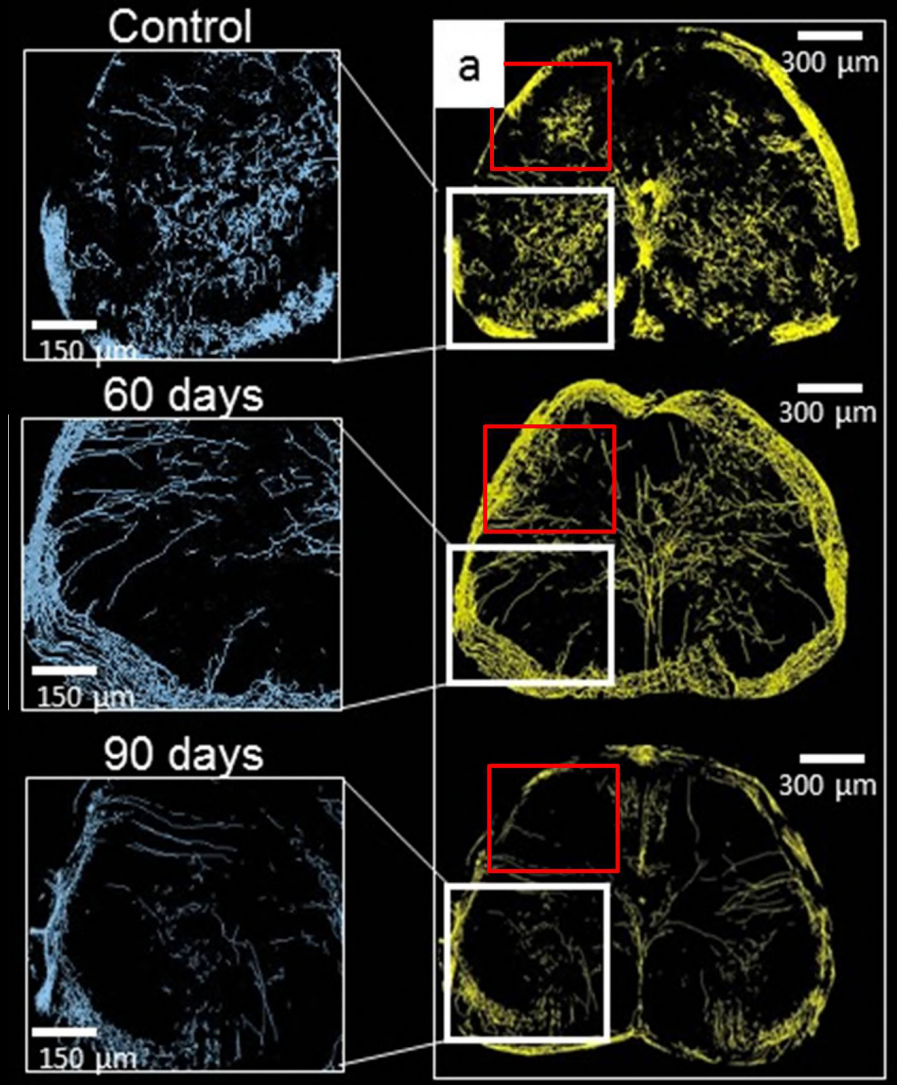
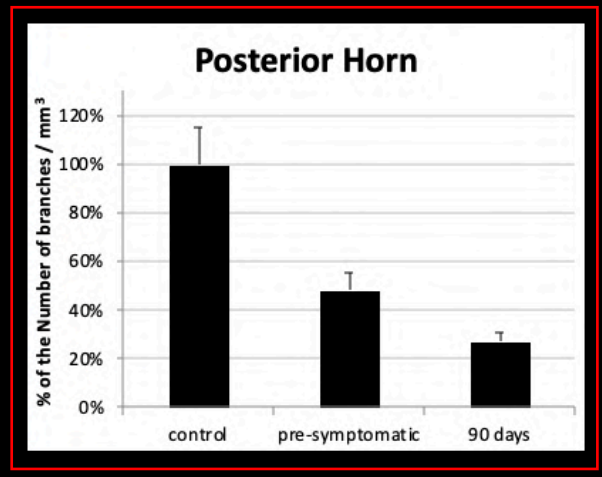
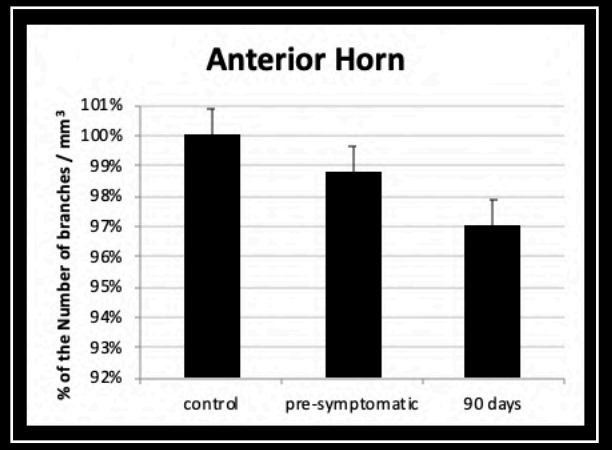


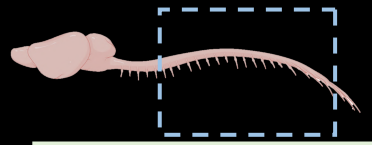
Vascular lesions

- Decrease of the number of branches in the vascular network as the disease progresses.





Begani Provinciali et al, J.Synchrotron Rad.(2020)



ALS Model: SOD1 mouse

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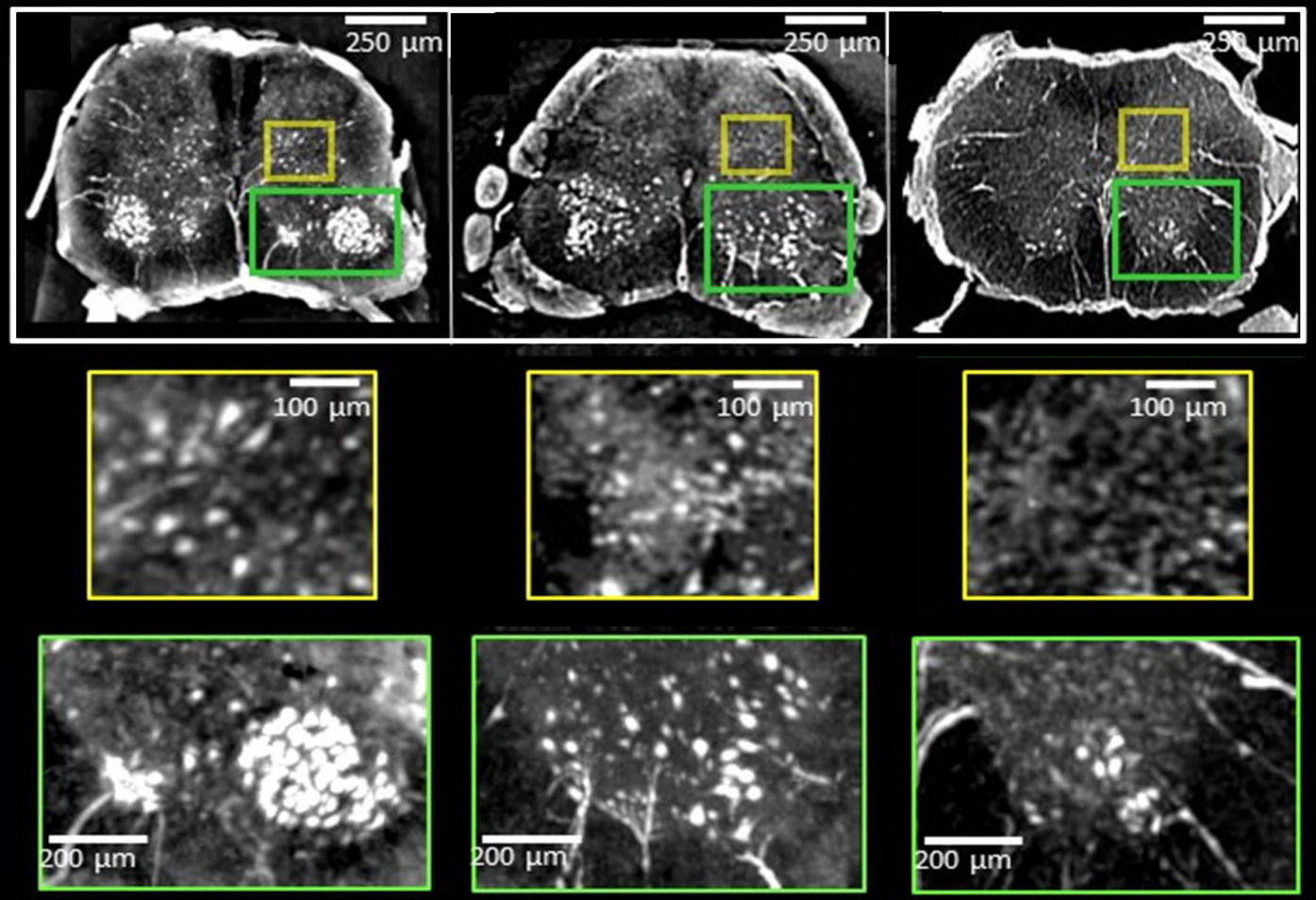
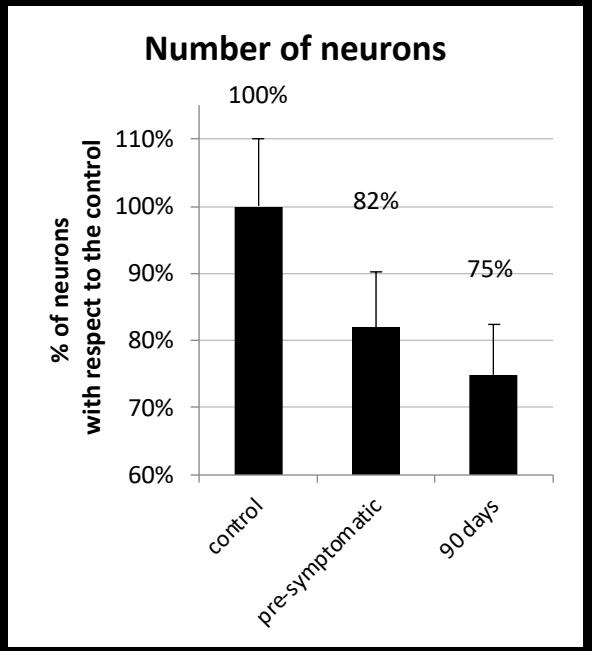


Vascular lesions

- Decrease of the number of branches in the vascular network as the disease progresses.

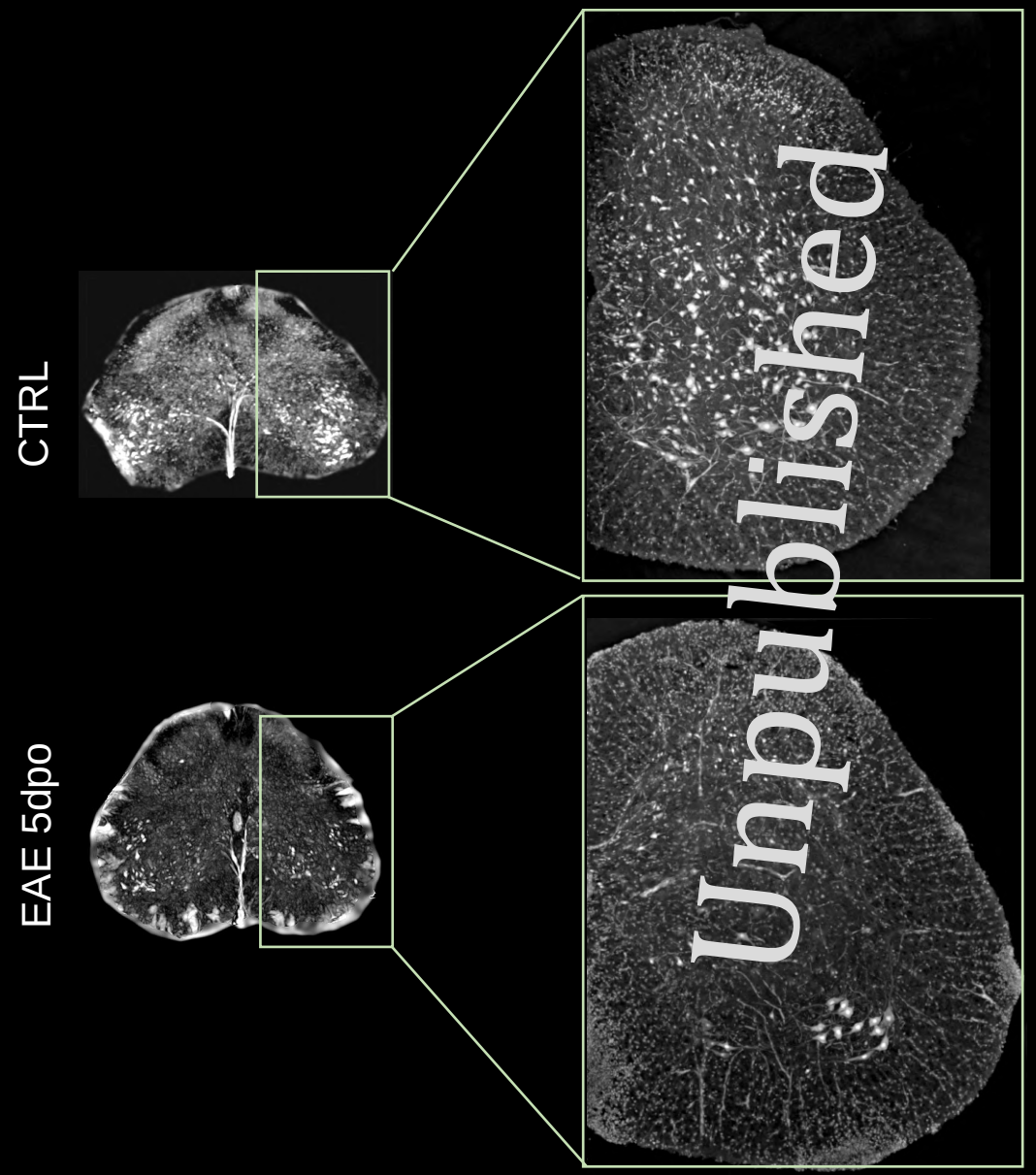
Neuron lesions

- Loss of motor neurons since pre-symptomatic. stage

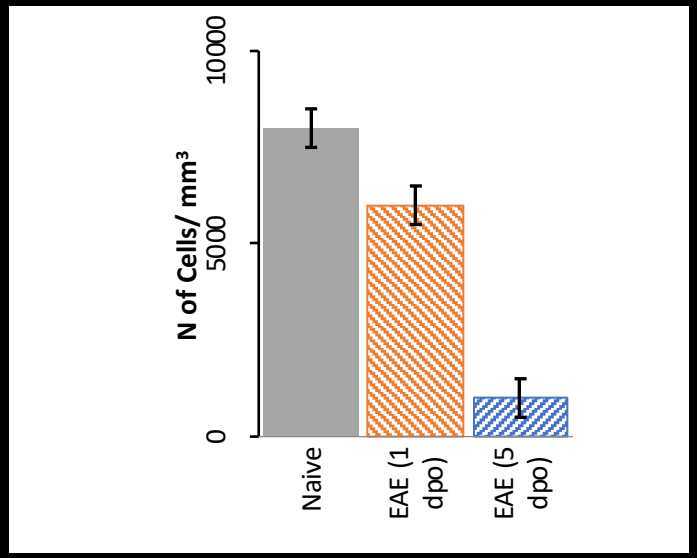


Begani Provinciali et al, J.Synchrotron Rad.(2020)

MS Model: EAE – Neuronal alteration

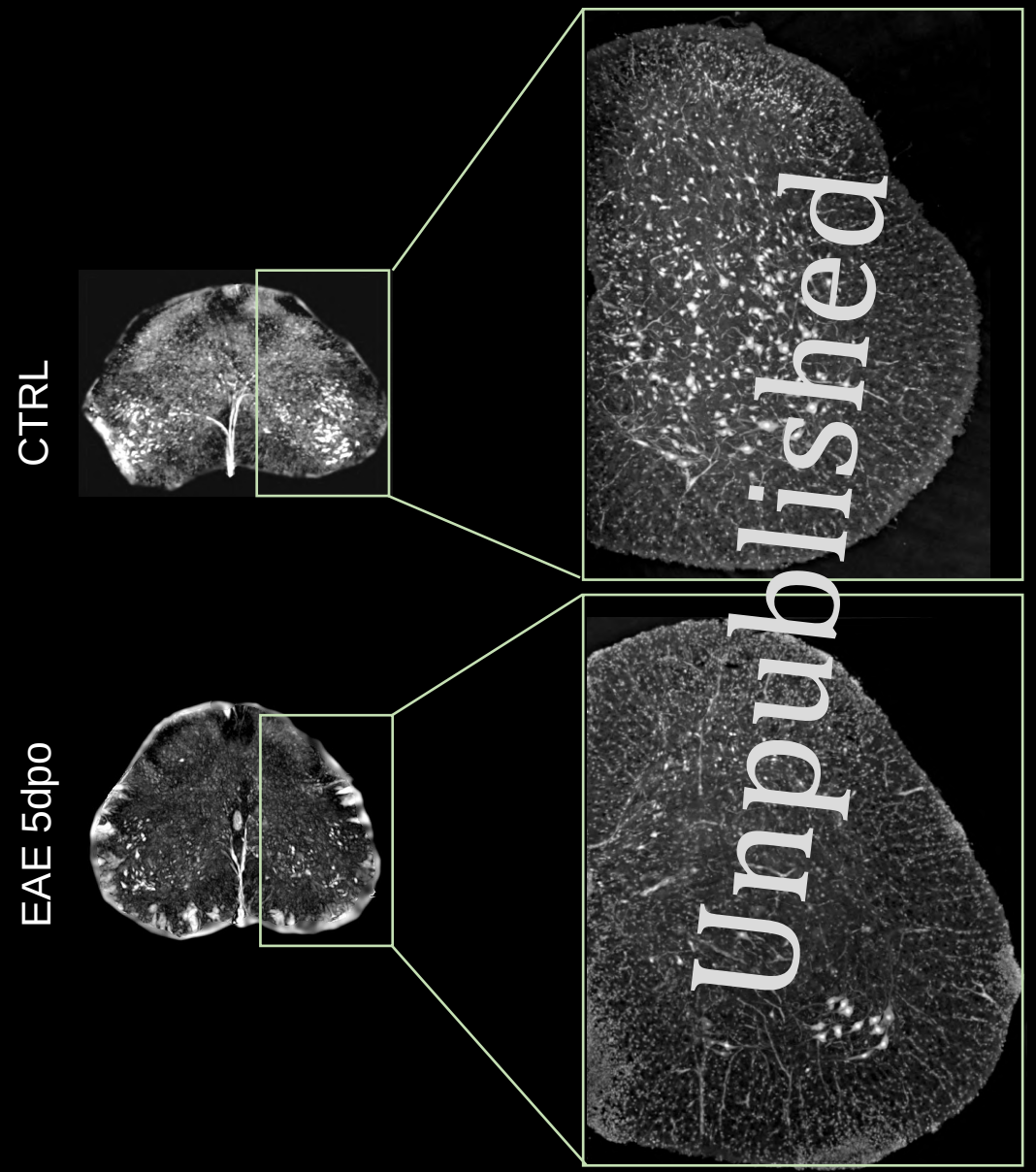


- Decrease of neurons in the advanced phase of EAE disease

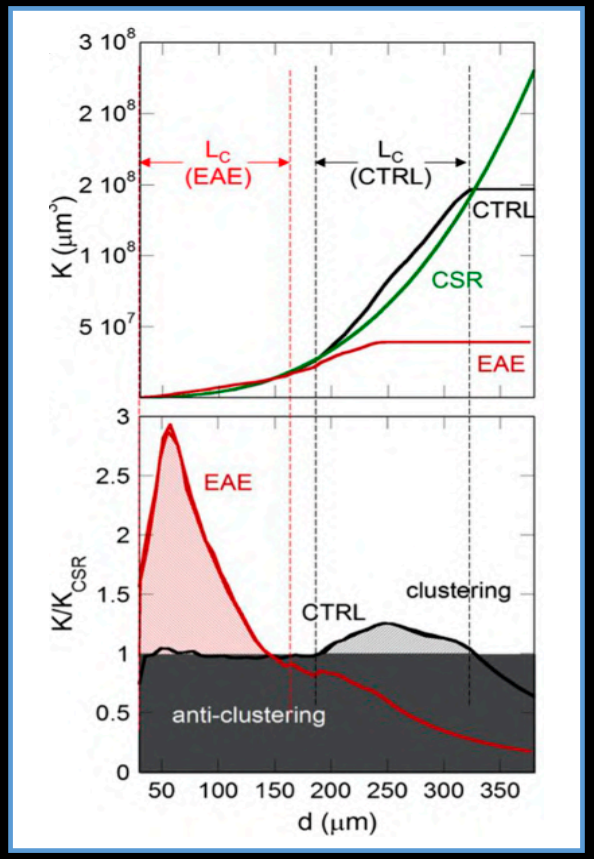


Cedola et al, Sci.Rep.(2017)

MS Model: EAE – Neuronal alteration



- Decrease of neurons in the advanced phase of EAE disease
- Local aggregation of neurons in advanced stage of EAE disease

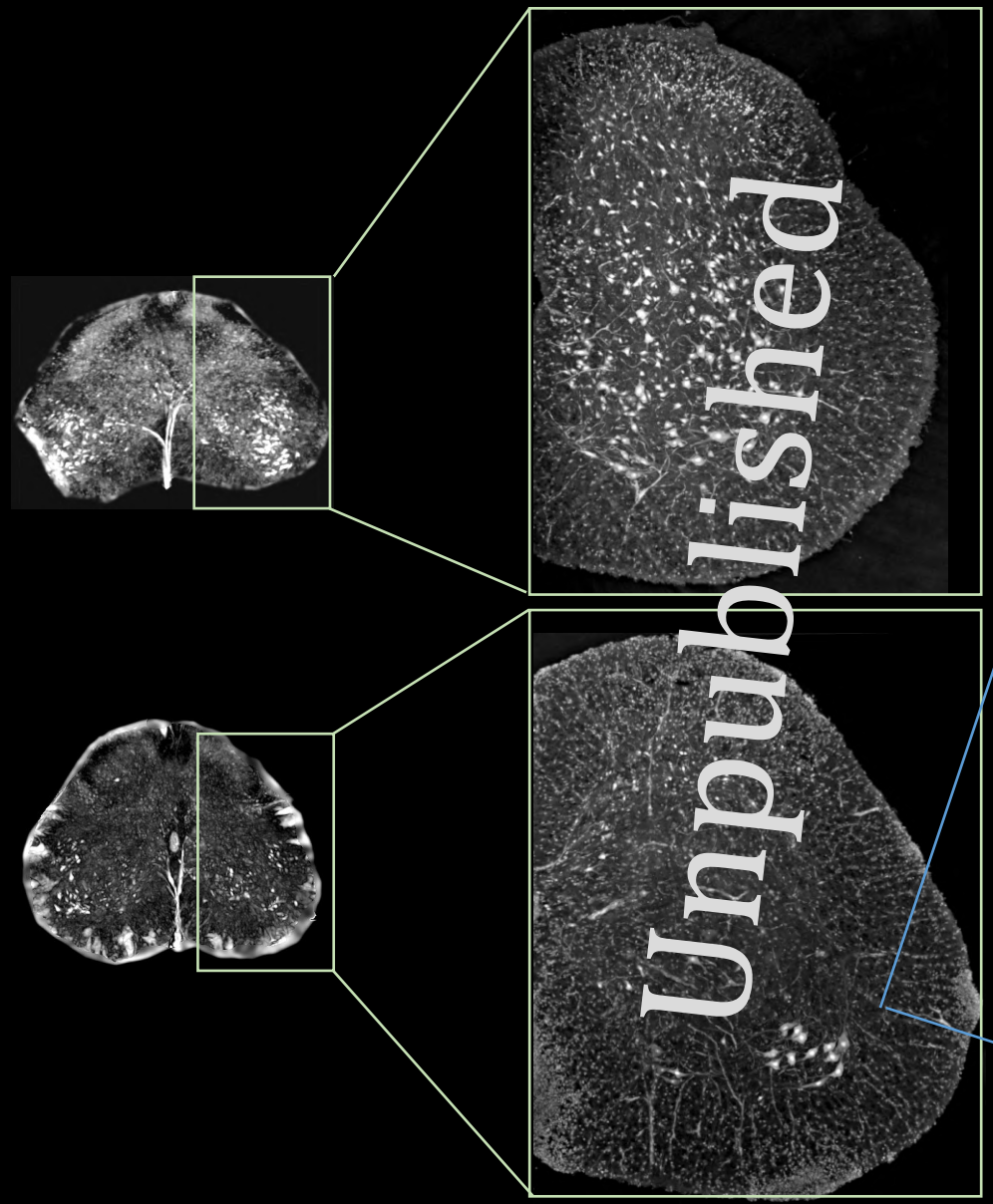


Bukreeva et al, Sci.Rep.(2017)

MS Model: EAE – Neuronal alteration

CTRL

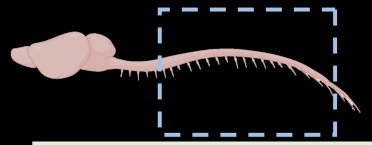
EAE 5dpo



- Decrease of neurons in the advanced phase of EAE disease
- Local aggregation of neurons in advanced stage of EAE disease
- Invading cells associated with damaged myelin in white matter

Nano-XPCT

Cedola et al, Sci.Rep.(2017)



MS Model: EAE – Vascular alteration

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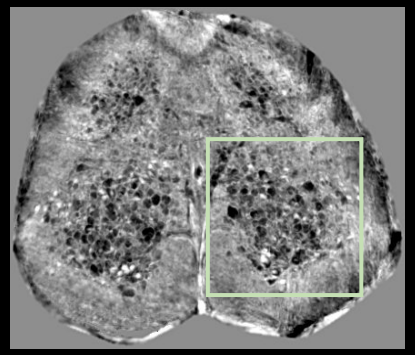
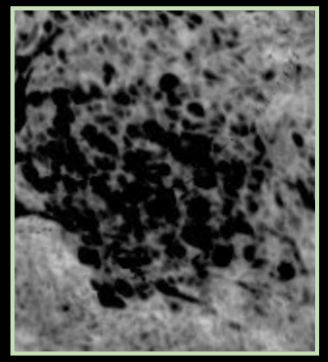
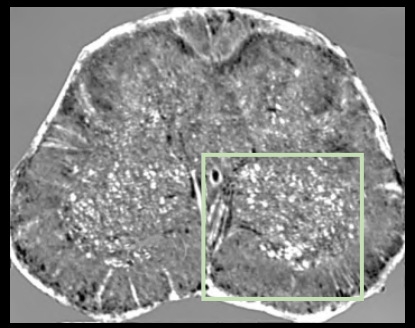
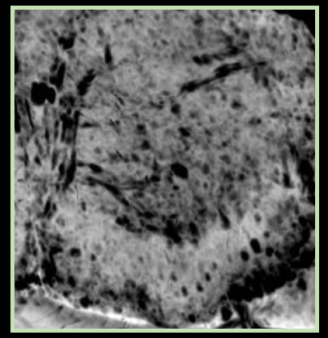
CTRL

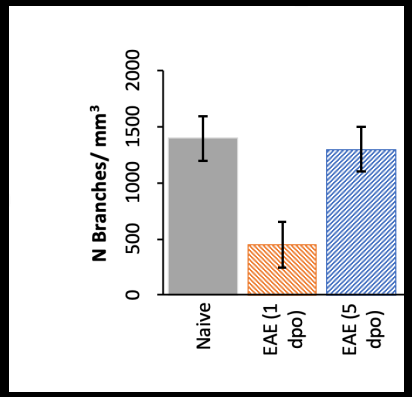
EAE-1dpo



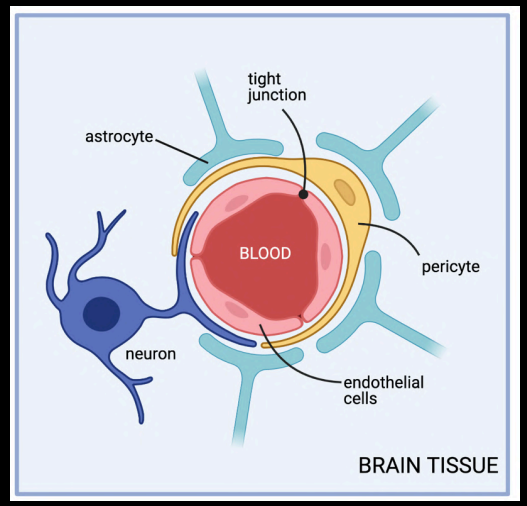








Blood barrier dysfunction

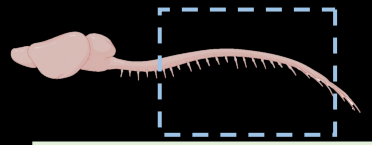


- Blood vessels decreasing 1 day post onset in EAE mice
- Angiogenic response after 5 gg

Sagittal view

CTRL EAE – onset

Cedola et al, Sci.Rep.(2017)



MS Model: EAE – Vascular alteration

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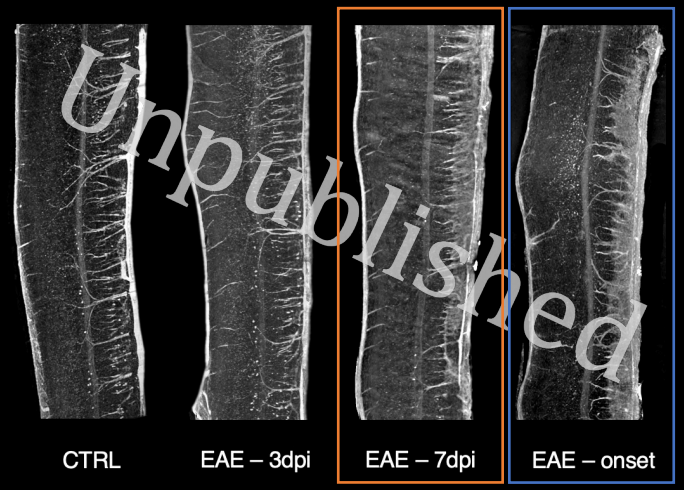
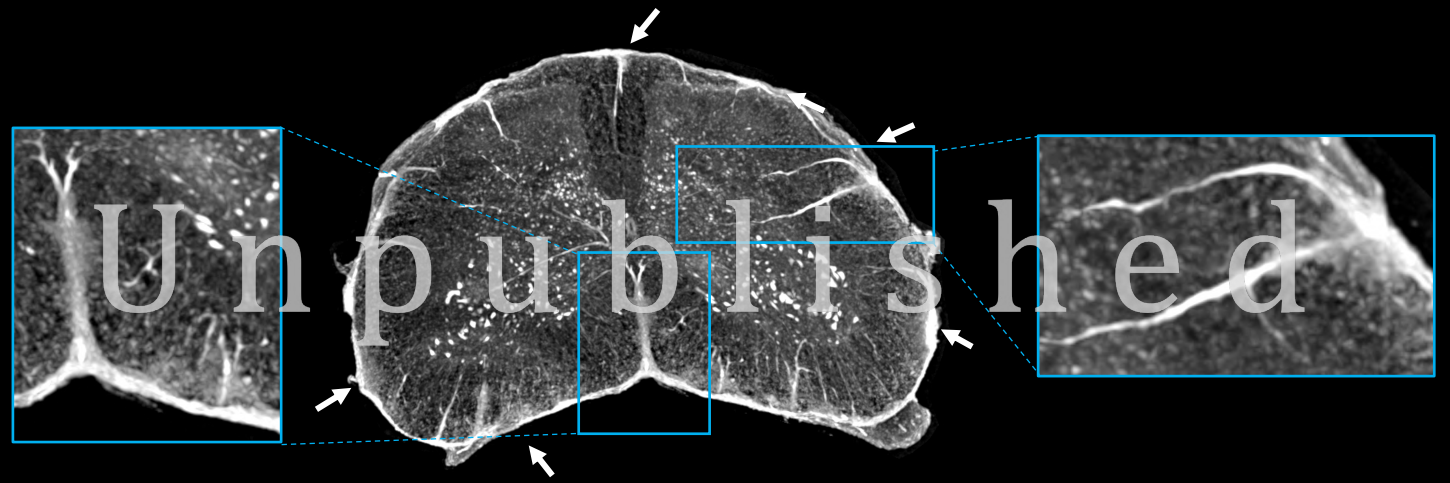
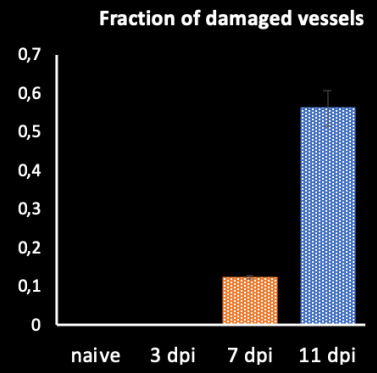
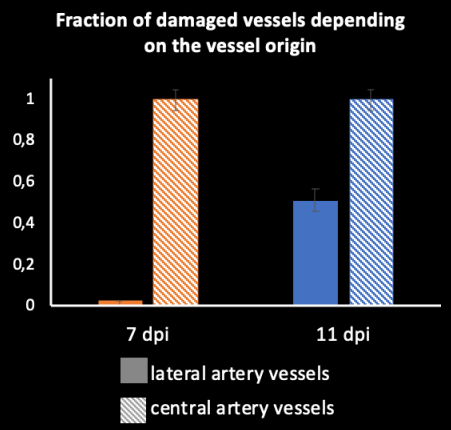








- Blood barrier damage appears at pre-syntomathic stage, before the onset
- Lesions become more extensive at the onset

MS Model: EAE – Blood barrier dysfunction

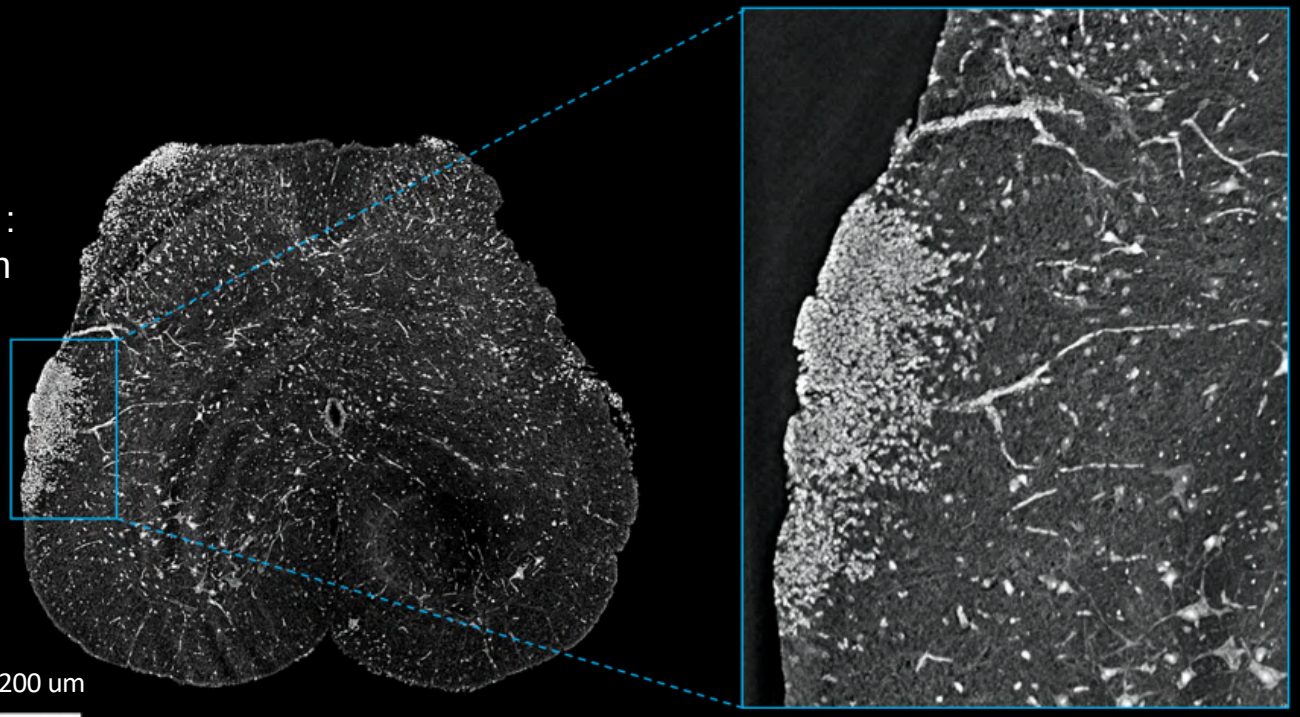
- The clouds appear to consist of a large accumulation of cells localized around the vessels, which would be typical of an EAE lesion with infiltrating inflammatory T-cells and macrophages

Pixel size : 3 micron

EAE – onset

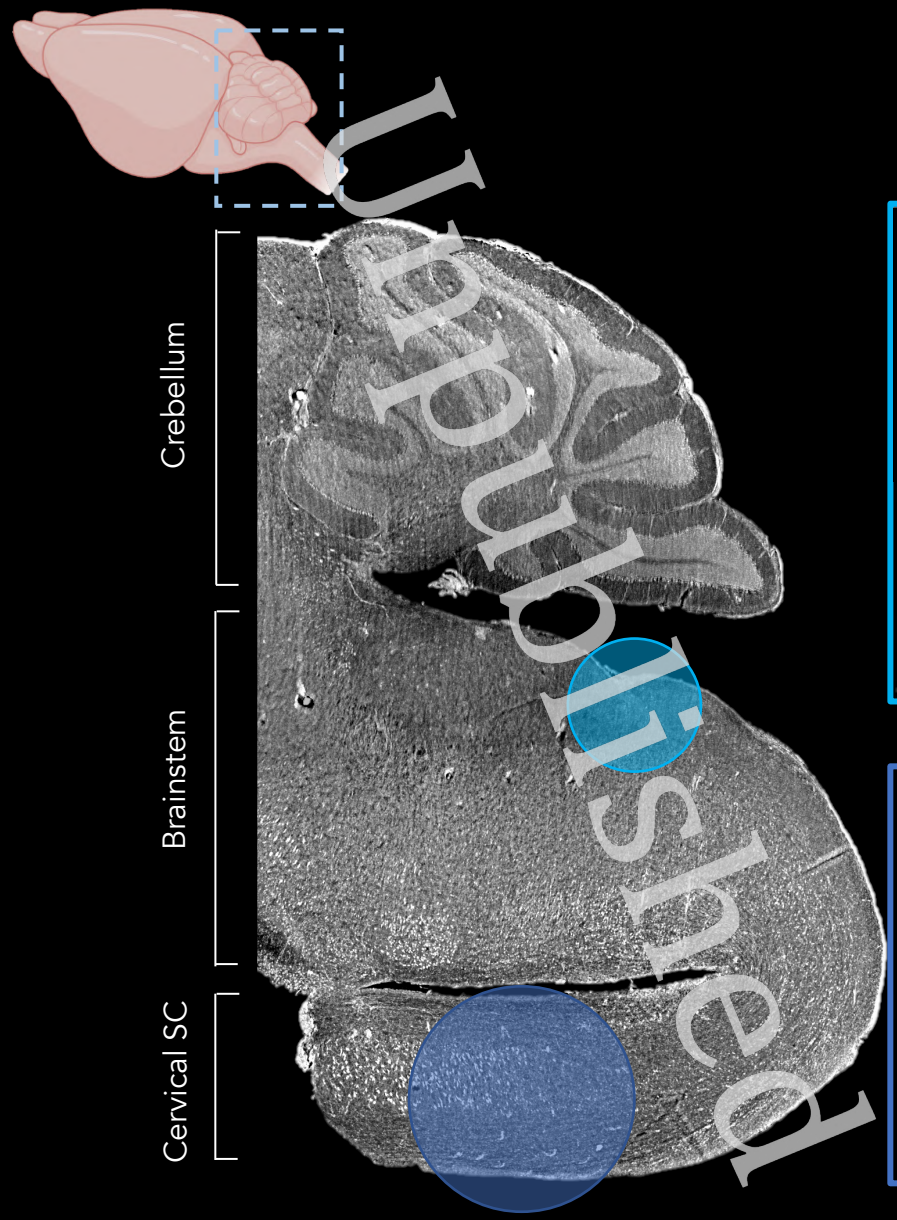
Higher resolution

Pixel size : 0.6 micron

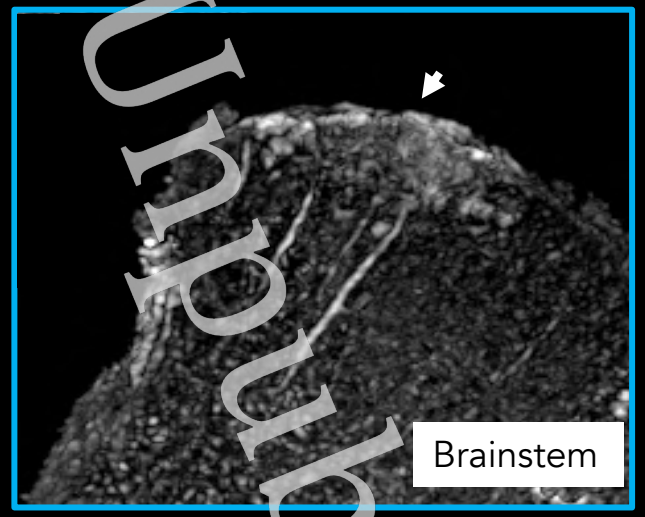


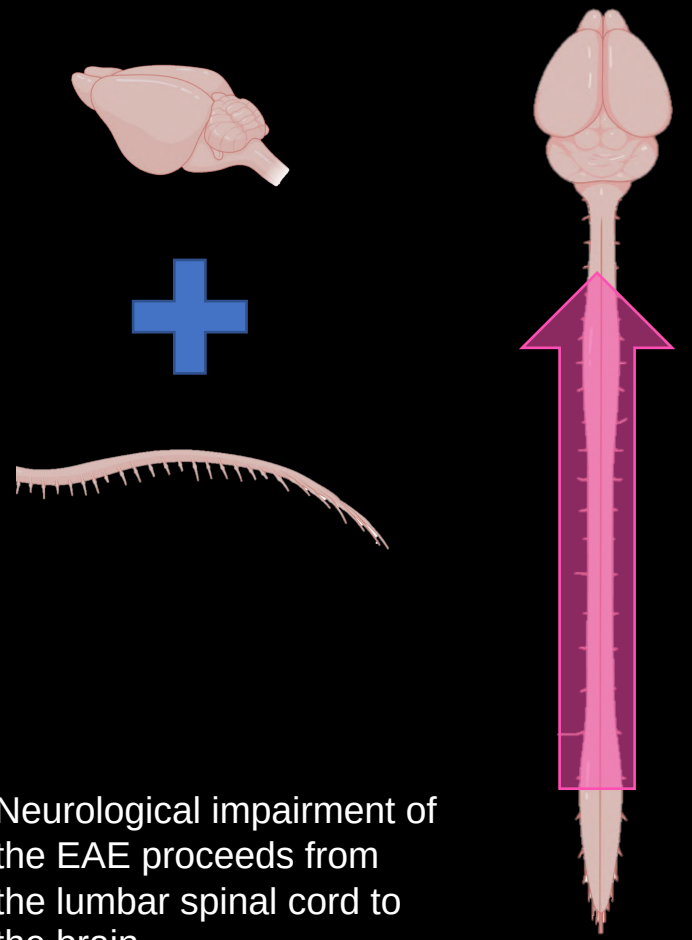
Palermo et al, Front. Neurosci. (2021)

MS Model: EAE – Blood barrier dysfunction



EAE – onset





- Neurological impairment of the EAE proceeds from the lumbar spinal cord to the brain

Testing new therapeutic strategies

TOMA Lab TOmography for Medical Applications

Alzheimer's Disease model

Multiple Sclerosis model

Testing new therapeutic strategies

TOMA Lab TOmography for Medical Applications

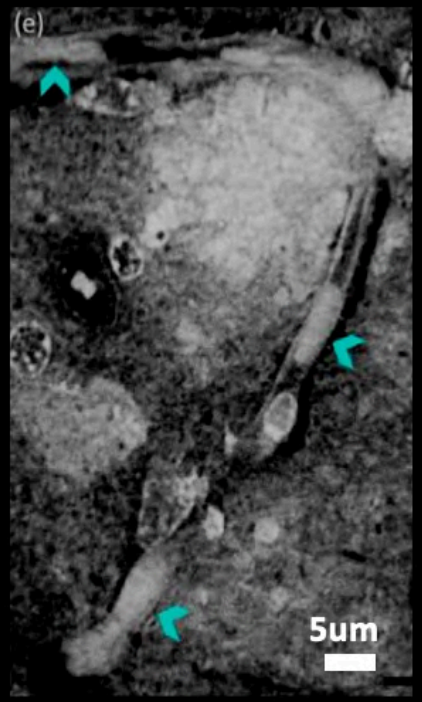
TecnoMedPuglia

Alzheimer's Disease model

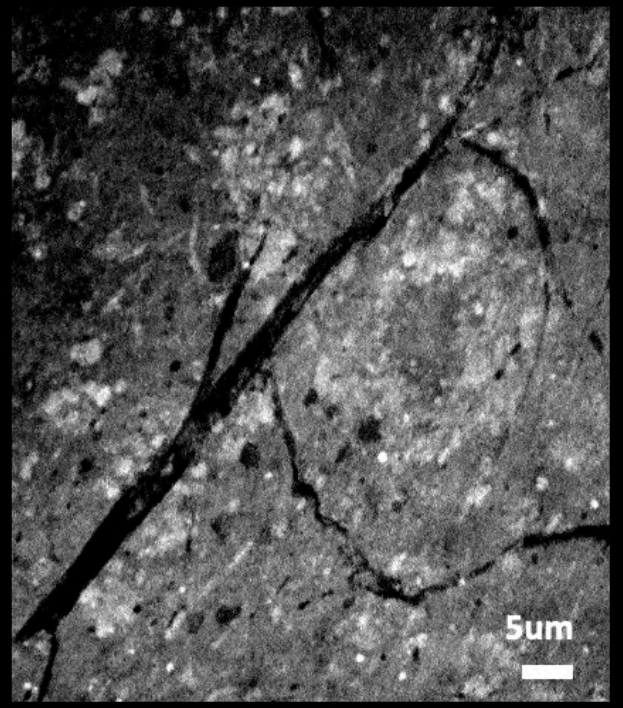
- Mesenchimal Stem Cell treatment

Multiple Sclerosis model

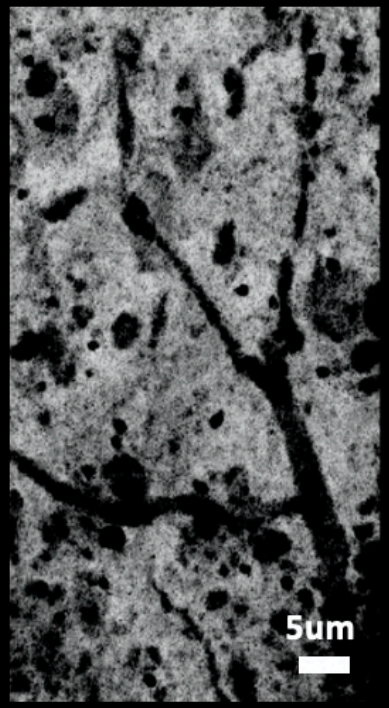
Disease-affected mouse



Disease-affected mouse + MSC-CS



Healthy mouse



Palermo et al, Front. Neurosci. (2021)

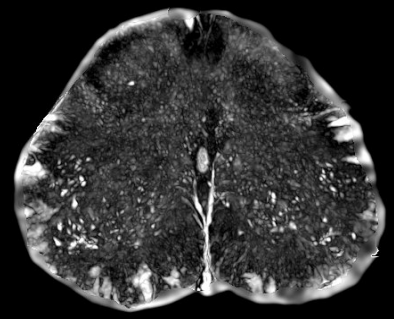
Testing new therapeutic strategies

Alzheimer's Disease model

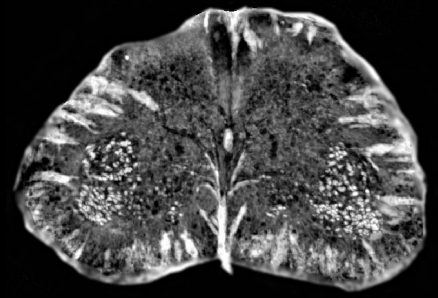
Multiple Sclerosis model

- Mesenchimal Stem Cell treatment
- Protective action of MSC on neuronal and vascular network

Neuronal network

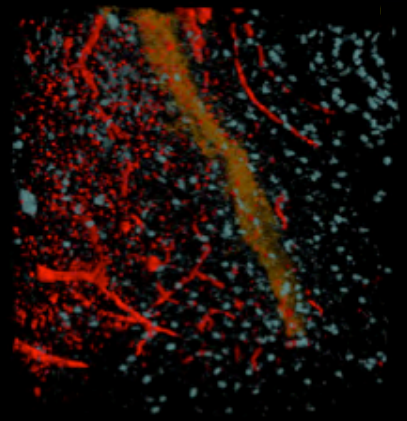


EAE mouse

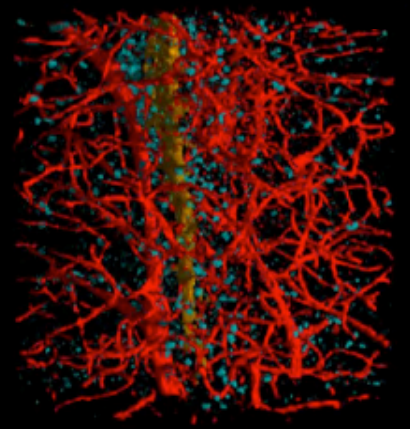


EAE + MSC

Vascular network



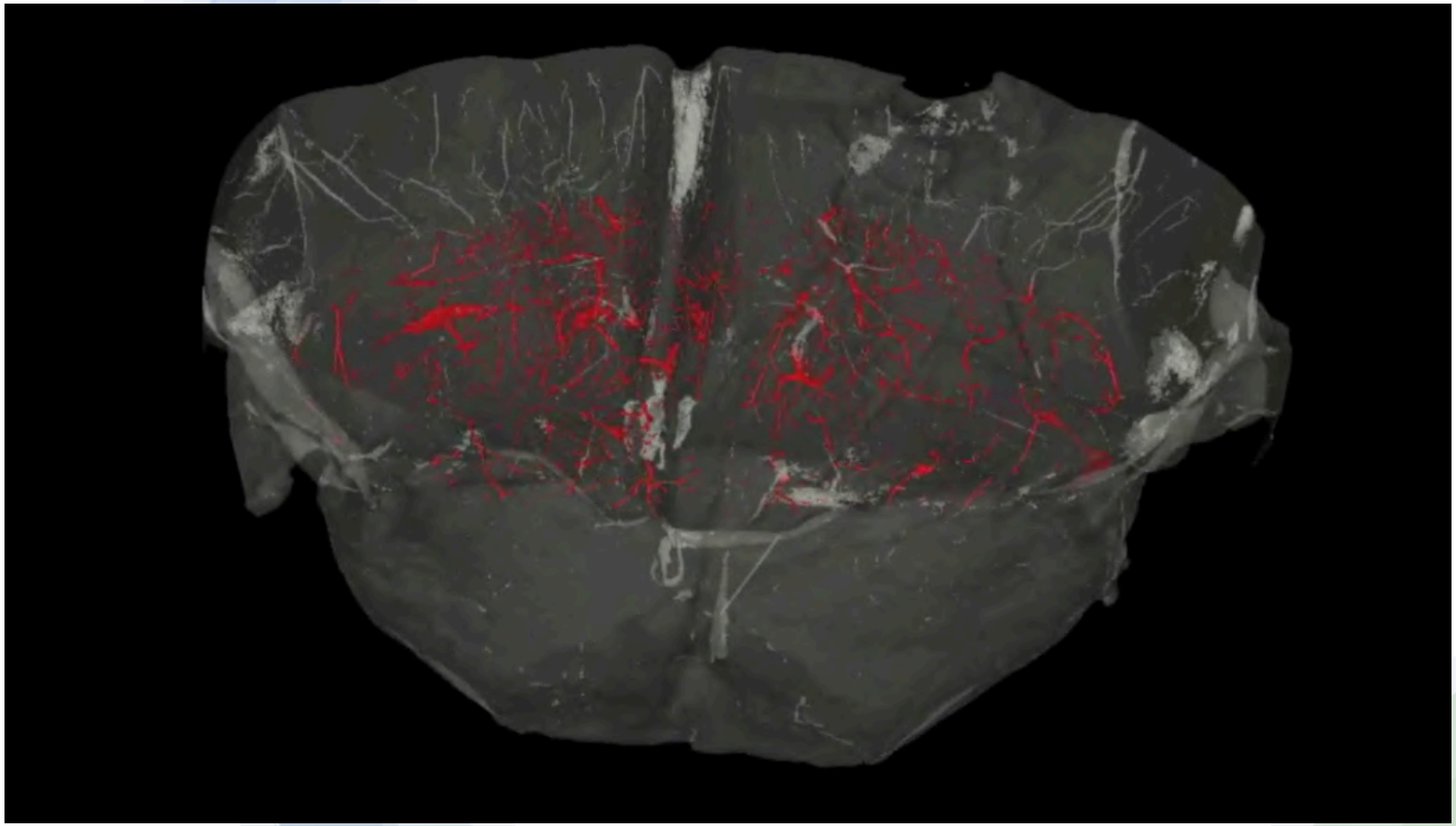
EAE mouse



EAE + MSC

Cedola et al, Sci.Rep.(2017)

Conclusions



- ✓ Histology-like resolution
- ✓ 3D information on large volumes
- ✓ Multiscale
- ✓ Simultaneous visualization of different structures
- ✓ Enabling qualitative AND quantitative analysis

CNR NANOTEC
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Thank you for your attention!

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