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Valérie Labas, Ana-Paula Teixeira-Gomes, Frédéric Andersson, Sébastien Ménigot, Martine Batailler, Hans Adriaensen, Martine Migaud, Elodie Chaillou

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2.5 D representation combining *in vivo* 3D MRI and *ex vivo* 2D MSI approaches to study the lipid distribution in the whole sheep brain

Labas V.¹⁻³ and Teixeira-Gomes AP.¹⁻⁴, Andersson F.⁵, Ménigot S.⁵, Batailler M.³, Adriaensen H.²⁻³, Migaud M.³, Chaillou E.³

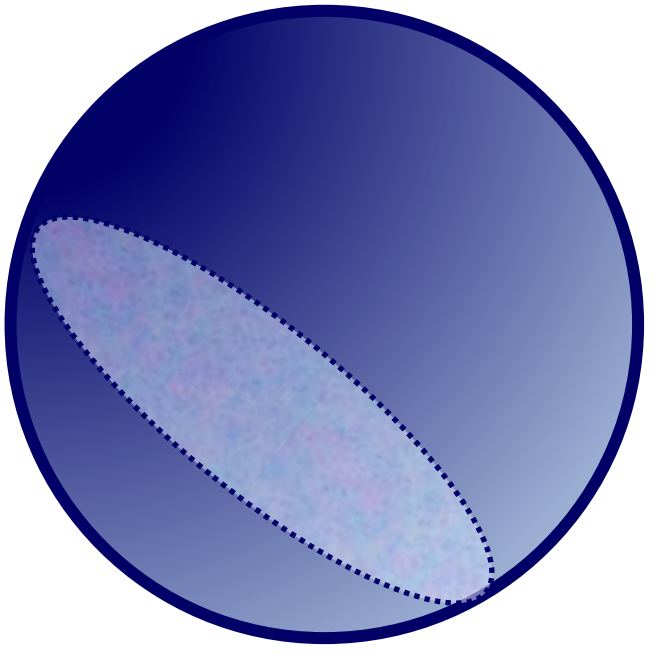
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- 3- INRA, UMR INRA 85 Physiologie de la Reproduction et des Comportements, CNRS 7247, Université François Rabelais, IFCE, F-37380 Nouzilly, France
- 4- INRA, UMR INRA 1282 Infectiologie et Santé Publique, Université François Rabelais, F-37380 Nouzilly, France.
- 5- INSERM, U930 Imagerie et Cerveau, Université François Rabelais de Tours, F-37000 Tours, France



INTRODUCTION

Mass Spectrometry Imaging (MSI) provides easily high spatially resolved masses allowing the characterization of endogenous lipids. These latter constitute about 70% of the composition of the white matter of the brain and are implicated in developmental and/or cognitive troubles. In order to examine the molecular distribution of lipids in whole sheep brain (gyrencephalic brain similar to human brain), we combined *in vivo* and *ex vivo* images, obtained in the same animals, using Magnetic Resonance Imaging (MRI) and MSI, respectively. In order to view the topology of the molecular species within the organ, we propose the construction of a 2.5 D representation where a single section imaged with 2D MSI is localized within the tissue volume obtained by 3D MRI. This study presents the steps required for multimodal imaging and modalities to combine *in* and *ex vivo* images with a good spatial co-registration.

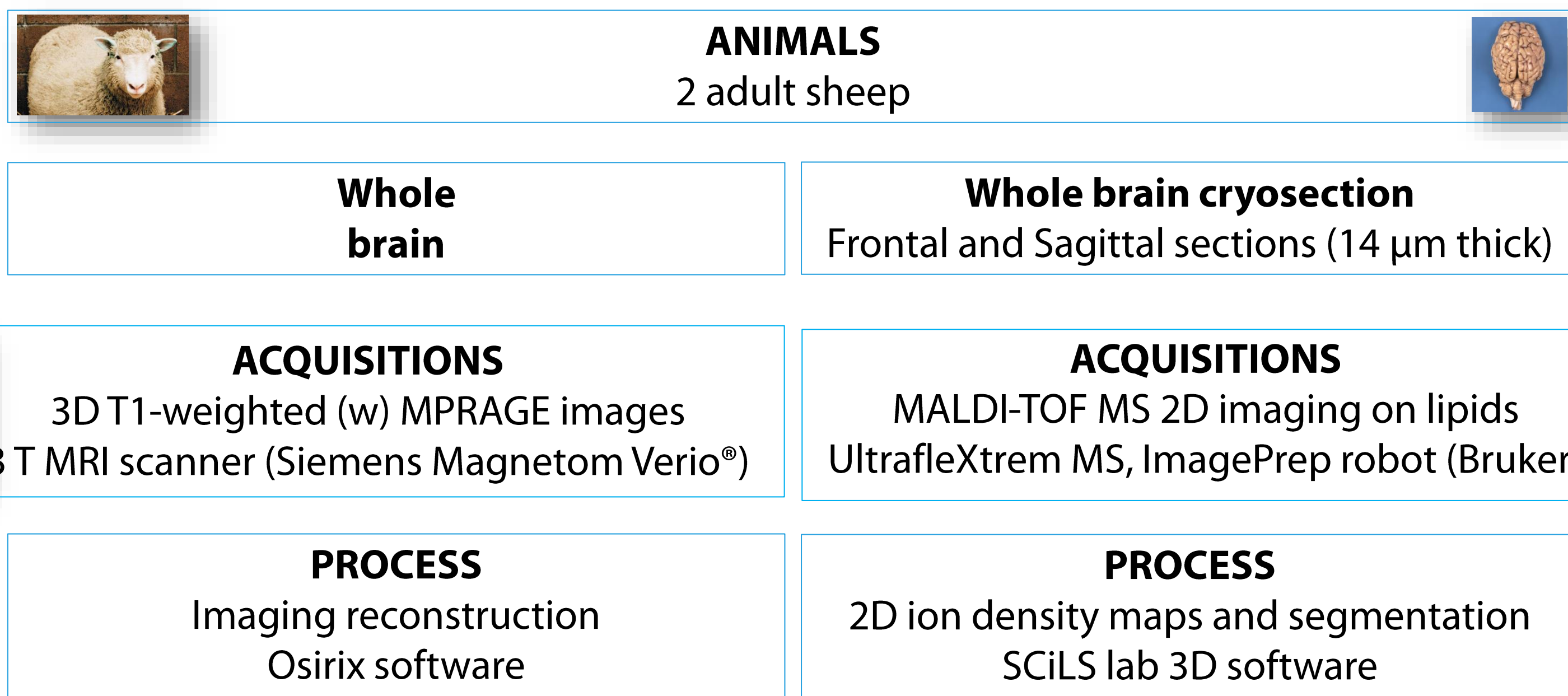
2.5 D representation



PROCEEDINGS AND RESULTS

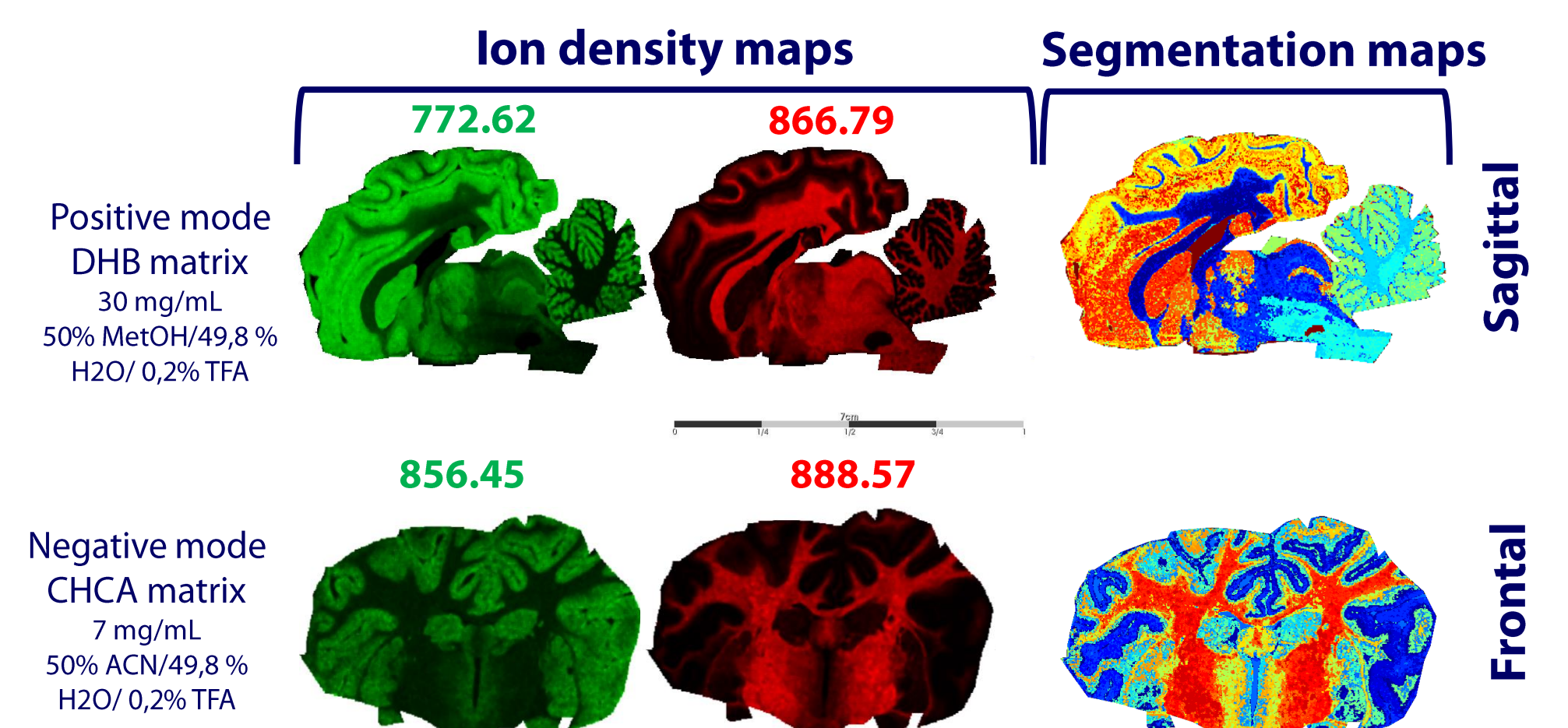
In vivo MRI

Ex vivo MSI



MOLECULAR HISTOLOGY

Lipidomic MSI analyses were performed in the 200–1200 m/z range with a spatial resolution set at 125 µm and treated with SCiLS Lab (TIC normalization, medium denoising), to generate 2D ion density maps (selected with ± 0,1 Da) and segmentation maps (bisecting k-Means).

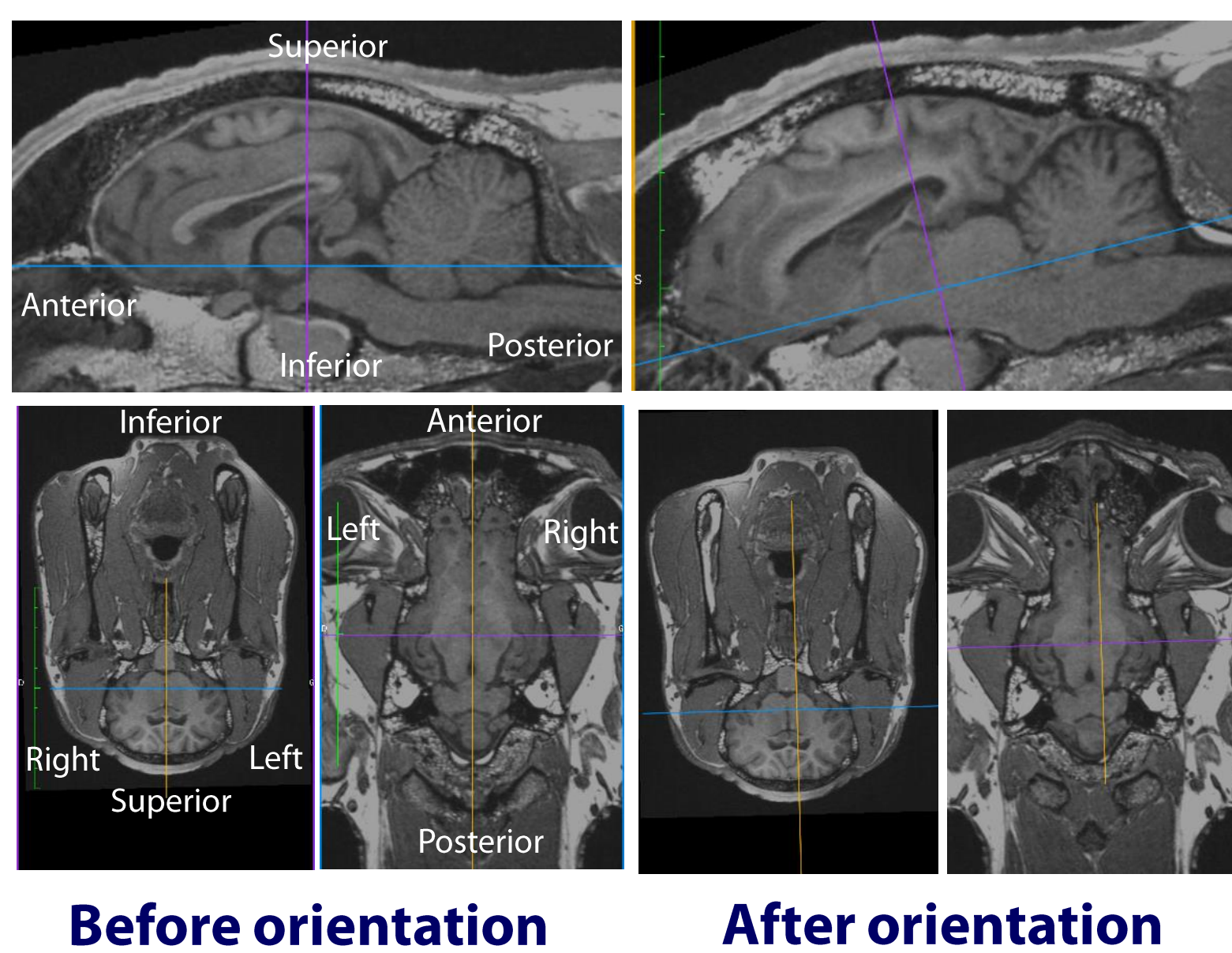


From ion density or segmentation maps, frontal and sagittal sections showed a clear difference in lipid distribution, especially between grey and white matter, to the point where the cerebral cortex presents circumvolutions. Furthermore, in complement of classical cresyl violet staining, molecular histology allowed to visualize more anatomical details within the tissues.

Multimodal and correlative *in/ex vivo* imaging

3D REORIENTATION

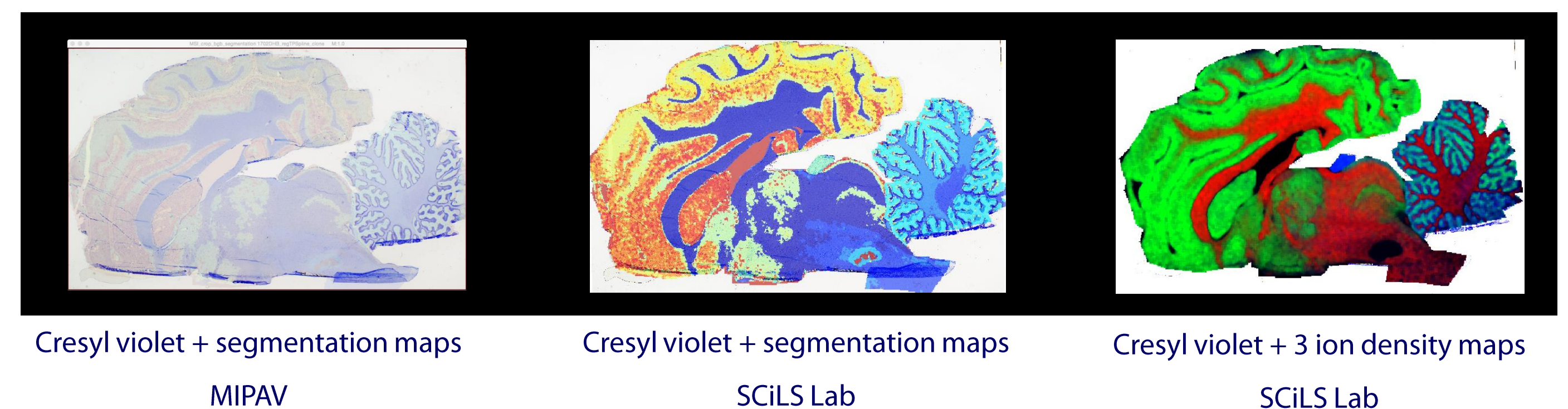
The aim of this step is to find the cutting planes corresponding to the 2D histological/MSI sections within the 3D volume of the whole brain. Here, we visualize the *axial*, *frontal* and *sagittal* 3D T1w MR images before and after manual 3D MRI reorientation using the anatomical information. We have easily reoriented the 3D volume in order to obtain an *in vivo* plan corresponding to the *ex vivo* sagittal sections which were analyzed by MSI. However, for *ex vivo* frontal sections, we did not find the right MRI plan since each step of tissue preparation (collection, dissection, freezing, cutting) induced too strong deformations.



MULTIMODAL EX VIVO IMAGING ALIGNMENT

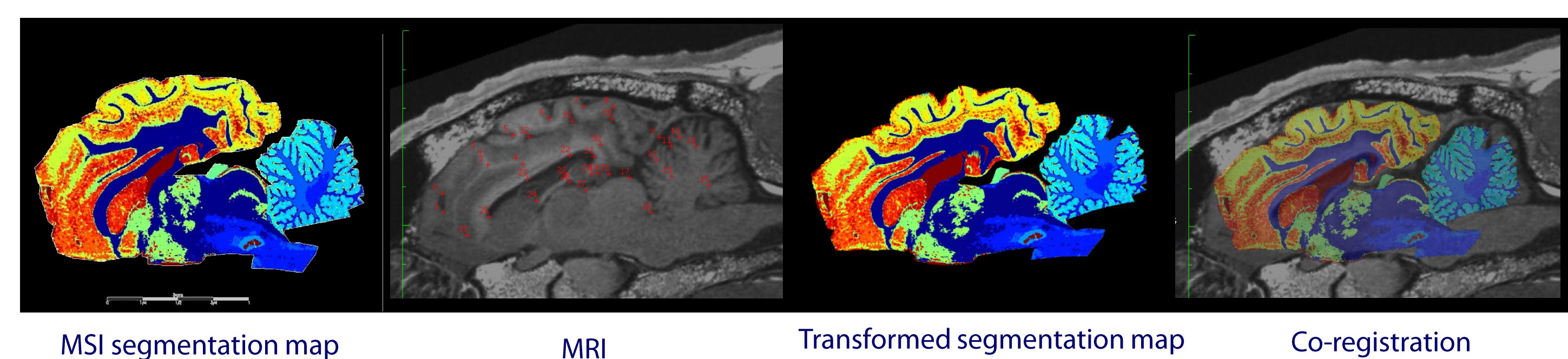
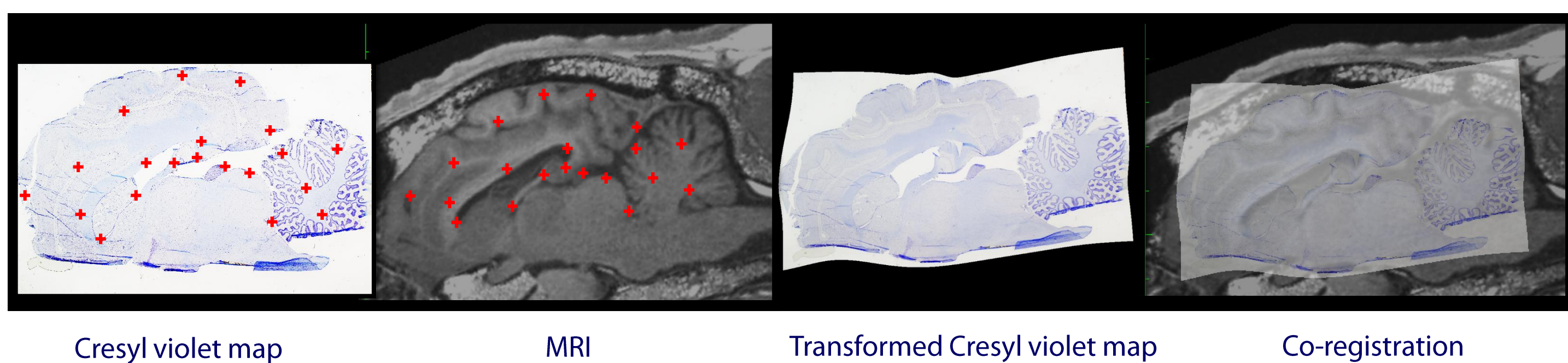
Cresyl violet map and MSI segmentation map were easily overlaid and co-registered (rigid transformation) using MIPAV software (Medical Image Processing and Visualization, National Institutes of Health, Bethesda, MD) and SCiLS lab software (SCiLS, germany).

In this context, SCiLS software is a tool of choice to visualize histological scans with multiple overlaid cartographies (772.62, 866.79, 872.71 m/z) in order to discover new histologic area using molecular profiles.



MULTIMODAL IN AND EX VIVO IMAGING CO-REGISTRATION

Due to the deformations induced by cutting and freezing of the organ, often encountered for large organs such as the brain, the alignment between *in vivo* (MRI) and *ex vivo* (MSI) images needed non-linear elastic co-registration. This transformation was carried out using semi-automated landmark-based method (non-linear coregistration, thin-plate-splines) available on the MIPAV software. Red crosses indicates landmarks that were chosen according to specific anatomical locations which were easily observed in all the imaging modalities : *in vivo* MRI and *ex vivo* cresyl violet or MSI segmentation map.

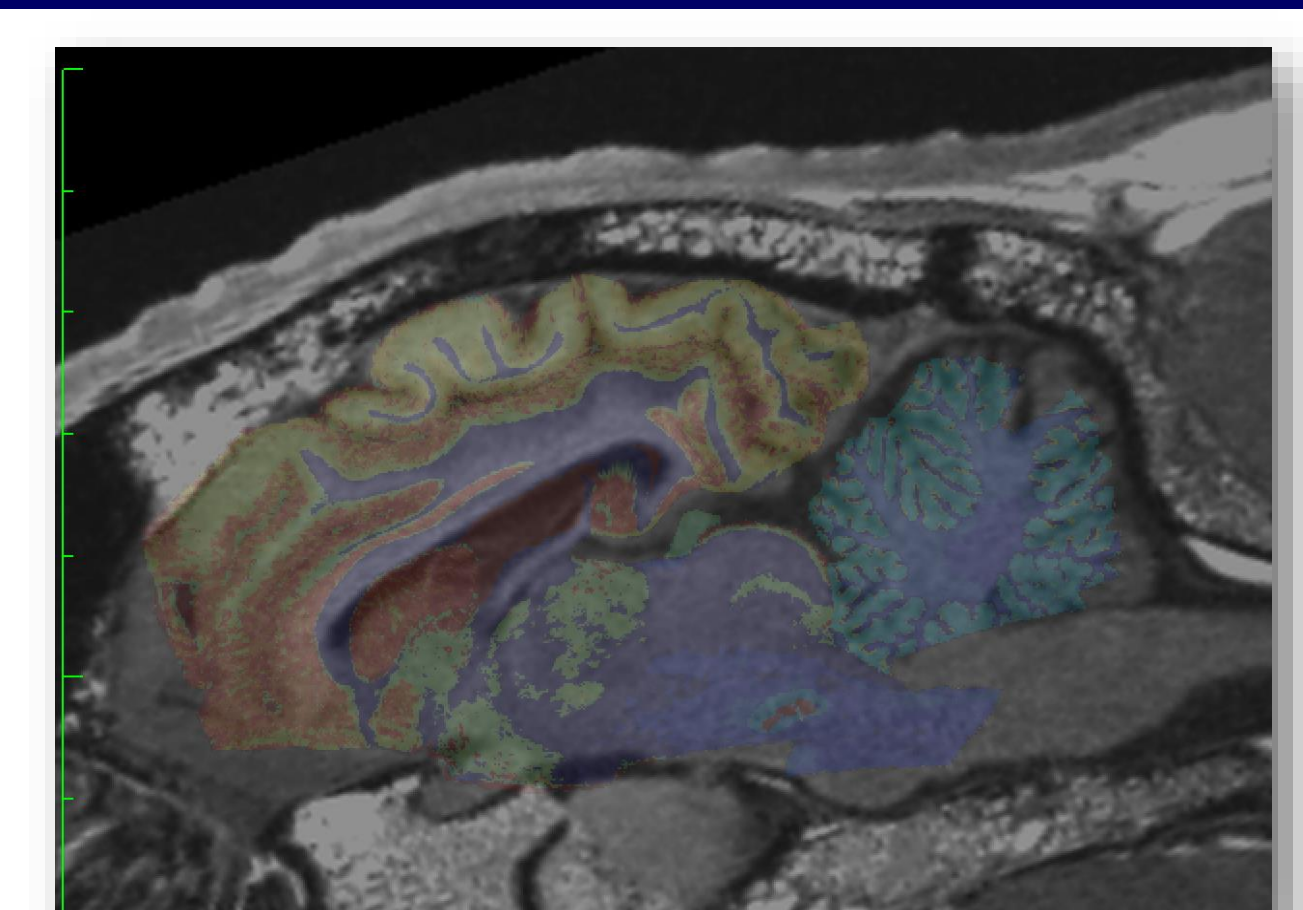
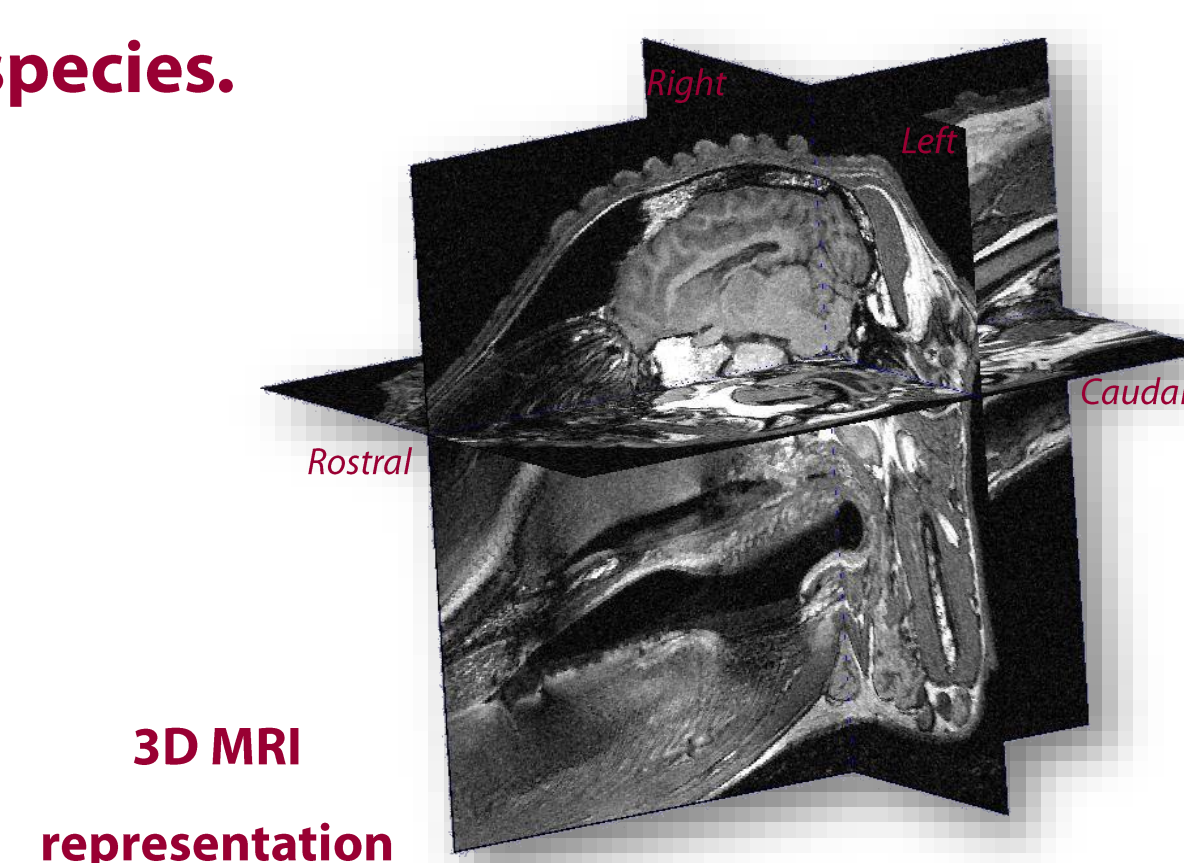


CONCLUSION

We presented a 2.5 D imaging pipeline for tissue analysis integrating three imaging modalities : (1) 3D *in vivo* Magnetic Resonance Imaging (MRI), (2) 2D *ex vivo* Cresyl violet scanning, (3) 2D *ex vivo* MALDI-TOF Mass Spectrometry Imaging (MSI) with lipidomic analysis. As a proof-of-principle-experiment, we applied the pipeline to the whole sheep brain. Here, the 2.5 D representation combining MRI and MSI (for the sagittal section) provided finer structural details on a whole large and circumvoluted brain and on the specific distribution of many lipid molecular species. We demonstrated that the 2.5 D representation is a tool of choice for exploring molecular distributions, with a perfect topology, throughout an entire complex organ such as the brain. Nowadays, the reported results may serve as a starting point for further experiments associating anatomic 3D imaging (MRI, Computerized Tomography (CT) scan) and structural 2D MSI to follow biological dynamic processes (tumors) in brain or in other organs.

2.5 D REPRESENTATION COMBINING MRI/MSI

Combined MRI and MSI is a unique approach to describe the precise distribution of each lipid species.



3D *in vivo* MRI images co-registered with 2D *ex vivo* segmentation map obtained by lipidomic MSI

FUNDINGS

