



HAL
open science

Effect of cerebral protein aggregates on tissue mechanical properties measured by Magnetic Resonance Elastography

Mathilde Bigot, Fabien Chauveau, Celine Mandon, Olivier Beuf, Simon Lambert

► To cite this version:

Mathilde Bigot, Fabien Chauveau, Celine Mandon, Olivier Beuf, Simon Lambert. Effect of cerebral protein aggregates on tissue mechanical properties measured by Magnetic Resonance Elastography. Journée Santé@labex, Dec 2016, Lyon, France. hal-01881078

HAL Id: hal-01881078

<https://hal.science/hal-01881078>

Submitted on 25 Sep 2018

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Effect of cerebral protein aggregates on tissue mechanical properties measured by Magnetic Resonance Elastography

Mathilde Bigot¹, Fabien Chauveau², Céline Mandon³, Olivier Beuf¹, Simon Lambert¹,

¹Univ. Lyon, INSA-Lyon, Université Claude Bernard Lyon 1, UJM-Saint Etienne, CNRS, Inserm, CREATIS UMR 5220, U1206, F-69000, LYON, France; ²Lyon Neuroscience Research Center, Centre National de la Recherche Scientifique UMR5292, Institut National de la Santé et de la Recherche Médicale, Univ. Lyon 1, Lyon, France ; ³Univ. Lyon1, CNRS, INSA, CPE-Lyon, ICBMS, UMR 5246, 43, Boulevard du 11 Novembre 1918, 69622 Villeurbanne Cedex, France

Contact : Mathilde.Bigot@creatis.insa-lyon.fr

Introduction

During the first stages of the development of neurodegenerative diseases, some endogenous proteins, usually in a monomeric shape, agglomerate to form beta-sheet stacks called fibrils [1]. The protein involved differs depending on the disease: α -synuclein in the case of Parkinson's disease, β -amyloid for Alzheimer's disease and Tau protein for frontotemporal dementia. Qualitative detection of β -amyloid and Tau fibrils is currently possible by Positron Emission Tomography (PET) using dedicated radiotracers [2]. In MRI, direct detection with contrast agents shows poor sensitivity, and the spatial resolution of structural MRI is not sufficient to discern micrometric scaled agglomerates. Thus, only a late diagnosis can be made, based on a loss in brain volume [3,4]. A non-irradiating, quantitative method to detect any type of aggregate through one unique exam would allow an improved efficiency of the diagnosis procedure. In the case of preclinical trials, being able to follow the evolution of the disease with imaging could be helpful for the development of new drugs.

We propose to develop an *in vivo* imaging technique based on the link between the microstructure of the aggregates and the macroscopic observables collected with an MRI experiment.

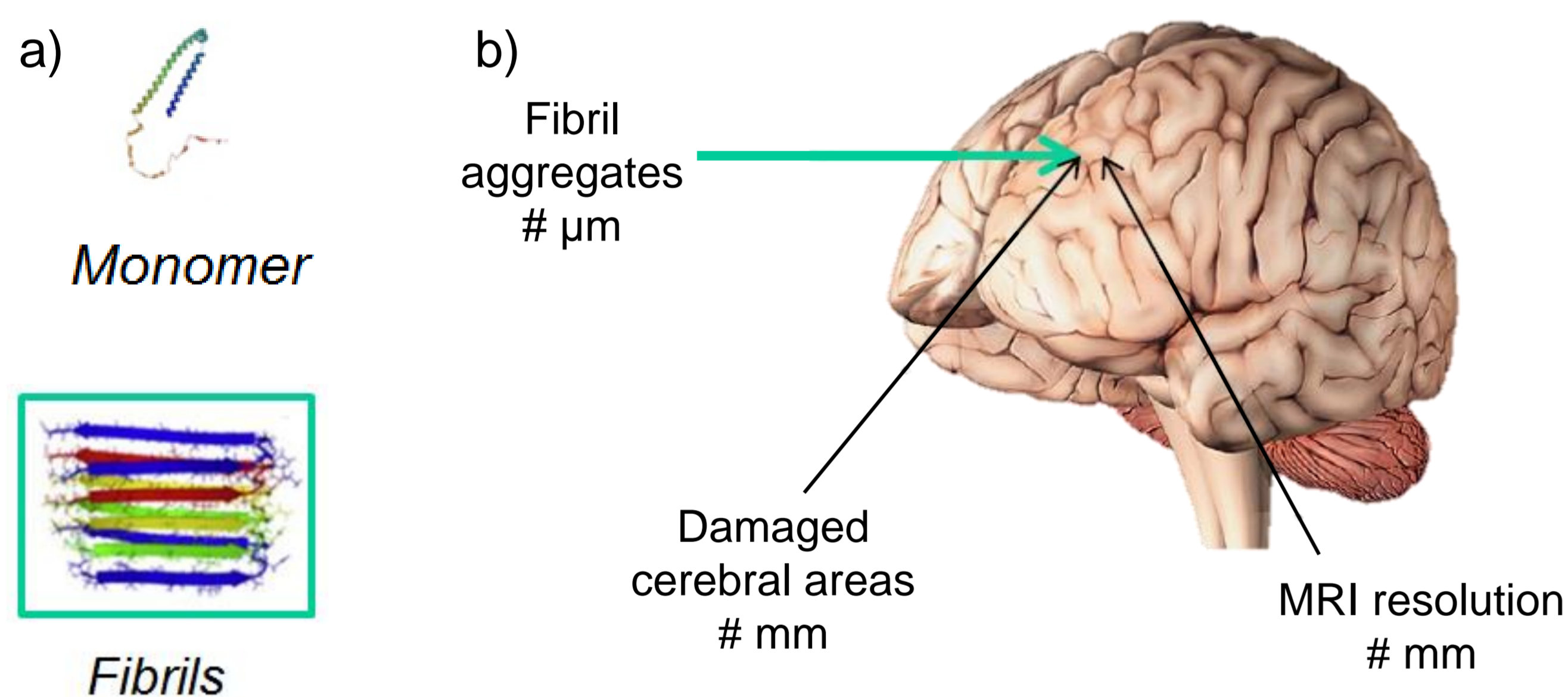


Figure 1. a) Endogenous proteins in their monomeric, healthy shape and grouped to form beta sheet agglomerates (fibrils); b) Presentation of the detection problem with MRI in terms of dimension for the fibril aggregates

Methods

Magnetic Resonance Elastography (MRE) consists in the *in situ* MR imaging of shear waves propagating within tissue. The registered wave is induced by an external driver synchronized with the MRE sequence. Images are acquired at different steps of the wave propagation, and after appropriate reconstruction, different mechanical such as wave speed, attenuation or shear modulus can be obtained.

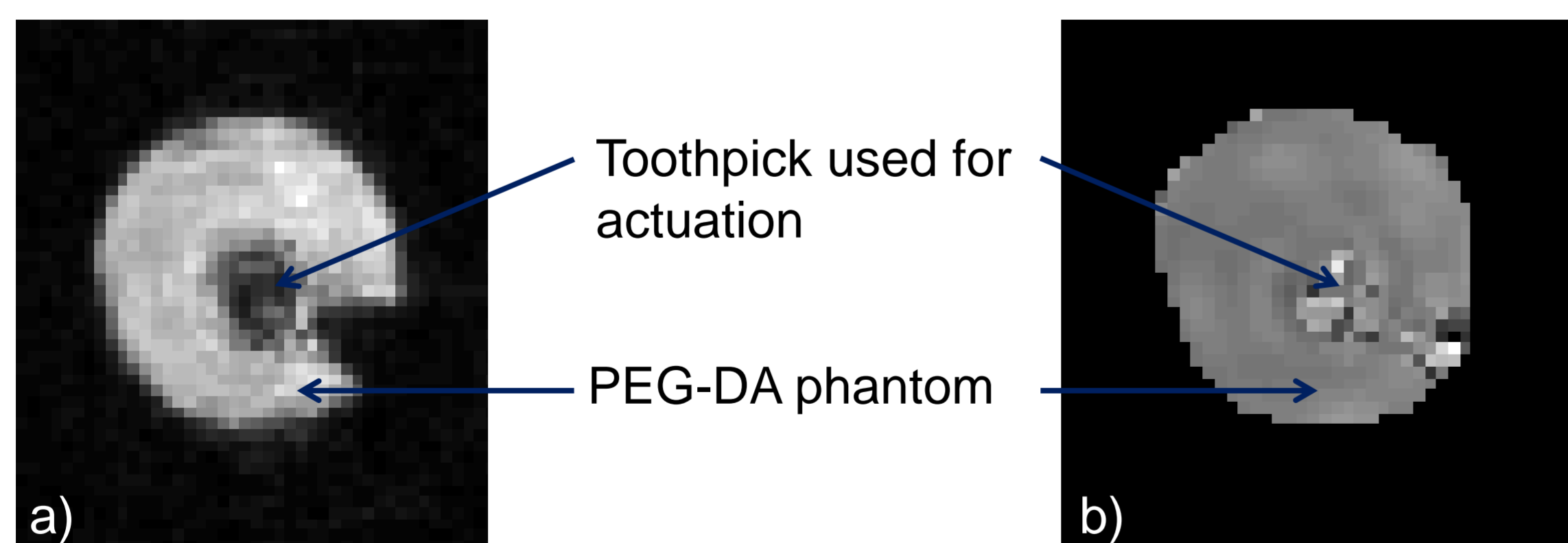


Figure 2. a) Magnitude and b) phase image of a 3D-printed phantom (PEG-DA hydrogel) and a toothpick (wood) used to propagate shear waves within the phantom. The wave propagation is visible around the toothpick. After analysis, the elasticity found for this sample was 2 kPa

In previous works it has been shown that the frequency dependence of these mechanical parameters can reveal the underlying microarchitecture at the macroscopic scale [5,6]. The behavior of the wave speed inside the material is linked to the multiple scattering undergone by the wave: as frequency (ν) increases, wave speed (c_s) increases, following a power-law of the type $c_s = \nu^y$, where y reflects the fractal aspect of the medium.

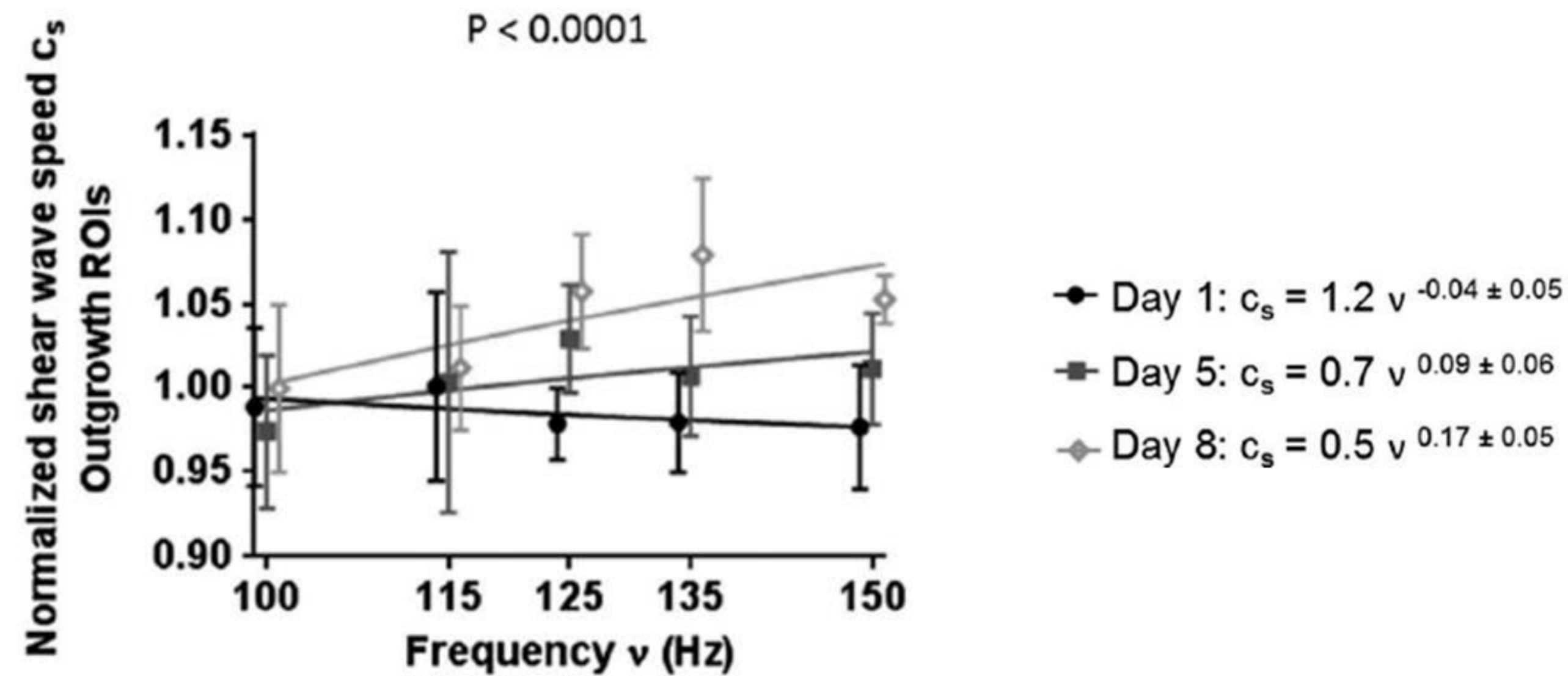


Figure 3. Evolution of the shear wave speed in a phantom where micro blood vessels are grown, the power factor of the law y increases as the vessels grow [6]

We believe that the fibrillary structure of the protein aggregates could leave its fingerprint in the macroscopic mechanical properties as well. Dedicated experimental developments are mandatory to obtain an adequate image spatial resolution compared to characteristic length of the experiment such as the wavelength.

Development of 3D-printed phantoms with fibril inclusions is ongoing. Those phantoms are, in the meantime, characterized with MRE. After the study of the effect of the fibrils on the mechanical properties of a homogeneous media, *ex vivo* and *in vivo* studies on mice bearing a focal injection of fibrils are scheduled. The main goal is to determine if the "micro/macro" link observed in phantoms persists *in vivo*, where the environment is more complex as it contains other sources of wave scattering than the fibrils.

Finally, a comparison of our results with PET images of the mice will be made to evaluate the MRE technique as a diagnosis tool of neurodegenerative diseases.

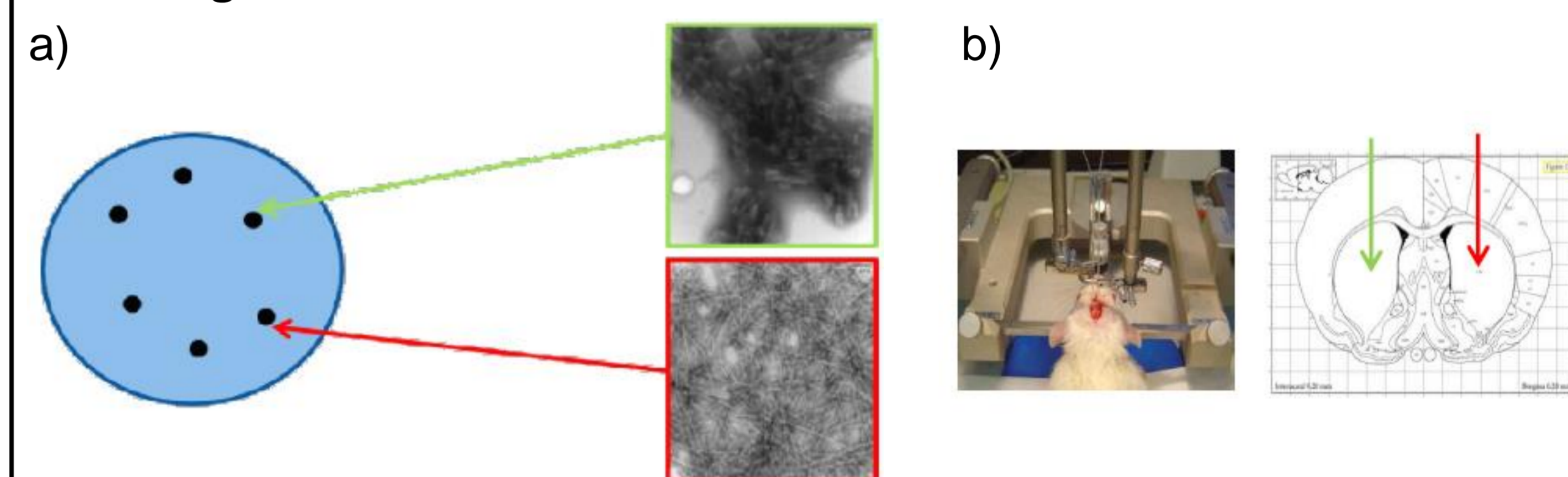


Figure 4. a) Schema of an agarose phantom containing inclusions of two types of fibrils; b) Inclusion of the same fibril aggregates in a mouse brain, *ex vivo*

Conclusion

Origin of contrast mechanisms in MRE are poorly understood [7]. This experimental approach will allow identifying the effect of a specific structure on the mechanical properties. By this approach we aim at disentangling the signal coming from the aggregation of proteins, which is the hallmark of neurodegenerative diseases from other structures.

References: (1) Verdurand M, et al. Differential effects of amyloid-beta 1-40 and 1-42 peptides on 5-HT1A serotonin receptors in rat brain. *Neurobiol Aging*. 2016 Apr;40:11-21. (2) Levigoureux E, et al. Binding of the PET radiotracer [¹⁸F]BF227 does not reflect the presence of alpha-synuclein aggregates in transgenic mice. *Curr Alzheimer Res*. 2014;11(10):955-60. (3) D. Martel, et al. Localized 2D COSY sequences: Method and experimental evaluation for a whole metabolite quantification approach. *J Magn Reson*. 2015 Nov;260:98-108. (4) Wadghiri YZ, et al. Detection of Amyloid Plaques Targeted by Bifunctional USPIO in Alzheimer's Disease Transgenic Mice Using Magnetic Resonance Microimaging. *PLoS ONE*. 2013;8(2): e57097 (5) Lambert SA, et al. Bridging Three Orders of Magnitude: Multiple Scattered Waves Sense Fractal Microscopic Structures via Dispersion. *Phys Rev Lett*. 2015 Aug 28;115(9):094301. (6) Jugé L, et al. Microvasculature alters the dispersion properties of shear waves – a multi-frequency MR elastography study. *NMR Biomed*. 2015;28(12):1763-1771. (7) Murphy Mc, et al. Regional brain stiffness changes across the Alzheimer's disease spectrum. *Neuroimage Clin*. 2015 Dec 19;10:283-90.

Acknowledgement: This work was supported by the LABEX PRIMES (ANR-11-LABX-0063) of Université de Lyon, within the program "Investissements d'Avenir" (ANR-11-IDEX-0007) operated by the French National Research Agency (ANR).

