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## Characterization of fibril aggregates in *ex vivo* rat brain with multifrequency MR Elastography – Preliminary results

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#### **Synopsis**

Fibrils are biomarkers for early stages of dementia. In this work,  $\alpha$ -synuclein fibrils were injected in rat striatum. Brains were imaged *ex-vivo* using multi-frequency MR Elastography. Estimation of the real part  $k_r$  of the complex wave number was made for each studied frequency in ROIs surrounding the inclusion, a contralateral control injection and the whole brain. Exponent of the frequency power law was derived from  $k_r$  maps acquired at different frequencies. No difference was observed between  $k_r$  values for the different ROIs, but the exponent was more important at the fibrils location, potentially indicating that multi-frequency MRE can detect fibrils.

#### Introduction

Accurate and early diagnosis of dementia represents a major challenge in an ageing society. Pathological hallmarks of these diseases are fibrils, formed by the aggregation of endogenous proteins misshaped to  $\beta$ -sheet conformation. Accurate localization of these fibrils could improve diagnosis given that diverse dementias protein accumulation starts in different locations.

We suggest using Multi-frequency Magnetic Resonance Elastography (MRE) to characterize those aggregates. MRE has already been used to characterize the spatial distribution of sub-voxel obstacles<sup>1,2</sup>. Other groups have found stiffness changes in transgenic mice<sup>3–5</sup>; however the substrate of these changes is not well characterized: effects of fibrils, neuronal loss, vascularization or inflammation are not discriminated. The purpose of this work is to characterize the local changes induced by injected fibrils on the brain mechanical properties.

#### **Methods**

Four Sprague Dawley rats were injected with  $10\mu$ L of  $\alpha$ -synuclein fibrils at  $200\mu$ M in the striatum area. The opposite hemisphere received a control injection of Phosphate Buffered Saline (PBS). Animals were sacrificed 2 to 4 weeks after injections. The brains were immediately embedded in 1% agarose gel (SIGMAF8630) with artificial cerebrospinal fluid<sup>6</sup>. The brain was then imaged on a Bruker 4.7T scanner with a home-designed volume coil dedicated to small sample MRE. RARE sequence was used as anatomical image. MRE measurements were performed at 800, 900, 1000 and 1200Hz. 1000Hz acquisition was done first and repeated before the last frequency was acquired, to confirm that brain

mechanical properties were not degraded during acquisition time (90 minutes). MRE sequence was derived from RARE sequence<sup>7</sup>. Motion was encoded in the three directions with the following parameters: 8 snapshot of the waves, 7 1-mm-thick slices, FOV of  $2.5 \times 2.5 \text{ cm}^2$ , in plane matrix of  $64 \times 64$ , leading to voxel size of  $0.391 \times 0.391 \times 1 \text{ mm}^3$ .

Processing involves a 3D direct curl inversion<sup>8</sup>. Reconstruction was performed with the application of a Gaussian filter ( $\sigma = 0.39 \times 0.39 \times 1 \text{ mm}^3$ , kernel = 3x3x3 voxels) on the unwrapped phase images. Real part k<sub>r</sub> (inversely proportional to wave speed) of the complex wave number was estimated in manually defined ROIs corresponding to the whole brain, the  $\alpha$ -synuclein injection localization and the contralateral injection. Those ROIs are reported on anatomical and k<sub>r</sub> reconstructed images (Fig.1). The exponent y of the frequency power law demonstrated by Lambert et al.<sup>2</sup> was derived from k<sub>r</sub> maps reconstructed at different frequencies for each ROI. Allometric fitting ( $a^*frequency^y$ ) was realized using Origin software (OriginPro 2016 64-bit, http://www.OriginLab.com). Paired sample Wilcoxon tests were performed to compare the dispersion in the ROIs.

#### **Results**

Mechanical parameters of the brain remained stable during whole imaging duration: for the two 1000Hz acquisitions, reconstructed  $k_r$  varied in average by 9 ± 6% for the whole brain, 13 ± 9% for the fibril injection and 4 ± 3% for the PBS injection. For the whole brain ROI, this variation is inferior to the standard deviations of each  $k_r$  measured at 1000 Hz.

No significant difference was found between  $k_r$  estimated from the three ROIs whatever the frequency investigated (Fig.2). Interestingly, y was superior in average in the  $\alpha$ -synuclein ROI (0.80 ± 0.09) compared to both the whole brain (0.65 ± 0.07) and the contralateral PBS injection (0.58 ± 0.04) (Fig.3). In two cases, y in the injection ROI was close to y in the whole brain. For two rats, y in PBS seemed close to y in the whole brain, but less for two others. Wilcoxon tests did not qualify this augmentation as significant.

#### **Discussion and conclusions**

Single-frequency MRE for fibril aggregates detection does not appear relevant as no change in  $k_r$  was detected whatever the frequency investigated. These results support recent findings in Alzheimer's transgenic animals suggesting that fibrils alone are not responsible for viscoelasticity changes at 1000Hz<sup>3</sup>.

This work shows for the first time that  $\alpha$ -synuclein fibrils, injected in an important quantity without over toxicity and inflammation at the sub-acute stage, can hardly be detected using multi-frequency MRE. An increase of the parameter y is observed at the fibril location. This parameter could be sensitive to microarchitecture alteration, as indicated by Schregel et al.<sup>9</sup>. A decrease of this same parameter is observed in a contralateral PBS injection. These changes are not significant, due to the small number of imaged animals, but also to some values, very close to whole brain dispersion. These values could be explained by a wrong estimation of the injection area when placing the ROIs, which will need validation from ongoing histological analysis.

Additional acquisitions are needed to confirm these results. The sensitivity of the method to detect the presence of fibrils must be studied by decreasing the concentration of injected fibrils.

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#### References

1. Jugé L, Petiet A, Lambert SA, et al.: Microvasculature alters the dispersion properties of shear waves--a multi-frequency MR elastography study. *NMR Biomed* 2015; 28:1763–1771.

2. Lambert SA, Näsholm SP, Nordsletten D, et al.: Bridging Three Orders of Magnitude: Multiple Scattered Waves Sense Fractal Microscopic Structures via Dispersion. *Phys Rev Lett* 2015; 115:094301.

3. Majumdar S, Mishra R, Lazarov O, Klatt D: Early-stage analysis of murine models of Familial Alzheimer's disease: Preliminary results. 1<sup>st</sup> MRE Workshop Berlin, Germany; 2017:25.

4. Murphy MC, Curran GL, Glaser KJ, et al.: Magnetic resonance elastography of the brain in a mouse model of Alzheimer's disease: initial results. *Magn Reson Imaging* 2012; 30:535–539.

5. Munder T, Pfeffer A, Schreyer S, et al.: MR elastography detection of early viscoelastic response of the murine hippocampus to amyloid  $\beta$  accumulation and neuronal cell loss due to Alzheimer's disease. *J Magn Reson Imaging* 2017; 47:234–245.

6. Preparation of Artificial CSF [http://www.alzet.com/products/guide\_to\_use/cfs\_preparation.html]

7. lefebvre P, Tse Ve Koon K, Brusseau E, et al.: Comparison of viscoelastic property characterization of plastisol phantoms with magnetic resonance elastography and high-frequency rheometry. *EMBC* Orlando, United States; 2016.

8. Sinkus R, Daire J-L, Beers BEV, Vilgrain V: Elasticity reconstruction: Beyond the assumption of local homogeneity. *C R Mécanique* 2010; 338.

9. Schregel K, Wuerfel E, Garteiser P, et al.: Demyelination reduces brain parenchymal stiffness quantified in vivo by magnetic resonance elastography. *Proc Natl Acad Sci U S A* 2012; 109:6650–6655.



Figure 1: a) Central slice of anatomical RARE image of an *ex vivo* brain embedded in agarose and b) reconstructed  $k_r$  map of the same brain, derived from MRE acquisitions. On both images are represented the ROIs used to calculate  $k_r$  in the whole brain (green), an  $\alpha$ -synuclein injection (blue) and a control PBS injection (yellow). Needle traces from the injection are visible in both blue and yellow ROIs on the anatomical image.



Figure 2: Plot of the  $k_r$  derived from MRE acquisitions in the whole brain, the  $\alpha$ -synuclein inclusion and its contralateral control for one rat. Fitting of a power law of the form  $a^*$  frequency<sup>y</sup> was performed and fitting curves are also represented



Figure 3: Plot of the y derived from  $k_r$  maps for 4 rats, in ROIs englobing the whole brain, an  $\alpha$ -synuclein injection and a PBS control injection and corresponding box charts