Gadolinium-based nanoparticles diffusion within the brain tissue following ultrasound induced Blood Brain Barrier permeabilization

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Context: For drug delivery to the brain, the knowledge of molecular transport processes within brain tissues is of great interest. In this study, we present a new method for the *in vivo*characterizationof the diffusion process of Gadolinium (Gd) based MRI contrast agents (MR-CA) through the brain extracellular space, following ultrasound-induced blood-brain barrier (BBB) permeabilization. **Methods:**Four Gd chelates presenting different hydrodynamic diameters were tested: Dotarem, Gadovist, MultiHance, and a new class of paramagnetic CA (AguiX).An ultrasound induced BBB permeabilization was performed [1] in the right striatum of Sprague-Dawley rats (n=3/compound, 120g, Janvier, France), followed by intravenous MR-CA injections. The Gd chelates diffusion starting from the BBB disruption site was dynamically followed by acquiring T_1-maps [2], from which Gd concentration maps were calculated. On each concentration map, a 2D Gaussian function was fitted (see figure), and the Apparent Diffusion Coefficient (ADC) was calculated from the parameters of the fit. The free diffusion coefficient (D_{free}) of each MR-CA was also measured by repeating T_1-maps acquisitions after an injection in a tube full of 0.3% (w/w) agarose gel. The same Gaussian fit was used as for *in vivo* measurements. The tortuosity was then calculated as the square root of the ratio of ADC over D_{free}. At last, the hydrodynamic diameter of each compound was calculated using the Stokes-Einstein relation. **Results:**We found tortuosity values of 1.7, 1.6, 1.6 and 1.5 with respectively Dotarem, Gadovist, MultiHance and AGUIX, which are in good accordance with values found in literature using optical techniques [3]. The measured hydrodynamic diameters were 1.5, 1.7, 2.3 and 5.8 nm for respectively Dotarem, Gadovist, MultiHance and AguiX, in good accordance with the values obtained with Dynamic Light Scattering (1.6, 1.8, 2.3 and 3.5 nm).**Conclusion:** Using ultrasound to deliver MR-CA enables to reliably measure brain tortuosity as well as to predict spatial distribution of nanomedicines along time.

References: [1] Marty et al, JCBFM, 2012. [2] Marty et al, CMMI, 2013. [3] Nicholson et al, Trends Neurosci. 1998.

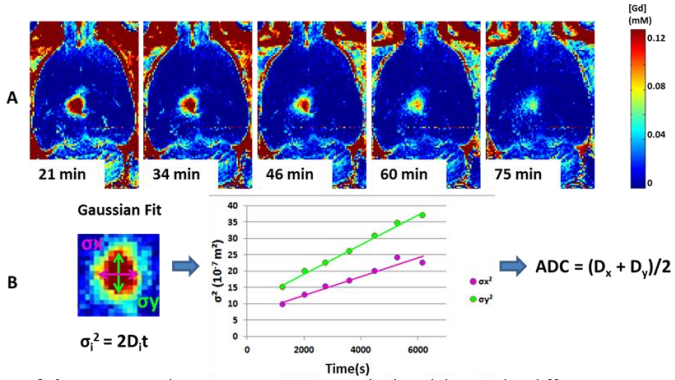

Figure: Calculation of the ADC. A. Gd concentration maps calculated during the diffusion process. B. A gaussian fit allows calculating the mean square displacement σ_i^2 along the gaussian main axes for each diffusion time. From this knowledge, the ADC is calculated as the average of the diffusion coefficients along these axes.