Measurements of diffusion at short and long time diffusion times at 17T in the rat brain in vivo and postmortem using OGSE and PGSE methods and a biexponential model

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Introduction: In biological tissues, microscopic obstacles encountered by water molecules, such as cell membranes, fibers or macromolecules make the diffusive transport non-Gaussian, so that the diffusion-weighted MRI signal behavior cannot be described using a monoexponential model [1]. Thus, MRI measurements of water diffusion coefficients might provide valuable information on those microscopic obstacles, if an adequate model can be used to link the diffusion-weighted MRI signal to those tissue features. Among the proposed approaches [2] two models have emerged as most robust and as potential candidates for clinical applications: the biexponential model [1,3] and the kurtosis model [4]. The kurtosis model provides a dimensionless measure of the diffusion profile deviation from the Gaussian distribution, but without a direct biological link. The biexponential model assumes the physical presence of fast and slow diffusion water pools with slow exchange between them, but the nature of those pools has remained elusive, as they do not necessarily coincide with the intra- and extra- cellular compartments [5]. The biexponential model can be improved by taking into account intercompartments exchange times using Karger equations [6], but those equations are valid only for very short gradient pulses. The limitation of most studies carried out on clinical/preclinical scanners is the necessity of using long diffusion times, resulting in 'averaging' effects, as molecules travel long distances across several cells or domains. The Oscillating Gradient Spin-Echo (OGSE) approach allows very short diffusion times to be reached by keeping diffusion distances short [7,8]. In this work we compare OGSE with the standard Pulsed Gradient Spin-Echo (PGSE) method in normal and post-mortem rat brains in order to study the dependence of the diffusion parameters on the diffusion time in the biexponential model.

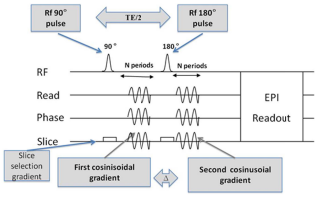

Fig. 1: OGSE cosinusoidal apodised sequence

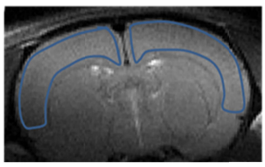

Fig. 2: T2w coronal slice (b=0 s/mm2) showing the ROI location in grey matter.

Materials and Methods: Diffusion images were obtained for 30 Malle Wistar rats at 17.2T (Biospec, Bruker) with maximum gradient strength of 1000mT/m using PGSE and the cosinusoidal OGSE with cosinusoidal apodised waveform gradients (Fig.1) sequences. Images were acquired *in vivo* and after the animals were sacrificed as a global ischemia model (keeping temperature constant). 40 b values were acquired (ranging from 4 to 4000s/mm^2) for each diffusion time: 1.9 and 3.8 ms as very short diffusion time with the OGSE sequence (using frequencies of 130 and 65 Hz with 1 and 2 periods), 10 and 16ms as intermediate diffusion time, and 40ms as long diffusion time with the PGSE sequence. TE ranged from 24 to 42ms and TR was of 3000ms. . The field of view was 25.6*25.6mm and matrix size of 64*64, resulting in a in plan resolution of 0.4*0.4*1.2 mm. The biexponential parameters: the slow diffusion fraction (f_{slow}) and the diffusion coefficients of the fast- and slow-diffusing water components (D_{fast} and D_{slow}) were estimated using the Levenberg-Marquardt nonlinear least-squares fitting routine (Matlab/Matworks) according to :

$$S/S_0=[(1-f_{slow}).\exp(-b.Dfast) + f_{slow}.\exp(-b.D_{slow}).$$

A global ADC was also calculated from the b=0 and b=2400s/mm² data, as ADC=ln(S_0/S)/2400. The data was analyzed in large ROIs in both side of the cortical (gray matter) region in the 4 acquired slices, separately (Fig.2) and pooled together. Parametric maps of f_{slow} D_{slow} and D_{fast} were also calculated on a voxel-by-voxel basis (not shown here).

			F slow	Dfast	D slow
normal	OGSE	1.9ms	0.12+/-0.03	0.87 +/-0.04	0.22+/-0.02
		3.8 ms	0.2+/-0.04	0.88+/-0.04	0.24+/-0.02
	PGSE	10 ms	0.28 +/-0.4	0.9 +/-0.04	0.25+/-0.02
		16 ms	0.33 +/-0.04	0.89 +/-0.03	0.25 +/- 0.02
		40 ms	0.39 +/-0.04	0.9 +/-0.04	0.28+/-0.04
dead	OGSE	1. 9ms	0.55 +/-0.02	0.8 +/-0.05	0.24+/-0.03
		3.8 ms	0.6+/-0.03	0.79 +/0.05	0.24+/-0.03
		10 ms	0.63 +/-0.03	0.78 +/-0.04	0.22 +/-0.03
	PGSE	16ms	0.65 +/0.02	0.7+/-0.04	0.22 +/- 0.04
		40 ms	0.73 +/-0.03	0.67+/-0.04	0.24+/-0.04

Table 1: Two compartment biexponential model fitting results with f_{slow}, D_{slow}, D_{fast}

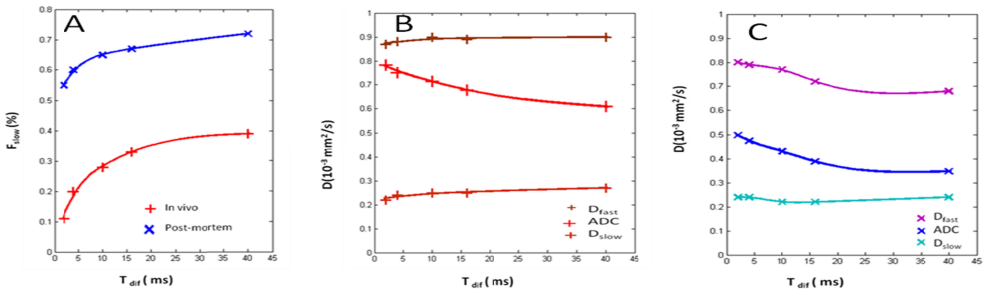

Fig 3: Variation of f_{slow} (a) and ADC, D_{slow} and D_{fast} in vivo (b) and post-mortem (c) rat brain with the diffusion time

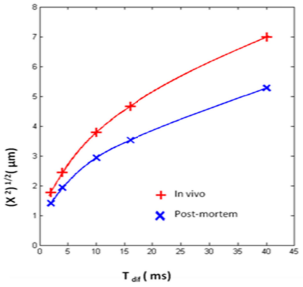

Fig 4 : Apparent diffusion distance calculated from ADC using Einstein's equation ($<X^2>^{1/2}=(2Dt_{diff})^{1/2}$

Results: An overall ADC decrease with the increase of diffusion time was observed (Fig.3). The apparent diffusion distances estimated based on the ADC values showed no true restricted diffusion patterns (plateau), but a curvature, suggesting that a growing fraction of water molecules were slowed down, as diffusion distances expanded beyond unique or multiple cell boundaries, especially upon death (Fig. 4). In the biexponential model in alive rats, f_{slow} increased dramatically with the diffusion time from 0.11 to 0.39 for 1.9msec and 40msec, respectively, while D_{slow} and D_{fast} were almost independent of the diffusion time (Table 1, Fig.3). Upon death the general trend of f_{slow} increase with diffusion time was preserved. f_{slow} was increasing at all diffusion times, but for short diffusion times the increase was the highest proportionally (Table 1, Fig.3). No significant change in D_{slow} was observed, except for D_{fast} decease at long diffusion times (PGSE sequence). For the same diffusion time no significant dependence of f_{slow} D_{slow} and D_{fast} on TE in the range of TE =24 and TE=42ms was observed.

Discussion: This study shows that the ADC decreases as the diffusion time increases, in agreement with a previously reported study [7]. Following the biexponential model used in the study, this ADC decrease was explained by a dramatic increase of the slow pool fraction, and not by changes in the fast and slow diffusion coefficients. These results rule out the view that the slow and fast fractions correspond to physical compartments, such as the intra- and extra- cellular compartments [5]. Instead, this result suggests that the diffusion pools are more functional in nature, with the slow pool originating from water molecules bound to or interacting with obstacles, most likely with membrane surfaces [1]. This pool is expected to increase with the diffusion time, as the probability to hit membranes increases, and with cell swelling, as membrane surface increases (in a fixed volume). Indeed, the slow pool fraction was also found to significantly increase upon cell death which is known to result in cell swelling. Interestingly, the observed behavior of f_{slow} increasing with the diffusion time, while D_{fast} and D_{slow} remain constant, is not predicted by the Karger model, which suggests that this model needs to be corrected for long diffusion times, when the compartment exchange with by water molecules occurs several times [9]. The impact of membrane permeability decrease on f_{slow} is also expected to be relatively greater at short diffusion times, as clusters of molecules close to membranes get 'trapped' for longer times, in agreement with our observations upon the death. Overall, the OGSE approach which allows controlling the time molecules spend near membranes, appears to be extremely powerful for elucidating the mechanisms of diffusion in tissues, and evaluating diffusion models, such as the biexponential model.

References [1] Le Bihan PMB(2007) 52:R57-R90, [2] Yablonskiy et al. NMR Biomed. 2010; 23: 661-681 [3]Niendorf et al MRM(1996) 36:847-857 [4]Jensen et al., NMR Biomed. 2010; 23: 698–710 [5]Sehi and al, MRM 48:765–770 (2002) [6] Karger. Advances in Magnetic Resonance (1988) 12, 1-89.[7]Does et al. MRM (2003) 49:206-215, [8] Gore et al. NMR Biomed. 2010; 23: 745–756, [9] Rebecca et al. ISMRM 2012 (submitted).