Local variations of magnetic susceptibility affect the contrast of Kurtosis maps: validation in phantom at 9.4T and in human brain at 3T.

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Introduction: The departure from purely mono-exponential decay of the pulse field gradient (PFG) signal, observed in brain tissue images obtained by a diffusion-sensitised sequence, prompted the search for alternative models able to characterise these non-Gaussian water diffusion dynamics. Diffusional Kurtosis Imaging (DKI) is one of the most popular non-Gaussian models [1,2] used to investigate brain tissue microstructure. In this model, the deviation from Gaussian behaviour is quantified using a convenient dimensionless metric called "the excess kurtosis", which is obtained from the first three terms of the expansion of the logarithm of the pulse field gradient (PFG) signal intensity in powers of b. DKI has been largely applied in the last years, thanks to its suitability for clinical applications and the solid theoretical framework [2,3]. Since its first applications in both healthy and diseased brains, DKI highlighted a different kind of information when compared to the outputs of Diffusion tensor Imaging (DTI). The link between microstructural tissue features and the measured kurtosis indices, such as the mean Kurtosis (MK) and the orthogonal Kurtosis (K_{ortho}), has been clarified in a recent review paper [4]. It is well known that when an internal gradient (G_i) is present, the PFG signal does not decay mono-exponentially, but exhibits signal changes that are proportional to the cross terms strength between internal and diffusion gradients. Moreover, Gi strength depends on magnetic susceptibility difference ($\Delta\chi$) at tissue interfaces, which in turns depend on the orientation of the main static magnetic field respect to the surface. As an example, in brain investigations, the static magnetic field is approximately perpendicular to the central zone of the genu and splenium of the corpus callosum. Conversely, it is approximately parallel to the white matter (WM) fibres of the internal capsule. However, to the best of our knowledge, there are no previous studies available that have investigated the relationship between Kurtosis contrast and internal gradients. The goal of the present work was therefore to investigate the influence of $\Delta\chi$ local variations (quantified by the T_2* parameter) on non-Gaussian water diffusion, as described using the Kurtosis method. The dependence of MK and K_{ortho} were first investigated in a controlled sample (a phantom characterized by pore sizes ranging from 4 to 10 µm and $\Delta\chi \approx 10^{-6}$ in SI), and then in the human brain in vivo.

Fig. 1

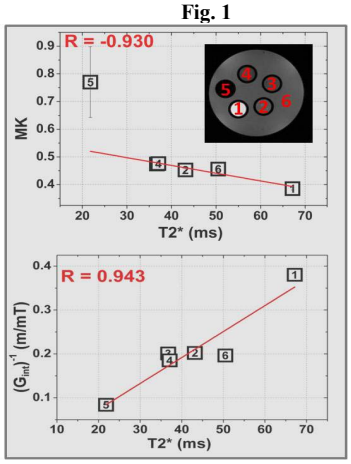


Fig. 2

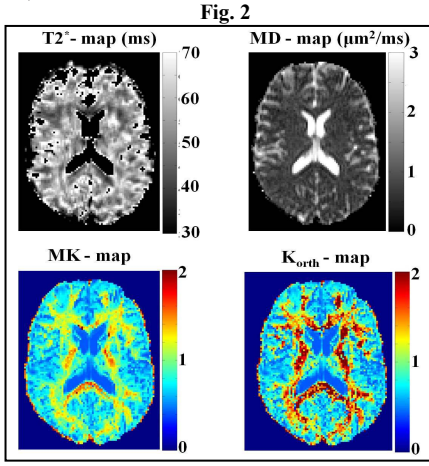
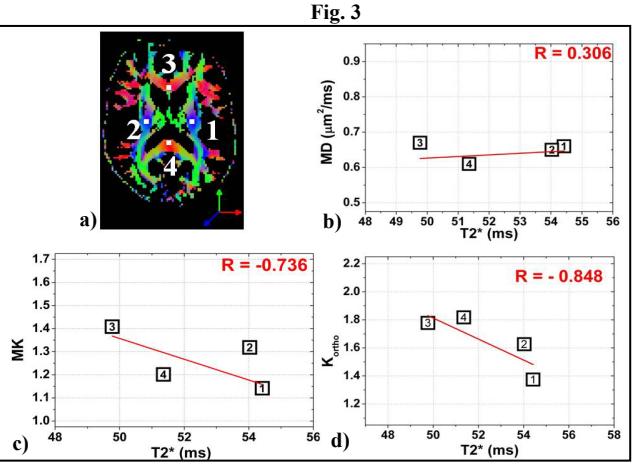


Fig. 3



Methods: In vitro experiments: Microcapillaries were filled up with 1) distilled water (capillary number 1, in reference image of Fig. 1); 2) polystyrene 6 µm beads monodispersed in water (capillary n. 2); 3) polystyrene 6+40 µm beads polydispersed in water (capillary n. 3); 4) polystyrene 6+40+140 µm beads polydispersed in water (capillary n. 4); 5) TiO_2 5 µm beads monodispersed in water. These five microcapillaries were immersed in a 8mm NMR tube containing 10µm packed polystyrene beads in water (region of interest [ROI] no. 6 in the reference image). $|\Delta\chi_m| = |\chi_m^{H2O} - \chi_m^{Polystyrene}| = 1.59 \times 10^{-6}$ in SI units, while $\Delta\chi$ between TiO_2 and water is approximately 10^{-5} (SI). All measurements were performed using a Bruker 9.4T Advance system, operating with a micro-imaging probe (10 mm internal diameter bore), and equipped with a gradient unit characterized by a maximum gradient strength of 1200 mT/m. An imaging version of the PGSTE sequence with Δ/δ=40/2ms, diffusion gradients along 15 non-coplanar directions, 10 b values ranging from 600 to 2500 s/mm^2, plus b=0, TE/TR=13/4000ms, slice thickness (STH)=1mm, FOV=10 mm, was used to obtain data for the MK maps, as previously described [2]. A MSME (multi slice multi echo) sequence, with *TR* = 3000 ms, 100 values of *TE* from 3.1 ms to 310 ms was used to extract the effective G_i map from the spin-echo (SE) decay, as previously reported [3]. Finally, T_2^* map was obtained by a GEFI (gradient echo fast imaging) sequence with *TR* = 3000 ms, 10 values of *TE* (from 1.6, to 65ms). All fitting procedures were based on the Levenberg-Marquardt algorithm , implemented in homemade scripts in MATLAB.

In vivo experiments: Three young healthy subjects (mean age 25 ± 2 years) underwent a MRI examination on a 3T scanner (Siemens Allegra), including gradient-echo (TR=5000ms,TE=10,20,35,65ms) and DTI acquisitions, using diffusion weighted SE EPI (TR=6400ms,TE=107ms, bandwidth 1860 Hz/px, STH=3mm, in plane resolution 1.8mm^2) acquired along 20 non collinear directions at 14 different b-values (0, 100, 200, 300, 400, 500, 700, 800, 1000, 2000, 2400, 3000, 4000, 5000) s/mm^2. Thirty-two contiguous axial slices were collected with NS=2. An algorithm implemented in MATLAB was used to perform a multidimensional fit of the diffusion signal decay in each pixel across the applied gradient directions. The fit generates as output conventional mean diffusivity (MD), colour coded fractional anisotropy (FA) maps, MK and K_{ortho} maps [4]. Four consecutive T2*-weighted gradient echo images were acquired using a segmented echo planar imaging sequence at different TEs:10, 20, 35, 65 ms (TR=5s, in plane resolution 1.8mm^2), from which maps of T2* values were obtained. ROIs were selected using the colour coded FA maps in the following structures: posterior limb of the internal capsule (ROIS 1 and 2); the central portion of the genu (ROI 3) and the splenium (ROI 4) of the corpus callosum (see Fig. 3a). Correspondent quantitative values were obtained and averaged across all subjects.

Results and Discussion: In vitro experiments: Experimental results displayed in Fig. 1 suggest that MK values depend on the strength of the G_i, as they are distributed at the interface of regions with different $\Delta\chi$. Specifically, as MK quantifies the departure from the purely monoexponential decay of water diffusion in heterogeneous systems, our findings indicate a strong correlation between the increase of G_i strength and the increase of non-Gaussian diffusion behavior of diffusing protons. **In vivo experiments:** in Fig.2, examples of T2* , MD, MK and K_{ortho} maps are displayed for one subject, while in Fig. 3b-c-d, MD, MK and K_{ortho} are plotted against the mean T2* for the four different ROIs selected in the brain. The squares indicate the SD obtained from all studied subjects. In vivo results confirm the observations obtained in vitro. Both MK and K_{ortho} values depend on the strength of the G_i, which are present at the interface of regions with different $\Delta\chi$. In particular, lower values of MK and K_{ortho} were found in internal capsule (ROIS 1 and 2), in which axonal fibres run approximately parallel to the main magnetic field. In contrast, K_{ortho} had higher values when measured in the corpus callosum (ROIS 3 and 4), whose fibers are perpendicular to the static magnetic field. It should be noted that the lower the T2* value, the higher the K value, i.e. the highest the deviation from mono-exponential behavior. It is well known that T2* strongly depends on the local $\Delta\chi$ variations, which affect the spin phase, thus causing a faster loss of coherence and shorter T2*. Here, we show for the first time that the amount of deviation from the mono-exponential behavior, quantified by MK and K_{ortho} is correlated with the $\Delta\chi$ strength.

Conclusion: Experimental results reported here show that local variations in $\Delta\chi$ are correlated with the amount of deviation from Gaussian behavior observed in diffusive decay of water in both controlled phantoms and human brains using Kurtosis approach. Diffusion sequences are based on the encoding of the spin phase by means of magnetic field gradients. When G_i due to local variations in $\Delta\chi$ are present, their coupling and overlap with the encoding gradients may affect the shape of recorded signals. We speculate that these results open a new scenario in the analysis of non-Gaussian diffusion-weighted data. If confirmed, the peculiar combination of diffusion and susceptibility can be used to characterize cerebral structures in an innovative fashion.

References: [1]De Santis S et al. MRI 2011; [2] Jensen JH et al. MRM 2005; [3] Tabesh A et al. MRM 2010; [4] Jensen JH, Helpern, JA. NMR Biomed. 2010;23:698.