

Double-PFG MR as a novel means for characterizing microstructures in grey matter

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Introduction. Diffusion MR has become one of the most important methods for characterizing microstructures in the central-nervous-system (CNS)¹. Diffusion-Tensor-Imaging (DTI) and the q-space approaches have proved extremely useful for characterizing white matter (WM) tracts, where ensemble anisotropy² (EA) exists (i.e. anisotropic compartments are coherently organized). However, current methodologies are extremely limited in characterizing scenarios where either spherical or randomly oriented anisotropic compartments exist; in both cases, EA is not present, and diffusion appears isotropic in conventional methods. Indeed, in grey matter (GM), which is characterized by rather spherical cell bodies and randomly oriented neurites, diffusion appears isotropic, and microstructural information is therefore scarce. The angular double-Pulsed-Field-Gradient (d-PFG) MR methodology is emerging as a novel means for characterizing the underlying microstructure even when EA is not present^{2,3}. The d-PFG sequences possess two unique parameters, namely the angle ψ between the two gradient vectors and the mixing time (t_m). The angular d-PFG methodology, where the angle ψ is varied at a constant q-value, yields $E(\psi)$ plots that have been predicted² and experimentally shown^{3,4} to be influenced by two novel parameters: microscopic anisotropy (μA), arising from geometrical restriction, and compartment shape anisotropy (csA), arising from the local compartment shape². The $E(\psi)$ plots at long t_m were predicted² and experimentally shown³ to manifest only csA; therefore, for spherical compartments that are locally isotropic, the $E(\psi)$ is constant (i.e. independent of ψ), while when anisotropic compartments are randomly oriented, the $E(\psi)$ plots appear as modulated curves³, and the extent of the modulation is dependent solely on compartment eccentricity².

Aims. (1) To apply the angular d-PFG methodology to isolated grey matter and study the signatures of μA and csA; (2) to compare the signatures in grey and white matter and (3) to apply d-PFG MRI and test the potential for delineating microstructures within grey matter regions.

Methods. Conventional s-PFG experiments were performed using a bipolar s-STE sequence with $\Delta/\delta=50/3$ ms. Angular d-PFG experiments in isolated pig grey matter were performed using a bipolar d-STE sequence using the following experimental parameters: $\delta_1=\delta_2=3$ ms, $\Delta_1=\Delta_2=50$ ms and $t_m=0$ or 28 ms. The same experiments were also performed on an isolated optic nerve. A double-PFG MRI sequence was written and calibrated using phantoms (data not shown). The imaging was performed on a rat brain using a d-PGSE sequence with $\delta_1=\delta_2=4$ ms, $\Delta_1=\Delta_2=20$ ms and $t_m=4.2$ ms. The field of view was 1.8×1.8 cm² and the matrix was 128×128 , yielding an in-plane resolution of 141×141 μ m². The slice thickness was 1.5 mm and the number of scans was 24.

Results and Discussion. Figure 1A shows the conventional bp-s-PFG experiments in the grey matter specimen. Clearly, the signal decay is isotropic, manifesting the lack of EA in grey matter, and it is impossible to infer on underlying microstructure. However, when the bp-d-PFG is performed with $t_m=0$ ms (Fig 1B), a pronounced modulation is observed, reporting on the presence of μA and csA; at longer t_m , the effects of μA are decoupled from the $E(\psi)$ plots, and the only anisotropy mechanism that can contribute to the signal decay is csA. The sharp modulation of $\sim 20\%$ that is observed between $E(0)$ and $E(90)$ at long t_m (Fig 1B) clearly indicates that this grey matter specimen is comprised of randomly oriented, anisotropic compartments. When similar experiments were performed on white matter, the bp-s-PFG clearly indicated on the presence of EA (Fig 1C). The angular bp-d-PFG experiment at $t_m=0$ ms however revealed also the presence of μA in the form of a bell shaped function, which is expected when EA exists² (Fig 1D), and is in good agreement with previous studies as well^{5,6}. However, at long t_m a slight angular dependence still remained (Fig 1D), despite theoretical predictions for a ψ -independent curve for coherently organized cylinders². This modulation most likely arises from a population of undulating axons that are not exactly aligned perpendicular to the plane of the experiment; these can be expected to be randomly oriented. Since the degree of modulation is directly dependent on the compartment eccentricity, one can infer that the randomly oriented compartments in the grey matter specimen are much more eccentric than those in the optic nerve specimen. Taken together, the four panels in Figure 1 show novel means of characterizing grey matter, as well as new sources of contrast in MRI within GM regions, angular d-PFG MRI was performed on a rat brain. The individual images for each value of ψ are shown in Figure 2, showing robust signal differences at different values of ψ . Three regions of interest (ROIs) were chosen in the cortex, and the CA1 and CA3 regions of the hippocampus. Figure 3 shows an overlay of a d-PFG image with a rat brain atlas and the ROIs (for one side only), and the extracted $E(\psi)$ plots. Clearly, the $E(\psi)$ plots are symmetrical in both sides; however, the $E(\psi)$ plots reveal different underlying microstructure for the three GM tissues. The modulation in the cortical grey matter is the largest, suggesting that it is characterized by very eccentric compartments, while the CA1 and CA3 regions of the hippocampus show a smaller modulation, suggesting that the microstructure is less eccentric there, with diffusion in the CA1 region experiencing the smallest compartment shape anisotropy. Mapping such parameters therefore should yield new forms of contrast in the GM.

Conclusions. The angular d-PFG appears very promising for characterizing underlying grey matter structures, showing different signatures for different GM regions in the brain based on csA and μA . Future studies will focus on quantifying these parameters and mapping it as a new source of contrast in MRI.

References. [1] Cohen Y and Assaf Y, NMR Biomed 2002, 15:516. [2] Özarslan E, J. Magn. Reson. 2009, 199:56. [3] Shemesh N et al., J. Chem. Phys. 2010, 133:044705. [4] Shemesh et al., NMR Biomed 2010, 23:757. [5] Koch MA and Finsterbusch J, Magn. Reson. Med. 2008, 60:90. [6] Weber T et al., Magn. Reson. Med. 2009 61:1001.

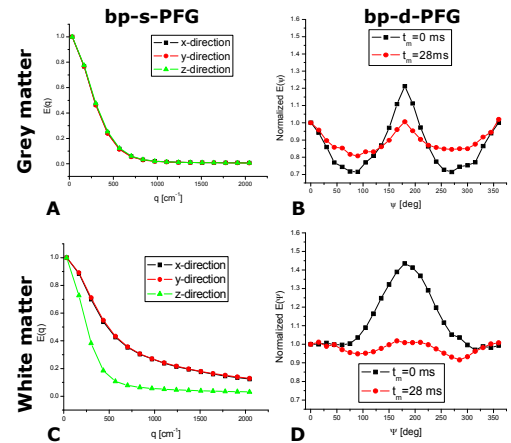


Figure 1. (A) bp-s-PFG experiments show isotropic diffusion in grey matter. (B) Angular bp-d-PFG experiments show modulated $E(\psi)$ curves for both short and long t_m in GM (C) bp-s-PFG experiments in WM show EA. (D) Angular bp-d-PFG experiments in WM reveal μA and csA.

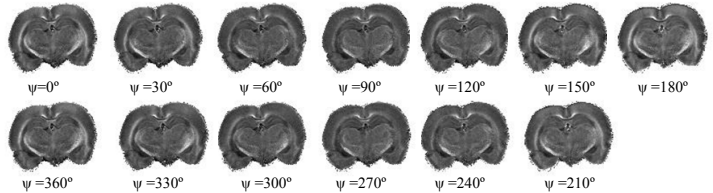


Figure 2. Angular d-PFG MRI in a rat brain. Each image corresponds to a different angle ψ as indicated.

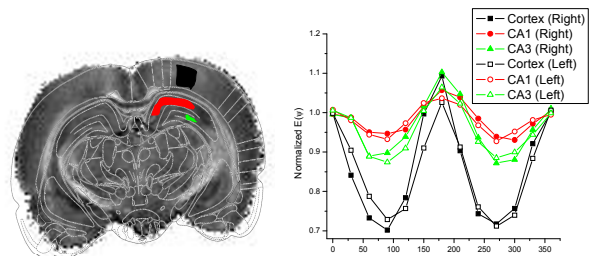


Figure 3. ROI definitions in a d-PGSE image of the rat brain (left) and $E(\psi)$ plots of these ROIs (right).