Multimodal fitting of diffusion MRI data for assessing the inflammatory/microvascularity relationship in a glioma rat model

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Target Audience: The present work may be addressed to people interested in the use of advanced models of DWI data fitting to assess the development of brain tumor in animal models.

Purpose: Alterations in inflammation and microvasculature underlie some of the most complicated brain diseases, like cancer. A deeper characterization of the inflammatory microenvironment in tumoral processes would improve its diagnosis, prognosis and help in the validation of new-targeted therapies. Magnetic resonance imaging (MRI) is a very well established and powerful tool for obtaining structural, functional and molecular information[1,2,3]. It is a widely used and versatile technique in neurooncology[4] that provides information about blood flow/volume, edema and cellularity[5]. In this line, this work was focused on the identification of DW parameters that allow characterizing the evolution of the blood perfusion and inflammatory microenvironment in a tumor as it grows. Our last goal, is to improve the knowledge of pathophysiological and biochemical basis of the coupling between inflammation and microvasculature alterations. We used for that a glioblastoma multiforme -the most frequent, aggressive and lethal intracranial tumor- animal model, DWI measurements at low and high b values, and three different models of data fitting in order to analyze the diffusion behavior and the perfusion contribution to the signal.

Methods: Adult male Wistar rats (n=5, 220-250g) were intracranial injected with C6 glioma cells and imaged in two stages of tumoral growth: small tumors (smaller than 50 mm^3) and big tumors (bigger than 75) mm^3 (Fig. 1). *DWI:* Animals were anesthetized with 1.5% isofluorane/oxygen during MRI protocols. We used a 7T Bruker Biospec scanner equipped with a 90mm gradient coil insert (360 mT/m) and a rat head resonator. DWI was acquired with 4 shot EPI-read gradient and in the L-R, A-P and H-F directions. Acquisition parameters were: δ/Δ=4/20ms, TR/TE=3000/31ms and a 273x273 μm^2 in plane resolution. We obtained 9 high b value (300<b<2000 s/mm2) and 9 low b value (10<b<600) acquisitions across 5 imaging planes centred in the tumoral area. *Data analysis:* The high b diffusion data set was fitted (MATLAB v7a) pixel by pixel either to a monoexponential $S(b)/S(0)=\exp(-b\cdot ADC)$ or to a biexponential model $S(b)/S(0)=SDP\cdot\exp(-b\cdot D_{slow})+FDP\cdot\exp(-b\cdot D_{fast})$, with slow (SDP) and fast (FDP) diffusion phases characterized by slow (D_{slow}) and fast (D_{fast}) diffusion coefficients. The calculated high b biexponential coefficients were used to obtain the perfusion components affecting the low b measurements, in which the signal decay was thus considered to be triexponential $S(b)/S(0)=f_{perf}\cdot\exp(-b\cdot D^*)+ SDP\cdot\exp(-b\cdot D_{slow})+FDP\cdot\exp(-b\cdot D_{fast})$, with a fraction of water molecules contributing to perfusion (f_{perf}) with a pseudodiffusion coefficient (D*). On each slice, two ROIs were studied, the tumor and an area of the contralateral (CL) region (Fig.1). Statistical tests were performed between conditions and area using ANOVA tests.

Results: Our results show significant differences between the mean values of ADC, SDP and f_{perf} in the glioma and CL areas (Fig. 2). ADC values are higher in the tumor regions than in the CL, especially in big tumors. On the contrary, the lowest SDP values are also found in big tumors. D_{slow} and D_{fast} coefficients showed some directionally dependent differences between areas and tumor conditions, with generalized higher D_{fast} values in tumor than in CL regions. In the DWI-perfusion analyses, small tumors showed the highest f_{perf} values. D* values showed high SD between animals and did not report robust changes between areas.

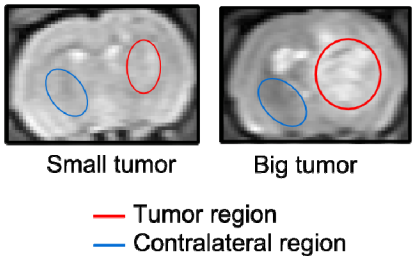

Figure1. Axial slices containing the analysed ROIs (tumor and contralateral), in the small tumor condition (left) and big tumor development (right) in the same rat.

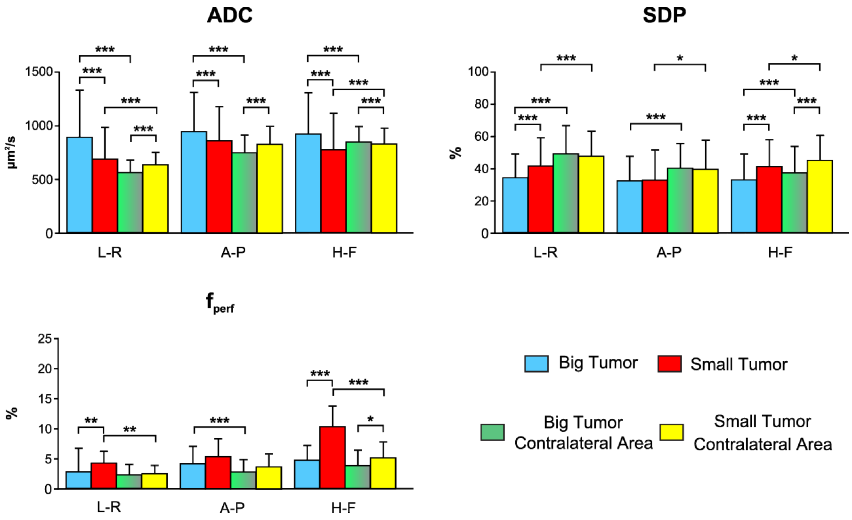

Figure2. Mean values (±SD) of tumor and CL area ADC, SDP, f_{perf} in the two tumor stages for the three directions of measurements. (*p<0.5,**p<0.01, ***p<0.001)

Discusion/Conclusion: We report that DWI can be used with high and low b weightings to emphasize different tumoral properties. At high b values, both mono&biexponential models revealed increased diffusion coefficients in big tumors. SDP fractions indicate diminished fractions of slow diffusion in big tumoral areas, suggesting that ADC increase might come from a shift of the number of molecule with slow to fast diffusion. Low b analyses indicate that small tumor have the highest perfusion components. This may reflect a major angiogenic state in the initial stage of the glioma development and/or a higher necrosis in the last phase of the tumors.

References : [1]Lizarbe B. Benitez A. et.al, *Neuroimage*, 2013, 64:448-457; [2]Lopez-Larrubia P. et.al, Cap.12, 2012, ISBN 978-953-307-284-5; Le Bihan D. ,Nat. Rev Neurosci.2003Jun;4(6):469-80.[4]Borges AR, Lopez-Larrubia P, et al. *AJNR. American Journal of neuroradiology*. 2012;33:24-36; [5]Calli C, et al. *European journal of radiology*. 2006;58:394-403