Microbeam Radiation Therapy effects on white matter assessed by Fiber Tractography

Yohan van de Looij[1,2], Audrey Bouchet[3,4], Benoit Pouyatos[3], Luc Renaud[5], Elke Bräuer-Krisch[4], Géraldine Le Duc[4], Jean A Laissue[6], and Raphaël Serduc[3]

[1]Division of Child Growth & Development, University of Geneva, Geneva, Switzerland, [2]Laboratory for Functional and Metabolic Imaging, Ecole Polytechnique Fédérale de Lausanne, Lausanne, Switzerland, [3]Grenoble Institut des Neurosciences UMR836, Université Joseph Fourier, Grenoble, France, [4]European Synchrotron Radiation Facility, Grenoble, France, [5]Centre de Recherche Cerveau et Cognition, Université de Toulouse, Toulouse, France, [6]Institute of Pathology, University of Bern, Bern, Switzerland

Introduction:

Microbeam Radiation Therapy (MRT) is a preclinical form of radiosurgery dedicated to brain tumor treatment. It uses micrometer-wide synchrotron-generated X-ray beams on the basis of spatial beam fractionation [1]. Due to the radioresistance of normal brain vasculature to MRT, a continuous blood supply can be maintained which would in part explain the surprising tolerance of normal tissues to very high radiation doses (hundreds of Gy *vs.* tens of Gy for conventional radiotherapy) [1]. Local axonal fiber disruptions might be of particular interest in neurological disease management such as epilepsy for which about two-third of the patients with medically refractory are non-eligible for surgery (gold standard). Microbeam arrays can be used to generate cortical transections or subcortical lesions, thus enabling the non-invasive modulation of brain networks [2]. Nevertheless, to our knowledge, no studies dealing with axonal fiber responses to spatially fractionated doses have been reported. Diffusion Tensor Imaging (DTI) probes white matter (WM) architecture through a full description of water diffusion in the tissue and allows for the reconstruction of WM fiber-tract trajectories in 3D as a result of fiber tractography (FT) algorithms. In this work, the effects of different irradiation patterns (microbeam width: beam width (BW)/deposition dose: peak dose (PD)) on rat brain white matter were assessed *ex-vivo* using DTI and FT.

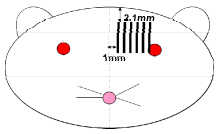

Fig. 1: Irradiation

Materials and methods:

Rats (n = 5 per group) were irradiated with microbeams centered on the external capsule as illustrated on figure 1 at the European Synchrotron Radiation Facility (ID17, ESRF, Grenoble, France) with three different PD (150, 280 and 500 Gy) associated to five different BW (25, 50, 100, 680 and 1000 µm). A control group (n=4, without any MRT exposition) was also assessed. Two months later, rats were sacrificed and brains were formalin-fixed for subsequent *ex-vivo* MRI and histology. All experiments were performed on an actively-shielded horizontal 9.4T/31cm magnet (Varian/Magnex) equipped with 12-cm gradient coils (400mT/m, 120µs) with a transceive 25-mm birdcage RF coil. A Spin-Echo sequence with addition of the Stejskal-Tanner diffusion gradients was used. Diffusion gradients were applied along the dual gradient diffusion gradient sampling scheme [3] with following parameters: G_d = 22 G/cm, δ = 3 ms and Δ = 20 ms, given a *b*-value of 1185 s.mm^{-2}, a FOV = 18 × 18 mm^2 was sampled on a 128 × 128 cartesian grid. 20 slices of 0.5 mm thickness were acquired in the axial plane with 10 averages and TE/TR = 30/2000 ms. Using in house Matlab script (Mathworks, Natick, MA), diffusivity values ($D_{//}$ and $D_{\perp}$) as well as fractional anisotropy (FA) was derived from the tensor and direction encoded color (DEC) maps computed. Regions of interest were manually delineated in the site of damage (external capsule) at six different levels of the brain (i.e. six slices). Significant differences of diffusivity and FA values between the irradiated and control groups were assessed by a Mann-Whitney test. FT of the whole brain was performed using ExploreDTI [www.exploredti.com] (wild-bootstrap algorithm) with an angle threshold = 30° and 3 different FA tracking thresholds: 0.2, 0.3 and 0.4.

Results and discussion:

For each BW, the decrease in FA was related to the dose deposition *i.e.* much more pronounced at 500Gy than at 280Gy or 150Gy. For the rats irradiated with the most severe combinations of PD/BW: 280Gy with 680µm and 1000µm as well as 500Gy with 680µm and 1000µm, a drastic significant decrease of FA was observed in the radiated external capsule when compared to control group as well as an increase of all the diffusivity values (MD, $D_{//}$ and $D_{\perp}$). This result demonstrates an increased mobility of the water in the damaged tissue in all the direction confirming a real 3D damage of the WM (not restricted to only one direction). Indeed, FT reconstruction (fig. 2) with a FA threshold of 0.2 already showed fiber disruption/loss, bigger with a FA threshold of 0.3 and 0.4. FT images showed clearly the region of fibers with very low FA, i.e. the site of injury centered on the external capsule with probable ruptured fibers following radiation. As a result, the FT reconstruction performed with a FA threshold of 0.2 seems already to be a good representation of the tissue shape.

For the other groups (i.e. 150Gy with 25µm, 50µm, 100µm, 680µm and 1000µm; 280Gy with 25µm, 50µm and 100µm as well as 500Gy with 25µm, 50µm and 100µm), no FA change was observed when compared to the control group. Indeed, the pattern of FT images was similar to the ones of control group. These results are also summarized in figure 3: the severity of the damage is as a function of the couple BW/PD. Very severe damages (i.e. high red peak of 1/FA on fig. 3) were observed for a couple of parameters mixing large BW/high PD. In the other hand, a large BW coupled with low PD or narrow BW coupled with high PD did not induce severe damages as depicted by the moderate 1/FA peak height. This result shows also a possible threshold effect as a function of the irradiation pattern: BW ≥ 680 µm associated to a PD ≥ 280 Gy leads to severe WM damages whereas under these values, the shape of the WM structure assessed by DTI derived parameters does not reveal damage.

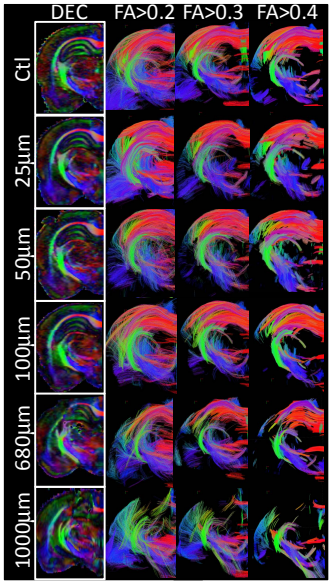

Fig. 2: Left panel, DEC maps of 5 typical rat irradiated hemispheres with a PD of 280 Gy and the 5 different BW. Right panel, 3D FT images of the irradiated hemispheres (FA thresholds of 0.2, 0.3 and 0.4).

Conclusion:

For the first time we present tractography results following microbeam radiation on rat brain white matter. This study shows the excellent ability of DTI to classify the degree of injury of diverse lesions by DTI derived parameters and 3D representation of the WM fibers in the injury. If with the very aggressive beam width/peak dose couples, the white matter is obviously extremely damaged, it appears more difficult to conclude about the exact shape of the fibers following radiation with lower beam width/peak dose couples. With these last patterns of radiation, no change was observed with DTI but histology staining are in progress to characterize more accurately the shape of the fibers as a function of the radiation pattern and conclude about the possible micro-transaction of the fibers following MRT.

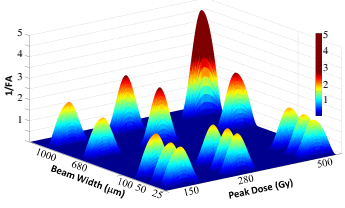

Fig. 3: 1/FA plotted as a function of the beam width and peak dose.

References: [1] Slatkin DN. Med Phys 1992; [2] Serduc R. PloS One 2010; [3] Basser PJ. MRM 1998.

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