White matter quantification in a model of schizophrenia mice using microscopic Diffusion Tensor Imaging

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Introduction STOP knockout (KO) mice have been proposed as a model of some schizophrenia-like symptoms [1]. KO mice exhibit brain anatomical abnormalities and the purpose of the study was to determine the WM alteration using microscopic Diffusion Tensor Imaging (DTI) [2] in the commissure of fornix which links hippocampus to mammillary bodies.

Methods *Preparation* – 12 mice (6 wild-type (WT) and 6 KO) were perfused and fixed in 4% paraformaldehyde solution. *Acquisition* – *Ex vivo* experiments were performed at 7.0T on a Bruker Avance III console with 600 mT/m maximum gradient strength using a volume/surface cross RF coil. Anatomical T2 weighted images were first acquired as a pilot image to place 7 slices of 0.7 mm in the coronal plane between -3.2 mm and 2.7 mm relative to the bregma. Diffusion sequence was a spin echo sequence (TE/TR equal to 35/2 000 ms) in which two identical diffusion gradients were applied with a duration of 5 ms and a separation time of 35 ms. 6 different gradient diffusion directions ([1 1 0],[1 -1 0],[0 1 1],[0 1 -1],[1 0 1],[-1 0 1]) with a b-value of 1000 s/mm^2 were used. The FOV and the plane resolution were set to 30 x 30 mm^2 and 59 x 59 μm^2 respectively. Total time of the DTI acquisition was about 12 hours with a number of averages equal to 12. *Data Analysis* – DTI analysis was done using house software implemented in Matlab (The MathWorks, Inc., Natick, MA). For each slice, an ROI of all the brain was manually selected. After DTI reconstruction fractional anisotropy (FA) maps and principal eigenvectors were calculated and color maps were obtained. Corpus callosum and dorsal fornix were segmented using a FA value threshold of 0.35 and a principal eigenvector in the X-Y plane / Z plane. Post-commissural fornix was selected by drawing a ROI.

Results/Discussion Fig.1 shows a color map of a WT mouse with magnification showing dorsal fornix and post-commissural fornix. This region appears in blue confirming the anteroposterior direction of the bundle. As shown in Fig.2a, a significant reduction in the brain volume (~16.2%) of the KO mice was found compared to WT mice. After a total brain volume normalisation, volume differences in the corpus callosum (~15.9) were also found between the two groups (Fig.2b). In Fig.3, the number of pixels was significantly reduced for high FA values [0.4 - 0.7]. Because high a FA value corresponds to the anisotropic tissue, this result shows that WM volume is significantly affected. A low FA value of 0.31 compared to 0.58 (Fig.2c) might confirm a net loss in the post-commissural fornix of the KO mice whereas no differences were obtained in the dorsal fornix (Fig.2d). This result is best shown in the FA maps in Fig.4.

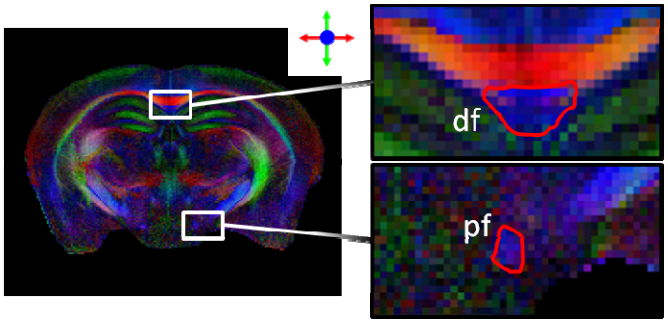

Fig.1 Color map of a WT mouse with ROI selections in the dorsal fornix (df) and post-commissural fornix (pf).

Conclusion In this study, we show that DTI is appropriate to detect the anatomical changes of WM in a model of schizophrenia mice. In addition to a total brain volume diminution, this study found that KO mice exhibit a global WM volume reduction observed in particular in the fornix region.

References

[1] A. Andrieux et al., The suppression of brain cold-stable microtubules in mice induces synaptic defects associated with neuroleptic-sensitive behavioral disorders, Genes Dev, 16, 2350-64.
[2] Y. Jiang, G. A. Johnson, Microscopic diffusion tensor imaging of the mouse brain, NeuroImage, 50, 2, 465-471

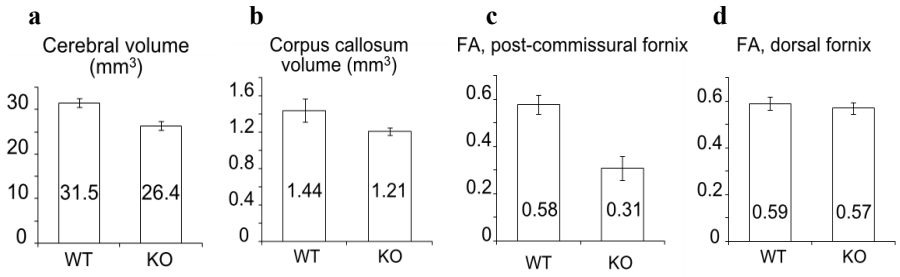

Fig.2 a- Total brain volumes of WT mice and KO mice. b- Corpus callosum volume of WT and KO mice. c- FA value of the post-commissural fornix in each group. d- FA value in the dorsal fornix.

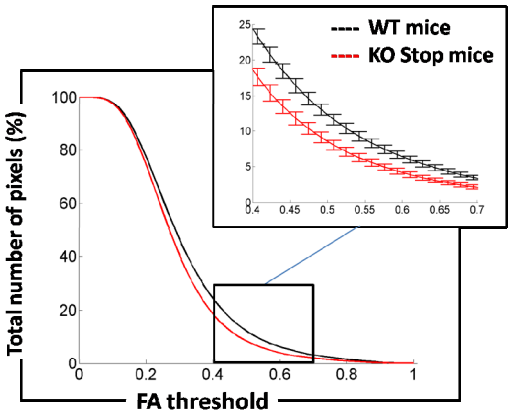

Fig.3 Cumulative histogram of FA values averaged on all mice of each group: intensity corresponds to a number of pixels having FA greater than FA threshold.

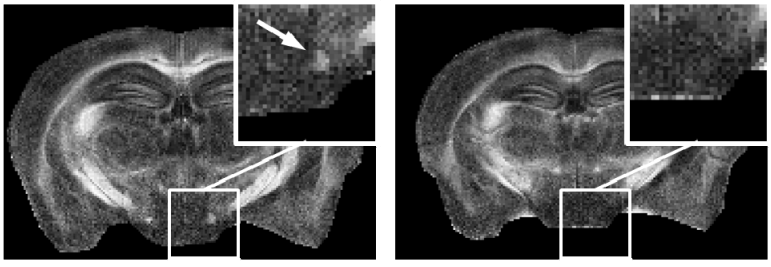

Fig.4 FA maps on a WT mouse (right) and on a KO mouse (left), image magnification on the post-commissural fornix (pf) showing that this structure might be considerably altered in KO mice.