Comparison of DTI and growth-associated protein expression as markers of neuronal plasticity after stroke.

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Introduction: Diffusion tensor imaging (DTI) allows microscopic probing of structure and architecture of neuronal tissue. The objectives of our project were to use a murine model of focal cerebral ischemia 1) to study the long-term evolution of the apparent diffusion coefficient (ADC) and fractional diffusion anisotropy (FA) *in vivo* after stroke induction, and 2) to compare the distribution of a plasticity-related protein (GAP-43) with qualitative and quantitative MRI changes in the striato-thalamic motor pathway, measured by high resolution *ex vivo* DTI.

Methods: Male ICR-CD1 mice were subjected to 30 min. middle cerebral artery occlusion (MCAo). Serial *in vivo* T1/T2/DTI scans were performed on a 4.7 T MRI system at days 5, 10, 15 and 21 (n=8 strokes and n=3 shams). The infarct was manually outlined on the DWI images and reflected in the contralateral hemisphere (CL). *Ex vivo* DTI was performed at 21 days and FA values and tract morphology of the striato-thalamic pathway were studied. The expression of GAP-43 was evaluated by immunohistochemistry and correlated with MRI data. Regions of interest were defined along the striato-thalamic motor pathway (striatum, forceps minor and thalamus) and in the hippocampus (CA1, CA3 and dentate gyrus regions) in the ipsilateral (IL) and the CL hemisphere. Neurological scores were recorded for all animals. Data were compared using the T-test, ANOVA and regression analysis.

Results: Our results showed that: **1)** ADC in the stroke area significantly increased up to 21 days after stroke ($p < 0.0001$) and correlated with functional outcome ($p<0.01$). **2)** GAP-43 expression was significantly higher in IL striatum and CL hippocampus (dentate gyrus) ($p<0.05$), Figure 1. **3)** FA in the IL striatum and the CL hippocampus are significantly different between strokes and shams ($p<0.05$); ADC data showed no significant differences between the stroke and sham groups. **4)** Qualitative fiber tract analysis showed fibers from CL striatum connecting to IL stroke region, which may related to the increased GAP43 and FA in this area, Figure 2. **5)** The difference between FA values in IL and CL dentate gyrus was significantly correlated with the difference between IL and CL GAP 43 expression in the same region ($p<0.05$); absolute values of IL and CL ADC in the striatum are correlated with IL GAP 43/CL GAP 43 ($p<0.05$).

Conclusion: DTI detects changes in water diffusion and "connectivity" after stroke that parallel histological remodeling and recovery of function and could be a valuable tool for *in vivo* monitoring of therapy aimes at stroke rehabilitation.

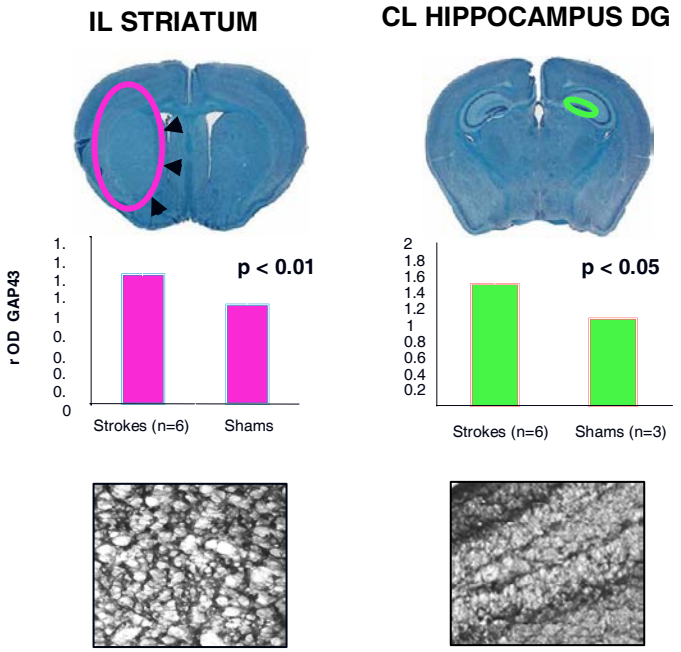

Figure 1. Left: Luxol blue myelin staining (top), relative Optical Density (r OD) GAP43 quantitative comparison between strokes and shams (middle) and GAP43 immunohistochemistry (bottom). Black arrows indicate the stroke area.

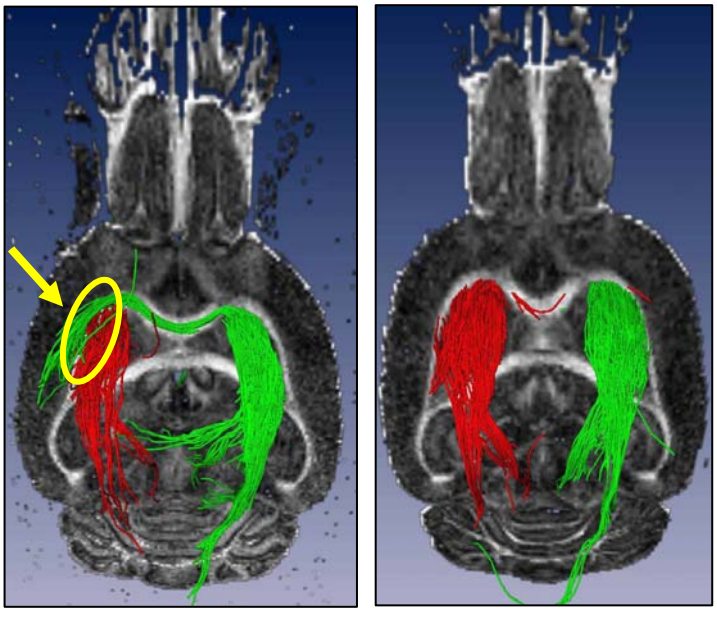

Figure 2 , Right: *Ex-vivo* image of the striato-thalamic tract in a mouse with stroke (top) and in a sham (bottom). Fiber trajectories connecting the CL striatum to the stroke area were evident in the stroke animal but not in the sham.