

Prediction of Behavioral Deficits using Diffusion Tensor Imaging in Experimental Hydrocephalus

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Introduction: Hydrocephalus is traditionally thought of as a straightforward disease; there is physical blockage to CSF outflow, either with clear evidence of blockage as in aqueductal stenosis or with assumed blockage more distally in the subarachnoid spaces. Treatments can also appear simple; ventricular shunting allows an alternate absorption path bypassing this blockage. Despite this seemingly simple picture, management remains a major challenge, with shunt failure often requiring surgical revision within 1-2 years (1), and residual functional deficits in up to 78% of patients even with successful shunting (2). A better understanding of the pathophysiology is needed, and in particular its relationship to severity and shunt outcome. As a first step, we investigated white matter pathology in a rat model of communicating hydrocephalus (CH) using diffusion tensor imaging (DTI) and its relationship to motor and cognitive function.

Methods: CH was induced in two groups of adult rats (225-250g) using kaolin injection into the basal cisterns (3). The model produces rapid and marked ventricular dilation. In group 1 (n=6 kaolin, n=5 saline control), DTI was compared at 2 weeks post-surgery. In group 2 (n=5 kaolin, n=5 saline), behavior was studied at 3 weeks post-kaolin including open field assessments, and balance beam tests. DTI was studied *in vivo* at 5-6 weeks and *ex vivo* at 6 weeks following euthanasia by cardiac perfusion (only n=4 kaolin, n=2 saline were studied *ex vivo*). DTI were collected on a 9.4T Varian scanner, with 6 directions (*in vivo* data) or 15 directions (*ex vivo* data), and 800 s/mm². High-directional *ex vivo* scans were used to explore DTI-behavior associations. In plane resolution was 230 μ m, slice was 1 mm, and respiratory gating used to minimize motion artifact. DTI images were analyzed with DTIstudio (S. Mori, Johns Hopkins); fractional isotropy (FA) and mean/radial/axial diffusivity were extracted for corpus callosum (CC), internal (IC) and external capsule (EC).

Results: 5/6 animals in the first group and 4/5 in the second developed signs of CH. Kaolin animals had moderate to severe motor deficits (3-20 slips on balance beam, compared to 0-1 in controls) and decreased exploration behavior in the open field (5-40 rears compared to 23-65 in controls). In group 1 (Fig 1), at two weeks post-kaolin, no differences in FA were detected. However, CH animals had a significant increase in CC and EC radial diffusivity (CC: $0.69 \pm 0.14 \times 10^{-3} \text{ mm}^2/\text{s}$ vs. 0.52 ± 0.04 , $p < 0.05$, EC: 0.82 ± 0.15 vs. 0.56 ± 0.02 , $p < 0.01$), and increased mean diffusivity in both regions. Differences were only found in mean and radial diffusivity for the *in vivo* group 2 scans; however, image quality issues with the FSE sequence may have masked any differences. There was no correlation between any behavior outcome and ventricular size, but significant correlations were found between FA in the CC splenium and both balance beam slips (Fig 2) and rears in the open field. Most interesting is the one animal (encircled) with severe ventricular dilation (540 μ l compared to 15 μ l in controls), yet display minimal motor deficit and near-normal CC FA.

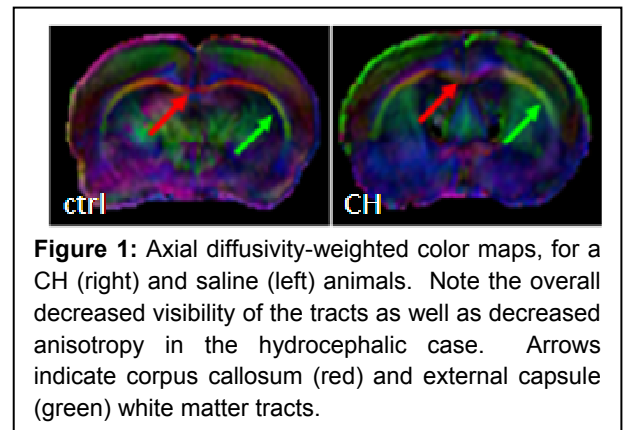


Figure 1: Axial diffusivity-weighted color maps, for a CH (right) and saline (left) animals. Note the overall decreased visibility of the tracts as well as decreased anisotropy in the hydrocephalic case. Arrows indicate corpus callosum (red) and external capsule (green) white matter tracts.

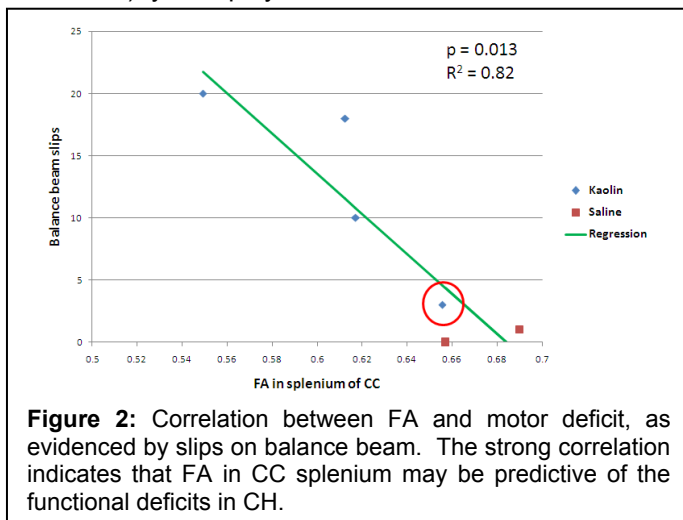


Figure 2: Correlation between FA and motor deficit, as evidenced by slips on balance beam. The strong correlation indicates that FA in CC splenium may be predictive of the functional deficits in CH.

Discussion: Changes in the white matter tracts following development of communicating hydrocephalus in the rat are detectable as early as two weeks following induction. While differences manifested mostly as increased radial diffusivity in the corpus callosum, high-resolution post-mortem scans showed decreased FA in the splenium of the CC. More importantly, these changes in FA appear to correlate with both motor and cognitive deficits in this model. This is strong supportive evidence for the utility of white matter tract pathology from DTI in predicting outcome in hydrocephalus. Future work will include improvements in *in vivo* techniques for detecting correlations in live animals, and using DTI pre- and post-shunting to identify correlates of successful shunting.

References:

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