3D MRI and DTI of *Cnp1* deficient mice: A model of axonal damage without affecting myelin

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Introduction

Cnp1 encodes the 2',3'-cyclic nucleotide 3'-phosphodiesterase (CNP) in oligodendrocytes, a myelin-associated protein which is essential for axonal survival. Genetically modified mice lacking the *Cnp1* gene develop axonal swelling and neurodegeneration throughout the brain without affecting the ultrastructure, periodicity, and physical stability of myelin [1]. The purpose of the study was to search for MRI surrogate markers of `pure' axonal damage using T1- and T2-weighted 3D MRI as well as diffusion tensor imaging (DTI) and thereby complement previous work on a mouse model of `pure' demyelination [2].

Methods

Eight *Cnp1* deficient and 8 wild type mice (at the age of 12 month) participated in the study. T1-weighted (3D FLASH, TR/TE = 17/7.58 ms, $\alpha = 25°$) and T2-weighted MRI (3D FSE, TR/TE = 3000/98.25 ms, 16 echoes, inter-echo-spacing = 12.5 ms) were obtained at 2.35 T (Bruker, Biospin) with an isotropic resolution of 117 µm. Nine mice (4 *Cnp1* deficient, 5 controls) additionally underwent a DTI measurement (HF DW STEAM, b=800, 140x200x1000 μm^3) from which maps of fractional anisotropy (FA) as well as radial and axial diffusivity were calculated. The total brain volume (excluding brain stem and cerebellum) and the ventricle size were manually determined in T1-weighted images by a single observer. For MRI examinations mice were anesthetized by i.p. injection of medetomidine and ketamine and subsequently intubated for artificial ventilation. After the final experiment the animals were sacrificed and prepared for histology.

Results and discussion

In comparison to controls *Cnp1* deficient mice showed a remarkable reduction of T2 contrast in white matter structures such as the corpus callosum, external capsule and hippocampal fimbria (Fig. 1, arrows), whereas T1 contrasts remained unchanged. Similar reductions of T2 contrast but also changes in T1 contrast have been observed during demyelination in cuprizone treated mice [2]. As a consequence the MRI contrast pattern of axonal damage (*Cnp1* deficient mouse) and demyelination (cuprizone mouse) turn out to be different. MR volumetry revealed a reduction of the total brain volume in *Cnp1* deficient mice whereas the ventricle size remain unchanged (Fig. 2).

Despite axonal damage in *Cnp1* mutants the FA in the corpus callosum did not significantly differ from that of controls. On the other hand, however, the apparent diffusion coefficient or more precisely, the axial (and radial) diffusivity were increased (Fig. 2). Although a recent study of DTI in the cuprizone mouse model [3] suggested radial diffusivity as a marker for demyelination, the present study demonstrates similar increases during axonal damage without demyelination.

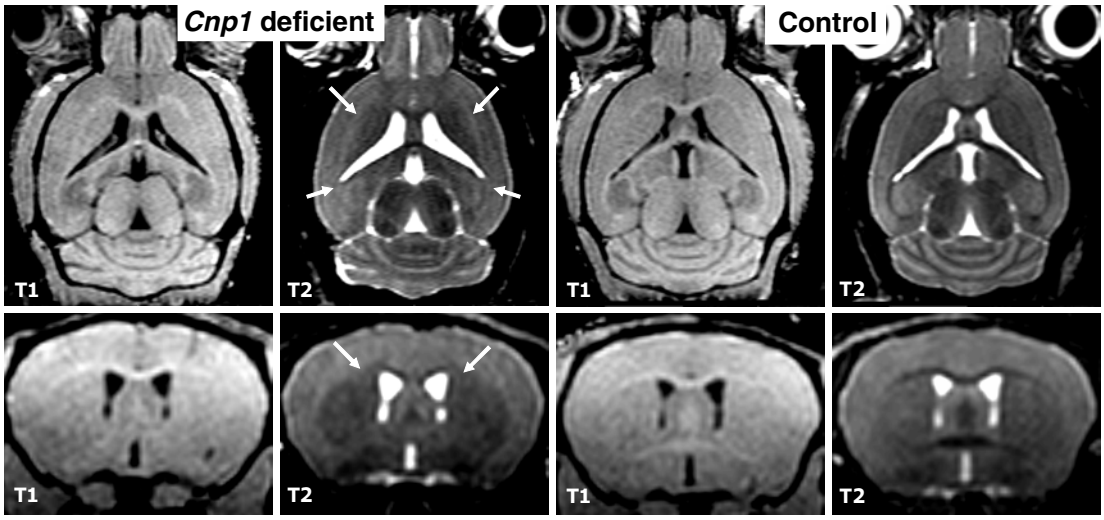

Fig.1: T1- and T2-weighted MRI of a *Cnp1* deficient mouse vs control. Arrows indicate reduced T2 contrast in white matter

Conclusion

Cnp1 deficient mice are a useful model to study axonal degeneration by MRI without additional contributions from inflammation or demyelination as usually encountered in conventional animal models of human MS such as EAE.

Here, the specific correlation of MRI contrast alteration due to axonal damage in the presence of unaltered myelin resulted in a decreased T2 contrast, an increased axial and radial diffusivity but no changes in T1 contrast and FA. Thus, intact myelination seems to be an important contributor to anisotropy in white matter of the mature brain, while ADC values are sensitive to axonal damage.

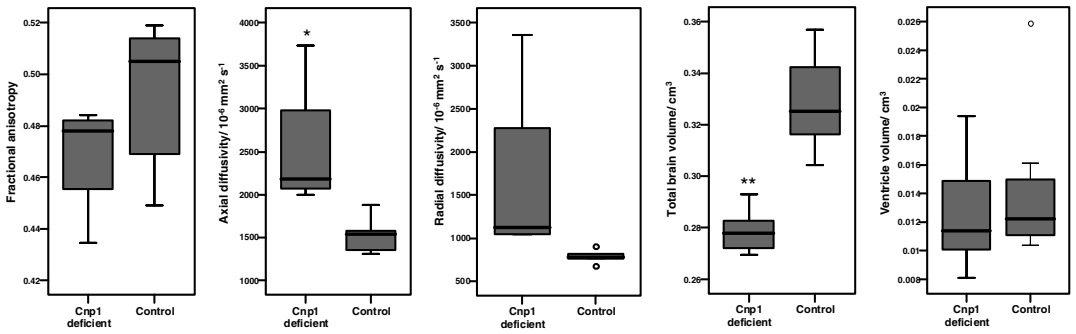

Fig.2: FA, axial and radial diffusivity as well as brain and ventricular volume of *Cnp1*deficient mice vs controls. * p<0.05, ** p<0.001

References

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