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Compact Myelin Detachment after metabolic Oligodendrocyte injury

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Introduction

Multiple sclerosis (MS) is characterized by demyelination and oligodendrocyte degeneration. The pathology of white matter injury induces neurodegeneration and in consequence accumulation of irreversible clinical disability. Mechanisms leading to oligodendrocyte and myelin degeneration are poorly understood, however centrifugal (early oligodendrocyte cell body pathology) and centripetal (early myelin sheath pathology) mechanisms have been described. Here we investigate structural consequences of Cuprizone-induced centrifugal oligodendrocyte degeneration.

Results

Centrifugal spread of oligodendrocyte damage in cuprizone lesions

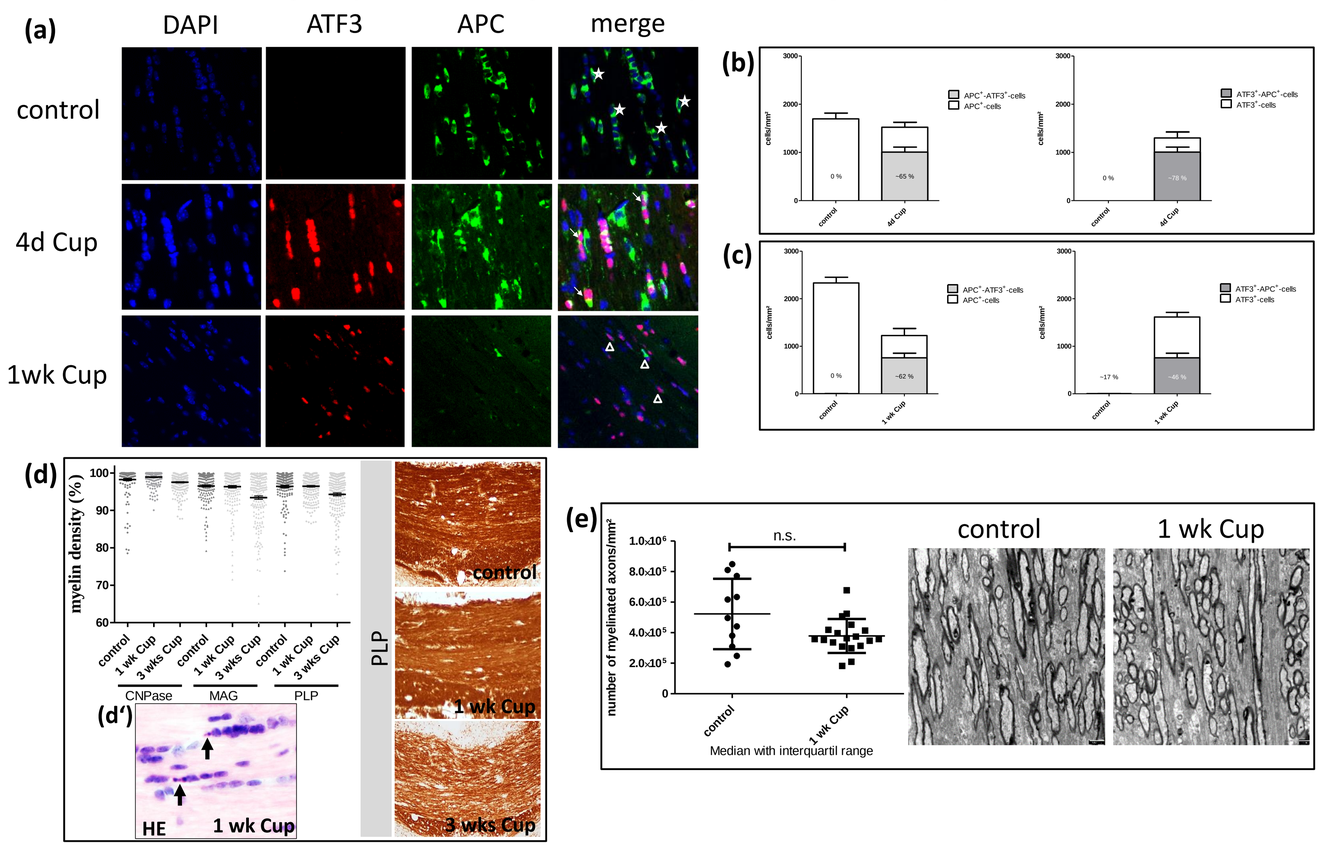

Figure 1 (**a**) Immunofluorescence double labelling against the mature oligodendrocyte marker protein APC and the cellular stress response marker protein ATF3. *Stars* highlight cytoplasmic APC, whereas the *arrows* highlight APC$^+$/ATF3$^+$ oligodendrocytes. (**b**) Quantification of APC/ATF3-expressing cell populations after 4 days cuprizone intoxication. (**c**) Quantification of APC/ATF3-expressing cell populations after 1 week cuprizone intoxication. (**d**) Quantification of myelin proteins densities at week 1 and week 3. *Arrows* highlight apoptotic oligodendrocytes in *d'*. (**e**) Quantification of demyelination on the ultrastructural level at week 1. Results point to a sequence of damage that starts with degeneration of oligodendrocyte followed by myelin loss (i.e., centrifugal oligodendrocyte pathology).

Compact Myelin Detachment (CoMyD) at the beginning of active demyelination (i.e., at week three)

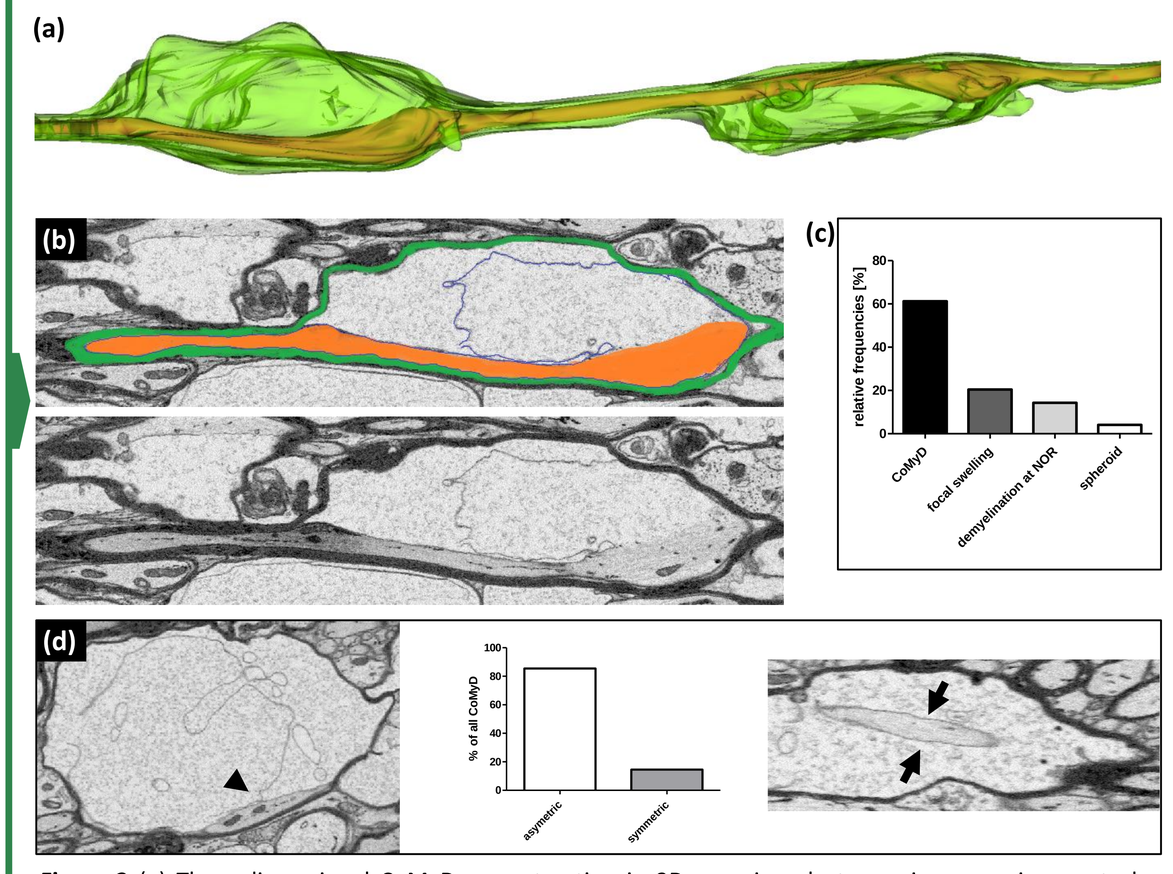

Figure 2 (**a**) Three-dimensional CoMyD reconstruction in 3D scanning electron microscopy image stacks (axon in orange, myelin in green). (**b**) Ultrastructural CoMyD appearance (axolemma in blue). (**c**) Quantification of different myelin pathologies at week 3. (**c**) Quantification of the spatial orientation of the detached myelin sheaths. *Arrowhead* highlights an asymmetrical, whereas *arrows* highlight symmetrical myelin detachment, respectively.

CoMyD characteristics

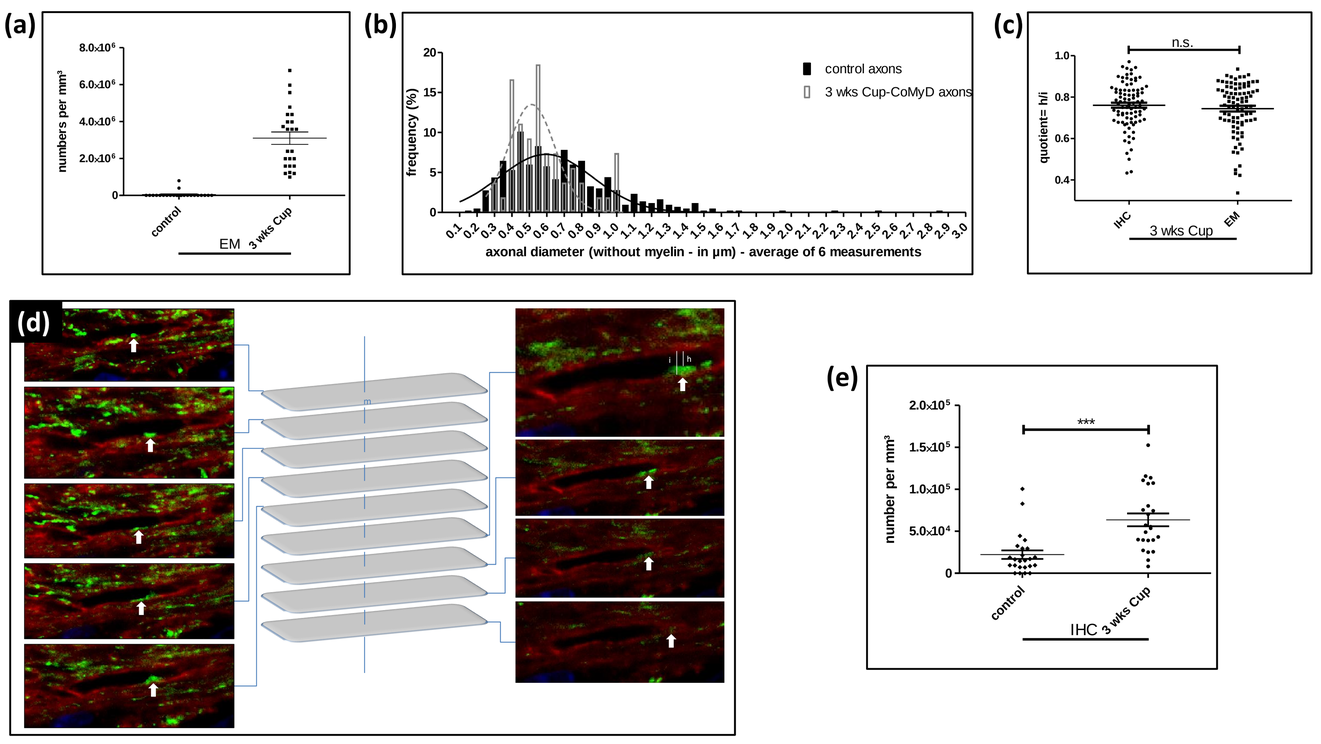

Figure 3 – (**a**) CoMyD numbers, analyzed in 3D scanning electron microscopy image stacks. (**b**) Quantification of axonal diameters showing CoMyD pathology. (**c**) Quantification of CoMyD dimensions, analyzed in confocal images. (**d**) Representative confocal CoMyD image stacks. Sections were labelled using antibodies directed against the myelin marker PLP (red) and a neurofilament marker SMI-312 (green). (**e**) CoMyD numbers, analyzed in confocal image stacks.

Electrophysiology analysis of corpus callosum axons

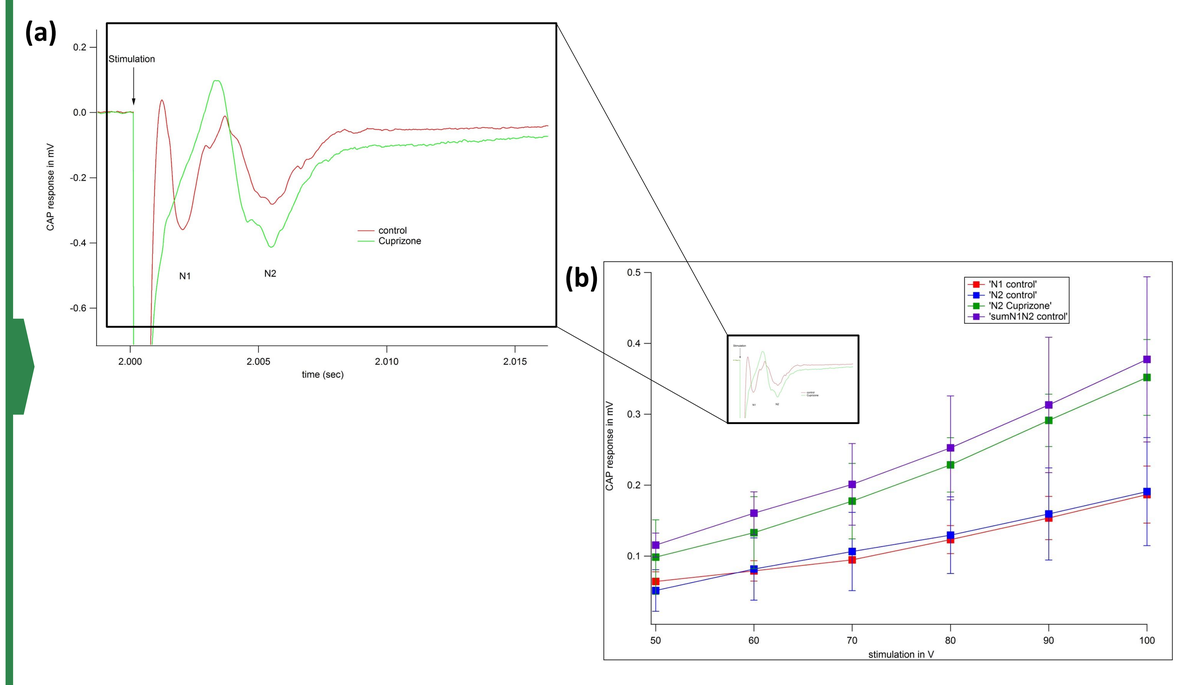

Figure 4 – (**a**) Representative compound action potential (CAP) recordings, obtained from acute brain slices containing corpus callosum of control and 3 wks cuprizone intoxicated mice. N1 indicates myelinated axons and N2 non-/de-myelinated axons. (**b**) Quantification of N1 and N2 CAP amplitudes . Note that the N2-Cuprizone response (green) does not reach the sum of N1N2-control response (purple).

Discussion

Our studies show a centrifugal progression of oligodendrocyte pathology during Cuprizone-induced metabolic injury. After initial oligodendrocyte cell body pathology, we propose that retraction of oligodendrocytes' processes leads to retraction forces, resulting in CoMyD eventually paralleled by axonal injury. Future studies have to show whether CoMyD as well occurs in MS, and which factors regulate this process.

Literature

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