PATHOLOGICAL SUBSTRATE OF MRI-DERIVED CORTICAL ATROPHY IN MULTIPLE SCLEROSIS

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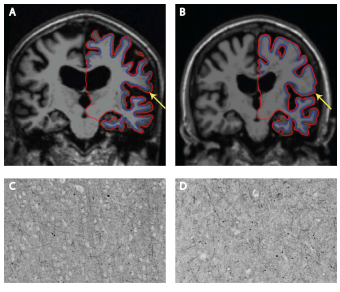
Background: In multiple sclerosis grey matter atrophy is clearly visible and correlated with disability and disease progression. It is still unknown which pathological changes are causing it. We aimed to investigate in a postmortem MRI study the histopathological correlates of MRI-measured cortical atrophy.

Methods: 11 postmortem MS donors of the Netherlands Brain Bank underwent at around 4h post-mortem whole-corpse in-situ MRI scan (1.5T, saggital direction, voxel size 1.2/1.2/1.2mm). Regional GM volumes were quantified after "lesion-filling" using FreeSurfer 5.3 with FLAIR pial refinement and manual editing. Tissue blocks were systematically sampled from the frontal superior, frontal inferior, cingulate, temporal superior, parietal inferior cortex. The following were histopathologically determined using semi-automated quantitation: neuronal numbers, shape and size, axonal, dendritic, synapse and myelin density, numbers of astrocytes, microglia, oligodendrocytes. Regional brain volumes from the same anatomical regions as the sampled cortical blocks were modeled using Generalized Estimating Equations correcting for anatomical region and false discovery rate.

Results: 7 out of 11 patients were men, 10 had SPMS, mean age was 68 years, mean disease duration 35 years, most frequent cause of death was pneumonia (5 patients).



Mean normalized brain volume was 1.27L (FSL-SIENAX), mean T2 lesion volumes 19.3mL. Two predictors survived the correction for false discovery rate: axonal density was positively correlated to grey matter volume in the inferior frontal gyrus (R^2=64%, see Figure), and astrocytes numbers correlated negatively with GM volume in/of the superior frontal gyrus (R^2=41%).

Discussion: These results suggest first, that there are regional differences in the neuropathological substrate of GM atrophy as measured with MRI. Second, GM atrophy appears to be predominantly driven by changes of the neuropilema and gliosis, and not by inflammation or demyelination.