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Characterization of Disease Dynamics in Multiple Sclerosis – Detection of New and Active Lesions and their Effect on Brain Parenchyma by Means of Voxel-Guided Morphometry

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This thesis reports a first-time application of voxel-guided morphometry (VGM), a Magnetic Resonance Imaging (MRI) based volumetry method, to multiple sclerosis (MS). VGM maps are sensitive to the detection of regional brain atrophy. The relationship of focal lesions and the development of brain atrophy was investigated. Two T1w MR datasets from 92 relapsing-remitting MS patients obtained each 12 months apart were analysed with VGM.

New lesions and volume changes in focal MS lesions as well as in the surrounding tissue were identified on colour coded VGM maps. Lesions were categorized in active and inactive lesions. Active lesions were either new lesions (NL) on T1-weighted (T1w) MRI (volume increase above 5% in VGM), chronic enlarging lesions (CEL) (pre-existent T1w lesions with volume increase above 5%), or chronic shrinking lesions (CSL) showing a volume reduction above 5% in VGM.

The frequency and spatial characteristics of active lesions were in line with the known frequencies and regional distribution of subcortical and cortical lesions in MS: NL per patient per year 2.0 (literature: 1-5), 7.1% GM lesions (literature: 5-10% GM lesions), and lesion size 6.0 mm (NL), 11.7 mm (CEL), and 9.6 mm (CSL) with a total range of 2-70 mm on T1w MRI.

Several patterns of regional brain volume shrinkage in relation to focal active lesions (NL, CEL, CSL) were detectable and subsequently also statistically analysed. Typically the focal active lesion was accompanied by an area of tissue shrinkage in an anatomically and functionally related region. Interestingly even CSL were associated with regional brain volume loss. For two anatomically well defined regions and predilection sites in MS further statistical analysis was performed. It was investigated whether the observed tissue shrinkage was due to an underlying connectedness to focal active lesions or were a chance finding. 1. Volume loss within the corpus callosum, a region frequently involved in MS patients, was highly correlated (point-biserial correlation) with the number of lesions in its close proximity. This was tested for the frontal and occipital callosal half separately. Significant results for (peri-)callosal NL (frontal: $\alpha < 0.02$, occipital: $\alpha < 0.05$) and CEL (frontal: $\alpha < 0.005$, occipital: $\alpha < 0.0005$) with callosal volume reduction were seen. In this context pericallosal CSL were significantly correlated with callosal volume loss only occipitally ($\alpha < 0.02$). 2. In addition volume reduction of the lateral geniculate nucleus (LGN) was also observed to be correlated with lesions along the optic radiation in keeping with the concept of retrograde transsynaptic degeneration. Point-biserial correlation of volume reduction within the LGN with NL, CEL, and CSL situated along the optic radiation revealed highly significant results ($\alpha < 0.0001$ for NL, $\alpha < 0.02$ for CEL, and $\alpha < 0.0001$ for CSL). The observed patterns of local brain volume loss may be interpreted as lesion-related tissue shrinkage, which is suggestive of and in line with tissue degeneration, e.g., Wallerian, retrograde, and/or (retrograde) transsynaptic degeneration.

In conclusion, VGM analyses provide strong evidence that all active lesion types (NL, CEL, and CSL) can contribute to brain volume reduction in the vicinity of lesions and/or in anatomically and functionally related areas of the brain.