Loss of Callosal Fibre Integrity in Healthy Elderly with Small Vessel Disease

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Background: Subtle but progressive clinical features like dysexecutive syndromes and dyspractic gait disturbances as well as urinary dysfunction with insidious onset are frequent in patients with cerebral small vessel disease (SVD). However, the pathophysiology beyond an increasing number and extent of white matter lesions is not known. We investigated the consequences of white matter lesions (as seen on FLAIR) on microstrutural tissue integrity (on DTI) in healthy appearing white matter. We hypothesized, that structural brain connectivity might be affected beyond the visible lesion load. With TBSS a whole brain voxelwise analysis of diffusion tensor imaging (DTI) and furthermore a quantitative analysis of corpus callosum (CC) area were performed as measure of white matter tract integrity.

Methods: In a prospective explorative approach clinical and MRI data (DTI, FLAIR, MP-RAGE) of 34 subjects with no or mild (n=22, Fazekas 0-1) and advanced (n=12, Fazekas 2-3) SVD were acquired on a 3T MRI scanner (Siemens Trio). DTI data (TR/TE 9200/95 ms, 128x128 matrix, 54 slices of 2.5mm thickness, b=0/900 s/mm² in 30 directions) were analysed in the TBSS framework (www.fmrib.ox.ac.uk/fsl). Fractional anisotropy (FA) maps were created and registered into standard space. A mean FA skeleton representation was generated and a voxelwise statistics was performed comparing mild with advanced SVD subjects. Mid-sagittal corpus callosum area (total and in subdivisions CC1-CC5) was calculated from MP-RAGE data and group statistics applied. White matter lesion volume was calculated from FLAIR images with a semiautomatic approach using MRIcron and a lesion probability map was created.

Results: The two groups did not differ significantly with respect to demographic parameters. The median MMSE value was lower in those with advanced SVD, though still in the normal range (29.0), while median MOCA was outside the normal range (24.5), but not significantly different between the groups. Furthermore, subjects with advanced SVD did not show an impaired motor performance.
TBSS analysis revealed lower FA values in subjects with advanced SVD in several white matter tracts: the large parts of the corpus callosum and several association tracts (see *Figure*). Projection fibres like the cortico-spinal tract were spared. These alterations affected also areas without white matter lesions (as shown in the lesion probability map). Corpus callosum area was reduced in subjects with advanced SVD with emphasis on the regions with lower FA values.

Discussion: TBSS demonstrates reduced FA in the corpus callosum and association fiber tracts, anatomical structures that themselves are typically not affected by T2-hyperintense lesions in SVD. The FA reduction might be the result of neurodegeneration due to lesions in the vicinity of the lateral ventricles, a frequent site of white matter lesions. Loss of white matter integrity in the corpus callosum might well explain dyspractic gait abnormalities and dysexecutive syndromes in SVD patients and appears to be already detectable in healthy elderly. This is also important background information to better understand changes of brain activation in reward learning paradigms.

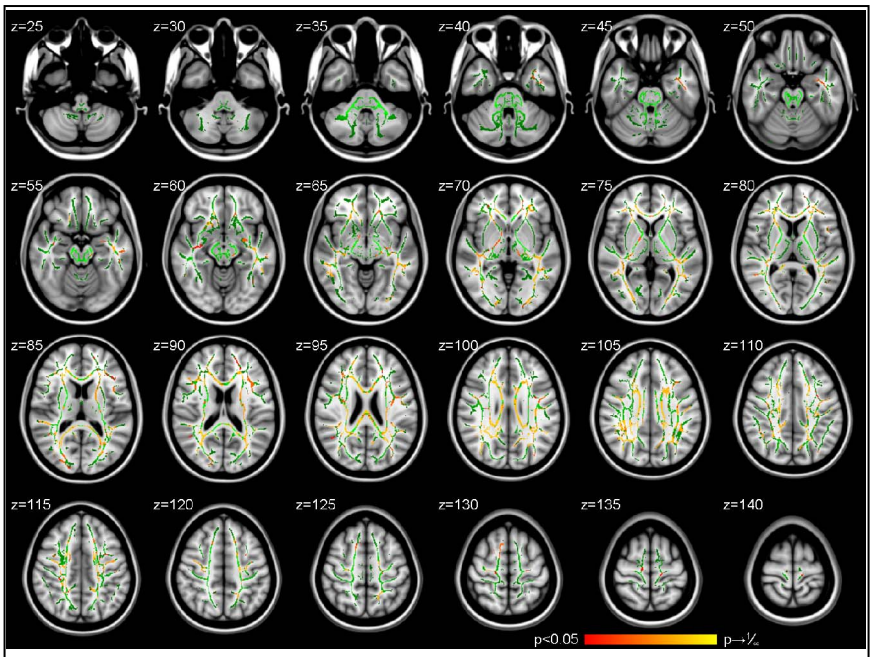

Figure: TBSS results superimposed on the MNI152 template: Significant FA decrease of the group with advanced SVD compared to the group with mild SVD. The colour green shows the group skeleton (without difference in FA value); the colour scale red to yellow indicates skeletal voxels with a significant FA reduction of at least p<0.05. Affected tracts include the corpus callosum (subdivision CC1, CC2, CC4, CC5), the inferior and superior longitudinal fasciculus and the uncinate fasciculus.

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