Grey and white matter atrophy in MS: Associations to corticospinal tract degeneration and upper spinal cord atrophy are restricted to relapsing-remitting MS

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Disease progression in multiple sclerosis (MS) is accompanied by degenerative processes both in the brain and spinal cord, including areas of grey and white matter that may appear normal on conventional MRI. Relapsing-remitting (RR) MS is characterized by acute inflammatory episodes which can regress to certain extend, while secondary progressive (SP) MS is dominated by a continuous progression of disability with chronic lesions, gliosis and irreversible axonal damage. Brain atrophy, which is a non-specific marker of tissue degeneration, can be observed already in early phases of the disease in both MS subtypes. However, regional atrophy evolves differently according to the MS subtypes: while RRMS is dominated by ventricular enlargement, cortical atrophy seems to be more important in SPMS [Pagani 2005]. Also, atrophy of the upper spinal cord (USC) is a common observation already in early MS. Previous studies have shown significant correlations of USC atrophy with disability [Edwards 1999, Lin 2003]. USC atrophy seems to be closer related to subtle degeneration in the normal appearing white matter of the spinal cord than to spinal cord lesions [Evangelou 2005] and it has been suggested that the decrease in spinal cord area seen in MS is related to anterograde Wallerian degeneration of axons which are transacted by distant focal lesions in the supratentorial brain [Hesseltine 2006, Bot 2004]. These processes would be mediated through the pyramidal tract, which comprises axons originating in the cortex (primary motor cortex, supplementary and premotor areas and others) and traveling downwards through the brainstem to the upper spinal cord.

Fiber integrity within the corticospinal tract can be assessed by DTI quantification, namely by the DTI indices fractional anisotropy (FA) and mean diffusivity (MD). FA decline is interpreted as a marker for axonal damage, while an increase in MD is largely complementary, but is also sensitive to the presence of edema and other processes leading to cellular barrier breakdown [Le Bihan 2001]. The pyramidal tracts are highly anisotropic and have a well defined anatomical course. Studies have shown that the pyramidal tracts are affected by MS already in early stages of the disease and are clinically relevant to motor impairment [Colombo 2000, Wilson 2003].

In order to assess the hypothesis of anterograde degeneration leading to spinal cord atrophy, we have investigated the degree of and the associations between -brain grey and white matter atrophy, -fiber integrity within the pyramidal tract and -upper spinal cord atrophy for patients with MS.
Methods and Materials

For 37 MS-patients (RRMS: n=19; SPMS: n=18) and 20 age and gender matched healthy controls grey matter volumes (GM), white matter volumes (WM), and the mean cross-sectional area of the USC were assessed. Additionally, FA and MD were quantified in the posterior limb of the corticospinal tract (CST) at the level of the internal capsule (FA\textsubscript{IC}; MD\textsubscript{IC}). Demographic and clinical information of the study cohorts are summarized in table 1 on page __. All volumetric quantification and DTI post-processing were done with NeuroQLab© software system as described below.

**MR-imaging:** Brain MRI was performed on a 1.5 T scanner and included in a single session for volumetry: sagittal high resolution T1-weighted (MPRAGE) acquisition with TE: 3.93 ms, TR: 1900 ms, TI: 1100 ms, resolution: [1 x 1 x 1.5] mm\textsuperscript{3}, 128 slices; for DTI: axial single shot EPI DTI datasets [6 gradient directions, b= 0 / 1000 s/mm\textsuperscript{2}, TE: 109 ms, TR: 8500 ms, resolution [2.5x2.5x2.5] mm\textsuperscript{3}, 47 slices volumes.

**Volumetry:** All volumes were derived from the same 3D MRI datasets. In particular brain and upper spinal cord volumes were calculated using a reliable semi-automated technique based on an interactive watershed transform and a fully automated histogram analysis. Measurement of the brain yielded the total brain volume (including the cerebellum and the brain stem), the corresponding volumes of WM and GM and the intra-cranial volume (ICC) (Figure 2 on page 6) [Lukas 2004]. The ICC was used to normalize all individual volumetric measures with respect to size, gender and age specific differences [Whitwell 2001]. For USC volumetry spinal cord volumes were segmented and quantified within a section of predefined length. The mean cross-sectional area within section was then calculated by dividing the volume by the defined section length (Figure 3 on page 7) [Lukas 2008]. Reliability and usefulness of these methods have been established in different types of neurodegenerative diseases, including SCA and multiple sclerosis [Lukas 2004, Lukas 2006].

**DTI quantification:** DTI parameters FA and MD were quantified using a probabilistic mixture model by which pure fiber tissue inside a region is separated from background and mixture voxels to effectively reduce partial volume effects and measurement variability [Schlüter 2004, Schlüter 2006, Schimrigk 2007]. In the post-processing procedure, three evaluation planes orthogonal to the main fiber direction of the CST have been chosen from the color-coded 3D dataset. Mean and standard deviation (SD) of the DTI metrics of the pure tissue fraction have been obtained from ROIs covering the posterior limb of the internal capsule (Figure 4 on page 8, Figure 5 on page 9). The effective FA\textsubscript{IC} and MD\textsubscript{IC} in the internal capsule was calculated as the mean value of the results of the left and right branch of the CST from the three distinct levels: (1) center of the internal capsule at maximal extension of the left and right thalamus, (2) caudal
border of the internal capsule at the level of the medial bend of the CST, (3) midbrain level of the cerebral peduncles.
**Fig. 0:** demographic and clinical data 1: mean+/-standard deviation 2: mean+/-standard deviation, [range: minimum - maximum]

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Fig. 0: Brain Volumetry: quantification of grey and white matter volume

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Fig. 0: Upper spinal cord volume

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**Fig. 0:** DTI: definition of evaluation planes along the corticospinal tract

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**Fig. 0:** DTI: tissue classification before quantification

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Results

Group differences between the MS patients and the control group

MRI characteristic of patients and normal controls are depicted in Figure 1 on page 13. Statistical significance of group differences has been assessed by an analysis of variance with age as a covariate and gender as a fixed factor. In MS patients atrophy was found in all assessed volumes, being most pronounced in SPMS patients.

Differences between SPMS patients and healthy controls were highly significant for all volumes. In contrast, the differences in the RRMS group did not reach significance, whereas WM atrophy was marginally significant on a level of p=0.067. In all MS patients DTI indices were significantly altered when compared to normal controls, in that FA_{IC} was reduced and MD_{IC} was elevated. However, no significant difference of DTI indices between RRMS and SPMS was found. Inspection of the dependency of FA_{IC} and MD_{IC} on disease duration (Figure 2 on page 13) revealed a continuous process of fiber degeneration in the RRMS phase, which reaches a constant level after about 5 years.

Correlations of the MR results with the clinical parameters

Correlations between the clinical parameters EDSS, maximum walking distance and disease duration with different CNS volumes and DTI indices in the CST were investigated by a partial correlation analysis controlled for age.

In RRMS correlations were significant for brain GM and WM, and mean USC area with EDSS (negative correlations: GM (k=-0.528 p=0.024), WM (k=-0.787 p<0.001), USC (k=-0.654 p=0.003)) and maximum walking distance (positive correlation GM (k=0.673 p=0.002), WM (k=0.637 p=0.005), USC (k=0.753 p<0.001)); but not with disease duration. Similarly, MD_{IC} correlated highly significant with the EDSS (positive correlation k=0.597 p=0.009) and maximum walking distance (negative correlation k=-0.757 p<0.001). In contrast, FA_{IC} correlated moderately only to the maximum walking distance (k=0.531 p=0.023).

In SPMS subjects we found only few correlations between the MR derived results and clinical parameters, namely: significant negative correlations between the USC mean area and disease duration (k=-0.597 p=0.011). A tendency for positive correlation between FA_{IC} and the maximum walking distance (k=0.477 p=0.053) did not reach significance in the SPMS group.

Correlations between the DTI indices and the CNS volumes
A partial correlation analysis with age as the control variable (Figure 3 on page 14) revealed highly significant correlations in RRMS patients between brain GM volume and FA<sub>IC</sub> and MD<sub>IC</sub>. The correlation between GM volume and mean cross-sectional USC area was borderline significant. Brain WM volume correlated moderately to MD<sub>IC</sub> and with high significance to the mean USC area.

In contrast, no significant correlation between GM volume and any DTI indices was found in SPMS subjects. However, brain WM was found to correlated significantly to FA<sub>IC</sub> in this subgroup.
### Fig. 0: MRI characteristics of patients and normal controls; 1: mean ± standard deviation 2: significance of the difference of the mean value in comparison to the healthy control group: ** highly significant, * significant, n.s. not significant, by GLM ANOVA with age as covariate and gender as fixed factor

<table>
<thead>
<tr>
<th></th>
<th>all patients(^1,2)</th>
<th>RRMS(^1,2)</th>
<th>SPMS(^1,2)</th>
<th>healthy controls(^1)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Grey Matter vol. / ml</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>589.0±56.7 **</td>
<td>621.7±29.5 n.s.</td>
<td>554.4±58.5 **</td>
<td>635.2±42.7</td>
</tr>
<tr>
<td></td>
<td>p=0.002</td>
<td></td>
<td>p&lt;0.001</td>
<td></td>
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<tr>
<td><strong>White Matter vol. / ml</strong></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>556.0±55.8 *</td>
<td>568.9±48.7 p=0.063</td>
<td>542.3±60.7 **</td>
<td>597.4±31.3</td>
</tr>
<tr>
<td></td>
<td>p=0.012</td>
<td></td>
<td>p&lt;0.001</td>
<td></td>
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<tr>
<td><strong>Upper Spinal Cord mean area / cm(^2)</strong></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>71.0±9.6 **</td>
<td>74.8±7.7 n.s.</td>
<td>67.0±9.9 **</td>
<td>79.3±6.9</td>
</tr>
<tr>
<td></td>
<td>p=0.002</td>
<td></td>
<td>p&lt;0.001</td>
<td></td>
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<tr>
<td>(A_{IC})</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.66±0.03 **</td>
<td>0.66±0.04 **</td>
<td>0.65±0.03 **</td>
<td>0.70±0.02</td>
</tr>
<tr>
<td></td>
<td>p&lt;0.001</td>
<td></td>
<td>p&lt;0.001</td>
<td></td>
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<tr>
<td>(MD_{IC})</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>0.72±0.03 **</td>
<td>0.72±0.03 **</td>
<td>0.72±0.03 **</td>
<td>0.69±0.01</td>
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<tr>
<td></td>
<td>p&lt;0.001</td>
<td></td>
<td>p&lt;0.001</td>
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**Fig. 0**: Scatterplots of MD and FA in the internal capsule in dependence on disease duration show a progressive phase during the first 2 to 5 years.

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<table>
<thead>
<tr>
<th></th>
<th>GM / ml</th>
<th>WM / ml</th>
<th>USC / cm²</th>
</tr>
</thead>
<tbody>
<tr>
<td>RRMS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FAIC</td>
<td>k=0.772 ** p&lt;0.001</td>
<td>n.s.</td>
<td>n.s.</td>
</tr>
<tr>
<td>MDIC</td>
<td>k=-0.860 ** p&lt;0.001</td>
<td>k=-0.470 * p=0.049</td>
<td>k=-0.495 * p=0.037</td>
</tr>
<tr>
<td>GM / ml</td>
<td>-</td>
<td>k=0.477 * p=0.046</td>
<td>n.s.</td>
</tr>
<tr>
<td>WM / m</td>
<td>k=0.477 * p=0.046</td>
<td>-</td>
<td>k=0.598 ** p=0.009</td>
</tr>
<tr>
<td>USC / cm²</td>
<td>k=0.461 p=0.054</td>
<td>k=0.598 ** p=0.009</td>
<td>-</td>
</tr>
<tr>
<td>SPMS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FAIC</td>
<td>n.s.</td>
<td>k=-0.510 * p=0.037</td>
<td>n.s.</td>
</tr>
<tr>
<td>MDIC</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
</tr>
<tr>
<td>GM / ml</td>
<td>-</td>
<td>n.s.</td>
<td>n.s.</td>
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<tr>
<td>WM / m</td>
<td>n.s.</td>
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<td>n.s.</td>
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<tr>
<td>USC / cm²</td>
<td>n.s.</td>
<td>n.s.</td>
<td>-</td>
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</table>

**Fig. 0:** Correlation analysis between DTI indices and CNS volumes; partial correlations controlled for age; k: correlation coefficient; p: significance, ** highly significant, * significant, n.s. not significant

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Conclusion

There has been evidence in several MS studies that spinal cord atrophy is clinically relevant and correlates well with patient disability [Furby 2008, Lin 2003]. Anterograde degeneration initiated by supratentorial pathology has been proposed as a mechanism leading to upper spinal cord atrophy [Bot 2004]. To test this hypothesis we have assessed WM and GM atrophy of the brain as a global marker for degeneration and correlated these with fiber integrity within the pyramidal tract and atrophy of the USC.

We found significant brain atrophy of GM and WM as well as atrophy of the USC in the SPMS group. In RRMS, GM and WM and USC area were also reduced in comparison to healthy controls, but did not reach statistical significance. However, fiber integrity within the pyramidal tracts at the level of the internal capsule, as quantified by the DTI indices was degraded similarly in both MS subtypes. The dependency of the DTI indices on disease duration gave rise to the interpretation, that fiber degeneration within the CST evolves in RRMS and possibly reaches a constant level in the secondary progressive phase of the disease.

Correlation analysis in the RRMS group showed highly significant associations between GM atrophy in the brain and FA_{IC} and MD_{IC} respectively, reflecting fiber degeneration in the pyramidal tracts. In contrast, WM atrophy was correlated only to MD_{IC} in the pyramidal tracts potentially reflecting the characteristic patterns of degeneration in RRMS, which is dominated by periventricular white matter lesions and acute inflammation. As MD_{IC} is more susceptible to inflammatory tissue changes than FA_{IC}, MD_{IC} in the CST may be correlated with WM atrophy, while FA_{IC} is not.

In contrast to WM, global GM volumes in RRMS did not correlate to USC atrophy although correlations between GM volume and fiber integrity in the pyramidal tract were highly significant. GM atrophy in RRMS has been shown to results mainly from deep grey matter affection, like the thalamus [Ceccarelli 2008]. The relatively close vicinity of the deep grey matter structures to the pyramidal tract may lead to secondary axonal degeneration in the CST, as reflected by our results. However in our study due to the technical limitations of our more global approach of assessing GM volumes, we were not able to investigate deep grey matter involvement in detail.

Correlations between MD_{IC} and mean USC atrophy were significant; as were the according direct correlations between brain WM atrophy und the decrease of the mean upper spinal cord area. This supports the hypothesis, that in RRMS white matter pathology within the brain is involved in USC atrophy possibly due to anterograde degeneration via the corticospinal tract.

In contrast, global GM atrophy in RRMS seems not to be involved in anterograde degeneration in the USC.
In the SPMS patients atrophy was pronounced in both brain and upper spinal cord volumes. Nevertheless we found no significant correlation between grey matter atrophy and the DTI indices. For brain WM and FA_{IC} a positive association was found. Additionally no significant correlations between brain atrophy and mean USC area or DTI indices and mean spinal cord area were observed. These results are in agreement with previous findings by Furby et al. [Furby 2008] showing that SPMS patients had very limited correlations between brain GM and WM with upper spinal cord area.

Thus in SPMS patients direct associations between the degenerative processes in the brain and the upper spinal cord by anterograde degeneration involving the corticospinal tract do not seem to be a major process. Our results give rise to the interpretation, that degeneration within the pyramidal tract reaches a constant, high level in the secondary progressive phase of MS. Thus local pathology in the spinal cord and the cerebral cortex may play a more dominant role.

One limitation of this study is the global approach to GM and WM volumetry, which is not sensitive to local atrophy distribution. Thus, an increasing fraction of infratentorial atrophy e.g. brain stem atrophy may mask correlations between degeneration of cortical areas which are connected with the corticospinal tract and the upper spinal cord atrophy. Therefore additional inclusion of central atrophy measures and brainstem volume into our analysis is currently undertaken to further clarify the interactions between degeneration in different part of the CNS.
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