CHAPTER 4
COGNITIVE IMPAIRMENT IN RELATION TO MRI-METRICS IN PATIENTS WITH CLINICALLY ISOLATED SYNDROME

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ABSTRACT

BACKGROUND: Cognitive deficits are frequent in MS and have been associated with morphologic brain changes. Less information exists on their extent and relation to MRI findings in clinically isolated syndrome (CIS). It is also unclear if structural changes as detected by magnetization transfer (MT) imaging may provide an additional explanation for cognitive dysfunction.

OBJECTIVE: To analyse the extent of cognitive deficits and their relation to MRI-metrics including MT-imaging in CIS compared to relapsing remitting MS (RRMS).

METHODS: Forty-four CIS and eighty RRMS patients underwent the Brief Repeatable Battery of Neuropsychological Tests (BRB-N) and a 3T MRI-scan.

RESULTS: BRB-N subtests revealed similar results in CIS and RRMS. Impaired mental processing speed was most prevalent in both groups (CIS 13.6%; RRMS 16.3%) and thus served for correlation with MRI-metrics. Using stepwise linear regression analyses, the strongest predictor for decreased mental processing speed was normalized cortex volume (p<0.001) followed by T2-lesion load (p<0.05) in RRMS, whereas cortical MT-ratio was the only MRI parameter associated with decreased mental processing speed in CIS (p<0.005).

CONCLUSION: Cognitive dysfunction occurs in CIS in a pattern similar to RRMS, with impaired mental processing speed being most prevalent. Cortical MTR changes may be an early sign for tissue changes related to impaired mental processing speed in CIS while this association shifts to increased signs of cortical atrophy and lesion load in RRMS.
INTRODUCTION

Cognitive impairment occurs frequently in multiple sclerosis (MS), with a prevalence of up to 40%-70% and a wide spectrum of deficits (Amato, et al. 2006, Bobholz and Rao. 2003, Chiaravalloti and DeLuca. 2008). Independent from physical disability, cognitive impairment significantly affects the patients’ quality of life and impacts on employment and social functioning (Bobholz and Rao. 2003, Rao, et al. 1991b). Although there is evidence for cognitive deficits to occur already early in the course of the disease (Achiron and Barak. 2006), only some studies have examined patients with a clinically isolated syndrome suggestive of MS (CIS) (Achiron and Barak. 2003, Feinstein, et al. 1992, Feuillet, et al. 2007, Glanz, et al. 2007, Potagas, et al. 2008, Zipoli, et al. 2010). Whether the pattern of neuropsychological dysfunction in CIS is comparable to that in relapsing-remitting MS (RRMS) and predicted by similar morphologic findings on MRI is largely unknown. Furthermore, it is also unclear if structural changes as detected by magnetization transfer (MT) imaging may provide an additional explanation for cognitive dysfunction.

We therefore conducted a prospective study to explore the extent of cognitive impairment in CIS and the relation to MRI measures of brain pathology. We also included MT-imaging as a tool for quantifying structural changes in MS lesions, cortex, and normal appearing brain tissue (NABT) (Ropele and Fazekas. 2009).

PATIENTS AND METHODS

Study participants were prospectively enrolled from our MS outpatient department (from 2006 to 2009) and gave informed consent to participate in this study. The local ethics committee approved the conduct of this study. Inclusion criteria were a diagnosis of CIS (Miller, et al. 2008, Polman, et al. 2005) or RRMS (Polman, et al. 2005), regular follow-up visits, and the patients’ willingness to undergo detailed clinical and neuropsychological testing and a comprehensive MRI examination at a 3T magnet. Demographic and clinical data recorded included age, gender, age at disease onset, disease duration, and treatment. Disability was measured with the Expanded Disability Status Scale (EDSS) (Kurtzke. 1983). In patients with RRMS, we also assessed the annualized relapse rate as a measure of clinical disease activity. Relapses were defined as the appearance or reappearance of at least one neurological symptom or as the worsening of an old symptom attributed to MS that lasted for at least 24 hours and which was preceded by a relatively stable or improving neurological state of at least 30 days. Forty-four patients with a CIS and 80 with RRMS fulfilled these criteria and contributed to the analysis (for demographical and clinical data see table 1). Seven CIS patients receiving interferon-beta and fifty RRMS patients (interferon-beta: 32, glatiramer-acetate: 10; intravenous immunoglobulins: 5, natalizumab: 3) were on immunomodulatory treatment.

Neuropsychological testing

Neuropsychological testing was based on the Brief Repeatable Battery of Neuropsychological Tests (BRB-N) (Boringa, et al. 2001, Rao, et al. 1991a, Rao, et al. 1991b). Briefly, the BRB-N consists of the following subtests:

1. The Selective Reminding Test (SRT) which tests for verbal learning and memory using a list of 12 words. From up to six test trials, two measures of Immediate Recall (Long-Term
Storage, Consistent Long Term Retrieval) plus a score for Delayed Recall (SRT-DR) were generated.

2. The 10/36-Spatial Recall Test (SPART), measuring visuospatial learning and delayed recall (SPART-DR).

3. The Symbol Digit Modalities Test (SDMT), measuring information processing speed, sustained attention, and concentration over a duration of 90 seconds.

4. The Paced Auditory Serial Addition Test (3-second-version; PASAT3) which examines sustained attention and information-processing speed by evaluating an addition task regarding acoustically presented digits.

5. The Word List Generation (WLG) which measures semantic verbal fluency by evaluating the spontaneous production of words of a given category within 90 seconds. The score equals the number of correct answers given (WORD).

The BRB-N, translated and validated in German (Scherer, et al. 2004), was applied in a standardized, single test session by a trained clinical neuropsychologist in the following order: SRT, SPART, SDMT, PASAT3, SRT-DR, SPART-DR, WORD and lasted for approximately 30 minutes.

To limit the number of comparisons we generated scores for the following domains by adding the z-values of respective subtests and adjustment for age, gender and education (Scherer, et al. 2004): Memory (Immediate recall) (Consistent Long Term Retrieval, Long-Term Storage, SPART), memory (Delayed recall) (SRT-DR, SPART-DR), mental processing speed (PASAT, SDMT), and executive functions (WORD). Z-values below or equal -1.68 were considered as abnormal, which equates the performance of the lowest 5th percentile of healthy controls (Scherer, et al. 2004).

**Magnetic resonance imaging**

Patients underwent MRI at 3 Tesla (Siemens Tim Trio, Siemens Healthcare, Erlangen, Germany) using a 12 element receiver coil array and a consistent imaging protocol. Structural imaging included a fast FLAIR sequence (TR/TE/TI = 9000 ms/69 ms/2500 ms, in plane resolution = 0.9x0.9 mm², slice thickness = 3 mm) and a T₁-weighted 3D MPRAGE sequence with 1 mm isotropic resolution (TR/TE/TI/FA = 1900 ms/2.19 ms/900 ms/9°).

MT data were acquired with a spoiled 3D FLASH sequences (TR/TE/FA = 40 ms/7.38 ms/15°, in plane resolution = 0.9x0.9 mm², slice thickness = 3 mm) with and without a Gaussian shaped saturation pre-pulse (offset frequency = 1.2 kHz, duration = 10ms, FA = 50°).

**Image Analysis**

All image analyses were performed by trained and experienced technicians and interpreters, blinded to clinical information.

**Atrophy**

Brain tissue volume, normalized for subject head size, was estimated using SIENAX (Smith. 2002, Smith, et al. 2004), as part of FSL (Smith, et al. 2004). SIENAX starts by extracting brain and skull images from the single whole-head input data (Smith. 2002). The brain image is then affine-registered to MNI152 space (Jenkinson and Smith. 2001, Jenkinson, et al. 2002) (using the skull image to determine the registration scaling); this is done primarily to obtain the volumetric scaling factor for use as normalization for head size. Next, tissue-type segmentation
with partial volume estimation is carried out (Zhang, et al. 2001) to calculate the total volume of brain tissue (including separate estimates of volumes of gray matter, white matter, peripheral gray matter and ventricular CSF).

Lesion load
MS lesions were outlined on a transparency overlaid on hard copies of the FLAIR sequence. Using these templates, lesion masks were then created using the DISImage program (Plummer. 1992). The lesion load was calculated by multiplying the area of all masks by the slice thickness.

Magnetization transfer
Magnetization transfer ratio (MTR) maps were calculated according to the formula $MTR = (M_{ss} - M_0) / M_0$, where $M_{ss}$ and $M_0$ are the signal intensities obtained with and without MT saturation, respectively. The MTR maps then were registered with the MPRAGE and FLAIR scans using an automated affine registration tool (FLIRT as part of FSL, www.fmrib.ox.ac.uk/fsl). A mean MTR was calculated for lesions, cortex, and normal appearing brain tissue (NABT, i.e. whole brain tissue without lesions), analyzed with a histogram technique.

To obtain NABT, brain areas showing T2-lesions were removed from the MTR maps after dilating the lesion masks by one pixel, Non-brain tissue was removed using a brain extraction tool (BET as part of FSL, www.fmrib.ox.ac.uk/fsl). All remaining voxels in the MTR maps then were considered for the MTR histogram analysis.

For each histogram, the peak position, the relative peak height, i.e. the relative voxel count at the peak position, as well as the mean MTR were calculated. To correct for differences in individual brain volumes, the histograms were normalized by the total number of voxels contributing to the histogram. Cortical MTR data were obtained by masking the whole-brain MTR data with the cortical masks provided by SIENAX, after registering the MTR maps to the MPRAGE scan.

To obtain within lesion MT metrics, a mean MTR was calculated for each lesion by masking the MTR maps with the lesion masks. To reduce partial volume effects, which might have taken place due to image registration and subsequent interpolation, all masks were eroded by 1 pixel. The MTR of all lesions were averaged to obtain a mean lesional MTR for each patient.

Statistical analysis
We used SPSS 15.0 (SPSS Inc., Chicago, Illinois, USA) for statistical analyses. The chi square test was applied to compare frequencies between subgroups. The distribution of continuous data was tested with the Kolmogorov-Smirnov test. Comparisons between groups were then performed by Mann-Whitney U test or 2 tailed t-test. Spearman and Pearson correlations served to calculate correlation coefficients between demographic, clinical, imaging, and neuropsychological data in the patient groups. Stepwise linear regression models were applied on continuous variables to identify factors independently predicting decreased mental processing speed performance. The z-values of mental processing speed constituted the dependent variable. Stepwise linear regression analyses were performed separately for CIS and RRMS. Variables showing the strongest correlation with z-values of mental processing speed in the correlation analysis were then added to each regression model. Thus, in CIS, independent variables considered were mean cortical MTR, relative MTR peak height of NABT and $T_2$ lesion load, whereas in RRMS lesion load, normalized cortex volume and mean lesional MTR. Other variables did not enter the models due
to multiple co-linearity. Since age at disease onset was significantly different between CIS and RRMS, this variable was additionally added to each regression model.

RESULTS

We examined a total of 124 patients (Table 1). The distribution of gender and mean age were similar in both groups, but CIS patients were significantly older at disease onset (p<0.005). The median EDSS and the proportion of patients receiving immunomodulatory treatment were lower in the CIS cohort (Table 1).

Z-values of neuropsychological test results are shown in Table 2. No statistically significant differences between patient-subgroups were detected when applying t-test analyses, except for the global cognitive index score, showing decreased z-values in RRMS (p=0.05) (Table 2). We then used a suggested cut-off level of z-values below or equal -1.68 to determine abnormal test results, which equates the performance of the lowest 5th percentile of healthy controls (Scherer, et al. 2004) (Table 3). Again the proportions of abnormal test results did not significantly differ between CIS and RRMS patients. Considering the global cognitive index score as a measure of global cognitive performance, none of the patients would have scored abnormal. Deficits in mental processing speed were most frequent in both groups (CIS 13.6% vs. RRMS 16.3%), 18.2% of CIS and 21.3% of RRMS patients showed abnormal test results in at least one cognitive domain.

Table 1. Clinical and demographical data

<table>
<thead>
<tr>
<th></th>
<th>CIS</th>
<th>RRMS</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (% female)</td>
<td>44 (70.5)</td>
<td>80 (65.0)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Age (y)</td>
<td>33.9 (10.0)</td>
<td>37.0 (9.6)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Age at disease onset (y)</td>
<td>32.8 (9.1)</td>
<td>27.3 (8.3)</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Disease duration * (y)</td>
<td>0.2 (0.1-0.8)</td>
<td>8.1 (4.2-13.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Annualized relapse rate *</td>
<td>NA</td>
<td>0.6 (0.3-1.1)</td>
<td>NA</td>
</tr>
<tr>
<td>EDSS *</td>
<td>1.0 (0.0-2.0)</td>
<td>2.0 (1.0-2.9)</td>
<td>0.06</td>
</tr>
<tr>
<td>N treated patients (%)</td>
<td>7 (15.9)</td>
<td>50 (62.5)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

CIS, clinically isolated syndrome; RRMS, relapsing remitting MS; N, number of patients; y, years; EDSS, expanded disability status scale; n.s., statistically not significant; NA, not applicable; values are given as mean (SD) or as *, median (interquartile range) (χ² contingency test, 2-tailed t test, * Mann-Whitney U-test).

Table 2. Mean z-values (SD) of neuropsychological test results

<table>
<thead>
<tr>
<th></th>
<th>CIS</th>
<th>RRMS</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Memory (Immediate Recall)</td>
<td>0.79 (1.04)</td>
<td>0.38 (1.19)</td>
<td>0.06</td>
</tr>
<tr>
<td>Memory (Delayed Recall)</td>
<td>0.31 (0.89)</td>
<td>0.03 (1.16)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Mental processing speed</td>
<td>-0.49 (0.79)</td>
<td>-0.75 (0.90)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Executive function</td>
<td>0.69 (1.38)</td>
<td>0.29 (1.04)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Global cognitive index score</td>
<td>0.12 (0.38)</td>
<td>-0.04 (0.46)</td>
<td>0.05</td>
</tr>
</tbody>
</table>

CIS, clinically isolated syndrome; RRMS, relapsing remitting MS; n.s., statistically not significant (2-tailed t test).
As expected, the \(T_2\)-lesion load was higher and brain volume measures were lower in the RRMS cohort (Table 4). More specifically, CIS patients showed larger normalized whole brain, total gray matter and cortical gray matter volumes and a lower ventricular volume than RRMS patients, while there was no significant difference regarding white matter volume (Table 4). MTR histogram parameters in normal appearing brain tissue (NABT) including mean MTR, relative MTR peak height (rPH), and MTR peak position (PP) indicated more severe tissue changes in RRMS compared to CIS patients (Table 4). This was also suggested by the mean lesional and cortical MTR (Table 4).

Correlations of patients’ characteristics and imaging variables with neuropsychological data focused solely on mental processing speed, as this was the only domain demonstrating a sizeable proportion of dysfunction (Table 2 and table 3).

In CIS, we found no association of clinical and demographical data with mental processing speed, including age, age at disease onset, disease duration and the EDSS. In RRMS patients, mental processing speed correlated with the EDSS score \((r=-0.2; p<0.05)\), but not with age, age at disease onset, disease duration or the annualized relapse rate.

Considering MRI metrics, \(z\)-values of mental processing speed in CIS correlated with a higher \(T_2\) lesion load \((r=-0.3; p<0.05)\), a lower relative MTR peak height of NABT \((r=0.3; p<0.05)\),

### Table 3. Number (%) of patients with abnormal neuropsychological test results

<table>
<thead>
<tr>
<th>Test</th>
<th>CIS</th>
<th>RRMS</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Memory (Immediate Recall)</td>
<td>0 (0.0)</td>
<td>6 (7.5)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Memory (Delayed Recall)</td>
<td>1 (2.3)</td>
<td>7 (8.8)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Mental processing speed</td>
<td>6 (13.6)</td>
<td>13 (16.3)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Executive function</td>
<td>2 (4.5)</td>
<td>5 (6.3)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Global cognitive index</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

CIS, clinically isolated syndrome; RRMS, relapsing remitting MS; n.s., statistically not significant \((\chi^2\) contingency test).

### Table 4. Morphological data

<table>
<thead>
<tr>
<th>Test</th>
<th>CIS Mean (SD)</th>
<th>RRMS Mean (SD)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normalized volume [ccm]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brain</td>
<td>1649.1 (82.6)</td>
<td>1582.3 (96.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gray matter</td>
<td>893.8 (83.1)</td>
<td>842.0 (82.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cortex</td>
<td>721.9 (55.1)</td>
<td>678.0 (62.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>White matter</td>
<td>755.3 (56.7)</td>
<td>740.3 (50.4)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Ventricle *</td>
<td>27.8 (20.2-33.0)</td>
<td>39.2 (25.7-50.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lesion load [ccm] *</td>
<td>4.2 (2.0-12.1)</td>
<td>14.8 (4.5-29.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MTR NABT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean [%]</td>
<td>32.8 (0.7)</td>
<td>31.9 (1.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Relative peak height</td>
<td>0.7 (0.1)</td>
<td>0.6 (0.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Peak position [%] *</td>
<td>39.0 (38.7-39.5)</td>
<td>38.6 (37.6-39.5)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Mean MTR lesions [%]</td>
<td>34.3 (2.8)</td>
<td>31.8 (2.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean MTR cortex [%]</td>
<td>29.2 (0.8)</td>
<td>28.8 (0.8)</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

CIS, clinically isolated syndrome; RRMS, relapsing remitting MS; MTR, magnetization transfer ratio; n.s., statistically not significant; NABT, normal appearing brain tissue; values are given as mean (SD) or as *, median (interquartile range) (2-tailed t test, * Mann-Whitney U-test).
and a lower mean cortical MTR \((r=0.4; \ p<0.05)\). Using a stepwise linear regression model, including the variables mean cortical MTR, relative MTR peak height of NABT, \(T_2\) lesion load and age at disease onset, mean cortical MTR was identified as the only independent predictor of decreased mental processing speed (Table 5). The model excluded the variables relative MTR peak height of NABT, \(T_2\) lesion load and age at disease onset.

In RRMS, \(z\)-values of mental processing speed correlated with increased \(T_2\) lesion load \((r=-0.5; \ p<0.001)\), a larger normalized ventricular volume \((r=-0.3; \ p<0.01)\), and lower normalized volumes of whole brain \((r=0.4; \ p<0.001)\), whole gray matter \((r=0.5; \ p<0.001)\), and cortical gray matter \((r=0.5; \ p<0.001)\). No significant correlation was found with white matter atrophy. Correlations were also seen with the peak position of NABT MTR \((r=0.3; \ p<0.01)\), the mean MTR of NABT \((r=0.3; \ p<0.01)\), the mean cortical MTR \((r=0.2; \ p<0.05)\), and the mean lesional MTR \((r=0.3; \ p<0.005)\). Using a stepwise linear regression model, including the variables lesion load, normalized cortex volume, mean lesional MTR and age at disease onset, normalized cortex volume was identified as the strongest predictor of decreased mental processing speed performance, followed by lesion load in the second and final step (Table 5). The model excluded the variables mean lesional MTR and age at disease onset.

### DISCUSSION

Using the BRB-N and a suggested grouping into cognitive domains (Scherer, et al. 2004) we found deficits in at least one cognitive domain in 18.2% of CIS patients. This is lower than in most earlier studies which reported prevalence rates of cognitive impairment in CIS ranging between 27.3%-80% (Achiron and Barak. 2003, Feuillet, et al. 2007, Kocer, et al. 2008, Potagas, et al. 2008). One likely explanation for these discrepancies is the usage of different cut-off levels and reference values for the BRB-N (Achiron and Barak. 2003, Feuillet, et al. 2007, Zipoli, et al. 2010). We used a conservative cut-off level, considering a test-result as abnormal if \(z\)-values were below or equal -1.68, which equates the performance of the lowest 5th percentile of healthy controls in a German-speaking population as in ours (Scherer, et al. 2004). Using a similarly restrictive approach, Potagas et al. and Zipoli et al. found prevalence rates of cognitive impairment in CIS of 27.3% (Potagas, et al. 2008) and 14.3%-25% (Zipoli, et al. 2010), which are closer to our observation. The use of different cognitive test batteries in some studies (Kocer, et al. 2008) is another likely reason for discordant results. Also, when considering the global cognitive index score as a measure of global cognitive performance, none of our patients would have scored abnormal, confirming that in early stages of the disease cognitive deficits may be

<table>
<thead>
<tr>
<th>Disease Course</th>
<th>Dependent variable</th>
<th>Step</th>
<th>Independent variable</th>
<th>Beta</th>
<th>Rho</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIS</td>
<td>Mental processing speed</td>
<td>1</td>
<td>Mean cortical MTR</td>
<td>0.5</td>
<td>0.5</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>RRMS</td>
<td>Mental processing speed</td>
<td>1</td>
<td>Normalized cortex volume</td>
<td>0.5</td>
<td>0.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2</td>
<td>Normalized cortex volume</td>
<td>0.4</td>
<td>0.5</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>T2-lesion load</td>
<td>-0.3</td>
<td>-0.4</td>
<td>&gt;0.05</td>
</tr>
</tbody>
</table>

CIS, clinically isolated syndrome; RRMS, relapsing remitting MS; MTR, magnetization transfer ratio.
rather domain specific (Amato, et al. 2008). In line with this, when using a different approach to define cognitive impairment (e.g. \( > 2 \) test \( > 2 \) SDs below the mean of normative values), only 2 out of 44 CIS and 6 out of 80 RRMS patients would have been classified as cognitively abnormal in our cohort. As a consequence, these small numbers precluded a comparison of cognitively impaired versus cognitively preserved patients using dichotomised analyses.

Here, we found deficits predominantly for mental processing speed. Previous studies have also shown cognitive deficits in tests for this domain as well as for visuospatial and verbal learning, attention, and semantic verbal fluency (Achiron and Barak. 2003, Feuillet, et al. 2007, Potagas, et al. 2008). Up to now, only scant information exists regarding a comparison of the pattern and frequency of cognitive impairment between CIS and RRMS (Potagas, et al. 2008). Interestingly, we found no significant differences between both subgroups, in line with Potagas et al. who noted a similar pattern of cognitive impairment throughout different MS subtypes including CIS (Potagas, et al. 2008). Although based on a limited number of individuals, these observations are intriguing as they suggest that cognitive deficits develop largely independent of MS relapses or the course of MS as characterized by other clinical findings.

In CIS patients, we also did not find any correlation of clinical and demographical characteristics with neuropsychological performance. This finding supports the assumption that in early stages of MS, cognitive deficits develop independently from or in advance of physical disturbances. Consistent with this notion, other studies in a CIS cohort (Feuillet, et al. 2007) and in patients with CIS or newly diagnosed MS (Glanz, et al. 2007) also failed to identify a relationship between cognitive performance and clinical data, including EDSS. Regarding RRMS, it has already been shown previously that both the EDSS and the time from disease onset are only poor predictors of cognitive dysfunction (Rao, et al. 1991a, Ron, et al. 1991). We also only found a weak to moderate correlation of EDSS scores with impaired mental processing speed. In this context it also has to be noted that our cohort of RRMS patients was only mildly disabled and certainly cannot be considered representative of the entire spectrum of relapsing MS.

At first, our observation of a similar pattern and frequency of cognitive deficits in CIS and RRMS certainly appears surprising, given the many significant differences in MRI findings between both patient groups. Distinct differences in the correlations between imaging variables and impairment in mental processing speed between CIS and RRMS may offer an explanation, however. In RRMS, stepwise linear regression analyses identified reduced cortical volume as the strongest independent predictor of reduced mental processing speed, followed by higher T2 lesion load. This is in accordance with previous reports on an association of neocortical volume decrease (Amato, et al. 2004, Benedict, et al. 2006, Calabrese, et al. 2009, Calabrese, et al. 2010) as well as higher lesion volume (Christodoulou, et al. 2003, Lazeron, et al. 2005) with cognitive impairment in MS patients. Although associations between poor cognitive performance and structural brain changes have been shown by other groups (including diffusion tensor imaging of gray and normal appearing white matter and NABT MT histogram analyses) (Filippi, et al. 2000, Rovaris, et al. 2008), none of the MTR parameters analyzed in our study demonstrated an independent predictive value for impairment in mental processing speed in RRMS. In CIS, patients with impairment in mental processing speed also had a significantly higher T1 lesion volume. However, when applying stepwise linear regression analysis, cortical MTR was the only variable independently associated with decreased mental processing speed. Altogether these findings suggest that structural cortical changes are the prevailing morphological correlate of the
early cognitive deficits seen in CIS. With advancing disease, other signs of tissue damage such as measures of brain atrophy and increasing T2 lesion load appear to factor in and gain in importance, which obscures this primary association. At that stage, MTR of the cortex then does no longer add independent information regarding the development of cognitive impairment, when cortical atrophy and T2 lesion load become its strongest predictors. While this explanation of our data is biologically plausible, it certainly will need confirmation from longitudinal observation.

Extending the conclusions drawn from associations of cognitive dysfunction with demographic and clinical data, these imaging results support the hypothesis that cognitive dysfunction develops independently from focal disease activity in the early phases of MS. This is also indicated by the results of other recent studies, which found no significant association between cognitive impairment and routine MRI measures (Achiron and Barak. 2003; Glanz, et al. 2007) in CIS and newly diagnosed MS patients. Altogether, these results provide evidence that cognitive impairment in CIS may develop in advance of evident morphological abnormalities detectable by routine MRI.

Our study has also several limitations that should be taken into account. One limitation is the lack of a control group of healthy subjects. Although we used a cut-off level of z-values below or equal -1.68, equating the lowest 5th percentile of healthy controls (Scherer, et al. 2004), to determine abnormal test results, direct comparisons with healthy subjects within the same study setting should be performed in future studies. Furthermore, the unequal number of CIS and RRMS patients in this study with an ensuing lower effect size in correlation analyses within the CIS group should be noted. Unfortunately we also did not collect information regarding depression or fatigue on our patients, which may be confounders of cognitive performance. However, these factors appear unlikely to have played a major role given the overall low prevalence of cognitive impairment in this study and the low disability of our patients. It would also have been interesting to see if patients with cognitive deficits differ in their future disease course from those without. A worse prognosis of cognitively impaired patients has been suggested by two recent studies (Portaccio, et al. 2009; Zipoli, et al. 2010). Unfortunately we do not yet have sufficient follow-up data to add to this discussion and this information is still being collected.

REFERENCES


