Quantitative Analysis of Magnetization Transfer Images of the Brain: Effect of Closed Head Injury, Age and Sex on White Matter

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Magnetization transfer (MT) imaging has an application in quantitative assessment of cerebral white matter. Previously published postprocessing methods have inherent problems, and therefore a new analysis technique is presented. This technique was found to be more sensitive for white matter changes in patients with a postconcussional syndrome, compared to other methods previously described. Because of the potential application of this technique in longitudinal and group studies, age and sex dependence of the MT ratio (MTR) of white matter were studied. In a group of 51 healthy subjects, a decrease in the mean MTR as well as an increasing distribution width of the MTR was found with increasing age. The mean MTR in males was higher than in females. These results stress the need to take age and sex into account when interpreting MTR data. Magn Reson Med 42:803–806, 1999. © 1999 Wiley-Liss, Inc.

Key words: magnetization transfer; quantitative imaging; normal aging; MRI

Conventional magnetic resonance (MR) imaging techniques provide a sensitive, noninvasive method for the detection of CNS pathology. Magnetization transfer imaging is a relatively new addition in this field. Because magnetization transfer (MT) readily occurs in the adult cerebral white matter, this technique has the potential to increase both sensitivity and specificity of MR imaging of white matter disease (1–7). Another advantage of MT-weighted imaging is that it is suitable for group analysis and longitudinal studies. There is a clinical application for quantitative MT imaging (MTI) in assessing the biological nature of tissue, especially of myelin in multiple sclerosis. In this field MT analysis is being increasingly used.

However, MT ratios (MTR) (8) are typically measured in a region of interest (ROI) and thus only a part of the brain is analyzed, and the results depend on the position of the ROI. Another approach is to analyze the entire data set by presenting the MTR data as a histogram (9). This method introduces a bias because the MT data of both gray and white matter are analyzed together and a change in gray/white ratio causes a change in the MTR histogram that is unrelated to a change in the MTR. A second issue is the effect of age and sex on MTR. Because MTI has the potential to be used in longitudinal and group studies, these effects on MTR need to be determined. Two studies have been published on this subject, with conflicting findings (10,11).

First we will propose an alternative method of postprocessing MT data. This method is tested on a patient population with a postconcussional syndrome (PCS). This patient group was selected because the (partially) organic etiology of PCS is still a matter of debate, as can be illustrated by the fact that PCS is often considered a psychosomatic syndrome. If a new imaging technique would show abnormalities in this group, it probably would do so in other conditions as well. Secondly, we will study the age- and sex-related changes of MTR of white matter in healthy subjects.

MATERIALS AND METHODS

Methods

MR images were acquired on a Philips ACS system operating at 1.5 T (Philips Medical Systems, Eindhoven, The Netherlands). MT-weighted imaging was performed with a spin-echo proton density weighted sequence (TR 1800 ms, TE 20 ms, slice thickness 6 mm, 0.6 mm gap, field of view 180 mm, scan matrix 128 × 90, two excitations). Two dynamic scans were acquired, one with and one without an off-resonance prepulse (prepulse 1000°, 20 ms, 1500 Hz offset). The slice orientation was coronal, and the part of the brain anterior to the splenium of the corpus callosum was included in the scan volume. The MT-weighted images were transmitted to a work station, and a MTR image was calculated as follows (8):

\[
MTR = (M_0 - M_p)/M_0,
\]

where \(M_0\) and \(M_p\) represent the signal intensity with the saturation prepulse off and on, respectively.

In the resulting image, the pixel gray scale value represents the local MTR. In a semiautomatic procedure the extracranial soft tissue, the skull, and CSF were removed, using the software program BrainImage (12). The resulting data set was used to generate a histogram. The histogram has a characteristic shape with a gradual slope on its left side, and a steep right slope. There are two peaks: one smaller gray matter peak at MTR 0.31, and a higher one for white matter at MTR 0.36 (Fig. 1).

First, the histograms were analyzed as described by van Buchem et al. (13); the shape and location of the histogram is characterized by the location and height of the white matter peak, the mean MTR and the 25, 50, and 75 percentile of the histogram. Correction for brain volume was achieved by normalizing the histogram area. Because the histogram is composed of data from gray as well as...
white matter, a change in ratio between these two will change the histogram peak height. Age-related changes in the gray/white matter ratio (14), as well as selective atrophy due to cerebral pathology (e.g., Alzheimer disease, multiple sclerosis), can change the histogram this way. Theoretically the peak height is therefore a less appropriate parameter to study MTR changes. The histogram width would be a more adequate parameter; however, the left slope of the white matter section of the histogram is overlapped by the gray matter peak. Curve fitting of the histogram proved unreliable. It was found that a third component was needed to allow for the gradual left slope, and a three component fit was highly variable and generally nonunique.

Since we are mainly interested in the white matter, we performed a segmentation on the MT-weighted images. A threshold-based technique was used in combination with successive erosions and dilations to ensure incorporation of all of the white matter. The MTR of the thalamus is close to the MTR of the cerebral white matter, and consequently this structure was partly included in the white matter segment.

The segmented volume is represented in a histogram, which has a single peak. Since the shape of this histogram resembles that of a Gaussian curve quite well (Fig. 1), we fitted the following function to the histogram:

\[ y = \alpha \cdot e^{-(MTR - \beta)^2/(2 \cdot \gamma^2)} \]

where \( \alpha \) is the amplitude of the curve, \( \beta \) the mean MTR of the curve, and \( \gamma \) the curve width or standard deviation (SD). The curve fitting procedure was implemented in SPSS (SPSS Inc., Chicago, IL) using the Levenberg-Marquardt estimation method. A curve fit was considered adequate when the correlation coefficient is greater than 0.99. In addition, all curve fittings were checked by visual inspection. The MTR distribution of white matter is thus characterized by the amplitude (\( \alpha \)), the mean MTR (\( \beta \)) and the curve width (\( \gamma \)). The basic assumption in this approach is that lesions lead to tissue heterogeneity, which manifests itself by a broadening and a shift of the histogram. The amplitude of the segmented white matter curve depends on the white matter volume or, after normalizing the histogram, the amplitude is inversely proportional to the curve width. Either way, the curve amplitude cannot provide unambiguous information on the MTR of the white matter, or the same information is presented in the curve width.

Statistical analysis was performed using parametric and nonparametric tests as appropriate. The relation between MTR histogram characteristics, age, and sex was studied with a multiple regression analysis.

Subjects
To assess the potential of this new postprocessing method, it was compared to the whole brain histogram analysis (13) using data of a group of 13 patients with a PCS (7 males, 6 females, mean age 40 years, range 21–62 years) and 13 controls, matched for age and sex (7 males and 6 females, mean age 40 years, range 20–62 years). The mean interval between the trauma and the MRI study was 4 years (1–12 years), and the median initial post-traumatic Glasgow Coma Scale (GCS) (15) score was 14 (9–15). All patients met the criteria of the DSM IV classification for the diagnosis postconcussional disorder (16).

For the analysis of age- and sex-dependent changes in MTR another group of subjects was assessed. Fifty-one healthy individuals [mean age of 55 years (range 21–77 years)], with a normal MRI study were recruited from the general population. The mean age of the males (\( N = 31 \)) is 53 years (range 26–76 years), the mean age of the females (\( N = 20 \)) is 58 years (range 21–76 years). The difference in mean age is not significant (\( p = 0.2 \)). All subjects had given informed consent to participate in the study, which was approved by the Medical Ethics Committee of the University Hospital Maastricht.

RESULTS
Histogram Analysis
The comparison of the results of the two methods of histogram analysis is shown in Table 1. The analysis of the whole brain histogram [approach according to van Buchem et al. (13)] showed a significant difference only for the histogram peak height (Table 1A). This parameter however depends on the gray/white matter ratio. The analysis of the segmented white matter shows the curve width to differ significantly between patients and controls (Table 1B). The amplitude also differs significantly between the two groups, but after histogram normalization, it contains the same information as the width. Although the mean MTR for the patients is lower than for the controls, the difference is not significant.

Clearly, the analysis of the segmented white matter is more sensitive for subtle white matter changes than the whole brain analysis. The parameter showing this white matter change, the curve width, does not depend on the gray/white matter ratio. This protocol was subsequently used for the second part of the study.
found that the curve width is sensitive to post-traumatic changes and shows a higher degree of significance than the descriptive histogram parameters of the gray and white matter together. This finding corroborates the hypothesis that the PCS has a partial organic etiology. At this point, the value of MT-weighted imaging in individual patients with PCS is still limited, because with a curve width of, e.g., 0.0182 as threshold, the sensitivity and specificity are 77% and 69%, respectively.

The analysis of the segmented white matter is useful in assessing MTR changes in pathologic conditions with a multifocal involvement of the white matter. When applying this method in group or longitudinal studies, it is important to gain understanding of the normal values and the effect of age and sex. We therefore used this new postprocessing method to establish the effects of age and sex on the MTR.

Our main finding is an age dependence of the mean MTR and the curve width. The mean MTR decreases with age, and the curve width increases with age. This stresses the need to take the age of individuals into account when interpreting MTR data. We also found a sex dependence of the mean MTR, males having a higher mean MTR than females. This is a new and unexpected finding. Age dependence of the MTR as observed by us was also found by Silver and co-workers (10). Metha et al. (11), however, did not find age-dependent changes of the MTR and neither of these studies reported sex difference in MTR.

The nature of the underlying structural changes of the brain in aging and in the post-traumatic brain is different, but both changes are shown by MTR analysis. In the chronic post-traumatic brain, reduction of MTR is most likely due to increased water content and gliosis in combination with structural changes to the myelin (17). It is unfortunate that neither for the aging brain nor for the normal-appearing white matter, pathologic anatomical correlation is available for regions with decreased MTR. Wong et al. showed a decrease of MTR in normal-appearing white matter in individuals with nonspecific periventricular high signal lesions as well as in the periventricular lesions (18). They assumed that the decreased MTR is caused by an increase of the water content due to gliosis. This might be an explanation for the decrease of the mean MTR and the increase of the distribution width of the MTR with age we found in our population.

A possible explanation for the difference between males and females is the different pattern of age-related changes in the brain. According to Murphy and co-workers (19), males show more frontal and temporal age-related volume loss, whereas females have age-related volume loss in the parietal lobe and the hippocampus. This loss of neurons will lead to Wallerian degeneration and subsequently to a decrease in the MTR (3) and an increase of the MTR distribution width. Because the scan volume in our study encompasses the brain anterior to the splenium, these

## DISCUSSION

MT imaging has shown abnormalities in normal-appearing white matter (5–7). To exploit the increased sensitivity of MT-weighted imaging, the entire volume of interest should be assessed, a demand not met by ROI measurements. One of the main parameters of the whole brain MTR histogram analysis (13), the histogram peak height, depends on the gray/white matter ratio. This ratio changes with age or selective atrophy of gray or white matter (e.g., Alzheimer or multiple sclerosis). We therefore performed the analysis on the MTR histogram of segmented white matter. It was found that the curve width is sensitive to post-traumatic

### Age- and Sex-Dependent Changes

The results of the analysis of age and sex dependence are shown in Tables 2 and 3. There is a correlation of the mean MTR with age: with increasing age the mean MTR decreases. This effect is seen in both males and females. Independent of the age effect, the mean MTR for males is higher than for females (Tables 2 and 3). There is also an effect of age on the curve width, as it increases with age. No significant sex differences were found for the curve width. To assess a possible effect of head size on the mean MTR, this parameter was added as a variable in the multiple regression analysis. Head size had no effect on the mean MTR ($\beta = 0.024$, $p = 0.82$).

### Table 1

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Patient mean (SD)</th>
<th>Control mean (SD)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histogram mean MTR</td>
<td>0.3010 (0.009)</td>
<td>0.3050 (0.010)</td>
<td>NS</td>
</tr>
<tr>
<td>Histogram peak height</td>
<td>31.78 (3.204)</td>
<td>34.06 (2.12)</td>
<td>0.044</td>
</tr>
<tr>
<td>Histogram peak perc.</td>
<td>0.2636 (0.010)</td>
<td>0.2700 (0.009)</td>
<td>NS</td>
</tr>
<tr>
<td>Histogram 50 perc.</td>
<td>0.3083 (0.009)</td>
<td>0.3113 (0.010)</td>
<td>NS</td>
</tr>
<tr>
<td>Histogram 75 perc.</td>
<td>0.3439 (0.009)</td>
<td>0.3469 (0.011)</td>
<td>NS</td>
</tr>
<tr>
<td>Histogram peak MTR</td>
<td>0.3515 (0.013)</td>
<td>0.3569 (0.013)</td>
<td>NS</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Male (SD)</th>
<th>Female (SD)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean MTR</td>
<td>0.3644 (0.007)</td>
<td>0.3523 (0.01)</td>
<td>&lt;0.000</td>
</tr>
<tr>
<td>Curve width</td>
<td>0.0181 (0.002)</td>
<td>0.0183 (0.002)</td>
<td>NS</td>
</tr>
</tbody>
</table>

1 The results of the combined gray and white matter analysis.

2 The results of the analysis of the segmented white matter.

## Table 2

### Results of Multiple Regression Analysis of Parameters of the Segmented White Matter Histogram in Healthy Subjects

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean MTR</th>
<th>Sex</th>
<th>$r^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean MTR</td>
<td>-0.44**</td>
<td>-0.51**</td>
<td>0.538</td>
</tr>
<tr>
<td>Curve width</td>
<td>0.41*</td>
<td>-0.02</td>
<td>0.164</td>
</tr>
</tbody>
</table>

**p < .001; *p < .005.

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**Table 3**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Male (SD)</th>
<th>Female (SD)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean MTR</td>
<td>0.3644 (0.007)</td>
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<td>Curve width</td>
<td>0.0181 (0.002)</td>
<td>0.0183 (0.002)</td>
<td>NS</td>
</tr>
</tbody>
</table>
age-related changes in the white matter can explain the higher correlation coefficient of the mean MTR and the curve width with age as well as the higher significance of these correlations for males as compared to females. This does not, however, fully explain the significantly different mean MTR of males and females, as this difference is also present in healthy controls below the age of 45. Our results therefore suggest a different composition of the cerebral white matter in males and females. Previous studies did not reveal significant sex differences in the T1 and T2 relaxation times of brain (20,21). There is no explanation for the sex difference presently found, and these findings clearly need replication.

The pulse-sequence applied by us is a spin-echo-based technique with a long repetition time to decrease the effect of the T2 relaxation on the MTR. The MTRs found with our technique with a long repetition time to decrease the effect clearly need replication.

The pulse-sequence applied by us is a spin-echo-based technique with a long repetition time to decrease the effect of the T2 relaxation on the MTR. The MTRs found with our pulse sequence are within the same range as published by others (10,11). The MTR of the genu of the corpus callosum in our study is typically 0.37 [0.36–0.40 (10,11)], and the MTR of CSF is below 0.05.

The new findings reported here need to be confirmed with improved segmentation methods including co-registration of MT-weighted images with T1- and T2-weighted images. Also the patho-anatomic basis of the age- and sex-dependent changes requires further study.

CONCLUSION

The analysis of the MTR histogram of segmented white matter seems to be a sensitive method to assess white matter changes, with potential applications in evaluating white matter disease. We have found MTR changes with age and a difference in mean MTR between males and females. The results of our study stress the need to take the age and sex of individuals into account when interpreting MTR data.

REFERENCES