MTI of white matter hyperintensities

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The severity of tissue changes associated with incidental white matter hyperintensities (WMH) in the elderly cannot be sufficiently determined by conventional MRI. We, therefore, performed a regional analysis of the magnetization transfer ratio (MTR) maps obtained on a 1.5 T scanner from 198 neurologically asymptomatic participants of the Austrian Stroke Prevention Study (mean age 70, age range 52–87 years) in regard to WMH and predefined areas of normal appearing brain tissue. Fluid attenuated inversion recovery MRI was used to grade lesion severity and for lesion volume measurements. The MTR of WMH was always significantly lower than that of normal appearing white matter (NAWM) with an overall relative reduction of ~10% and decreased significantly with increasing scores of WMH severity (P = 0.02) and WMH volume (r = −0.24, P = 0.0016). NAWM MTR was not different between subjects with very few and extensive WMH and the WMH volume was associated with NAWM MTR of the frontal lobes only. Concerning a possible impact on cerebral functioning the MTR of the frontal NAWM was significantly associated with fine motor dexterity (P = 0.04) but not with cognitive performance. A significant decline of the MTR with aging was seen in both NAWM and cortex but not in WMH. We conclude that MTR measurements can serve to quantify WMH associated tissue damage. It is predominantly focal, relatively mild, increases with lesion size and may have remote effects on the frontal white matter.

Keywords: ageing; cerebral small vessel disease; magnetization transfer imaging; white matter injury

Abbreviations: ASPS = Austrian Stroke Prevention Study; FLAIR = fluid-attenuated inversion recovery; MS = multiple sclerosis; MTI = magnetization transfer imaging; MTR = magnetization transfer ratio; NAGM = normal appearing grey matter; NAWM = normal appearing white matter; PVH = periventricular hyperintensities; ROI = region of interest; WMH = white matter hyperintensities


Introduction

Incidental hyperintensities of the deep and subcortical white matter on proton density, T2-weighted, and fluid-attenuated inversion recovery (FLAIR) MRI, i.e. so called white matter hyperintensities (WMH), are increasingly common with advancing age. Many lines of evidence imply a vascular aetiology (Pantoni and Garcia, 1995). Histopathologic studies suggest a rather wide range of tissue damage associated with these lesions. In general, the severity of tissue changes appears to increase with lesion size irrespective of identical signal abnormality on conventional MRI (Fazekas et al., 1998). A recent long-term follow-up study also suggests differences in WMH according to their size. Punctate lesions tended to remain unchanged while more severe WMH frequently expanded quite rapidly with time (Schmidt et al., 2003). From this it has been speculated that lesion progression would be indicative of focal spreading of tissue damage due to microangiopathy (Schmidt et al., 2004). However, WMH enlargement could also result from a ‘surfacing’ of pre-existing diffuse abnormality of the white matter which is not seen by conventional MRI.

Magnetization transfer imaging (MTI) has proven superior to conventional MRI regarding the detection and quantitation of subtle tissue changes especially affecting cerebral white matter (Tofts et al., 2003). This has been demonstrated most convincingly in multiple sclerosis (MS). Calculation of the magnetization transfer ratio (MTR) served to demonstrate alterations of otherwise normal-appearing white matter and it has been speculated that this kind of occult damage may contribute significantly to MS patients’ disability (Filippi, 2003). MTR measurements also provide a quite
accurate estimate of the severity of tissue destruction within MS lesions as shown by correlative histopathologic studies (Van Waesberge et al., 1999; Schmiter et al., 2004).

Based on these considerations we decided to use MTI for a quantitation of WMH lesion severity in a normal elderly population. We also attempted to search for coexisting changes in brain tissue that appears normal on conventional MRI. A few earlier MTI studies on the composition of the ageing brain have based their analysis primarily on MTR histograms (Hofman et al., 1999; Ge et al., 2002; Van der Flier et al., 2002; Rovaris et al., 2003). This allows for the acquisition of rapid and robust information on large tissue volumes. However, such data strongly depend on the quality of tissue segmentation and contain limited regional information. In view of our goals and following other reports (Mehta et al., 1995; Silver et al., 1997; Armstrong et al., 2004), we, therefore, decided to use a region of interest (ROI) approach. In a second step we also attempted to correlate the MTR data with the individuals’ cognitive and fine motor performance. To limit the number of correlations, we decided to do this for only those regions that would show MTR changes in relation to WMH volume.

Methods

Subjects

The study cohort was drawn from the Austrian Stroke Prevention Study (ASPS). This is a single-centre prospective follow-up study in our community which attempts to examine the frequency of cerebrovascular risk factors and their effects on cerebral morphology and function in the normal elderly as described earlier (Schmidt et al., 1997). The criteria for participation in this study are the absence of a history of neuropsychiatric and severe general diseases, and a normal neurologic exam. A randomly selected sub-sample of ASPS participants also undergoes neuroimaging studies including brain MRI. Following appropriate technical adaptation MTI was added to the scanning protocol and performed on 234 individuals. For the present analysis, we excluded 36 for the following reasons: motion artefacts on FLAIR or three dimensional-MTI scans: 22; silent infarcts: 6; single large lesions (>20 mm) or diffuse white matter changes of uncertain aetiology: 6; hydrocephalus: 2. This left a total of 198 individuals (136 female, 62 male; with a mean age of 70 years; age range 52–87). Informed consent was given by all participants in this study.

Magnetic resonance imaging

MRI was performed on a 1.5 T superconducting magnet (ACS-Intera, Philips Medical Systems) with a protocol that included a T2-weighted fast spin-echo sequence and a FLAIR sequence. Slice thickness was 5 mm with a 10% interlice gap. MTI was performed with a spoiled three dimensional gradient echo sequence (TR = 26 ms, TE = 4 ms, FA = 20°, THK = 3 mm, FOV = 250 mm, matrix = 256 × 256) that was performed with and without a binomial on-resonance saturation pulse (1-2-1, B1max = 21 μT).

Image analysis

MTR maps were calculated according to the formula \( MTR = \frac{M_{ss} - M_0}{M_0} \), where \( M_{ss} \) and \( M_0 \) are the signal intensities obtained with and without MT saturation, respectively. The MTR maps then were registered to the FLAIR scans using an automated affine registration tool (FLIRT, FMRIB Image Analysis Group Oxford) (Jenkinson and Smith, 2001).

Assessment of WMH and the definition of normal appearing white matter (NAWM) and normal appearing grey matter (NAGM) were based on the FLAIR scans. First, WMH were specified and graded according to our scheme into absent, punctate, early confluent, and confluent (Fazekas et al., 1993). Then, WMH were outlined on transparencies, and the volume of the WMH were measured semi-automatically by one person with the program Dispiimage (Plummer, 1992) using the transparencies as reference, as described earlier (Fazekas et al., 2000). In addition, the WMH were converted into WMH masks and the MTR was calculated for every WMH. To reduce partial volume effects with NAWM these mask were eroded by 1 pixel. Because of the exquisite sensitivity of FLAIR images only 6% of examined normal volunteers had no WMH. When comparing MTR measurements according to WMH severity we, therefore, grouped individuals into those with no or up to 2 punctate WMH, individuals with ≥3 punctate WMH and those with early confluent or confluent WMH. As expected WMH severity was paralleled by increasing subjects’ age, volume and number of WMH (Table 1).

For the regional MTR analysis we used predefined templates to position the ROIs in similar locations of normal-appearing brain tissue (Fig. 1). For most structures we used circular ROIs with a diameter of ~10–14 mm, while irregular ROIs were used in cortical grey matter and in the corpus callosum. Cortical ROIs were drawn manually by outlining the inner and outer grey matter boundaries on the zoomed (×4) display of the respective cortical region. ROIs were placed in the right and the left hemisphere, and the mean MTRs of both sides were averaged for the statistical analysis. In the analysis we also considered the respective standard deviations as they reflect tissue homogeneity within the ROI. Great care was taken not to overlap with any of the outlined WMH.

Neuropsychological testing

A neuropsychologic test battery assessing memory and learning abilities, conceptional reasoning, attention and speed as well as fine motor dexterity was administered to every subject. The tests employed have been widely used in the German-speaking area and were always applied in the same order and under the same laboratory conditions. Bäumler’s ‘Lern- und Gedächtnistest’

<table>
<thead>
<tr>
<th>WMH severity</th>
<th>Punctate WMH</th>
<th>≥3 Punctate WMH</th>
<th>Early confluent</th>
<th>Confluent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects</td>
<td>29 (14.6%) 113 (57%) 33 (16.6%) 23 (11.6%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>66.6 (5.5) 69.5 (6.5) 71.4 (5.8) 74.3 (5.1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WMH volume (cm³)</td>
<td>1.2 (2.8) 2.8 (2.6) 10.1 (5.2) 30.6 (21.2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WMH number</td>
<td>0.9 (0.9) 28.3 (24.8) 64.0 (30.7) 89.3 (38.1)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Numbers refer to mean and standard deviation (SD) except for number of subjects.
LGT-3 assessed learning capacity and intermediate memory recall (Ba¨ umler, 1974). The Wisconsin Card Sorting Test was used as a measure of conceptual reasoning (Heaton, 1981). Attention and speed were assessed with the ‘Alters-Konzentrations-Test’ of Gatterer (Gatterer, 1990), form B of the Trail Making Test (Army Individual Test Battery, 1944), the Digit Span from the Wechsler Adult Intelligence Scale—Revised (Tewes, 1991) and with a complex reaction time task (Dr. Schuhfried Ges.m.b.H., 1991). Fine motor dexterity was evaluated with Purdue’s Pegboard Test (Tiffin and Asher, 1948). A detailed description of the tests was given previously (Schmidt et al., 1999). To reduce floor and ceiling artefacts and other forms of measurement error, we used summary measures of cognitive function in analysis rather than individual tests. We formed composite measures of the specific domains of cerebral function. Each summary measure was calculated by converting individual tests to Z-scores and by computing the average of the scores in each cognitive domain when multiple tests had been employed.

Statistical analysis
We used the Statistica™ package for Windows™ (StatSoft, Inc.) for data analysis. For comparison of regional MTR values, we used a Student’s t-test after checking that the data were normally distributed. One-way ANOVA was performed to study the MTR changes as a function of WMH severity. Univariate linear regression analysis was used to explore the association of the MTR with continuous variables. Multiple linear regression analysis served to assess the relationship of regional MTR values with age, with lesion severity and with lesion volume. For studying the correlations with cerebral functioning we performed multiple regression analyses with performance in the respective domain as dependent and the MTR as independent variable. Other variables considered were age and WMH volume.

Results
Regional MTR variations
The MTR of NAWM showed significant regional differences throughout the brain (Fig. 2). MTR was highest in the genu and in the splenium of the corpus callosum, and it was lowest in the parieto-occipital white matter. The MTR of grey matter structures was consistently lower than that of white matter. The highest MTR values of grey matter were observed in the thalamus.

White matter hyperintensities and MTR
The mean MTR of WMH was significantly lower than that of NAWM in all regions assessed (Fig. 2). In relative terms, the mean MTR reduction was ~10%. A more detailed analysis of the extent of MTR reductions according to WMH severity is shown in Table 2. As can be seen there was a constant albeit weak decrease of the MTR with increasing WMH severity which was significant by one-way ANOVA ($P = 0.022$). In parallel, univariate linear regression analysis showed a significant negative association between the lesional MTR and the total volume ($r = -0.24$, $P = 0.0016$) and number ($r = -0.25$, $P < 0.001$) of WMH. Age had no effect on the MTR of WMH.

WMH and MTR of normal appearing brain tissue
Global MTR of NAWM, i.e. the mean of all NAWM ROIs, was not different between volunteers with no to two punctate WMH, three or more punctate WMH, early confluent or confluent WMH (Table 2). On a regional basis, the MTR of frontal white matter was decreasing ($P = 0.044$) and the standard deviation in the corpus callosum ($P = 0.041$) was increasing with greater WMH severity scores. In a linear regression model including age, WMH volume and WMH severity, WMH volume and age turned out as independent predictors of MTR changes in these regions (Table 3).

The MTR of NAGM of the cortex also appeared to decrease significantly with lesion severity (Table 2). However, this association disappeared when correcting for age. No association between WMH severity and regional MTR was seen in subcortical grey matter structures (Table 2).

Age and MTR
Irrespective of the presence of WMH the individuals’ age showed a modest but significant effect on the MTR of normal
appearing brain tissue. Assuming a linear relationship with age, the relative annual MTR decrease in NAWM was found to be 0.05% \( (P < 0.01) \) (Fig. 3). An even greater age dependence was found for the frontal and parieto-occipital cortex, where we observed a relative annual MTR decrease of 0.16% and 0.21%, respectively \( (P < 0.01) \). In all white matter regions, except the splenium of the corpus callosum, we also observed significant increases of the standard deviation of the MTR with age \( (P \text{ at least } <0.01) \). Such evidence for increased tissue inhomogeneity was not seen in the cortical grey matter.

**MTR and cognitive performance**

Correlations between cognitive performance and regional MTR were assessed only for the frontal lobe because this was the only area where we had found a significant relation between the MTR of NAWM and WMH volume. For the

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**Table 2 MTR of WMH and of normal appearing brain structures according to scored WMH severity**

<table>
<thead>
<tr>
<th>WMH severity</th>
<th>( \leq 2 ) Punctate WMH</th>
<th>( \geq 3 ) Punctate WMH</th>
<th>Early confluent</th>
<th>Confluent</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>WMH MTR (%)</td>
<td>50.4 (2.9)</td>
<td>49.6 (2.2)</td>
<td>49.4 (1.7)</td>
<td>48.2 (2.7)</td>
<td>0.02</td>
</tr>
<tr>
<td>NAWM MTR (%)</td>
<td>53.3 (1.3)</td>
<td>53.4 (1.5)</td>
<td>53.5 (1.7)</td>
<td>53.6 (1.7)</td>
<td>0.82</td>
</tr>
<tr>
<td>Cortical MTR (%)</td>
<td>40.6 (1.9)</td>
<td>40.2 (2.1)</td>
<td>39.9 (2.3)</td>
<td>39.3 (2.9)</td>
<td>0.03</td>
</tr>
<tr>
<td>Deep GM MTR (%)</td>
<td>42.2 (3.0)</td>
<td>42.1 (3.1)</td>
<td>42.3 (3.2)</td>
<td>41.8 (3.2)</td>
<td>0.86</td>
</tr>
</tbody>
</table>

Numbers indicate mean and standard deviation (SD). Levels of significance refer to ANOVA.

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**Table 3 Effect of age and WMH volume on regional MTR of normal appearing brain structures as determined by multiple regression analysis (regions without a significant relationship between WMH volume and MTR are not listed)**

<table>
<thead>
<tr>
<th></th>
<th>Age</th>
<th>WMH volume</th>
<th>R</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Beta</td>
<td>( P )</td>
<td>Beta</td>
</tr>
<tr>
<td>Frontal NAWM</td>
<td>Mean</td>
<td>-0.24</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>0.27</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Genu of CC</td>
<td>Mean</td>
<td>-0.20</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>0.25</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Splenium of CC</td>
<td>Mean</td>
<td>-0.02</td>
<td>0.73</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>0.07</td>
<td>0.35</td>
</tr>
</tbody>
</table>

CC = corpus callosum.
Z-scores of all cognitive domains assessed (learning capacity and intermediate memory recall, confectional reasoning, attention and speed, fine motor dexterity), there was a highly significant association with age ($P$ at least $\leq 0.001$). A parallel association with the MTR of the frontal NAWM was seen with fine motor dexterity only ($P = 0.04$). After adjustment for WMH volume there remained a non-significant trend ($P = 0.07$). WMH volume itself was not associated with the performance on Purdue’s Pegboard Test ($P = 0.29$).

**Discussion**

This study is the first to provide a more detailed analysis of WMH and of associated changes in normal appearing brain tissue using MTI. Examining a large cohort of neurologically asymptomatic elderly volunteers, we observed a decrease of the MTR of WMH with increasing WMH severity scores and volume. This parallels histopathologic observations (Fazekas et al., 1998). In these studies punctate lesions consisted of only minimal perivascular demyelination or frequently were not identified at all, while early confluent WMH consisted of more extensive rarefaction of myelinated fibres. The extent of tissue damage was felt to be even more pronounced in areas corresponding to confluent WMH (Fazekas et al., 1993). The range of MTR decreases seen with WMH, in this study, was relatively small and the overall MTR reduction was in the order of only $\sim 10\%$ relative to NAWM. This is in line with the definition of WMH, which should not be associated with signal changes on T1-weighted MRI. As known from MS T1-hypointensity is indicative of more severe tissue destruction (Van Walderveen et al., 1998). A mild reduction of the MTR also fits well with the fact that WMH in normal ageing rarely have clinical sequels unless they become more extensive (Schmidt et al., 1998; Pantoni et al., 1999). For comparison, an earlier study on the MTR of periventricular hyperintensities (PVH) reported a relative reduction of 11% in non-demented individuals with ischaemic cerebrovascular events compared to controls, while the relative reductions found in the PVH of patients with Binswanger’s disease and in infarctions were 20% and 35%, respectively (Hanyu et al., 1999). MTR reductions associated with MS lesions appear more pronounced, as well, and have been reported in the order of 20–30% (Dousset et al., 1992; Gass et al., 1994; Fazekas et al., 2002).

Our findings indicate that most parts of the NAWM neither differ in MTR between individuals with and without WMH nor in relation to lesion severity. This argues against a diffuse pathologic process as the origin of WMH in the ageing brain and supports the concept of focal damage most likely related to microangiopathy (Schmidt et al., 2004). Accordingly, a most recent comparison of MTR histograms of the NAWM between two groups of elderly individuals also failed to find an association with WMH severity (Spilt et al., 2005).

However, we observed an interaction between WMH volume and the MTR of NAWM of the frontal lobes. As the frontal lobes are especially rich in connecting fibre tracts this may indicate an accumulation of remote effects from WMH dispersed throughout the brain. Along these lines, a recent study found that in nondemented subjects WMH, irrespective of their location, impair frontal lobe function as measured by tests of executive function and PET glucose metabolism (Tullberg et al., 2004). We also found subtle but significant
decreases of the MTR of cortical grey matter with increasing WMH severity. However, these changes turned out to be primarily a consequence of aging by itself. In this context we could not confirm a preliminary study on 12 elderly subjects using MTR histogram analysis which reported primarily cortical grey matter changes in association with WMH (Mezzapesa et al., 2003).

Apart from new insights into WMH and associated changes of normal appearing white matter, this study also substantiates the high sensitivity of MTR for depicting regional differences in tissue composition (Silver et al., 1997; Armstrong et al., 2004) and concerning alterations in relation to the aging process per se. Earlier studies have been controversial on this issue with some investigators reporting no association between MTR histogram metrics with age (Rovaris et al., 2003), while these were seen by others (Hofman et al., 1999; Ge et al., 2002). The reasons for this are likely to have been both technical and related to the relatively small sample sizes of individuals examined, especially as the absolute changes with ageing appear very small. In addition, our study, along with another more recent study, shows that age effects vary regionally throughout the brain (Armstrong et al., 2004). In contrast to the work of Armstrong et al., however, we failed to observe an increase of the MTR with age in any of the regions examined (Armstrong et al., 2004). This regional variance may add to an underestimation of age-related MTR changes of NAWM when investigated by means of whole brain histograms only. Otherwise, such approach might be better suited to explore possible additional effects of cerebrovascular risk factors like increased blood pressure or disturbances in glucose and lipid metabolism on cerebral tissue composition displayed by MTI.

It is also noteworthy that we saw a stronger age-related decline of the MTR in cortical grey matter than in white matter regions. On one hand this is surprising because current concepts and available histopathologic data for the interpretation of MTR changes stress primarily the high sensitivity of MTI for myelin (Barkhof et al., 2003; Schmierer et al., 2004). On the other hand, this observation confirms the notion that MTI may be a valuable technique for the investigation of degenerative cortical disorders as well (Van der Flier et al., 2002).

As a measure of the homogeneity of white matter structures, we also included the standard deviation of the MTR in our analysis. In line with an earlier report higher age was associated with an increasing standard deviation of normal appearing white matter MTR (Hofman et al., 1999). This is likely to be explained by the inclusion of minute changes that do not yet represent recognizable WMH on conventional MRI. An association with WMH severity or volume was not observed, however, except for the frontal lobes and the corpus callosum. As the corpus callosum consists mainly of interconnecting fibres this probably reflects a secondary phenomenon similar to that discussed for the frontal lobe. On the other hand, the absence of an association between WMH severity or volume and the standard deviation of NAWM MTR in other regions of the brain argues against a distortion of our results by partial volume effects of WMH.

We also explored if observed MTR changes of NAWM in the frontal lobe were related to the individuals' cognitive performance. While the performance in all cognitive domains assessed (learning capacity and intermediate memory recall, confectional reasoning, attention and speed, fine motor dexterity) was significantly associated with the individuals’ age we found a parallel association between the MTR of the frontal NAWM with fine motor dexterity only. In this context, it must be noted that both the study design and the population examined would not appear ideal to study such correlations. In this situation, the ROI analysis of the NAWM MTR is likely to provide only limited information and correlations are further complicated by a small range of MTR changes and of neuropsychologic test scores in an otherwise healthy population.

The observation of an association between the MTR of the frontal NAWM and a test related primarily to motor abnormality, despite these drawbacks is intriguing. Some support comes from a recent study of 478 elderly persons which also found a stronger relation between the extent of WMH and poor motor performance (including low scores on the Purdue Pegboard test) than with other cognitive functions (Sachdev et al., 2005). Our findings also suggest that NAWM MTR is a more sensitive indicator of morphologic changes related to cerebral dysfunction than WMH volume. However, both these aspects certainly need to be confirmed by further studies.

In conclusion, this study shows that MTI is a valuable technique for the quantitation of tissue damage associated with WMH and concurrent changes of the ageing brain. Different from other white matter disorders like MS, the severity of tissue destruction within 'incidental' WMH appears relatively mild but increases with lesion size. Distant effects are seen only in the frontal lobes and in the corpus callosum while the remaining white matter appears to alter with aging per se. Even more pronounced age-related changes occur within the cortex. Further examination will reveal if either of these abnormalities contribute to cerebral dysfunction of the elderly and, if so, the extent of such contribution.

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