Teaching Course 11 MAGNIMS

Quantitative MR imaging in the management of multiple sclerosis

Chairs: A. Rovira (Barcelona, ES)
        H. Vrenken (Amsterdam, NL)

23  Focal lesion load quantitative MR measures
    H. Vrenken (Amsterdam, NL)

24  Brain and spinal cord volume measurements
    A. Rovira (Barcelona, ES)

25  Advanced quantitative brain MR measures
    M. Filippi (Milano, IT)
Wednesday, 7 October, 10.30 – 12.00

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Focal lesion load quantitative measures

H. Vrenken, VU University Medical Center, Amsterdam, the Netherlands.

Focal lesions in the white matter (WM) were long considered the pathological hallmark of MS, and play an important role in the diagnostic criteria for MS (Polman, 2011). And although grey matter lesions and atrophy of both white and grey matter have gained prominence (e.g., Geurts, 2012; Sastre-Garriga, 2004; Shiee, 2012), focal WM lesions still remain important to this day. Most work on automated measurement has been done on WM lesions in the brain, while far less has been done towards contrast-enhancing, grey matter, or spinal cord lesions. In view of the usability in the clinical management of MS, WM lesions are also most easily accessible through standard clinical MS imaging protocols. We therefore focus this lecture on the quantitative measurement of brain WM lesion volumes and their change over time.

Since many of the disease modifying treatments currently available for MS act primarily on the inflammatory component of the disease, the focal WM lesions provide an important indicator of the success of treatment. As we will see in this lecture, the exploitation of quantitative measures to assess focal lesion loads is lagging.

Current use of MRI of lesions

Diagnosis

As prescribed in the diagnostic criteria of MS (Polman, 2011), the emphasis in the diagnostic evaluation of focal lesions is on the number of lesions and their locations. Although the size
of the lesions plays a role in discriminating MS from other disorders, lesion sizes or total lesion volumes are not generally quantitatively assessed in routine clinical diagnosis.

Prognosis

While some studies have related (early) lesion load to later clinical worsening (e.g., Popescu, 2013), there are no guidelines on how such information might be used in individual patient cases to predict the evolution of disease. Leaving aside the problem of how to account for variable treatment regimens in assessing this relation, the absence of reliable methods to measure and gauge quantitative focal lesion loads certainly also contributes to this problem.

Treatment response

The latest treatments for MS are successful in reducing the numbers of new relapses and new lesions. One might therefore argue that in a patient with a substantial amount or volume of new lesions under treatment, the treatment may be partially or wholly ineffective, and a change of treatment may be considered. However, it is also possible that the same patient may have had a much less favorable course without the treatment, and therefore a change of treatment may not result in any improvement. Here too, there are no guidelines to help the clinician make their decision based on an observed increase in focal lesion load. And again, the absence of reliable methods for the assessment of lesion volume change hampers its clinical use.

Questions

Three key questions may be identified, that are inter-connected, and together summarize the challenges.

1. Will it be useful to include quantitative measures of focal lesion load?
2. Is it possible to measure them in a clinical setting?

3. How will the clinician use the focal lesion load measures?

We will discuss these questions and their answers now.

**Will it be useful to include quantitative measures of focal lesion load?**

First we have to assess the clinical need for quantitative measures of focal lesion load.

In diagnosing MS, precise volumetric information of the focal lesion volumes does not appear to add information over the existing information.

By contrast, to assess treatment efficacy, reliable quantitative information on lesion volume change over time may yield important insights into individual patient pathology worsening – information that is currently only available in a qualitative sense. Since there are now several treatments that can reduce the incidence of new lesions, precise quantitative measurement of lesion change may help to identify the best treatment for an individual patient. Possibly, quantitative lesion volume and lesion volume change assessment may also help to improve prognostic accuracy, if the influence of other factors, most notably past and current medication, can be adequately modeled.

Clearly, on both issues, appropriate steps will also have to be taken in order to allow the neurologists to use this information in their practice.

**Is it possible to quantitatively measure focal lesion load (change) in a clinical setting?**

**Requirements**

If the focal lesion load and its change over time are to be measured in a clinical setting, two things are required. First, image acquisition should include suitable images for assessing small lesion changes over time. Preferably these should be of the 3D Flair or 3D T2-weighted type, with sufficiently small voxel size to allow reliable quantification of small changes between
imaging time-points (see, e.g., Vrenken, 2013). The 2015 revision of the recommended standardized MS imaging protocol specifically emphasizes the use of 3D acquisition for this purpose (http://www.mscare.org/?page=MRI_protocol; Simon, 2006).

Second, quantification of lesion loads and their change over time should be reliably possible. An important challenge for both cross-sectional and change measurement, is that the automated methods should perform well independent of the scanner and pulse sequence used to acquire the data.

Lesion volume measurement

A very nice review of automated methods for MS lesion segmentation is provided by Mortazavi and colleagues (Mortazavi, 2012). A fairly large number of methods have been developed, based on various principles which may, with Mortazavi, be characterized as data driven, statistical, “intelligent”, or deformable contours methods. Some methods require additional reference images with lesion labels in order to work, others are fully independent. Many methods require optimization of parameters to improve performance for the data at hand.

Despite serious advances over the past years, including recently (e.g., Guizard, 2015; Roura, 2015; Wang, 2015), the performance of automated methods still leaves substantial room for improvement. The comparison of segmentations by automated methods with those by expert manual raters shows that at the voxel level, there is substantial disagreement between them. Dice similarity indices, which can range between 0 and 1 where 1 indicates perfect agreement and 0 no overlap, seldom reach values above 0.7 (Mortazavi, 2012), implying a volume of disagreement that is on the order of 30% of the lesion volume. Rates of false positive voxels, i.e., image voxels labelled as lesion voxels by the automated method but not by the expert, are generally on the order of 10-20%. The same holds for the rates of false negative voxels, i.e.,
those lesion voxels missed by the automated methods; these too are generally around 10-20% for optimized methods.

It should be noted here that the manual expert labels, often referred to as the “gold standard”, generally exhibit substantial variability both within and between raters. For example, in Flair images with 1x1x1 mm resolution, the Dice similarity index between two expert manual raters was 0.84 (Steenwijk, 2013). This highlights one of the difficulties in further optimizing automated methods: if the manual reference is not perfect, an automated segmentation that is superior to the manual one will be interpreted as being inferior because of its disagreement with the imperfect reference. By combining multiple labels from different raters e.g. using STAPLE software (Warfield, 2004), such problems may be somewhat alleviated, but the fundamental problem that one cannot outperform the reference remains.

For individual patient treatment, these errors have to be reduced, or the uncertainty in the automated methods has to be taken into consideration when interpreting the lesion volumes in a clinical situation.

**Lesion volume change measurement**

For a very nice overview of MS lesion change detection and quantification methods, the paper by Lladó and colleagues is recommended (Lladó, 2012). Methods may be separated into detection of lesion change, and quantification of the volumetric effects involved, including both the change of the actual lesions, and the change of the surrounding tissue due to any mass effects that may be present, e.g., due to edema. In case of two time points, subtraction of the images obtained on the two time points may be of help, especially for visual change analysis. In case of multiple time points, modeling of the signal intensities as a function of time may be more appropriate.
Most methods have been tested in relatively small datasets, but have yielded reasonable reproducibility, with inter-scan coefficients of variation down to just under 1%, and reasonable agreement with manual assessment yielding Dice similarity coefficients around 0.6 to 0.8. Lladó and colleagues conclude that improvement is needed before clinical application is feasible. Recently, there have been efforts directed at obtaining more reliable measures of lesion volume change in MS in a coordinated way (http://iall.ece.jhu.edu/MSChallenge).

**How will the clinician use the focal lesion load measures?**

So far, we have addressed requirements and performance of current methods from a technical perspective. An equally important perspective perhaps, is how clinicians would use the information on lesion volume and change of lesion volume if reliable measurements were to become available. We leave aside here, apart from this brief mention, the necessity to have analysis methods developed according to certified protocols, and regulatory approval for their use in a clinical setting, according to standardized guidelines. What is of concern to us now, is that such guidelines for clinical use of lesion volumes and lesion volume changes, have to be developed in order to give the treating physician sufficient guidance to make well-informed decisions incorporating the lesion volume information. It will likely not be possible to provide precise information on how to interpret an observed lesion volume increase in a patient for any disease duration, and any possible combination of past treatments, relapses, and progression of disability. Nevertheless, it is important that at least basic clinical guidelines become available. Even if imaging-related technical challenges are all overcome, use of lesion volume measures in the clinic can only take place if supported by such guidelines.

**Conclusion**
While much work has been done over the past decades, there are still no completely satisfactory automated methods for MS WM lesion volume measurement or for lesion volume change measurement. Remaining disagreements with an, albeit imperfect, manual reference, generally remain at least 10-20% of the lesion volume or lesion volume change under investigation, warranting some caution for individual patient application. Robustness across scanners and pulse sequences remains an important requirement to provide a feasible clinical tool.

References


New Therapies Allow Re-evaluation of Treatment Goals and Greater Consideration of the Patient Perspective

Clinical disease activity

MRI disease activity

MR imaging Biomarkers in Multiple Sclerosis

Purpose | Measure
--- | ---
Disease activity | New/enlarging T2 lesions, gadolinium enhancing lesions, Gd-DTPA (combined unique activity lesions)
Disease burden or load | T1/T2 lesion load, MRI
Demyelination / Remyelination | MTR, DTI (FA, MD)
Neuroaxial loss | Myelin, NAA, MRI (global, regional), PBV, UZCC, T2 lesion load
Brain plasticity | Functional (BOLD, fMRI), MTR
Iron content | T2 maps, CEM

Road map for validating brain atrophy as a proxy for (long-term) disability progression

- Global marker of neuroaxial loss in MS,1,2
- Occurs in all clinical stages of MS at a rate of 0.5–1.3%/year vs. 0.1–0.3%/year in healthy subjects1,2
- Measures of global brain atrophy are robust, sensitive and relatively easy to standardise2
- Correlates with and predicts disability progression on group-wise level
- Generally measured on 2D/3D T1-weighted images

Two overlapping pathogenetic components of MS

Preclinical | Relapsing–remitting | Secondary progressive
--- | --- | ---
Lack of evidence suggests that strongest surrogate marker correlation with disability in MS is brain (spinal cord) atrophy

Active lesions | Inflammation | Neurodegeneration
--- | --- | ---
Anti-inflammatory/immunomodulatory therapies | Myelin/neural repair/neuroprotection

Lesion load

T2

Brain atrophy measures

Time (years)

Weight of evidence suggests that strongest surrogate marker correlation with disability in MS is brain (spinal cord) atrophy
Brain volume loss
Healthy adults vs. multiple sclerosis

Measures of overall brain atrophy predict disability and disability progression

GM atrophy in MS

Subcortical GM atrophy in MS

Clinical impact of early brain atrophy in CIS

Clinical relevance of WM and GM atrophy

GM atrophy in MS

Localized grey matter atrophy in multiple sclerosis: A meta-analysis of voxel-based morphometry studies and associations with functional disability

Regions of GM loss (A) participants with RRMS + CIS
• (B) RRMS only subgroup

Deep grey matter bilaterally / pre- and post-central bilaterally / lingual bilaterally

Thalamic atrophy
• Occurs within the first five years of MS onset, when most patients are still minimally disabled (Howie et al., 2005; Henry et al., 2006)
• Inversely correlated with lesion load in MS (Brune et al., 2012)
• Associated with a wide range of clinical manifestations: cognitive decline, motor deficits, disability, fatigue, painful syndromes, and ocular motility disturbances (Brune et al., 2011; Brune et al., 2012; Beretta et al., 2011; Huh et al., 2012)
• Associated with conversion from CIS to definite MS over 2 years (Ghidoni et al., 2012; Venkatachalam et al., 2010)
Clinical correlates of regional brain atrophy

- **EDSS score:**
  - In early RRMS patients (N = 425): most significant correlations between cortical thickness and EDSS score for the anterior pole of the left inferior temporal gyrus, the middle and superior frontal gyri bilaterally, and the bilateral anterior cingulate cortex and left post-central cortical area

- **Cognitive impairment:**
  - Hippocampal atrophy associated with impaired memory encoding and retrieval
  - Atrophy of the putamen predicts poor performance in tests assessing cognitive performance

- **Fatigue:**
  - Atrophy in the frontal lobes and progression of corpus callosum atrophy over 5 years associated with severity of fatigue

### Effects of DMTs on Brain Atrophy (RRMS)

**Reported data from CTs**

<table>
<thead>
<tr>
<th>DMT</th>
<th>Trials</th>
<th>Treatment</th>
<th>Healthy</th>
<th>NAT</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Teriflunomide 7mg vs 14mg vs placebo</td>
<td>Ph. III, n=540, 2y</td>
<td>FTY 0.5mg vs FTY 1.25mg vs placebo</td>
<td>Ph. III, n=1153, 1y</td>
<td>Teriflunomide 7mg vs 14mg vs placebo</td>
<td>Ph. III, n=1003, 2y</td>
</tr>
<tr>
<td>Neflumab 12mg vs 24 mg vs sc IFN</td>
<td>Ph. II, n=334, 3y</td>
<td>Neflumab 12mg vs sc IFN</td>
<td>Ph. III, n=581, 2y</td>
<td>Neflumab 12mg vs sc IFN</td>
<td>Ph. III, n=581, 2y</td>
</tr>
<tr>
<td>Teriflunomide 7mg vs 14mg vs placebo</td>
<td>Ph. III, n=1003, 2y</td>
<td>FTY 0.5mg vs FTY 1.25mg vs im IFN</td>
<td>Ph. III, n=799, 1y extension phase</td>
<td>Neflumab 12mg vs sc IFN</td>
<td>Ph. III, n=581, 2y</td>
</tr>
<tr>
<td>Derilimus 12mg vs Placebo</td>
<td>Ph. III, n=942, 2y</td>
<td>Teriflunomide 7mg vs 14mg vs placebo</td>
<td>Ph. III, n=1003, 2y</td>
<td>Teriflumab 12mg vs sc IFN</td>
<td>Ph. III, n=581, 2y</td>
</tr>
</tbody>
</table>

### Atrophy measurements

Capturing temporal patterns of structural brain changes requires:

- adequate MRI protocols
- accurate and robust image analysis tools

It might be challenging the use of MRI-based assessments on individual basis to reliably classify subjects into patient versus normal, as opposed to assessing significant group differences

### Measurement errors

- **White brain measurement errors**
  - Mean: 0.25%, SEM: 0.15%
  - Small: 0.3% vs large: 0.6%

- **Gray matter measurement errors**
  - Mean: 0.25%, SEM: 0.15%
  - Small: 0.3% vs large: 0.6%

### Brain atrophy in MS: MRI-based methods

**Segmentation-based**

- Single time-point
- Global or regional automated segmentation
- BPF=brain parenchymal fraction
- PBVC=percentage of brain volume loss

**Registration-based**

- Two time-points
- PBVC=percentage of brain volume loss

- Heterogeneous results
- Influenced by the quality of T1-weighted images
- Not recommended for longitudinal studies
- Designed to analyse regional volumes

### Brain atrophy in MS: segmentation-based

Multiple regression model used to calculate the normalised brain volume (NBV) according to baseline characteristics (age, gender, disease duration, EDSS, T2UL)

**Small NBV**

- Higher risk of disability progression
- Higher treatment effect

**EDSS, Expanded Disability Status Scale; RRMS, relapsing-remitting MS; HC, healthy control; NAT, natalizumab treated; Placebo group; English group**

**Courtesy of Wim Van Hederaen, Isometrica**
Brain regional atrophy measurement (regional)

GM and WM volumes can also be calculated separately, using SIENA, SPM.

Lesion filling and GM atrophy measure

52% of lesion voxels misclassified as GM (Chard, et al. Brain 2002)

Effect: \( \uparrow \) Lesion volume \( \rightarrow \) GM volume

SIEMA [Structural Image Evaluation using Normalization of Atrophy]

Lesion filling and GM atrophy measure

Error in GM volume estimation as a function of lesion volume for all patients included.

Lesion volume errors: 0.3-2.5%

Lesion segmentation

Methods

- Expectation maximization segmentation (Van Leemput et al., 2001)
- Lesion-TOADS (Shiee et al., 2010)
- Lesion segmentation toolbox (LST) (Schmidt et al., 2012)
- CASCADE (Damangir et al., 2012)
- HAMMER-White matter lesion (Yu et al., 2002)
- Lesion segmentation tool for 3D slicer (Scull et al., 2010)
- Msmetrix (Jain et al., 2015)

Lesion filling and GM atrophy measure

FLAIR+LST mask

Segmentation (without and with LST)

Registration-based measures

SIENA [Structural Image Evaluation using Normalization of Atrophy]

\( \Delta \) aPBVC first year: -1.6%

\( \Delta \) aPBVC second year: -1.8%
Segmentation-based measures

Brain atrophy in MS: registration-based

<table>
<thead>
<tr>
<th>PBVC cut-offs (%)</th>
<th>Specificity (%)</th>
<th>Sensitivity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>-0.50</td>
<td>85%</td>
<td>49%</td>
</tr>
<tr>
<td>-0.46</td>
<td>90%</td>
<td>54%</td>
</tr>
<tr>
<td>-0.40</td>
<td>80%</td>
<td>65%</td>
</tr>
</tbody>
</table>

Cut-off values that identify a PBVC distinguishing healthy controls from MS patients

Concept of no evidence of disease activity (NEDA)

In 0-7 years: 46%-85% (Rotstein et al. JAMA Neurol 2014)
NEDA at 2 years had a positive predictive value (78%) for no progression at 7 years
Associated with lower brain volume loss

NEDA 3
Free of clinical activity/progression
Free of disability progression
Free of MRI activity

Brain atrophy in MS: translation to clinical practice

Challenges

- Pipelines
  - Non-standardised
  - Variability
  - Off-line
  - Resources
- MRI-related factors
  - Variation in imaging protocols
  - Artefacts: signal heterogeneity, spatial distortions, motion, etc.
  - Lack of normative data acquired with the same MR protocol
- MS-related factors
  - Pseudoatrophy effect (long-term follow-up required)
- Non-MS related factors (accelerate brain volume decrease)
  - High body mass index
  - Genetic factors: glycated haemoglobin, APOE ε4
  - High alcohol consumption
  - Smoking
  - Dehydration
  - Cardiovascular risk factors
Brain atrophy in MS

Mechanisms producing brain volume loss

- Tissue loss (i.e., loss of myelin, glial cells, neurons and axons due to the inflammatory demyelination and neurodegeneration).
- Change in non-tissue components (i.e., fluids shifts).

The respective contribution of each component to brain volume loss may depend on many factors, such as disease stage, brain region affected, type of pharmacological treatment, presence of comorbidities and other factors unrelated to the disease.

Atrophy measurements: off-line

- Errors: Technically demanding, Time consuming.
- Strategies for extracting atrophy: Pre-processing of data, Segmentation and registration of data.

Atrophy measurements: actions

- Fully automated pipelines:
  - Cross-sectional/longitudinal volumetric analysis
  - Automated lesion filling
  - Quality control
  - Normative data
- Commercially available (NeuroQuant®, IcoMetrix®)
- Integrated in all major MR vendors post-processing software
- Information transferred into PACS
- Reimbursement (public health systems, private insurance)

Pipelines for atrophy measurements (in MS)

<table>
<thead>
<tr>
<th>Software Library/Tool</th>
<th>Institution</th>
<th>License</th>
<th>Language</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARMC/BrainSuite</td>
<td>Penn Imaging Informatics Laboratory, University of Pennsylvania, Philadelphia, USA</td>
<td>Open source</td>
<td>C++/depends on the Insight Toolkit</td>
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<tr>
<td>FIRST</td>
<td>Freesurfer</td>
<td>Free</td>
<td>C++/depends on the Insight Toolkit</td>
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<td>NeuroQuant</td>
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<td>Advanced Radiology, Baltimore, Maryland, USA</td>
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<td>MRV/MSI Segment</td>
<td>Missckeen Trust Centre for Neurorehabilitation, London, UK</td>
<td>Open source</td>
<td>C++/depends on the Insight Toolkit</td>
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</tbody>
</table>

Brain volume loss: hydration

Ventricular volume change

- Hyperhydration > Dehydration
- Measurement timepoints

Ventricular volume change, obtained using FreeSurfer segmentation results, in percent in comparison to normal hydration (set to 100%).
Effects of DMTs on Brain Atrophy (RRMS)

Reported data from CTs

### Table 1: DMTs and their effects on brain volume

<table>
<thead>
<tr>
<th>Drug</th>
<th>Initial effect on brain volume</th>
<th>Immediate effect on brain volume</th>
<th>Delayed effect on brain volume</th>
<th>Able to cross Blood-Brain Barrier</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alemtuzumab</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Natalizumab</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
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<tr>
<td>fingolimod</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>teriflunomide</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
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<tr>
<td>Interferon</td>
<td>No</td>
<td>No</td>
<td>No</td>
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<tr>
<td>Dimethyl</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
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</table>

### Brain atrophy from CARE MS I study

Alemtuzumab treatment has a consequence on brain volume loss.

### Effects of DMTs on Brain Atrophy (RRMS)

Reported data from CTs

### Brain atrophy from FREEDOMS extension study

Fingolimod treatment has a consequence on brain volume loss.

### Pseudotrophy effect in the first year of treatment with Natalizumab

Early brain pseudotrophy while on natalizumab therapy is due to white matter volume changes.
Exclude brain atrophy changes during the first months after treatment onset:

- Multivariate analysis: 2 MRI markers evaluated during the first 12 months after treatment onset

- White matter T2 relaxometry

- Grey matter assessment (insensitive to fluctuations in water content)
  - Normalisation
    - Degree of inflammatory activity (Gad lesions)
    - White matter T2 relaxometry

Alternatives to brain volume assessment (as a measure of atrophy):

- Corpus callosum index
- Spinal cord area

Corpus callosum atrophy

- Corpus callosum area change

Value of corpus callosum (CC) area change for predicting conversion to CDMS

- Assessment of relationship between MRI measures and clinical status in 181 highly active RRMS patients from Avonex-Steroid-Azathioprine study (mean age 31.2 yr, disease duration 5.5 yr; EDDS 1.9) over 9 yr
  - Multivariate analysis: 2 MRI markers evaluated during the 1st yr on treatment were predictive of sustained disability progression over 9 yr:
    - T1 lesion volume at mo 12 (HR 1.16; P=0.009)
    - CC change mo 12-6 (HR 0.92; P=0.009)

Corpus callosum atrophy

- Corpus callosum area

Value of corpus callosum (CC) volume change for predicting disability progression after 9 yr

- CC volume and T1 lesion volume seem to predict about half of pts who will have sustained disability progression over 9 yr of interferon β treatment.
Spinal cord atrophy in MS

- Affects the majority of MS patients (++) SPMS, + PPMS), progressive over time
  (Stevenson, 1998; Lin, 2003; Furby, 2008, 2010; Rocca, 2011, Lukas 2013, Lukas 2014)
- Moderate association with clinical status
- Faster in MS patients with disability progression over time
  (Lukas 2014)
- Relevant for disability in the long term
  (Kearney, 2014)

Spinal cord atrophy in MS: correlation with clinical disability

440 MS patients

Multivariate linear regression

- Motor per cent predicting EDSS
  UCCA: $R^2=0.01$,
  T1 lesion volume: 0.003
  Diffuse spinal cord abnormalities: 0.002
  Number of spinal cord segments: 0.004

MR imaging-derived UCCA was found to be the most significant spinal cord parameter for explaining EDSS score.

Spinal cord atrophy in MS: changes over time

352 MS patients (two centers)

- SC atrophy develops mostly independently from brain pathology, but not to number of SC segments involved by lesions and the presence of diffuse SC abnormalities
- UCCA was significantly higher in patients with disease progression (~2.3% per year) than in stable patients (~1.2% per year; p<0.001)
- cUCCA did not differ between subtypes (RRMS: 0.43% per year; SPMS: 0.60% per year; PPMS: 0.46% per year), not between progressive and stable patients (p=0.015)

Grey matter spinal cord atrophy in MS: correlation with clinical disability

113 MS patients: 20 controls

<table>
<thead>
<tr>
<th>Parameter</th>
<th>UCCA</th>
<th>T2 lesion volume</th>
<th>Diffuse spinal cord abnormalities</th>
<th>Number of spinal cord segments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EDSS</strong></td>
<td>0.32</td>
<td>0.004*</td>
<td>0.06*</td>
<td>0.01*</td>
</tr>
<tr>
<td><strong>MMSE</strong></td>
<td>0.39</td>
<td>0.005*</td>
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<td><strong>MOCA</strong></td>
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Spearman Rank Correlations between PSIR and Clinical Measures:

- PSIR: control

Spinal cord atrophy in MS: brain/spinal 3D T1-PSIR

Advantages:
- Easy to measure
- “Summary measure” of the irreversible/destructive pathological process of MS
- Whole brain atrophy is highly reproducible and sensitive to disease-related changes
- Correlates with disability, cognitive impairment and fatigue

Disadvantages:
- End-stage phenomenon
- Pseudotrophy effect (first 6–12 months)
- Fluctuations: steroids, hydration
- Co-morbidities: smoking, alcohol, body mass...
- Technically demanding / time consuming: reimbursement?
- Not enough evidence to use atrophy measures to assess and predict individual treatment response
Special thanks to:

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Advanced quantitative brain MR measures
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Introduction
Conventional magnetic resonance imaging (MRI) sequences (i.e., dual-echo, FLAIR, pre- and post-contrast T1-weighted scans) provide important pieces of information for diagnosing multiple sclerosis (MS), understanding its natural history, and assessing treatment efficacy. Disappointingly, the strength of the association between conventional MRI findings and the clinical manifestations of the disease remains modest in patients with MS. This is likely due to the relative lack of specificity of conventional MRI in the evaluation of the heterogeneous pathological substrates of the disease, its inability to provide accurate estimates of damage outside focal lesions, and the fact that it cannot provide information on central nervous system (CNS) functional reorganization after tissue injury has occurred. Several advanced MRI techniques have been applied to estimate overall MS burden in the different phases of the disease. Their use has allowed to grade in vivo the heterogeneity of MS pathology in focal lesions, normal-appearing white matter (NAWM) and gray matter (GM).

Heterogeneity of WM lesions
Variable degrees of magnetization transfer ratio (MTR) reduction have been reported in acute and chronic MS lesions, with the most prominent changes found in T1-hypointense lesions. Recently, MRI contrast agents composed of iron particles, known as ultrasmall particles of iron oxide (USPIO) or super-paramagnetic iron particles of oxide (SPIO), have been introduced to monitor different aspects of the MS inflammatory process. These particles are taken by cells of the monocyte/macrophage system. As a consequence, USPIO-enhancement reflects cellular infiltration and may complement Gd-enhancement.[1]

High-field (3.0-4.0 Tesla) and ultra-high field (7.0 Tesla and higher) MRI scanners are becoming progressively available and contribute to detect a greater number and a larger volume of T2 and enhancing brain lesions. These MR scanners also provide a better definition of lesions in terms of location in the WM and GM, morphology, architecture and association with vasculature, at a resolution which resembles that of pathological assessment.[2-4] Due to the better definition of the relationship between demyelinating lesions and the deep venous system, several studies have shown that MS plaques form around the microvasculature.[4, 5] This feature has been reinforced by the investigation of blood-brain barrier abnormalities in MS at 7.0 Tesla, which showed that the majority of enhancing lesions are perivenular, and that the smallest lesions have a concentric pattern
of enhancement, suggesting that they grow outward from a central vein. [5] The presence of a central small vein and a rim of hypointensity on 7.0 Tesla T2*-weighted magnitude images can also assist in the differentiation of WM lesions found in MS patients from those of patients with other neurological conditions that can mimic MS.

**Cortical lesions**

Although imaging the cortex is technically difficult, due to its morphology and location, and the nature of the pathology within this structure, the development of specialized MRI sequences that can suppress the signal from WM and cerebrospinal fluid simultaneously, named “double inversion recovery” (DIR), has enabled substantial improvements in cortical lesions (CLs) detection. [6] Using DIR, MRI studies revealed that CLs develop early in MS and increase in number and size with progression of the disease. [7] On the other hand, they are sparse in benign forms of the disease [8] and in children with MS. [9] CLs contribute to explain both locomotor disability and cognitive impairment, [10] and their presence is associated with other MRI indexes of damage such as $T_2$ lesion load and WM and GM atrophy. [11] In patients presenting with a clinically isolated syndrome (CIS) suggestive of MS the accuracy of MRI diagnostic criteria for MS increases when considering CLs on baseline scans. [12] Importantly, CLs have not been identified in migraine patients with multiple brain WM hyperintensities and patients with neuromyelitis optica, thus suggesting a high specificity for MS. Measuring CLs might also represent a valuable marker to monitor treatment effect. [13]

**Diffuse NAWM damage**

Outside T2 lesions, quantitative MRI techniques allow estimating the presence and extent of abnormalities in the NAWM of MS patients. Several studies with serial MR investigations have shown that, at least in some cases, subtle WM changes can be seen in areas which days to weeks later develop into classical enhancing lesions. These changes consist of a reduction of MTR, increase in mean diffusivity (MD), and mild to moderate reduction of N-acetylaspartate. NAWM MTR histogram-derived measures evolve at different rates in the major MS clinical phenotypes. NAWM MTR reduction has also been shown to predict the accumulation of clinical disability over the subsequent five years in patients with definite MS. A voxelwise assessment of the regional distribution of abnormalities of diffusion tensor (DT) MR indexes has been shown to be a rewarding strategy for understanding the heterogeneity of MS clinical phenotypes. In a recent study, [14] this method has been applied to 172 MS patients with different clinical phenotypes and it has been found that compared with healthy controls, CIS patients had significantly increased MD,
axial diffusivity, and radial diffusivity in the majority of WM tracts of the brain. Compared to controls, patients with primary progressive (PP) MS also showed a diffuse fractional anisotropy (FA) decrease involving the majority of WM tracts. No relevant difference in diffusivity measures was found between CIS and relapsing-remitting (RR) MS patients. Compared with benign MS patients, those with RRMS had reduced FA values in all WM tracts and a decreased axial diffusivity in the majority of the tracts. Secondary progressive (SP) MS had a pronounced damage to the majority of tracts and, compared with benign MS, a pronounced FA alteration of the tracts relevant for motor impairment. Significant DT MRI abnormalities of brain WM tracts, which were only partially correlated with focal WM lesions, were also found in very young pediatric MS patients.[15]

Several approaches have been developed to investigate damage to selected WM tracts with the ultimate goal of improving the correlation with clinical measures. In patients with CIS, diffusivity measures of the corticospinal tract correlate with clinical measures of motor impairment.[16] In patients with optic neuritis, reduced structural connectivity values in the optic radiations compared with controls have been shown.[17] Diffusivity abnormalities in optic radiations have been related to trans-synaptic degeneration secondary to optic nerve damage and Wallerian degeneration due to local lesions in a recent study in which patients were classified according to the presence of previous optic neuritis and lesions along these tracts.[18] In cognitively impaired MS patients damage of specific corticothalamic tracts explained global cognitive dysfunction and impairment of selected cognitive domains better than MRI measures of thalamic and cortical damage.[19]

Advances in DT MRI and tractography have spurred the development of brain connectivity techniques, which allow defining and quantifying anatomical links between remote brain regions.[20] The use of these approaches has revealed reduced network efficiency in the WM structural networks of MS patients,[21] including those at the earliest stages of the disease.[22]

**Diffuse GM damage**

The application of modern MR techniques can contribute to the assessment of different aspects of GM damage, including the presence of diffuse disease-related abnormalities (measured using quantitative techniques such as MT and DT MRI), metabolic abnormalities (measured by means of proton MR spectroscopy), irreversible tissue loss (atrophy) and iron deposition (quantified using $T_2/T_2^*$-weighted imaging), thought to reflect neurodegeneration. Several studies have demonstrated reduced MTR and increased MD in the GM of patients with different MS phenotypes including those at the earliest clinical stages of the disease.[23, 24] These abnormalities are more severe in patients with the progressive disease phenotypes. Analogous findings have been shown when
measuring cortical atrophy.[25] Diffuse cortical damage is not stable, but tends to worsen over time, independent of the progression of damage within the WM.[26] The clinical relevance of measuring such a damage has been demonstrated by several studies which have shown correlations with clinical disability and cognitive impairment.[25] A longitudinal study has found an increased rate of cortical tissue loss in patients with progressing disability compared to those with stable disease,[27] whereas another study demonstrated that progressive neocortical loss is relevant to MS-associated cognitive impairment.[28, 29] A recent 13-year longitudinal study demonstrated that GM damage is one of the key factors associated with both long-term accumulation of disability and cognitive impairment in MS patients.[29]

Analysis of the spatial distribution of GM damage has demonstrated that different regions might have different vulnerabilities to MS-related pathological processes. Overall, MRI studies have agreed in identifying the frontal, temporal and parietal lobes as the most affected cortical regions in MS patients. However, the patterns of GM loss differs between the major MS clinical phenotypes.[30] The quantification of diffuse GM damage provides robust prognostic measures of disease progression. In RRMS patients, GM MTR was found to be an independent predictor of the accumulation of disability over the subsequent eight years[31] and baseline GM fraction was found to be an independent predictors of the development of SPMS over a 13-year period,[29] while in PPMS, GM MD predicted the accumulation of disability over a five-year period.[26]

Assessment of atrophy of strategic GM structures could contribute to explain deficits in selective cognitive domains, as well as the occurrence of specific symptoms and disability progression. Hippocampal atrophy has been associated with deficits in memory encoding and retrieval.[32] In this perspective, a recent study showed that hippocampal subregions have a different vulnerability to MS-related damage, with a relative sparing of the head of the left hippocampus.[33] Atrophy of the frontal and parietal lobes has been correlated with the presence and severity of fatigue.[34] Thalamic atrophy has been correlated with accumulation of disability after a eight year follow up period in patients with relapse-onset MS[35] and after a five year follow up period in PPMS patients.[36]

**Brain functional reorganization**

Studies with functional MRI (fMRI) of the visual, cognitive and motor systems have consistently demonstrated functional cortical changes in all MS phenotypes, with altered activation of regions normally devoted to the performance of a given task and/or the recruitment of additional areas in comparison to healthy subjects.[37] fMRI abnormalities in MS patients occur relatively early in the course of the disease, even in patients with CIS and pediatric MS,[38] and tend to vary over the
course of the disease, not only after an acute relapse, but also in clinically stable patients.[37] Functional and structural MRI abnormalities in MS patients are strictly correlated,[37] suggesting that increased recruitment of “critical” cortical networks helps to limit the functional impact of MS-related damage. However, increased cortical recruitment cannot continue indefinitely, and a lack of, or exhaustion of, the “classical” adaptive mechanisms has been considered as a possible factor responsible for unfavorable clinical evolution or accelerated cognitive decline.[37, 39]

Several studies have attempted to develop sophisticated statistical approaches to establish the strength of activations and the synchrony between specific cortical areas, through the analysis of functional and effective connectivities.[40] The combination of measures of functional connectivity with measures of structural damage to specific WM fiber tracts is also likely to improve our understanding of the relationship between structural and functional abnormalities.

Recently, the analysis of brain activity at rest has shown an increased synchronization of the majority of the resting-state networks (RSN) in patients with CIS,[41] a reduced functional connectivity (FC) of anterior regions of the default-mode network in patients with progressive MS[42] and cognitive impairment,[40] and a complex reorganization of the visual network in normal-sighted patients who recovered from a previous optic neuritis.[43] Distributed abnormalities of RS FC within and between large-scale neuronal networks have been shown in RRMS and pediatric MS patients and have been related to the extent of T2 lesions.[44, 45] Active and RS fMRI have also been applied to assess modifications of the patterns of activations and FC following cognitive rehabilitation in a few single-centre studies.[46, 47] A recent study demonstrated that changes in RS FC of cognitive-related networks contributes to the persistence of the effects of cognitive rehabilitation after six months in RRMS patients.[48]

Graph theory is a mathematical framework which allows to describe a network as a graph consisting of a collection of nodes (i.e., brain regions) and edges (i.e., structural and functional connections). The application of this approach to RS fMRI data has allowed to investigate the topological organization of functional brain network connectivity. In a recent study an impairment of global integration, that likely reflects a reduced competence in information exchange between distant brain areas, has been demonstrated in MS patients. Such a modification of regional network properties contributed to cognitive impairment and phenotypic variability of MS.[49]

**Conclusions**

Conventional and advanced MRI techniques have been applied extensively to the study of MS and such an effort has contributed to improve our ability to diagnose and monitor the disease, as well as our understanding of its pathophysiology and treatment efficacy. Nevertheless, many challenges
remain. Quantitative, metabolic and functional imaging techniques need to be optimized and standardized across multiple centres to monitor adequately disease evolution. In addition, from the large body of available literature, it results clear that none of these quantitative techniques, taken in isolation is able to provide a complete picture of the complexity of the MS process. A multiparametric approach, combining aggregates of different MR quantities might improve our ability to monitor the disease. With the increased availability of high field and ultra-high field MR scanners, such an issue is now becoming extremely critical. Furthermore, the practical utility of modern MR approaches from a research setting to daily-life clinical practice still needs to be investigated.

References


