INSIGHTS INTO MULTIPLE SCLEROSIS PATHOLOGY FROM HIGH FIELD MRI

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Disclosures

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Learning Objectives

At the conclusion of this activity, the participant will be able to:

1. To understand the use of ultra-high field MRI as a methodology for probing multiple sclerosis brain pathology
2. To understand the use of quantitative techniques to describe pathologic change in the spinal cord in multiple sclerosis
3. To describe how these novel imaging techniques can lead to a better understanding of multiple sclerosis and help evaluate the impact of therapies on pathologic change
Outline

• Incomplete picture provided by standard MRI
• How high field MRI may provide more information
• 7T MRI in MS Project
  • Cortical Lesions
  • Thalamic Lesions
  • Diffusion Tensor Spectroscopy (DTS)
  • Quantitative Susceptibility Mapping (QSM)
  • Meningeal Pathology
• Conclusion
Standard MRI in Multiple Sclerosis

- T2/FLAIR Lesions
- Gadolinium Enhancement
- T1 “black holes”
- Atrophy
What are we missing?

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Brain (2005), 128, 2705–2712

Cortical demyelination and diffuse white matter injury in multiple sclerosis

Alexandra Kutzelnigg,1 Claudia F. Lucchinetti,3 Christine Stadelmann,5 Wolfgang Brück,5,6 Helmut Rauschka,2 Markus Bergmann,7 Manfred Schmidbauer,2 Joseph E. Parisi4 and Hans Lassmann1

Table 1 Quantitative differences in pathological features between different subgroups of multiple sclerosis values

<table>
<thead>
<tr>
<th></th>
<th>AMS</th>
<th>RRMS</th>
<th>SPMS</th>
<th>PPMS</th>
<th>Controls</th>
<th>Alzheimer’s disease</th>
<th>P-value group comparison</th>
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</thead>
<tbody>
<tr>
<td>Number of cases</td>
<td>11</td>
<td>6</td>
<td>20</td>
<td>14</td>
<td>15</td>
<td>15</td>
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<tr>
<td>Mean age (years); range</td>
<td>45.27 (28–68)</td>
<td>50.5 (20–67)</td>
<td>46.4 (28–61)</td>
<td>53.9 (28–75)</td>
<td>74.6 (46–89)</td>
<td>79.7 (60–92)</td>
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<tr>
<td>Female/male ratio</td>
<td>1.75</td>
<td>1</td>
<td>1.44</td>
<td>1.33</td>
<td>1.14</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Disease duration (months)</td>
<td>1.5 (0.2–7)</td>
<td>2.1 (0.48–15.6)</td>
<td>192 (72–408)</td>
<td>198 (30–411)</td>
<td>8</td>
<td>n.a.</td>
<td>P &lt; 0.001</td>
</tr>
<tr>
<td>WML area forebrain (%)</td>
<td>22.66 (0–85.05)</td>
<td>10.3 (1.01–53.25)</td>
<td>24.1 (2.79–60.36)</td>
<td>6.54 (0.46–76.54)</td>
<td>0</td>
<td>Atrophy</td>
<td>P = 0.06</td>
</tr>
<tr>
<td>Cortical lesion area forebrain (%)</td>
<td>0 (0–3.93)</td>
<td>2.96 (0–14.14)</td>
<td>13.29 (0–6.83)</td>
<td>12.54 (0–36.68)</td>
<td>0</td>
<td>Plaques + tangles</td>
<td>P &lt; 0.001</td>
</tr>
<tr>
<td>Active WMLs (%)</td>
<td>100 (90–100)</td>
<td>11.4 (0–100)</td>
<td>0 (0–50)</td>
<td>0 (0–50)</td>
<td>n.a.</td>
<td>n.a.</td>
<td>P &lt; 0.001</td>
</tr>
<tr>
<td>Slowly expanding WMLs (%)</td>
<td>0 (0)</td>
<td>10.42 (0–100)</td>
<td>14.29 (0–53.85)</td>
<td>12.5 (0–50)</td>
<td>0</td>
<td>n.a.</td>
<td>P &lt; 0.001</td>
</tr>
<tr>
<td>Inactive WMLs (%)</td>
<td>0 (0–10)</td>
<td>35.3 (0–85.71)</td>
<td>85.71 (12.5–100)</td>
<td>77.78 (14.29–100)</td>
<td>0</td>
<td>n.a.</td>
<td>P &lt; 0.001</td>
</tr>
<tr>
<td>Inflammatory infiltrates meninges (per 100 mm)</td>
<td>0.56 (0.196–2.793)</td>
<td>0.42 (0–0.824)</td>
<td>0.86 (0–4.752)</td>
<td>0.64 (0–4.506)</td>
<td>0</td>
<td>n.a.</td>
<td>P = 0.58</td>
</tr>
<tr>
<td>Perivascular inflammatory infiltrates NAWM (per mm²)</td>
<td>0.04 (0.015–0.12)</td>
<td>0.05 (0.03–0.21)</td>
<td>0.27 (0.015–0.79)</td>
<td>0.13 (0.015–0.88)</td>
<td>0</td>
<td>0.009 (0.0–0.03)</td>
<td>P &lt; 0.001</td>
</tr>
<tr>
<td>Microglia activation NAWM</td>
<td>1.5 (1–4)</td>
<td>2 (2–4)</td>
<td>4 (2–5)</td>
<td>4 (2–5)</td>
<td>1 (l)</td>
<td>2 (1–4)</td>
<td>P &lt; 0.001</td>
</tr>
<tr>
<td>Axonal spheroids NAWM (per mm²)</td>
<td>2.69 (0–7)</td>
<td>4.67 (1.65–7.5)</td>
<td>10.25 (0–35.06)</td>
<td>16.8 (2.5–81.5)</td>
<td>0.5 (0–5.75)</td>
<td>3.775 (0.78–7.8)</td>
<td>P &lt; 0.001</td>
</tr>
</tbody>
</table>

These values represent medians, the range for values are given in brackets; n.a.: not applicable.
Values in bold indicate those contributing to the significant differences.
What are we missing?

Normal Appearing White Matter

- Magnetization Transfer Ratio (MTR) is reduced\(^1\)
- Diffusion Tensor Imaging (DTI) indices are altered\(^2\)
- Both correlate with disability\(^1,3\)

What are we missing?

Gray matter pathology

- Cortical lesions
- Deep gray matter lesions
- Neuronal injury
- Demyelination


What are we missing?

Between and Within Plaque Heterogeneity

- Lucchinetti pathologic subtypes⁴
  - Type I: Perivenular demyelination, activated macrophages
  - Type II: Perivenular demyelination, Ig and complement deposition
  - Type III: Poorly defined borders, not-perivenular, oligodendorycte apoptosis, loss of MAG
  - Type IV: Perivenular demyelination, extensive oligodendorycte loss, lack of signs of re-myelination

- Iron deposition and/or loss in and around lesions⁵

Meningeal Pathology

Meningeal inflammation is widespread and linked to cortical pathology in multiple sclerosis

Owain W. Howell,²•• Cheryl A. Reeves,¹•• Richard Nicholas,¹ Daniele Carassiti,¹ Bishan Radotra,¹ Steve M. Gentleman,¹ Barbara Serafini,² Francesca Aloisi,² Federico Roncaroli,³ Roberta Magliozi² and Richard Reynolds¹

• 40% subjects with meningeal plasma cells, T-cells, and follicular dendritic cells
Meningeal Pathology

- Howell et al found F+ MS subjects had:
  - Greater cortical lesion burden
  - Earlier age of disease onset
  - More rapid disability progression
  - Earlier time to death
Why use higher field MRI?

- Signal-to-noise ratio (SNR)
- Resolution
- Wider separation of metabolic spectra
- Greater susceptibility effects
Initial Studies at 7T

- Kollia et. al. (2009):\textsuperscript{6}
  Comparison 7T to 1.5T.
  - 23\% increased white matter lesion detection
  - Lesion heterogeneity on T\textsuperscript{2}* GRE images

- Mainero et al. 2009:\textsuperscript{7}
  - Cortical lesions identified and characterized by known pathologic subtypes
  - Subtype proportions noted same as autopsy studies
  - Sub-pial type III/IV cortical lesions found more in SPMS

Adapted from Mainero et al. 2009
Perivascular Lesions

- Tallantyre et al. 2009:
  - Identification of lesions with central vessel by use of T2* sequence
  - Perivascular lesions: 45% at 3T, 87% at 7T

MS Center 7T MRI project

- 7-tesla Philips Achieva scanner with volume transmit, 32-channel receive head coil (Novamedical)
  - MPRAGE
  - MPFLAIR
  - 3D-GRE
  - Diffusion Tensor Spectroscopy
  - DTI
- MS participants ages 25 – 65, any subtype, EDSS 0 – 6.5, with no relapse in the 30 days prior to MRI study visit.
- EDSS
- MSFC
- MACFIMS
CORTICAL LESIONS
MPRAGE
- 0.5mm isotropic resolution
- repetition time 5.2ms
- delay time 4500ms
- echo time 2.3ms
- flip angle 7 degrees

MPFLAIR
- 1.0mm isotropic resolution
- repetition time 8107ms
- inversion time 2175ms
- echo time 293ms
- flip angle 90 degrees
Cortical lesion subtypes

<table>
<thead>
<tr>
<th>MPRAGE</th>
<th>Leukocortical</th>
<th>Intracortical</th>
<th>Subpial</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Type 1</td>
<td>Type 2</td>
<td>Type 3</td>
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</table>

<table>
<thead>
<tr>
<th>MPFLAIR</th>
<th>Leukocortical</th>
<th>Intracortical</th>
<th>Subpial</th>
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<tbody>
<tr>
<td></td>
<td>Type 1</td>
<td>Type 2</td>
<td>Type 3</td>
</tr>
</tbody>
</table>
Cortical Lesion Count / Volume

* = p < 0.05 for difference from healthy volunteers. † = p < 0.05 for difference from RRMS.

* = p < 0.05 for difference from healthy volunteers. † = p < 0.05 for difference from RRMS.
## Cortical Lesions and Disability

<table>
<thead>
<tr>
<th>Cortical Lesions</th>
<th>( R_{	ext{Spearman}} )</th>
<th>( R_{	ext{Spearman}} )</th>
<th>( R_{	ext{Spearman}} )</th>
<th>( R_{	ext{Spearman}} )</th>
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<th>( R_{	ext{Spearman}} )</th>
<th>( R_{	ext{Spearman}} )</th>
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<tbody>
<tr>
<td>Cortical GM</td>
<td>-0.13</td>
<td>0.36*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Cortical lesion</td>
<td>0.63*</td>
<td>0.65*</td>
<td>0.44*</td>
<td>0.44*</td>
<td>0.59*</td>
<td>0.63*</td>
<td>0.41*</td>
<td>0.34*</td>
<td>-0.64*</td>
<td>-0.51*</td>
<td>-0.13</td>
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<tr>
<td>BPF</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>0.27</td>
<td>0.53*</td>
<td>-0.27</td>
<td>0.03</td>
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<tr>
<td>WM Volume</td>
<td></td>
<td></td>
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<tr>
<td>Cortical lesion</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.44*</td>
<td>0.65*</td>
<td>0.44*</td>
<td>0.59*</td>
<td>0.63*</td>
<td>-0.13</td>
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<tr>
<td>EDSS</td>
<td></td>
<td>0.27</td>
<td>0.53*</td>
<td>-0.27</td>
<td>0.03</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>WM lesion</td>
<td></td>
<td>-0.13</td>
<td>0.36*</td>
<td></td>
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</tr>
<tr>
<td>PASAT-3</td>
<td>-0.03</td>
<td>-0.13</td>
<td>0.00</td>
<td>0.10</td>
<td>0.00</td>
<td>-0.099</td>
<td>-0.05</td>
<td>0.10</td>
<td>0.27</td>
<td>0.53*</td>
<td>-0.27</td>
</tr>
<tr>
<td>COWAT</td>
<td>-0.34*</td>
<td>-0.32</td>
<td>-0.24</td>
<td>-0.17</td>
<td>-0.20</td>
<td>-0.30</td>
<td>-0.19</td>
<td>0.04</td>
<td>0.35*</td>
<td>0.50*</td>
<td>-0.10</td>
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<tr>
<td>JLO</td>
<td>-0.29</td>
<td>-0.28</td>
<td>-0.19</td>
<td>-0.27</td>
<td>-0.35*</td>
<td>-0.31</td>
<td>-0.25</td>
<td>-0.38*</td>
<td>0.11</td>
<td>0.12</td>
<td>0.07</td>
</tr>
<tr>
<td>CVLT, mean total learning score</td>
<td>-0.28</td>
<td>-0.37*</td>
<td>-0.19</td>
<td>-0.09</td>
<td>-0.34*</td>
<td>-0.46*</td>
<td>-0.16</td>
<td>0.05</td>
<td>0.43*</td>
<td>0.47*</td>
<td>0.06</td>
</tr>
<tr>
<td>CVLT, mean delayed recall score</td>
<td>-0.28</td>
<td>-0.37*</td>
<td>-0.04</td>
<td>-0.20</td>
<td>-0.42*</td>
<td>-0.46*</td>
<td>-0.04</td>
<td>-0.07</td>
<td>0.41*</td>
<td>0.38</td>
<td>0.14</td>
</tr>
<tr>
<td>BVMT, mean total recall score</td>
<td>-0.25</td>
<td>-0.44*</td>
<td>0.51*</td>
<td>-0.06</td>
<td>-0.40*</td>
<td>-0.51*</td>
<td>-0.13</td>
<td>-0.12</td>
<td>0.36*</td>
<td>0.34</td>
<td>0.03</td>
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<tr>
<td>BVMT, mean delayed recall score</td>
<td>-0.29</td>
<td>-0.48*</td>
<td>-0.16</td>
<td>-0.08</td>
<td>-0.44*</td>
<td>-0.56*</td>
<td>-0.18</td>
<td>-0.14</td>
<td>0.29</td>
<td>0.26</td>
<td>0.05</td>
</tr>
<tr>
<td>SDMT, mean total correct</td>
<td>-0.33*</td>
<td>-0.48*</td>
<td>-0.23</td>
<td>-0.09</td>
<td>-0.35*</td>
<td>-0.50*</td>
<td>-0.28</td>
<td>0.02</td>
<td>0.58*</td>
<td>0.58*</td>
<td>-0.06</td>
</tr>
<tr>
<td>DKEFS, mean # of sorts</td>
<td>-0.24</td>
<td>-0.42*</td>
<td>0.01</td>
<td>-0.09</td>
<td>-0.34*</td>
<td>-0.47*</td>
<td>0.02</td>
<td>0.04</td>
<td>0.28</td>
<td>0.22</td>
<td>0.06</td>
</tr>
<tr>
<td>DKEFS, mean description score</td>
<td>-0.18</td>
<td>-0.38*</td>
<td>0.04</td>
<td>-0.02</td>
<td>-0.26</td>
<td>-0.42*</td>
<td>0.04</td>
<td>0.13</td>
<td>0.33</td>
<td>0.29</td>
<td>0.05</td>
</tr>
</tbody>
</table>

### Table: Correlation with disability

Shown are spearman rank correlation coefficients. * \( p < 0.05 \) for correlation. EDSS = Expanded Disability Status Scale. MSSS = Multiple Sclerosis Severity Score. MSFC = Multiple Sclerosis Functional Composite. PASAT-3 = Paced Auditory Serial Addition Test – 3 second delay. COWAT = Controlled Oral Word Association Test. JLO = Judgment of Line Orientation Test. CVLT = California Verbal Learning Test. BVMT = Brief Visuospatial Memory Test. SDMT = Symbol Digit Modalities Test. DKEFS = Delis-Kaplan Executive Function System Test.
Cortical Lesions and Cognitive Impairment

- OR for log [Total Cortical Lesion Volume] predicting cognitive impairment (adj age, gender) = 3.36 (1.07 – 10.59), p = 0.038
- OR for log [Total Cortical Lesion Volume] predicting cognitive impairment (adj age, gender, WM lesions, atrophy) = 14.26 (1.06 – 192.37), p = 0.045
THALAMIC LESIONS
7T Imaging of Thalamus in MS

MPFLAIR – A, C
MPRAGE – B, D
Orange Arrows – Ovoid Lesion
Yellow Arrows – Periventricular Lesion
- The total thalamic lesion burden and ovoid lesion burden were increased in SPMS/PPMS subjects compared to RRMS.
- There was no difference between subgroups for periventricular lesion burden.
- * = p < 0.05 for comparison to healthy volunteers. ** = p < 0.05 for comparison to RRMS.
7T Imaging of Thalamus in MS

- Spearman rho = 0.30, p = 0.034
- Spearman rho = 0.34, p = 0.049
- Spearman rho = 0.13, p = 0.474
- Spearman rho = 0.16, p = 0.365
- Spearman rho = 0.36, p = 0.037
- Spearman rho = 0.40, p = 0.020
Diffusion Tensor Spectroscopy (DTS)

- DTI – Provides quantification of directional diffusion in anisotropic tissues. Susceptible to inflammation, demyelination, and degeneration.
- MRS – Provides quantification of metabolites in tissue, but no structural information.
- DTS – Measures diffusion properties of metabolites. Prelim studies show sensitivity of DTS of N-acetyl-aspartate (NAA) to axonal tract geometry.\textsuperscript{10}

Figure 1. Voxel location and spectra. a, sagittal and c, coronal T1-weighted images demonstrating voxel location in red. b, DTI axial color map. d, non-diffusion-weighted spectrum (black) and diffusion-weighted spectra with gradient direction primarily parallel to fiber tract (red & blue).

Figure 2. Parallel diffusivity ($\lambda_||$) of NAA and water. a, NAA $\lambda_||$ is negatively correlated with $\text{avgDTI}_\text{water} \lambda_||$ (all subjects, $R^2=0.16$, $p=0.02$). b, NAA $\lambda_||$ and $\text{avgDTI}_\text{water} \lambda_||$ for multiple sclerosis patients (MS) and healthy controls (HC) (*$p<0.05$, **$p<0.001$, error bars represent 95% confidence intervals).

Figure 3. NAA parallel diffusivity ($\lambda_||$) is correlated with clinical severity of disease ($\rho=-0.61$, $p=0.015$). EDSS=Expanded Disability Status Scale.

DTS – Clinical Data

QUANTITATIVE SUSCEPTIBILITY MAPPING
Magnetic Susceptibility in MS

- Diffuse subpial T2* changes seen in MS
- Corresponding to cortical demyelination? Iron deposition?

Figure from Cohen et al. Neuroimage 2011;57:55-62.
Magnetic Susceptibility in MS

• Hammond et al. 2008:¹¹
  • Local field shift increased in basal ganglia compared to controls
  • Phase contrast seen in 74% of lesions
  • Peripheral phase ring in 6% of lesions
  • Phase contrast also identified additional lesions

• Absinta et al 2013:¹²
  • Phase rim present in acute, centripetal enhancing lesions, which later disappears
  • Phase rim also present in subset of chronic lesions
  • Iron rich macrophages or oligos?
  • Blood brain barrier breakdown?

Phase contrast is filter dependent

- Phase contrast also changes with orientation of head
- Phase contrast also changes with lesion geometry
Quantitative Susceptibility Mapping (QSM)

- Quantitative technique to measure inherent tissue susceptibility
  - No non-local phase effects
  - Head orientation independent analyses possible
- 3D-Gradient Echo (GRE) images acquired at 7T
Magnetic Susceptibility in MS – Iron or Myelin?

- Iron = paramagnetic effect
  - Iron in macrophages and oligodendrocytes
  - Decreased axonal movement of iron in injured neurons
  - Blood-brain barrier leakage
- Myelin = diamagnetic effect

Image from Stuber et al. Neuroimage 2014: in press
Magnetic Susceptibility in MS – Iron or Myelin?

• Loss of gray/white contrast in shiverer mice on QSM. (Liu et al. Neuroimage 2011;56:930-938)

• Myelin contribution to QSM signal larger and opposite of iron (below)

• Taken together,

\[ R2^* \downarrow + \chi \uparrow = \text{myelin loss} \]
\[ R2^* \uparrow + \chi \uparrow = \text{iron deposition} \]

Image from Stuber et al. Neuroimage 2014: in press
Figure: Examples of common lesion types on R2*, Phase, and QSM. On phase imaging, 42% were isointense with no rim (thus invisible) and 29% were hyperintense with no rim. Thirteen percent of lesions were surrounded by either a hypo- or hyperintense rim. On QSM, 52% of lesions were hyperintense with no rim and 36% were isointense with no rim (thus invisible). Eight percent of lesions were surrounded by either a hypo- or hyperintense rim.
Interpretation of Subtypes

- Demyelination w/o oligo loss¹
- ? Lucchinetti type I/II lesions³

- Demyelination w/ oligo loss²
- ? Lucchinetti type III/IV lesions³
- ? Chronic-active lesions with M1 polarized, iron laden macrophage rim⁴

MENINGEAL DISEASE
Meningeal Pathology

- Leptomeningeal carcinomatosis and infectious leptomeningeal disease seen on post-contrast FLAIR > post-contrast T1 (Fukuoka et al. AJNR 2010)
- Could post-contrast FLAIR provide similar findings in MS?
Subarachnoid spill/fill pattern
Nodular Pattern
<table>
<thead>
<tr>
<th></th>
<th>MS cases (n = 29)</th>
<th>Healthy Volunteers (n = 2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enhancing leptomeningeal foci present, n (%)</td>
<td>26 (90%)</td>
<td>1 (50%)</td>
</tr>
<tr>
<td>Number of enhancing foci, median (range)</td>
<td>2.0 (0 – 8)</td>
<td>1.5 (0 – 3)</td>
</tr>
<tr>
<td>Subarachnoid spill/fill foci present, n (%)</td>
<td>20 (69%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Number of subarachnoid spill/fill foci, median (range)</td>
<td>1 (0 – 6)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Nodular foci present, n (%)</td>
<td>17 (59%)</td>
<td>1 (50%)</td>
</tr>
<tr>
<td>Number of nodular foci, median (range)</td>
<td>1 (0 – 7)</td>
<td>1.5 (0 – 3)</td>
</tr>
</tbody>
</table>

Trend towards subarachnoid spill/fill more common in older patients with higher EDSS, lower SDMT, and higher MFIS.
Meningeal Pathology

- Similar findings in 3T NIH study (Absinta et al. Neurology 2015), but only seen in 25% there.
- Post-contrast subarachnoid space enhancement is stable on re-scan and over time.
- Autopsy showed diffuse leptomeningeal inflammation and perivascular inflammation in regions with subarachnoid post-contrast FLAIR enhancement.
A Gradient of Neuronal Loss and Meningeal Inflammation in Multiple Sclerosis

Roberta Magliozzi, BSc,1,2 Owain W. Howell, PhD,1 Cheryl Reeves, PhD,1 Federico Roncaroli, MD,1 Richard Nicholas, MD,1 Barbara Serafini, PhD,2 Francesca Aloisi, PhD,2 and Richard Reynolds, PhD1

ANN NEUROL 2010;68:477–493
Comparison to segmented volumes

- Cortical GM fraction correlated with the number of spreading/filling foci (Spearman rho -0.383, p = 0.049).
- No significant relationship between leptomeningeal enhancement and white matter fraction or white matter lesion volume.
Conclusions

• High field MRI allows for *in vivo* quantification of MS pathology previously only noted in *ex vivo* studies
• Cortical and deep gray matter lesions are visible by high field MRI, and contribute significantly to disability
• DTS reveals reduced axonal integrity in MS
• QSM and R2* imaging can combine to quantify myelin and iron content in lesions, revealing lesion heterogeneity
• Meningeal pathology may be directly or indirectly visible
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Quantitative Characterization of the Spinal Cord in MS - MRI

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Department of Biomedical Engineering
Department of Ophthalmology
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Disclosures

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Clinical Neurology

• FLAIR
  – 1992 (Bydder)
• Questions?
  – Sensitive
  – Specific
  – R1/R2?
  – Quantification?
• Answers a Dx question
T2 lesion load vs. EDSS

Correlation coefficient ($r$) vs. number of patients ($n$)

Courtesy: Daniel Reich
What does MR bring to the table?

Structure

Macro Structure

Function

Micro structure
Clinical Questions

Metabolic Biochemical (CEST) MRI

Tissue Integrity - DTI

Myelin Sensitivity

Function

Mathematical Modeling

Ultra High Field
What is the Spinal Cord
Vertebral Body

Dorsal Columns (vibration)

Lateral Column (motor)

Spine diameter at C2: ~1.5 cm RL
Spinal Cord MRI

T₁w

Healthy

MS

T₂w
What does the spinal cord do?
The peripheral nervous system is the network of nerves strands that branch off from the left and right sides of the spinal cord through openings between each vertebra on the spinal canal. These nerve pairs spread throughout your body to deliver commands from your brain and spinal cord to and from parts of your body.

What does the spinal cord do? - University of Alabama at ... www.uab.edu/...spinal-cord.../what-d... University of Alabama at Birmingham
Multiple Sclerosis

• Attack of the Central Nervous system
  – Automimmune
  – Involves all of the CNS

• Characterized by
  – Axonal Damage
  – Demyelination
  – Tissue Atrophy

• Recovery
  – Transient
  – Unpredictable course
  – Treatments?
Coronal and curved reformat

Carswell, Illustrations of the Elementary Forms of Disease 1838.
More Than Expected

Healthy

3T T2*w 0.8 x 0.8mm²

T1w 0.8 x 0.8mm²

MS

H K

I L

J M
Existing MRI Knowledge and Technique Gaps
Structure

Anatomical
Knowledge Gap 1

- Conventional MRI does not provide excellent contrast like the Brain
If we can improve contrast...
Axial 3D gradient-echo imaging for improved multiple sclerosis lesion detection in the cervical spinal cord at 3T

Arzu Ozturk · Nafi Aygun · Seth A. Smith · Brian Caffo · Peter A. Calabresi · Daniel S. Reich
Macro Structure

Magnetization Transfer

Myelin
Knowledge Gap 2

- Magnetization Transfer is slow, cumbersome (with modeling), and provides poor contrast in the cord
Magnetization Transfer

Off-resonance RF

Free water pool

Solid phase proton pool

$\omega_o$

Reference: $S_o$

MT weighted: $S(\omega)$

semi-solid lattice
Basis for the MT Effect: Macromolecules
Basics of Quantitative MT (qMT)

Pathology: Inflammation

- 1. Long $T_2$ (~10 ms)
- 2. Mobile
- 3. Directly Imaged

Pathology: Demyelination

1. Short $T_2$ (~ms)
2. Solid phase
3. Silent to conventional MRI
\[ \alpha_e = 360^\circ \]

\[ D = 1 \text{ kHz} \]

\[ D = 1.5 \text{ kHz} \]

\[ D = 2 \text{ kHz} \]

\[ D = 2.5 \text{ kHz} \]

\[ D = 8 \text{ kHz} \]

\[ a = 360 \]

\[ e = 820 \]

Pool Size Ratio (PSR)

Myelination Content

\[ r^2 = 0.61 \quad (p < 0.01) \]

\[ \text{PSR} = 0.4 \times \text{OD} + 12.3 \]
Magnetization Transfer

PSR: Pool Size Ratio
Sensitive to Myelin Density
0.6 x 0.6 x 3mm³
5-8 minutes scan time
Pool Size Ratio Maps

Voxel Fraction (%) vs. PSR

Controls
MS Patients
Micro Structure

Diffusion Tensor Imaging

Axons
Knowledge Gap 3

- DTI is challenging: long acquisition times, low resolution, and susceptibility artifacts
Anisotropic Diffusion (WM)

- $MD = \frac{1}{3}(\lambda_1 + \lambda_2 + \lambda_3)$
  - Average Displacement

- $\lambda_\perp = \frac{1}{2}(\lambda_2 + \lambda_3)$
  - Displacement Perpendicular to Axon Bundle

Isotropic Diffusion (GM, CSF)

- $\lambda_\parallel = \lambda_1$
  - Displacement Along Axon Bundle

- $FA = \sqrt{\frac{1}{2} \left( \frac{(\lambda_1 - \lambda_2)^2 + (\lambda_1 - \lambda_3)^2 + (\lambda_2 - \lambda_3)^2}{\lambda_1^2 + \lambda_2^2 + \lambda_3^2} \right)}$
Diffusion Tensor Imaging

DTI: 15 directions
b = 0, 750 s/mm²
0.9 x 0.9 x 3mm³
Zoom EPI
5-10 min scan time
Tractography – scaled by FA
Clinical Applicability

FA 6 15 32 4.5 min 9 min 2.42 3.0 2.37 1.72 2.5 3.31
AD 6 15 32 4.5 min 9 min 1.72 2.5 3.31
Localizer FA 6 15 32 4.5 min 9 min 1.72 2.5 3.31
mFFE FA 4.63 2.24 2.09
RD μm²/ms
TLSC AD 6 15 32 4.5 min 9 min 1.72 2.5 3.31
mFFE FA 4.63 2.24 2.09
RD μm²/ms
## DTI vs. Function/Clinical Measures

<table>
<thead>
<tr>
<th></th>
<th>Hip Flexion Strength</th>
<th>Vibration Sensation Threshold</th>
<th>EDSS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Regression coefficient</td>
<td>p-value*</td>
<td>Regression coefficient</td>
</tr>
<tr>
<td><strong>FA</strong></td>
<td>43.43</td>
<td>0.08</td>
<td>-46.78</td>
</tr>
<tr>
<td><strong>MD</strong></td>
<td>-33.49</td>
<td><strong>&lt;0.001</strong></td>
<td>13.62</td>
</tr>
<tr>
<td><strong>λ⊥</strong></td>
<td>-30.92</td>
<td><strong>&lt;0.001</strong></td>
<td>17.79</td>
</tr>
<tr>
<td><strong>λ∥</strong></td>
<td>-23.46</td>
<td><strong>&lt;0.001</strong></td>
<td>3.57</td>
</tr>
<tr>
<td><strong>MTR</strong></td>
<td>56.41</td>
<td>0.12</td>
<td>-74.68</td>
</tr>
<tr>
<td><strong>Lesion count</strong></td>
<td>-1.43</td>
<td>0.13</td>
<td>1.27</td>
</tr>
</tbody>
</table>

Jiwon Oh, Kathleen Zackowski, Min Chen, Scott Newsome, Shiv Saidha, Seth Smith, Marie Diener-West, Jerry Prince, Peter A. Calabresi, Daniel S. Reich
Micro Structure

Chemical Exchange Saturation Transfer (CEST)

Molecules
Knowledge Gap 4

- CEST – approach to biochemical specificity – non-existent in SC

![Graph showing S/S% vs offset (ppm) for different chemical components: amides, amines, lipids, water, and macromolecules. The graph compares healthy control and MS patient images with mFFE and APT maps.](image)
What is CEST?

• **Chemical Exchange Saturation Transfer**
  – Transfer of spin information from mobile protons to surrounding water
  – Occurs through direct chemical exchange

• **Sensitivity**
  – Mobile protons (NH$_x$, OH)
  – Sufficient concentration (~mM)
  – Slow to intermediate exchange rate
    • Chemical Shift ($\Delta \omega$) > $k_{ex}$

• **MRI Method**
  – Apply off-resonance RF irradiation (saturation)
  – Observe water signal decrease
MT vs. CEST

Magnetization Transfer (MT)

- Rigid/solid-like structures
- Broad line-shape
- Dipole + Chemical Exchange

Chemical Exchange Saturation Transfer (CEST)

- Mobile structures
- Narrow line-shape
- Chemical exchange
What is CEST Sensitive to?

Glycogen

• Energy Metabolism
• $\Delta \omega \sim 0.5$-1.5ppm

Glutamate (GluCEST)

• Excitatory Neurotransmitter
• $\Delta \omega \sim 3.0$ppm

Myoinositol (miCEST)

• Related to Glial Cells
• $\Delta \omega \sim 0.6$-1.0ppm

Proteins/Peptides (APT)

• Everywhere $\rightarrow$ accumulation
• $\Delta \omega \sim 3.5$ppm
Function

Functional MRI (fMRI)

Function/Activity
Knowledge Gap 5

- fMRI? In the cord? Really?

M. Pasin¹, M.C. Yiannakas¹, H. Kearney¹, A. Toosy², C.A.M. Wheeler-Kingshott. ISMRM 2014
Physicist Viewpoint

Courtesy: Etsy

Courtesy: Seth
Functional Connectivity – Spinal Cord

Irene Tracy et al (eLife 2013)
Resting State fMRI at 3T

mFFE

fMRI

13 mm
Future Opportunities

7T
Importance of Field Strength

- Exchange Effects (CEST, T1rho)
- Spectral Dispersion (Spectroscopy/CEST)
- Susceptibility Effects (fMRI)
- Prolonged T1 (MT)

Other Significant Benefits
7T

Courtesy: Julien Cohen-Adad, Wei Zhao, Larry Wald
Application to MS

Healthy

T2*W  T1W

0.5 x 0.5mm²  0.5 x 0.5mm²

MS

B C D

E F G

H I J

K L M
Spinal Cord fMRI at 7 Tesla

Anatomical

Functional
Resting State fMRI - SC

tSNR

Connectivity
Summary

• Description and Characterization of the Spinal Cord
  – Anatomy
  – Function

• Role of SC in disease and Why Care
  – Multiple Sclerosis
  – Relatively Underrepresented in qMRI studies

• Knowledge Gaps/Technique Limitations
  – Focus on Clinical Field Strength
  – Anatomical, Magnetization Transfer, Diffusion, CEST, fMRI
  – Improvement is necessary and possible

• 7T
  – Brief but looking forward
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Hakmook
Kristin
Alex
Sam
Lydia
Bailey
Bailey
Ben
Who’s Who

Seth

Saikat

Sid

Kristin

Francesca

Alex

Hakmook

Sam

Richard

Bailey

Lydia

Ben
Until Next Time
Thank You
Quick Picture of Multiple Sclerosis

- Progressive-relapsing multiple sclerosis
  - Steady decline since onset with superimposed attacks.

- Secondary progressive multiple sclerosis
  - Initial relapsing-remitting multiple sclerosis that suddenly begins to have decline without periods of remission.

- Primary progressive multiple sclerosis
  - Steady increase in disability without attacks.

- Relapsing-remitting multiple sclerosis
  - Unpredictable attacks which may or may not leave permanent deficits followed by periods of remission.
Improvement on Clinical Standard
MRI shows Inflammation

Normal

ALD
No inflammation, No MR contrast

• Defect in β-oxidation of very-long chain fatty acids (peroxisomomal)

• Adult Variant: Adrenomyeloneuropathy
  – Slowly progressing Axonopathy (years)
  – Demyelination of spinal cord (dorsal column)

• Conventional MRI not able to see the damage
MT shows Injury in AMN

MT weighted Images

Healthy

Mildly Affected

Severely Affected

Post-mortem Reprinted with permission from:
Powers J, et al.
Journal of Neuropathology and Experimental Neurology, 2000, 59: 89-102

Smith et al, MRM (2005)
Multiple Sclerosis

CEST in MS

Healthy WM

NAWM

GM

Lesion

CSF

Frequency Offset (ppm)

$\text{CEST}_{\text{asym}} (%)$