Imaging Disease Progression in MS
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- Stock in GlaxoSmithKline
Disease progression in MS: the acute plaque

Inflammatory cells (blue) Myelin (green) Axons (in red)

Acute demyelination initiates local remyelination

Myelin structure is distinct in healthy myelinated and demyelinated segments

RJ Franklin, C ffrench-Constant
Acute demyelination initiates local remyelination

Myelin structure is distinct in healthy myelinated and demyelinated segments

Brains from 3 patients with demyelination (red) and remyelination (blue)

Disease progression in MS: the chronic plaque

Astrocytic “scar” (orange)

T1-weighted MRI

Courtesy of Dr. D. Arnold, McGill Univ, adapted from animation courtesy of Bruce D. Trapp, 2002, © Cleveland Clinic Foundation
Neuronal and axonal loss is the major pathological mechanism for disability

Pathological sodium channel expression along demyelinated axons

Sections of post-mortem spinal cord of white matter from healthy subjects (A,B) and patients with MS (C-L) immunostained to show:
- Nav1.6 (red)
- Nav 1.2 (red)
- Caspr (paranodal junctions) (green)
- Neurofilaments (blue)
Chronic macrophage or microglia mediated damage

- Axonal injury correlates with active demyelination and inflammation
- Antibody destruction via Fc / complement receptors
- Release of inflammatory mediators cytokines
  - TNF-a
  - Nitric Oxide
  - Proteases

Kuhlmann T et al. Brain 2002;125:2202-2212

Imaging Markers for Myelin

<table>
<thead>
<tr>
<th>Technique</th>
<th>Marker</th>
<th>Influenced by</th>
<th>Usability (Practicality for Clinical Trials)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myelin Water Imaging</td>
<td>Myelin Water Fraction (MWF)</td>
<td>Myelin (intact, debris)</td>
<td>Not yet available as product sequence</td>
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<tr>
<td>Magnetisation Transfer Imaging</td>
<td>Magnetisation Transfer Ratio (MTR)</td>
<td>Changes in myelin protein associated water</td>
<td>Commonly available but not standardized</td>
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<tr>
<td></td>
<td></td>
<td>Axons</td>
<td>Varies between vendors</td>
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<tr>
<td></td>
<td></td>
<td>Myelin</td>
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<tr>
<td></td>
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<td>Other macromolecules</td>
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</table>
Myelin Water has a shorter T2 “relaxation time” than free water

Myelin water images of the whole cerebrum, derived from T2 relaxation, can be acquired in less than 15 minutes.

Content courtesy of S Kolind, C Laule, A MacKay, A Traboulsee, I Vavasour (University of British Columbia).

Myelin water: imaging of MS lesions and remyelination

Content courtesy of S Kolind, C Laule, A MacKay, A Traboulsee, I Vavasour (University of British Columbia).
Principles of magnetisation transfer ratio (MTR) imaging

Magnetisation Transfer (MT) Image
- Selectively excite bound water
- Magnetisation is transferred to free water
- Pre-excited molecules provide less signal on T1W images

T1W=T1 weighted; RF=radio frequency.
Content courtesy of Prof. Doug Arnold (McGill University).

Magnetisation transfer ratio (MTR) image generation

Content courtesy of Prof. Doug Arnold (McGill University).
**MTR: imaging remyelination with MS**

- **New lesions on MTR show demyelination**
- **Resolving lesions on MTR show repair**

**Baseline**

**+4 Months**

**Difference (ΔMTR)**

MTR=magnetisation transfer ratio.

Content courtesy of Prof. Doug Arnold (McGill University).

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**Microstructure of the grey and white matter**

- **GM components:**
  - Neuronal cell bodies
  - Dendritic arborisation
  - Some myelin fibres

- **WM components:**
  - Axons (~45%)
  - Myelin (~25%)
  - Glial cells (~17%)
  - Blood vessels and tissue fluids (~13%)

GM, grey matter; WM, white matter

Whole brain atrophy in MS

Healthy Control
- RRMS (EDSS: 1.5, MS Duration: 5 years)
  - BPF 0.89
- RRMS (EDSS: 4.0, MS Duration: 10 years)
  - BPF 0.80
- SPMS (EDSS: 6.5, MS Duration: 18 years)
  - BPF 0.70

MS=multiple sclerosis; RRMS=relapsing-remitting MS; SPMS=secondary progressive MS; BPF=brain parenchymal fraction.

The absolute rate of brain atrophy is similar through the disease course

De Stofano et al. Neurology 2010;74:1868-1876
Atrophy arises from multiple pathophysiological mechanisms

Factors causing brain-volume reduction:
- Tissue loss (such as myelin, axons and possibly also astrocytes)¹
- Fluid shift¹
- Ageing²
- Alcohol³
- Smoking³
- ApoE?⁴

Factors causing brain-volume increase:
- Neuronal repair⁶
- Remyelination¹
- Astroglisis¹
- Fluid shift¹

Optical coherence tomography (OCT): retinal structure reflects axonal injury in MS

- OCT allows rapid, noninvasive quantification of retinal layers by low-coherence near-infrared light¹–³
- Characterizes neuronal injury in the retina¹–³
**OCT: Retinal Nerve Fiber Layer (RNFL) Thinning with Progressive MS**

RNFL Comparisons Between Controls and MS Subgroups by History of Optic Neuritis (ON)

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<tr>
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<th>Microns</th>
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<tr>
<td>Controls</td>
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<td>MS Eyes Not</td>
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<td>Affected by ON of MS</td>
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<td>ON Patients</td>
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<td>Unaffected Eyes</td>
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RNFL Comparisons in MS Subtypes

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<tr>
<td>RRMS</td>
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<td>PPMS</td>
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<td>SPMS</td>
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*P<0.05; †P<0.01; ‡P<0.001; §P<0.0001.

OCT=optical coherence tomography.


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**Sodium MRI**

A measure of both intracellular sodium accumulation and cell loss

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Imaging of activated microglia with PET using 18 kD mitochondrial translocator protein (TSPO) radioligands

Visit 1
Before natalizumab (failing IFNβ)

Visit 2
After 6 months of natalizumab treatment

[18F]PBR111 microglial imaging for treatment monitoring?

 Modify from Fig. 5 in Colasanti A et al. J Nucl Med. 2014;55:1112-1118.

IFN=interferon beta
Content courtesy of Prof. Paul Matthews (Imperial College London).
Summary: advanced imaging measures in MS provide new tools for assessing disease and treatment response

Positron Emission Tomography (PET) Imaging
- Microglial activation
- Rapid, direct measure of retinal pathology

Myelin Water Imaging
- Pathological myelin microstructure

Magnetisation Transfer Ratio (MTR)
- Completeness of recovery

Sodium imaging
- Pathological sodium accumulation and cell loss

Retinal Optical Coherence Tomography (OCT)
- Rapid, direct measure of retinal pathology

Cortical mapping

Why do we care about imaging measures of disease progression?

70% test negative
30% test positive

Benefits from treatment
No benefit from treatment

Greater increase of lesion volume in SPMS over the first 5 years

CIS, clinically isolated syndrome; RRMS, relapse-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis

Fisniku LK, et al. Brain 2008;131;808–817

Median T2 lesion volume

CIS
RRMS
SPMS

Brain atrophy in MS: correlation with disability

Rate of atrophy and annualised change in EDSS vs. PBVC/year

EDSS, Expanded Disability Status Scale; GMF, grey-matter fraction; PBVC, percentage brain volume change; MS, multiple sclerosis; SDMT, Symbol Digit Modalities Test; WMF, white-matter fraction

Meta-analysis of randomised clinical trials in RRMS
Lesions, brain atrophy and clinical disability as predictors of subsequent disability progression over 2 years

Includes data from >13,500 patients
Defining brain volume cut-offs to predict disability progression in MS: analysis of a large cohort of RRMS patients

- Baseline NBV (assessed by SIENAX) was comparable across different trials
- Patients with a small NBV (adjusted for age and MS disease characteristics) were at higher risk of subsequent disability progression over 2 or 4 years


MS, multiple sclerosis; NBV, normalised brain volume; RRMS, relapsing remitting multiple sclerosis

Standardising automated T2 lesion change measures

High correlation ($r=0.77$, $p<0.001$) between automated PD difference imaging over 76 weeks and cumulative Gd-enhancing lesion count with serial MRI
Standardising automated brain volume measures

http://applications.eu-decide.eu/gridmriseg

GridMRI Seg Report

Physician: Griffin
Patient ID: DEC15
Sec: F, Age: 81

ACM-AdaBoost Results

Model: L15

Left Volume: 2653 mm³
Right Volume: 2847 mm³

Every colored line represents the Prediction Percentile for the hippocampus volume of a normal age matched subject.

http://applications.eu-decide.eu/gridmriseg