Neuroplasticity in Multiple Sclerosis – Evidence from TMS

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Little correlation between functional deficit and lesion load

MRI T2 lesion burden in multiple sclerosis
A plateauing relationship with clinical disability

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Disability and T2 MRI lesions: a 20-year follow-up of patients with relapse onset of multiple sclerosis

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Neuroplasticity Predicts Outcome of Optic Neuritis Independent of Tissue Damage

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Objectives: To determine whether lateral occipital complex (LOC) activation with functional magnetic resonance imaging (fMRI) predicts visual outcome after clinically isolated optic neuritis (ON). To investigate the reasons behind good recovery following ON, despite residual optic nerve demyelination and neuroaxonal damage.

Methods: Patients with acute ON and healthy volunteers were studied longitudinally over 12 months. Structural MRI, visual evoked potentials (VEPs), and optical coherence tomography (OCT) were used to quantify acute inflammation, demyelination, conduction block, and later to estimate remyelination and neuroaxonal loss over the entire visual pathway. The role of neuroplasticity was investigated using fMRI. Multivariable linear regression analysis was used to study associations between vision, structure, and function.

Results: Greater baseline fMRI responses in the LOCs were associated with better visual outcome at 12 months. This was evident on stimulation of either eye (p = 0.007 affected; p = 0.020 fellow eye), and was independent of measures of demyelination and neuroaxonal loss. A negative fMRI response in the LOCs at baseline was associated with a relatively worse visual outcome. No acute electrophysiologic or structural measures, in the anterior or posterior visual pathways, were associated with visual outcome.

Interpretation: Early neuroplasticity in higher visual areas appears to be an important determinant of recovery from ON, independent of tissue damage in the anterior or posterior visual pathway, including neuroaxonal loss (as measured by MRI, VEP, and OCT) and demyelination (as measured by VEP).

ANN NEUROL 2010;67:99–113
Neuroplasticity in multiple sclerosis

Rapid onset plasticity
Interregional plasticity
Local network plasticity
Neuroplasticity in Multiple Sclerosis

Rapid onset plasticity
Interregional plasticity
Local network plasticity
Synaptic plasticity impaired by:

- *demyelinating lesion*: possible loss of synchronicity
- *Atrophy of grey matter*: (glial (-36%), neuronal (-10%), synaptic (-47%): Wegner, Neurology, 2006; Sicotte, Brain, 2008)

Synaptic plasticity improved by:

- *Ciliary neurotrophic factor (CNTF) signalling* (Dutta, Brain, 2007)
- *Endocannabinoids?* (Centonze, Brain 2006)
Paired associative stimulation

Stefan et al. Brain. 2000
Temporally asymmetric Hebbian rule


Dan. Physiol Rev. 2006

M1

S1

P25-Amplitude prä/post

Interstimulus interval (ms)

Normalized EPSP slope (%)

Pre/post spike interval (ms)

Prozent des Ausgangswertes

Interstimulus interval (ms)

Synaptic plasticity in multiple sclerosis

Zeller, aufm Kampe, Neurology, 2010
Force window performance of 21 patients with multiple sclerosis (MS) and 22 matched control subjects over the course of the training. Each symbol refers to mean of 100 attempts (2 blocks of 50 each). Error bars indicate the SEM.

Zeller, aufm Kampe, Neurology, 2010
Normal baseline-normalized motor learning in a simple motor training task

Leocani et al., NeuroRehab NeurRepair, 2007
Functional brain reorganization for hand movement in patients with multiple sclerosis: defining distinct effects of injury and disability

H. Reddy,1 S. Narayanan,2 M. Woolrich,1 T. Mitsumori,1 Y. Lapierre,2 D. L. Arnold2 and P. M. Matthews1
Synaptic plasticity retained also in high brain injury

Table 3  Paired associative stimulation-induced plasticity and motor learning performance in patients with multiple sclerosis with good hand function, stratified into those with high and low CNS injury according to corticomuscular latency or NAA/Cr spectra

<table>
<thead>
<tr>
<th>Hand function and CNS injury</th>
<th>9-Hole peg board test, s</th>
<th>Tapping</th>
<th>n</th>
<th>CNS injury index</th>
<th>Maximum MEP% after PAS</th>
<th>p Value (vs PHF)</th>
<th>Force production performance increment</th>
<th>p Value (vs PHF)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PHF</td>
<td>45.1 ± 51.8</td>
<td>64.9 ± 14.5</td>
<td>6</td>
<td>123.2 ± 31.8</td>
<td>—</td>
<td>—</td>
<td>5.3 ± 4.4</td>
<td>—</td>
</tr>
<tr>
<td>GHF</td>
<td>19.0 ± 3.2</td>
<td>104.3 ± 19.2</td>
<td>16</td>
<td>133.6 ± 35.7</td>
<td>0.537</td>
<td>3.9 ± 5.0</td>
<td>0.578</td>
<td></td>
</tr>
<tr>
<td>CML</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GHF-LBI</td>
<td>20.8 ± 2.9</td>
<td>99.1 ± 18.8</td>
<td>4</td>
<td>18.9 ± 1.1</td>
<td>119.3 ± 8.4</td>
<td>0.823</td>
<td>0.5 ± 4.0</td>
<td>0.121</td>
</tr>
<tr>
<td>GHF-HBI</td>
<td>18.5 ± 3.2</td>
<td>106.0 ± 19.8</td>
<td>12</td>
<td>22.9 ± 1.1</td>
<td>138.3 ± 40.2</td>
<td>0.433</td>
<td>5.2 ± 4.8</td>
<td>0.977</td>
</tr>
<tr>
<td>NAA/Cr</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>GHF-LBI</td>
<td>18.7 ± 3.4</td>
<td>95.6 ± 10.7</td>
<td>7</td>
<td>1.6 ± 0.1</td>
<td>126.0 ± 28.1</td>
<td>0.869</td>
<td>3.2 ± 4.9</td>
<td>0.451</td>
</tr>
<tr>
<td>GHF-HBI</td>
<td>21.2 ± 4.7</td>
<td>106.7 ± 21.4</td>
<td>3</td>
<td>1.4 ± 0.1</td>
<td>113.6 ± 2.3</td>
<td>0.630</td>
<td>5.3 ± 7.8</td>
<td>0.984</td>
</tr>
</tbody>
</table>

Abbreviations: CML = corticomuscular latency; Cr = creatine; GHF = good hand function; HBI = high CNS injury; LBI = low CNS injury; MEP = motor evoked potential; NAA = N-acetyl aspartate; PAS = paired associative stimulation; PHF = poor hand function.

Zeller, aufm Kampe, Neurology, 2010
Long-term potentiation-like plasticity and rapid motor learning of a simple motor task are not compromised in MS.

In mild-to-moderately affected patients, rapid-onset plasticity does not appear to be a factor determining good hand function in the presence of variable degrees of brain injury.
Neuroplasticity in Multiple Sclerosis

Rapid onset plasticity

Interregional plasticity

Local network plasticity
MS patients without impairment of hand function
  – Activation of ipsilateral sensorimotor cortex (Reddy, Brain 2000).

Reddy, Brain, 2000
Exploring interregional plasticity by neuronavigated TMS
Regional plasticity in MS - reaction time task

Zeller, Dang, JNNP, 2011

Increase of reaction time task (% of baseline (MO))

- Controls
- Patients

*r=-0.52, P=.006*
Non-canonical (motor) brain regions are involved in the execution of simple motor tasks in MS.

Activation of these regions is functionally relevant, but compensation likely is limited by disease-related brain injury.
Neuroplasticity in Multiple Sclerosis

Rapid onset plasticity
Interregional plasticity
Local network plasticity
Extracting complex parameters of motor control by TMS-mapping of finger movements

• Somatotopical representation

• Efficiency of motor control
Somatotopical organisation of finger movements as revealed by TMS

A

Thumb  Index finger  Middle finger  Ring finger  Little finger

B

Gentner, Neuron, 2006
Homuncular finger movement representation

Healthy control

△ Little
◆ Ring
■ Middle
▼ Index
● Thumb

Nagel, Gentner
Expansion of homuncular representation in professional musicians – mapping finger movts. = plasticity paradigm

Violinists (red=right M1)  Healthy control  Dystonia

Little
Ring
Middle
Index
Thumb

Nagel et al., in preparation
Disruption of homuncular motor representation in multiple sclerosis patients

Violinists (red=right M1)  Healthy control  Dystonia  MS patients

▲ Little  ◆ Ring  ■ Middle  ▼ Index  ● Thumb

Nagel et al., in preparation
Disruption of homuncular motor representation covaries with hand function in multiple sclerosis patients

Nagel et al., in preparation
Disruption of homuncular motor representation covaries with hand function - in multiple sclerosis patients

Violinists (red=right M1)  Healthy control  Dystonia  MS (all)  MS (poor HF)

Distance

d1-d5 (mm)

Nagel et al., in preparation
Magnetic stimulation TMS induced movements

Extraction of modules

4 modules explain ≥90% of data variance

reconstruction

Grasping at virtual objects

Natural grasping movements

Nagel et al., in preparation
Impairment of modular control of precision movements in MS – independent of hand function in timed motor tests

Nagel et al., in preparation
Increased functional connectivity indicates the severity of cognitive impairment in multiple sclerosis

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Short-term plasticity, resembling long-term potentiation of excitatory neuronal synapses is was not compromised, in patients with mild-to-moderate MS.

Activation of non-canonical brain regions is functionally relevant.

Reduced efficiency of motor control of dexterous movements may provide a pathophysiological model for impairment of behavioral control beyond that detectable in conventional functional assessments.