Epidemiology of cognitive impairment in MS: an update

Maria Pia Amato
University of Florence, Italy
Disclosures

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Bayer, Biogen, Merck, Novartis, Sanofi Genzyme, Teva, Almirall, Roche
Agenda

- Prevalence and profile of CI
  - In the MS population at large
  - In different disease subtypes: CIS, RRMS, SPMS, PPMS
  - In «special» populations: RIS, Benign MS, Pediatric MS, «Cortical variant»

- Functional impact and prognostic role

- Conclusions & future perspectives
Variables that can influence prevalence rates

- Study setting
  - clinic-based versus community-based
- Study epoch
  - Poser’s versus MacDonald’s criteria
- Study sample
  - demographic and clinical characteristics
- Assessment tools
  - Single test
  - Brief /intermediate/extensive batteries
  - Computerized batteries
- Criteria for defining CI
Criteria for defining CI in MS: a review of the literature
(Fisher et al., 2014)

- 3 basic classification strategies
  - Performing 1.5 SD or 2.0 SD below normative means in 20-30% of tests (most common)
  - Impairment in >2 cognitive domains
  - Composite indices (eg mean of all normalized scores; grading each test score in respect to mean and SD of normative values)
  - [Combination of the above systems]

- More stringent criteria correspond to lower prevalence rates (and vice versa)
Criteria for CI in MS: are they reliable?
(Fisher et al., 2014)

- Inter-rater reliability across all criteria was moderate

- However, between criteria of comparable stringency reliability was strong

- «Take home»: Criteria for defining CI in MS should be better homogenized
Prevalence of CI in the MS Population

- Prevalence range: 40-65%
  - Nearly 40% in community-based studies
  - >65% in clinic-based studies

Review article: Chiaravalloti ND, DeLuca J. Lancet Neurol 2008
Community-based study: 100 MS pts. versus 100 HCs, extensive NP battery

**Prevalence of CI in the MS sample 43%, (weak) correlation with EDSS**

![](chart.png)

Adapted from Rao *et al.* *Neurology*, 1991

<table>
<thead>
<tr>
<th>Cognitive Domain</th>
<th>Percentage of MS Group Scoring &lt; 5th Percentile for Healthy Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Episodic Memory</td>
<td>22–31%</td>
</tr>
<tr>
<td>Information Processing Speed</td>
<td>22–25%</td>
</tr>
<tr>
<td>Verbal fluency</td>
<td>13–19%</td>
</tr>
<tr>
<td>Conceptual Reasoning</td>
<td>12–19%</td>
</tr>
<tr>
<td>Visual-spatial Abilities</td>
<td>8–9%</td>
</tr>
<tr>
<td>Language</td>
<td>7–8%</td>
</tr>
<tr>
<td>Simple Attention</td>
<td></td>
</tr>
</tbody>
</table>
Prevalence of CI in different MS subtypes

**CIS**: range 14-57%
- 25-30%*

**Early RRMS (≤ 5 years)**: range 20-60%
- 30-40%*

**SPMS**: range 37-83%
- In most of the studies ≥60%*

**PPMS**: range 7-87%
- In most of the recent studies ≥50%*
  - Comparing PP and SPMS, prevalence of CI in PPMS is reported to be inferior, comparable or superior to that reported in SPMS

* Criterion for CI: > 2 tests failed, 1.5 – 2.0 SDs
Neuropsychological profile: comparative studies

- Huijbregts et al., *Neurology 2004*: 108 RRMS, 71 SPMS, 55 PPMS, 67 HCs, BRB
- Ruet et al., *Neurology 2013*: 41 PPMS, 60 RRMS, 415 HCs, extensive NP battery

- No consistent findings about "specific profiles” related to different disease subtype.
- (early) RRMS usually show prominent involvement of IPM and WM
- Both SP and PPMS compared with RRMS exhibit more frequent and severe deficits, involving a wider range of cognitive domains, including language in a few studies
- Only subtle (and inconsistent) differences in NP profile between SP and PPMS
MINIMUS: an Italian collaborative study

(Ruano et al., MSJ 2017)

Cognitive performance was assessed in 1040 patients using a battery validated for MS:

- Selective Reminding Test (SRT)
- 10/36 Spatial Recall Test (SPART)
- Paced Auditory Serial Addition Test (PASAT)
- Symbol Digit Modalities Test (SDMT)
- Word List Generation (WLG)
- Stroop Test (ST)

- Test failure was defined as a score ≤ 2 SDs, using Italian normative values adjusted for age, sex and education as reference.
- Cognitive impairment was defined as impairment in ≥ 2 cognitive domains.

Rao’s Brief Repeatable Battery
## Clinical and demographic characteristics of the study sample

(Ruano et al., MSJ 2017)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total n=1040</th>
<th>CIS n=167</th>
<th>RR n=759</th>
<th>SP n=114</th>
<th>PP n=40</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (mean, years)</strong></td>
<td>40.1</td>
<td>33.9</td>
<td>39.9</td>
<td>51.6</td>
<td>49.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Sex (% female)</strong></td>
<td>67.7</td>
<td>66.5</td>
<td>69.7</td>
<td>58.1</td>
<td>52.3</td>
<td>0.015</td>
</tr>
<tr>
<td><strong>Education (mean, years)</strong></td>
<td>12.2</td>
<td>12.7</td>
<td>12.3</td>
<td>11.0</td>
<td>10.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Age at onset (mean, years)</strong></td>
<td>29.7</td>
<td>32.5</td>
<td>28.6</td>
<td>32.2</td>
<td>36.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Disease duration (mean, years)</strong></td>
<td>10.3</td>
<td>1.4</td>
<td>11.2</td>
<td>19.4</td>
<td>12.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Relapses in the previous year (mean)</strong></td>
<td>0.9</td>
<td>1.0</td>
<td>1.3</td>
<td>0.3</td>
<td>0.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>EDSS (mean, years)</strong></td>
<td>2.6</td>
<td>1.5</td>
<td>2.4</td>
<td>5.5</td>
<td>5.1</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

* Student’s t test for independent samples or \( \chi^2 \) test adjusted for multiple comparisons
Prevalence of cognitive impairment by clinical subtype

(Ruano et al., MSJ 2017)

![Bar chart showing the frequency of cognitive impairment by clinical subtype.](chart.png)

**Significant differences**: CIS vs. SP, CIS vs. PP, RR vs. SP and RR vs. PP
(p<0.001, χ² test adjusted for multiple comparisons)
Cognitive impairment by age group (all patients)

(Ruano et al., MSJ 2017)

OR=1.75 [1.54; 2.00] p-value<0.001
Clinically isolated syndrome

<table>
<thead>
<tr>
<th>Patient age (years)</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>18-30</td>
<td>23%</td>
</tr>
<tr>
<td>30-40</td>
<td>40%</td>
</tr>
<tr>
<td>40-50</td>
<td>36%</td>
</tr>
<tr>
<td>50-60</td>
<td>60%</td>
</tr>
<tr>
<td>60-70</td>
<td></td>
</tr>
</tbody>
</table>

Relapsing remitting

<table>
<thead>
<tr>
<th>Patient age (years)</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>18-30</td>
<td>30%</td>
</tr>
<tr>
<td>30-40</td>
<td>37%</td>
</tr>
<tr>
<td>40-50</td>
<td>51%</td>
</tr>
<tr>
<td>50-60</td>
<td>60%</td>
</tr>
<tr>
<td>60-70</td>
<td>79%</td>
</tr>
</tbody>
</table>

Secondary progressive

<table>
<thead>
<tr>
<th>Patient age (years)</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>18-30</td>
<td>66%</td>
</tr>
<tr>
<td>30-40</td>
<td>69%</td>
</tr>
<tr>
<td>40-50</td>
<td>78%</td>
</tr>
<tr>
<td>50-60</td>
<td>93%</td>
</tr>
</tbody>
</table>

Primary progressive

<table>
<thead>
<tr>
<th>Patient age (years)</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>18-30</td>
<td>75%</td>
</tr>
<tr>
<td>30-40</td>
<td>83%</td>
</tr>
<tr>
<td>40-50</td>
<td>100%</td>
</tr>
<tr>
<td>50-60</td>
<td>100%</td>
</tr>
<tr>
<td>60-70</td>
<td></td>
</tr>
</tbody>
</table>
Cognitive impairment by disability level (all patients)

(Ruano et al., MSJ 2017)

OR=1.99 [1.68; 2.36] p-value<0.001

Frequency of Cognitive Impairment

EDSS score
Clinically isolated syndrome

Secondary progressive

Relapsing remitting

Primary progressive

Frequency of Cognitive Impairment

EDSS score

(Ruano et al., MSJ 2017)
### Multivariate logistic regression model for cognitive impairment in MS
(Ruano et al., MSJ 2017)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Crude OR [95% CI]</th>
<th>Adjusted OR [95% CI]</th>
<th>p-value (multivariate)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (10 years)</strong></td>
<td>1.75 [1.54; 2.00]</td>
<td>1.62 [1.42; 1.86]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>EDSS (2 points)</strong></td>
<td>1.99 [1.68; 2.36]*</td>
<td>1.80 [1.51; 2.15]</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Variables not in the model*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Crude OR [95% CI]</th>
<th>Adjusted OR [95% CI]</th>
<th>p-value (multivariate)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex (female)</strong></td>
<td>1.08 [0.82; 1.43]</td>
<td>1.10 [0.81; 1.49]</td>
<td>0.55</td>
</tr>
<tr>
<td><strong>Fatigue (FSS)</strong></td>
<td>1.01 [1.00; 1.19]</td>
<td>1.00 [0.99; 1.02]</td>
<td>0.32</td>
</tr>
<tr>
<td><strong>Depression (MADRS)</strong></td>
<td>1.02 [1.00; 1.15]</td>
<td>1.00 [0.98; 1.03]</td>
<td>0.84</td>
</tr>
<tr>
<td><strong>Disease duration (10 years)</strong></td>
<td>1.68 [1.44; 1.97]</td>
<td>1.01 [0.99; 1.03]</td>
<td>0.47</td>
</tr>
<tr>
<td><strong>Clinical course</strong></td>
<td></td>
<td></td>
<td>0.30</td>
</tr>
<tr>
<td>CIS vs. RR</td>
<td>1.84 [1.26; 2.71]</td>
<td>1.10 [0.75; 1.63]</td>
<td>0.63</td>
</tr>
<tr>
<td>CIS vs. SP</td>
<td>4.80 [2.57; 9.01]</td>
<td>1.42 [0.69; 2.92]</td>
<td>0.35</td>
</tr>
<tr>
<td>CIS vs. PP</td>
<td>13.11 [3.05; 56.04]</td>
<td>3.64 [0.80; 16.57]</td>
<td>0.10</td>
</tr>
</tbody>
</table>
In brief: prevalence and profile of CI in MS

The prevalence of cognitive impairment in this large sample was \textbf{46.3\%} (n=1040).

\textbf{CIS vs. RR:} Prevalence of 34.5\% vs 44.5\%.

\textbf{SP vs. PP:} 79.4\% vs 91.3\%;

\textbf{CIS and RR vs. SP and PP:}

\begin{itemize}
  \item \textbf{In the progressive} forms the \textbf{prevalence of CI} was \textbf{two-fold higher} when compared with the relapsing forms.
  \item The impairment in the different cognitive domains was also proportionally increased.
\end{itemize}

(Ruano et al., MSJ 2017)
Modeling of Cognitive Impairment by Disease Duration in Multiple Sclerosis: A Cross-Sectional Study

- Study design: cross-sectional, mono-centric
- Assessment through a computerized tool, the Mindstream GAB (NeuroTrax Corp., Bellaire, TX, USA)
- 1500 MS patients

- In a cluster analysis, CIS and RR patients and, respectively, SP and PP patients had a similar cognitive pattern
- Predictors of worse cognitive performance (linear regression):
  - Older age
  - Higher EDSS score
  - Longer disease duration
  - Sharper decline after 5 years from onset
Cognitive impairment was evident only at five years from onset suggesting a therapeutic window during which patients may benefit from interventions to maintain cognitive health.
Frequency of cognitive impairment dramatically increases during the first 5 years of multiple sclerosis

Françoise Reuter,¹,² Wafaa Zaaraoui,² Lydie Crespy,¹,² Anthony Faivre,² Audrey Rico,¹,² Irina Malikova,¹,² Elisabeth Soulier,² Patrick Viout,² Jean-Philippe Ranjeva,² Jean Pelletier,¹,² Bertrand Audoin¹,²

JNNP 2011

Cl at baseline 29%
Cl after 5 years 54%

Figure 1 Percentages of patients with impaired function on each cognitive domain at baseline and year 5. For each cognitive domain, patients were classified as cognitively impaired if they obtained a grade at or above 2.
A 10-year longitudinal study

50 patients with early MS (untreated) compared with 70 HCs

Study onset
CI = 26%

Mean duration 1.6 years
Mean EDSS 1.9

4.5 years
CI 49%

10 years
CI 56%

Predictors of a worse cognitive outcome after 10 years:
• Older age
• Higher EDSS
• Shift from RRMS to SPMS

0% 20% 40% 60% 80% 100%

No impairment (0-2 failed subtests)
Mild impairment (3-5 failed subtests)
Moderate impairment (>5 failed subtests)
Prevalence of cognitive impairment tends to increase over the disease course
None of the RIS had a strictly normal cognitive function and 10/26 failed at least 1 test (PASAT or Digit Span)
It could be suggested that these patients are MS patients with an undiagnosed isolated symptom presenting as cognitive dysfunction.
CI in Radiologically Isolated Syndrome (RIS)

(Amato et al., Neurology 2012)

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Characteristics of the study sample</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RIS</td>
</tr>
<tr>
<td>No. of subjects</td>
<td>29</td>
</tr>
<tr>
<td>Gender (men/women)</td>
<td>10/19</td>
</tr>
<tr>
<td>Education, y, mean ± SD</td>
<td>12.7 ± 3.8</td>
</tr>
<tr>
<td>Age, y, mean ± SD</td>
<td>36.6 ± 9.2</td>
</tr>
<tr>
<td>Disease duration, y, mean ± SD</td>
<td>8.7 ± 7.1</td>
</tr>
<tr>
<td>EDSS, mean ± SD</td>
<td>1.6 ± 1</td>
</tr>
<tr>
<td>OBs presence, n (%)</td>
<td>16/23 (70)</td>
</tr>
<tr>
<td>VEPs, n (%)</td>
<td>8/23 (35)</td>
</tr>
<tr>
<td>Cognitive Impairment, n (%)</td>
<td>8/29 (27.6)</td>
</tr>
<tr>
<td>At least 2 tests failed</td>
<td>8/29 (27.6)</td>
</tr>
<tr>
<td>One test failed</td>
<td>5/29 (17.2)</td>
</tr>
<tr>
<td>FSS, n (%)</td>
<td>4/25 (16.0)</td>
</tr>
<tr>
<td>MADRS, n (%)</td>
<td>4/24 (16.7)</td>
</tr>
</tbody>
</table>

Rao’s battery
Relationships between NP performance and MRI variables

In RIS subjects the number of tests failed was associated with higher T1LV and with lower NCV

- T1LV: $r = 0.52$, $p = 0.02$
- NCV: $r = 0.48$, $p = 0.04$
Cognitive impairment in “Benign MS”

Benign multiple sclerosis

Cognitive, psychological and social aspects in a clinical cohort

163 patients with “benign” MS (disease duration ≥15 years and EDSS ≤3.0):

• 45% cognitive impairment
• 49% fatigue
• 54% depression

In 38% of cases, cognitively impaired patients had reduced their social and work activities measured on the Environmental Status Scale (ESS)

A reliable definition of BMS should include the preservation of cognitive functioning as an additional requisite

(Rovaris et al., Neurology 2008)
Cognitive impairment in «benign» MS is associated with
- Greater T1 lesion loads in the WM
- More pronounced cortical tissue changes (reduced volumes, total and regional MTR values)

Higher risk of progression to a no longer benign status after 5 years
Results confirmed in a 12-year follow-up (unpublished data)
A «cortical variant» of MS?

**Clinica findings**
- prominent cognitive and/or psychiatric disorders at presentation
- most often PP course
- Positive CSF OB

**Neuropsychological findings**
Severe cognitive deficits, sometimes with a «cortical pattern» (aphasia, apraxia)

**MRI findings**
- both discrete and confluent, diffuse WM abnormalities
- severe brain atrophy at presentation
- higher reduction of GM fraction compared with WM fraction
- high number of CLs with DIR
## CI in pediatric onset MS

(Amato et al, Neurology 2016 Suppl 2)

| Study          | Region            | MS/HC     | Definition of CI                                                                 | % CI  | Major areas of impairment  
<table>
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<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>MacAllister 2005</td>
<td>U.S.</td>
<td>MS 37</td>
<td>&gt; 2 test scores &gt;1.5 SDs below normative data</td>
<td>35.1%</td>
<td>Complex attention, Verbal memory [Naming 18.9%]</td>
</tr>
<tr>
<td>Amato 2008</td>
<td>Italy, multi-center</td>
<td>MS 63 HC 63</td>
<td>performance on &gt; 3 tests &lt; 5th percentile of HC performance</td>
<td>31%</td>
<td>Verbal and visual memory Complex attention, Executive functions, <em>Expressive and receptive language</em> IQ reduced in 8% (younger age at onset)</td>
</tr>
<tr>
<td>Till 2011</td>
<td>Canada</td>
<td>MS 35 HC 33</td>
<td>≥3 test scores &lt;1.5 SDs below normative data</td>
<td>29.4%</td>
<td>Attention, IPS, Visuomotor integration, Verbal fluency, <em>Spelling abilities</em></td>
</tr>
<tr>
<td>Julian 2013</td>
<td>U.S., multi-center</td>
<td>MS 187 CIS 44</td>
<td>≥33% of test scores &lt;1 SD below normative data</td>
<td>35%</td>
<td>Fine motor speed, Visuomotor integration, IPS</td>
</tr>
</tbody>
</table>

### Notes

- Naming: Verbal memory may be impaired, with a 18.9% reduction in naming.
- IQ: Reduced IQ in 8% of patients, particularly younger age at onset.
- Executive functions: Impaired in various tasks including attention, expression, and fluency.
- Spelling abilities: Reduced in 18% of patients.
- Visuomotor integration: Important for fine motor speed and coordination.
Patients with paediatric-onset multiple sclerosis are at higher risk of cognitive impairment in adulthood: An Italian collaborative study

Luis Ruano, Mariana Branco, Emilio Portaccio, Benedetta Goretti, Claudia Nicolai, Francesco Patti, Clara Chisari, Paolo Gallo, Paola Grossi, Angelo Ghetti, Marco Roscio, Flavia Mattioli, Chiara Stampatori, Marta Simone, Rosa Gemma Viterbo and Maria Pia Amato

Figure 2. Comparison of the prevalence of cognitive impairment by age group in patients with paediatric-and adult-onset multiple sclerosis.
How do cognitive problems affect the lives of people with MS?

<table>
<thead>
<tr>
<th>Activity and Participation</th>
<th>Safety</th>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Employment</td>
<td>Driving</td>
<td>Medical decisions</td>
</tr>
<tr>
<td>Relationships</td>
<td>Falls</td>
<td>Medication adherence</td>
</tr>
<tr>
<td>Social function</td>
<td></td>
<td>Rehabilitation benefit</td>
</tr>
<tr>
<td>Daily activities</td>
<td></td>
<td>Symptom management</td>
</tr>
<tr>
<td>Physical independence</td>
<td></td>
<td>Risk appraisal</td>
</tr>
<tr>
<td>Leisure activities</td>
<td></td>
<td>Coping strategies</td>
</tr>
<tr>
<td>Mood</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>General</strong></td>
<td></td>
<td>Life satisfaction, Quality of Life of pts. and CGs</td>
</tr>
</tbody>
</table>

Review article: Langdon DW, Curr Opin Neurol. 2011 Jun;24(3):244-9.
CI: a factor in prognosis - Longitudinal studies

▷ In CIS subjects CI predicted more rapid conversion to CDMS after a 3 year follow-up (Zipoli et al. Mult Scler 2010)

▷ In early RRMS patients (mean duration at baseline 23 months) baseline IPS and verbal memory impairments predicted higher EDSS score after 5 and 7 years (Deloire et al., Mult Scler 2010)

▷ In newly diagnosed MS patients CI predicted faster progression to EDSS 4 and shift to SPMS in a 10-year follow-up (Moccia et al., Mult Scler 2015)
Cognitive impairment at diagnosis predicts 10-year multiple sclerosis progression

Marcello Moccia, Roberta Lanzillo, Raffaele Palladino, Kiara Chu-Mei Chang, Teresa Costabile, Cinzia Russo, Anna De Rosa, Antonio Carotenuto, Francesco Saccà, Giorgia Teresa Maniscalco and Vincenzo Brescia Morra

67 MS pts. followed-up from the diagnosis for a mean of 10 years

Pts. with CI HR 3.2, p<0.001
Pts. with CI HR 2.5, p=0.008
A brief cognitive assessment tool is needed. Cognition self-report is unreliable.

Confounders

- Depression
- Anxiety
- Fatigue
- Perceived stress
- Self-efficiency
- Conscientiousness
1 in 4 patients has a miscalculated EDSS score $\leq 4.0$ if we use the EDSS scale without considering cognition.

2 in 3 patients have CI not detected at standard neurol exam.

*Saccà et al, MSJ 2016*
Conclusions

- CI is part of many people’s experience of MS, independent of the disease subtype
- It has a negative impact on many aspects of life, also independent of physical disability
- It can also have a negative prognostic role: implications for therapeutic decision-making?
- Brief assessment and regular monitoring of cognition is therefore highly advisable in everyday practice and could contribute to therapeutic decisions
Future perspectives

• The search for effective management strategies needs to remain a key focus in this research field

• Potential risk/protective factors are poorly understood

• Risk factors
  ◦ aging
  ◦ disease severity (EDSS, progression) and duration
  ◦ MRI variables (LL, WM and GM atrophy, altered connectivity)
  ◦ Male gender (less well documented)
  ◦ Other potential risk factors?
    — genetics (HLA, BDNF, APOE...)
    — lifestyle
    — comorbidities

• Protective factors
  o Brain reserve and cognitive reserve
  o Others?
Acknowledgements

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N. De Stefano
M. Battaglini
A. Giorgio
M.L. Stromillo
A. Federico

University of Siena

Italian MS Society (AISM)
Back up slides
fMRI in MS cognition activation & cognitive impairment in MS

Penner et al., J. Neurology 2007

Loitfelder et al, Neurology 2011
The role of inflammation

- EAE models

- PASAT scores show transient decline when there are gadolinium enhancing MRI lesions\(^1\)

- SDMT scores show transient decline (nearly 4 points) during a physical relapse\(^2\)\(^-\)\(^3\)

- SDMT scores show transient decline (3.5 points or 6%) during MS relapses (confirmed by gd-pos. lesions at MRI), associated with perceived cognitive problems and worsening EDSS. Recovery after 3 months, with steroid treatment\(^3\)

- Possible fluctuations of cognitive performance depending on inflammation

\(^1\)Bellmann-Strobl J, Neurology 2009;\(^2\)Morrow SA, J Neurol 2011;\(^3\)Benedict RHB, MSJ 2014

\(^4\)Pardini M, J NNP 2014
Isolated Cognitive Relapses (ICR)

- “Isolated cognitive relapses”, defined as SDMT score decreased by $\geq 4$ points, detected in patients with
  - stable neurological condition (EDSS)
  - no change in depression (HADS), fatigue (MIFFS), self-assessed cognition (MSNQ)
  - Gd-enhancing lesions, mainly frontoparietal, followed by absence of enhancing lesions at 6 and 12 months