Cognition in MS

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Disclosures

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Multiple sclerosis

An immunomodulatory chronic degenerative condition

Prevalence of 50–300 per 100 000 people

About 2·3 million people are estimated to live with multiple sclerosis globally

No cure, but drugs slow down disease progression

Constellation of physical, psychiatric and cognitive symptoms

About half of people with MS experience cognitive difficulties
Clinical Course of MS

Pre-symptomatic  Relapsing–remitting  Secondary progressive

Plan

• Cognition in MS overview
• Assessment options
• MS cognition in clinical trials
## Negative impact of cognitive deficits in MS

<table>
<thead>
<tr>
<th>Participation</th>
<th>Safety</th>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Employment</td>
<td>Driving</td>
<td>Medical decisions</td>
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<tr>
<td>Relationships</td>
<td>Falls</td>
<td>Medication adherence</td>
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<tr>
<td>Social function</td>
<td></td>
<td>Rehabilitation benefit</td>
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<tr>
<td>Daily activities</td>
<td></td>
<td>Symptom management</td>
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<tr>
<td>Physical independence</td>
<td></td>
<td>Coping</td>
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<td>Leisure activities</td>
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<tr>
<td>Mood</td>
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<tr>
<td>General</td>
<td></td>
<td>Life satisfaction</td>
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<tr>
<td></td>
<td></td>
<td>Health-related quality of life</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Quality of Life</td>
</tr>
</tbody>
</table>

Langdon. Curr Opin Neurol 2011;24:244-249.

Percentage of people with MS in employment

Kobelt et al. (MSCOI Study Group) Mult Scler 2017;23:1123-1136
Cognitive dysfunction in MS: Prevalence of impairment by cognitive domain

Why do we need formal assessment of MS cognition?

• Patient report confounded by depression, fatigue, anxiety and other psycho social variables

• Poor correlation with disease variables
  – Disease duration
  – MRI
  – EDSS (Disability)

• Neurologists’ detection of cognitive impairment at routine consultation is 50%
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Assessment of Cognition

Routine in the office

Routine NP exam.

Differential diagnosis
Disability questions
Rehabilitation programs

Screening tests
BRB
SEFCI

Brief Batteries

Intermediate length Batteries
MACFIMS

Comprehensive Batteries
Ad hoc
Recommendations for a Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS)

DW Langdon¹, MP Amato², J Boringa³, B Brochet⁴, F Foley⁵, S Fredrikson⁶, P Härmäläinen⁷, H-P Hartung⁸, L Krupp⁹, IK Penner¹⁰, AT Reeder¹¹ and RHB Benedict¹²

Abstract
Background: Cognitive impairment in MS impacts negatively on many patients at all disease stages and in all subtypes. Full clinical cognitive assessment is expensive, requiring expert staff and special equipment. Test versions and normative data are not available for all languages and cultures.

Objective: To recommend a brief cognitive assessment for multiple sclerosis (MS) that is optimized for small centers, with one or few staff members, who may not have neuropsychological training and constructed to maximize international use.

Methods: An expert committee of twelve members representing the main cultural groups that have so far contributed considerable data about MS cognitive dysfunction was convened. Following exhaustive literature review, peer-reviewed articles were selected to cover a broad spectrum of cultures and scales that targeted cognitive domains vulnerable to MS. Each was rated by two committee members and candidates scales were rated on psychometric qualities (reliability, validity, and sensitivity), international application, ease of administration, feasibility in the specified context, and acceptability to patients.

Results: The committee recommended the Symbol Digit Modalities Test, if only 5 minutes was available, with the addition of the California Verbal Learning Test – Second Edition and the Brief Visuospatial Memory Test – Revised learning trials if a further 10 minutes could be allocated for testing.

Conclusions: A brief cognitive assessment for MS has been recommended. A validation protocol has been prepared for language groups and validation studies have commenced.
What BICAMS adds to EDSS alone...

• “our study shows the potential advantages of using the BICAMS ....in everyday clinical practice. If the cognitive status is not properly measured, one out of four patients with an EDSS<=4 has a miscalculated score with an underestimation of disability. More stunning is that two out of three patients have a cognitive impairment that is not recorded during clinical practice in the CFS.”

Sacca et al., The EDSS integration with the Brief International Cognitive Assessment for Multiple Sclerosis and orientation tests. Mult Scler. 2016 Nov 1:1352458516677592.
Validity of BICAMS in employment context

Brief International Cognitive Assessment for MS (BICAMS): international standards for validation

Ralph HB Benedict*, Maria Pia Amato, Jan Borlinga, Bruno Brochet, Fred Foley, Stan Fredrikson, Palvi Hamalainen, Hans Hartung, Lauren Krupp, Iris Penner, Anthony T Reder and Dawn Langdon

Abstract

An international expert consensus committee recently recommended a brief battery of tests for cognitive evaluation in multiple sclerosis. The Brief International Cognitive Assessment for MS (BICAMS) battery includes tests of mental processing speed and memory. Recognizing that resources for validation will vary internationally, the committee identified validation priorities, to facilitate international acceptance of BICAMS. Practical matters pertaining to implementation across different languages and countries were discussed. Five steps to achieve optimal psychometric validation were proposed. In Step 1, test stimuli should be standardized for the target culture or language under consideration. In Step 2, examiner instructions must be standardized and translated, including all information from manuals necessary for administration and interpretation. In Step 3, samples of at least 65 healthy persons should be studied for normalization, matched to patients on demographics such as age, gender and education. The objective of Step 4 is test-retest reliability, which can be investigated in a small sample of MS and/or healthy volunteers over 1–3 weeks. Finally, in Step 5, criterion validity should be established by comparing MS and healthy controls. At this time, preliminary studies are underway in a number of countries as we move forward with this international assessment tool for cognition in MS.
BICAMS sensitive to physical relapses

<table>
<thead>
<tr>
<th>Test</th>
<th>MS group during relapse N=60</th>
<th>MS group 1 month after relapse</th>
<th>MS group 3 month after relapse</th>
<th>ANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td>SDMT</td>
<td>40.18 (11.42)</td>
<td>46.2 (12.28)</td>
<td>46.62 (10.96)</td>
<td>F=43.08 P&lt;.001</td>
</tr>
<tr>
<td>BVMT-R (0-36)</td>
<td>22.57 (6.07)</td>
<td>26.30 (4.56)</td>
<td>26.93 (4.62)</td>
<td>F=34.73 P&lt;.001</td>
</tr>
<tr>
<td>CVLT-II (0-80)</td>
<td>52.02 (9.61)</td>
<td>58.45 (8.36)</td>
<td>60.57 (2.04)</td>
<td>F=65.87 P&lt;.001</td>
</tr>
</tbody>
</table>

Giedraitiene et al., Cognition during and after multiple sclerosis relapses as assessed with the Brief International Cognitive Assessment for Multiple Sclerosis. Scientific Reports. 2018;8:8169
BICAMS (Brief International Cognitive Assessment for MS) is an international initiative to recommend and support a cognitive assessment that is brief, practical and universal.
Calculate Norms

Register

Click the button below to register.

Sign In

Username:

Password:

Sign In

Forgot your password?
American Academy of Neurology

Multiple Sclerosis

Quality Measurement Set

Approved by the Multiple Sclerosis Quality Measurement Development Work Group on February 12, 2015, by the AAN Quality and Safety Subcommittee on February 20, 2015; by the AAN Practice Committee on March 10, 2015; and by the AANI Board of Directors on March 24, 2015.

This measurement set was endorsed by the American Association of Neuroscience Nurses on March 13, 2015.
BICAMS current status

• 17 countries have published peer review BICAMS national validation studies
• Nearly 20 peer review papers recommend BICAMS for routine cognitive assessment
• 11,000 PwMS assessed annually in clinics around the world
• Over 50 peer review scientific studies of MS cognition reporting BICAMS data

https://researchoutreach.org/articles/bicams-cognition-multiple-sclerosis/
Experimenter

Participant
Tablet capture of cognitive data

• Requirements
  – Tablets for centres
  – Wi-fi
  – Assessment for specific patient profile
  – Interface for specific patient profile

• Advantages
  – Accurate test administration
  – Data automatically scored and sent straight to server
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Disability outcome measures in Phase III RRMS trials

**Fig. 1** Disability outcomes measures used in phase III relapsing multiple sclerosis or RRMS trials (n = 16). Includes unpublished trials and trials published from 2012 onwards (with the exception of the DEFINE and CONFIRM trials, which are included in the review by Lavery et al. [20]). EDSS Expanded Disability Status Scale, FDA freedom from disease activity, MSFC Multiple Sclerosis Functional Composite, MSIS Multiple Sclerosis Impact Scale, NEDA no evidence of disease activity, SF-36 Medical Outcomes Study Short-Form (36-item) Health Survey, RRMS relapsing-remitting multiple sclerosis.
Early studies indicating that DMD’s may have a weak effect on cognitive function

- **IFNβ-1a**: significant effect on information processing and learning / memory\(^1\)
- Early IFNβ-1b treatment was associated with improved PASAT scores at 5-year follow-up\(^2\)

IFN, interferon; PASAT, Paced Auditory Serial Addition Test

Mean change from baseline in PASAT-3 scores (number of correct answers) in the pooled FREEDOMS studies

- Mean change from baseline in PASAT-3 scores:
  - Fingolimod 0.5 (n=783):
    - 0.035 at Month 6
    - 0.015 at Month 12
    - 0.016 at Month 24
  - Placebo (n=773):
  - p-values fingolimod vs placebo:
    - 0.035 at Month 6
    - 0.015 at Month 12
    - 0.016 at Month 24

Dawn W. Langdon, Iris-Katharina Penner, Pasquale Calabrese, Gary Cutter, Dieter A. Häring, Frank Dahlke, Davorka Tomic, Ludwig Kappos. Fingolimod effects on PASAT score and baseline determinants of PASAT in a large cohort of RRMS patients. Poster AAN 2016
BICAMS’ trials

• Improving Cognition in People With Progressive Multiple Sclerosis Using Aerobic Exercise and Cognitive Rehabilitation
  – N=360, 6 centres across Europe and North America, funded by Canadian MS Society

• CLARIFY QoL and cognition study
  – Phase IV, n=445, 2-Year Prospective Study to Assess Health-related Quality of Life In Subjects With Highly-Active Relapsing Multiple Sclerosis Treated With Mavenclad®, Merck

• MS-STAT-2
  – 2-year phase III trial of simvastatin. N=1,180 PwSPMS. UK MS Society funded.
MS trial design - challenges

• MS is changing\textsuperscript{1,2}  
  \begin{itemize}  
  \item 1993–2002 ARRs 0.5 to .87, modern ARRs 0.16 to .37\textsuperscript{3}  
  \end{itemize}  
• Changing diagnostic criteria and their adoption\textsuperscript{4}  
• Increasing DMD options, combinations and availability  
• Personalised medicine\textsuperscript{5}  
• Symptom management improving\textsuperscript{6}  
  \begin{itemize}  
  \item Improved health and life expectancy, awareness of cognitively harmful medication  
  \end{itemize}  
• Brain Health  
• Recruitment and attrition biases

MS trial design - challenges

- MS is changing\(^1,2\)
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Definition of MS endophenotypes based on response to DMT’s

Figure 1. The definition of multiple sclerosis (MS) endophenotypes (EPs) will be based on response to disease-modifying therapies (DMTs) in prospective validating cohorts. Disease classifying biomarkers (DCBs) constitute the most reliable multivariate model recognizable from biomarker portfolios in each MS subpopulation. The implementation of new endophenotypes translates the current clinical and paraclinical subtypes of MS into finite biomarker-based MS endophenotypes.

Endophenotype (EP)-based therapeutic interventions are most effective within their corresponding MS endophenotype.

New endophenotype (EP)-based multiple sclerosis (MS) trial design versus the status quo

Following an enrichment trial design, new disease-modifying therapies (DMTs) will be assessed against intraendophenotype patient-DMT controls.

Conclusions

• Cognition in MS is an important outcome for patients
• Increasingly included in major trials
• Changing MS landscape poses challenges for trial design
• Enriched/endophenotype designs?