Teaching Course 9

Cognition

Chairs:  
M.P. Amato (Florence, IT)  
J. DeLuca (New Orange, US)

25 Epidemiology of cognitive impairment in MS: an update  
M.P. Amato (Florence, IT)

26 Assessment: Pros and cons of available tools  
D. Langdon (Egham, UK)

27 Current approaches to management  
J. DeLuca (New Orange, US)
Epidemiology of cognitive impairment in MS: an update

Maria Pia Amato, University of Florence (Italy)

Introduction

The subtle and often insidious changes in cognition, unspoken of for years and seen in all subgroups of Multiple Sclerosis (MS) irrespective of age or disease pattern, are finally being given the profile and importance their impact warrants.

The last decade in particular has seen a stream of high quality studies addressing some of the key issues pertaining to this area: documenting the extent and severity of cognitive impairment (CI) and its evolution over time; identifying and developing appropriate clinical measures with which to assess the impact on the patient, their family and society; understanding the mechanisms underpinning these changes and, as a direct consequence, the attempts made to compensate for them and, lastly, the potential for therapeutic intervention, be it medication, training or rehabilitation. In addition, hypotheses such as the concept of cognitive reserve and the protective potential of cognitive enrichment in ameliorating decline provide scope for additional therapeutic approaches.

However this is an area that is still in its infancy, the evidence base to drive interventions is limited and much more needs to be done in all the areas mentioned earlier if we are to make a real difference to the impact on our patient population.

This teaching course provides an up-to-date coverage of some key areas in which there have been recent developments.

Prevalence and profile of CI in the general MS population

The prevalence of CI in the MS population at large is around 40% in a few, more representative, community-based studies and around 60% or higher in several clinic-based studies. In the seminal study published by Rao et al., 100 community-based MS patients were compared with 100 demographically matched healthy controls (HCs) using an extensive neuropsychological battery. Forty-eight MS patients were impaired on ≥ 4 tests, giving a CI prevalence rate of 43%. In this study, the cognitive domains most frequently involved resulted to be information processing
speed (IPS) and complex attention, episodic memory, aspects of executive functions and visual-spatial abilities, whereas language and general intelligence were relatively preserved. This pattern has been largely confirmed in subsequent surveys.

The main variable that can influence the estimates of prevalence rates are represented by the study setting (clinic-based versus community-based); the time when the study was performed and published, since in more recent studies the new MacDonald’s criteria were used, providing diagnostic anticipation and therefore implicating the inclusion of samples of patients in an earlier stage of their disease; the sample composition, particularly in terms of disease subtype, disease duration and disability levels; the use of different assessment tools with different sensitivity and specificity levels: single test, brief and intermediate batteries, extensive batteries and, more recently, computerized batteries; finally, different criteria used for defining CI.

In a recent review Fisher et al., 2014[^3] identified the most common criteria used in the MS literature to define CI (Table 1). Interestingly, inter-rater reliability across all criteria was moderate. However, between criteria of comparable stringency reliability was strong, implicating that results from studies using more stringent criteria are more robust and that criteria for defining CI in MS should be better homogenized, in order to allow comparison between studies and pooling of different datasets.

### Prevalence and profile of CI in different MS subtypes

Over the past decade, it has been clarified that CI can be detected in all disease stages and subtypes, starting from the very beginning of the disease.

Mild cognitive deficits consistent with the profile of MS-related CI have been found even in subjects with radiologically isolated syndrome (RIS), that may represent a sub-clinical or pre-clinical form of MS. In a study comparing 29 RIS subjects with a group of RRMS patients and a group of HCs, combining cognitive assessment with quantitative MRI assessment, the prevalence of CI in the RIS group was 27.6%, comparable to that observed in the RRMS group. Moreover, cognitive defects in the RIS group were associated with decreased neocortical volumes and T1-lesion volume.
In subjects with clinically isolated syndrome (CIS) the range of prevalence figures in the literature is 14-57%. However, focusing on studies that have used more stringent criteria (> 2 tests failed, 1.5 – 2.0 SDs) the figures become much more consistent, around 25-30% of subjects 5-7.

Similarly, in early relapsing-remitting MS (RRMS) (<2-5 years of duration) a wide range of prevalence is reported, between 20 and 60%, but using the above stringent criteria the range is 25-30% 5-7.

The frequency of cognitive impairment is clearly increased in secondary progressive MS (SPMS), with a reported range between 37 and 83%. However, the prevalence in most of the studies using reliable criteria is ≥60% 5-7.

As for primary progressive MS (PPMS), there is much more variability in the prevalence figures, with a reported range from 7 and 87%. In different studies, prevalence of CI in PPMS is estimated to be inferior, comparable or superior to that observed in SPMS. In the majority of the recent studies, however, the prevalence is ≥ 50% 5-7.

Taking into account difficulties in matching for age, disease duration and disability levels, studies attempting to identify specific cognitive profiles according to different disease subtypes have in general provided conflicting findings, or have reported only minor differences.

However, it is consistently recognized that progressive MS patients can exhibit more frequent and severe deficits as compared with RRMS, involving a wider range of cognitive domains, that may include more pronounced visual-spatial deficits and also linguistic skills.

Therefore, the prevalence and severity of cognitive impairment are bound to increase over the disease course, with increasing disease burden in the brain and decreased brain plasticity/compensatory abilities.

In a large, collaborative study 8, using the Brief Repeatable Battery and the Stroop Test in consecutive patients with MS referred to six Italian centres, CI was defined as impairment in ≥2 cognitive domains. The study included 1040 patients, 167 with CIS, 759 with RR, 74 with SP and 40 with PP disease course. Overall, the prevalence of CI tended to increase over the disease course (Fig. 1). In SP and PPMS the severity of impairment and the number of involved domains was significantly higher than in CIS and RRMS subjects. The profile of CI in different disease sub-types reported in this study is shown in Table 2.
In multivariable logistic regression analysis, the presence of CI was significantly associated with higher physical disability on the EDSS and older patient age. Male gender—that has been associated with a worse disease and cognitive outcome in a few studies—was not retained in the analysis. The conclusions from these findings were that CI is present in all MS subtypes since the clinical onset and its frequency is increased in the progressive forms, but these differences seem to be more associated with patient age and disability than to disease subtype per se. Furthermore, the results concur with the hypothesis of “cognitive reserve”, as aging has previously been associated with decreased plasticity and capability of functional reorganization in MS, that probably results from the interaction between cerebral aging and the accumulation of structural brain damage. However, with the possible exception of studies on cognitive reserve and intellectual enrichment in MS, there is a dearth of research on potential risk factors/protective factors for cognitive impairment in MS.

### Prevalence and profile of CI in pediatric MS

In comparison with the large body of evidence on cognitive functioning in adults with MS, there is limited information on cognition in pediatric onset MS (POMS). Unique vulnerabilities in POMS can derive from having a disease that occurs during key periods of age-expected brain growth, active myelination in the central nervous system and maturation of neural networks; moreover, during the “learning curve” and key formative years in the academic career of the subject. Until the last decade, research in the pediatric population was mainly represented by small clinical series, often limited by the narrow scope of neuropsychological assessment and lack of adequate control groups. Over the past decade, however, cognitive functioning and mood related difficulties have become an increasing concern as awareness of this population has grown and a few specialized MS Centers have begun performing more systematic research in the field. Table 3 summarizes the key findings of the main studies published in the field. It is noteworthy that the prevalence of CI in different pediatric populations, in different countries, and using different assessment tools and criteria for CI has been consistently reported around 30%. The cognitive profile largely overlaps with that known in adults with MS, but also includes, in a few studies, linguistic deficits and reduced intelligence quotient (IQ). Moreover, there is increasing evidence that subjects with younger age at onset (less than 10 years) can be at higher risk of cognitive difficulties, language and IQ deficits, as well as more likely to show progression of their cognitive deficits over time. Finally,
in the pediatric population, CI is clearly dissociated from the level of physical disability on the EDSS and has a profound negative impact on school performance and function in everyday activities. Only carefully designed, longitudinal studies can clarify the definitive cognitive outcome in POMS subjects and their work and social attainment in adult life.

**Conclusions**

CI is part of many people’s experience of MS, independent of the disease subtype. Information processing speed and memory are most often affected. It has negative impact on many aspects of life, also independent of physical disability. Systematic assessment of cognition is therefore highly advisable in MS patients, not only for research purposes but also in everyday practice, through the use of brief and reliable assessment tools. The search for effective management strategies needs to remain a key focus in this research field.
References


Table 1: Classification strategies for defining cognitive impairment in MS (Fisher et al., 2014)

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

- More stringent criteria correspond to lower prevalence rates (and vice versa)
Table 2: Profile of cognitive impairment in different MS subtypes (Ruano et al., submitted)

- In the whole MS sample (#1040)
  - IPS → 47.9%
  - Executive function → 40.8%
  - Verbal learning → 31.1%
  - Visuospatial learning → 20.5%
- In CIS and RRMS: prominent involvement of IPS and executive functions
  - No differences in the cognitive profile between CIS and RR patients
- In the progressive forms: significantly higher number of affected domains and severity of impairments
  - No differences in the cognitive profile between SP and PP patients
Table 3: prevalence and profile of cognitive impairment in pediatric MS (Amato et al., in press)

<table>
<thead>
<tr>
<th>Study</th>
<th>Region</th>
<th>MS/HC</th>
<th>Definition of CI</th>
<th>% CI</th>
<th>Domains involved</th>
</tr>
</thead>
<tbody>
<tr>
<td>MacAllister, 2005</td>
<td>U.S.</td>
<td>MS 37</td>
<td>≥ 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</td>
<td>Performance on ≥ 3 tests &lt; 5th percentile of HC performance</td>
<td>31%</td>
<td>Verbal and visual memory</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HC 63</td>
<td></td>
<td></td>
<td>Complex attention, Executive functions, Expressive and receptive language, IQ</td>
</tr>
<tr>
<td>Till, 2011</td>
<td>Canada</td>
<td>MS 35</td>
<td>≥3 test scores &lt;1.5 SDs below normative data</td>
<td>29.4%</td>
<td>Attention, IPS, Visuomotor integration</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HC 33</td>
<td></td>
<td></td>
<td>Verbal fluency, Spelling abilities</td>
</tr>
<tr>
<td>Julian, 2013</td>
<td>U.S., multi-center</td>
<td>MS 187</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>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>18% in CIS</td>
<td></td>
</tr>
</tbody>
</table>

Note: HC = Healthy Control
Fig. 1: Cognitive impairment tends to increase over the disease course.
Assessment: pros and cons of available tools

The basic dementia screens, such as the Mini Mental State, are insensitive to the majority of MS cognitive impairment (Aupperle at al., 2002). The Montreal Cognitive Assessment has been validated in MS, but again its sensitivity is not optimal (Dagenais et al., 2013).

The Screening Examination for Cognitive Impairment was specifically designed for MS (SEFCI; Beatty et al., 1995). It consists of SDMT, a short word list and delayed recall, the Shipley Institute of Living Scale Vocabulary and SLS Verbal Abstractions. Compared to a long neuropsychological battery, the SEFCI correctly identified 86% of the patients with impairment on any of the 11 measures from the longer battery, 100% of the patients with impairments in at least three cognitive domains, and 90% of the patients without cognitive impairment.

The Brief Repeatable Battery of Neuropsychological Tests (BRB-N, or “Rao Battery”) was devised after identifying which tests from an extensive battery best distinguished between people with MS and matched healthy controls (Rao et al., 1991). It consists of the Selective Reminding Test, the 10/36 spatial recall tests, SDMT, PASAT and COWAT. In a study which compared the BRB-N with the SEFCI, 42% of the MS group and 14% of the control group were impaired on the BRB-N, whereas 31.5% of the MS group and 11% of the controls were impaired on the SEFCI (Solari et al., 2002). The BRB-N has been described as the “gold standard” of MS cognitive batteries. There are translations of the BRB-N in many languages, but not all are validated. It is the most widely-published cognitive assessment battery, with 55 studies on medline being identified by a search for “BRB-N” alone.

The minimal assessment for cognition in MS (MACFIMS; Benedict et al., 2002) was an attempt by an expert committee to develop a more comprehensive cognitive battery for MS, including executive function and visuo-spatial skills. The MACFIMS comprises the COWAT, Judgement of Line Orientation, SDMT, PASAT, CVLT-II, BVMT-R, DKEFS sorting. A direct comparison with the BRB-N demonstrated a marginal advantage for the MACFIMS in terms of effect sizes on the information processing speed and spatial memory tests (Strober et al., 2009). There are a number of national validations outside of the US (e.g. Dusankova et al., 2012; Eshagi et al., 2012; Migliore et al., 2016).

Responding to the need for a shorter cognitive battery that does not require neuropsychological expertise to administer, another expert committee has recommended the Brief International Cognitive Assessment for MS (BICAMS; Langdon et al., 2012). BICAMS comprises the SDMT, the five learning trials of the CVLT-II and the three learning trails of the BVMT-R. Comparisons with the longer MACFIMS battery have demonstrated equal sensitivity for cognitive impairment in MS (Dusankova et al., 2012). A study comparing BICAMS with BRB-N using the whole BRB as the gold standard, demonstrated an overall BICAMS sensitivity of 58.2 %, specificity 86.7 %, with an accuracy of 75 % (Niccolai et al., 2015). There is an established international validation protocol (Benedict et al., 2012) and an extensive international validation programme (Dusankova et al., 2012; Eshagi et al., 2012; Migliore et al., 2016).
It has been suggested that BICAMS could become a routine annual cognitive assessment for MS patients (Langdon, 2016).

<table>
<thead>
<tr>
<th>Battery</th>
<th>Domains tested</th>
<th>Time to administer</th>
<th>Required expertise</th>
<th>Published studies</th>
<th>International validations</th>
</tr>
</thead>
<tbody>
<tr>
<td>SEFCI</td>
<td>IPS</td>
<td>30 mins</td>
<td>*</td>
<td>*</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Vocabulary</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Verbal memory</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BRB-N</td>
<td>IPS</td>
<td>45 mins</td>
<td>***</td>
<td>*****</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Verbal memory</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Spatial memory</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Verbal Fluency</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MACFIMS</td>
<td>IPS</td>
<td>90 mins</td>
<td>*****</td>
<td>***</td>
<td>**</td>
</tr>
<tr>
<td></td>
<td>Verbal memory</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Spatial Memory</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Visuo-spatial EF</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BICAMS</td>
<td>IPS</td>
<td>15 mins</td>
<td>**</td>
<td>**</td>
<td>****</td>
</tr>
<tr>
<td></td>
<td>Verbal Memory</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Spatial memory</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

References


Benedict RH, Drake AS, Irwin LN, Frndak SE, Kunker KA, Khan AL, Kordovski VM, Motl RW, Weinstock-Guttman B. Benchmarks of meaningful impairment on the


Current Approaches to Management of Cognitive Impairment in Multiple Sclerosis

John DeLuca, Ph.D.
Kessler Foundation

It is now well established that up to 70% of persons with multiple sclerosis (MS) suffer from cognitive impairment. Given the frequency and degree of cognitive involvement in persons with MS, and how it affects so many aspects of a person’s life (e.g., vocational, familial, social, emotional, cultural) the need for cognitive rehabilitation therapies and programs is clear. This presentation will describe the research data on the effectiveness of cognitive rehabilitation in persons with MS.

Compared to studies in stroke and traumatic brain injury, relatively few studies of cognitive rehabilitation exist in persons with MS. Three recent Cochrane reviews on cognitive rehabilitation (Rosti-Ostajarvi & Hamalainen, 2011, 2014; das Nair et al, 2012) have yielded mixed conclusions. However, beyond the Cochrane approach, there is emerging support that behavioral interventions can significantly improve targeted cognitive processes. Recent studies have also shown that cognitive rehabilitation not only improves neuropsychological functioning, but also results in increased functional brain activity on fMRI and functional connectivity in the brain, as well as improved everyday life activity and quality of life. A review of these data will be presented. There is also preliminary evidence that physical activity (e.g., physical fitness, physical activity, exercise training) may be associated with improved cognition in MS. However the research is inconsistent and lacks methodological rigor. These data will be reviewed. Lastly, several studies have examined various pharmacological approaches (e.g., DMT’s; symptomatic therapies) to improve cognition in MS. These data are also inconsistent and suffer methodological problems. There are no approved medications to treat cognitive problems in MS. These data will be reviewed.


Cognitive Impairment in MS – treatment
Neuropsychological rehabilitation for multiple sclerosis
(Review)

Rost-Ojani & Hamalainen, 2014

20 studies with
966 MS
20 HC

Low evidence found
18 of 20 studies showed evidence
of positive effects of
neuropsychological
rehabilitation

Kessler Foundation

Treatment of cognitive impairment in multiple sclerosis:
position paper
Maria van Aalst • Horst Langen • Xavier Michallet •
Magali M. Marescot • Julie Demaille • Laurence B. Brière •
Axel J. Thiery • Giancarlo Cirino

• Literature review of behavioral and
pharmacological interventions for cognition
• Behavioral studies
  – Information Processing speed
  – Learning and memory

Amato et al., 2013, J Neurol

Behavioral Treatment and Learning
and Memory in MS

Support  No Support

12  5

1 week support

Amato et al., 2013, J Neurol
An RCT to treat learning impairment in multiple sclerosis
The MEM/REHAB trial

Nancy D. Chiaravalloti, PhD
Nancy B. Moore, MA
Olga M. Nikishpur, PhD
John DeLuca, PhD

Classification of evidence: This study provides Class I evidence that the mSMT behavioral intervention improves both objective memory and everyday memory in patients with MS over 8 weeks, with treatment effects lasting over a 6-month period. Neurology® 2013;81:2016-2020

Learning by Group: Post-treatment

* No significant group difference at baseline
p<.02, controlling for baseline

Everyday Life Self-Report

FAMS General Contentment

Chiaravalloti et al, Neurology, 2013
Increased cerebral activation after behavioral treatment for memory deficits in MS

Stacy B. Chiaravalloti - Glenn Wylie - Victoria Levent - John DiLuna

Brain changes after behavioral treatment for memory impairment in MS using fMRI

Changes in Brain Functioning in MS

- Pre-training
- Treatment minus control

- Post-training
- Treatment minus control

Increased activation in frontal and occipital regions in treatment group that is not evident prior to treatment (p<.05)

Chiaravalloti et al., 2012, J Neurol

Multiple Sclerosis: Effects of Cognitive Rehabilitation on Structural and Functional MR Imaging Measures—An Explorative Study

Matteo Rigo, MD
Glenna Roddell, PhD
Kathy Robitaille, MD
Robert Copo, MD
Chloe Thompson, PhD
Evaluative Project, Inc.
Paisano Performance, Inc.
Maximilian Court, PhD
Archimedes, MD
Giancarlo Cirelli, MD
Marta Ascanio, MD

20 RR MS randomly assigned to 2 groups
* Computerized cognitive treatment for attention, information processing and executive function
* No treatment group
12 weeks of treatment
Pre-post Neuropsych test and MR imaging

Data from Mattioli et al J Neural Sci, 2010
Changes of brain resting state functional connectivity predict the persistence of cognitive rehabilitation effects in patients with multiple sclerosis

Laura Parisi1, Maria A Rocca1, Flavia Mattioli2, Massimilano Copetti2, Ruggero Capra3, PaolaValsesia1, Chiara Stampatori2 and Massimo Filippi1,2

6 month follow-up of 12-week cognitive Rehabilitation on cognition and resting state functional connectivity

What RSFC changes between T0 and T1, best predict NP scores at T2?

6 best RSFC predictors of improved cognitive performance at 6 months post TK
Using random forest analysis

(a)

Cognitive Total Score

Filippi et al, Radiology, 2012

Paris et al (2014), MSJ
Computer-aided cognitive rehabilitation improves cognitive performances and induces brain functional connectivity changes in relapsing remitting multiple sclerosis patients: an exploratory study

S. Bonavita - R. Nazar - M. Della Curta - S. Gnesi - M. Spurio -
S. Chiodini - M. Vincenzi - A. Pratesi - G. Leverger - B. Cerbo -
S. Candeo - M. G. C. Lim - L. E. Annese - C. Tedeschi

Cog impaired RR assigned to cog rehab (n=18) or control (n=18)
9 weeks TX, 2x per week
Pre-post RS-fC and structural imaging (brain volume; lesion load)
RehaCom – computer-based cognitive rehabilitation: Sessions:
Attention and concentration
Plan a day
Divided attention
reaction behavior
Logical thinking


Computer-Assisted Cognitive Rehabilitation of Attention Deficits for Multiple Sclerosis: A Randomized Trial With fMRI Correlates

Antonio Coraza, PhD1, Maria Cecilia Gioia, PhD2, Paula Valentini, MD3,
Rita Nistico, MD3, Carmela Chiabrera, PhD2, Domenico Pizzirano, MD2,
Francesco Tomassoni, PhD2, Grazia Alfonsi Mangone, MD, Maria Testa, MD1,
Tiziana Talarico, MD1, Giacinta Billiteri, MD1, and Aldo Quattrone, MD1,3

RR with impaired PS, attention, WM or EF assigned to cog rehab (n=12) or control (n=11)
6 weeks TX, 2x per week
Pre-post fMRI during PVSAT; Lesion load
RehaCom – computer-based cognitive rehabilitation: Sessions:
Attention and concentration
Divided attention
Vigilance
Multiple Sclerosis: Changes in Thalamic Resting-State Functional Connectivity Induced by a Home-based Cognitive Rehabilitation Program[^1]

24 MS cognitively impaired RRMS randomized to:
- Tx: home-based computerized intervention
- Wait list control
- NPI testing
- RS MRI
  - Looking at Thalamic RSFC

[^1]: De Gli e et al (2016), Radiology
Cognitive Rehabilitation and Cognition in MS

- Conclusions
  - Consistent data to support effectiveness
    - Neuropsychological performance
    - Functional neuroimaging support
- Future studies
  - Design studies to look at everyday life
  - More studies on long term outcomes
- Ready for clinical practice
  - Paucity of adequately trained clinicians

Exercise Training and Cognition in MS

- Inconsistent evidence from 5 RCTs of exercise training and cognition in MS.
  - Not in-line with literature from the general population on exercise and cognitive function.
  - Methodological concerns of MS RCTs
  - Importance of considering Class II, III, and IV evidence for informing better RCTs (i.e., for better prescribing exercise training).

---

5 Chen et al., 2004; 6 Huisenga et al., 2005; 7 Bokan et al., 2014; 8 Carter et al., 2014; 9 Hoog et al., 2016; 10 Hui et al., 2013; 11 Sandroff, 2013; 12 Sandroff et al., 2014
Exercise and Cognition in MS

- Conclusions
  - No consistent data to support effectiveness
    - Exercise
    - Physical activity
    - Physical fitness

- Future studies
  - Design studies to look specifically at cognition
  - Replication is required

Pharmacological Approaches

- In principle, DMTs potentially improve cognition
  - approved DMTs reduce T2 & T1 brain lesions
  - some reduce the progression of brain atrophy
  - decrease of inflammatory activity may contribute to better cognitive performances

- Symptomatic drugs may have specific effects
- Review RCT's
**Pharmacology and Cognition in MS**

<table>
<thead>
<tr>
<th></th>
<th>Support</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interferons</td>
<td>1 of 3</td>
</tr>
<tr>
<td>Acetylcholinesterase Inhibitors</td>
<td>2 of 6</td>
</tr>
<tr>
<td>L-amphetamine</td>
<td>2 of 3</td>
</tr>
<tr>
<td>Other agents</td>
<td>1 of 8</td>
</tr>
</tbody>
</table>

**Pharmacology and Cognition in MS**

- Conclusions
  - No consistent data to support effectiveness
    - DMT's
    - Symptomatic
- Future studies
  - Design studies to look specifically at cognition
  - Replication is required

**What is Needed?**

- Improved methodology
- Most studies with RRMS
- More Class I studies
  - Active control groups
- Larger samples
- Examine impact on everyday life
- Rehab works for:
- Multidimensional approach to research and treatment
  - Cognitive, medication, exercise