Cognition in MS: An Overview

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• Speaker, Sanofi - Genzyme
• Grant funding, Biogen IDEC
• Grant funding, EMD Serono
• Grant funding, NMSS
• Grant funding, CMSC
Overview

• Cognition in MS
  – impact on daily life
  – assessment
  – brain imaging parameters

• Cognitive Rehabilitation

• Exercise and Medication

• Conclusions
Charcot
(1868)

Cognitive experience of patients with MS:

"a marked enfeeblement of the memory; conceptions are formed slowly ..."
MS - Historical

- By 1960’s, medical students taught
  - cognitive change not characteristic of MS
- Early 1970’s: cognitive impairment in about 3%
- Today, cognitive impairments up to 65% in MS
Cognitive Deficits in MS

- Information processing speed/efficiency
- Learning and Memory
- Executive functions
  - planning, organization, initiation
- Perceptual processing
Cognitive Impairment in MS

Chiaravalloti & DeLuca, 2008, *Lancet Neurol*
The frequency of cognitive impairment tends to increase over MS course.

Figure 1: Cognitive Impairment in Patients with MS from 6 Italian Centers

Adapted from Ruano et al (2017), MSJ
Preclinical Disease Activity in Multiple Sclerosis: A Prospective Study of Cognitive Performance prior to First Symptom

Marianna Cortese MD,1,2,3 Trond Riise MSc, PhD,2,3 Kjetil Bjørnevik MD,2,3 Alok Bhan MD,4 Elisabeth Farbu MD, PhD,4 Nina Grytten PhD,3,5 Ineke Hogenesch MD,6 Rune Midgard MD, PhD,7,8 Cecilia Smith Simonsen MBChB,9 Wenche Telstad MD,10 Alberto Ascherio MD, DrPH,11,12,13 and Kjell-Morten Myhr MD, PhD3,5,14

Examine MS symptoms prior to clinical onset (or dx)

Prospectively investigate potential signs of preclinical MS activity

Cognitive performance of all Norwegian men born 1950-1995 who underwent conscription between 18-19yo

Linked this list to the Norwegian MS registry

924 MS cases
19,530 HC

Men who later dx with MS had lower cognitive scores at conscription
Men who developed PPMS up 20 years later had lower cognitive scores at conscription.

Cognitive sx may be an early sign of MS.

Mean stanine score (SEM) p<.03

Stanine range 1-9; mean = 5, sd = 2

# Evolution of Cognitive Impairment in MS over 10 year period

<table>
<thead>
<tr>
<th>Cognitive impairment</th>
<th>Initial Testing</th>
<th>4 year follow-up</th>
<th>10 year follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>74%</td>
<td>51%</td>
<td>44%</td>
</tr>
<tr>
<td>Mild</td>
<td>8%</td>
<td>33%</td>
<td>34%</td>
</tr>
<tr>
<td>Moderate</td>
<td>18%</td>
<td>16%</td>
<td>22%</td>
</tr>
</tbody>
</table>

Amato et al, (2001), *Archives Neurol*
<table>
<thead>
<tr>
<th>Some Factors which affect Cognition in MS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Disease Course</strong></td>
</tr>
<tr>
<td><strong>Duration of disease</strong></td>
</tr>
<tr>
<td><strong>Physical Disability</strong></td>
</tr>
<tr>
<td><strong>Fatigue</strong></td>
</tr>
<tr>
<td><strong>Depression</strong></td>
</tr>
<tr>
<td><strong>Stress</strong></td>
</tr>
<tr>
<td><strong>Gray Matter atrophy</strong></td>
</tr>
<tr>
<td><strong>Gender</strong></td>
</tr>
<tr>
<td><strong>Smoking</strong></td>
</tr>
<tr>
<td><strong>Ambient temperature</strong></td>
</tr>
<tr>
<td><strong>Cannabis</strong></td>
</tr>
</tbody>
</table>
Cognitive Impairment and Everyday Life
Cognitive Problems and Everyday Life Functioning

- Cognitive deficits in MS have been shown to negatively affect daily life including:
  - Employment
  - Driving
  - Social and vocational activities
  - Household activities
  - Sexual functioning
  - Family activities
  - Overall QOL
  - Increased psychiatric illness

- Beyond physical disability alone

VR-Driving System

Figure 4. Number of years after diagnosis before people with MS stopped working*

*People with MS who are not currently employed

97 employed MS
At 3.5 year follow-up, 45% declined in employment status

DES- deteriorated employment
SES- stable employment

Morrow et al. [Clin Neuropsychologist, 2011]
Processing Speed can affect Higher-order Cognition
Processing Speed

- Symbol Digit Modalities Test (SDMT: Oral Version)

- HCs faster than persons with MS
  \( (F = 14.95, p < .001, \eta_p^2 = .17) \)

- Consistent with MS-related processing speed deficits documented throughout the MS literature.

Leavitt et al (2014), *Rehab Psychol*
Executive Function: Inhibition

Color Word Interference Test (D-KEFS: Inhibition Trial)

HCs outperformed persons with MS
\( (F = 14.95, p < .001, \eta_p^2 = .17) \)

HOWEVER

Group differences disappeared when controlling for the speed aspect of the task (Color Naming)
\( (F = 0.01, p > .5, \eta_p^2 = .00) \)

Leavitt et al (2014), Rehab Psychol
Executive Function: Switching

Trail Making Test (D-KEFS: Number-Letter Switching)

HCs outperformed persons with MS (F = 6.87, p = .01, $\eta_p^2 = .08$)

HOWEVER

Group differences disappeared when controlling for the speed aspect of the task (Letter Sequencing Trial) (F = 0.16, $p > .5$, $\eta_p^2 = .00$)

Leavitt et al (2014), Rehab Psychol
Brain atrophy is associated with slower processing speed.

Leavitt et al (2014), *Rehab Psychol*
Executive Function: Inhibition

Color Word Interference Test (D-KEFS: Inhibition Trial)

Brain atrophy is associated with worse “Stroop” performance

HOWEVER

Group differences disappeared when controlling for the speed aspect of the task (Color Naming)

Leavitt et al (2014), Rehab Psychol
Executive Function: Switching

Trail Making Test (D-KEFS: Number-Letter Switching)

Brain atrophy is associated with worse Trail Making performance

HOWEVER

Group differences disappeared when controlling for the speed aspect of the task (Letter Seq.)

Leavitt et al (2014), *Rehab Psychol*
Conclusions

• Processing Speed may underlie many of the cognitive problems
What are the Radiologic Parameters that Correlate with Cognition?
Cognition and MRI

- Numerous studies have consistently shown a clear relationship between cognition and MRI metrics
- MS with cognitive impairment vs without
  - WM and GM lesions
  - WM and GM atrophy
  - Global, cortical, subcortical atrophy
- Advanced imaging sensitive to cognitive dysfunction
  - DTI, MRS, MTR
- Functional imaging sensitive to cognitive dysfunction
  - Task related activation and connectivity
  - Resting state activation and connectivity
Cognition and MRI

- Gray matter atrophy correlates with cognition and
  - predicts long term outcome 13 years later (Filippi et al, Neurology, 2013)
  - predicts conversion from CIS to definite MS (Dalton et al., 2004)

- Early cognitive impairment
  - predict conversion RR to PMS (Pittieri et al, 2016)
  - predict disability progression (Pittieri et al, 2016)
  - Predict cortical thinning 8 years later (Pittieri et al, 2016)

- Regional atrophy may be particular useful in cognition
  - Thalamus (Benedict et al., 2013; Debernard et al., 2015)
  - Hippocampus (Koenig et al., 2014; Sacco et al., 2015; Sicotte et al., 2008)

- Functional imaging metrics have been useful in cognitive rehabilitation studies
  - fMRI, functional connectivity
Cognitive Reserve

Impact on Cognition and Imaging in MS
Cognitive Reserve Hypothesis

Persons with higher lifetime intellectual enrichment can better withstand disease-related neuropathology without suffering cognitive impairment or dementia, likely due to more efficient neurocognitive processing.

Stern et al., *JINS* 2002;8:448-460.
Does Cognitive Reserve Moderate the Relationship between Brain Imaging and Cognitive status in multiple sclerosis?

MRI accounts for 17-27% of variance in cognition
(Pinter et al, 2015, Neuroimage: Clinical)
Cognitive Reserve in MS

Assessing Cognitive Impairment in MS

Objective vs Self-report Measures of Cognitive Impairment and Everyday life
CMSC Member Survey on Cognitive Screening Practices
Respondents (N=207) to CMSC member survey asking, “How are patients screened for cognitive problems/changes at your practice?” Respondents were instructed to check all that apply.

- 29% formal testing
- 52% not assessed
- 19% self report

How Assess Cognition?

- **Neurologist assessment**
  - No greater than chance (Peyser, 1982; Romero et al, 2015)
  - Clinical interview and neurological exam not sufficient

- **Patient Self report**
  - Predicts emotional distress
  - Not objective cognitive impairment

- **Neuropsychological Evaluation (gold standard)**
  - Correlated with brain imaging
  - Predicts everyday life activity
    - Employment
    - Cooking
    - Driving
    - Internet functional tasks (book airline ticket)
    - Other ADL’s
Validity of Patient Self-Report

Self-report DOES NOT correlate with:
- Everyday life functional activity
- Neuropsychological performance

Self-report DOES correlate with:
- Emotional distress

Neuropsychologic performance DOES correlate with:
- Everyday life functional activity

## Cognitive Batteries

<table>
<thead>
<tr>
<th></th>
<th>MACFIMS</th>
<th>BRB</th>
<th>NINDS</th>
<th>MSCOG</th>
<th>BICAMS</th>
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<tbody>
<tr>
<td>PS</td>
<td>SDMT PASAT</td>
<td>SDMT PASAT</td>
<td>SDMT PASAT</td>
<td>SDMT PASAT</td>
<td>SDMT PASAT</td>
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<td>Verbal Memory</td>
<td>CVLT2</td>
<td>SRT</td>
<td>CVLT2</td>
<td>SRT</td>
<td>CVLT2</td>
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<td>Visual memory</td>
<td>BVMT-R</td>
<td>10/36 test</td>
<td>BVMT-R</td>
<td>BVMT-R</td>
<td>BVMT-R</td>
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<td>Expressive Language</td>
<td>COWA</td>
<td>COWA</td>
<td>COWA</td>
<td></td>
<td></td>
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<tr>
<td>Executive functions</td>
<td>DKEFS Sort</td>
<td></td>
<td>DKEFS Sort</td>
<td></td>
<td></td>
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<tr>
<td>Spatial processing</td>
<td>JLOT</td>
<td></td>
<td>JLOT</td>
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</tbody>
</table>

BRB – Brief Repeatable Battery
Recommendations for a Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS)

California Verbal Learning Test Second Edition [CVLT2]

Trial 1 __/16
Trial 2 __/16
Trial 3 __/16
Trial 4 __/16
Trial 5 __/16
Total Learning __/80

Delayed Recall __/16
Delayed Recognition __

Brief Visuospatial Memory Test Revised [BVMTR]

Trial 1 __/12
Trial 2 __/12
Trial 3 __/12
Total Learning __/36

Delayed Recall __/12

Symbol Digit Modalities Test

Carrot
Sweater
Hammer
Baseball
Football
Chisel
Pants
Beans
Shoes
Screwdriver
Basketball
Corn
Saw
Golf
Dress
Lettuce

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

Carrot
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Symbol Digit Modalities Test
Many Studies Show PS Best Predictor of Future Decline

SDMT (not PASAT) was best predictor of cognitive deterioration (Amato et al, 2010)

Similar results in others studies (Deloire et al, 2010)
What Should be Routinely Done Clinically?
Recommendations for Cognitive Screening and Management in Multiple Sclerosis Care


- **Purpose:** promote understanding of cognitive impairment in MS
  - recommend optimal screening, monitoring, and treatment strategies
  - address barriers to optimal management.

- **Methods:** NMSS convened experts in cognitive dysfunction (clinicians, researchers, people with MS) to review literature, reach consensus on optimal strategies for screening, monitoring, & treating cognitive changes; propose strategies to address existing barriers to optimal care.

- **Recommendations:** NMSS makes the following recommendations, endorsed by:
  - Consortium of Multiple Sclerosis Centers (CMSC)
  - International Multiple Sclerosis Cognition Society (IMSCOGS):

*Multiple Sclerosis Journal (Accepted)*
Recommendations for the Management of Cognitive Dysfunction

- **Education and Awareness**
  - Persons with MS and family members need information about cognitive changes and their impact on daily life
  - Treating clinicians need information about cognitive changes and impact on daily life to help with patient care
  - Clinicians need information about referral resources in the community for assessment and treatment.
  - Patients and their providers should discuss the importance of cognition on a routine basis, and recognize the need for early and ongoing assessment to identify and address problems.
Recommendations for the Management of Cognitive Dysfunction

• **Assessment and Management**

• **Baseline cognitive screening with the Symbol Digit Modalities Test (SDMT) or other validated screening tool, as a *minimum*:**
  - For *all* adults and children 8 years or older diagnosed with MS
  - For adults who have experienced a first clinical event or have evidence on MRI of asymptomatic white matter lesions that are consistent with MS (RIS), or evidence of early gray matter damage
  - For any patient or family member who reports changes in cognitive functioning at home or work

• **Annual re-assessment *with the same instrument, or more often as needed*, recommended for all adults & children 8 yrs or older with MS.**
NMSS Recommendations for the Management of Cognitive Dysfunction

- Assessment and Management (cont)
- Depression screening at least yearly with the Beck Depression Inventory – Fast Screen$^{85}$ or the Hospital Anxiety and Depression Scale$^{86}$ for adults, or an age-appropriate screening tool for children, to identify mood changes that may be impacting cognition.
- Routine monitoring is recommended for academic and behavioral changes for all children

Table 1: Kalb et al, *Multiple Sclerosis Journal*, In Press
Assessment and Management (cont)

A more comprehensive neuropsychological assessment (including assessment of mood) is recommended for:

- any adult who initially screens positive for cognitive deficits
- or whose yearly screening demonstrates a clinically significant drop from a previous assessment (e.g., 4-point change or reduction of 10% on SDMT)
- any adult, with or without a positive screen, who reports problems at work or poor performance reviews
- any child under age 18 whose academic or behavioral functioning declines significantly for unexplained reasons, in collaboration with the school
- any individual who is applying for private disability, Social Security Disability Insurance (SSDI) or Supplemental Security Income (SSI) because of cognitive problems
- any individual who needs cognitive remediation to help manage existing deficits
Recommendations for the Management of Cognitive Dysfunction

- Assessment and Management (cont)
- **Remedial interventions** by appropriately trained professionals are recommended to address objectively-measured cognitive deficits and impact on everyday functional activity.
Recommendations for the Management of Cognitive Dysfunction

- **Access:**
- Steps are required to obviate barriers to adequate diagnosis and management of cognitive deficits, including:
  - Insufficient knowledge about MS-related cognitive dysfunction on the part of people with MS, family members, healthcare providers or school personnel
  - Stigma associated with cognitive changes
  - Insufficient numbers of adequately trained clinicians to offer screening, assessment or remediation
  - Insufficient financial resources
Cognitive Rehabilitation in MS
It works!

Improves cognition
Improves everyday life
Functional brain plasticity
Cognitive Rehabilitation Studies

- 42 total studies
- 63% of all studies
- 2010-2015: 25 studies
- 2004-2009: 9 studies
- 1998-2003: 5 studies
- 1993-1997: 2 studies

42 total studies
Memory rehabilitation for people with multiple sclerosis (Review)

das Nair R, Martin KJ, Lincoln NB

15 studies
989 persons with MS

Support effectiveness of memory intervention on:
Objective assessments of immediate and long term follow-up
QOL in immediate follow-up

Cochrane Database of Systematic Reviews 2016, Issue 3
Classified studies on level of evidence based on AAN criteria for therapy trials

Yielded **40** studies (2007-2016)

contrasts with **16** studies (ALL prior years)

**Results:**

1. Practice Standard  Learning/Memory
2. Practice Guidelines  Attention, nonspecific tx
5. Practice Options  Learning/Memory; Attention
<table>
<thead>
<tr>
<th>Practice Standards</th>
<th>Practice Guidelines</th>
<th>Practice Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attention</td>
<td>mSMT&lt;sup&gt;9&lt;/sup&gt;</td>
<td>APT&lt;sup&gt;6&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>RehaCom&lt;sup&gt;7&lt;/sup&gt;</td>
</tr>
<tr>
<td>Learning and memory</td>
<td></td>
<td>Music&lt;sup&gt;10&lt;/sup&gt; Self-generation&lt;sup&gt;18-20&lt;/sup&gt;, Spaced trials&lt;sup&gt;21&lt;/sup&gt;, Visual Imagery&lt;sup&gt;14,15&lt;/sup&gt;</td>
</tr>
<tr>
<td>Working memory and processing speed</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Executive Functions</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Metacognition</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Nonspecific/multi cognitive domains</td>
<td>RehaCom&lt;sup&gt;41,44,45&lt;/sup&gt;</td>
<td></td>
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</tbody>
</table>
Systematic review of the impact of cognitive rehabilitation to enhance brain plasticity yielded 10 studies

Methodological quality (PEDRo scale)
- 5 – excellent
- 2 – good
- 3 – fair

9 of 10 studies showed positive - improving cognitive performance
10th positive trend likely secondary to sample size

All 10 showed increased activation or connectivity in TX group vs Ctl group
9 of 10: increased activation/connectivity significantly associated with cognitive improvements

Brain regions which showed increased activation/connectivity varied across studies
Most consistent regions:
- cingulate, precuneus and cerebellum
Cognitive Rehabilitation: Behavioral Approaches

Sample RCT results
An RCT to treat learning impairment in multiple sclerosis
The MEMREHAB trial

Nancy D. Chiaravalloti, PhD
Nancy B. Moore, MA
Olga M. Nikelskaya, 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 5 weeks, with treatment effects lasting over a 6-month period. Neurology® 2013;81:2066-2072
Memory Retraining in MS

- 86 participants with MS
  - with objective impairment in new learning
- Method
  - Random assignment into two groups:
    - memory retraining group
    - control group
  - Double blinded conditions

Chiaravalloti et al, 2013, *Neurology*
Learning by Group: Post-treatment*

* No significant group difference at baseline
p=.02, controlling for baseline
Everyday Life Self-Report

FAMS General Contentment

FrSBe Total Score, Family Form

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

Nancy D. Chiaravalloti · Glenn Wylie · Victoria Leavitt · John DeLuca

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*
BOLD activation change from pre- to post-treatment

parahippocampal gyrus

superior temporal gyrus

Chiaravalloti et al., 2012, *J Neurol*

MS – red
HC - blue
BOLD activation change from pre- to post-treatment

middle frontal gyrus  precuneus

MS – red  
HC - blue

Chiaravalloti et al., 2012, *J Neurol*
Increased connectivity from L Hippocampus to Insula bilaterally in treatment group after TX.

- L post-central gyrus
- precentral gyrus
- middle frontal gyrus
- cingulate gyrus

Red line tx; blue line controls

Increased connectivity from R Hippocampus to cluster comprised of:

Leavitt et al, *Brain Imaging and Beh*, 2012
6 month follow-up
Behavioral Performance

CVLT SDFR Performance

- Control group mean
- Treatment group mean

Pre-intervention | Post-intervention | 6 months Post-intervention

Dobryakova et al., 2014
Brain areas activated in association with encoding

Area more activate in the treatment group vs control group during memory encoding

pre-intervention x post-intervention

post-intervention x 6months post-intervention

Dobryakova et al., 2014
Home-based cognitive rehabilitation using the internet
Double blind, randomized, active placebo controlled trial
135 MS randomized (all with cognitive impairment)
    adaptive online cognitive training   n=74
    ordinary computer games            n=61
Training was remotely delivered and supervised
    60 hours over 12 week
Primary outcome:
    neuropsychological composite score
Results: significant improvement in Tx group
Class I evidence
Change from pre to post assessment

Mean NP composite z-score

Mean rating cognitive improvement

Charvet et al, (2017) PLOS ONE

p < .007

p < .029
Evaluate a cognitive rehabilitation "App" in cognitively impaired MS
- "COGNI-TRAcK" – Cognitive Training Kit
- For portable devices
- 28 cognitively impaired MS randomized to:
  - **ADAT-gr**: adaptive training – automatic adjustment of task difficulty
  - **CONST-gr**: trained at a constant difficulty level
- Based on working memory exercises
- 8 weeks, five 30-min sessions per week
  - Self-administered at home
Table 3: Performance on the neuropsychological battery of the two groups (ADAPT-gr and CONST-gr) before (PRE) and after (POST) the cognitive rehabilitative intervention.

<table>
<thead>
<tr>
<th>Test</th>
<th>CONST-gr PRE</th>
<th>POST</th>
<th>ADAPT-gr PRE</th>
<th>POST</th>
<th>p values</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Value (Mean)</td>
<td>(Range)</td>
<td>Value (Mean)</td>
<td>(Range)</td>
<td></td>
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<tr>
<td>SRT-LTS</td>
<td>32.14 (10.43)</td>
<td>(18.77–54.17)</td>
<td>24.59 (8.45)</td>
<td>(6.55–41.56)</td>
<td>NS</td>
</tr>
<tr>
<td>SRT-CLTR</td>
<td>19.98 (10.92)</td>
<td>(5.44–42.12)</td>
<td>15.80 (10.01)</td>
<td>(1.91–32.62)</td>
<td><strong>0.003</strong></td>
</tr>
<tr>
<td>SPART</td>
<td>13.64 (4.91)</td>
<td>(3.94–23.56)</td>
<td>13.82 (4.58)</td>
<td>(8.31–23.78)</td>
<td>NS</td>
</tr>
<tr>
<td>SDMT</td>
<td>36.70 (9.54)</td>
<td>(21.24–50.53)</td>
<td>39.10 (11.60)</td>
<td>(22.24–61.38)</td>
<td><strong>0.0001</strong></td>
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<tr>
<td>PASAT-3</td>
<td>33.43 (8.74)</td>
<td>(20.08–46.06)</td>
<td>28.11 (14.15)</td>
<td>(-1.02–43.68)</td>
<td><strong>0.0002</strong></td>
</tr>
<tr>
<td>PASAT-2</td>
<td>22.17 (8.98)</td>
<td>(7.29–31.10)</td>
<td>18.10 (9.83)</td>
<td>(-0.67–35.45)</td>
<td><strong>0.0002</strong></td>
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<tr>
<td>SRT-D</td>
<td>6.08 (2.54)</td>
<td>(2.48–10.88)</td>
<td>5.37 (1.88)</td>
<td>(1.87–7.88)</td>
<td><strong>0.0002</strong></td>
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<tr>
<td>SPART-D</td>
<td>4.16 (2.48)</td>
<td>(0.72–9.59)</td>
<td>4.56 (1.22)</td>
<td>(2.18–7.92)</td>
<td>NS</td>
</tr>
<tr>
<td>WLG</td>
<td>33.21 (10.88)</td>
<td>(7.88–64.88)</td>
<td>38.15 (5.96)</td>
<td>(23.88–49.12)</td>
<td><strong>0.0002</strong></td>
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<tr>
<td>WCST</td>
<td>2.50 (1.74)</td>
<td>(0–5)</td>
<td>3.15 (1.46)</td>
<td>(0–5)</td>
<td>NS</td>
</tr>
</tbody>
</table>

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
Cognitive Rehabilitation in MS

It works!
Video Games and Cognitive Rehabilitation

– Can I tell my client to use “brain games” or “video games” for cognitive rehabilitation?

A Consensus on the Brain Training Industry from the Scientific Community

75 Leading Cognitive Psychologists & Cognitive Neuroscientists Representing 48 Universities

“We object to the claim that brain games offer consumers a scientifically grounded avenue to reduce or reverse cognitive decline when there is no compelling scientific evidence to date that they do.”

Lumosity to Pay $2 Million to Settle FTC Deceptive Advertising Charges for Its “Brain Training” Program

• “Lumosity preyed on consumers’ fears about age-related cognitive decline, suggesting their games could stave off memory loss, dementia, and even Alzheimer’s disease, But Lumosity simply did not have the science to back up its ads.”

• Lumosity claimed that training would:
  – 1) improve performance on everyday tasks, in school, at work, and in athletics
  – 2) delay age-related cognitive decline and protect against mild cognitive impairment, dementia, and Alzheimer’s disease
  – 3) reduce cognitive impairment associated with health conditions, including stroke, traumatic brain injury, PTSD, ADHD, the side effects of chemotherapy, and Turner syndrome, and that scientific studies proved these benefits.


Federal Trade Commission Press release, 1/6/2015
Exercise and Cognition
Exercise and Cognition in MS

- Exercise training may be a behavioral approach for managing cognitive dysfunction in MS, but understudied.

- Potential effects in MS based on the well-established literature in the general population across the lifespan.

- Of the existing MS studies
  - most are not RCTs
  - suffer from significant methodological flaws including
    - small sample sizes
    - poorly-defined interventions
    - lack of adequate control groups
    - inclusion of cognition as a non-primary outcome

Sandroff, 2015, *Neuroscience and Biobehavioral Reviews*
Exercise Training and Cognition in MS

- Inconsistent evidence from 5 RCTs of exercise training and cognition in MS: \(^5\text{-}^9\)
  - Not in-line with literature from the general population on exercise and cognitive function\(^10\)
  - Need to considering Class II, III, and IV evidence for informing better RCTs (i.e., for better prescribing exercise training)\(^11\text{-}^12\)

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\(^5\) Oken et al., 2004; \(^6\) Romberg et al., 2005; \(^7\) Briken et al., 2014; \(^8\) Carter et al., 2014; \(^9\) Hoang et al., 2016; \(^10\) Voss et al., 2011; \(^11\) Sandroff, 2015; \(^12\) Sandroff et al., 2016
Systematically developed pilot randomized controlled trial of exercise and cognition in persons with multiple sclerosis

Brian M. Sandroff\textsuperscript{a}, Julia M. Balto\textsuperscript{b}, Rachel E. Klaren\textsuperscript{b}, Sarah K. Sommer\textsuperscript{b}, John DeLuca\textsuperscript{a} and Robert W. Motl\textsuperscript{b}

pilot, single-blind RCT on treadmill walking exercise training intervention on processing speed (SDMT), cardiorespiratory fitness and walking (6 min walk) 10 fully-ambulatory RRMS females randomly assigned into:

• exercise training intervention (n=5)
• waitlist control (n=5)

12-weeks of supervised, progressive treadmill walking exercise training

Results - Large effects on:

- Processing speed \((d = 0.95)\)
- Walking performance \((d = 0.76)\)
- Cardiorespiratory fitness \((d > 1.08)\)

Change in cardiorespiratory fitness significantly associated with:

- Processing speed \((r = .60)\)
- NOT walking performance

Preliminary conclusions:

- Treadmill walking may improve processing speed perhaps by improving fitness \((\text{VO}_2\text{peak})\)
Treadmill exercise improved Cognition in MS

TX grp | ctl grp
--- | ---
SDMT | Sandroff et al, (2016) *Neurocase*
Treadmill walking exercise training and brain function in multiple sclerosis: Preliminary evidence setting the stage for a network-based approach to rehabilitation

Brian M Sandroff, Glenn R Wylie, Brad P Sutton, Curtis L Johnson, John DeLuca and Robert W Motl

- pilot, single-blind RCT on treadmill walking exercise training intervention on RSFC & cognition
- 8 fully-ambulatory RRMS females randomly assigned into:
  - exercise training intervention (n=5) or waitlist control (n=3)
- 12-weeks of supervised, progressive treadmill walking exercise training
- Pre-post of thalamocortical RSFC
- intervention increased RSFC between thalamus and:
  - R superior frontal gyrus (SFG; d=1.92)
  - L medial frontal gyrus (MFG; d=1.70)
- Intervention improved SDMT performance (d=0.72)
- Change in SDMT associated with RSFC change between thalamus and:
  - R SFG (r=.59)
  - L MFG (r=.63)
- Preliminary supports for exercise as adaptive compensatory mechanism

Kessler Foundation Research Center

Sandroff et al, (2018) MSJ-ETC
Figure 1: Areas in which thalamic RSFC significantly increased following treadmill walking exercise training compared with waitlist control.
Exercise and Cognition in MS

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

- Future studies
  - Improve methodology
  - Design studies to look specifically at cognition
  - Replication is required
Pharmacological Approaches
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
Pharmacological Approaches

- Methodological problems in DMT RCT’s
  - cognition a secondary or even a tertiary outcome
  - explorative outcome often single cognitive test
  - patients’ cognitive status not an entry criterion
  - studies not powered on cognitive parameters
    - not appropriate to detect cognitive changes

- Observational studies on DMT studies
  - vast majority are non-randomized
  - small samples with different clinical characteristics
  - heterogeneous cognitive assessment tools and outcome measures

- Results must be viewed with caution
Pharmacology and Cognition in MS

No Support
13

Support
7
Pharmacology and Cognition in MS

<table>
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<tr>
<th>Category</th>
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Conclusions

- Cognitive impairment in up 2/3 of persons with MS
- Significantly impacts everyday life
- Must be assessed objectively
- New NMSS guidelines include:
  - Education for family and patient
  - Initial baseline assessment
  - Annual re-assessment
  - Full neuropsychological examination when indicated
  - Intervention with a trained professional
- Cognitive Rehabilitation is effective
  - Challenge is finding appropriately trained professionals
- Exercise and Medication insufficient data
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**After Viewing Archived Presentation** - pause the presentation, copy the links below and type into your web browser.

Evaluation: [https://www.surveymonkey.com/r/CognitiveCareinMS](https://www.surveymonkey.com/r/CognitiveCareinMS)

Post Test and CME/CE Certificate: [https://www.classmarker.com/online-test/start/?quiz=yq75ba1be4f371cb](https://www.classmarker.com/online-test/start/?quiz=yq75ba1be4f371cb)

Questions? Contact kathleen.costello@nmss.org

Thank you for your participation.
Thank You