Cognition in MS: Remembering Not To Forget

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Disclosures

• none
Objectives

• Recognize common cognitive deficits in MS
• Understand the neurophysiologic basis of cognitive deficits in MS
• appreciate standard treatments for cognitive deficits in MS including important lifestyle modifications
Background

- Cognitive impairment in 40-60% (Rao, 1991)
- 1/3 of patients with early RRMS (Amato, 2010)
- Most common cause of employment disability
- Typical domains impacted
  - Information processing speed
  - Episodic memory
  - Executive functioning
  - Complex attention
COGNITIVE DYSFUNCTION IN MS

Prevalence of Impairment by Cognitive Domain*

Screening cognitive impairment in MS

- Bedside clinical exam too insensitive
- Self-report unreliable (Benedict, 2004)
  - Over-reporting with depression
  - Under-reporting with loss of insight
- Brief International Cognitive Assessment for Multiple Sclerosis – BICAMS (Langdon, 2012)
  - 5 minutes – Symbol Digit Modalities Test (SDMT)
  - Additional 10 minutes
    - California Verbal Learning Test, 2nd Ed.
    - Brief Visuospatial Memory Test
Example of the stimuli of the SDMT type
CVLT-2 and BVMT

Example stimuli of the CVLT type

Example stimuli of the BVMT type
Assessing Cognitive Impairment in MS

- Brief Repeatable Neuropsychological Battery (BRNB) – 30-60 minutes
- Minimal Assessment of Cognitive Function in MS (MACFIMS) – 90 minutes
<table>
<thead>
<tr>
<th>Screening Battery</th>
<th>Component Tests</th>
<th>Cognitive Domain Assessed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brief Repeatable Battery of Neuropsychological Tests</td>
<td>Buschke Selective Reminding Test</td>
<td>Verbal learning and memory</td>
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<td></td>
<td>7/24 Spatial Recall Test</td>
<td>Visual learning and memory</td>
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<tr>
<td></td>
<td>Paced Auditory Serial Addition Test (PASAT)</td>
<td>Working memory and resistance to interference</td>
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<td></td>
<td>Controlled Oral Word Association Test (COWAT)</td>
<td>Verbal fluency and word retrieval</td>
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<tr>
<td></td>
<td>Symbol Digit Modalities Test (SDMT)</td>
<td>Processing speed and working memory</td>
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<tr>
<td></td>
<td>SDMT</td>
<td>Processing speed and working memory</td>
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<tr>
<td></td>
<td>California Verbal Learning Test-II</td>
<td>Verbal learning and memory</td>
</tr>
<tr>
<td></td>
<td>Brief Visuospatial Memory Test-Revised</td>
<td>Visual learning and memory</td>
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<td></td>
<td>Delis-Kaplan Executive Function System</td>
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<tr>
<td></td>
<td>Judgment of Line Orientation</td>
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<td></td>
<td>COWAT</td>
<td>Verbal fluency and word retrieval</td>
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Cognitive Reserve

• Maximal lifetime brain growth (MLBG) and greater lifetime intellectual enrichment protect against cognitive decline in MS (Sumowski, 2014)

• Behavioral adaptation acquired through experience – results in variable neuropsych manifestation of anatomical deficits

• Profile of patients with cognitive dysfunction
  – Typically over 40 yo
  – Less educated – 79% have education level of 9 years or less (Sartori, 2006)
  – Fewer professionals
Treating Cognitive Impairment in MS

- DMTs
- Symptom meds
- Cognitive rehabilitation
- Physical exercise
DMTs and Cognition

• Study design variable
• RCT of IFN β-1a IM(n=166; improvement in information processing, learning/memory; delayed the deterioration in PASAT processing rate compared to placebo (Fischer, 2000)
• RCT of IFN β-1a SQ 22 vs.44 mcg – high dose 32% risk reduction in impairment at 3 years (Patti, 2010)
• RCT Glatiramer Acetate – no difference at years 1 and 2 compared to placebo – large practice effect in both groups and minimal baseline cognitive deficits (Weinstein, 1999)
• No RCT data available for natalizumab, fingolimod, or dimethyl fumarate
Symptom Meds

• **Attention** – minimal/no benefits
  – Amantadine
  – Methylphenidate
  – L-amphetamine
  – Lizdexamfetamine
  – Modafinil
Lisdexamfetamine – Improved SDMT/CVLT2 scores

Morrow, 2013
Symptom Meds

• Potassium channel blockers
  – Largely negative pilot studies

• Acetylcholinesterase inhibitors
<table>
<thead>
<tr>
<th>Reference</th>
<th>Drug</th>
<th>Number treated</th>
<th>Design</th>
<th>Duration</th>
<th>Primary outcome</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smits et al. [80]</td>
<td>4 aminopyridine</td>
<td>20</td>
<td>DB, PC, RCT, CO</td>
<td>4 weeks</td>
<td>Cognitive function</td>
<td>−</td>
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<tr>
<td>Bever et al. [74]</td>
<td>3,4 diaminopyridine</td>
<td>28</td>
<td>DB, PC, RCT, CO</td>
<td>2 × 30 days</td>
<td>Leg strength</td>
<td>−</td>
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<tr>
<td>Rossini et al. [76]</td>
<td>4 aminopyridine</td>
<td>49</td>
<td>DB, PC, RCT, CO</td>
<td>6 months</td>
<td>Fatigue (NP Tests secondary)</td>
<td>−</td>
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<tr>
<td>Geisler et al. [61]</td>
<td>Amantadine or pemoline</td>
<td>16</td>
<td>DB, PC, RCT</td>
<td>6 weeks</td>
<td>Multiple NP Tests</td>
<td>−</td>
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<tr>
<td>Wilken et al. [72]</td>
<td>Modafinil</td>
<td>23</td>
<td>Randomized, evaluator blind</td>
<td>4 months</td>
<td>Multiple NP Tests</td>
<td>+</td>
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<tr>
<td>Lange et al. [69]</td>
<td>Modafinil</td>
<td>8</td>
<td>DB, PC, RCT</td>
<td>8 weeks</td>
<td>D2 Alertness Test</td>
<td>+</td>
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<tr>
<td>Stankoff et al. [71]</td>
<td>Modafinil</td>
<td>59</td>
<td>DB, PC, RCT</td>
<td>5 weeks</td>
<td>MFIS cognitive dimension</td>
<td>−</td>
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<tr>
<td>Möller et al. [68]</td>
<td>Modafinil</td>
<td>62</td>
<td>DB, PC, RCT</td>
<td>8 weeks</td>
<td>Symbol Digit Modalities Test Paced Auditory Serial Addition Test</td>
<td>−</td>
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<tr>
<td>Harel et al. [64]</td>
<td>Methylphenidate</td>
<td>14</td>
<td>DB, PC, RCT</td>
<td>Single dose</td>
<td>Paced Auditory Serial Addition Test</td>
<td>+</td>
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<tr>
<td>Benedict et al. [65]</td>
<td>l-amphetamine</td>
<td>19</td>
<td>Counterbalanced, within-subject</td>
<td>4× single doses</td>
<td>Multiple NP Tests</td>
<td>+</td>
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<tr>
<td>Morrow et al. [66]</td>
<td>l-amphetamine</td>
<td>108</td>
<td>DB, PC, RCT</td>
<td>4 weeks</td>
<td>Symbol Digit Modalities Test</td>
<td>−</td>
</tr>
<tr>
<td>Sumowksi et al. [67]</td>
<td>l-amphetamine (re-analysis of 66)</td>
<td>108</td>
<td>DB, PC, RCT</td>
<td>4 weeks</td>
<td>California Verbal Learning Test 2; Brief Visuospatial Memory Test Revised</td>
<td>+</td>
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<tr>
<td>Krupp et al. [77]</td>
<td>Donepezil</td>
<td>35</td>
<td>DB, PC, RCT</td>
<td>24 weeks</td>
<td>Selective Reminding Test; Self Report</td>
<td>+</td>
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<tr>
<td>Krupp et al. [78]</td>
<td>Donepezil</td>
<td>61</td>
<td>DB, PC, RCT</td>
<td>24 weeks</td>
<td>Selective Reminding Test; Self Report</td>
<td>−</td>
</tr>
<tr>
<td>Shaygannejad et al. [79]</td>
<td>Rivastigmine</td>
<td>30</td>
<td>DB, PC, RCT</td>
<td>12 weeks</td>
<td>Wechsler Memory Scale</td>
<td>−</td>
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<tr>
<td>Lovera et al. [81]</td>
<td>Memantine</td>
<td>58</td>
<td>DB, PC, RCT</td>
<td>16 weeks</td>
<td>Paced Auditory Serial Addition Test and Selective Reminding Test</td>
<td>−</td>
</tr>
</tbody>
</table>

Number treated is the number who received the active drug

Amato, 2013
Overview of Cognitive Rehab In MS

• Mixed results with in-home, computer-based “non-specific cognitive training”
• Cochrane Review - No evidence to support effectiveness of memory rehab in patient with MS (das Nair, 2012)
  – Limited quality of the primary studies
Treating Processing Speed and Memory in MS

• Improvement seen in normal aging (Ball, 2007)

• No studies specifically targeting processing speed in MS

• Improved fMRI utilizing training in context and imagery (Chiaravalloti, 2012)
Treating Attention in MS

• Mixed results
• Increased cerebellar activation after 5 weeks of computer aided and non computed aided exercises targeting attention (Sastre-Garriga, 2011)
• IHAMS in normal aging (Wolinsky, 2013)
Treating Executive Functioning in MS

• Fink Study (2010)
  – Textbook exercises 30 minutes, 4 x weekly
  – Feedback with psychologist weekly
  – 6 week treatment
  – Improvement in executive functioning and verbal learning
Elements of Cognitive Exercising

- Repetition
- Novelty
- Adaptability
- Targeting
- Generalizing
- Feedback
“Brain Training” Industry

- Brain health software grew from $600 million in 2009 to $1 billion by end of 2012 – forecasted to reach $4-10 billion by 2020
Leading Products

- **CogMed** (Pearson)
  - targeting ADHD
  - licensed to psychologists and schools
- **RehaCom** (CogniPlus; Schuhfried)
  - Founded in 1986
  - Established in over 1000 hospitals/clinics through Europe
- **BrainHQ** (PositScience)
- **Lumosity**
  - 60 million subscribers worldwide
Computerized Cog Rehab in MS

• Studies utilizing RehaCom
  – “Plan a Day” and “Divided Attention”
  – 1 hour sessions, 3 sessions/wk
• Flavia, 2010
  – 20 patients with cog deficits on neuropsych
  – Improvement in attention, information processing, executive functioning, and depression
• Filippi, 2012
  – 10 study patients, 10 controls
  – Improved attention, info processing, exec fxn
  – MRI – no changes in grey matter volume or WM architecture
  – fMRI – modifications during Stroop Test and resting state
• Cerasa, 2012
  – Utilized “Divided Attention,” 2 sessions/week for 6 weeks
  – fMRI modifications during Stroop Test
Parisi, 2012

• 12-week computer-based rehabilitation programme of attention and executive functions was shown to be effective in improving neuropsychological performance in the trained domains in patients with relapsing–remitting (RR) MS (Mattioli, 2010)
“Plan a Day” by RehaCom

- Trains ability to organize, plan and develop solution strategies
- Set of scheduled dates and duties to be organized at specific places in a small city map
- Timed completion; 55 levels of difficulty
- Requires executive functioning, short term memory, and working memory
“Divided Attention” by RehaCom

- Simulate the actions of a train driver
- Carefully observe the control panel and the countryside
- Several distractions, such as crossing animals, and train speed must be taken into account with increasing levels of difficulty
- Requires attention and information processing speed
Computerized “brain training” in Aging

• Studies utilizing BrainHQ
  – ACTIVE Study
  – IMPACT Study
  – IHAMS (Wolinsky, 2013) – 620 participants
    • 10-14 hrs Brain HQ vs. crossword puzzles in healthy aging
    • “Double Decision” – expands useful field of view (UFOV)
    • Improvement on Trails A, Trails B, SDMT, Stroop Word
Cognitive Exercise in Aging

• ACTIVE study (Ball, 2002; Rebok, 2014)
  – 2832 participants, 65 and older
  – 3 treatment types – memory, reasoning, processing speed
  – 10 one-hour sessions over 6 weeks; 4 booster sessions 1-3 years later
  – Results showed slower decline in instrumental ADLs in processing and reasoning groups
    • Benefits observed 5 and 10 years after training completed
Brain HQ “Double Decision”

How the visual speed of processing training program appears to the user
Double Decision At-a-Glance

<table>
<thead>
<tr>
<th>What you do</th>
<th>What it improves</th>
<th>How the exercise changes</th>
<th>How you're scored</th>
</tr>
</thead>
<tbody>
<tr>
<td>Choose which car you saw at the center of the screen and locate where the Route 66 sign appeared in the periphery</td>
<td>• Useful field of view and visual processing speed</td>
<td>• Distractors are added</td>
<td>Your score is in milliseconds. As you improve, the cars and road signs flash for fewer milliseconds, giving you a lower (better) score.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Distance from the center increases</td>
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<tr>
<td></td>
<td></td>
<td>• Cars get more similar</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>• Backgrounds get more complex</td>
<td></td>
</tr>
</tbody>
</table>
Lumosity training

• Impact of time of day (Sternberg, 2013)
  – Working memory and attention tasks – AM
  – Executive function/creativity tasks - PM

• Impact of age and training interval (Ballard, 2012)
  – Best when training repeated every 1-3 days
  – Better improvement with younger age
  – Younger individuals can retain benefits with longer gaps in between training
Physical Exercise and Cognition

• Cognitive benefits seen in animal models and normal human aging with both strengthening and aerobic exercise (Nagamatsu, 2014)

• Change in fitness status through a telephone-based health promotion intervention over 12 weeks improved executive functioning in MS (Beier, 2014)
  – Did not improve processing speed
Summary
References

- Ballard K, Sternberg DA, Hardy JL, et al. Training related improvements in cognitive performance persist over time but depend on age; an online study including > 140,000 participants. Society for Neuroscience Annual Meeting,, 2012: 693.10.
References

References

• Sternberg DA, Hardy JL, Scanlon M. Cognitive performance peaks at different times of day depending on the task. *Entertainment Software and Cognitive Neurotherapeutics Society Annual Meeting*, 2013: