Cognitive Rehabilitation in Multiple Sclerosis: Its About Time!

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Disclosures

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   – Biogen-Idec: Consultant
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Overview

• Cognitive problems in MS
• Cognitive Rehabilitation
  – Learning and Memory
  – Executive dysfunction
• Cognitive Reserve
• What is needed for the future?
Multiple Sclerosis

• MS is a progressive disease producing widespread:
  – plaques in white matter
  – axonal damage
  – damage to grey matter

• Results in range of symptoms
  – Sensory/motor
  – Fatigue
  – Cognitive
  – Neuropsychiatric
MS - Background

- Affects about 400,000 persons in the US
- Approximately 2.1 million worldwide
- Age of Onset: 20-40 years
- Almost 2 times more frequent in females
- **Etiology** - Unknown, thought to be an autoimmune disease triggered by a viral infection in genetically susceptible individuals
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 Impairment in MS

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

Chiaravalloti & DeLuca, 2008, Lancet Neurol
Cognitive Impairment in MS

percent impaired

- fluency
- visuospatial perception
- memory (immediate)
- memory (delayed)
- working memory / speed
- speed
- concept formation

Cognitive domain
Cognitive Problems and Everyday Life Functioning

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

• Beyond physical disability alone

Rao et al., 1991
Cognitive Impairment in MS - treatment

Memory Rehabilitation for people with multiple sclerosis (Review)

das Nair R, Ferguson H, Stark DL, Lincoln NB

8 RCT for memory rehabilitation involving 521 participants

“…no evidence to support the effectiveness of neuropsychological rehabilitation in MS… well-designed high quality studies are needed”

Das Nair et al, 2012
Cognitive Impairment in MS - treatment

Neuropsychological rehabilitation for multiple sclerosis (Review)

Rosti-Otajärvi EM, Hämäläinen PI

14 studies with
770 MS
20 HC

Low evidence found

12 of 14 studies showed evidence of positive effects of neuropsychological rehabilitation

Rosti-Otajarvi & Hamalainen, 2011
Systematic Reviews: Comments

• “A lack of evidence; however, does not equate to evidence against a procedure”
• “To draw firm conclusions that are based on systematic reviews that synthesize evidence from small numbers of randomized controlled trials of sometimes poor methodological quality, is undoubtedly overly simplistic”

Freeman & Playford, 2012, MSJ, p 1380
Evidenced-Based Cognitive Rehabilitation for Persons With Multiple Sclerosis: A Review of the Literature

Amanda R. O’Brien, PhD, Nancy Chiaravalloti, PhD, Yael Goverover, OT, PhD, John DeLuca, PhD


Objectives: To conduct evidence-based review of cognitive rehabilitation intervention research conducted in persons with multiple sclerosis (MS), to classify level of evidence, and to generate recommendations for interventions in this area. learning and memory received support for a practice guideline and practice option, respectively.

Conclusions: Cognitive rehabilitation in MS is in its relative infancy. More methodologically rigorous research is needed to determine the effectiveness and efficacy of various cognitive rehabilitation interventions. Specific recommendations for future research are given.

Key Words: Cognition disorders; Cognitive therapy; Multi-
Conclusions
Evidence-Based Cognitive Rehabilitation Review

• Little attention for Cog rehabilitation in MS
  – Yielded only 16 studies
  – Contrasts with 258 studies in TBI
• Only 1 practice guideline recommended
  – Single technique, based on 1 study
• Missing are studies on processing speed

O’Brien et al., 2008, Arch PM&R
Treatment of cognitive impairment in multiple sclerosis: position paper

Maria Pia Amato · Dawn Langdon · Xavier Montalban · Ralph H. B. Benedict · John DeLuca · Lauren E. Krupp · Alan J. Thompson · Giancarlo Comi
Position paper on treatment of cognitive impairment in MS

- Literature review of behavioral and pharmacological interventions for cognition
- Behavioral studies
  - Information Processing speed
  - Learning and memory
  - Attention
  - Executive functioning

Amato et al., 2013, J Neurol
Methodological Problems with many Existing Behavioral Studies

- Small sample size
- Lack of control group, or inadequate control (e.g., “historic controls”)
- Interventions are multifaceted and difficult to quantify
- Inadequate selection of targeted sample
  - e.g., cognitively intact patients often included
- Inclusion criteria for cognitive impairment based on self-report rather than objective assessment
- Treatment is often not impairment specific (e.g., “improve cognition”)
- Frequency and intensity of treatment often not reported
- Specific details of how treatment was delivered often not reported
  - (e.g., non-specific cognitive training)
- Unsupervised training sessions (compliance not monitored)
- Use of poor outcome measures (e.g., “positive clinical response”)
- Outcome measurements lack relevance to everyday life
- Lack of long-term follow-up

Amato et al., 2013, J Neurol
General Procedure: Processing Speed

• No cognitive studies specifically designed to improve processing speed found
General Procedure: Learning and Memory

- 44 potential papers identified
  - Not all of these assessed memory
- 17 considered for inclusion
  - Intervention was memory-based
  - Memory was an outcome measure
- Reviewed independently by 2 experts
Behavioral Treatment and Learning and Memory in MS

Support: 12

No Support: 5

1 weak support

Amato et al., 2013, J Neurol
Learning and Memory
Learning and Memory Process

- Encoding
- Consolidation
- Retrieval

Learning
Identifying the Cause

- Retrieval failure hypothesis?
- Acquisition deficits?
The Nature of Memory Impairments in Multiple Sclerosis: Acquisition versus Retrieval*

John DeLuca¹,²,³, Susan Barbieri-Berger¹,², and Susan K. Johnson²

¹ Kessler Institute for Rehabilitation, West Orange, New Jersey and Departments of Physical Medicine and Rehabilitation², and Neurosciences³ University of Medicine and Dentistry of New Jersey New Jersey Medical School, Newark, New Jersey
SRT Trials to Criterion

DeLuca et al., *JCEN*, 1994
Recall and Recognition

Mean correct words

Recall | Recognition
---|---
MS | HC

DeLuca et al., *JCEN*, 1994
Learning Impairment is Associated With Recall Ability in Multiple Sclerosis*

Heath A. Demaree, Elizabeth A. Gaudino, John DeLuca, and Joseph H. Ricker
Kessler Medical Rehabilitation Research and Education Corporation, Neuropsychology and Neuroscience Laboratory, West Orange, New Jersey and UMDNJ-New Jersey Medical School, Departments of Physical Medicine and Rehabilitation, and Neurosciences, Newark, New Jersey
Logical Memory: Trials to Criterion

Logical Memory: Delayed Recall

Paired Associate: Delayed Recall

Facial Recognition: Trials to Criterion

Facial Recognition: Delayed Recall

Learning and Memory in MS

- Primary deficit in MS is in the acquisition of information
- Cognitive rehabilitation the focus in improving acquisition/learning
Hippocampal Imaging Protocol

A. Sagittal T2-weighted scout image with the superimposed slice prescription for the 16 coronal high-resolution structural images covering the medial temporal lobe.

B-C. Coronal T2-weighted scan acquired at 3T with in-plane resolution of 400µm x 400µm

D. Subregional segmentation
MS with lower hippocampal volumes required more learning trials for unrelated word-pairs

MS divided into 4 groups according to Hippocampal volumes using 25,50,75 Percentiles as cutoff

Length of box – range
Center dot – mean
Horizont line – median

Sicotte et al. 2008, Brain, 131, 1134-1141
Hippocampus and Cognition in MS

- MS with **intact** memory no hippocampal structural damage
  - Subtle decreased functional connectivity
  - During memory encoding see *INCREASED* activation on fMRI
- Functional problems precedes memory decline
- Over time, structural damage increases, leading to learning and memory decline

Cognitive Rehabilitation: Behavioral Approaches

Sample Non-RCT results
Cognitive Rehabilitation: Four Areas of Research

• Techniques Borrowed from Cognitive Psychology
  – Generation Effect
  – Spacing Effect
  – Testing Effect
  – Combined interventions

• Clinical trial to improve learning
ORIGINAL ARTICLE

Self-Generation to Improve Learning and Memory of Functional Activities in Persons With Multiple Sclerosis: Meal Preparation and Managing Finances

Yael Goverover, PhD, OT, Nancy Chiaravalloti, PhD, John DeLuca, PhD, ABPP

Archives of Physical Medicine & Rehabilitation, (2008), 89(8), 1514-1521
The generation effect is the observation that items generated by subjects are remembered better than items simply presented.

- Robust effect in Healthy subjects
- Little work in Clinical samples
Self-Generation and Everyday Life Activities

Food Preparation

Managing Finances

Spacing Effect

New learning in healthy individuals is significantly improved when trials:

✓ Are **SPACED** or distributed over time

compared to

✓ **MASSED** or consecutive learning trials

Ebbinghaus, 1885/1994
Spaced Learning or “Spacing Effect”

- Instructions on how to perform tasks were presented three times in two conditions:
  - Massed condition          1/2/3
  - Spaced condition          1_____2______3
  - Within-group design

Paragraph from Newspaper in MS

Combined Self-Generation and Spaced Learning
Examining the benefits of combining two learning strategies on recall of functional information in persons with multiple sclerosis

Yael Goverover¹,², Michael Basso³, Hali Wood², Nancy Chiaravalloti²,⁴ and John DeLuca²,⁴
Mean Recall of Appointments

Chart Title

- Sp-Gen
- spaced
- massed

Goverover, Basso, Wood Chiaravalloti & DeLuca, (2011)
Retrieval practice or “Testing Effect”

• Testing provides better retention than re-studying
• study trial - re-study - assess vs.
• study trial - testing trial – assess
Testing Effect in MS (Mean Words recalled)

25%↑  78%↑

Learning and Memory

Randomized Control Trials
Treating learning impairments improves memory performance in Multiple Sclerosis: a randomized clinical trial

Nancy D. Chiaravalloti, Ph.D.
John DeLuca, Ph.D.
Nancy B. Moore, M.A.
Joseph H. Ricker, Ph.D.

*Multiple Sclerosis*, 2005, 11, 58-68

Funded by NMSS grant PP0752
Context and Imagery
Memory Retraining in MS

- 28 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, 2005, *Mult Scler*
HVLT-R Mod/Severe vs. Control Baseline to follow-up

$\text{p}<.01$

Baseline to immediate change

Baseline to long-term change

Chiaravalloti et al, *Multiple Sclerosis*, 2005
Self-report Memory Impairment (n=28)
Baseline to follow-up

Remember things that occur in everyday life

<table>
<thead>
<tr>
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<th>Treatment Group</th>
<th>Control Group</th>
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Baseline to immediate change

Baseline to long-term change

Chiaravalloti et al, *Multiple Sclerosis*, 2005
A Randomized Clinical Trial to treat Learning Impairment in Multiple Sclerosis: The MEMREHAB trial

Nancy D. Chiaravalloti, Ph.D.
Nancy B. Moore, M.A.
Olga Nikelshpur, Ph.D.
John DeLuca, Ph.D.

Neurology, In Press

Funded by NIH R01
The MEMREHAB trial

- Double Blind, placebo controlled RCT
  - Screened into study based on learning deficit
- 86 MS with impaired learning & memory
- 6 month follow-up
- Outcome measures
  - Neuropsychological performance
  - Everyday life
  - Neuroimaging (subset of s’s)
Learning by Group: Post-treatment*

No significant group difference at baseline, p = .02, controlling for baseline
Improvement on CVLT Slope

% of group showing improvement

Treatment Placebo

Improvement defined as $\geq 10\%$ increase from T1 to T4 on CVLT

p<.05

Chiaravalloti et al., *Neurology*, In Press
Everyday Life Self-Report
FAMS General Contentment

p<.05

Chiaravalloti et al., *Neurology*, In Press
Everyday Life Self-Report
FrSBe Total Score, Family Form

*lower score indicates less symptoms

Chiaravalloti et al., *Neurology, In Press*
Brain changes after behavioral treatment for memory impairment in MS using fMRI
Increased cerebral activation after behavioral treatment for memory deficits in MS

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

Chiaravalloti et al., 2012, *J Neurol*
Resting state functional connectivity following cognitive rehabilitation in MS

Increased connectivity from L Hippocampus to Insula bilaterally in treatment group after TX

Increased connectivity from R Hippocampus to cluster comprised of L post-central gyrus, precentral gyrus middle frontal gyrus and cingulate gyrus in treatment Group after TX

Increased connectivity from PCC to thalamus bilaterally in treatment group after TX

Red line tx; blue line controls

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

- Pre- to Post-intervention
  - Significant memory improvements in treatment group

- Post-intervention to 6 months Post-intervention
  - Groups maintain the level of performance observed at Post-intervention

CVLT Performance

- CVLT SDFR

Dobryakova et al, Submitted
6 month follow-up at Encoding: main effect of Treatment

Parameter Estimates (Beta Weights)

- Visual Cortex
- MTL
- DLPFC

Treatment (green) vs. Control (red)

* $p < 0.005$
** $p < 0.001$

Dobryakova et al, Submitted
Encoding Results

• Increased activity ONLY in the treatment group
  – Dorsolateral Prefrontal Cortex
    • DLPFC
  – Medial Temporal Lobe
    • MTL
  – Visual cortex

Dobryakova et al, Submitted
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 6 months post-intervention

Dobryakova et al, Submitted
Executive Functions
<table>
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<tr>
<th>Study (Year)</th>
<th>Training Description</th>
<th>Effect</th>
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<tr>
<td>Mattioli et al (2012)</td>
<td>Computer training of Attn, PS, EF vs no tx</td>
<td>YES</td>
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Efficacy and specificity of intensive cognitive rehabilitation of attention and executive functions in multiple sclerosis

Mattioli Flavia a,*, Chiara Stampatori a, Deborah Zanotti a, Giovanni Parrinello b, Ruggero Capra c
Cognitive Rehab in RRMS

• Evaluate efficacy of computer-based intervention (RehaCom) for attention, PS and executive functions in RRMS

• 20 RRMS randomized into TG or CG:

  Treatment Group (TG): intensive computer-assisted (RehaCom software) cognitive rehabilitation of attention, information processing and executive functions for 12 weeks (1 hr session, 3 days a week).

  Control Group (CG): no rehabilitation.

• Pre (T0) and post (T1) Neuropsych testing

Mattioli et al (2010), J of Neurol Sci
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NO impact on memory performance

Mattioli et al (2010), *J of Neurol Sci*
Multiple Sclerosis: Effects of Cognitive Rehabilitation on Structural and Functional MR Imaging Measures—An Explorative Study

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 Neurol Sci, 2010
MR changes following Cognitive Rehabilitation

In treatment group, Functional MR changes Correlated with cognitive improvement

No structural MR changes
In GM volume or NAWM observed with treatment

Filippi et al, Radiology, 2012
Cognitive rehabilitation correlates with the functional connectivity of the anterior cingulate cortex in patients with multiple sclerosis

Laura Parisi · Maria A. Rocca · Paola Valsasina · Letizia Panicari · Flavia Mattioli · Massimo Filippi
Functional connectivity following Cognitive Rehabilitation

TG ONLY: Increased FC of ACC with:
- R MFG
- R IPL

PASAT correlated with increased FCC of ACC with:
- R MFG
- R IPL

CG ONLY: decreased FCC of ACC with:
- R cerebellum
- R ITG

No correlation with cognition

Parisi et al (in press), *Brain Imaging and Behavior*
Persistence of the effects of attention and executive functions intensive rehabilitation in relapsing remitting multiple sclerosis

F. Mattioli a,∗, C. Stampatori a, C. Scarpazza a, G. Parrinello c, R. Capra b

6 mo follow-up data: Mattioli et al, 2012, JNS study
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NO impact on memory performance

6 mo follow-up data: Mattioli et al, 2012, MSRD
Cognitive Rehabilitation in MS

It works!
“When my memory started failing, I knew I had to see my doctor. He put me on ARICEPT®. Now I’m doing better.”

ARICEPT® is well tolerated but may not be for everyone. Some people may experience nausea, diarrhea, not sleeping well, vomiting, muscle cramps, feeling very tired, or not wanting to eat. In studies, these side effects were usually mild and went away over time. Some people taking ARICEPT® may experience tachycardia. People at risk for ulcers should tell their doctors because their condition may get worse.

Please get additional important product information or accompanying leaflet.

Kessler Foundation Research Center
Cognitive Reserve
Clinical Expression of Neurologic Disease

- Not everyone with Alzheimer’s Disease develops dementia

- Alzheimer’s Disease (AD)
  - Persons without clinical dementia can meet post-mortem neuropathological criteria for AD

  - Numerous studies show that lower educational attainment is a risk factor for AD-related dementia.
The Cognitive Reserve Hypothesis

- Persons with greater life-time intellectual enrichment results in greater cerebral efficiency, which provides protection against the expression of disease, in this case, cognitive impairment - “cognitive reserve”

Cognitive Reserve in MS

- Sumowski et al., *Neurol.* 2010
Cognitive Reserve and MS

- Higher cognitive reserve protects MS subjects from MS-related cognitive decline

- What about “Brain Reserve”?
Brain Reserve Hypothesis

Persons with larger lifetime brain growth/size (estimated with intracranial volume) can withstand more severe neuropathology without suffering cognitive impairment or dementia.

Persons with larger lifetime brain growth/size have more brain to lose before suffering cognitive decline.

Stern et al., *JINS* 2002;8:448-460.
Brain Reserve in MS

Does larger maximal lifetime brain growth (estimated with intracranial volume) protect MS patients from disease-related cognitive deficits?
Results: Brain Reserve

Sumowski et al (2013), *Neurology*
Results: Brain Reserve

Sumowski et al (2013), *Neurology*
Brain Reserve Results

- Higher “brain reserve” (larger brain size) protects against expression of cognitive impairment in persons with MS
Question

Does intellectual enrichment (cognitive reserve) protect MS patients from cognitive impairment independently of maximal lifetime brain size (brain reserve)?

Do people have control over their own destiny?
Results: Cognitive Reserve

\[
p < .001
\]
Results: Cognitive Reserve after factoring our Brain Reserve

Sumowski et al (2013), *Neurology*
Brain Reserve and Cognitive Reserve

- Higher “cognitive reserve” can protect against expression of cognitive impairment in MS over and above the influence of “brain reserve” (larger brain size)
Cognitive Reserve and Rehabilitation

• Higher cognitive reserve protects MS subjects from MS-related cognitive decline
• Can we identifying “at risk” patients for cognitive impairment?
• Can one build up a “cognitive reserve”?  
  – “neuroprotective” against developing cognitive impairment?
What is needed for the future?
Cognitive Rehabilitation

• Effective cognitive rehabilitation programs do not employ only techniques to improve specific cognitive domains
• but also typically include therapy for:
  – Emotional issues
  – Family issues
  – Behavioral/personality issues
  – Vocational/everyday life issue

Amato et al, 2013, *J of Neurol*
What is Needed?

• Despite the Cochrane reviews, there is significant evidence that non-pharmacological approaches can significantly improve cognitive functioning

• How do we incorporate such work into practice?

• Still an important area for research
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
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Nancy Moore, M.S.
Helen Genova, Ph.D.
Victoria Leavitt, Ph.D.
Gianna Riccitelli, Ph.D.
Massimo Filippi, M.D.
Thank You
Correlation between Brain Reserve & Cognitive Reserve

Brain size is correlated with education and intelligence

Witelson et al., *Brain*; 2006;129:386-398
Deary et al., *Nat Rev Neurosci* 2010;11:201-211

Brain size is genetically determined

Posthuma et al., *Nat Neurosci* 2002;5:83-84.
Thompson et al., *Nat Neurosci* 2001;4:1253-1258
Deary et al., *Nat Rev Neurosci* 2010;11:201-211