Cognitive Impairment in MS: What Does it Mean to Me?

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“Appointment after appointment Dr. xxx listened to my complaints, but didn’t take them seriously or relate them to MS. Compared to her patients in wheelchairs, my thinking symptoms must have appeared minor, but they were very powerful, and had the potential to be just as devastating as the physical difficulties”

Gingold (2006) Facing the cognitive challenges of MS, 39
Overview

• Cognitive problems in MS
• Impact on Everyday Life
• Key Cognitive problems
• Can we improve cognitive problems?
• Cognitive Reserve and MS
• Exercise
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
Affects about 450,000 persons in the US
Approximately 2.3 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
Cognitive experience of patients with MS:

“a marked enfeeblement of the memory; conceptions are formed slowly …”

Charcot
(1868)
Early 1900’s saw a great debate on cognition!

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
“I thought I was losing my mind. It was difficult to explain to others what was happening when I didn’t know myself. I do remember the fear and loneliness that went along with all this. I silently begged God, ‘Do what you will to my body, but please leave my mind alone”

Hall (1999) *Inside MS, 17, 52-53*
What is Cognition?

Dictionary:
“the act or process of knowing”
What is Cognition?

• **Receptive Functions**
  – Sensory input, paying attention, rapid processing incoming information

• **Learning and Memory**
  – Acquiring, storing, retrieving

• **Thinking**
  – Mental organization and manipulation

• **Execution and expressive functions**
  – Acting upon and communicating intentions
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*
Spared Cognition in MS

- Basic Attention
- Essential verbal skills
  - Comprehension
  - Expression
  - Naming
  - Repetition
- Intelligence
### Some Factors which affect Cognition in MS

<table>
<thead>
<tr>
<th>Disease Course</th>
<th>RR &lt; SP</th>
</tr>
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<tbody>
<tr>
<td>Duration of disease</td>
<td>Sometimes</td>
</tr>
<tr>
<td>Physical Disability</td>
<td>Not always</td>
</tr>
<tr>
<td>Fatigue</td>
<td>Not well known</td>
</tr>
<tr>
<td>Depression</td>
<td>It may, not always</td>
</tr>
<tr>
<td>Stress</td>
<td>It may, not always</td>
</tr>
<tr>
<td>Gender</td>
<td>Males at increased risk</td>
</tr>
</tbody>
</table>
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

Chiaravalloti & DeLuca, 2008, *Lancet Neurol*
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

97 employed MS
At 3.5year f/up, 45% declined in employment status

DES- deteriorated employment
SES- stable employment

Morrow et al. [Clin Neuropsychologist, 2011]
Information Processing Efficiency

Processing speed
Working Memory
“Often I have a 5-15 second delay in recognizing what is going on, what is being said, who I am talking to….Don’t ask me a compound question unless you want me to shut down completely. One thing at a time and wait…Up until about a year ago, I thought MS would just be a physical battle”
Risk Estimates (Odds Ratios)

What are the odds or relative risk of having a PS or WM Deficit in MS compared to that of the general population?
## Risk Estimates (Odds Ratios) of PS vs WM impairment in MS

<table>
<thead>
<tr>
<th></th>
<th>All MS vs. Controls</th>
<th>RRPM vs. Controls</th>
<th>SMPM vs. Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds Ratio</td>
<td>Odds Ratio</td>
<td>Odds Ratio</td>
</tr>
<tr>
<td>Processing Speed Index</td>
<td>10.4</td>
<td>5.3</td>
<td>65.2</td>
</tr>
<tr>
<td>Working Memory Index</td>
<td>2.7</td>
<td>1.3</td>
<td>9.0</td>
</tr>
</tbody>
</table>

DeLuca et al, *JCEN*, 2004
Summary

• Information processing deficit in MS is primarily processing *speed* and not working memory *accuracy*
Learning and Memory
Defining Learning

- **Learning** - “The *process* of acquiring new information”
- **Memory** - “The *persistence* of learning in a state that can be revealed at a later time”
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 vs Retrieval

John DeLuca, Ph.D.
Susan Barbieri-Berger, M.D.
Susan K. Johnson, Ph.D.

SRT Trials to Criterion

Trials To Criterion

Recall and Recognition

DeLuca et al., 1994, *J Clin Exp Neuropsych*
Learning impairment is associated with recall ability in multiple sclerosis

Heath A. Demaree, Ph.D.
Elizabeth A. Gaudino, Ph.D.
John DeLuca, Ph.D.
Joseph H. Ricker, Ph.D.

Journal of Clinical & Neuropsychology, 2002, 22, 865-873
Facial Recognition  (Demaree et al., 2000)

Trials to Criterion

Recall

Learning and Memory in MS

- Primary deficit in MS is in the acquisition of information
- Cognitive rehabilitation the focus in improving acquisition/learning
What can we do to Improve Cognition?

Cognitive Rehabilitation
Cognitive Rehabilitation: Four Areas of Research

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

• Clinical trial to improve learning
The generation effect is: items generated by subjects are remembered better than items presented.

Robust effect in Healthy subjects.

Little work in Clinical samples.
Tasks

- Participants were asked to complete two tasks:
  - Meal preparation
  - Financial management
Self-Generation and Everyday Life Activities

Meal 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 Goverover\textsuperscript{1,2}, Michael Basso\textsuperscript{3}, Hali Wood\textsuperscript{2}, Nancy Chiaravalloti\textsuperscript{2,4} and John DeLuca\textsuperscript{2,4}

Mean Recall of Appointments

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

- Which do you prefer for new learning
  - 4 opportunities to learn something
  - 1 opportunity then tested 3 times
Active Retrieval during Learning enhances deep and conceptual encoding

SSSS – study 4 times
SSSR – study 3 times then recall once
SRRR – study 1 time then recall 3 times

Reading educational texts

Testing Effect in MS (Mean Words recalled)

- Massed Restudy: 25% ↑
- Spaced Restudy: 78% ↑

Graphs showing delayed recall after 45 minutes and one week:
- Delayed Recall after 45 Minutes:
  - Massed Restudy: 15%
  - Spaced Restudy: 25%
  - Retrieval Practice: 77%
- Delayed Recall after One Week:
  - Massed Restudy: 1.3%
  - Spaced Restudy: 5.0%
  - Retrieval Practice: 27.5%

Context and Imagery

Clinical Trial to Improve Learning and Memory
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

\[ p < .01 \]

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

\[ p < .01 \]

\[ p < .001 \]

Remember things that occur in everyday life

Baseline to immediate change
Baseline to long-term change

Chiaravalloti et al, *Multiple Sclerosis*, 2005
An RCT to treat learning impairment in multiple sclerosis
The MEMREHAB trial

ABSTRACT

Objective: To examine the efficacy of the modified Story Memory Technique (mSMT), a 10-session behavioral intervention teaching context and imagery to facilitate learning, to improve learning and memory abilities in persons with multiple sclerosis (MS).

Methods: This double-blind, placebo-controlled, randomized clinical trial included 86 participants...
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
Everyday Life Self-Report FrSBe Total Score, Family Form

*lower score indicates less symptoms

Chiaravalloti et al., *Neurology*, 2013
Imaging data and Rehabilitation

• Brain changes after treatment
  – Functional:
    • fMRI
    • functional connectivity

• Does this 10 session behavioral treatment change brain structure or function?
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., *J Neurol*, 2012
BOLD activation change from pre- to post-treatment

parahippocampal gyrus

superior temporal gyrus

Chiaravalloti et al., *J Neurol*, 2012

MS – red

HC - blue

Chiaravalloti et al., *J Neurol*, 2012
BOLD activation change from pre- to post-treatment

middle frontal gyrus

precuneus

MS – red
HC - blue

Chiaravalloti et al., J Neurol, 2012
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
A pilot study examining functional brain activity 6 months after memory retraining in MS: the MEMREHAB trial

Ekaterina Dobryakova • Glenn R. Wylie • John DeLuca • Nancy D. Chiaravalloti
Behavioral Performance

CVLT SDFR Performance

- Control group mean
- Treatment group mean

Pre-intervention Post-intervention 6 months

Dobryakova et al., 2014
6 month follow-up at Encoding: main effect of Treatment

Parameter Estimates (Beta Weights)

- Visual Cortex
- MTL
- DLPFC

Treatment: * P < 0.005 ** p < 0.001
Control: * P < 0.005 ** p < 0.001

Dobryakova et al., 2014
Encoding Results

• Main effect of group (treatment x control)
  – Dorsolateral Prefrontal Cortex
    • DLPFC
  – Medial Temporal Lobe
    • MTL
  – Visual cortex

Dobryakova et al., 2014
Area more activate in the treatment group vs control group during memory encoding

pre-intervention x post-intervention

Brain areas activated in association with encoding

post-intervention x 6months post-intervention

Dobryakova et al., 2014
Changes in Brain Functioning in MS

- Increased activity in brain areas associated with memory and imagery
- Increased connections with other parts of the brain

Chiaravalloti et al., 2012; Leavitt et al, 2012
"When my memory started failing, I knew I had to see my doctor. He put me on ARICEPT. Now I'm doing better."

Time Magazine 1/20/2003
Cognitive Reserve and MS

• Not all persons with Alzheimer’s exhibit dementia
• Lifetime intellectual enrichment results in increased cerebral complexity, resulting in resistance to expression of disease
• Is this observed in MS?
Cognitive Reserve in MS

Cognitive Reserve and Rehabilitation

- Higher cognitive reserve protects MS subjects from MS-related cognitive decline
- Clinical implications: can we identify “at risk” patients
- Can one build up a “cognitive reserve”? – that can be “neuroprotective” against the expression on developing cognitive impairment?
Exercise
Exercise, Cognition and the Brain: Non-MS

- Aerobic exercise training in animals
  - stimulates hippocampal neurogenesis
  - Improves memory
- Exercise-induced hippocampal neurogenesis has been shown in healthy humans (Pereira et al., 2007)
- RCT of aerobic exercise in non-demented elders
  - Aerobic group
    - Increased hippocampal volume
    - Increased memory
  - Non-aerobic group
    - age-related decline in hippocampal volume
    - and memory (Erickson et al., 2011)
Aerobic exercise increases hippocampal volume and improves memory in multiple sclerosis: Preliminary findings


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2 RRMS patients randomized to aerobic vs non-aerobic training
30 min sessions, 3x/week for 3 months
Memory and Aerobic Exercise

<table>
<thead>
<tr>
<th></th>
<th>Aerobic</th>
<th>Stretching</th>
</tr>
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<tbody>
<tr>
<td>Hippocampus</td>
<td>+ 16.5%</td>
<td>+ 2.8%</td>
</tr>
<tr>
<td>Cerebral Grey Matter</td>
<td>+ 2.4%</td>
<td>+ 2.9%</td>
</tr>
<tr>
<td>Memory</td>
<td>+ 53.7%</td>
<td>+ 0.0%</td>
</tr>
<tr>
<td>Non-Memory Cognition</td>
<td>+ 0.0%</td>
<td>+ 0.0%</td>
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Leavitt et al., *Neurocase*, 2013
Memory and Aerobic Exercise

Leavitt et al., Neurocase, 2013
Overall Summary

- Cognitive impairment in 2/3 persons with MS
- PS and learning & memory primary problems
- Significantly affects everyday life activities
- Work with your clinicians to get assessed
- Rehabilitation can improve cognitive symptoms
- Can we build a cognitive reserve?
- Exercise
THANK YOU

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