

# IMPROVING COGNITIVE, EMOTIONAL & PHYSICAL HEALTH

## An Educational Conference for People with Multiple Sclerosis



# WELCOME

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Kessler Foundation

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National Multiple Sclerosis Society, New Jersey Metro Chapter



# ACKNOWLEDGEMENTS



National  
Multiple Sclerosis  
Society

**Kessler**  
**INSTITUTE FOR REHABILITATION**  

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*Select Medical*

**ACORDA**  

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**THERAPEUTICS**

**Genentech**  
*A Member of the Roche Group*

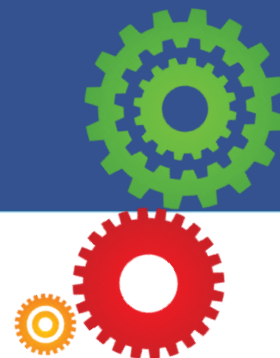
# TODAY'S AGENDA

## MORNING SESSION

Cognition & MS

## AFTERNOON SESSION

Panel Discussion I – Fatigue, motivation & physical activity  
Panel Discussion II – Everyday life, employment, wellness & social cognition



# Please note...

In your folder you will find:

Materials pertaining to today's discussions

A list of current studies at Kessler Foundation

A contact sheet (Please hand in at the recruitment table)

For today:

Please complete questions cards (Hand in before lunch)

Please stop by our vendors and exhibitors tables

Parking assistance will be available throughout the day



# Please note...

After you leave today:

Podcasts of today's talks will be available at:  
[Kesslerfoundation.org/MS2017](http://Kesslerfoundation.org/MS2017)

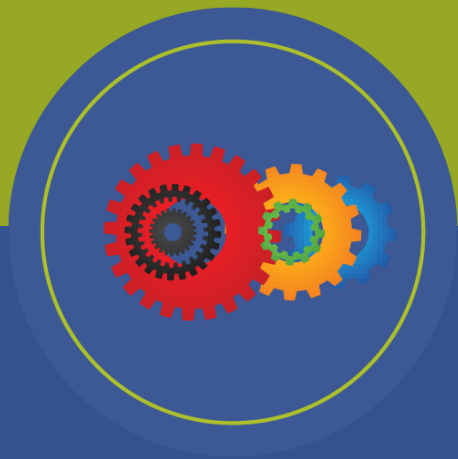
Look for our follow-up survey



# IMPROVING COGNITIVE, EMOTIONAL & PHYSICAL HEALTH

## An Educational Conference for People with Multiple Sclerosis





# National MS Society-NJ Metro Chapter Highlights

Moyra Rondon, LCSW



# Getting to know the National MS Society

*The National MS Society is focused on helping people affected by MS live their best lives through connection, support and information, no matter their location, needs or circumstances.*

- Founded in 1946 by Sylvia Lawry
- A nationwide network of chapters across the country
- Programs and Services
- Advocacy at the national and state level
- Volunteer engagement opportunities
- Fund-raising events
- Investment in MS research

# Funded Research

*National MS Society is a driving force of MS Research*



Stop the disease in it's tracks



Restore what's been lost



End the disease forever

Over 300 projects funded annually and \$974 million in research funding to date

# What services are available across the Society?

- MS Navigator Services:  
Information & referrals and link to case management as needed  
Phone: 1-800-344-4867      Email: [ContactUsNMSS@nmss.org](mailto:ContactUsNMSS@nmss.org)
- Website and Publications: [www.nationalMSSociety.org](http://www.nationalMSSociety.org)
- MS online community: [MSConnection.org](http://MSConnection.org)
- Nationwide Core Programs
  - Connections Program: Peers helping Peers
  - Scholarship Program
  - Monthly Tele-learning/webinar
  - Healthcare Access Partnerships

# What programs are available locally?

## Chapter developed programs:

- Wellness activities
- Locally based education programs
- Local in person self-help groups (30 in NJM)
- Nursing Home Outreach
- Collaborative programs with community partners
- Hispanic Family Day (NYC area)
- African American/Black Families Affected by MS (NYC area)

# Coming soon in our area!

- Sign up for Fall Wellness Series  
- free yoga and tai chi classes
- Impact Series 2017 – Sunday, December 3<sup>rd</sup>  
Join us for our new approach to our annual meeting!  
Register online at [nationalMSSociety.org/NJM](http://nationalMSSociety.org/NJM) or call  
1-800-344-4867.
- WALK MS: April 28<sup>th</sup> and 29<sup>th</sup> 11 sites throughout chapter area.

# Getting Involved

## ADVOCATE

Spread the word. Make a change.

## EDUCATE

Increase awareness. Help others learn about the disease.

## PARTICIPATE

Join us for our client programs or annual fundraising events: WALK MS, Bike MS, and Muckfest.

## VOLUNTEER

Give your time and talents. Help others by doing what you love.



# IMPROVING COGNITIVE, EMOTIONAL & PHYSICAL HEALTH

## An Educational Conference for People with Multiple Sclerosis



# Cognitive Deficits

John DeLuca, PhD, ABPP

Senior Vice President for Research  
Kessler Foundation

Professor, Physical Medicine and Rehabilitation  
Rutgers-New Jersey Medical School





# Overview

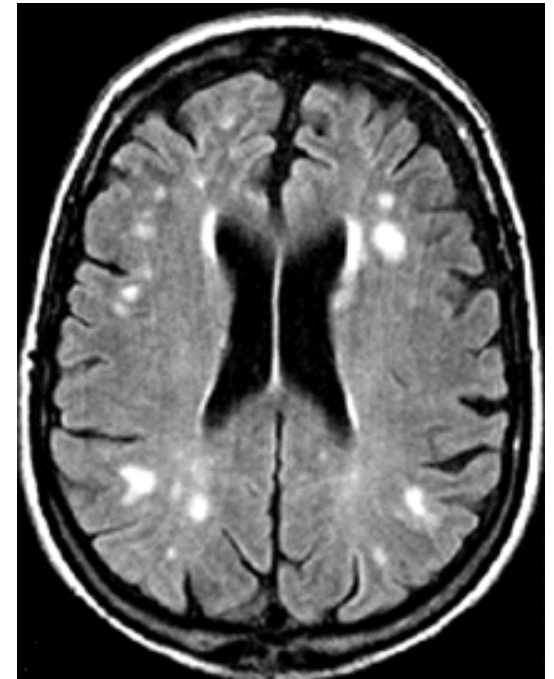
- Cognitive problems in MS
- Factors that affect cognition
- Impact on everyday life
- Key cognitive problems
- Medication

# From Persons with MS

“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”

# 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 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

# Charcot

(1868)

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Cognitive experience of patients with MS :

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

# MS - Historical

- 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

# From Persons with 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’”

# What is Cognition?

Dictionary:

“the act or process of knowing”



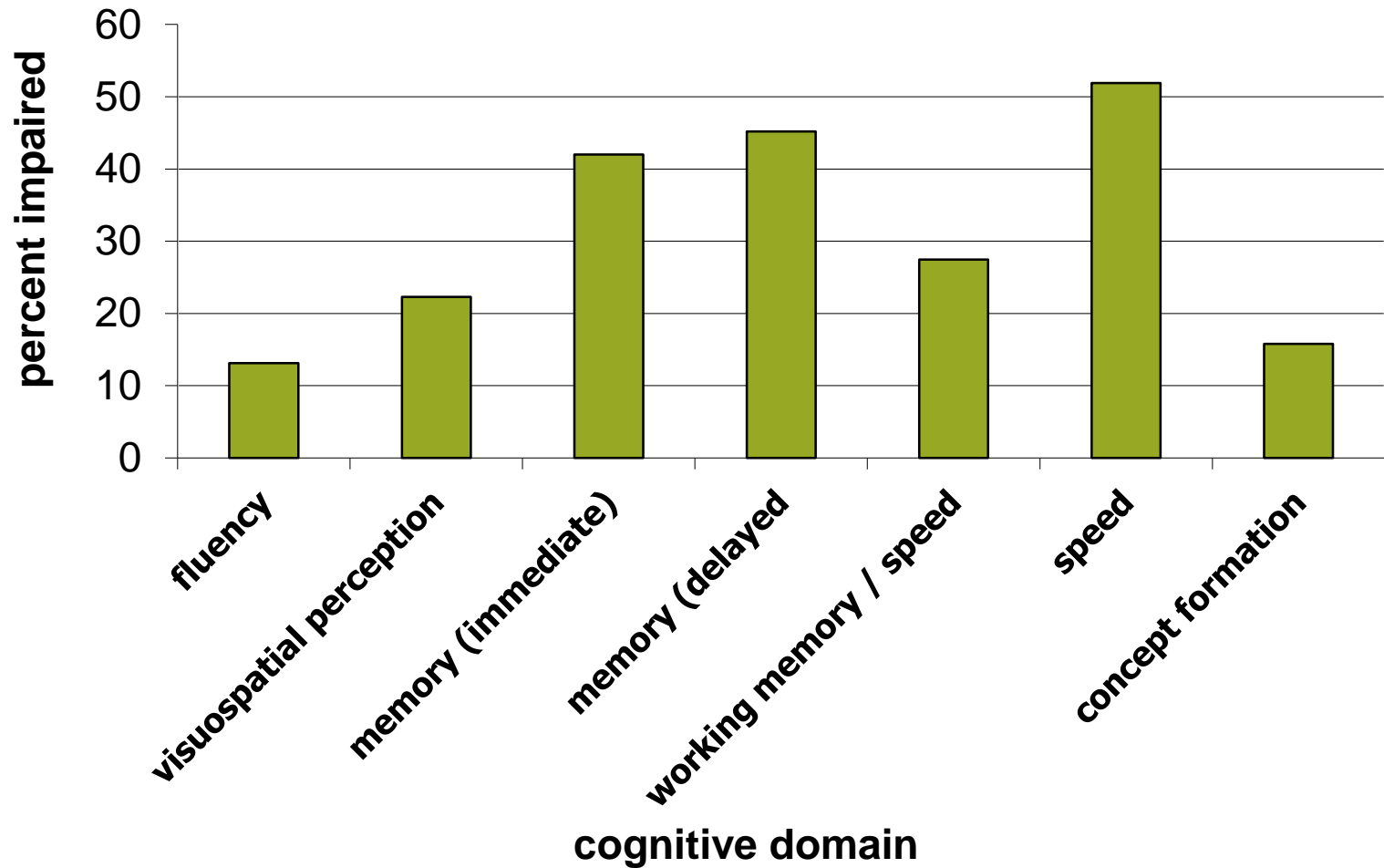
# What is Cognition?

- 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

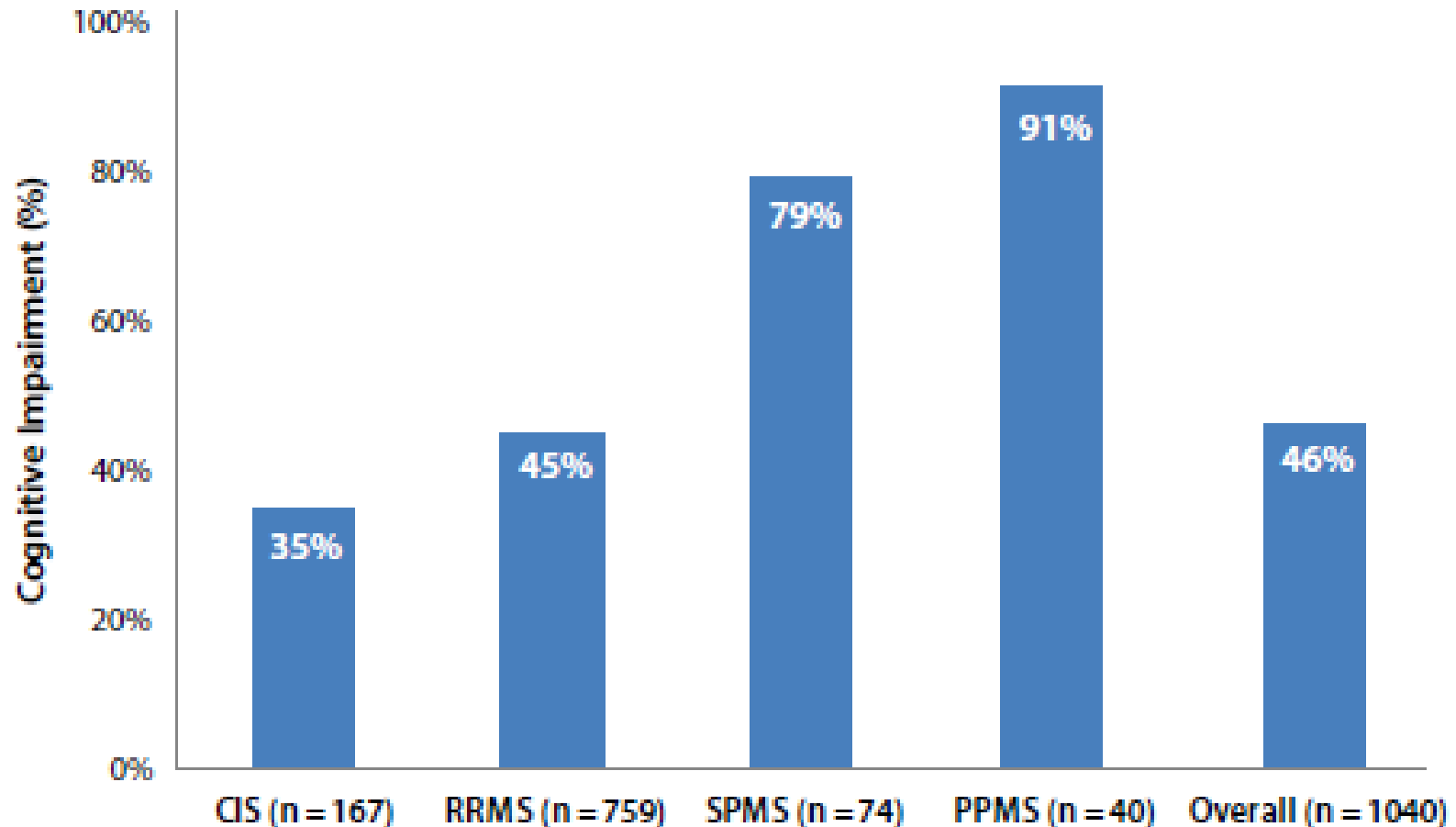
- Information processing speed/ efficiency
- Learning and Memory
- Executive functions
  - planning, organization, initiation
- Perceptual processing
- Social cognition

# Cognitive Impairment in MS



The frequency of cognitive impairment tends to increase over MS course

Figure 1: Cognitive Impairment in Patients with MS from 6 Italian Centers<sup>3</sup>



# Spared Cognition in MS

- Basic Attention
- Essential verbal skills
  - Comprehension
  - Expression
  - Naming
  - Repetition
- Intelligence

# Evolution of Cognitive Impairment in MS over 10 year period

	Initial Testing	4 year follow-up	10 year follow-up
Cognitive impairment			
None	<b>74%</b>	<b>51%</b>	<b>44%</b>
Mild	<b>8%</b>	<b>33%</b>	<b>34%</b>
Moderate	<b>18%</b>	<b>16%</b>	<b>22%</b>

# Some Factors which affect Cognition in MS

Disease Course	RR < SP
Duration of disease	Sometimes
Physical Disability	Not always
Fatigue	Not well known
Depression	It may, not always
Stress	It may, not always
Gray Matter atrophy	Strong predictor
Gender	Males at increased risk

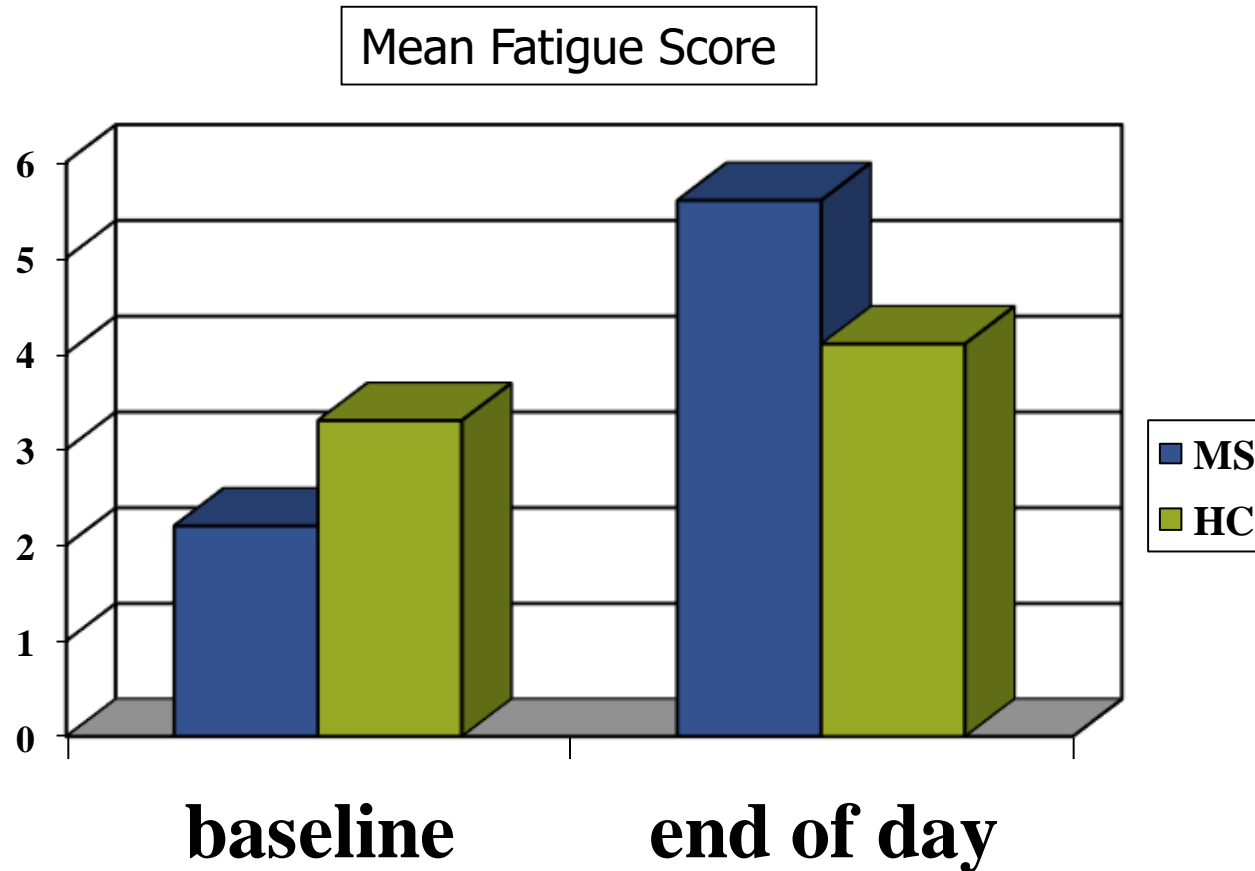
# Some Factors which Influence Neuropsychological Profiles in MS

FATIGUE



# Fatigue and Cognition

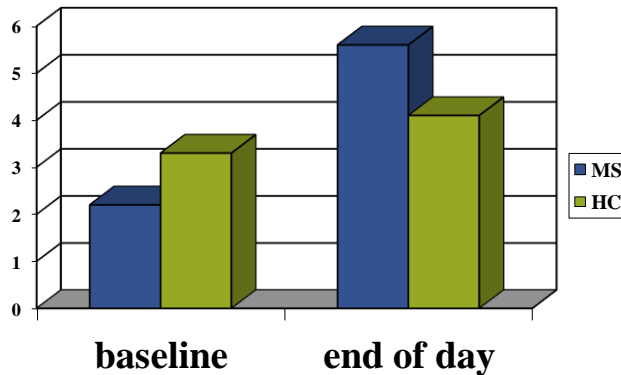
## Subjective Fatigue Across the Workday



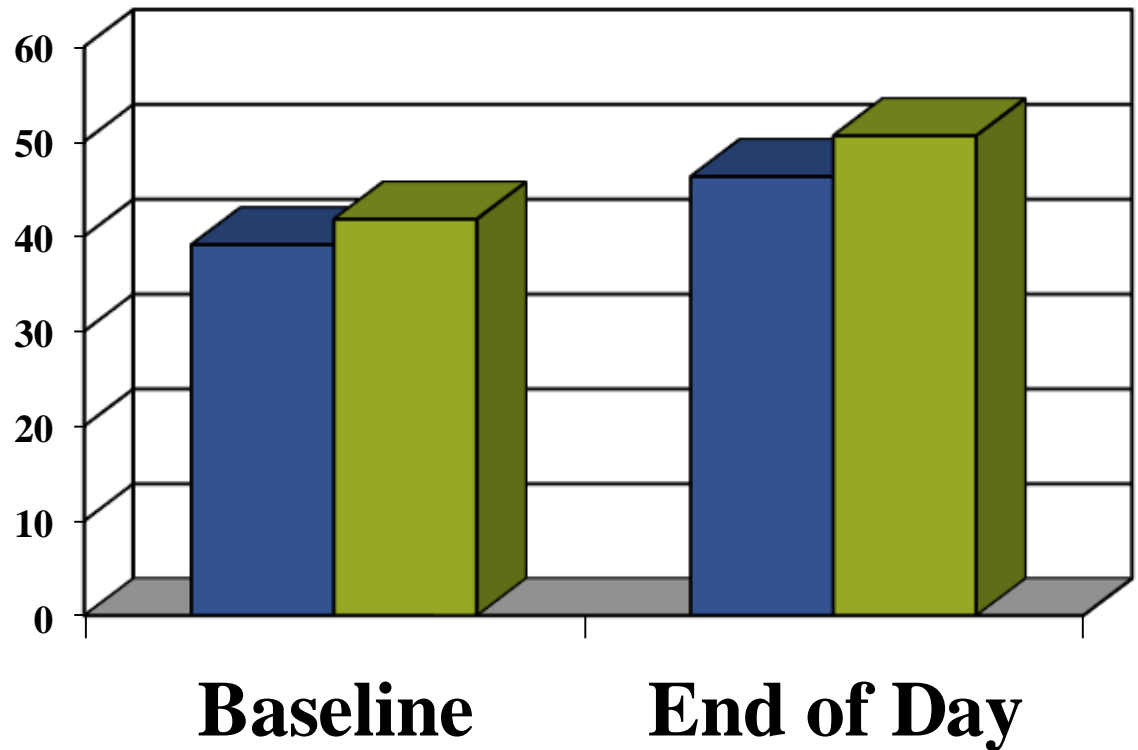
# Fatigue and Cognition

## Subjective Fatigue Across the Workday

Mean Fatigue Score



PASAT Mean Correct

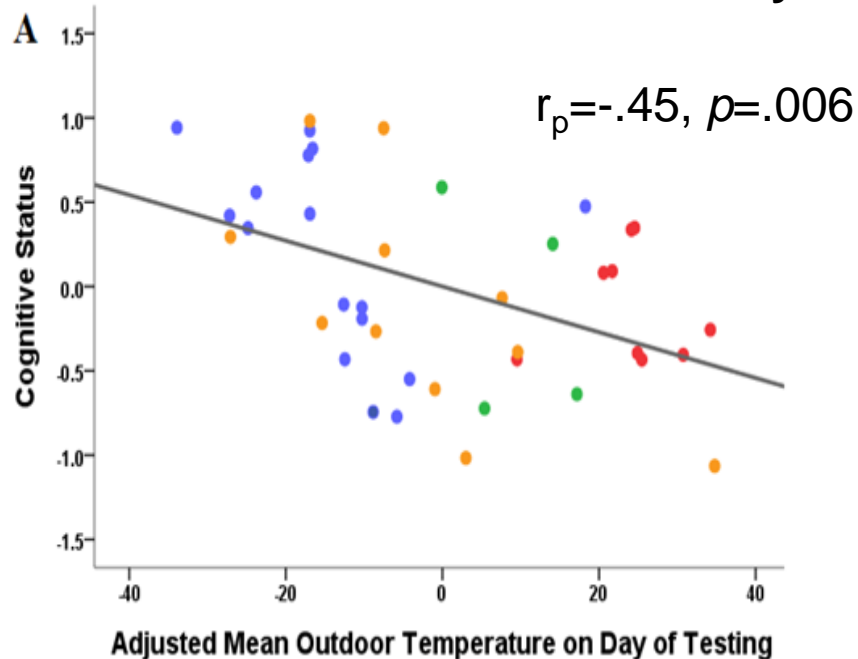


# Some Factors which Influence Neuropsychological Profiles in MS

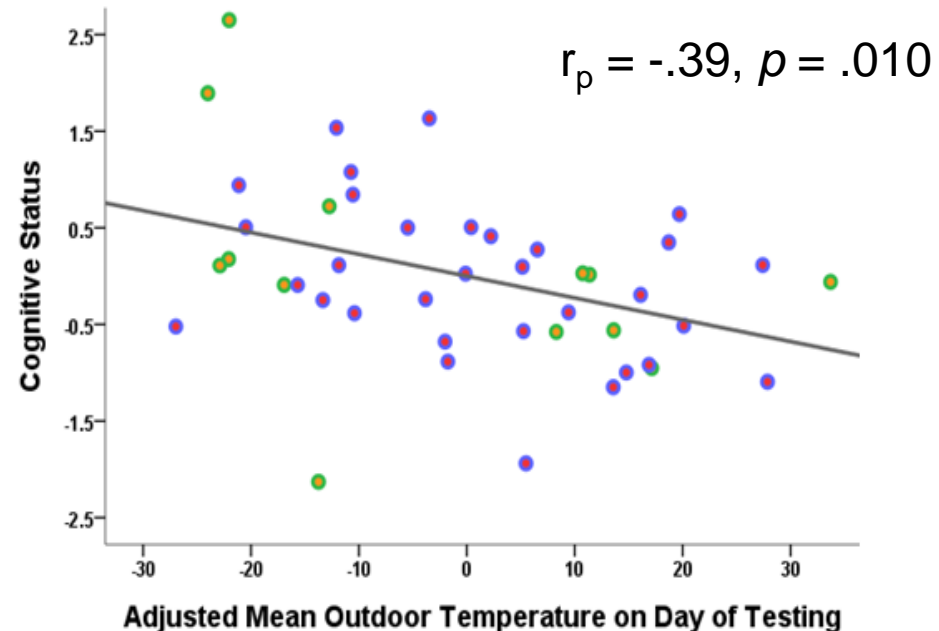
AMBIENT  
TEMPERATURE

# Association between temperature and cognitive status in MS patients

## Cross sectional Study



## Longitudinal Study



# Some Factors which Influence Neuropsychological Profiles in MS

CANNABIS

**Table 3** Cognitive test comparisons between MS cannabis users and nonusers

Cognitive domain	Cognitive test	Cannabis users, mean (SD)/n (%) Impaired	Nonusers, mean (SD)/n (%) Impaired	t or $\chi^2$	p
Learning and memory	CVLT-II immediate recall	49.5 (10.9)	52.5 (11.2)	t = -0.969	0.337
	CVLT-II long delay recall	10.6 (3.6)	11.2 (2.7)	t = -0.681	0.499
	BVMT-R total recall	22.1 (8.3)	22.8 (7.6)	t = -0.284	0.777
	BVMT-R delayed recall	8.2 (3.1)	8.7 (3.1)	t = 0.545	0.588
Verbal fluency	COWAT total score	31.0 (11.9)	33.7 (10.8)	t = -0.845	0.403
Visuospatial perception	JLO score <sup>a</sup>	23.9 (4.7)	26.7 (3.5)	t = -2.417	0.020
Executive functioning	D-KEFS sorting score	8.4 (2.4)	10.3 (2.7)	t = -2.704	0.009
	D-KEFS description score	31.4 (9.5)	37.4 (10.4)	t = -2.127	0.039
Information processing speed	PASAT 3.0	36.0 (12.0)	44.0 (11.4)	t = -2.402	0.020
	PASAT 2.0	26.1 (7.6)	35.0 (11.7)	t = -3.188	0.003
	SDMT Total	42.4 (11.4)	50.4 (12.9)	t = -2.329	0.024
Global cognitive Impairment	≤1.5 SD on 2 or more of 11 cognitive tests, n (%)	16 (64.0)	8 (32.0)	$\chi^2 = 5.128$	0.024

No group differences on psychiatric variable

“Whatever subjective benefits patients may derive from using street cannabis (e.g., pain and spasticity) should be weighed against the associated cognitive side effects”

# Some Factors which Influence Neuropsychological Profiles in MS

CIGARETTE  
SMOKING

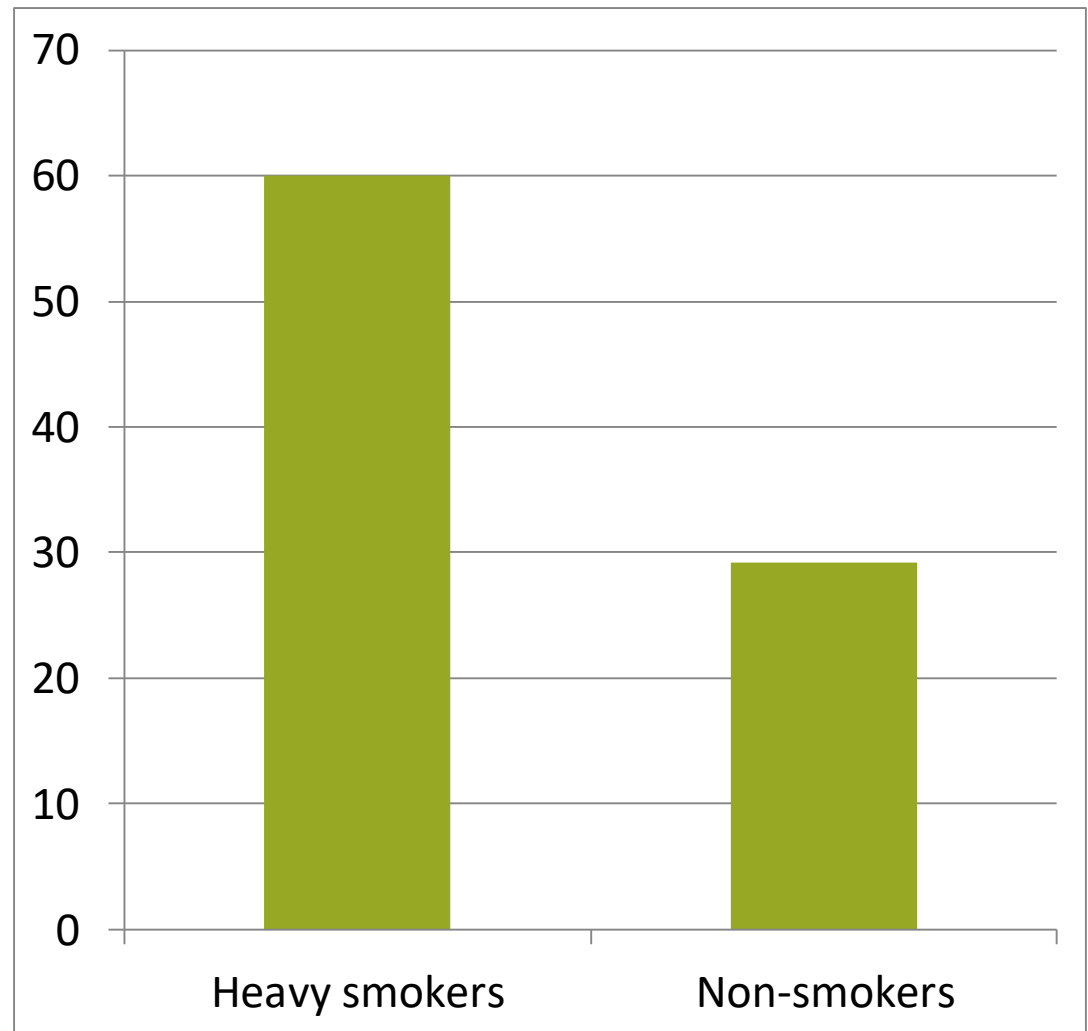


# Smoking and Cognition in MS

## Cigarette smoking:

- May trigger MS
- Facilitate transformation from CIS to MS
- Increase relapse frequency
- Promote progression of MS

## % of MS with Cognitive Impairment



*Original Research Paper*

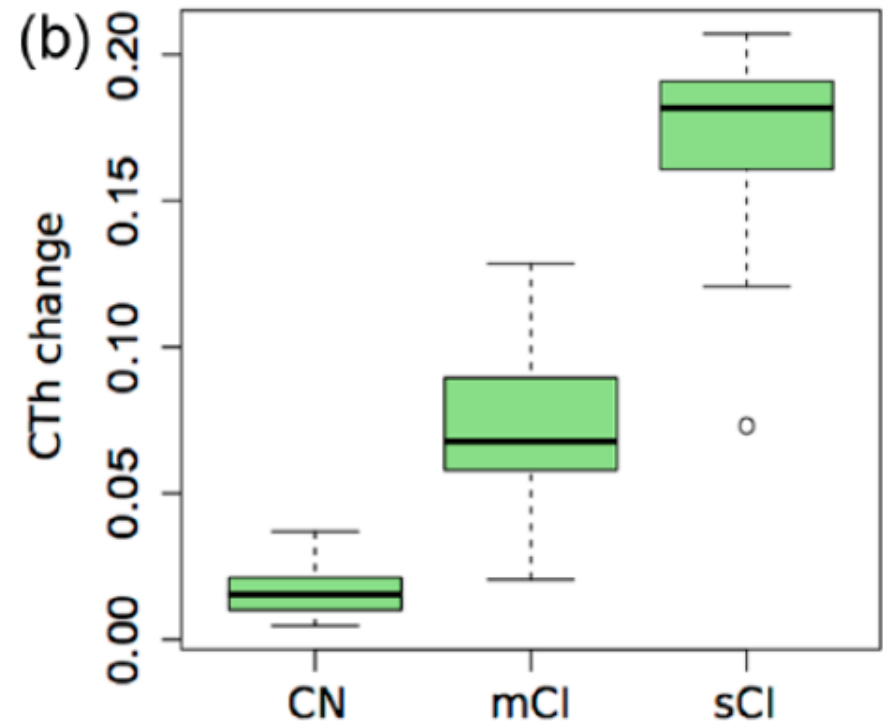
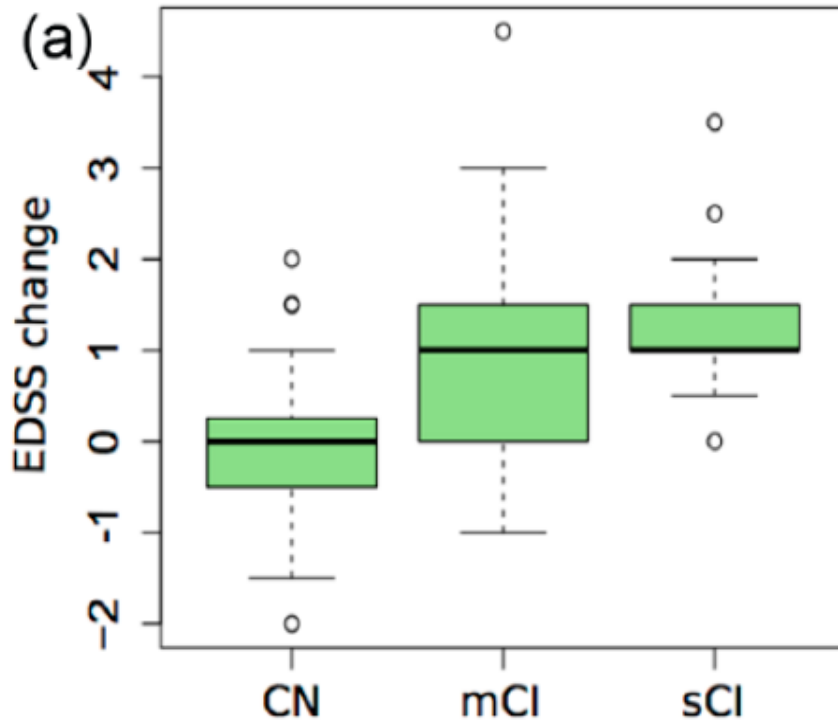
# **Cognitive impairment predicts disability progression and cortical thinning in MS: An 8-year study**

**Marco Pitteri, Chiara Romualdi, Roberta Magliozzi, Salvatore Monaco and Massimiliano Calabrese**

Cognitive Impairment at time of diagnosis is a good predictor of:

- conversion to definite MS
- disability progression
- transition to secondary progressive MS
- cortical thinning

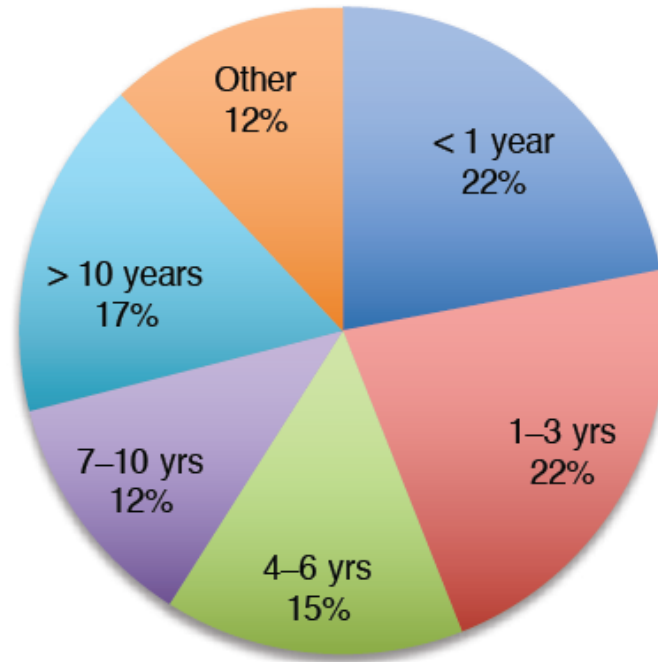
# Change in disability and cortical thinning across groups over 8 years



CN: cognitive normal  
mCI: mild cognitive impairment  
sCI: severe cognitive impairment  
cTh: cortical thinning

# 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**



59% not working  
5 years post dx

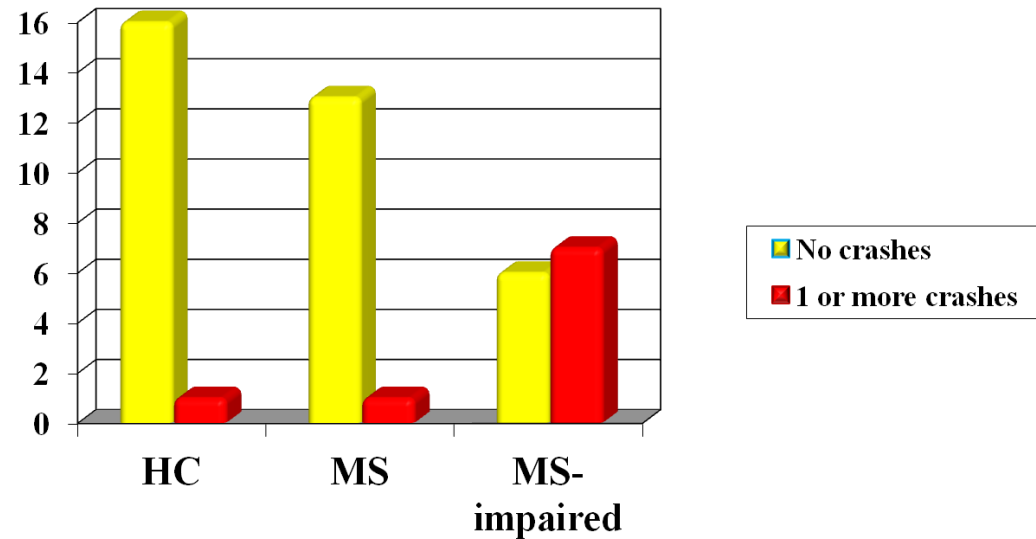
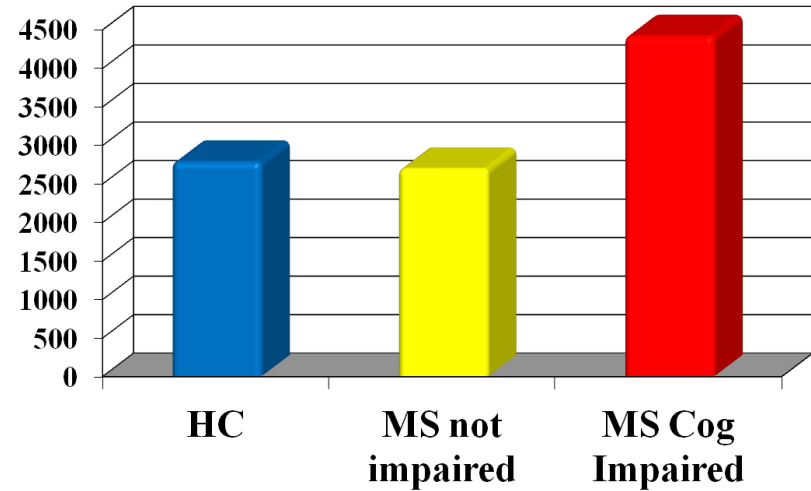
**Figure 4.**

**Number of years after diagnosis before people with MS stopped working\***

\*People with MS who are not currently employed

Source: MS International Foundation. Global MS Employment Report 2016. Available at: <http://www.ms-sep.be/userfiles/files/MSEmploymentReport2016.pdf>

# VR-Driving System



# Assessing Cognitive Impairment in MS

- Neurologist judgment poorly associated with actual cognitive impairment
  - No greater than chance
    - Romero, Shammi & Feinstein, (2015), *Mult Scler Relat Disord*. Jul;4(4):291-5
    - Peyser et al (1980) *Arch Neurol*, 37, 577-9
- Clinical interview and neurological exam not sufficient
- What about patient self report?

# How to Assess Cognition?

- 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



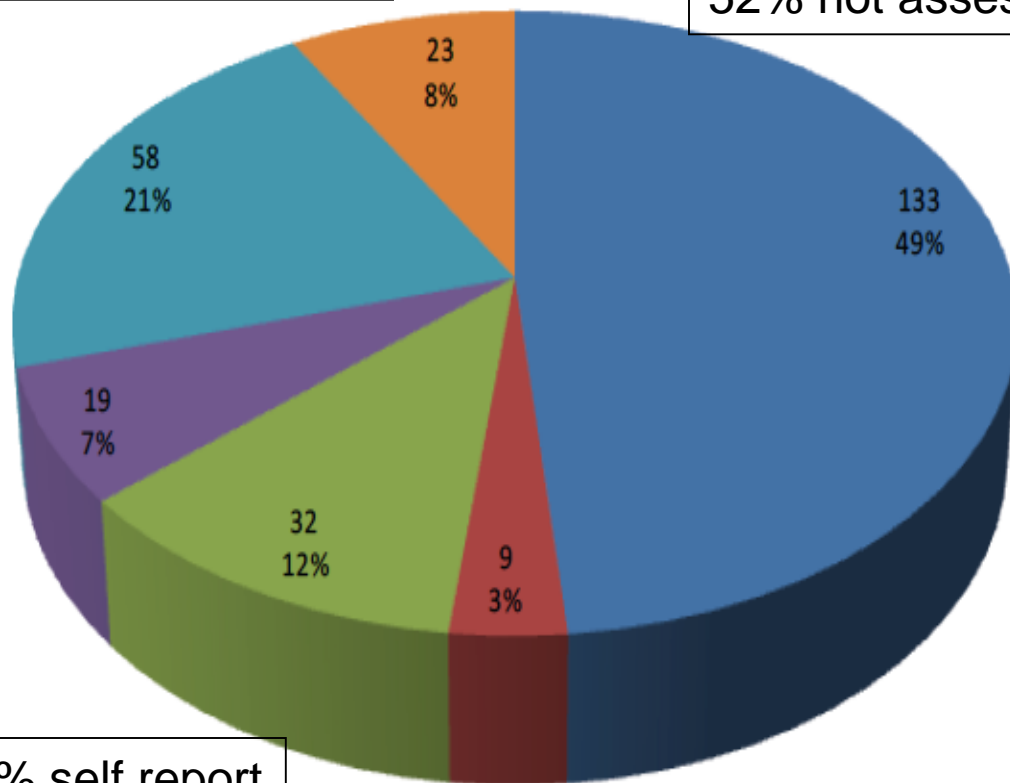
# CMSC Member Survey on Cognitive Screening Practices

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.

## Respondents

29% formal testing

52% not assessed



- There is no formal procedure but clinicians are very attuned to symptoms and signs of cognitive impairment and routinely assess and query patients
- There is no formal procedure and little specific attention to the problem by clinicians
- Self-report instruments such as the Multiple Sclerosis Neuropsychological Questionnaire
- Informant-report instruments such as the Multiple Sclerosis Neuropsychological Questionnaire
- Cognitive Performance tests such as the PASAT or Symbol Digit Modalities Test
- Cognitive Performance tests administered with computer

19% self report

Source: Foley FW et al. *Int J MS Care*. 2012;14:58-64.

# Overview

- Cognitive problems in MS
  - Factors affect cognition
  - Impact on Everyday Life

## –**Key Cognitive problems**

- Can we improve cognitive problems?
- Cognitive Reserve and MS
- Exercise
- Medication

# Information Processing Efficiency

Processing speed  
Working Memory

# From Persons with MS

“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”

# Speed of Processing Defined

- **Amount of time to complete a given amount of work**

**OR**

- **Work completed given a limited amount of time**

# WM Defined

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**temporary storage and active  
maintenance and manipulation of  
thinking for on-line use**

**(Baddeley, 2000)**

# Risk Estimates (Odds Ratios)

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**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

All MS vs. Controls

	<b>Odds Ratio</b>
Processing Speed Index	10.4
Working Memory Index	2.7

RRPM vs. Controls

	<b>Odds Ratio</b>
Processing Speed Index	5.3
Working Memory	1.3

SMPM vs. Controls

	<b>Odds Ratio</b>
Processing Speed Index	65.2
Working Memory Index	9.0



# 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**

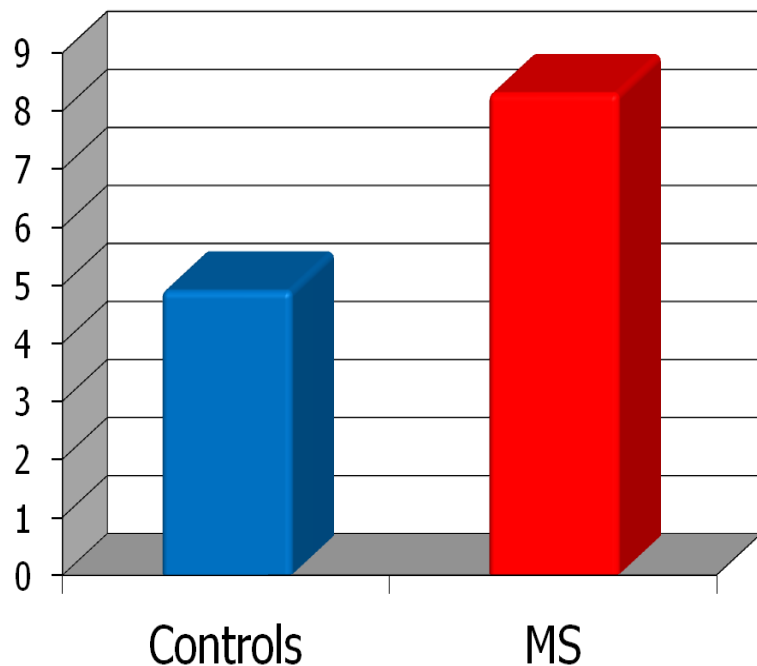
# Identifying the Cause

- Retrieval failure hypothesis ?
- Acquisition deficits?

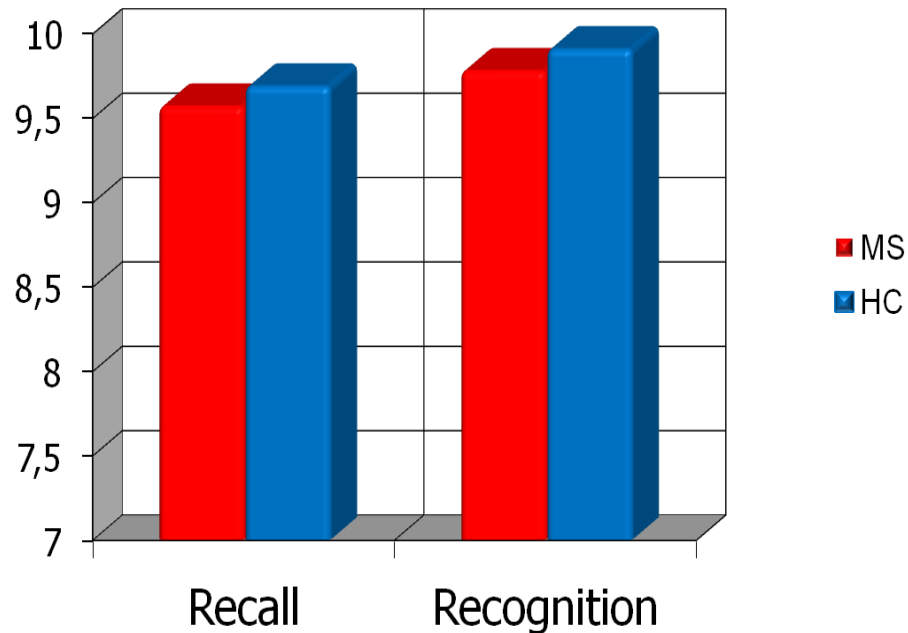
Train subjects to a learning criterion

# SRT Trials to Criterion

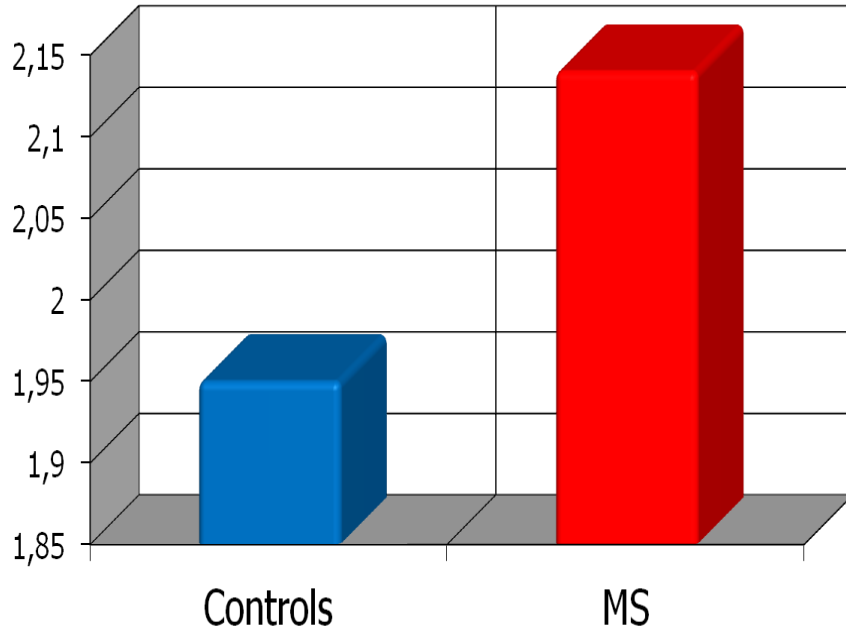
Trials To Criterion



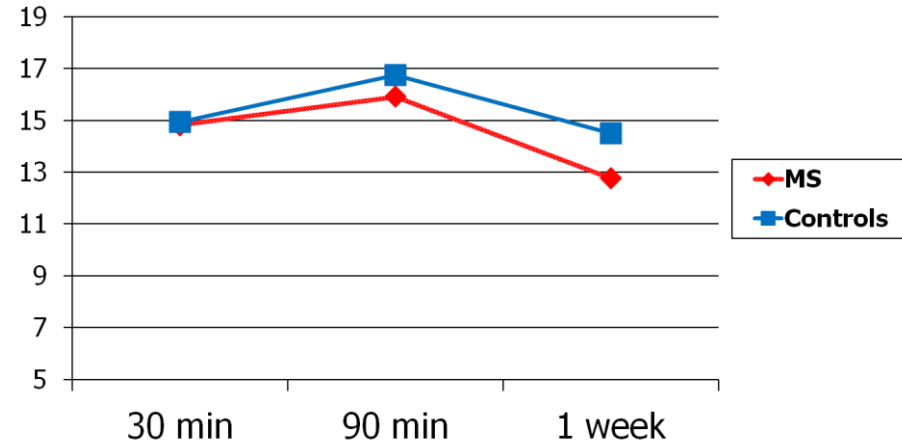
Recall and Recognition



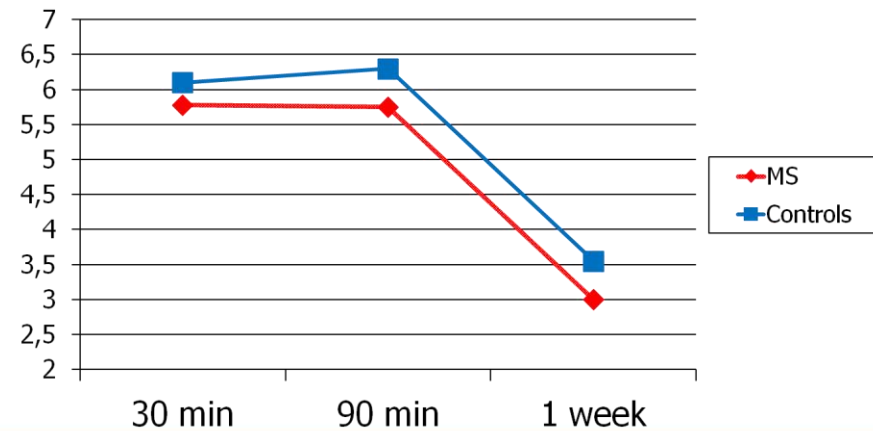
### Logical Memory: Trials to Criterion



### Logical Memory: Delayed Recall



### Paired Associate Learning: Delay Recall



# Learning and Memory in MS

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



# Overview

- Cognitive problems in MS
  - Factors affect cognition
  - Impact on Everyday Life
  - Key Cognitive problems
- **Can we improve cognitive problems?**
- Cognitive Reserve and MS
- Medication

What can we do to improve  
cognition?

**Cognitive Rehabilitation**  
Learning and Memory



## Memory rehabilitation for people with multiple sclerosis (Review)

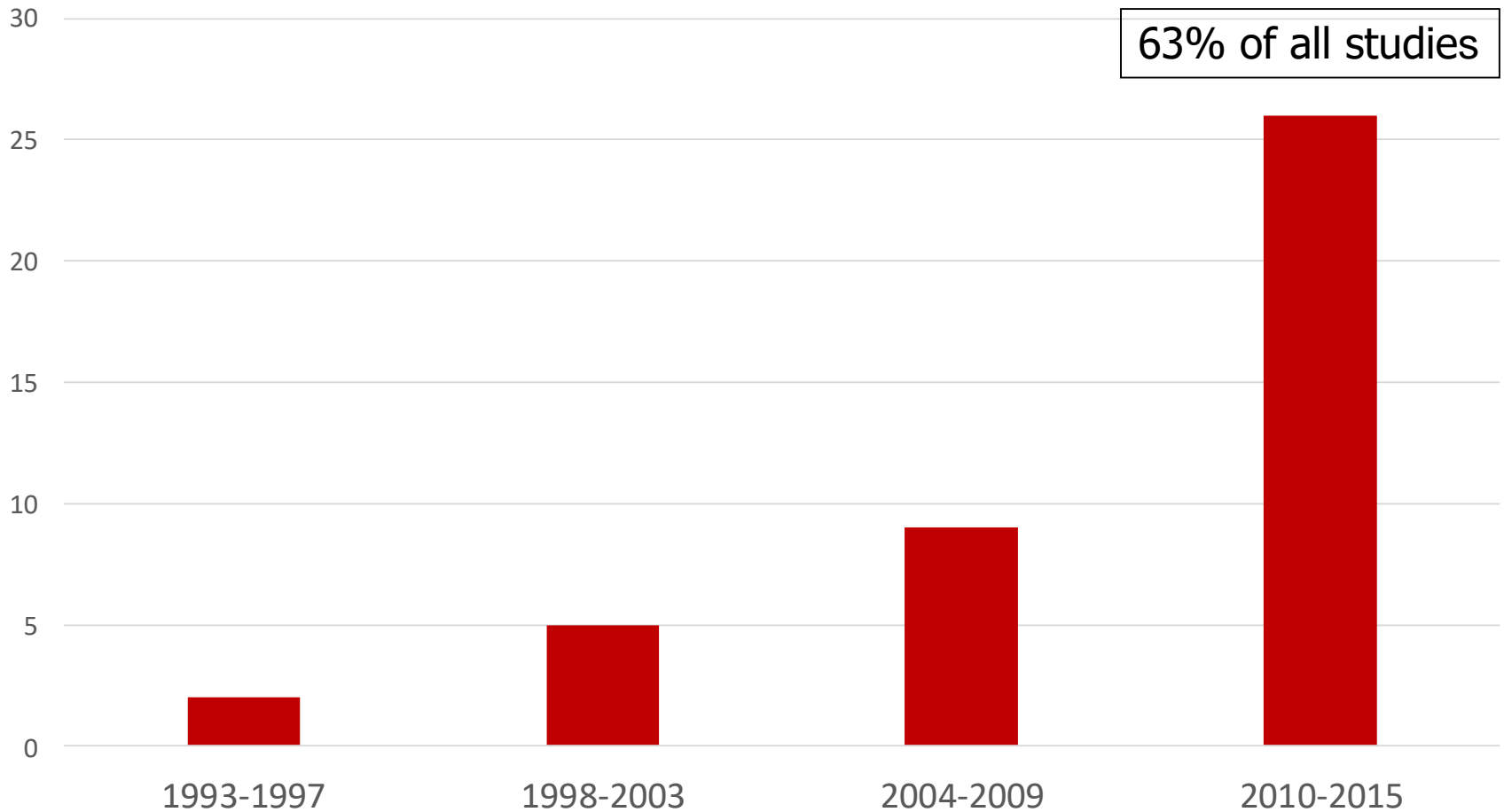
das Nair R, Martin KJ, Lincoln NB

15 studies  
989 persons with MS

Significant effect of memory intervention on:

Objective assessments of immediate and long term follow-up  
QOL in immediate follow-up

# Cognitive Rehabilitation Studies



# 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

Max-Planck-Institut für Bildungsforschung  
Max Planck Institute for Human Development

October 20, 2014



### **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.

<https://www.ftc.gov/news-events/press-releases/2016/01/lumosity-pay-2-million-settle-ftc-deceptive-advertising-charges>

# 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 performance
- 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

	<b>Support</b>
Interferons	<b>1 of 3</b>
Acetylcholinesterase Inhibitors	<b>2 of 6</b>
L-amphetamine	<b>2 of 3</b>
Other agents	<b>2 of 8</b>

# 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
  - Its time MS patients get treated
- Can we build a cognitive reserve?
- Exercise
- Medication

# THANK YOU

## Acknowledgments

Nancy Chiaravalloti, Ph.D.

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Helen Genova, Ph.D.

Victoria Leavitt, Ph.D.

Ekaterina Dobryakova, Ph.D.



# IMPROVING COGNITIVE, EMOTIONAL & PHYSICAL HEALTH

## An Educational Conference for People with Multiple Sclerosis



# Cognitive Rehabilitation

Nancy D. Chiaravalloti, PhD

Director of Neuroscience and Neuropsychology  
Kessler Foundation  
Research Professor, Physical Medicine and Rehabilitation  
Rutgers-New Jersey Medical School



# OUTLINE

- The Literature
- Other ongoing work at Kessler Foundation
  - Processing Speed
  - Executive Functioning
    - Wonderkins





# The Literature

- Recent Systematic Review (2017)
  - Examined CR literature by cognitive domain
  - Since 2007 – substantial progress

Domain	# of studies	Comment
Attention	3 studies	1 practice standard; 1 option
Learning and Memory	15 studies	1 practice standard; 4 options
Processing Speed	4 studies	
Executive Functions	2 studies	
Non-specific & Multiple	14 studies	1 practice guideline
Metacognition	2 studies	

# The Literature

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Processing Speed	4 studies	
Executive Functions	2 studies	
Non-specific & Multiple	14 studies	1 practice guideline*
Metacognition	2 studies	

# Attention

**3 studies**

**1 practice standard: APT**

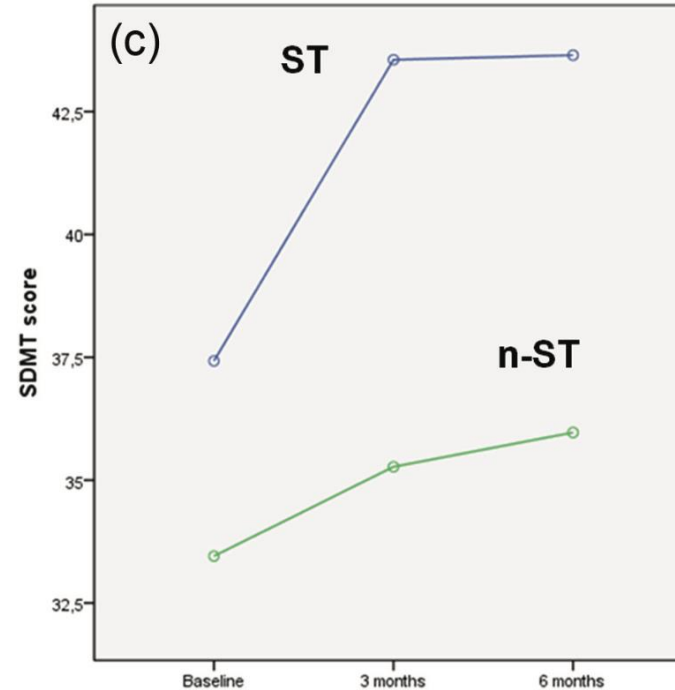
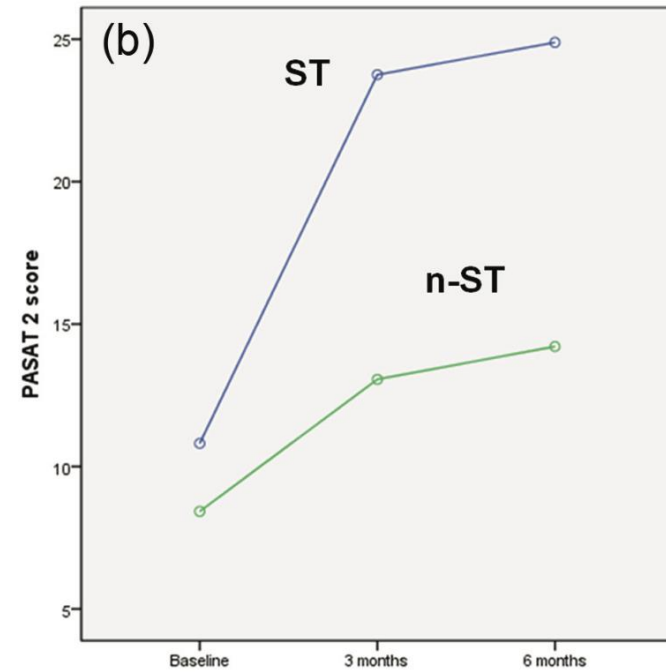
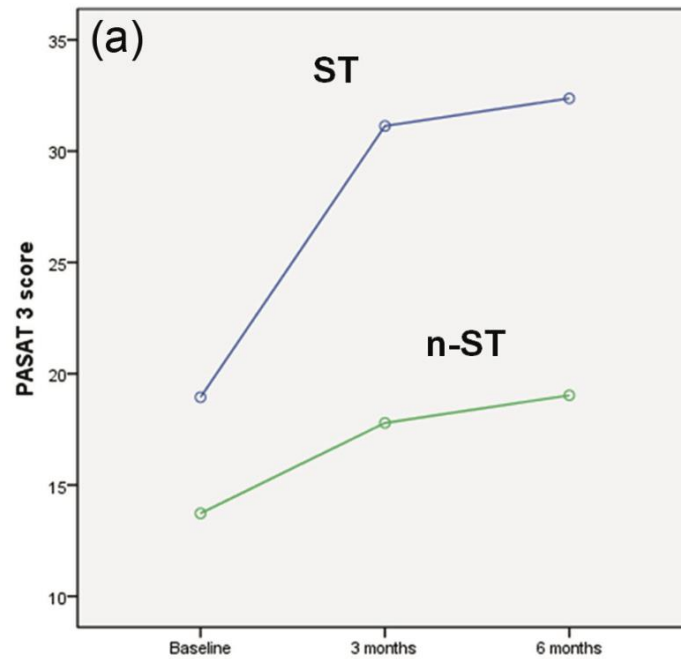
**1 option: RehaCom**

# Attention

## *Attention Process Training (APT)*

## APT Group:

Increase on 3 tests requiring attention



# Attention

**3 studies**

**1 practice standard: APT**

**1 option: RehaCom**

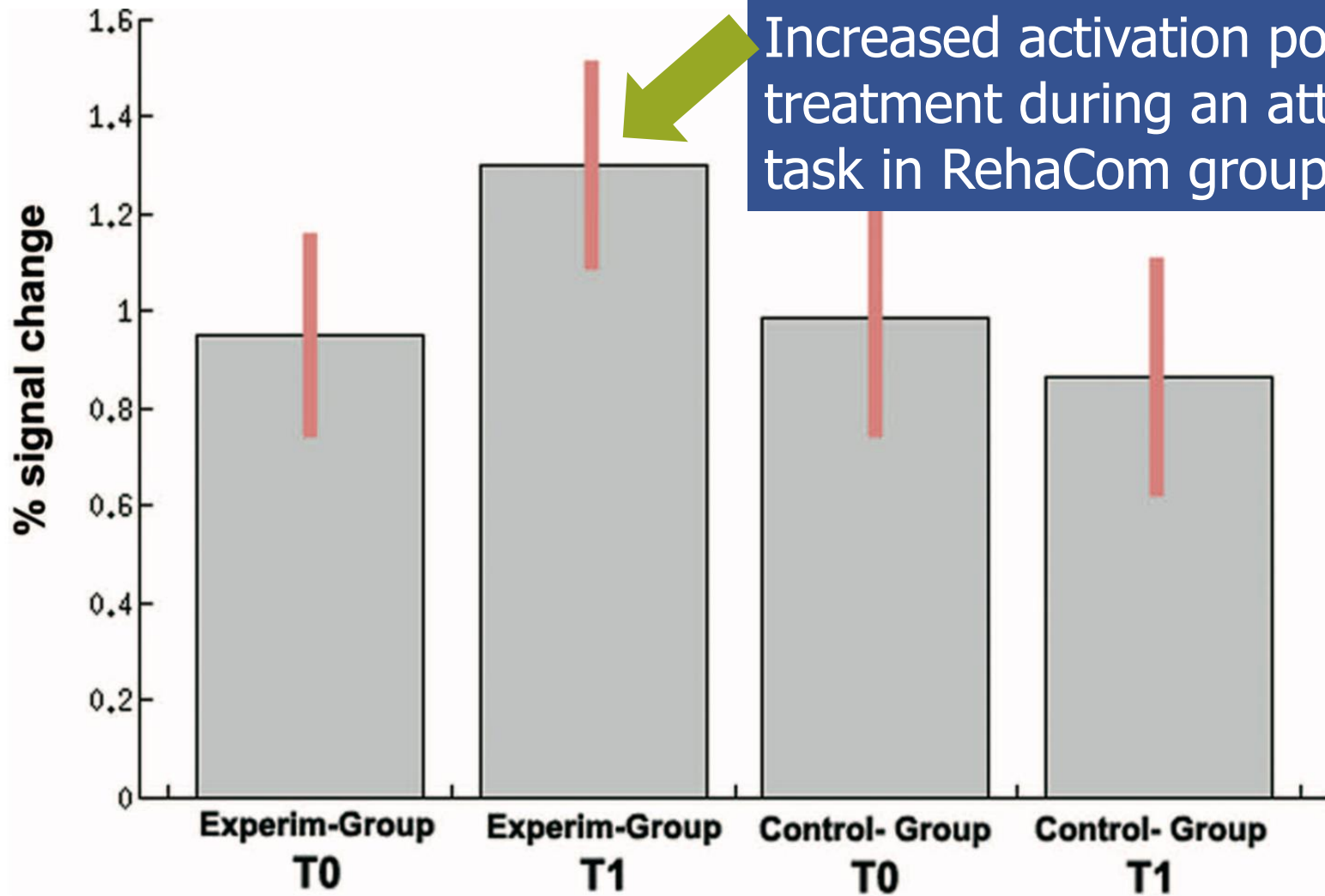
# Attention

## *RehaCom*

*Multiple modules available*

*practice option for treating attention*  
*practice guideline for other cognitive domains*  
*(executive functioning)*

# RehaCom





# Learning and Memory

**15 studies**

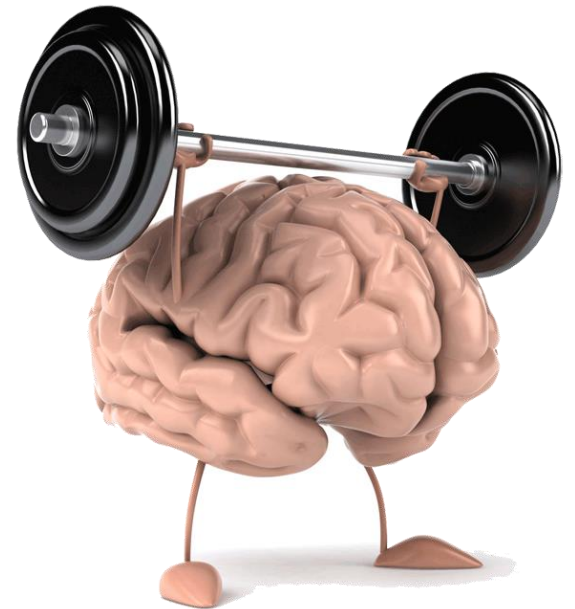
**1 practice standard: mSMT**

**4 options:**

- **Imagery (basis of mSMT)**
- **Music**
- **Self-generation**
- **Spaced trials**

# Learning and Memory

mSMT



# Treating learning impairments improves memory performance in multiple sclerosis: a randomized clinical trial†

Nancy D Chiaravalloti<sup>1,2,2</sup>, John DeLuca<sup>1,2,3</sup>, Nancy B Moore<sup>3</sup> and Joseph H Ricker<sup>2,2</sup>  
<sup>1</sup>Kessler Medical Rehabilitation Research and Education Corporation, 1199 Pleasant Valley Way, West Orange, NJ 07052, USA; <sup>2</sup>UMDNJ-New Jersey Medical School, Department of Physical Medicine and Rehabilitation, Newark, NJ, USA; <sup>3</sup>UMDNJ-New Jersey Medical School, Department of Neurosciences, Newark, NJ, USA

## ARTICLES

# An RCT to treat learning impairment in multiple sclerosis

The MEMREHAB trial



Nancy D. Chiaravalloti,  
PhD

Nancy B. Moore, MA  
Olga M. Nikelshpur, PhD  
John DeLuca, PhD

## ABSTRACT

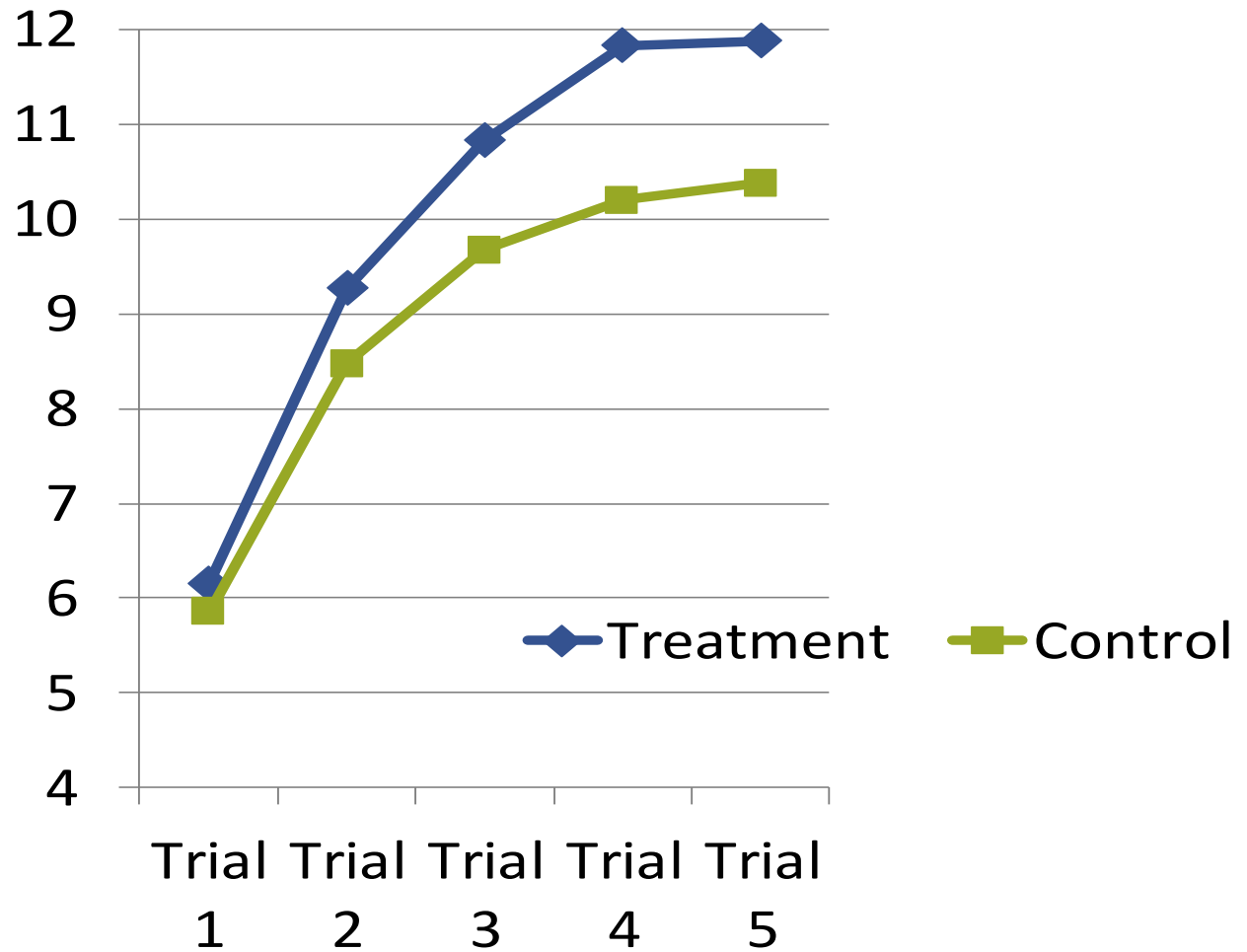
**Objective:** To examine the efficacy of the modified Story Memory Technique (mSMT), a 10-session behavioral intervention teaching context and imagery to facilitate learning, to improve learning and memory abilities in persons with multiple sclerosis (MS).

**Methods:** This double-blind, placebo-controlled, randomized clinical trial included 86 participants

# Can context and imagery facilitate learning?

- **Memory Retraining Treatment Protocol**
  - Randomized Control Trial
  - Modified Story Memory Technique (mSMT)
  - 10 sessions
    - ✓ 2 times per week for 5 weeks
    - ✓ 30 to 90 minutes in duration
- **Does it work?**
  - Assessments before and after treatment
  - Neuropsychological assessment, neuroimaging, assessment of daily life

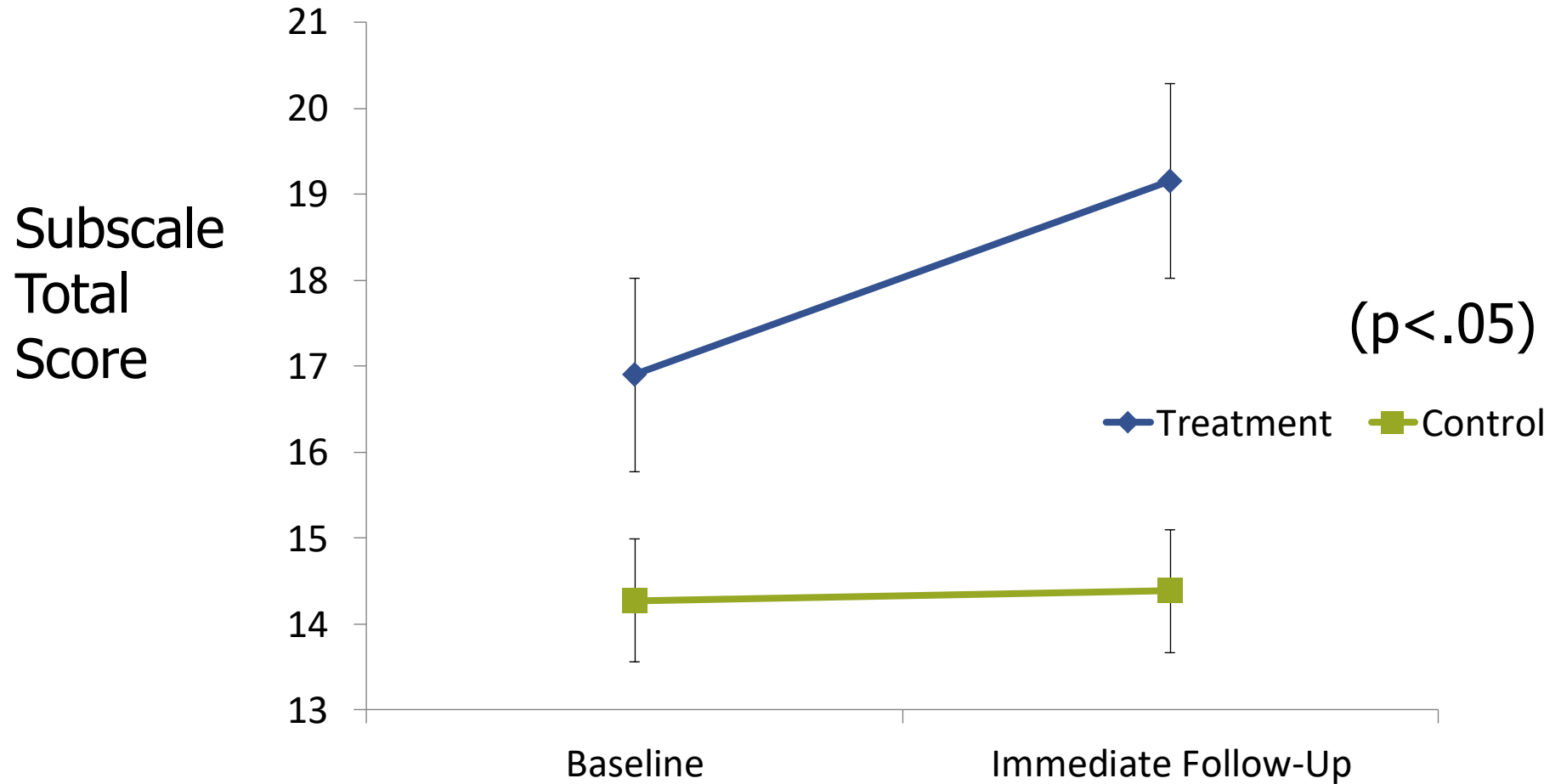
# Learning by Group



CVLT  
Learning  
Trials

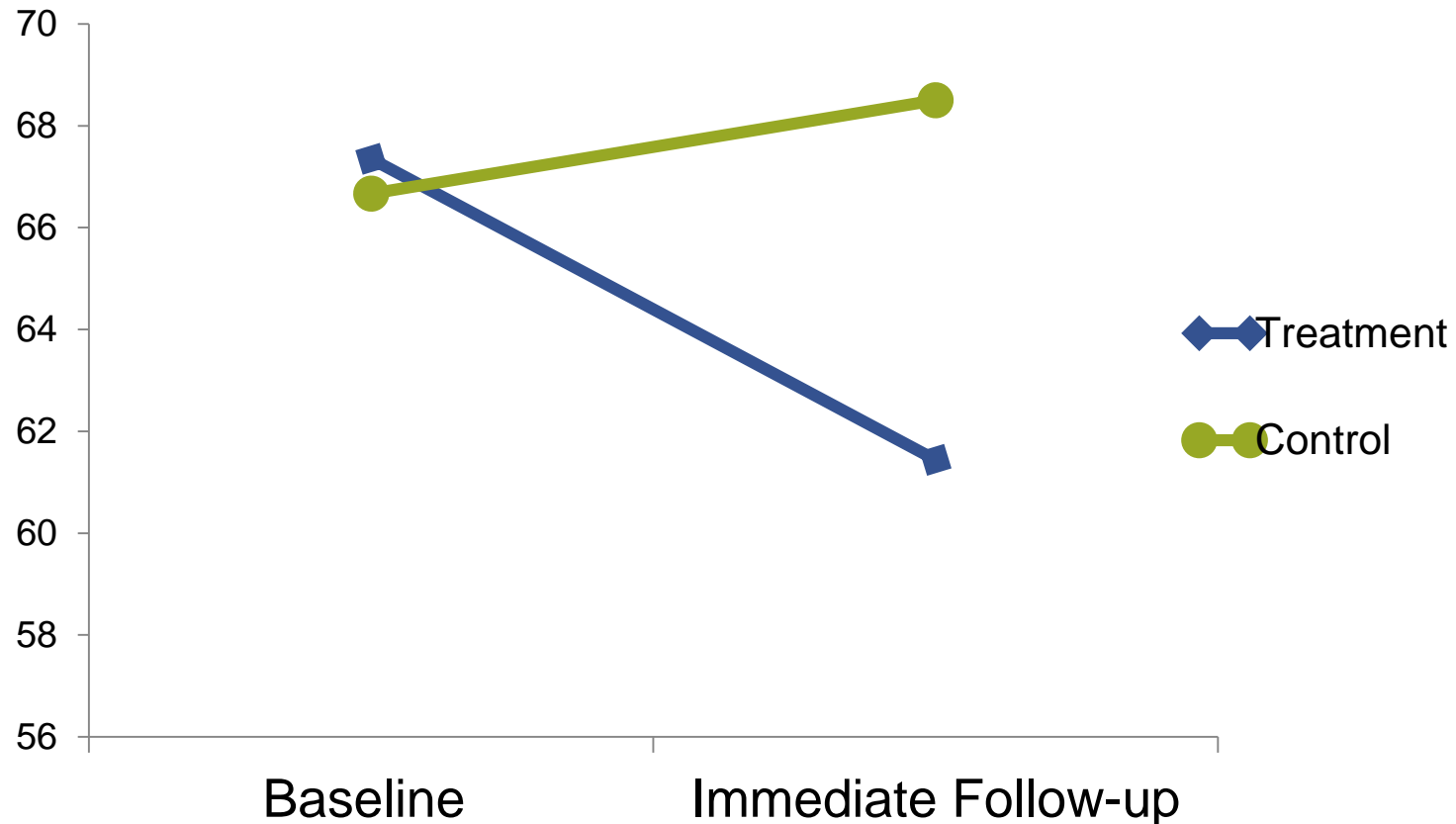
# Everyday Life Self-Report

## FAMS General Contentment



# Family Report of Daily Life

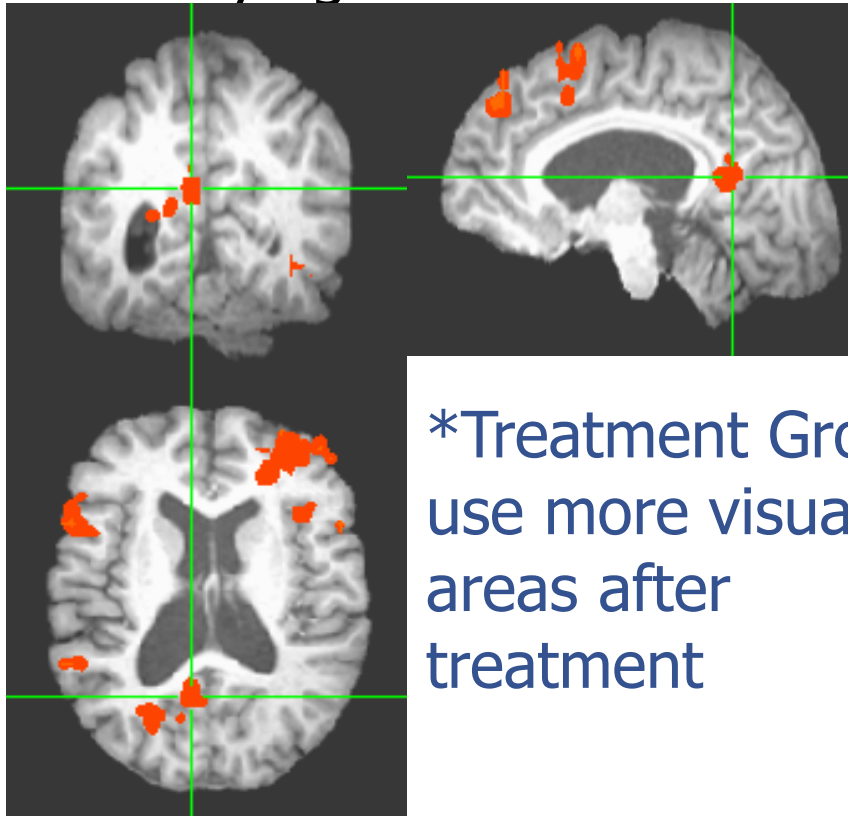
FrSBe Total Score, Family Form



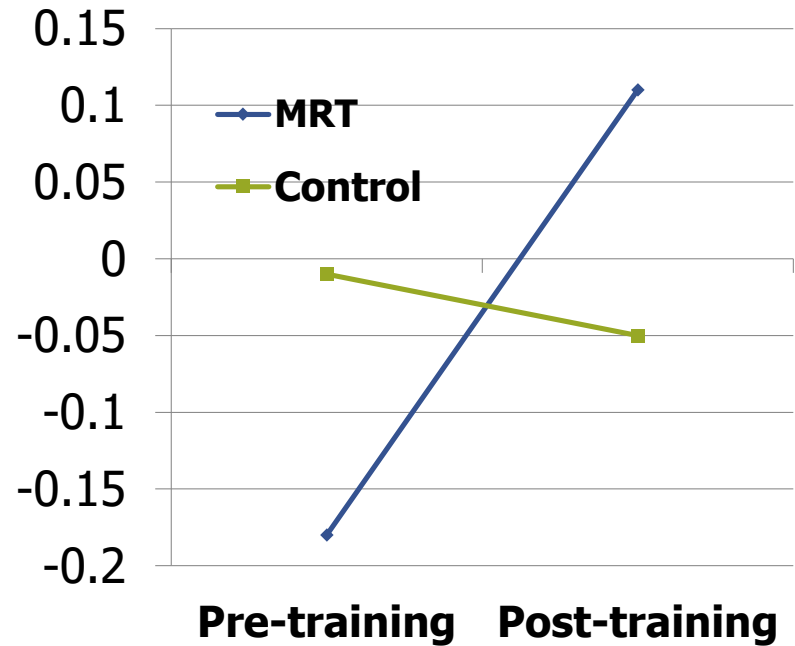
# Changes on Functional MRI Scans

## *Before and After mSMT treatment*

fMRI shows increased activity after treatment only in areas underlying the treated function

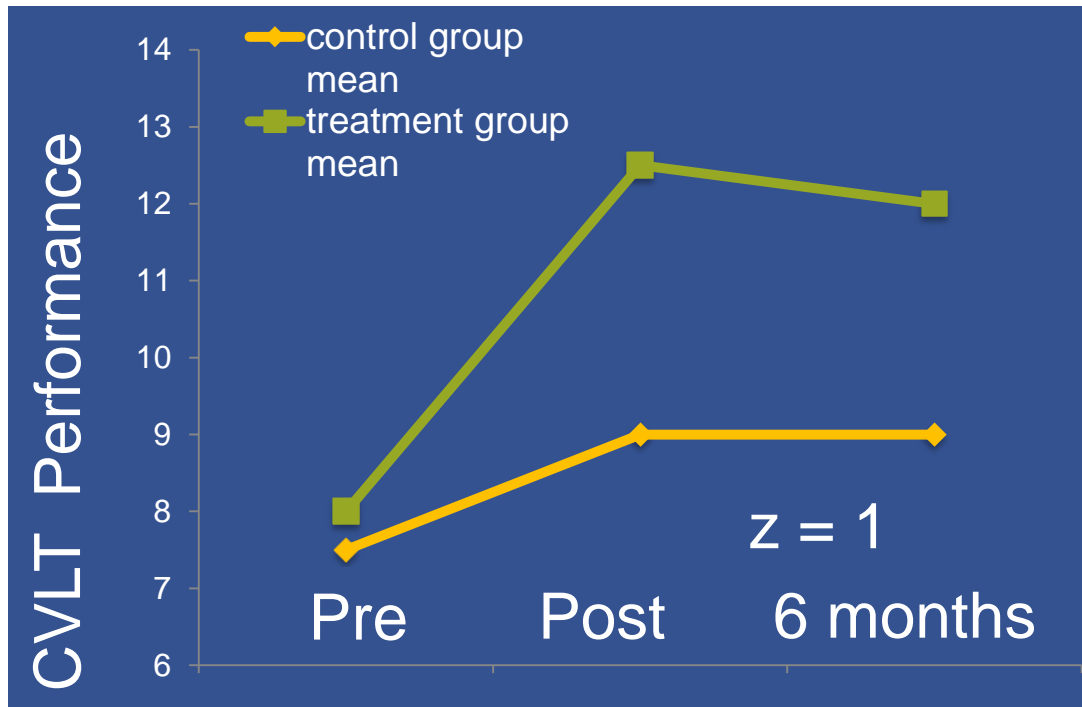


\*Treatment Group use more visual areas after treatment

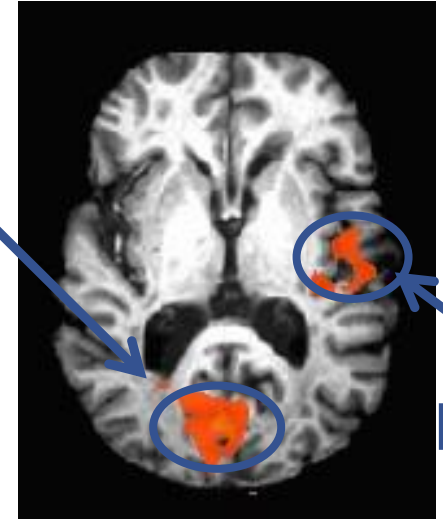




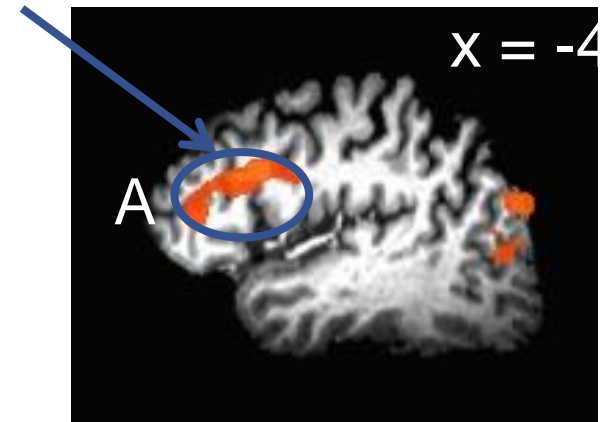
# mSMT Long-Term Effects



Occipital Gyrus



MFG



# Learning and Memory

15 studies

1 practice standard: mSMT

4 options:

- Imagery (basis of mSMT)
- **Music**
- Self-generation
- Spaced trials

# Learning and Memory

## *Music*

2 studies by same group



# Music mnemonics aid verbal memory and induce learning – related brain plasticity in multiple sclerosis

Michael H. Thaut<sup>1\*</sup>, David A. Peterson<sup>2,3</sup>, Gerald C. McIntosh<sup>4</sup> and Volker Hoemberg<sup>5</sup>

<sup>1</sup> Center for Biomedical Research in Music, Colorado State University, Fort Collins, CO, USA

<sup>2</sup> Computational Neurobiology Laboratory, Salk Institute for Biological Studies, La Jolla, CA, USA

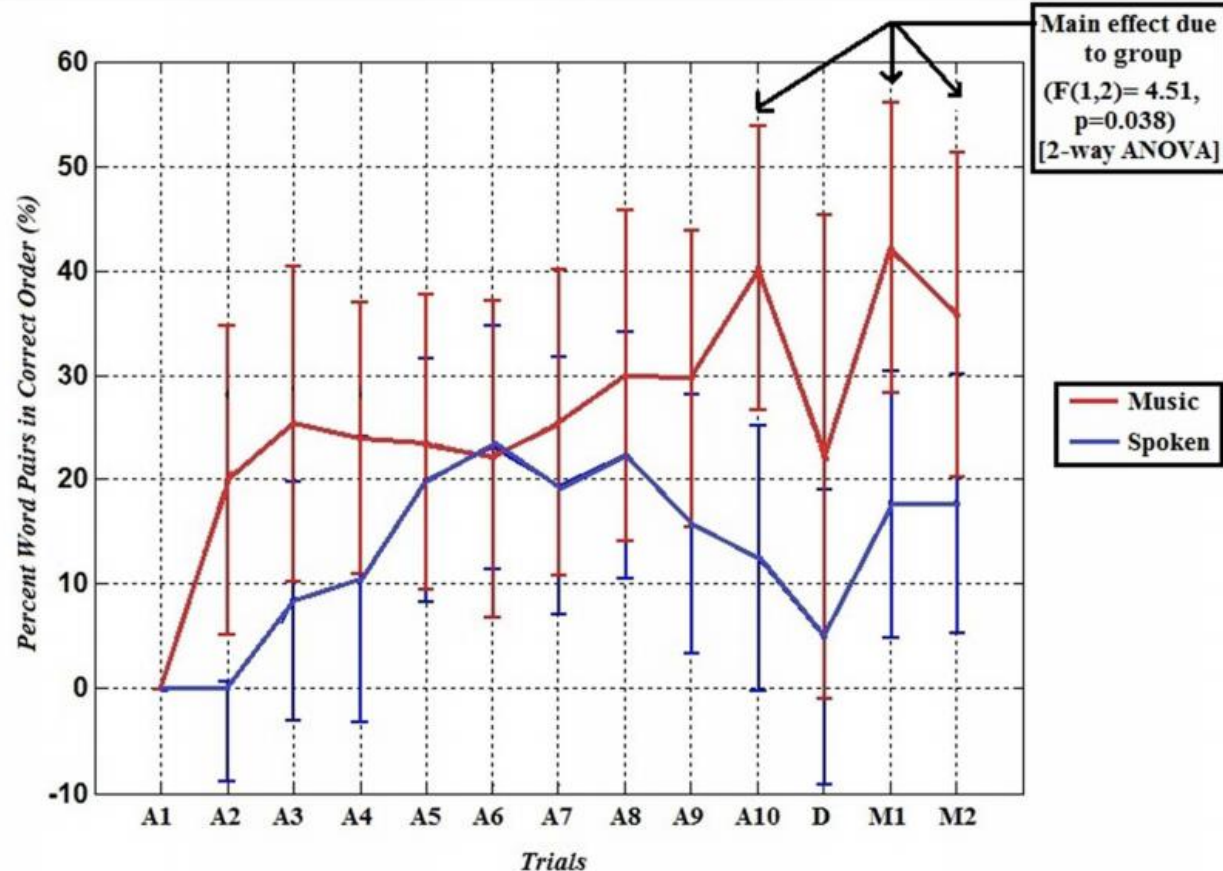
<sup>3</sup> Institute for Neural Computation, University of California San Diego, La Jolla, CA, USA

<sup>4</sup> Department of Neurology, University of Colorado Health, Fort Collins, CO, USA

<sup>5</sup> Department of Neurology, SRH Rehabilitation Hospital Bad Wimpfen, Bad Wimpfen, Germany

*Spoken vs sung*  
list of words.

Sung: recalled  
more word and  
had more  
frontal activity



# Learning and Memory

**15 studies**

**1 practice standard: mSMT**

**4 options:**

- **Imagery (basis of mSMT)**
- **Music**
- **Self-generation**
- **Spaced trials**

# Learning and Memory

Self-generation  
& Spaced Learning

**STEM**

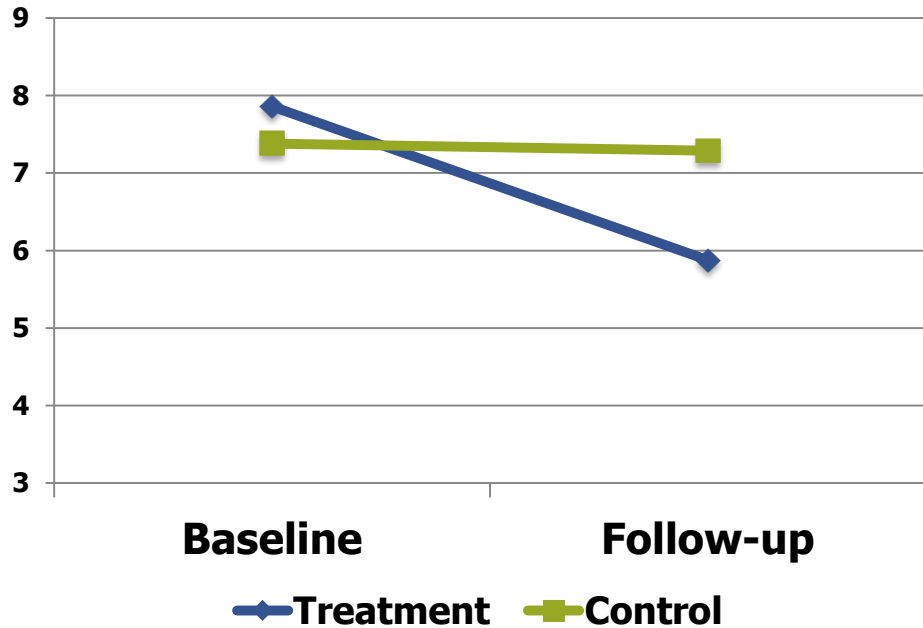
# Strategy-based Treatment to Enhance Memory (STEM)

- Teaches persons and significant others how to apply novel techniques in daily life
- Teaching application of:
  - Generation effect
  - Spacing effect
  - Testing effect
- 8 session treatment protocol for:
  - Persons with MS
  - Significant Other

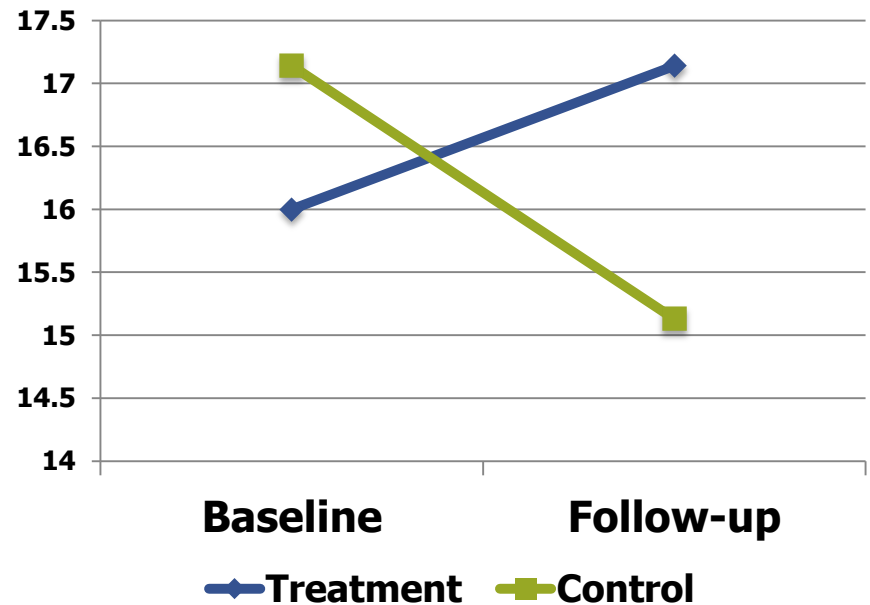


# STEM Results

## Perceived Deficits



## Quality of Life





# OUTLINE

- The Literature
- Other ongoing work at Kessler Foundation
  - Processing Speed
  - Executive Functioning
    - Wonderkins



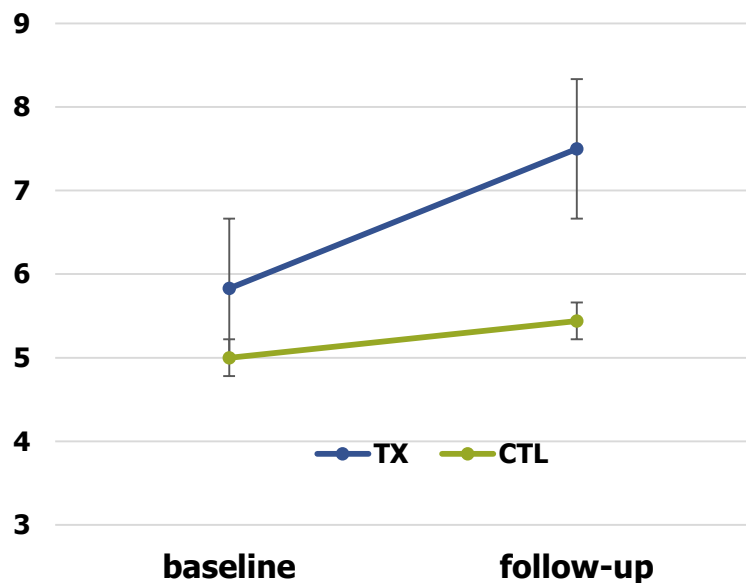
# Speed of Processing Training

- 10 session computerized PS treatment
  - Laptop administration
  - Highly manualized
  - Used extensively in normal aging
- 3 levels: 1) single discrimination
  - 2) discrimination task with peripheral target
  - 3) discrimination task with peripheral target embedded among distractors

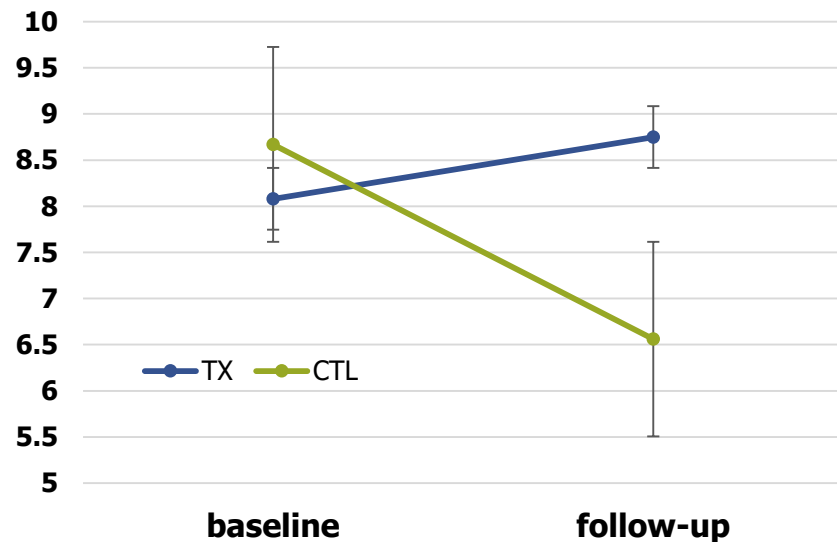


# Speed of Processing Training RESULTS

## Processing Speed (Coding)

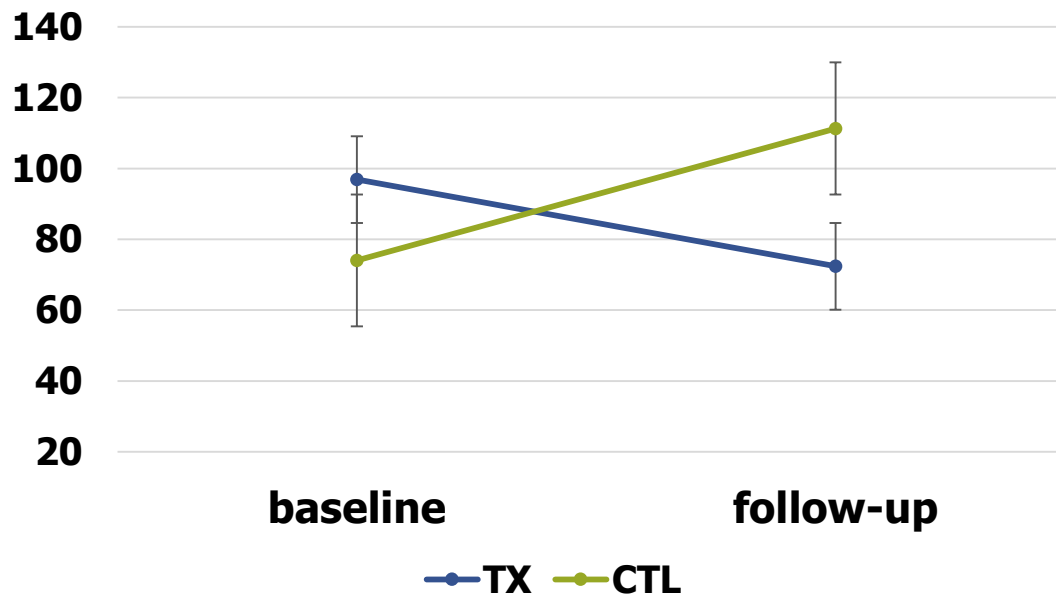


## Memory (CVLT)



# Speed of Processing Training RESULTS

## Daily Living (TIADL)



# OUTLINE

- The Literature
- Other ongoing work at Kessler Foundation
  - Processing Speed
  - Executive Functioning
    - Wonderkins



# Wonderworks: More engaging Cog Rehab?

Development grant....

Uses Virtual Reality to make  
cognitive rehabilitation more  
engaging

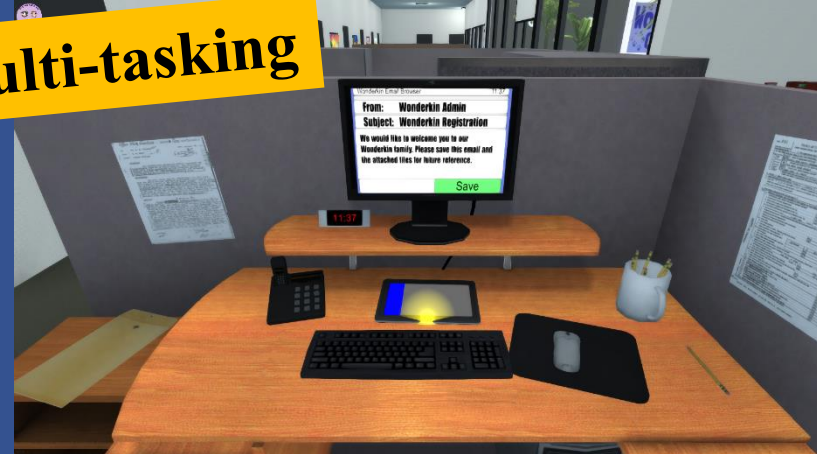
Focuses on executive functioning  
-Task switching  
-multitasking

# Virtual Reality & Cognitive Rehab

## Task Switching



## Multi-tasking



## Task Switching



## Multi-tasking



# Collaborators

John DeLuca, PhD

Yael Goverover, PhD

Glenn Wylie, D.Phil

Ekaterina Dobryakova, PhD

Helen Genova, PhD

Lauren Strober, PhD

Denise Krch, PhD

Silvana Costa, PhD

Nancy Moore, MA

Angela Smith, MA



# Funding Sources



# IMPROVING COGNITIVE, EMOTIONAL & PHYSICAL HEALTH

## An Educational Conference for People with Multiple Sclerosis



# Staying Cognitively Active

John DeLuca, PhD, ABPP

Senior Vice President for Research  
Kessler Foundation

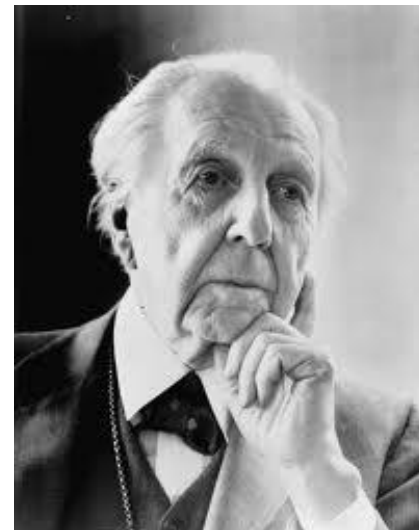
Professor, Physical Medicine and Rehabilitation  
Rutgers-New Jersey Medical School



# Overview

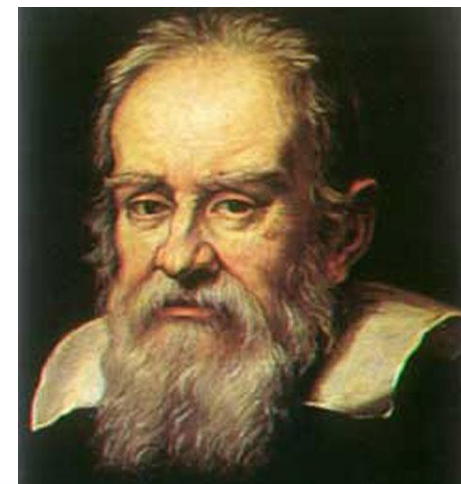
- Can we keep mentally fit?
- What is cognitive reserve
- Cognitive Reserve in MS
- Brain reserve
- Exercise & Cognition

Frank Lloyd Wright  
Started designing the Guggenheim  
Museum at age 76, completed at age 89



Goethe finished his masterpiece  
"Faust" at age 81

Galileo published his last paper at age  
74, when life expectancy was 35



# The Alzheimer's Association Website

## Keep your brain active every day:

- Stay curious and involved — commit to lifelong learning
- Read, write, work crossword or other puzzles
- Attend lectures and plays
- Enroll in courses at your local adult education center, community college or other community group
- Play games
- Garden
- Try memory exercises

alzheimer's  association

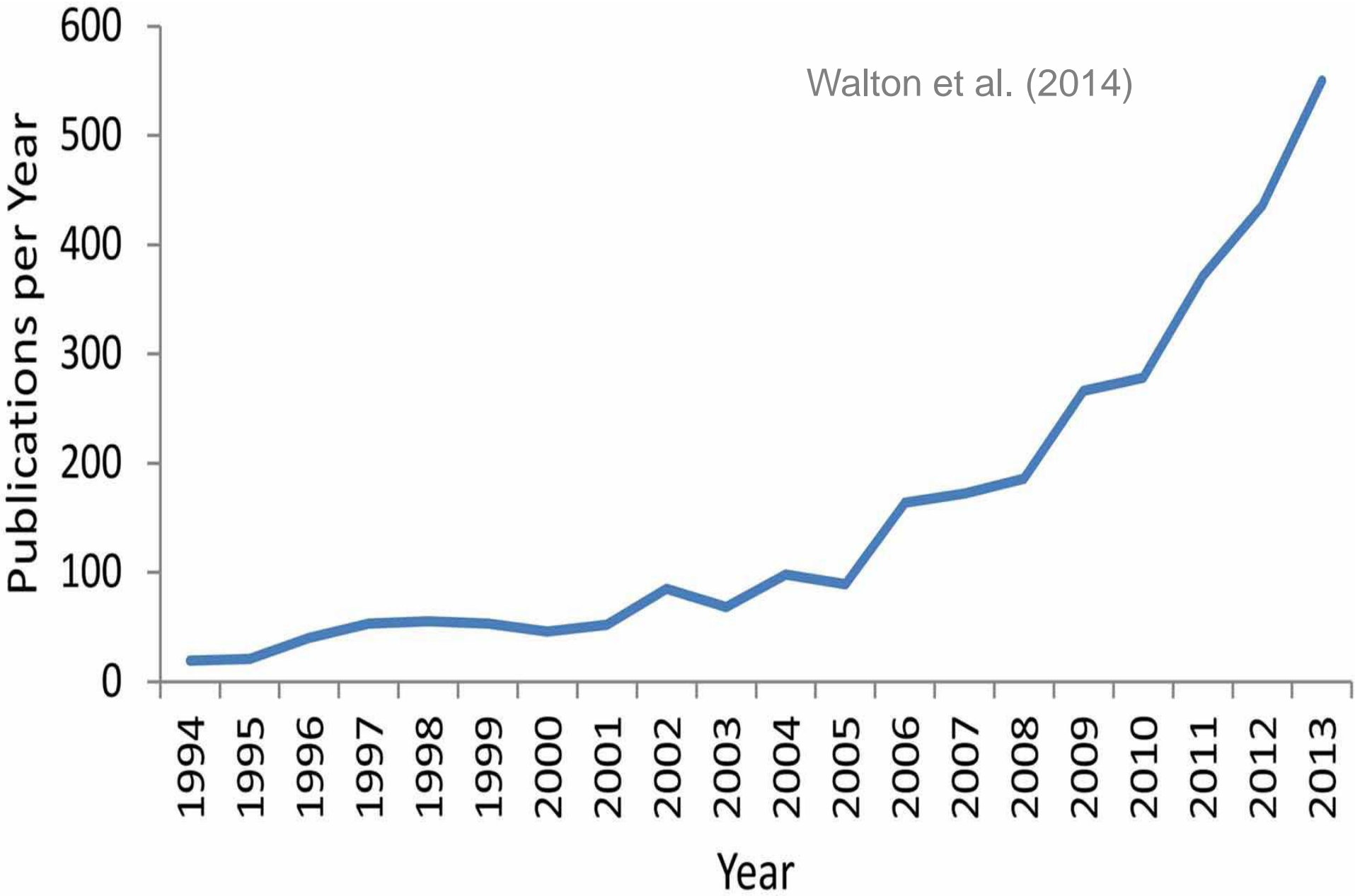
# Cognitive training: Introduction

# What is cognitive training?

- Guided practice on set of tasks related to memory, attention, or other brain functions
- Uses repetitive exercises for a single cognitive ability (e.g., memory) or multiple abilities (e.g., memory and reasoning)
- May be computer-assisted or delivered in person to an individual or small groups
- Based on idea of brain plasticity
- NOT just puzzles or “brain games”



# Growth of cognitive training studies

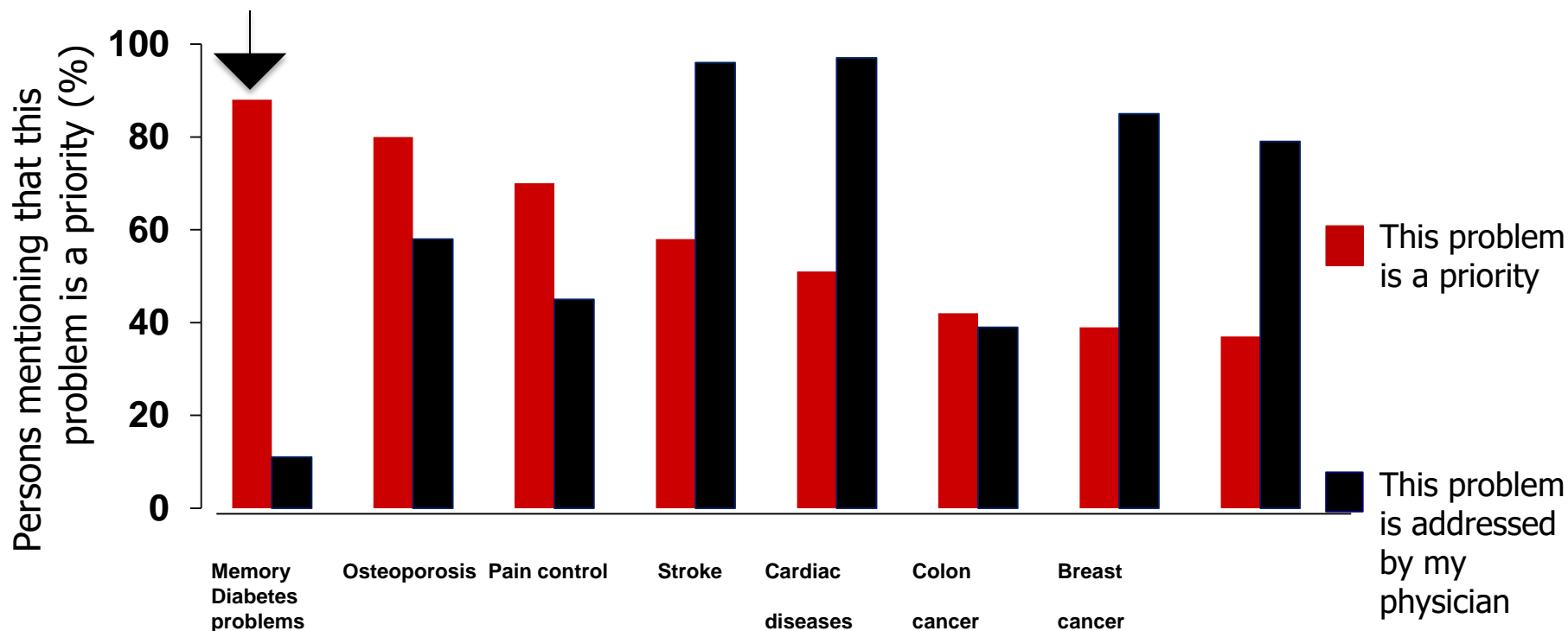


# Why cognitive training in aging is important

- 65+ population is growing
  - 20% of population (72 million) by 2030
- Cognitive decline is most feared aspect of growing older
- Cognitive impairments heavily affect aging population
  - 1 in 4 adults 70 years or older have an impairment without dementia
  - About 5.3 million people in the U.S. have Alzheimer's disease

Drug trial results are disappointing

# Health priorities in older adults



Older women's health priorities and perceptions of care delivery: results of the WOW health survey

N= 2161 older Canadian women

Cara Tannenbaum, Nancy Mayo, Francine Ducharme



**Evidence from the ACTIVE  
Trial:**

**Advanced Cognitive Training  
for Independent and Vital  
Elderly**

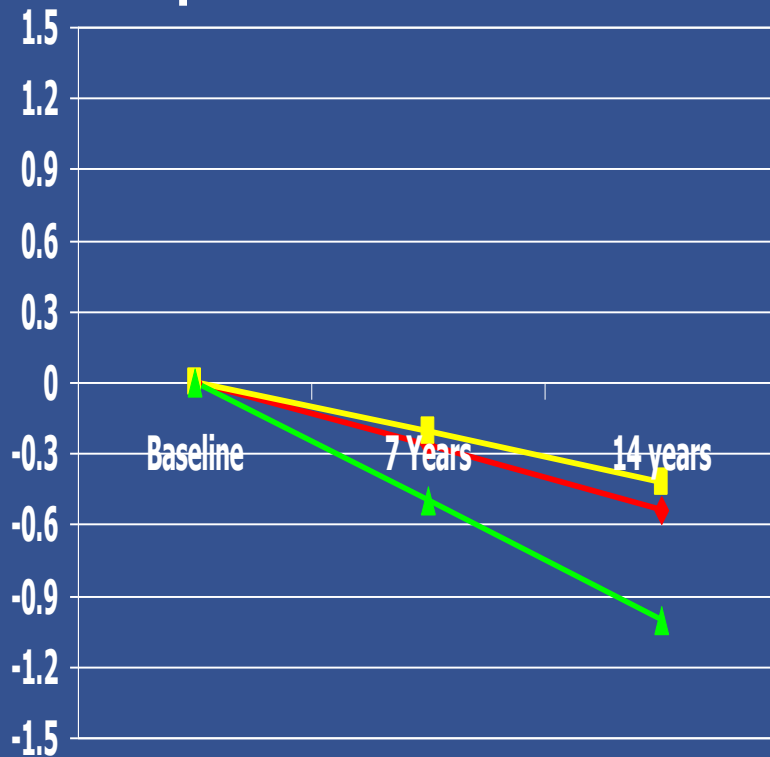
# **ACTIVE Interventions: Common Structural Features**

- Small-groups (3-5 participants per group)
- Led by a certified trainer with a scripted manual
- 10 sessions over a 6-week period
- 60-75 minutes per session
- Pre-specified order of sessions and rules for make-ups
- 80% compliance for successful completion

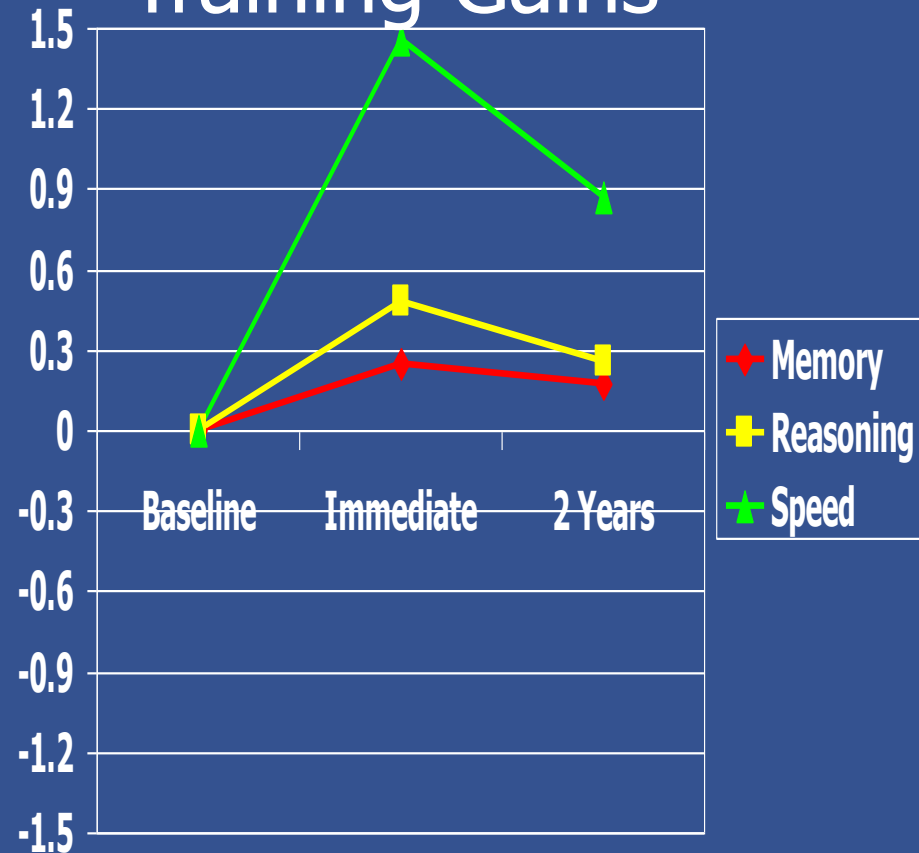
**ACTIVE**

# Initial Effect Sizes *(JAMA 2002)*

## Expected Decline

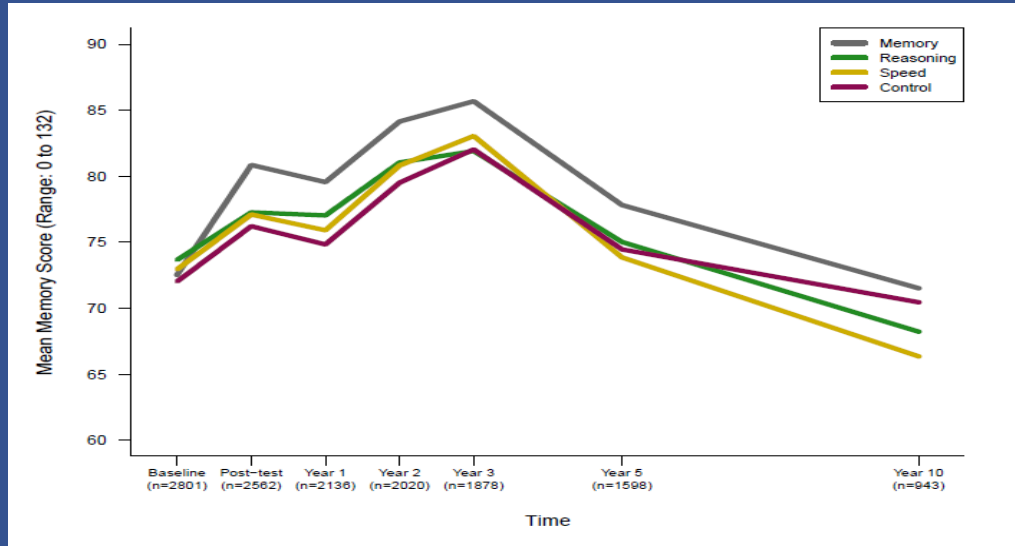


## Training Gains



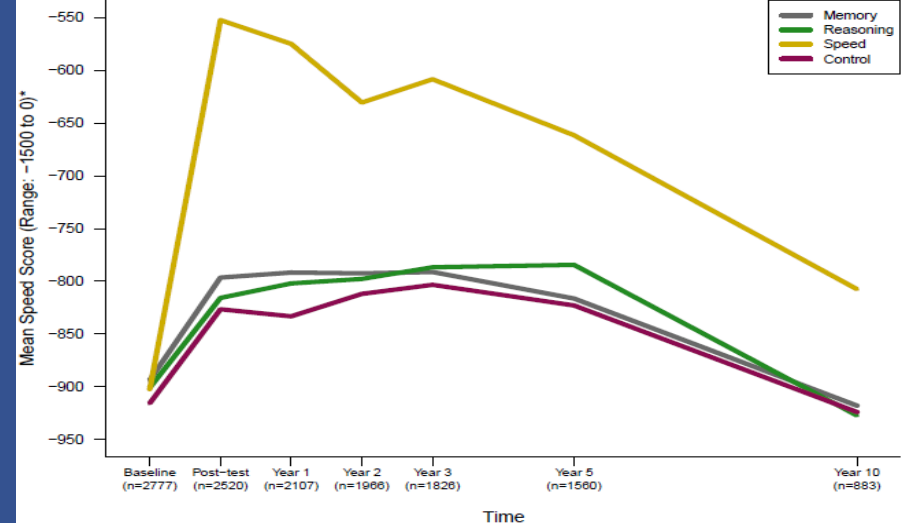
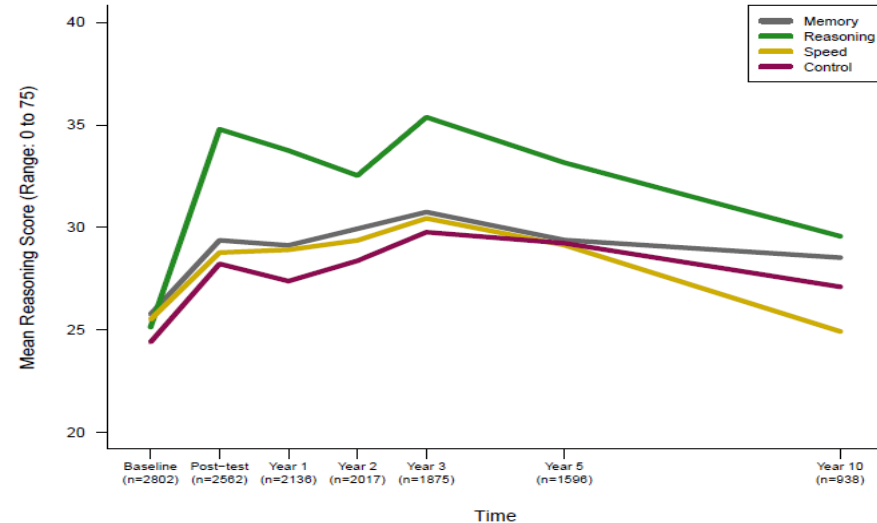
# 10-year trajectory of memory, reasoning, and speed, by training group (JAGS 2014)

## Memory



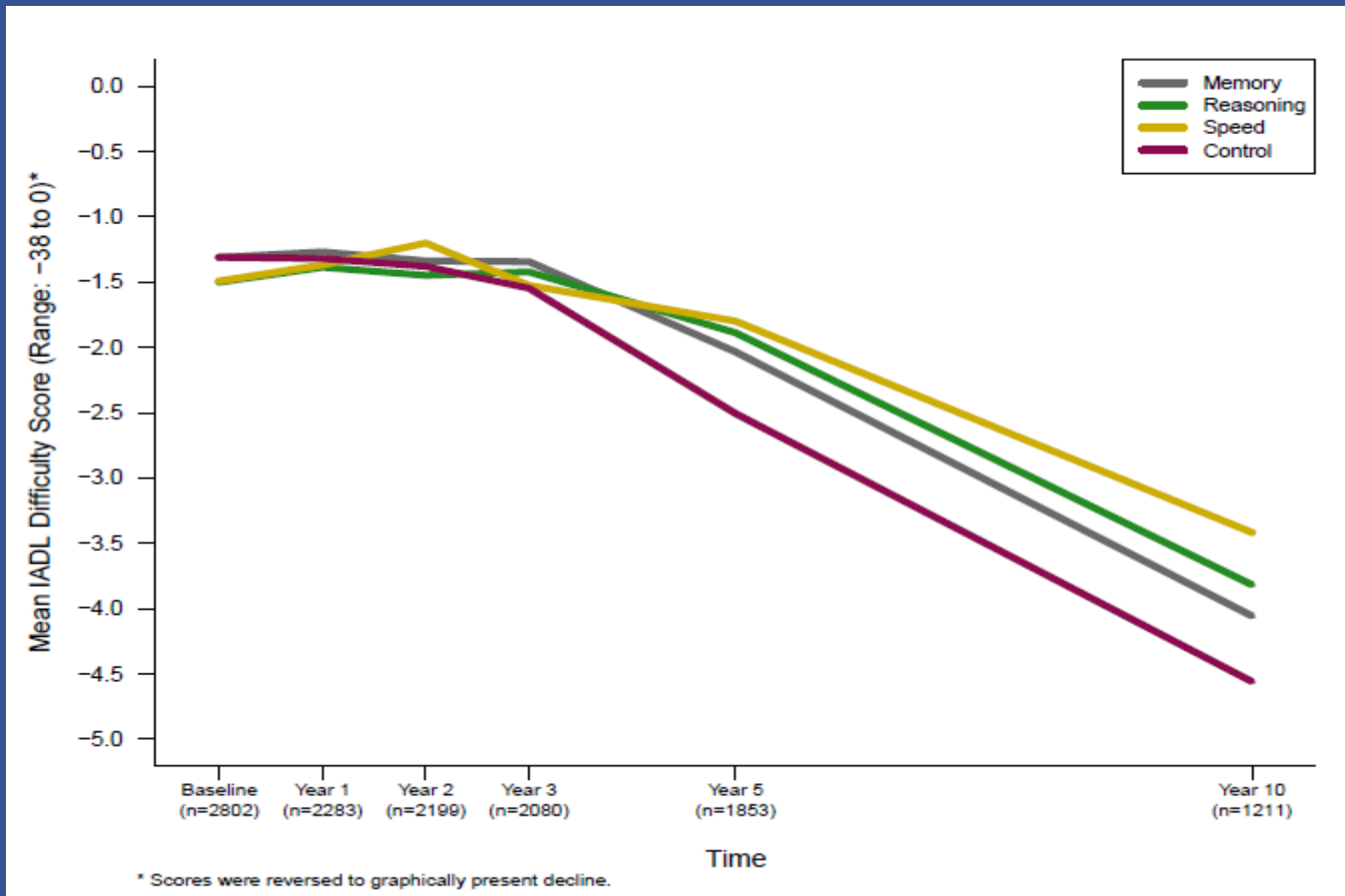
## Reasoning

## Speed



\* Scores were reversed to graphically present decline.

# 10-year trajectory of self-reported IADL difficulty, by training group (*JAGS 2014*)





# Secondary outcomes related to everyday functioning: Findings at 5-,10-yr follow-up

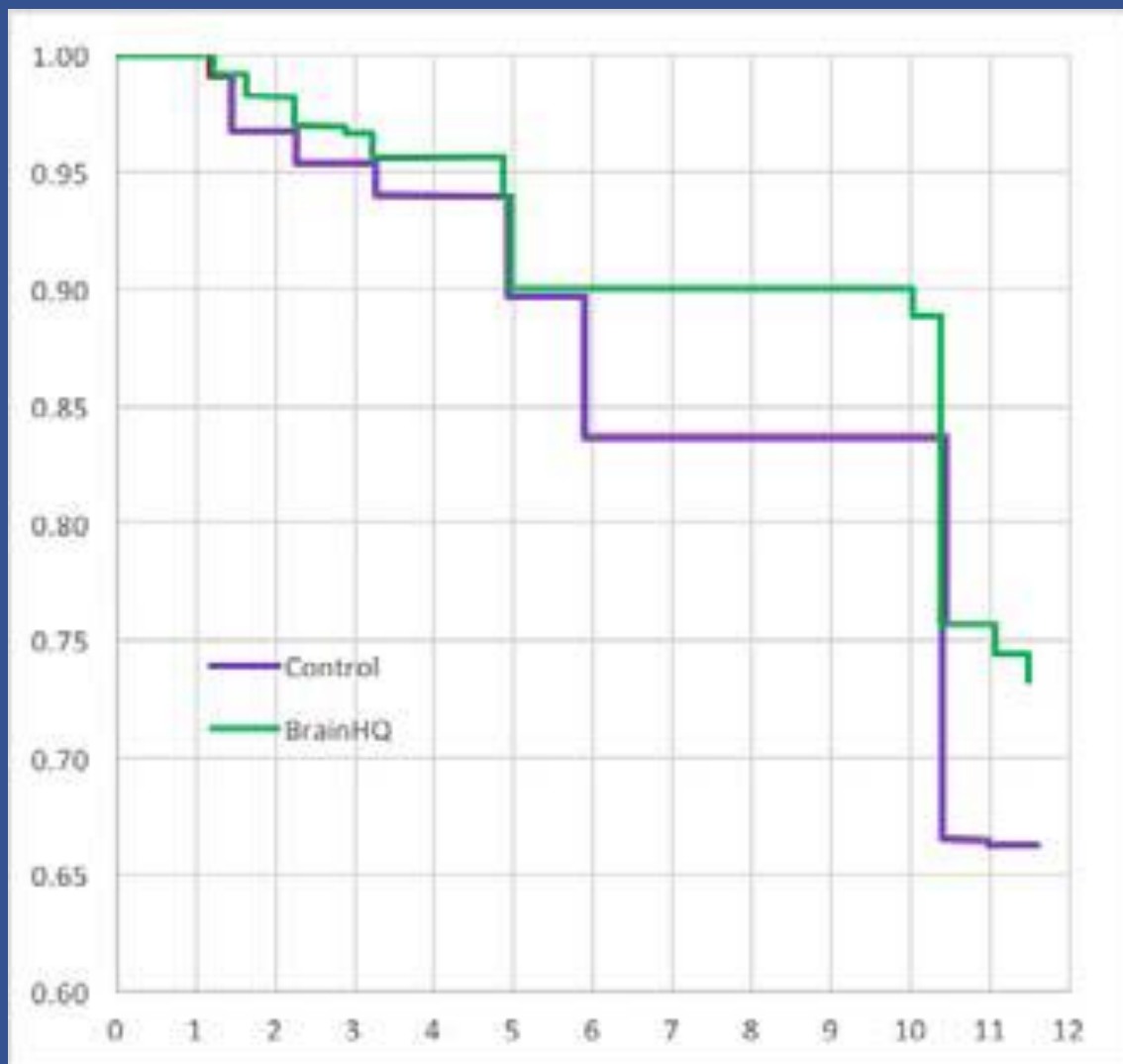
- Mobility and Driving
  - Reduction in Auto Crashes: Speed & Reasoning Training
- Internal Control
  - Increase in Control Beliefs: Speed & Reasoning Training
- Depression
  - Fewer depressive symptoms in Speed training
  - Subjects in Memory & Reasoning Training with depressive symptoms profit from training
- Health-Related Quality of Life (HRQoL)
  - Less decline in HRQoL in Memory, Reasoning, & Speed training

# Dementia findings: 10-yr follow-up

N=2785 participants in analyses,  
n=296 met dementia criteria (10.6%)

*Edwards et al. (2016), AAIC*

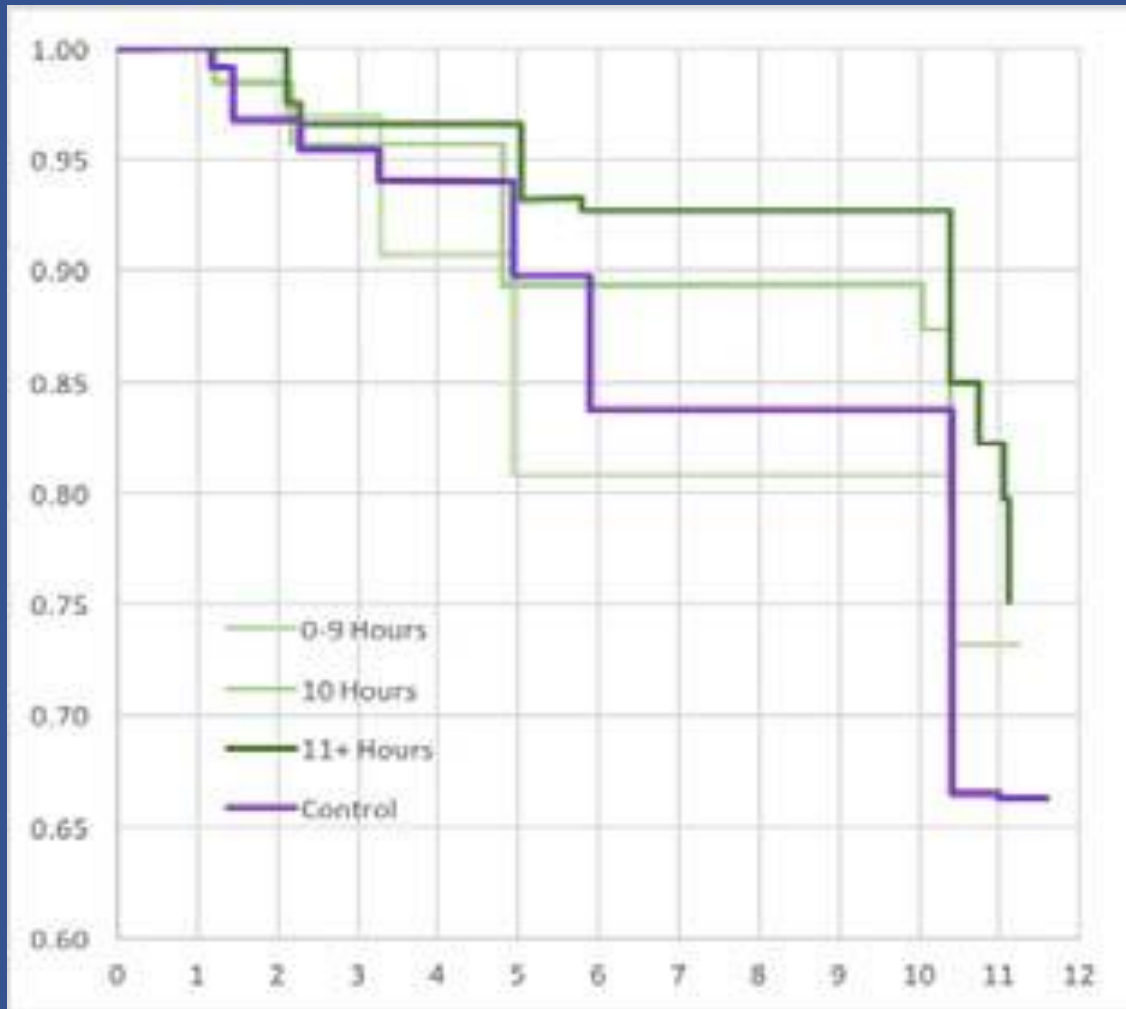
# Speed training delays dementia onset



*33% risk reduction*

*HR=0.67, 95%CI 0.49-0.91, p=.012*

# Effects of speed training are dose dependent



*48% risk reduction*

*HR=0.52, 95%CI 0.33-0.82, p=.005*

# 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
    - Katzman, *et al.*, (1988), *Ann Neurol*, 23, 138-144
    - Crystal, *et al.*, (1988), *Neurology*, 11, 1682-1687
    - Price & Morris, (1999), *Ann Neurol*, 45, 358-368
  - Numerous studies show that lower educational attainment is a risk factor for AD-related dementia.

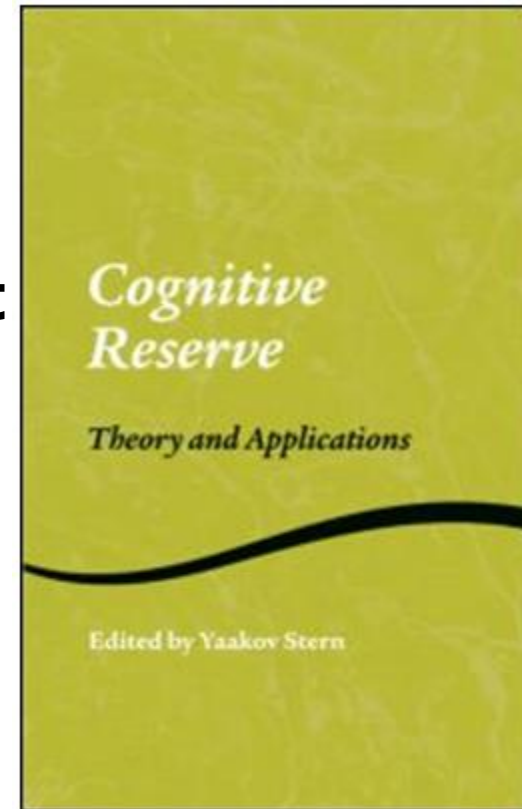
For review: Stern, (2006), *Alzheimer Dis Asso Disord*, 20, S69-74

# Cognitive Reserve Hypothesis

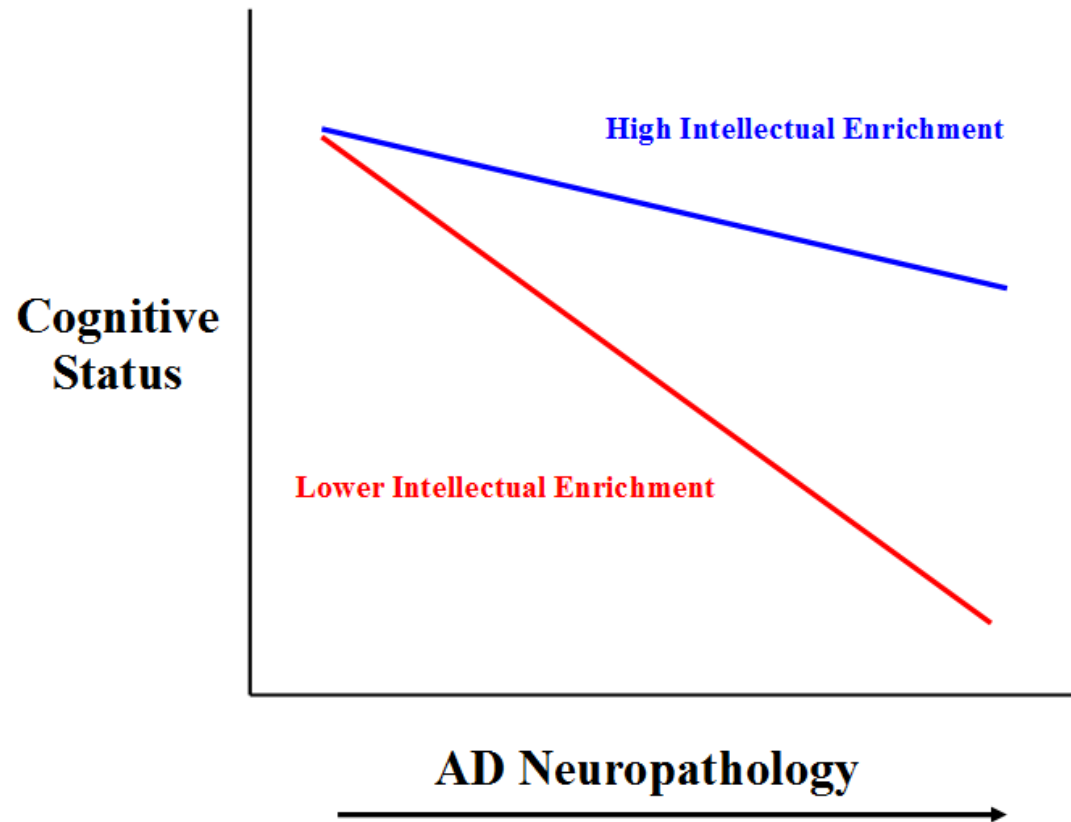
**Persons with higher lifetime intellectual enrichment can better withstand disease-related neuropathology without suffering cognitive impairment or dementia, likely due to more efficient neurocognitive processing.**

**Stern et al., *JINS* 2002;8:448-460.**

**Stern et al., *Cereb Cortex*  
2005;15:394-402.**



# Evidence of Cognitive Reserve in Alzheimer's Disease





# How is Cognitive Reserve Measured?

- Cognitive reserve is a construct. Thus is measured by proxy
  - Years of education
  - Pre-morbid IQ
    - Vocabulary
    - word reading
  - Cognitively-stimulating leisure activity

# What about MS?

Cognitive Reserve

Does cognitive reserve moderate  
the relationship between MS  
diagnosis and development of  
cognitive impairment?

## Cognitive reserve protects against cognitive dysfunction in multiple sclerosis

James F. Sumowski,<sup>1,2</sup> Nancy Chiaravalloti,<sup>1,2</sup> and John DeLuca<sup>1,2,3</sup>

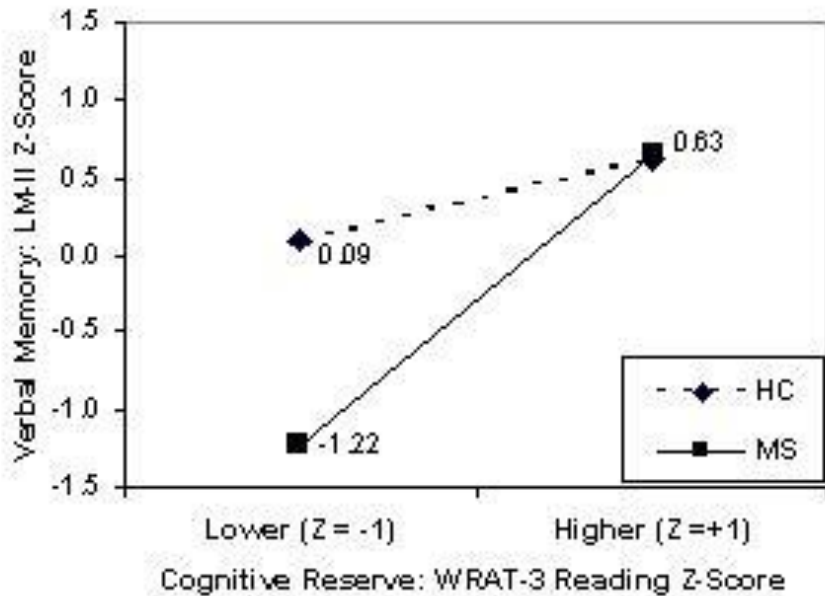
<sup>1</sup>Kessler Foundation Research Center, Neuropsychology and Neuroscience Laboratory, West Orange, NJ, USA

<sup>2</sup>UMDNJ–New Jersey Medical School, Department of Physical Medicine and Rehabilitation, Newark, NJ, USA

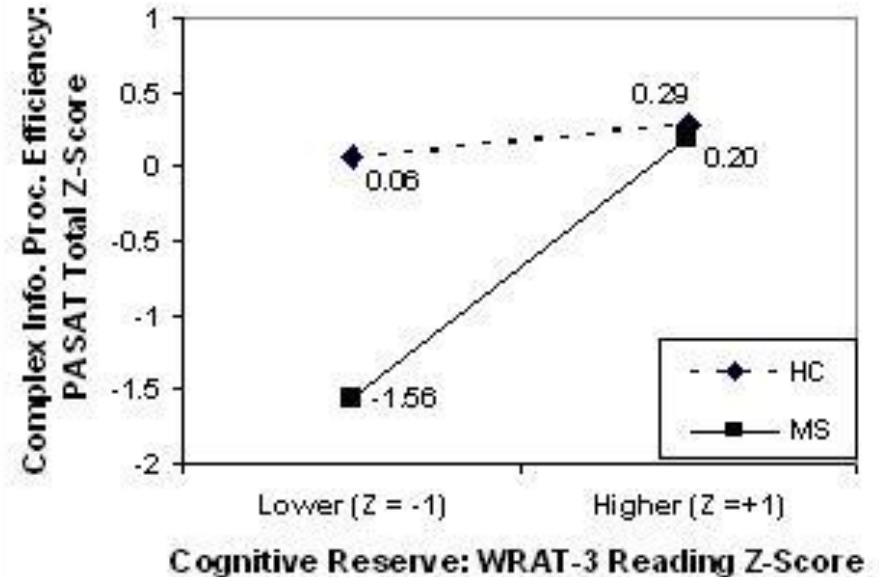
<sup>3</sup>UMDNJ–New Jersey Medical School, Department of Neurology and Neurosciences, Newark, NJ, USA

# Cognitive Reserve and Cognition in MS

## Memory



## Cognitive Efficiency



# Cognitive Reserve and Brain Imaging

- Brain atrophy predicts Cognition in MS
- Prediction is incomplete:
  - $R^2$ s vary between approximately 25 and 45
- Does cognitive reserve moderate the relationship between brain atrophy and cognition in MS?

## ARTICLES

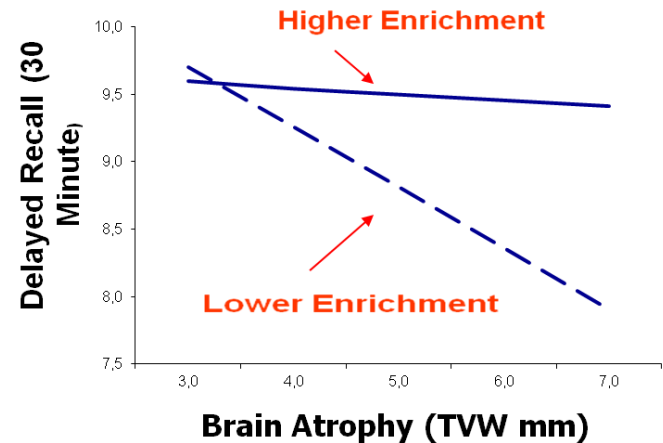
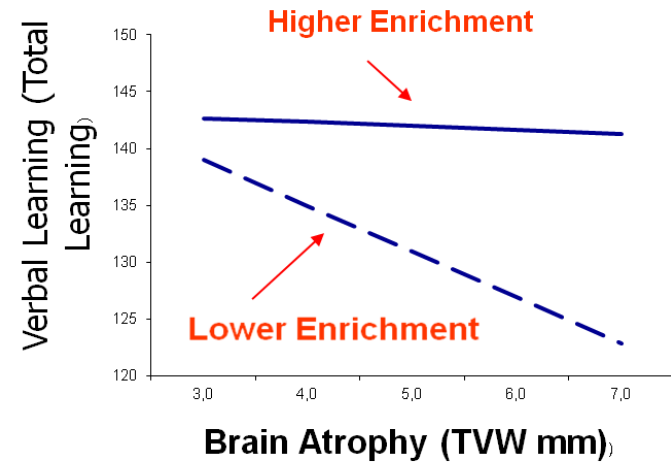
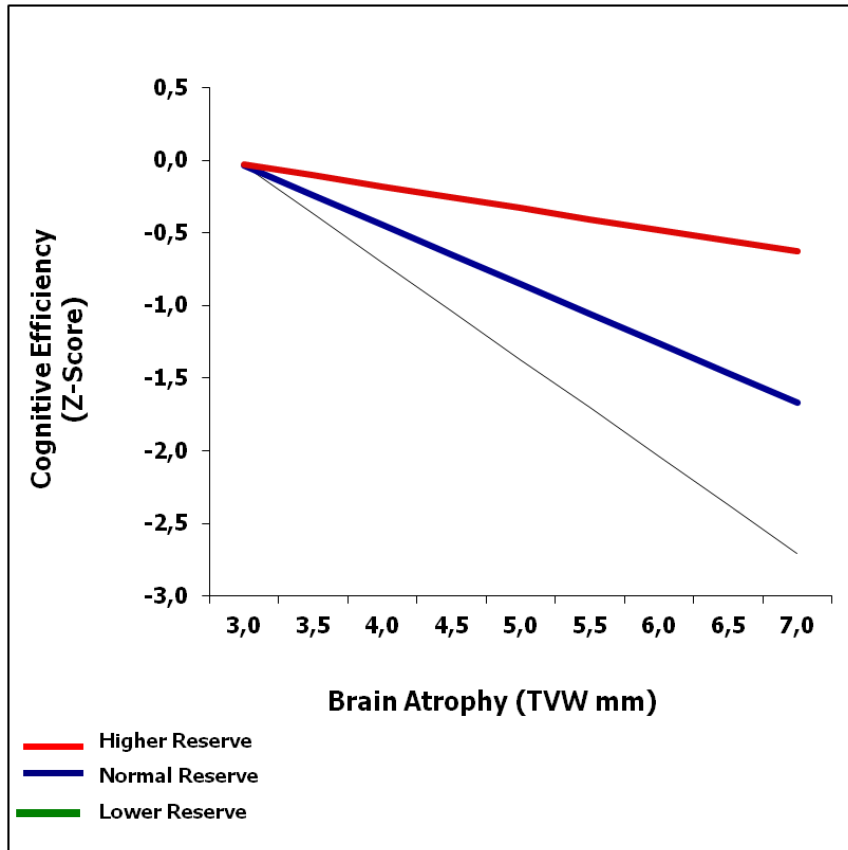
# Intellectual enrichment lessens the effect of brain atrophy on learning and memory in multiple sclerosis

James F. Sumowski, PhD  
Glenn R. Wylie, DPhil  
Nancy Chiaravalloti, PhD  
John DeLuca, PhD

## ABSTRACT

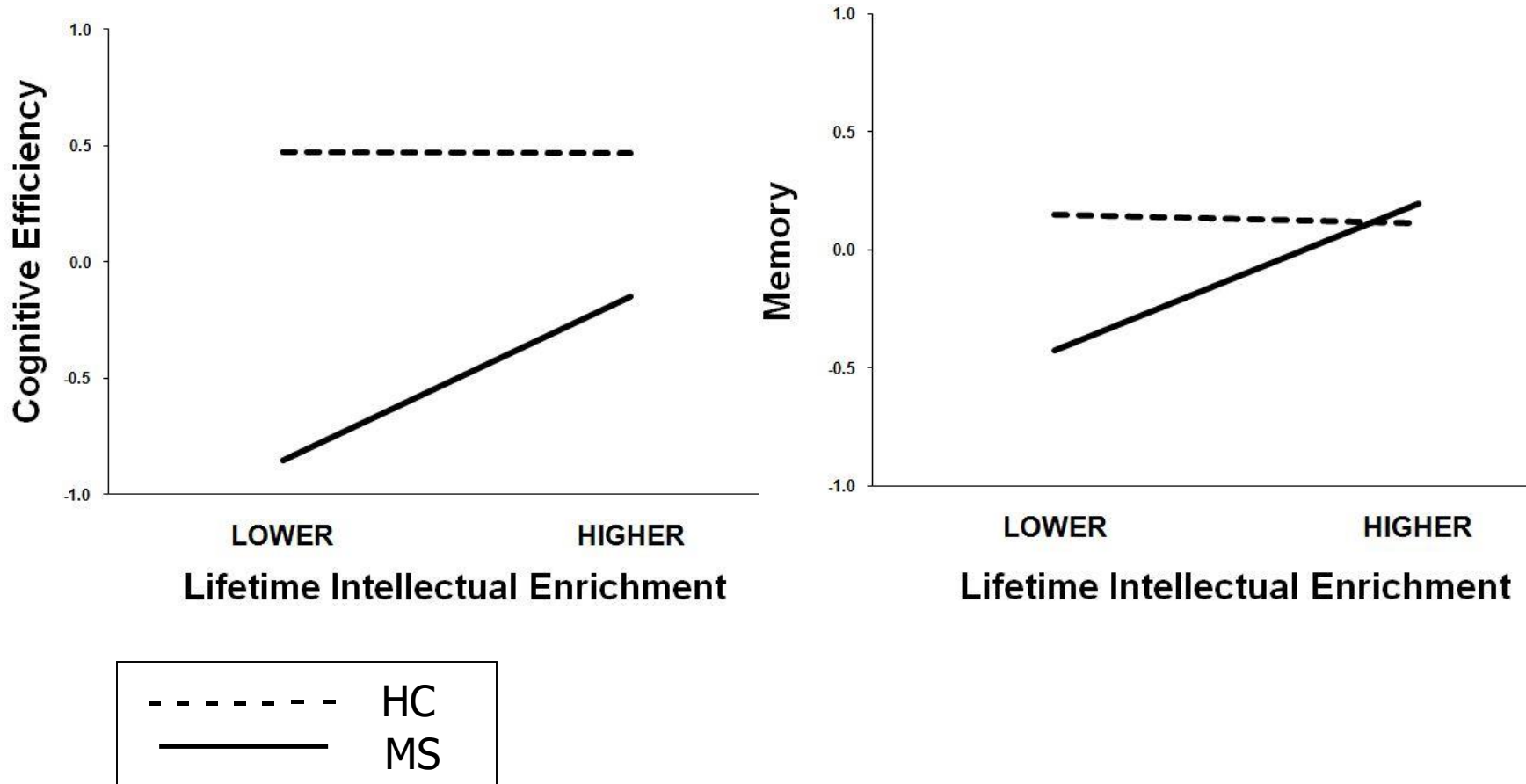
**Objective:** Learning and memory impairments are prevalent among persons with multiple sclerosis (MS); however, such deficits are only weakly associated with MS disease severity (brain atrophy). The cognitive reserve hypothesis states that greater lifetime intellectual enrichment lessens the negative impact of brain disease on cognition, thereby helping to explain the incomplete relation-

# Cognitive Reserve in MS





# Cognitive Reserve in SPMS



# Benefits of Early Life Cognitive Leisure Activity and Aerobic Exercise in Multiple Sclerosis

# Premorbid cognitive leisure independently contributes to cognitive reserve in multiple sclerosis

J.F. Sumowski, PhD  
G.R. Wylie, DPhil  
A. Gonnella, EdM  
N. Chiaravalloti, PhD  
J. DeLuca, PhD

## ABSTRACT

**Objective:** Consistent with the cognitive reserve hypothesis, higher education and vocabulary help persons with Alzheimer disease (AD) and multiple sclerosis (MS) better withstand neuropathology before developing cognitive impairment. Also, premorbid cognitive leisure (e.g., reading, hobbies) is an independent source of cognitive reserve for elders with AD, but there is no research on the contribution of leisure activity to cognition in MS. We investigated whether premorbid cognitive leisure protects patients with MS from cognitive impairment.

## Leisure Activity Scale

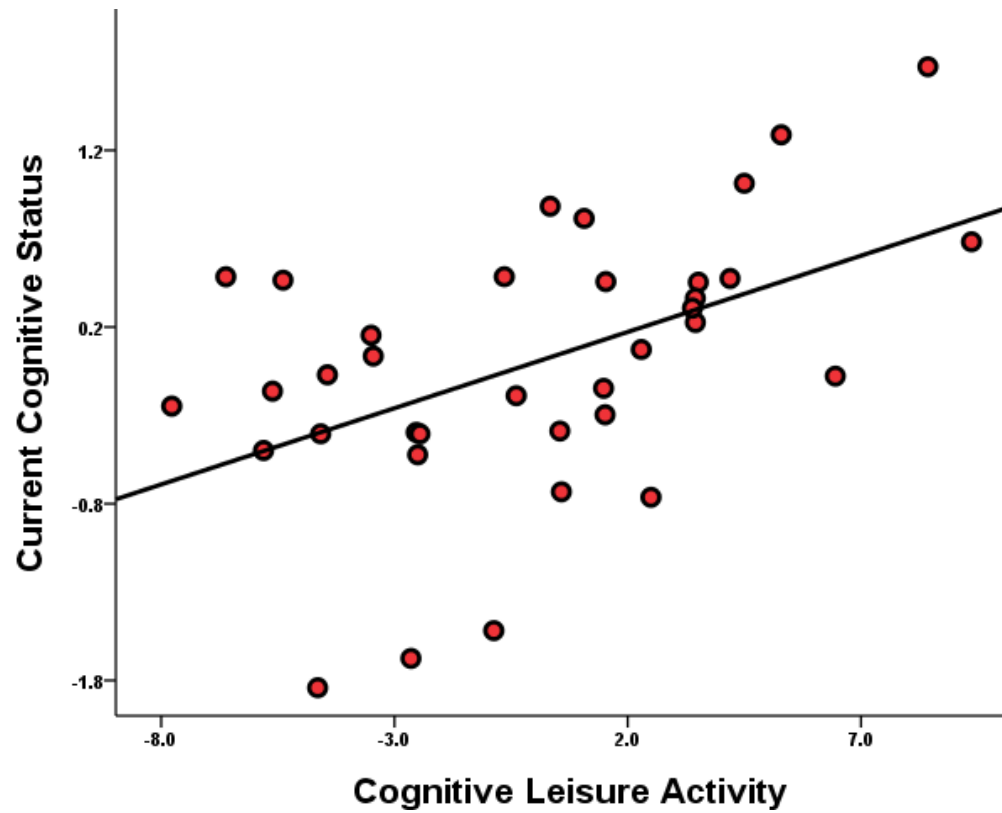
Several leisure activities are listed below. Please read each item and indicate how frequently you performed the activity **during your early 20's before you developed MS**. Respond by circling the number that represents your typical participation in each activity **during your early 20's before you developed MS**. Only report on activities that were performed for leisure, not activities performed to fulfill educational or occupational requirements. If you are unsure of the exact frequency of your participation, please provide your best estimate. Please circle one number for each item rather than marking between numbers.

**During your early 20's before you developed MS, how often did you...**

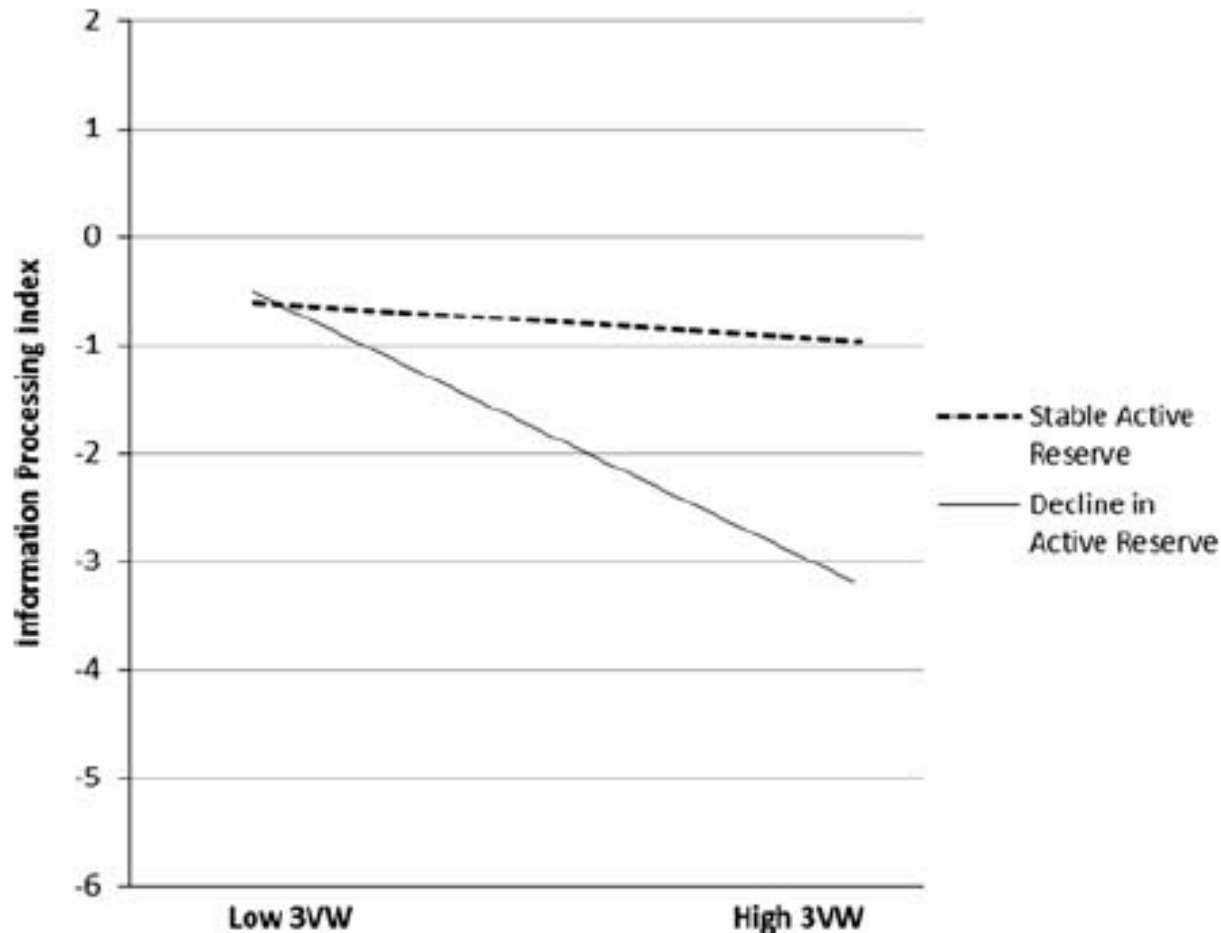
	Daily	Several Times per Week	Several Times per Month	Several Times per Year	Once / Less per Year
Read books	5	4	3	2	1
Read magazines or newspapers	5	4	3	2	1
Produce art (e.g., painting, poetry, sculpture, song writing, ballet, etc.)	5	4	3	2	1
Produce non-artistic writing (e.g., diary, newsletter, essay, blogs, etc.)	5	4	3	2	1
Play a musical instrument	5	4	3	2	1
Play structured games (e.g., cards, board games, crossword puzzles, etc.)	5	4	3	2	1
Participate in hobbies (e.g., gardening, model building, web design, etc.)	5	4	3	2	1

# Results

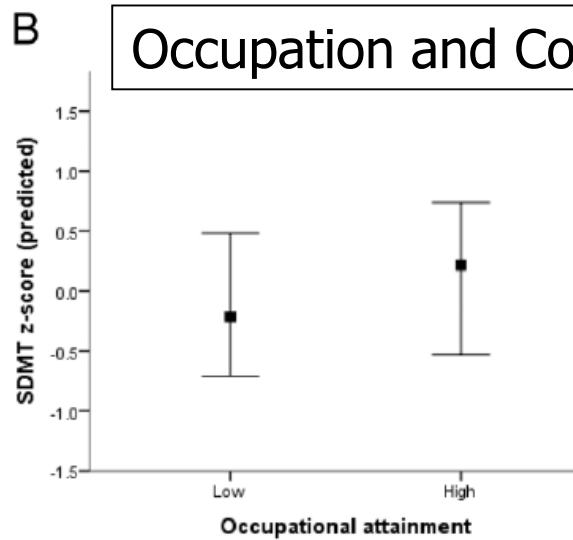
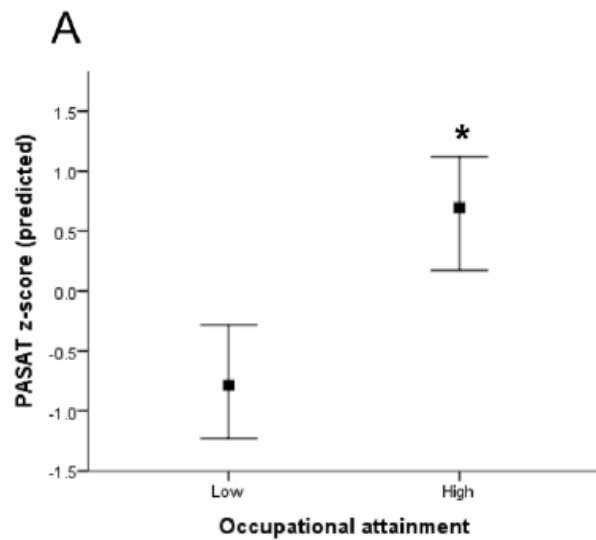
Cognitive Leisure Activity is positively associated with current cognitive status ( $r_p = .49, p < .01$ )



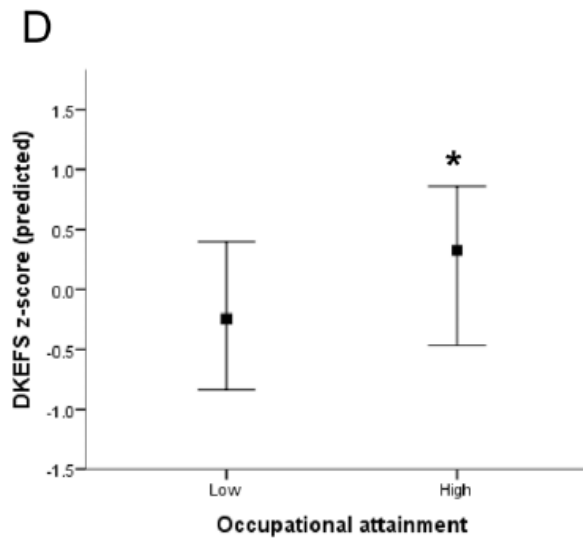
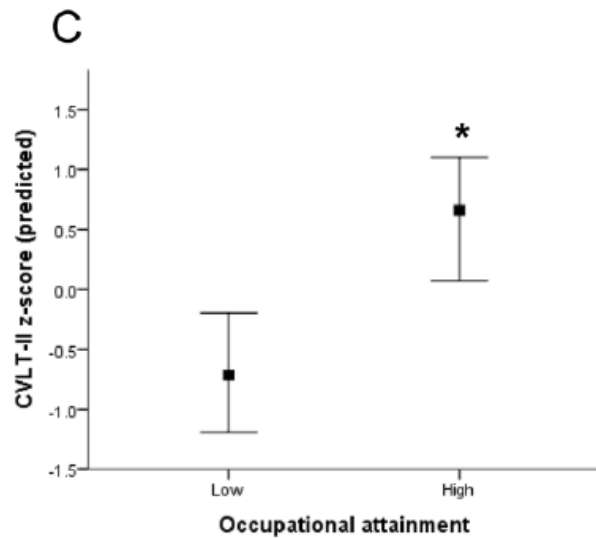
# Maintenance vs decline in recreational activity since MS diagnosis



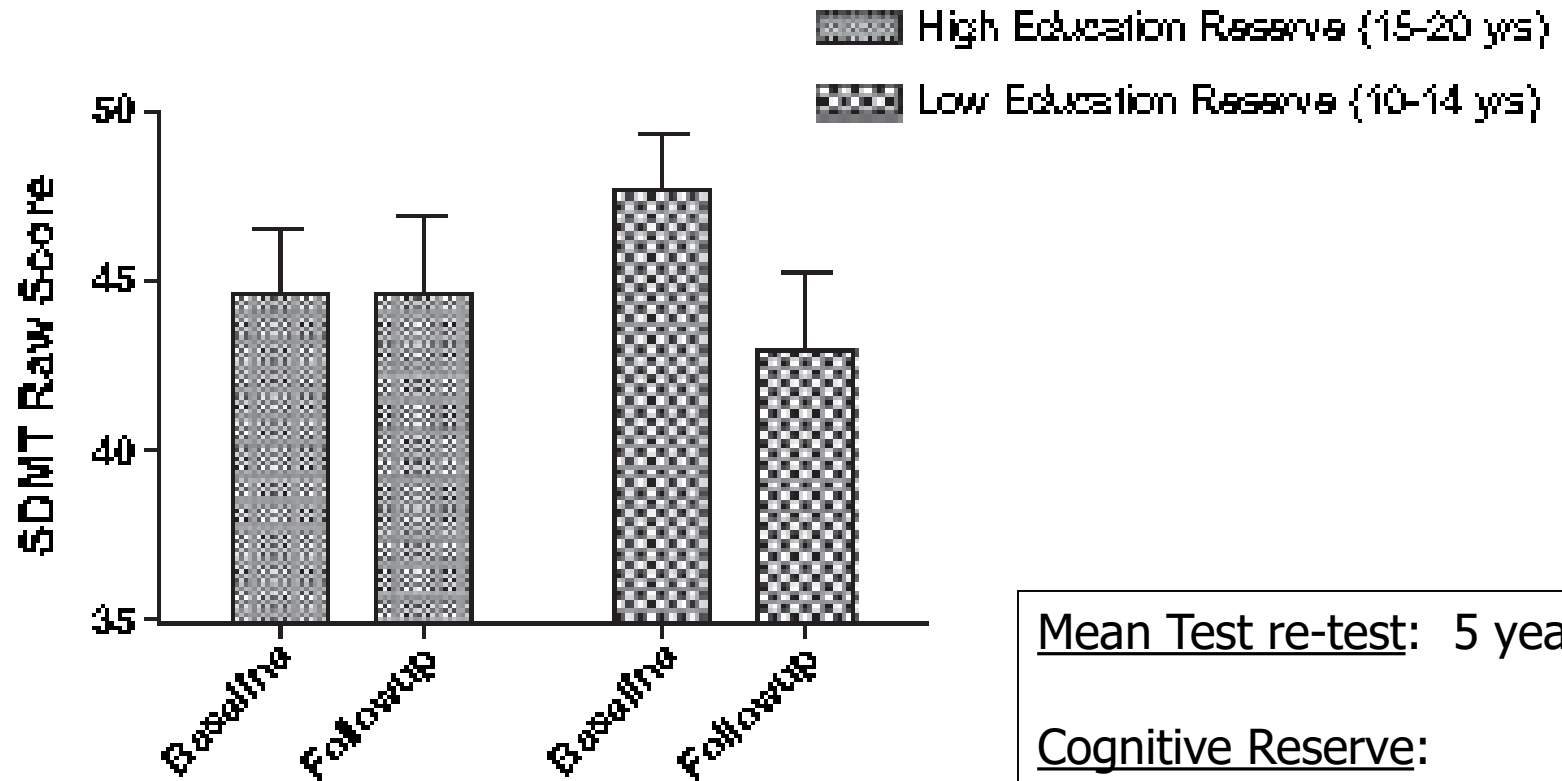
# Occupation and Cognitive Reserve in MS\*



Adjusted for atrophy and IQ



# Longitudinal analysis of Cognitive Reserve in MS



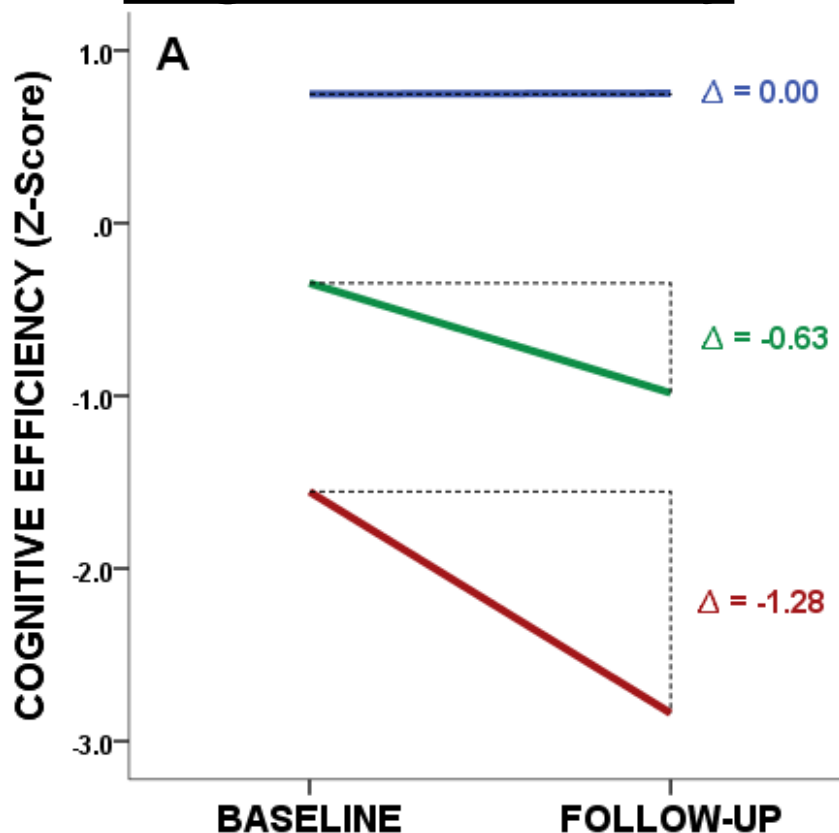
Mean Test re-test: 5 years

Cognitive Reserve:  
Yrs education  
NAART

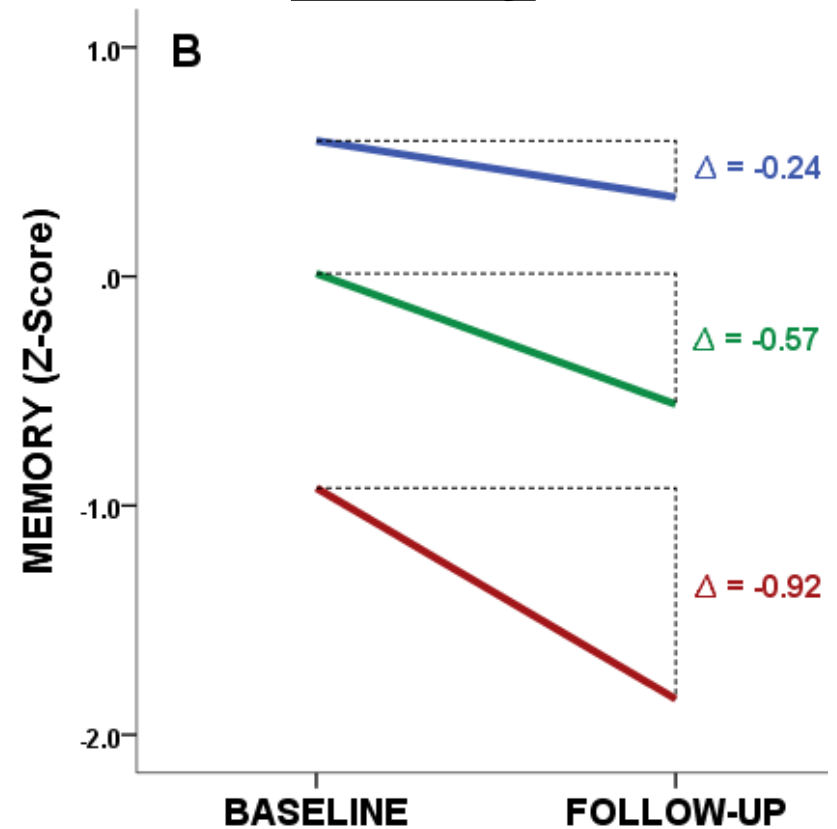


# Cognitive Decline over Time in MS: 4.5 year follow-up

## Cognitive Efficiency



## Memory



# Reserve Concepts and MS

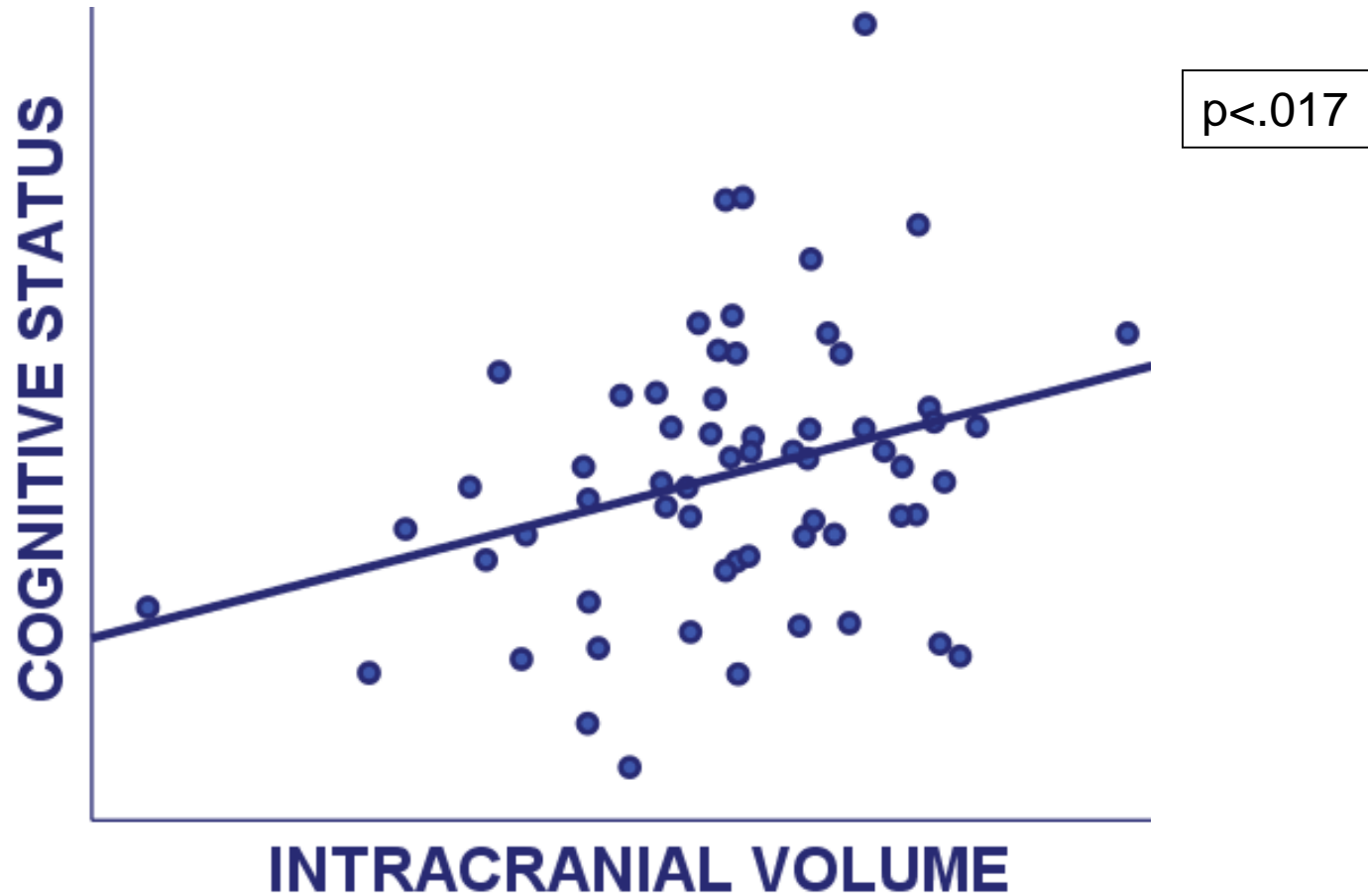
- Higher cognitive reserve protects MS subjects from MS-related cognitive decline
- What about “Brain Reserve”?

# Brain Reserve Hypothesis

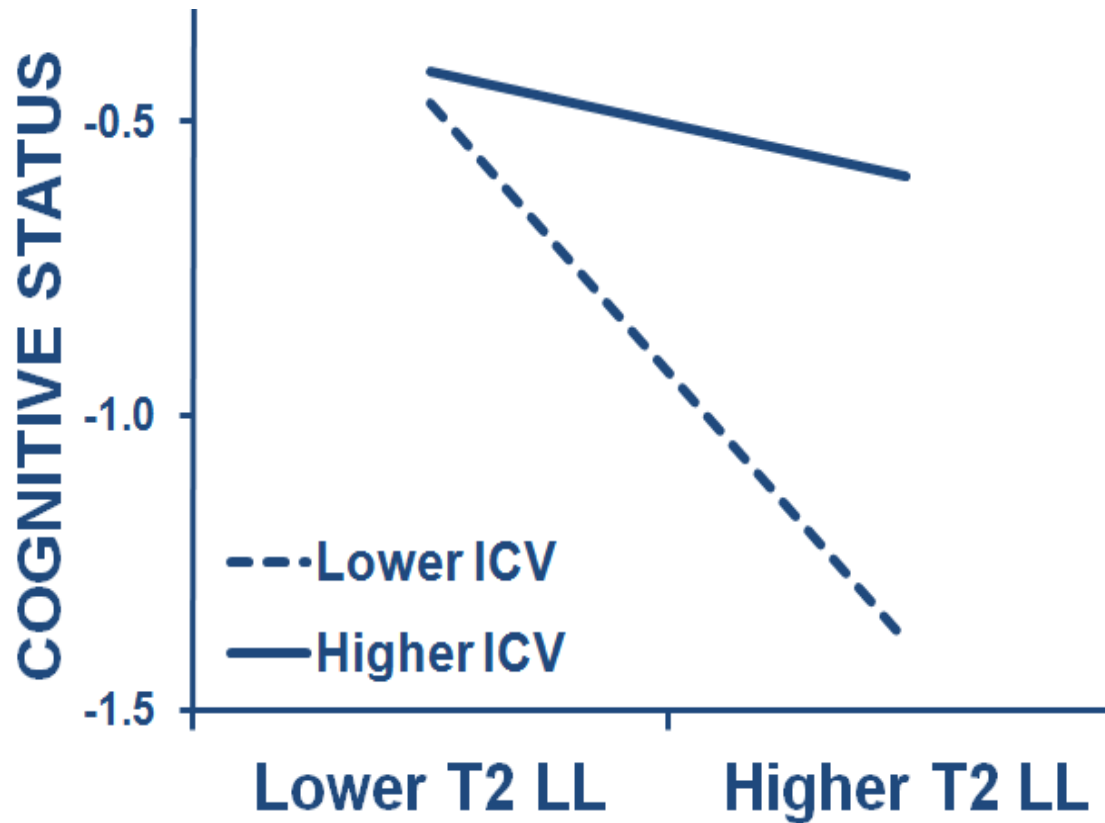
**Persons with larger lifetime brain growth/size (estimated with intracranial volume) can withstand more severe neuropathology without suffering cognitive impairment or dementia.**

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

# Results: Brain Reserve



# Results: Brain Reserve



# 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**

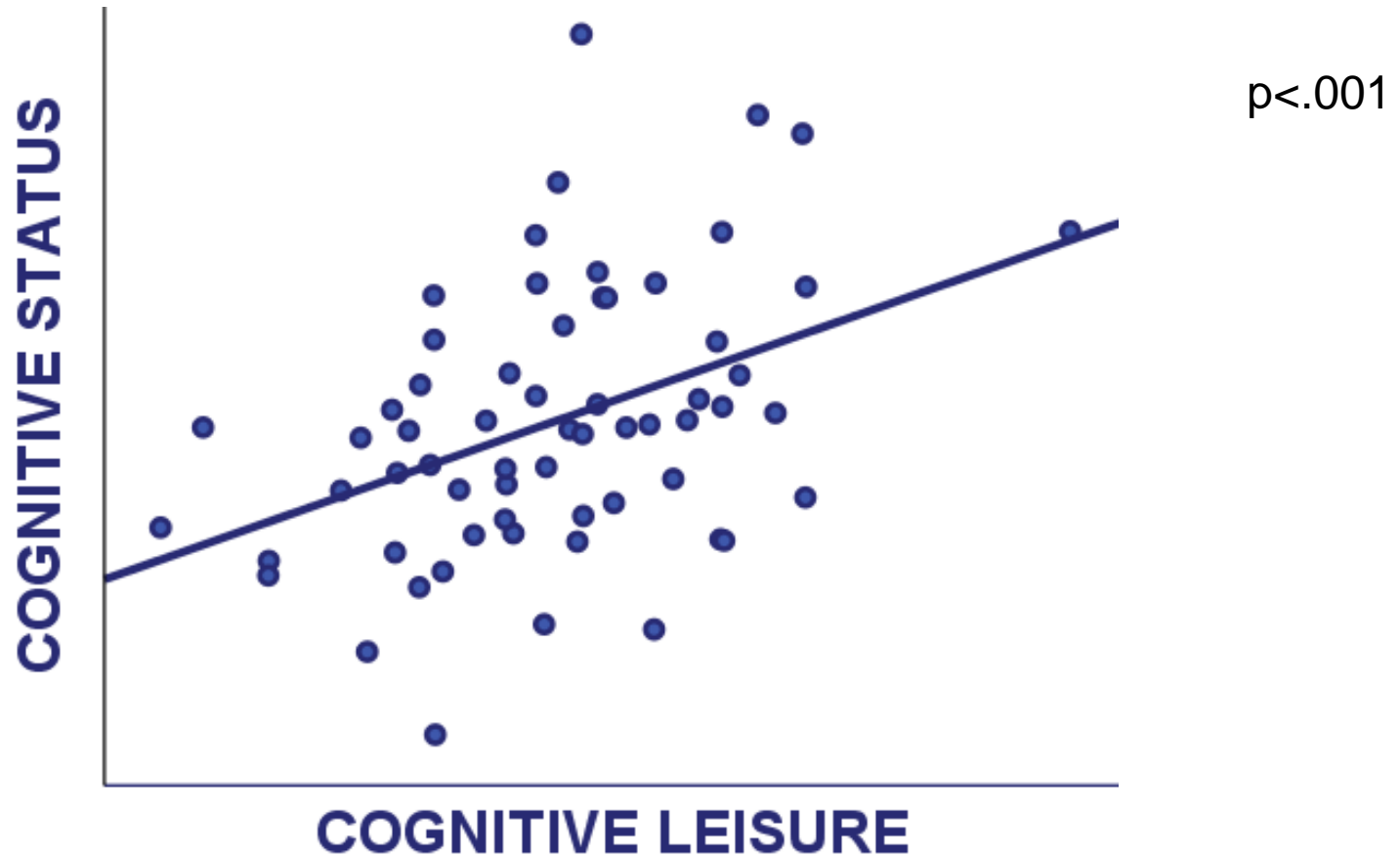
**Deary et al., *Nat Rev Neurosci* 2010;11:201-211**

# QUESTION

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

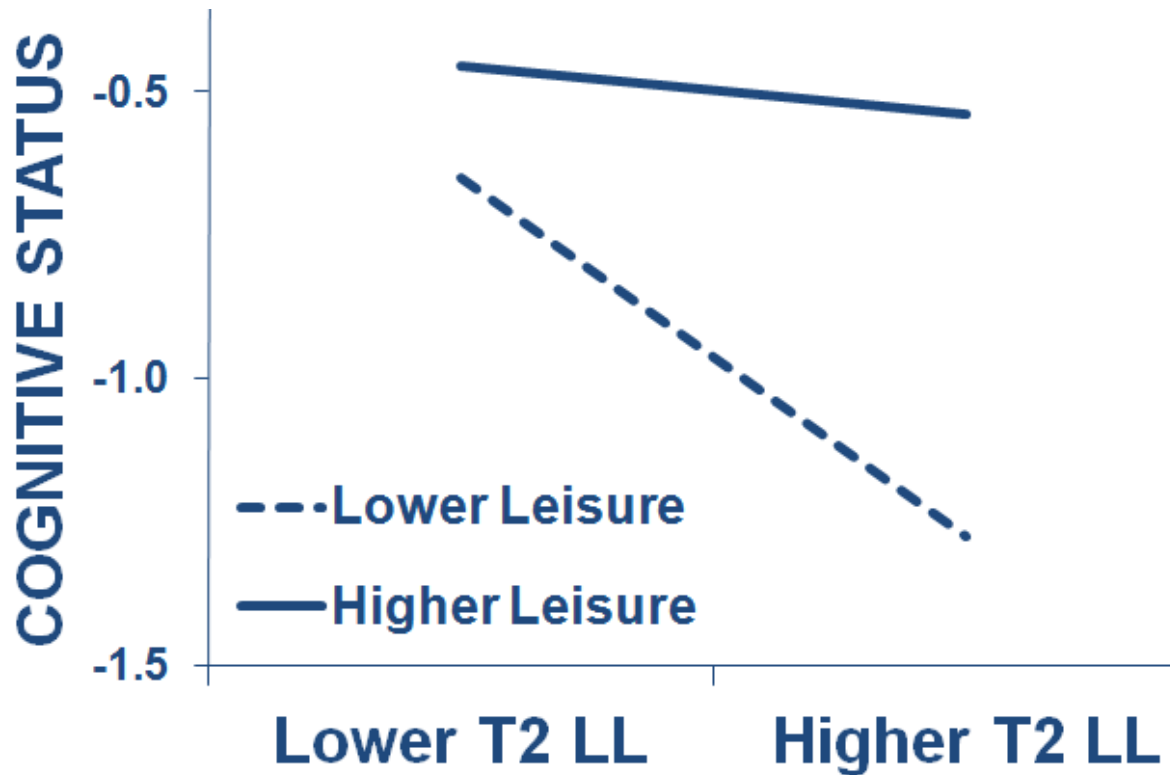
**Do people have control over their own destiny?**

# Results: Cognitive Reserve





# Results: Cognitive Reserve after factoring out Brain Reserve



# 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 identify “at risk” patients?
- Can one build up a “cognitive reserve”?
  - “neuroprotective” against developing cognitive impairment?

# The Alzheimer's Association Website

## Keep your brain active every day:

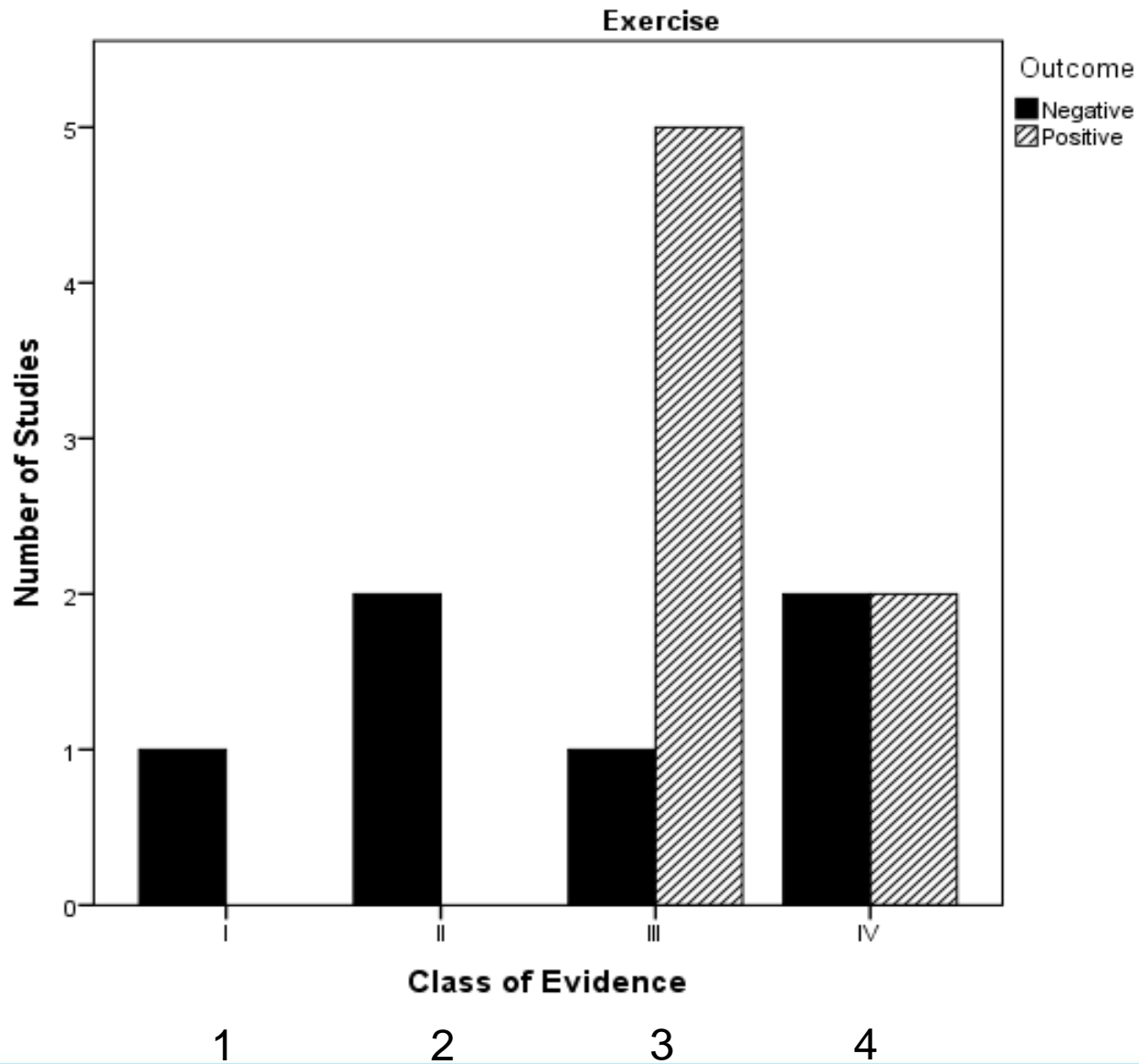
- Stay curious and involved — commit to lifelong learning
- Read, write, work crossword or other puzzles
- Attend lectures and plays
- Enroll in courses at your local adult education center, community college or other community group
- Play games
- Garden
- Try memory exercises

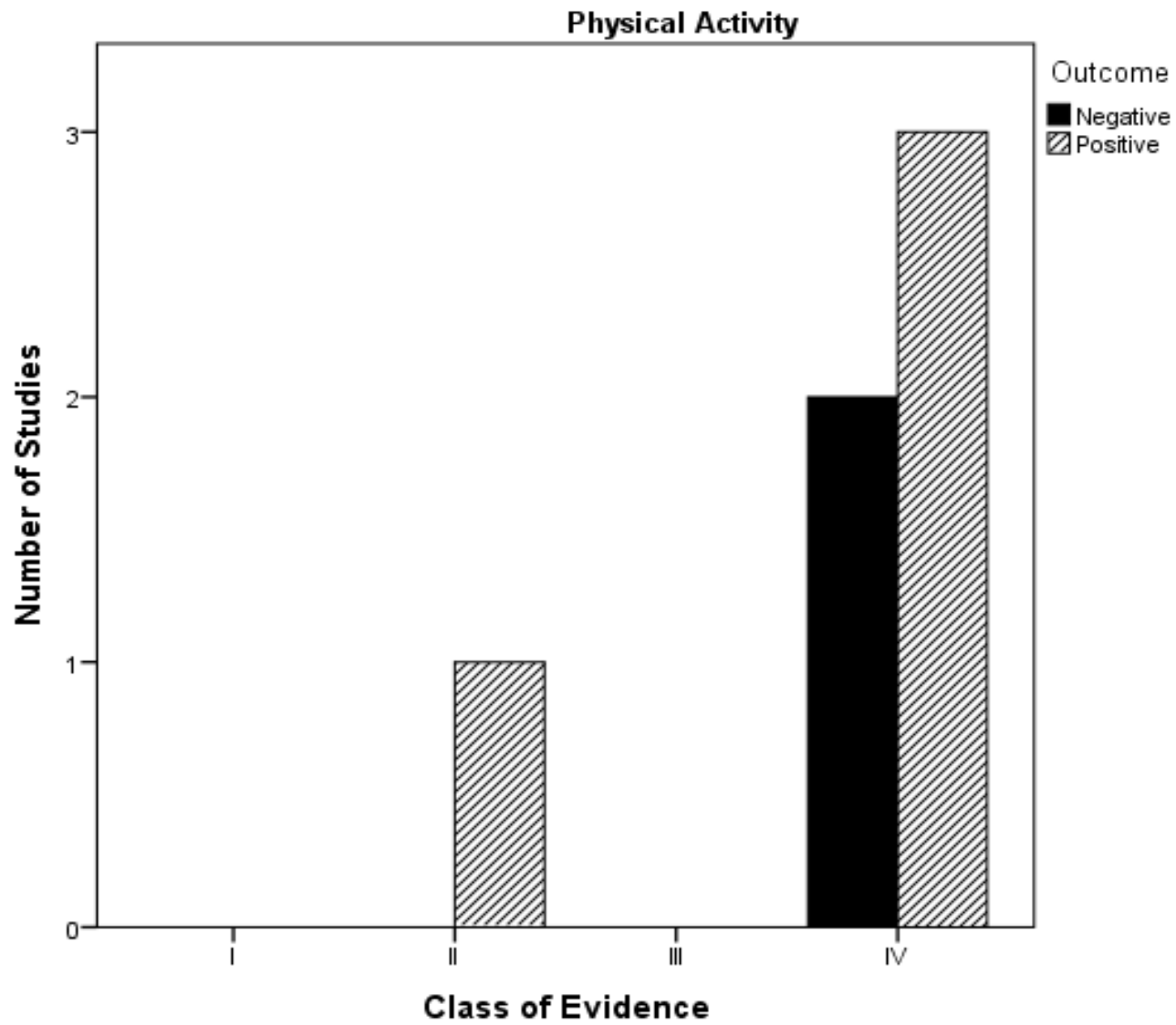
alzheimer's  association

# Exercise and Cognition

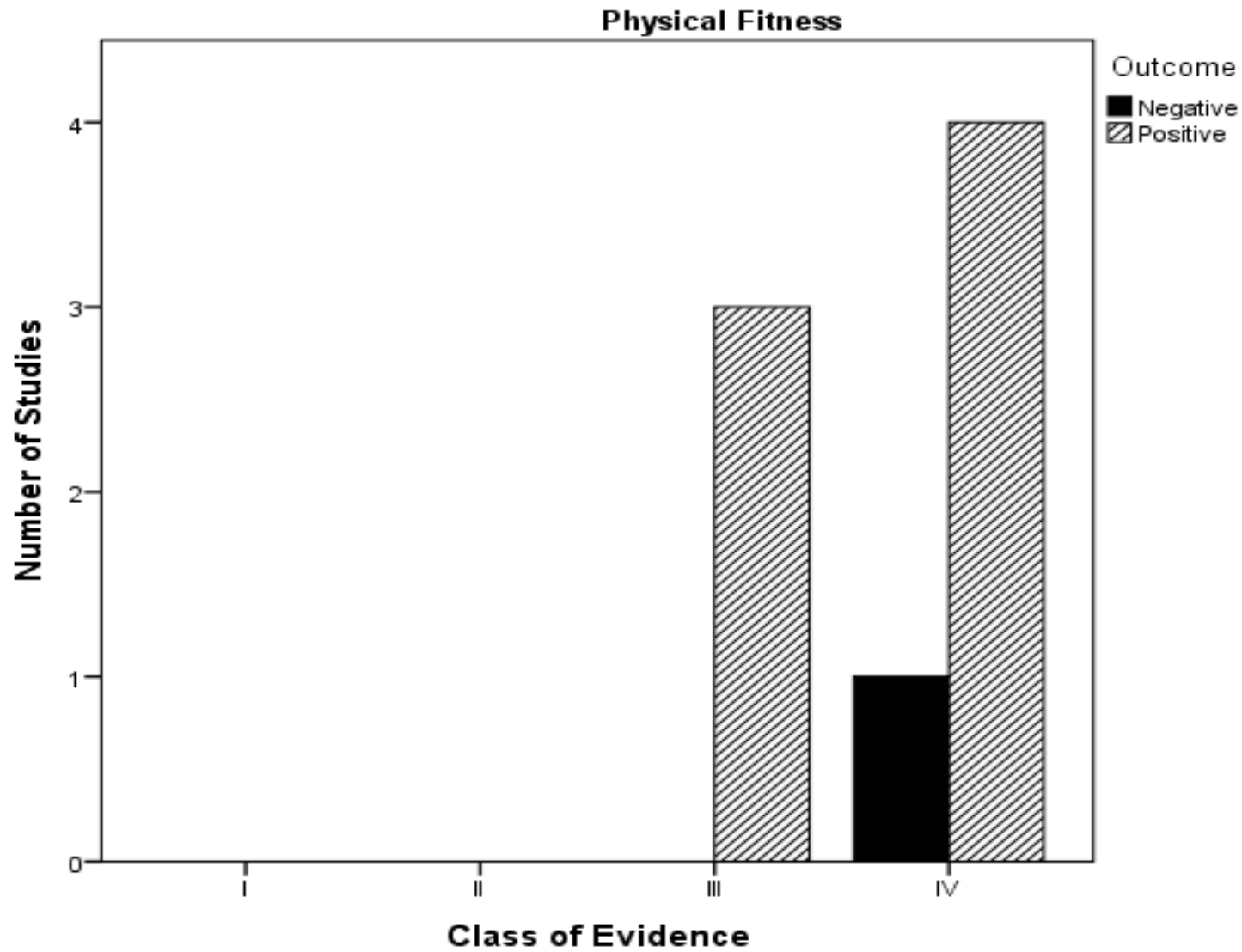
# Exercise and Cognition in MS

- Exercise training may be a behavioral approach for managing cognitive dysfunction in MS, but understudied
- Well-established literature in the general population
- 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
- Data in the literature on MS is mixed









# **Aerobic exercise increases hippocampal volume and improves memory in multiple sclerosis: Preliminary findings**

**V. M. Leavitt<sup>1,2</sup>, C. Cirnigliaro<sup>3</sup>, A. Cohen<sup>1</sup>, A. Farag<sup>3</sup>, M. Brooks<sup>3</sup>, J. M. Wecht<sup>3</sup>,  
G. R. Wylie<sup>1,2</sup>, N. D. Chiaravalloti<sup>1,2</sup>, J. DeLuca<sup>1,2</sup>, and J. F. Sumowski<sup>1,2</sup>**

<sup>1</sup>Kessler Foundation Research Center, West Orange, NJ, USA

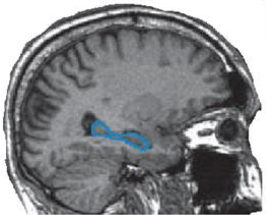
<sup>2</sup>Rutgers – New Jersey Medical School, Newark, NJ, USA

<sup>3</sup>James J. Peters VA Medical Center, Bronx, NY, USA

<sup>4</sup>Kessler Institute of Rehabilitation, West Orange, NJ, USA

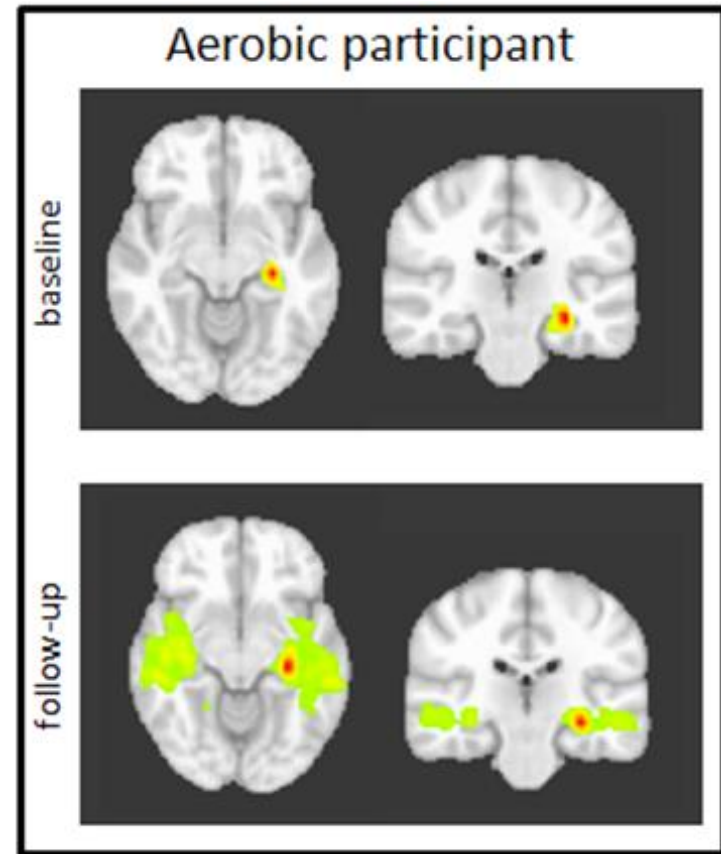
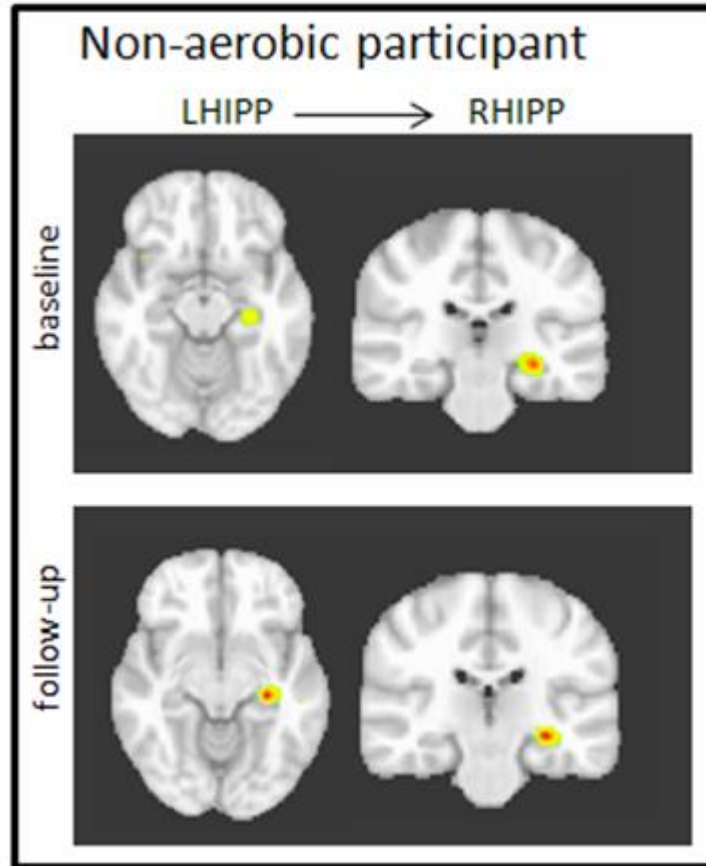
2 RRMS patients randomized to aerobic vs non-aerobic training  
30 min sessions, 3x/week for 3 months

# Memory and Aerobic Exercise



	Aerobic	Stretching
Hippocampus	+ 16.5%	+2.8%
Cerebral Grey Matter	+ 2.4%	+2.9%
Memory	+ 53.7%	+ 0.0%
Non-Memory Cognition	+ 0.0%	+ 0.0%

# Memory and Aerobic Exercise



# Treadmill Walking Exercise Training and Brain Function in Multiple Sclerosis: Setting the Stage for a Network-Based Approach to Rehabilitation

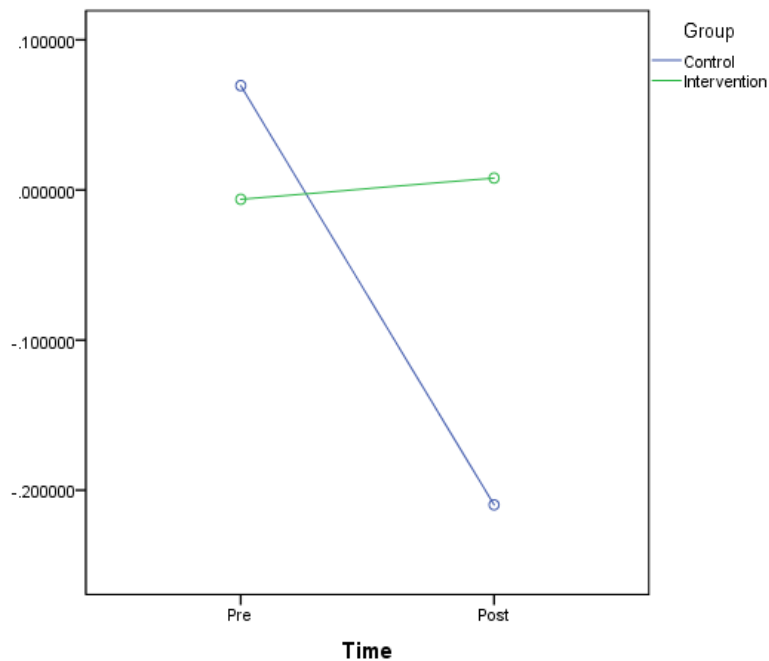
Brian M. Sandroff, Ph.D., Glenn R. Wyllie, Ph.D., Brad P. Sutton, Ph.D., Curtis L. Johnson, Ph.D., John DeLuca, Ph.D. & Robert W. Motl, Ph.D.

- 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:
  - right middle frontal gyrus (MFG;  $d=1.92$ )
  - anterior cingulate cortex (ACC;  $d=1.70$ )
- Intervention improved SDMT performance ( $d=0.72$ )
- Change in SDMT associated with RSFC change between thalamus and:
  - right MFG ( $r=.42$ )
  - ACC ( $r=.53$ )
- Supports exercises as adaptive compensatory mechanism

# RSFC with Thalamus Following Exercise

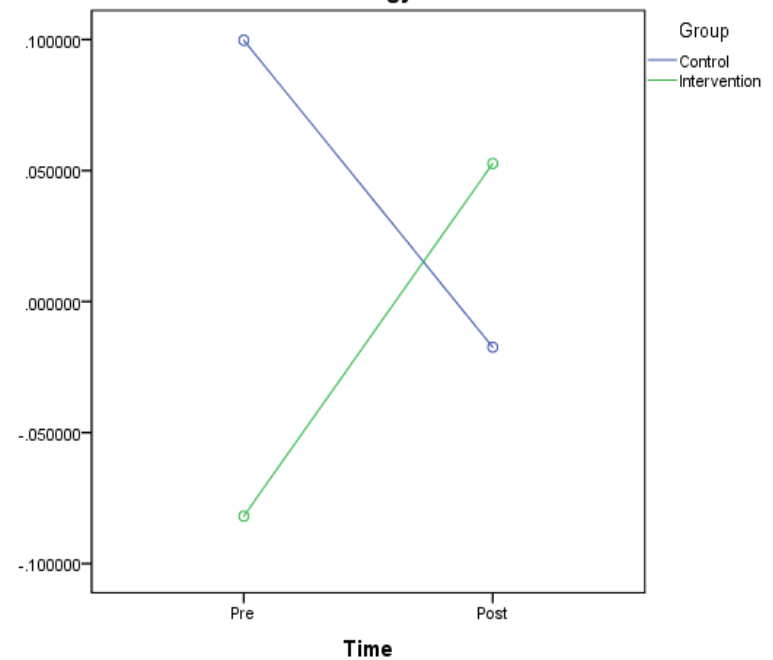
ACC

Resting-state functional connectivity between thalamus and anterior cingulate cortex



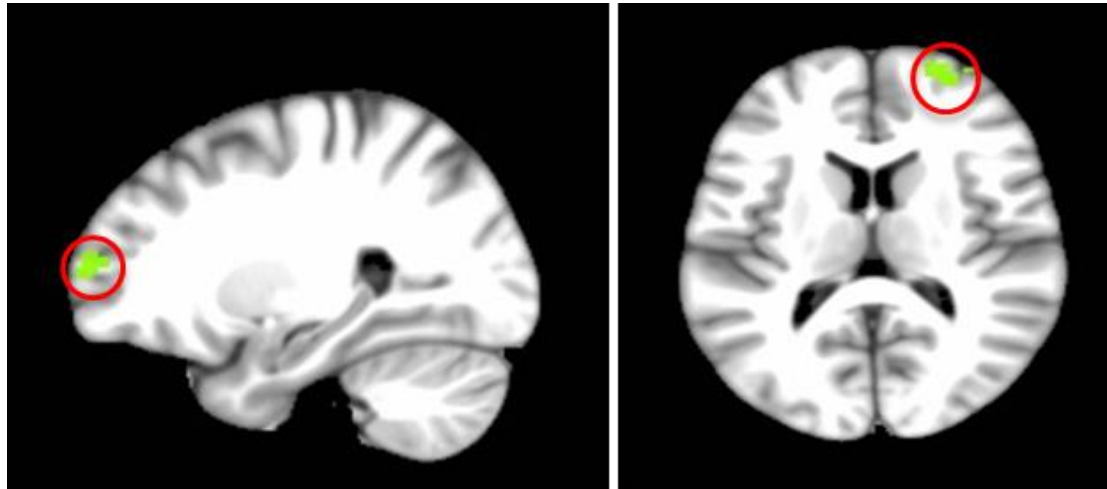
R Middle frontal gyrus

Resting-state functional connectivity between thalamus and right middle frontal gyrus

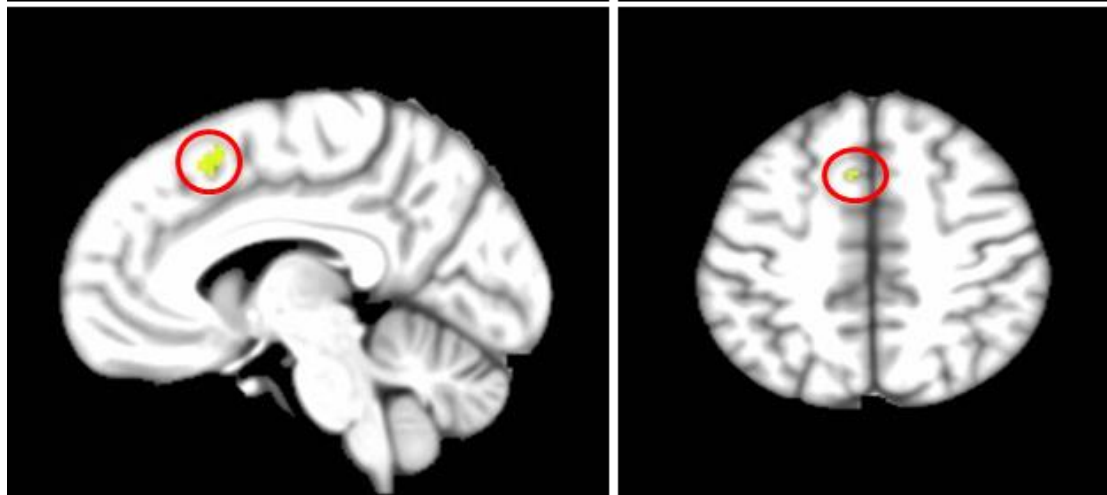


# Areas in which thalamic RSFC significantly increased following treadmill walking exercise training compared with waitlist control

MFG



ACC



# 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



# Overall Summary

- Cognitive Reserve and Brain Reserve protect against the negative effects of brain dysfunction in MS
  - Protects against cognitive decline
- Impact of Cognitive Reserve on cognition found over and above impact of Brain Reserve
- Environmental enrichment should be a major focus of rehabilitation on MS
  - Can we build cognitive reserve?
- Exercise may hold promise to improve cognition, but data is preliminary

# THANK YOU

## Acknowledgments

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Helen Genova, Ph.D.

Victoria Leavitt, Ph.D.

Ekaterina Dobryakova, Ph.D.



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# PANEL DISCUSSION I

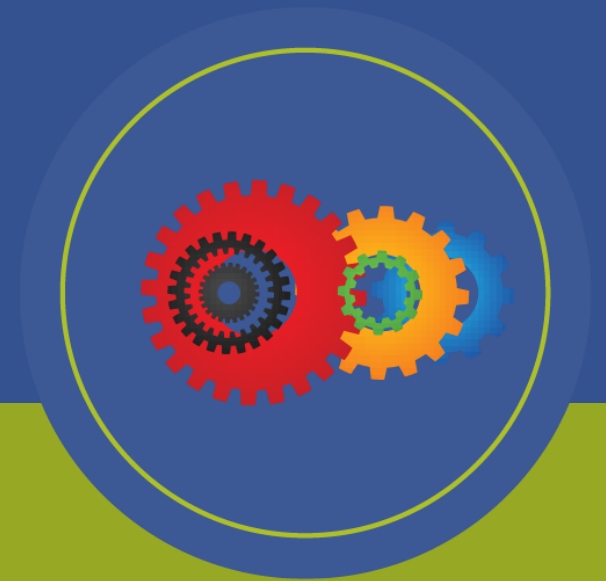
## Fatigue, Motivation & Physical Activity

Ekaterina Dobryakova, PhD

Helen Genova, PhD

Glenn Wylie, PhD

Moderator: Michele Pignatello



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# PANEL DISCUSSION II

## Wellness, Social Cognition, Everyday Life & Employment

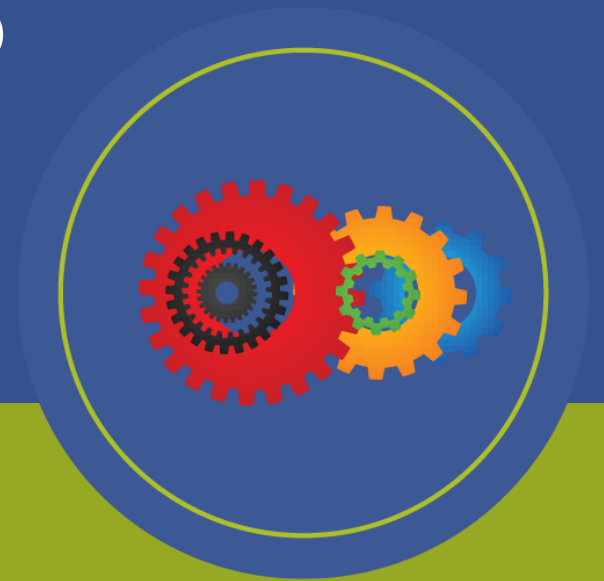
Helen Genova, PhD

Yael Goverover, PhD

Kimberly Beckwith-McGuire, PhD

Lauren Strober, PhD

Moderator: Michele Pignatello



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# CLOSING REMARKS

REMINDER Podcasts available at:  
[Kesslerfoundation.org/MS2017](http://Kesslerfoundation.org/MS2017)

THANK YOU!





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