A Behavioral and Neuroimaging Analysis of Cognitive Rehabilitation in Multiple Sclerosis

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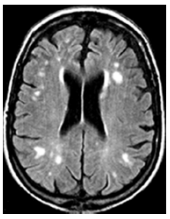
Overview

- Cognitive problems in MS
- Neuropsychological Profiles
  - Learning and Memory
  - Processing speed
- Cognitive Rehabilitation
  - Non RCT studies
  - RCT studies
- Cognitive Reserve, Imaging and Cognition

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
- 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 …"

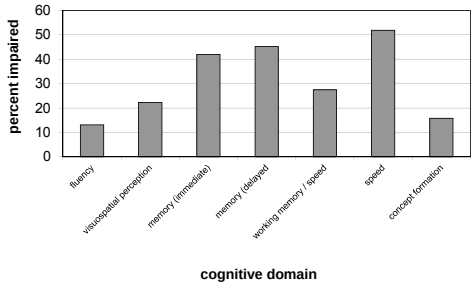
MS - Historical

- 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 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*

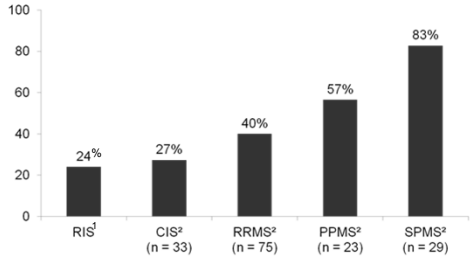
Spared Cognition in MS

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

Some Factors which affect Cognition in MS

Disease Course	RR < SP
Duration of disease	Sometimes
Physical Disability	Not always
Fatigue	Not necessarily
Depression	It may, not always
Stress	It may, not always
Gender	Males at increased risk

The frequency of cognitive impairment tends to increase over MS course



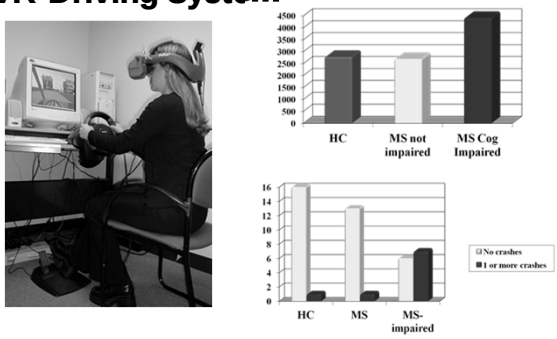
RIS, radiologically isolated syndrome; CIS, clinically isolated syndrome
[1] Amato, Neurology 2012; [2] Potagas, J Neurol Sci 2008

Cognitive Problems and Everyday Life Functioning in MS

- **Cognitive deficits negatively affect daily life including:**
  - Employment
  - Driving
  - Social and vocational activities
  - Household activities
  - Sexual functioning
  - Family activities
  - Internet functional activity (purchase airline tickets)
  - Overall QOL
  - Increased psychiatric illness
- **Beyond physical disability alone**

Goverover et al, 2010; Schultheis et al, 2001;Rao et al., 1991

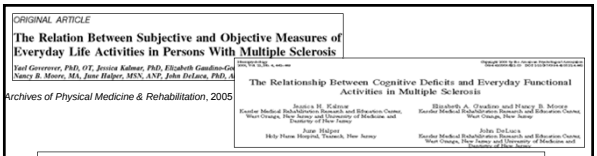
VR-Driving System



Schultheis et al (2001) Neurology, 56(8), 1089-94

How Assess Cognition?

- Neurologist assessment
  - No greater than chance (Peyser, 1982; Feinstien, 2015)
- Patient Self report
  - Predicts emotional distress
- Neuropsychological Evaluation
  - Correlated with brain imaging
  - Predicts everyday life activity
    - Employment
    - Cooking
    - Driving
    - Internet functional tasks (book airline ticket)
    - Other ADL's


ORIGINAL ARTICLE

The Relation Between Subjective and Objective Measures of Everyday Life Activities in Persons With Multiple Sclerosis

Yael Goverover, PhD, OT, Jessica Kalmar, PhD, Elizabeth Gaudino-Go
Nancy B. Moore, MA, June Halper, MSN, ANP, John DeLuca, PhD, A

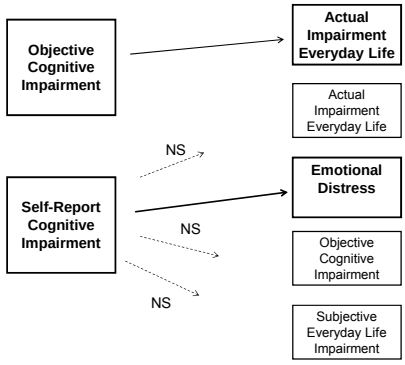
Archives of Physical Medicine & Rehabilitation, 2005

The Relationship Between Cognitive Deficits and Everyday Functional Activities in Multiple Sclerosis

Cognition and Everyday Life

- Objective cognitive impairment
- Subjective cognitive impairment
- Objective everyday functional activity
- Subjective everyday functional activity
- Emotional distress

Goverover et al., 2005; Kalmar et al., 2008



Goverover et al., 2005; Kalmar et al., 2008

Neuropsychological Profiles in MS

Information Processing Efficiency

speed of processing
and
working memory

WM Defined

temporary storage and active maintenance and manipulation of internal representations for on-line use (Baddeley, 2000).

Speed of Processing Defined

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

OR

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

Purpose

Examine whether Speed or WM ability is the primary Information Processing problem experienced by persons with MS

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

All MS vs. Controls

	Odds Ratio
Processing Speed Index	10.4
Working Memory Index	2.7

RRPM vs. Controls

	Odds Ratio
Processing Speed Index	5.3
Working Memory	1.3

SPMS vs. Controls

	Odds Ratio
Processing Speed Index	65.2
Working Memory Index	9.0

DeLuca et al, *JCEN*, 2004

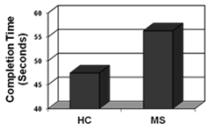
Can Processing Speed affect other Cognitive Functions?

Processing Speed and Executive Functions

Executive Function: Inhibition

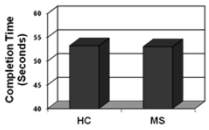
Color Word Interference Test (D-KEFS: Inhibition Trial)

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



HOWEVER

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

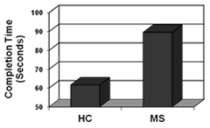


Leavitt et al (2014), *Rehab Psychol*

Executive Function: Switching

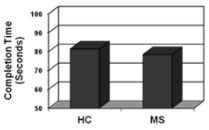
Trail Making Test (D-KEFS: Number-Letter Switching)

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



HOWEVER

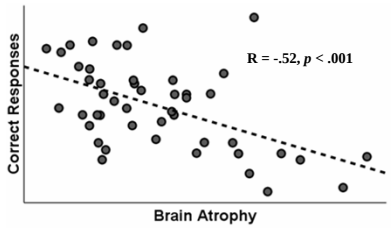
Group differences disappeared when controlling for the speed aspect of the task (Letter Sequencing Trial)
($F = 0.16$, $p > .5$, $\eta_p^2 = .00$)



Leavitt et al (2014), *Rehab Psychol*

Processing Speed

Symbol Digit Modalities Test (SDMT: Oral Version)



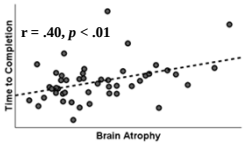
Brain atrophy is associated with slower processing speed.

Leavitt et al (2014), *Rehab Psychol*

Executive Function: Inhibition

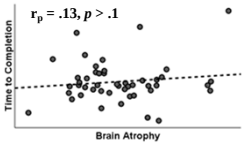
Color Word Interference Test (D-KEFS: Inhibition Trial)

Brain atrophy is associated with worse "Stroop" performance



HOWEVER

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

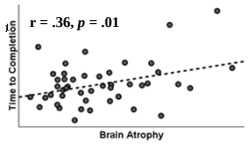


Leavitt et al (2014), *Rehab Psychol*

Executive Function: Switching

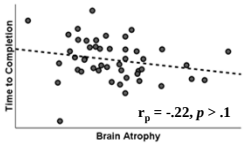
Trail Making Test (D-KEFS: Number-Letter Switching)

Brain atrophy is associated with worse Trail Making performance



HOWEVER

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



Leavitt et al (2014), *Rehab Psychol*

Conclusions

- Primary Cognitive problems in MS
  - Learning and Memory
  - Executive dysfunction
- Processing Speed may underlie many of the cognitive problems

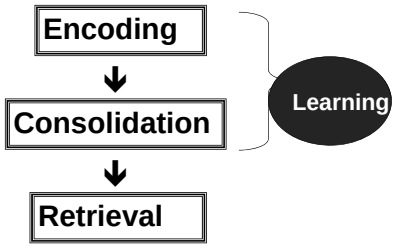
Learning and Memory

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"

Squire, 1987

Learning and Memory Process



Identifying the Cause

- Retrieval failure hypothesis ?
- Acquisition deficits?

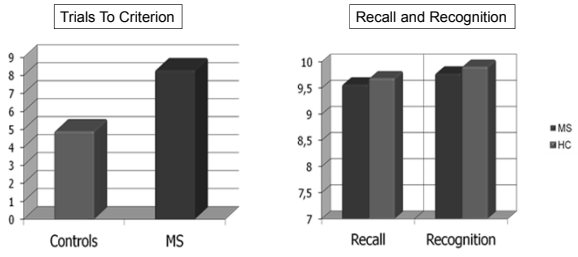
Train subjects to a learning criterion

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.

Journal of Clinical and Experimental Neuropsychology, 1994*, 16*, 183-189

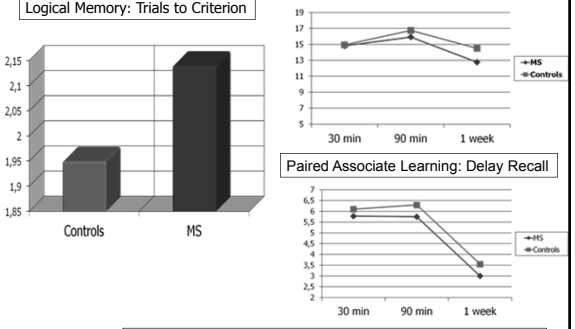
SRT Trials to Criterion



DeLuca et al., 1994, *J Clin Exp Neuropsych*

Logical Memory: Delayed Recall

Logical Memory: Trials to Criterion

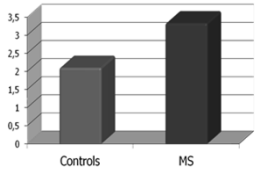


Paired Associate Learning: Delay Recall

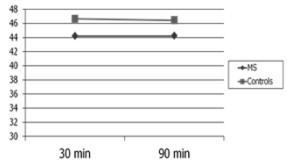
Demaree, et al. (2000). *Journal of Clinical and Experimental Neuropsychology,* 22(6), 865-873.

Facial Recognition (Demaree et al., 2000)

Trials to Criterion

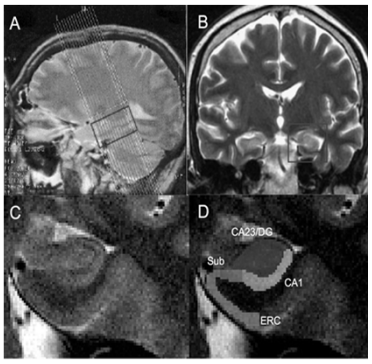


Recall



Demaree, et al. (2000). *Journal of Clinical and Experimental Neuropsychology,* 22(6), 865-873.

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

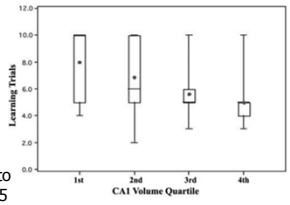
D. Subregional segmentation

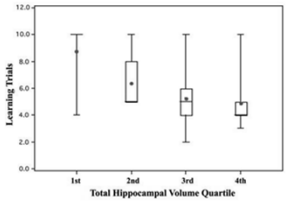
Sicotte et al. 2008, *Brain*

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

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
- Learning and Memory
- **Cognitive Rehabilitation**
  - **Non-RCT studies**
    - RCT studies
- Cognitive Reserve, Imaging, and Cognition

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

Self-generation as a means of maximizing learning in Multiple Sclerosis: An Application of the Generation Effect

Nancy Chiaravalloti, Ph.D
John DeLuca, Ph.D.

Archives of Physical Medicine & Rehabilitation
2002, 83, 1070-1079

Generation Effect

- 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

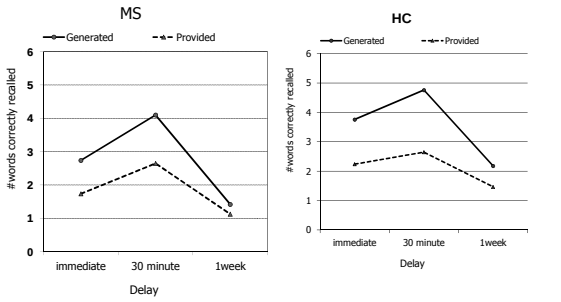
Generation Effect
Procedure

- 32 sentences presented individually
  - Generated Condition: 16 sentences with the last word omitted. S fill's in the blank.
  - Provided Condition: 16 sentences with full sentence. S has to recall the last word in the sentence
- Within group design

Sample Sentences
Generation Effect

- Provided Items
  - The bad boy was sent to his room.
  - The old milk tasted very sour.
- Generated Items
  - Water and sunshine help plants to _____.
  - It's unlucky to walk under a _____.

Recall- HC vs. MS



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

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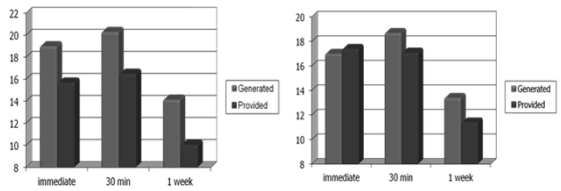
Arch Physical Medicine & Rehabilitation, (2008), 89(8), 1514-1521

Self-Generation and Everyday Life Activities

Meal Preparation

Managing Finances



Goverover et al., *Arch Physical Med & Rehab*, (2008)

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

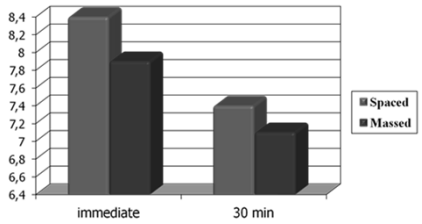
Ebbinghaus, 1885/1994

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

Goverover et al., *J Exp Clin Neuro Psych*, (2009)

Paragraph from Newspaper in MS



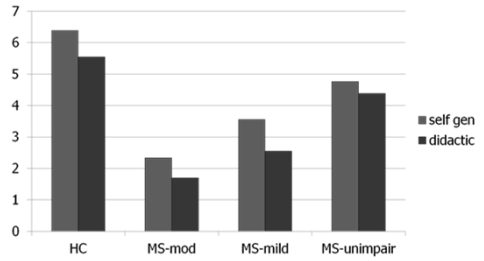
Goverover et al., *J Exp Clin Neuro Psych*, (2009)

Self-generated Learning in People with Multiple Sclerosis

Michael R. Basso
Natasha Lowery
Courtney Ghormley
Dennis Combs
Jay Johnson

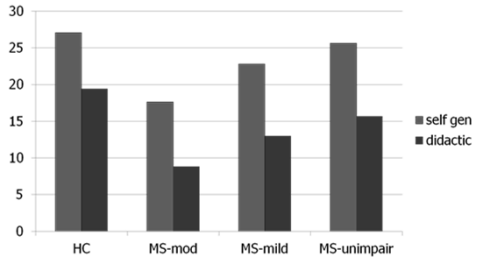
Journal of Clinical Experimental Neuropsychology, 2006, 12, 640-648

Recall of Names



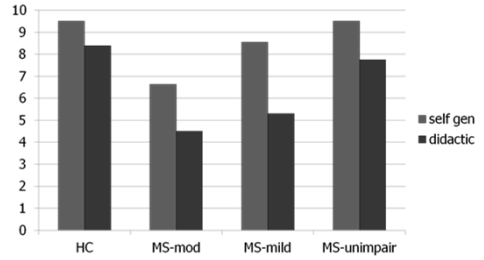
Basso et al., 2006

Recall of Appointments



Basso et al., 2006

Recall of Object Locations



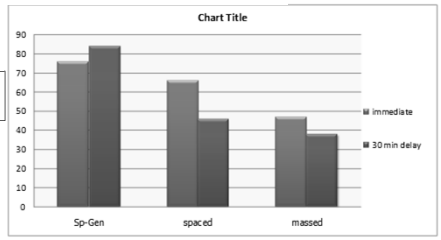
Basso et al., 2006

Combined Self-Generation and Spaced Learning

Research Paper

Examining the benefits of combining two learning strategies on recall of functional information in persons with multiple sclerosis

Yael Goverover[1,2], Michael Basso[3], Hali Wood[3], Nancy Chiaravalloti[3,4] and John DeLuca[3,4]



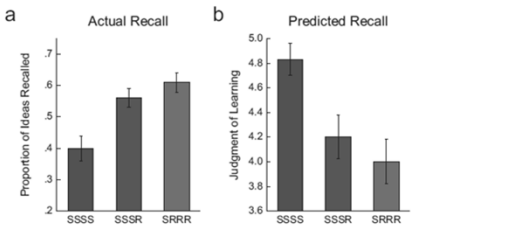
Mean Recall of Appointments

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



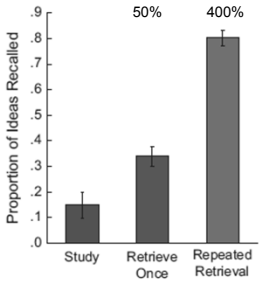
SSSS – study 4 times
SSSR – study 3 times then recall once
SRRR – study 1 time then recall 3 times

Reading educational texts

Karpicke (2012) Psychological Science, 21(3) 157-163.

Active Retrieval during Learning enhances deep and conceptual encoding

One week recall



RED – study once
BLUE- study, recall, re-study
GREEN – alternate study/recall 4 times

Karpicke (2012) Psychological Science, 21(3) 157-163

Neuropsychology
2010, Vol. 24, No. 2, 267-272

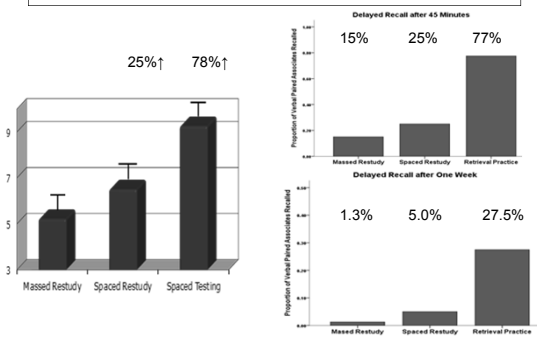
0894-4105/10/$12.00 DOI: 10.1037/a0017533

BRIEF REPORTS

Retrieval Practice Improves Memory in Multiple Sclerosis: Clinical Application of the Testing Effect

James F. Sumowski, Nancy Chiaravalloti, and John DeLuca
Kessler Foundation Research Center and University of Medicine and Dentistry of New Jersey

Testing Effect in MS (Mean Words recalled)



Sumowski, et al., *Neuropsychology,* 2010; Sumowski et al *MSJ.* In Press

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- **Cognitive Rehabilitation**
  - **Non-RCT studies**
  - **RCT studies**
- Cognitive Reserve, Imaging, and Cognition

Cognitive Rehabilitation: Behavioral Approaches

Sample RCT results

Learning and Memory

Multiple Sclerosis 2005; 11: 58–68
www.multiplesclerosisjournal.com

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

Nancy D Chiaravalloti[1,2,*], *John DeLuca*[1,2,3], *Nancy B Moore*[2] *and Joseph H Ricker*[2,*]
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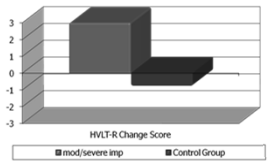
Context and Imagery

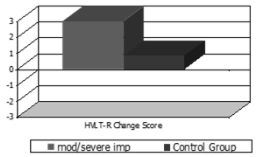
HVLT-R Mod/Severe vs. Placebo
Baseline to follow-up

p<.01



Baseline to immediate change

p<.05

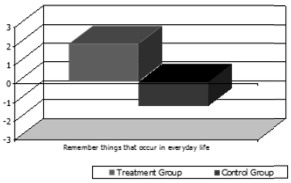


Baseline to long-term change

Chiaravalloti et al, *Multiple Sclerosis*, 2005

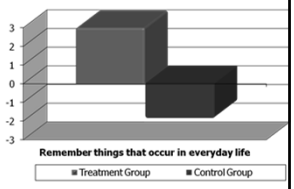
Self-report Memory Impairment (n=28)
Baseline to follow-up

p<.01



Baseline to immediate change

p<.001



Baseline to long-term change

Chiaravalloti et al, *Multiple Sclerosis*, 2005

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

Context and Imagery

Classification of evidence: This study provides Class I evidence that the mSMT behavioral intervention improves both objective memory and everyday memory in patients with MS over 5 weeks, with treatment effects lasting over a 6-month period. *Neurology*® 2013;81:2066-2072

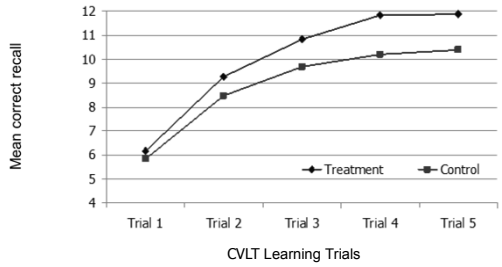
AMERICAN ACADEMY OF NEUROLOGY®

Memory Retraining in MS

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

Chiaravalloti et al, 2013, *Neurology*

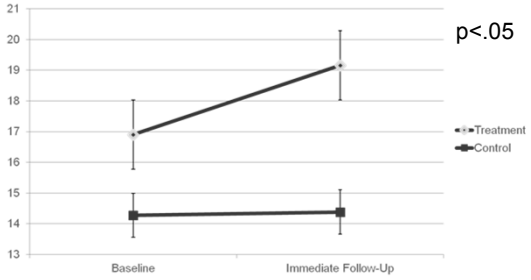
Learning by Group: Post-treatment*



* No significant group difference at baseline

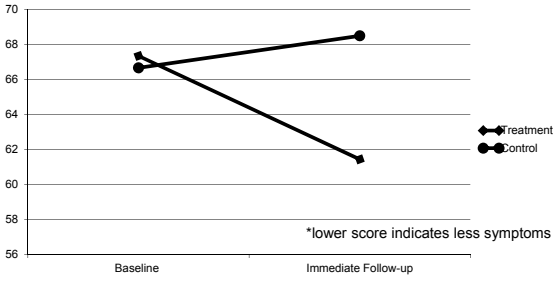
p=.02, controlling for baseline

Everyday Life Self-Report
FAMS General Contentment



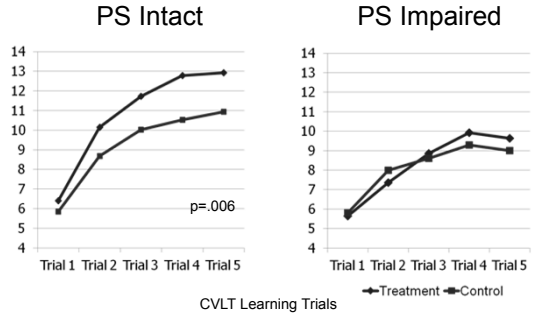
Chiaravalloti et al., *Neurology*, 2013

Everyday Life Self-Report
FrSBe Total Score, Family Form



Chiaravalloti et al., *Neurology*, 2013

Learning by Group (post-treatment*)



* No significant group difference pre-treatment

J Neurol
DOI 10.1007/s00415-011-6353-x

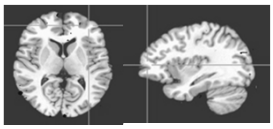
ORIGINAL COMMUNICATION

Increased cerebral activation after behavioral treatment for memory deficits in MS

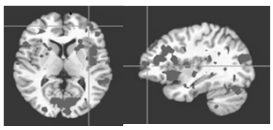
Nancy D. Chiaravalloti · Glenn Wylie · Victoria Leavitt · John DeLuca

Brain changes after behavioral treatment for memory impairment in MS using fMRI

Changes in Brain Functioning in MS



- Pre-training
- Treatment minus control



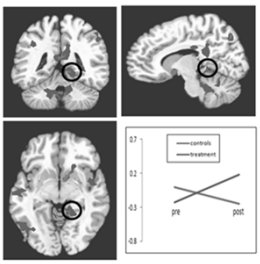
- Post-training
- Treatment minus control

Increased activation in frontal and occipital regions in treatment group that is not evident prior to treatment (p<.05)

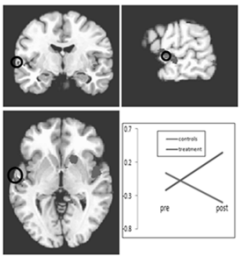
Chiaravalloti et al., 2012, *J Neurol*

BOLD activation change from pre- to post-treatment

parahippocampal gyrus



superior temporal gyrus

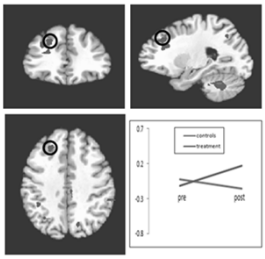


MS – red
HC - blue

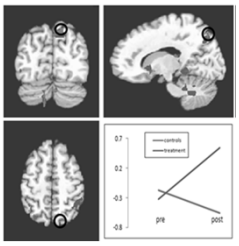
Chiaravalloti et al., 2012, *J Neurol*

BOLD activation change from pre- to post-treatment

middle frontal gyrus



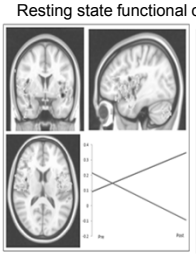
precuneus



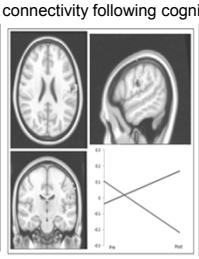
MS – red
HC - blue

Chiaravalloti et al., 2012, *J Neurol*

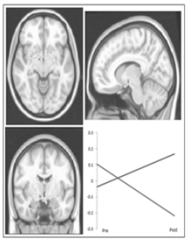
Resting state functional connectivity following cognitive rehabilitation in MS



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



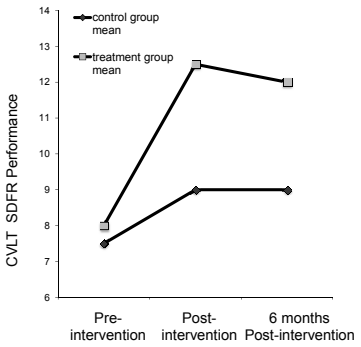
Increased connectivity from PCC to thalamus bilaterally in treatment group after TX

Red line tx; blue line controls

Leavitt et al, *Brain Imaging & Beh*, 2013

6 month follow-up

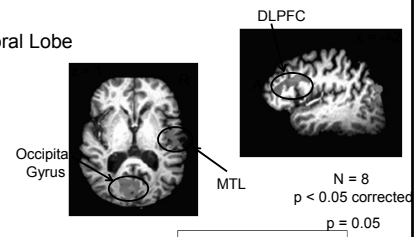
Behavioral Performance



Dobryakova et al., 2014

Encoding Results

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

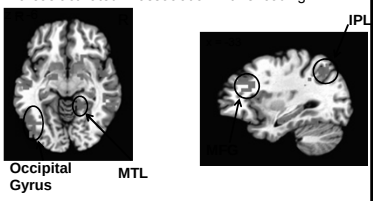


Dobryakova et al., 2014

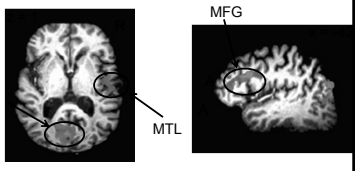
Area more activate in the treatment group vs control group during memory encoding

pre-intervention x post-intervention

Brain areas activated in association with encoding



post-intervention x 6months post-intervention



Dobryakova et al., 2014

Executive Functions, PS and Attention

Contents lists available at ScienceDirect
Journal of the Neurological Sciences
journal homepage: www.elsevier.com/locate/jns

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]

- computer-based intervention (RehaCom) for attention, PS & EF in RRMS
- 20 RRMS randomized into Treatment vs control:

TG: RehaCom cognitive rehabilitation for 12 weeks (1 hr session, 3 days a week).
CG: no rehabilitation.

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

Mattioli et al (2010), *J of Neurol Sci*

Median change score from T0 to T1

	CG =10	TG=10	p-value
PASAT 2	0	22	.004
PASAT 3	7	36	.023
WCST te	45	20	.037
WCST pr	37	17.5	.08
WCSTpe	28.5	14.5	.051
SDMT	38	34.5	ns
MADRS	14	4.5	.01
MSQoL	155	189	ns

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[1]

Massimo Filippi, MD
Gianna Riccitelli, PhD
Flavia Mattioli, MD
Ruggero Capra, MD
Chiara Stampatori, PhD
Elisabetta Pagani, MSc
Paola Valsasina, MSc
Massimiliano Copetti, PhD
Andrea Falini, MD
Giancarlo Comi, MD
Maria Assunta Rocca, MD

Radiology, 2012

20 RR MS randomly assigned to 2 groups

* Computerized cognitive treatment for attention, information processing and executive function

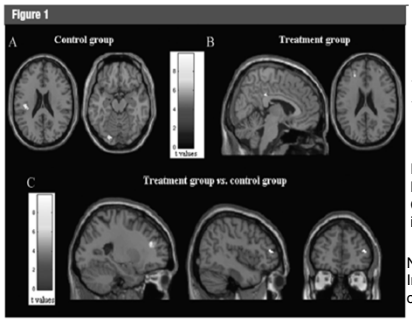
* no treatment group

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

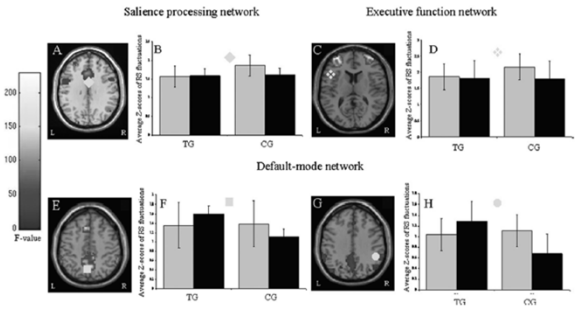


Increased Dorsolateral PFC bilaterally in Treatment group after treatment

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



Significant increase (or stability) of resting state FCC over time in TG vs CG

Grey – baseline black- f/up

Filippi et al, *Radiology,* 2012

DOI 10.1007/s11682-012-9160-9

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

TG ONLY: Increased FC of ACC with:

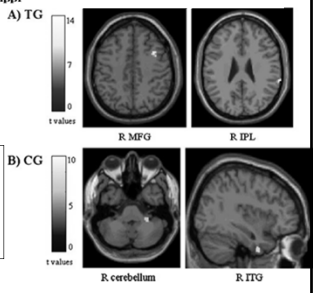
R MFG
R IPL

correlated with PASAT

CG ONLY: decreased FCC of ACC with

R cerebellum
R ITG

No correlation with cognition



Functional connectivity following Cognitive Rehabilitation

Multiple Sclerosis and Related Disorders 1 (2012) 168–173
Contents lists available at SciVerse ScienceDirect
Multiple Sclerosis and Related Disorders
journal homepage: www.elsevier.com/locate/msard
ELSEVIER

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

Median change score from T2 & T0

	CG =11	TG=13	p-value
PASAT 2	0	13	ns
PASAT 3	3	20	.05
WCST te	17	40.3	ns
WCST pr	14	31.5	ns
WCSTpe	15	27	.05
SDMT	2	3	ns
MADRS	3	8	.05
MSQoL	13	33	.05

NO impact on memory performance

6 mo follow-up data: Mattioli et al, 2012, MSRD

Slide 92

j7 jdeluca, 5/25/2012

J Neurol (2015) 262:91–100
DOI 10.1007/s00415-014-7528-z

ORIGINAL COMMUNICATION

Computer-aided cognitive rehabilitation improves cognitive performances and induces brain functional connectivity changes in relapsing remitting multiple sclerosis patients: an exploratory study

S. Bonavita · R. Sacco · M. Della Corte · S. Esposito · M. Sparaco · A. d'Ambrosio · R. Docimo · A. Bisecco · L. Lavorgna · D. Corbo · S. Cirillo · A. Gallo · F. Esposito · G. Tedeschi

Cog impaired RR assigned to cog rehab (n=18) or control (n=18)
8 weeks TX, 2x per week
Pre-post RS-FC and structural imaging (brain volume; lesion load)

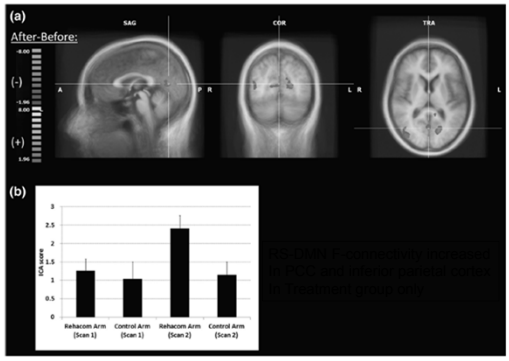
RehaCom – computer-based cognitive rehabilitation. Sessions:
- Attention and concentration
- Plan a day
- Divided attention
- reaction behavior
- Logical thinking

	RRMS before cCR (no. 18) (corrected score: mean ± SD)	RRMS after cCR (no. 18) (corrected score: mean ± SD)	RRMS before vs. RRMS after cCR *p* value
LTS	37.44 ± 3.82	39.42 ± 10.97	0.69
CLTR	25.05 ± 1.09	29.08 ± 8.36	0.26
10/36 SPART	13.98 ± 3.09	16.81 ± 5.14	0.07
SDMT	23.45 ± 4.22	28.22 ± 7.99	**0.01**
PASAT 3″	30.62 ± 9.41	40.00 ± 7.76	**0.00**
PASAT 2″	20.85 ± 3.54	24.42 ± 6.11	**0.03**
SRT-D	6.87 ± 1.27	8.17 ± 1.77	**0.02**
10/36 SPART-D	4.13 ± 1.50	5.65 ± 2.35	**0.04**
WLG	17.11 ± 4.24	16.84 ± 2.82	0.85
SCWIT	100.46 ± 0.53	89.66 ± 28.42	0.10

NO significant pre-post differences on NP in control group

NO significant pre-post differences in brain volume or lesion load in either group

Bonavita et al (2015) *J of Neurol*



RS-DMN F-connectivity increased in PCC and inferior parietal cortex in Treatment group only

Bonavita et al (2015) *J of Neurol*

Computer-Assisted Cognitive Rehabilitation of Attention Deficits for Multiple Sclerosis: A Randomized Trial With fMRI Correlates

Neurorehabilitation and Neural Repair
27(4) 284–295
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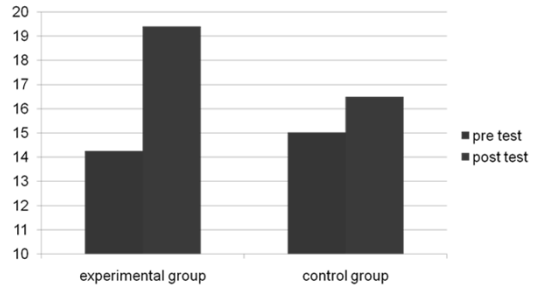
DOI: 10.1177/1545968312465194
nnr.sagepub.com
SAGE

Antonio Cerasa, PhD[1], Maria Cecilia Gioia, PhD[1], Paola Valentino, MD[2], Rita Nisticò, MD[2], Carmelina Chiriaco, PhD[1], Domenico Pirritano, MD[2], Francesco Tomaiuolo, PhD[3], Graziella Mangone, MD[1], Maria Trotta, MD[2], Tiziana Talarico, MD[2], Giacinta Bilotti, MD[2], and Aldo Quattrone, MD[1,2]

RR with impaired PS, attention, WM or EF assigned to cog rehab (n=12) or control (n=11)
6 weeks TX, 2x per week
Pre-post fMRI during PVSAT; Lesion load

RehaCom – computer-based cognitive rehabilitation. Sessions:
- Attention and concentration
- Divided attention
- Vigilance

Stroop Performance

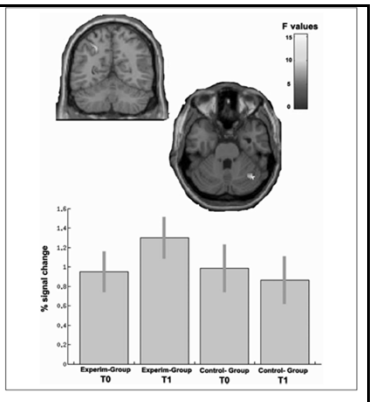


Cerasa et al (2012), *Neurorehab & Neural Repair*

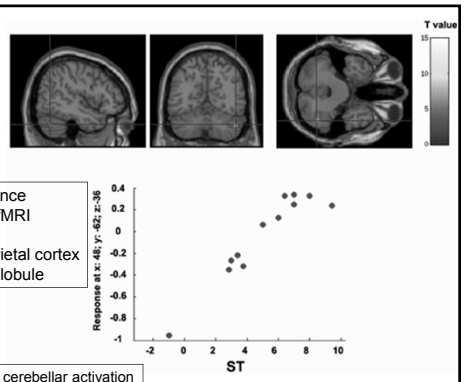
Tx group vs control showed:

Increased activation in
L posterior parietal cortex
R posterior cerebellar lobule

(group x time interaction)



Cerasa et al (2012), *Neurorehab & Neural Repair*



Stroop performance
Correlated with fMRI activation in:
Left superior parietal cortex
Right cerebellar lobule

Figure illustrates cerebellar activation

Cerasa et al (2012), *Neurorehab & Neural Repair*

Cognitive Rehabilitation in MS

It works!

Video Games and Cognitive Rehabilitation

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

A Consensus on the Brain Training Industry from the Scientific Community

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

STANFORD CENTER ON LONGEVITY

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."

"A Consensus on the Brain Training Industry… ", accessed (April 29, 2015), http://longevity3.stanford.edu/blog/2014/10/15/the-consensus-on-the-brain-training-industry-from-the-scientific-community/

Overview

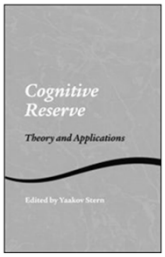
- Cognitive problems in MS
- Learning and Memory
- Cognitive Rehabilitation
- **Cognitive Reserve, Imaging and Cognition**

Clinical Expression of Neurologic Disease

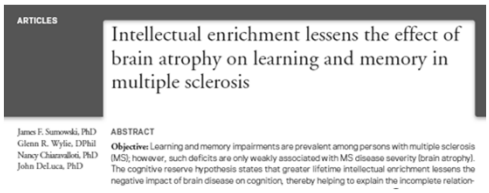
- Not everyone with Alzheimer's Disease develops dementia
- Alzheimer's Disease (AD)
  - Persons without clinical dementia can meet post-mortem neuropathological criteria for AD
    Katzman, *et al., (1988), Ann Neurol*, 23, 138-144
    Crystal, *et al.,* (1988), *Neurology,* 11, 1682-1687
    Price & 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.



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

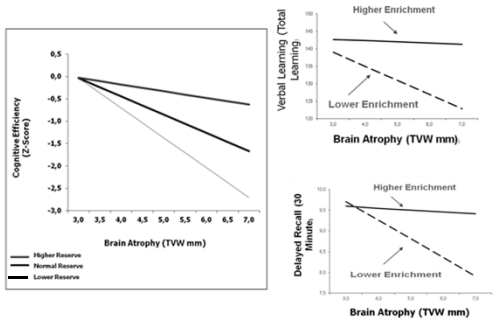
ABSTRACT

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-

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

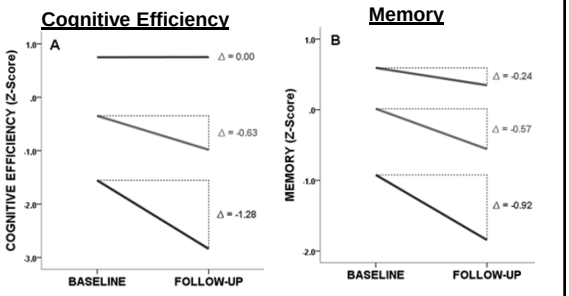
Does Cognitive Reserve Moderate the Relationship between Brain Imaging and Cognitive status in multiple sclerosis?

Cognitive Reserve in MS



Sumowski et al., *J. Clin. Exp. Neuropsyc.* 2009
Sumowski et al., *J. Int. Neuropsych. Soc.* 2009

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



Blue=Hi; **Green** Mod; **Red** Low CR | Sumowski et al, *Neurology, 2014*

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.

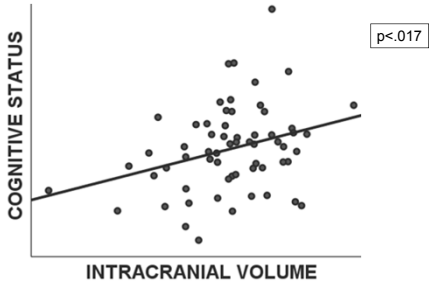
Persons with larger lifetime brain growth/size have more brain to lose before suffering cognitive decline.

Satz., *Neuropsychology;* 1993;7:273-295.
Stern et al., *JINS* 2002;8:448-460.

Brain Reserve in MS

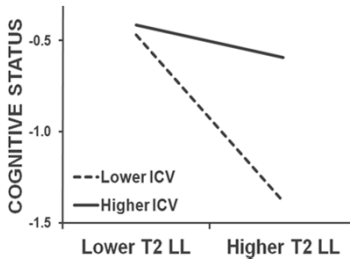
Does larger maximal lifetime brain growth (estimated with intracranial volume) protect MS patients from disease-related cognitive deficits?

Results: Brain Reserve



Sumowski et al (in Press), *Neurology*

Results: Brain Reserve



Sumowski et al (in Press), *Neurology*

Brain Reserve Results

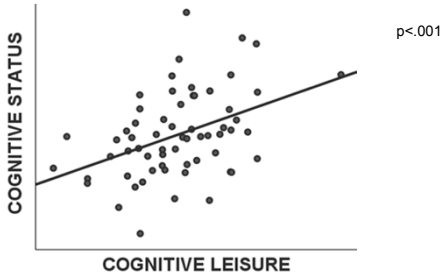
- Higher "brain reserve" (larger brain size) protects against expression of cognitive impairment in persons with MS

Question

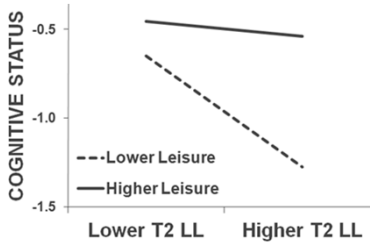
Does intellectual enrichment (cognitive reserve) protect MS patients from cognitive impairment independently of maximal lifetime brain size (brain reserve)?

Do people have control over their own destiny?

Results: Cognitive Reserve



Results: Cognitive Reserve after factoring our Brain Reserve



Sumowski et al (in Press), *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?

Overall Summary

- Cognitive impairment in 2/3 persons with MS
- Significantly affects everyday life activities
- Learning & memory, Processing speed major cognitive problems
- Rehabilitation can improve cognition and everyday life activity
- Cognitive Reserve protects against the negative effects of brain dysfunction in MS

Cognitive Rehabilitation: 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:
  - Whom? What? How? When? Dosage? (boosters)
- Multidimensional approach to research and treatment
  - Cognitive, medication, exercise