COGNITIVE AND BRAIN CHANGES IN MULTIPLE SCLEROSIS

MARCH 27, 2017

Esther Fujiwara, Ph.D. (efujiwara@ualberta.ca)
Department of Psychiatry, University of Alberta

Objectives

1. Identify cognitive challenges in multiple sclerosis and their measurement.
2. Understand the importance of brain and cognitive reserves.
3. Learn about how to keep and build active minds and healthy brains.

Overview

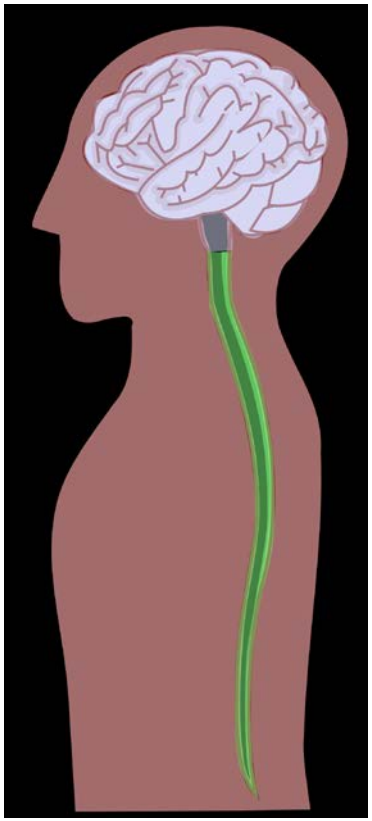
- Brain & Cognition in MS
- Measuring Cognitive Challenges in MS
- Brain/Cognitive Reserve
- What To Do

Overview

- Brain & Cognition in MS
- Measuring Cognitive Challenges in MS
- Brain/Cognitive Reserve
- What To Do

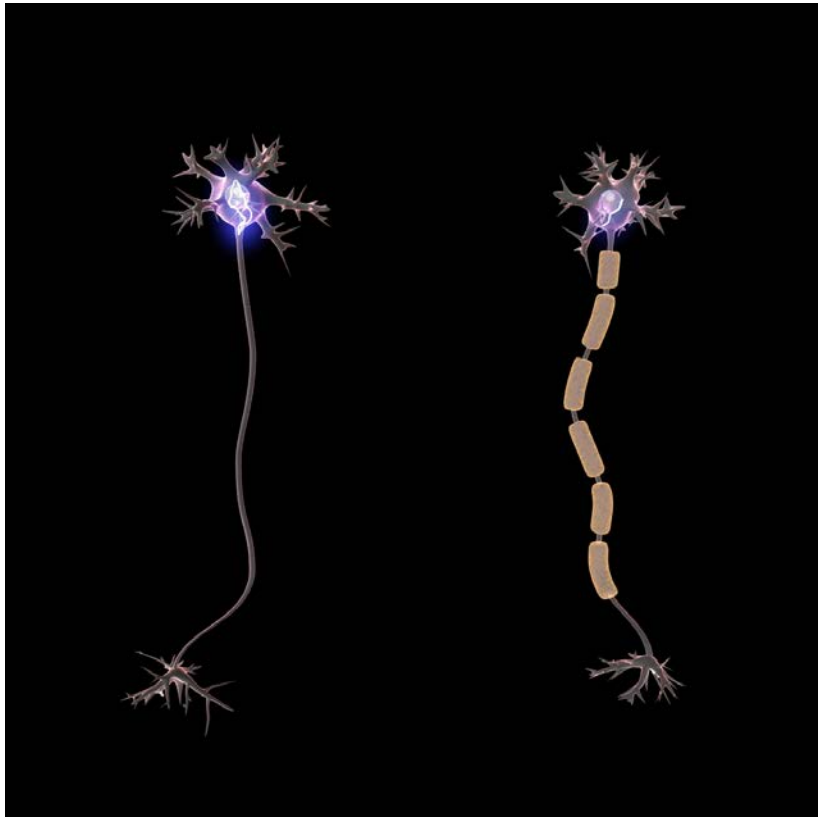
Brain changes in MS

- In MS, the immune system mistakenly attacks and damages the central nervous system (CNS).



Brain changes in MS

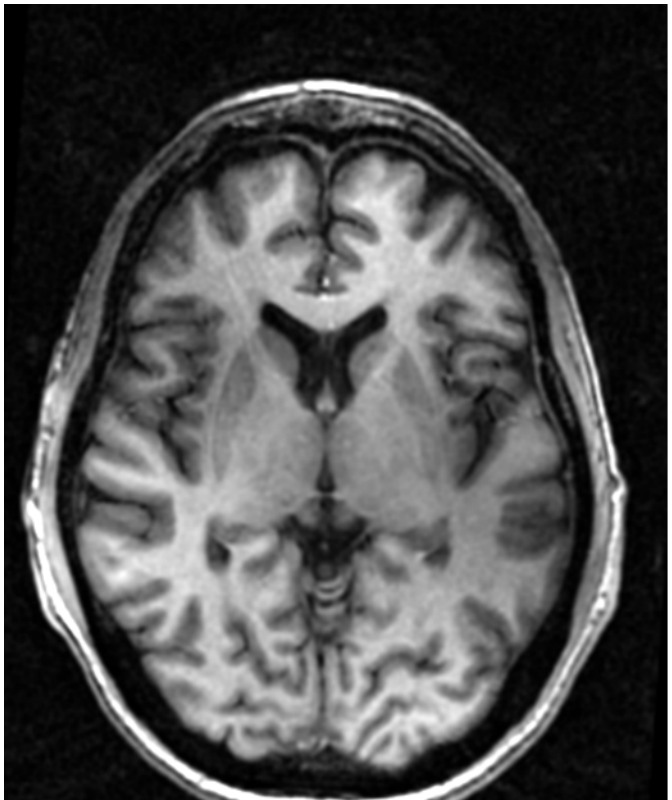
- Damage to the brain's white matter slows information throughput.

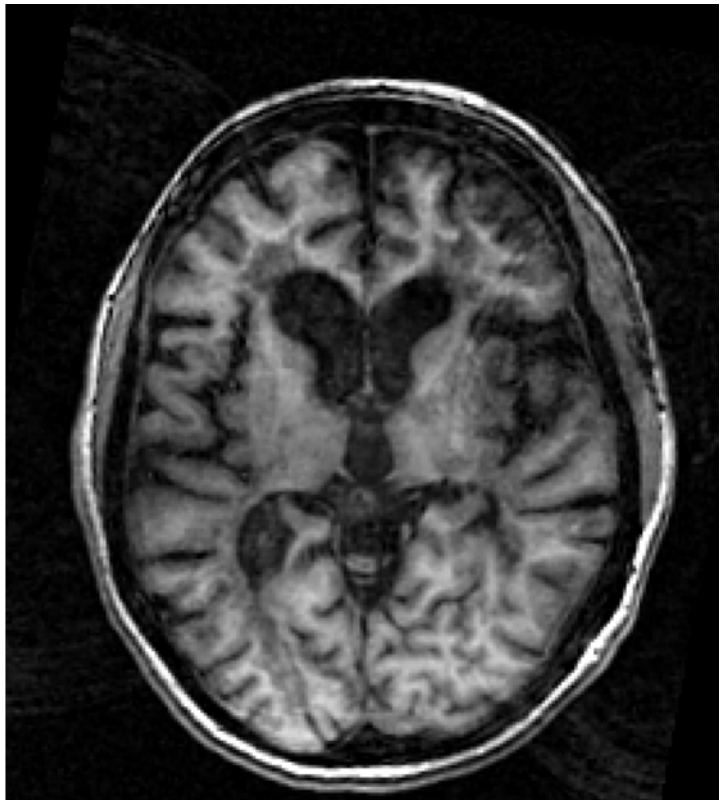


By Dr. Jana - http://docjana.com/#/saltatory

Brain changes in MS

- In addition to lesions, there is brain tissue loss (atrophy).
- If MS is left untreated, tissue loss is faster and more pronounced in pwMS (~ premature “brain aging”).



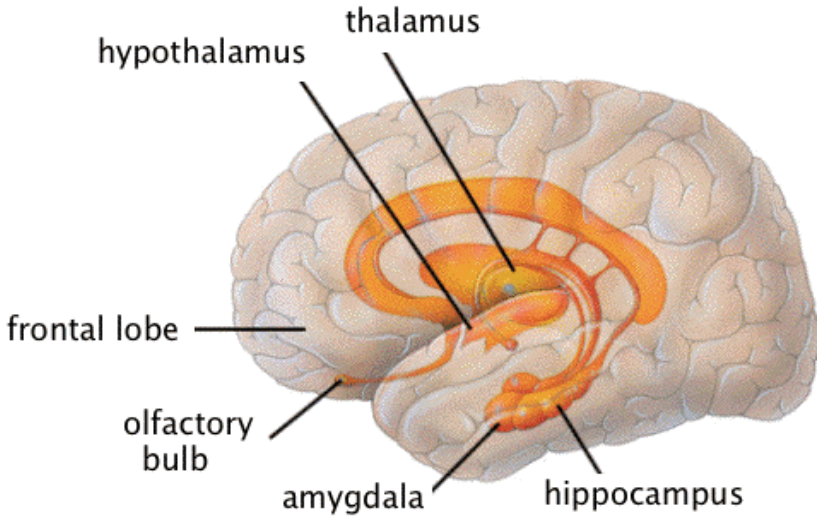


Cognition and brain changes in MS

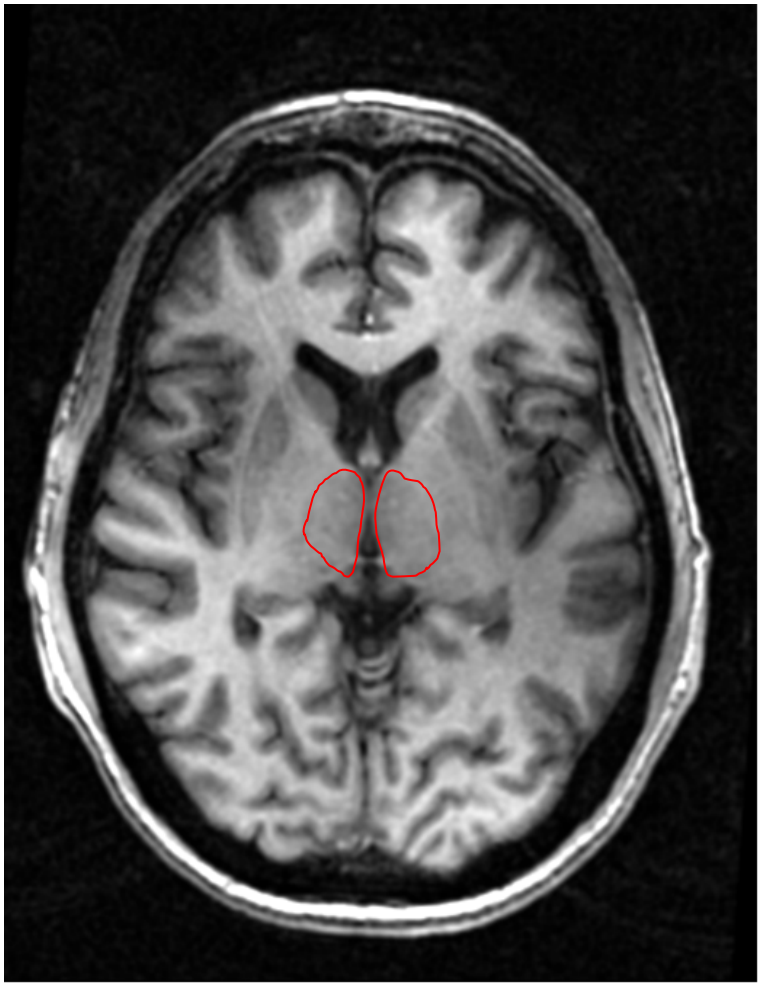
- Most of the brain changes observed in MS relate to changes in cognitive functions.

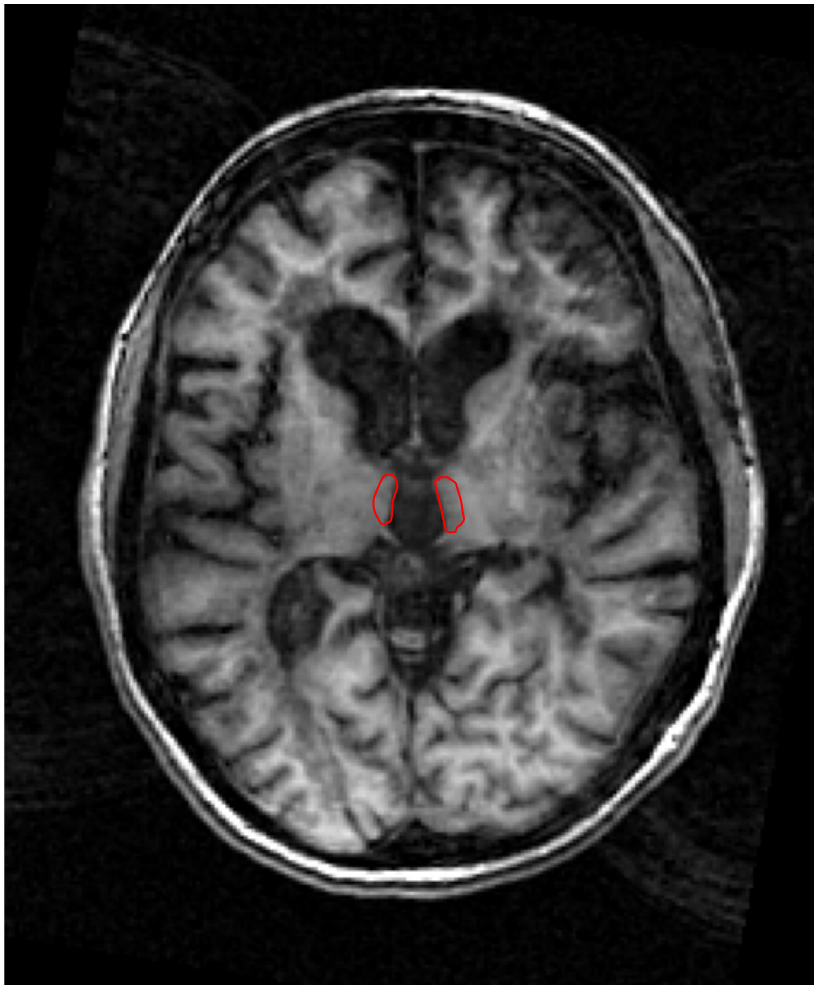
In particular:

- Thalamus
- Hippocampus
- Pre-frontal/ frontal cortex
- Connections between these

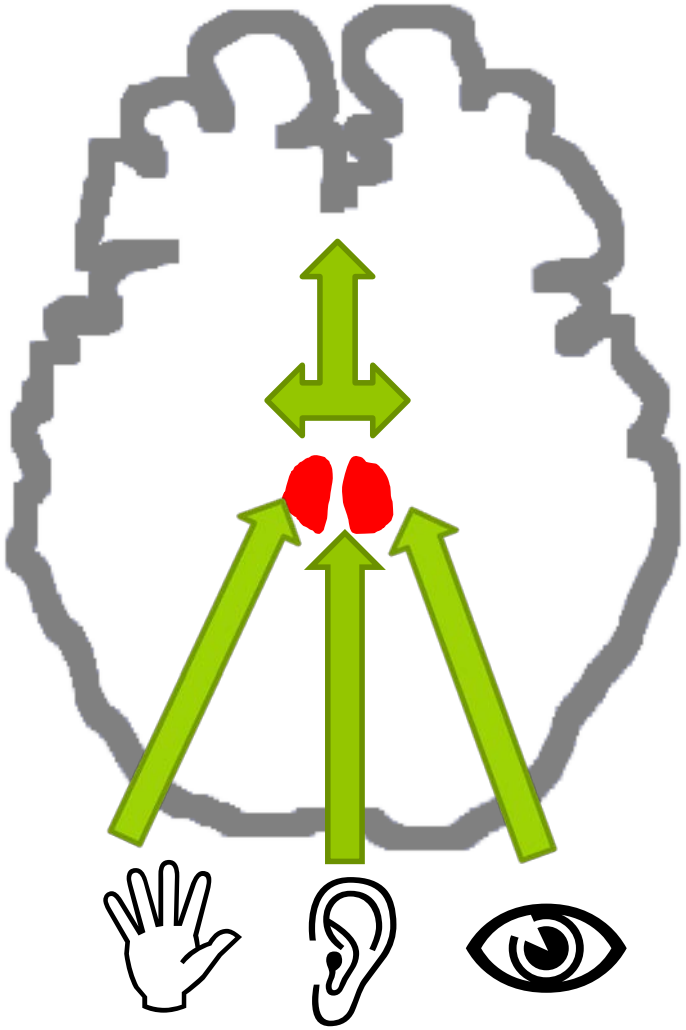


Thalamus & cognition in MS



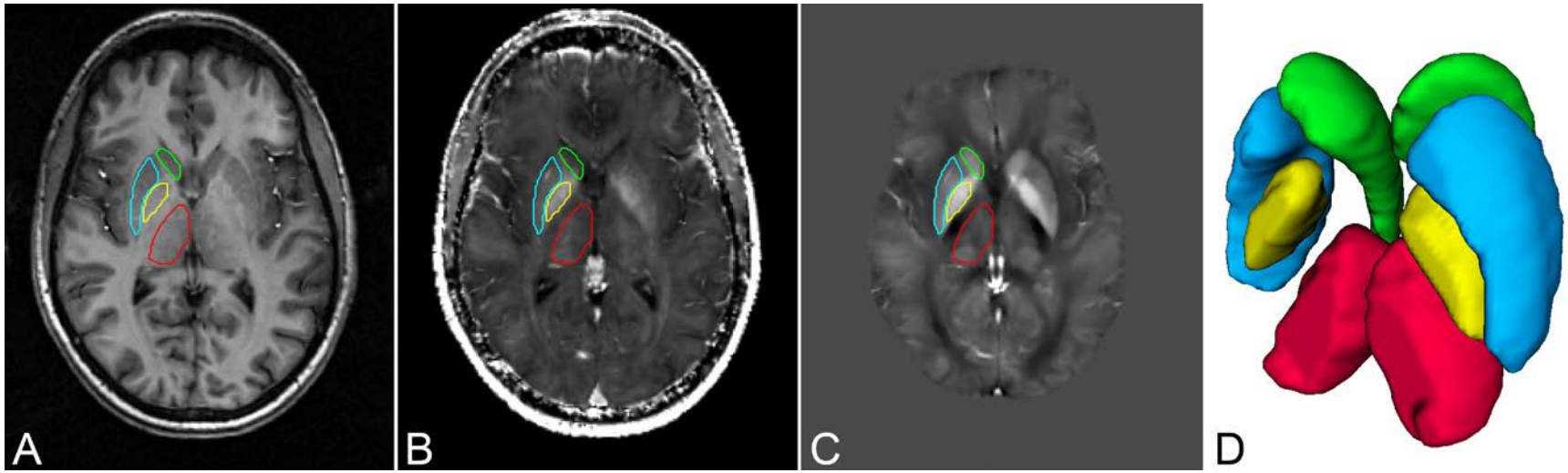


Thalamus & cognition



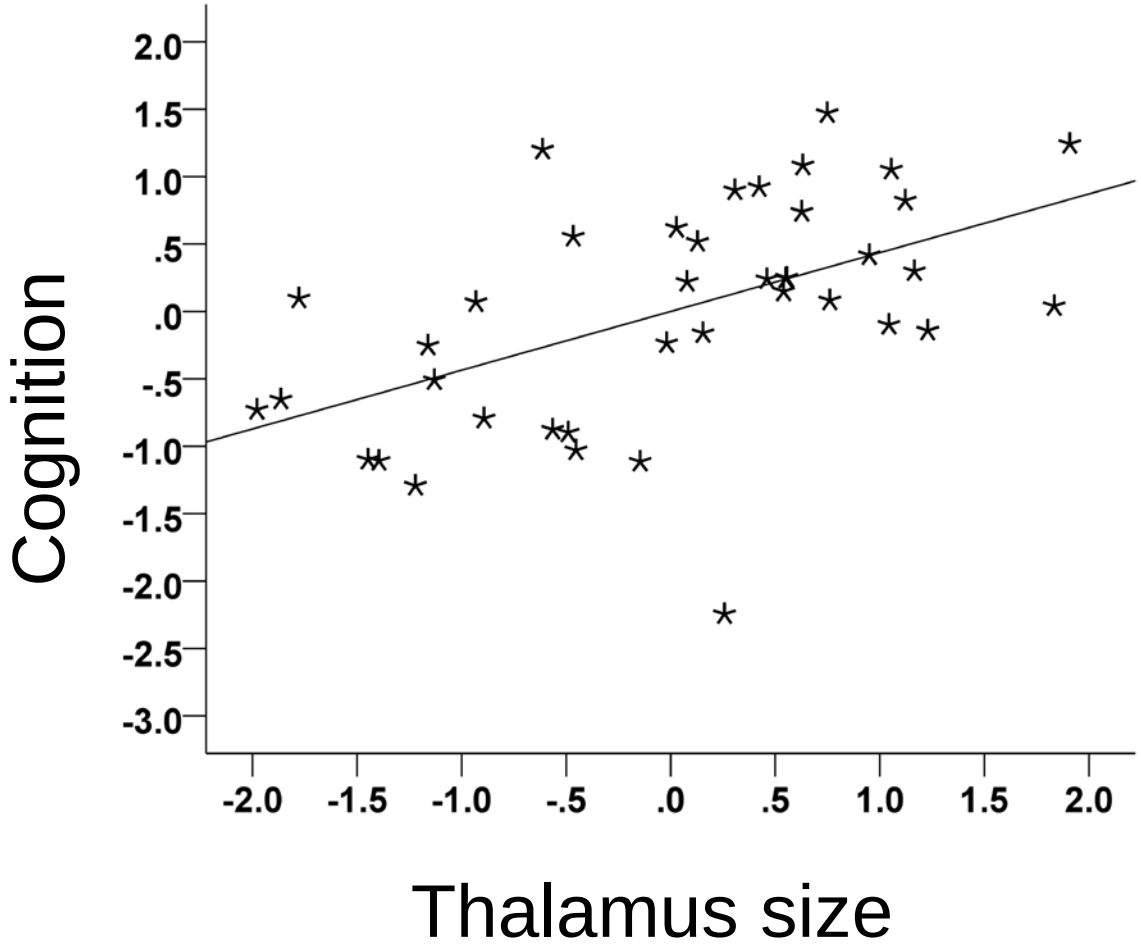
Almost all sensory information passes through the thalamus.

Thalamus & cognition



Fujiwara et al. (2017). American Journal of Neuroradiology

Thalamus & cognition

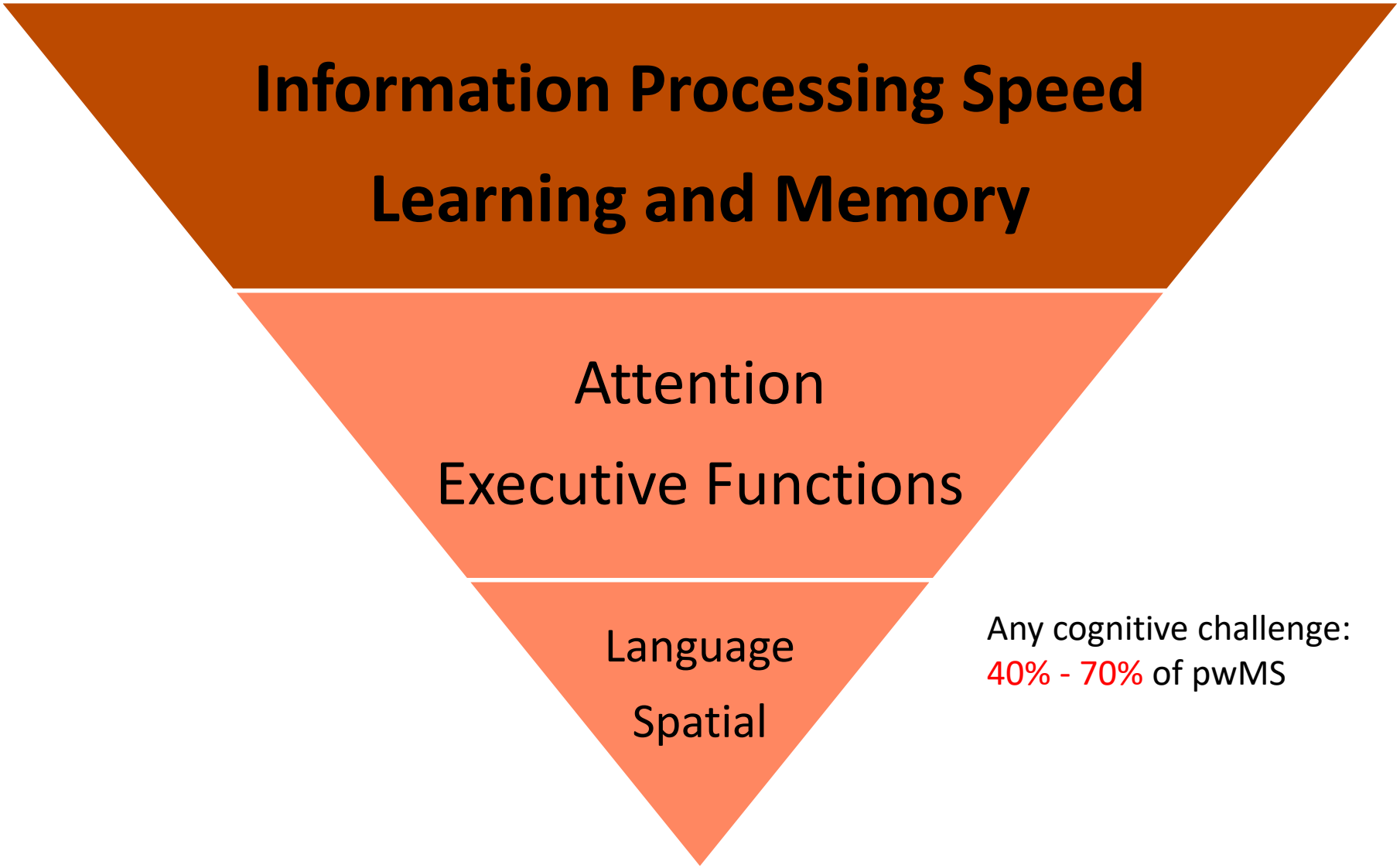


Fujiwara et al. (2017). American Journal of Neuroradiology

Overview

- Brain & Cognition in MS
- Measuring Cognitive Challenges in MS
- Brain/Cognitive Reserve
- What To Do

Cognitive challenges in MS



Any cognitive challenge:
40% - 70% of pwMS

Cognitive functions

- **Information processing speed**
  - How fast (sensory) information is passed on and evaluated
- **Learning and Memory**
  - Learning: Acquiring and storing new information
  - Memory: Retrieving stored information
- **Attention**
  - Divided: Concentrating one two (or more) things at once
  - Selective: Concentrating on one thing, ignoring others
- **Executive functions**
  - Umbrella term: Cognitive flexibility, planning, prioritizing
  - Orchestrating the other cognitive functions

Cognitive functions

- **Language**
  - Production, comprehension, reading
- **Visuo-spatial functions**
  - Visual perception & construction, navigation

Less or unaffected

Cognitive challenges in MS

- Can go unnoticed and/or are attributed to depression, fatigue, or stress.
- Are only weakly related to other disease characteristics and disability (motor ≠ cognitive).
- Can occur at any time, but are more common later in the disease.
- Possible in any disease course, but are more likely in progressive MS.

MS is not dementia

- Cognitive challenges in MS are usually milder than in dementia, like in Alzheimer's Disease.
- The progression of cognitive deficits is also less severe in MS than in AD.
- There is no evidence that the risk for getting AD is higher in pwMS.
- The biology of the two conditions is different.
- Largely unsuccessful intervention studies with AD medications (like donepezil) in MS.

Measuring cognition

REPORT

- Subjective report of cognitive issues.

MSNQ (Benedict et al. (2003). Screening for multiple sclerosis cognitive impairment using a self-administered 15-item questionnaire. Multiple Sclerosis Journal, 9(1), 95-101).

15 questions for pwMS & informant.

But the MSNQ also reflects mood.

Measuring cognition

REPORT

- Subjective report of cognitive issues.

NEUROPSYCHOLOGICAL TESTING

- Objective assessment of cognitive functions with standardized and normed test instruments.

Neuropsychological testing

- Full examination
- Neuropsychological screening

- Neuropsychological tests are:

Standardized: Applied in the same way.

Normed: Healthy people's performance is known.

Neuropsychological examination

- Has to be led by a clinical neuropsychologist.
- Usually guided by a specific question (like “Can I drive a car safely?”).
- 1-3 hours, sometimes several sessions.

Neuropsychological screening batteries

- Minimal Assessment of Cognitive Function in MS (**MACFIMS**)
  - 7 tests (90 min.)

MACFIMS: Benedict et al. 2002; *Clinical Neuropsychologist,* 16, 381–397

Processing speed/working memory
Learning and memory
Executive function
Visual-spatial processing
Verbal fluency

Neuropsychological screening batteries

- Brief Repeatable Battery of Neuropsychological Tests (**BRB-NT**)
  - 5 tests (30 min.)

BRBN: Rao, S. M., & the Cognitive Function Study Group of the National Multiple Sclerosis Society. (1990). Milwaukee, WI: Medical College of Wisconsin.

Processing speed/working memory
Learning and memory
Verbal fluency

Neuropsychological screening batteries

- Symbol-Digit Modalities Test
- CVLT-2
- BVMT-R

Langdon et al. (2012). Multiple Sclerosis Journal, 18, 891-898.

Benedict et al. (2012) BMC Neurology, 12,55

Neuropsychological screening batteries

- Symbol-Digit Modalities Test
- CVLT-2
- BVMT-R

~ 15 min.
Material: Paper, pen, stopwatch
Initial expert training

Langdon et al. (2012). Multiple Sclerosis Journal, 18, 891-898.

Benedict et al. (2012) BMC Neurology, 12,55

Symbol Digit Modalities Test

Faux Example

‖	₸	Π	“O	∞	m̸	Ξ	⌂	¬
1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**

Ξ	⌂	Π	¬	∞	¬	⌂	₸	∞	m̸	₸	“O	⌂	‖	Ξ

⌂	₸	‖	Ξ	m̸	¬	Π	‖	m̸	Ξ	∞	“O	₸	Π	⌂

....

Symbol Digit Modalities Test

Faux Example

‖	₸	Π	‟O	∞	⁒	Ξ	⌂	¬
1	2	3	4	5	6	7	8	9

Ξ	⌂	Π	¬	∞	¬	⌂	₸	∞	⁒	₸	‟O	⌂	‖	Ξ
7	8	3	9	5	9	8	2	.	.	.				

⌂	₸	‖	Ξ	⁒	¬	Π	‖	⁒	Ξ	∞	‟O	₸	Π	⌂

.... Outcome: Number of correct responses in 90 seconds

CVLT-2

Faux Example

Apple				
Tiger				
Car				
Shoes				
Orange				
Boat				
Lion				
Socks				
Puma				
Banana				
Airplane				
Gloves				
Hat				
Leopard				
Bike				
Pear				

CVLT-2

Faux Example

Apple				
Tiger				
-				
-				
Orange				
-				
Lion				
-				
-				
-				
-				
-				
-				
-				
Bike				
Pear				

CVLT-2

Faux Example

6 / 16	Boat			
	Tiger			
	Car			
	Lion			
	Leopard			
	Apple			
	Shoes			
	Airplane			
	Puma			
	Bike			
	Hat			
	Pear			
	Socks			
	Orange			
	Banana			
	Gloves			

CVLT-2

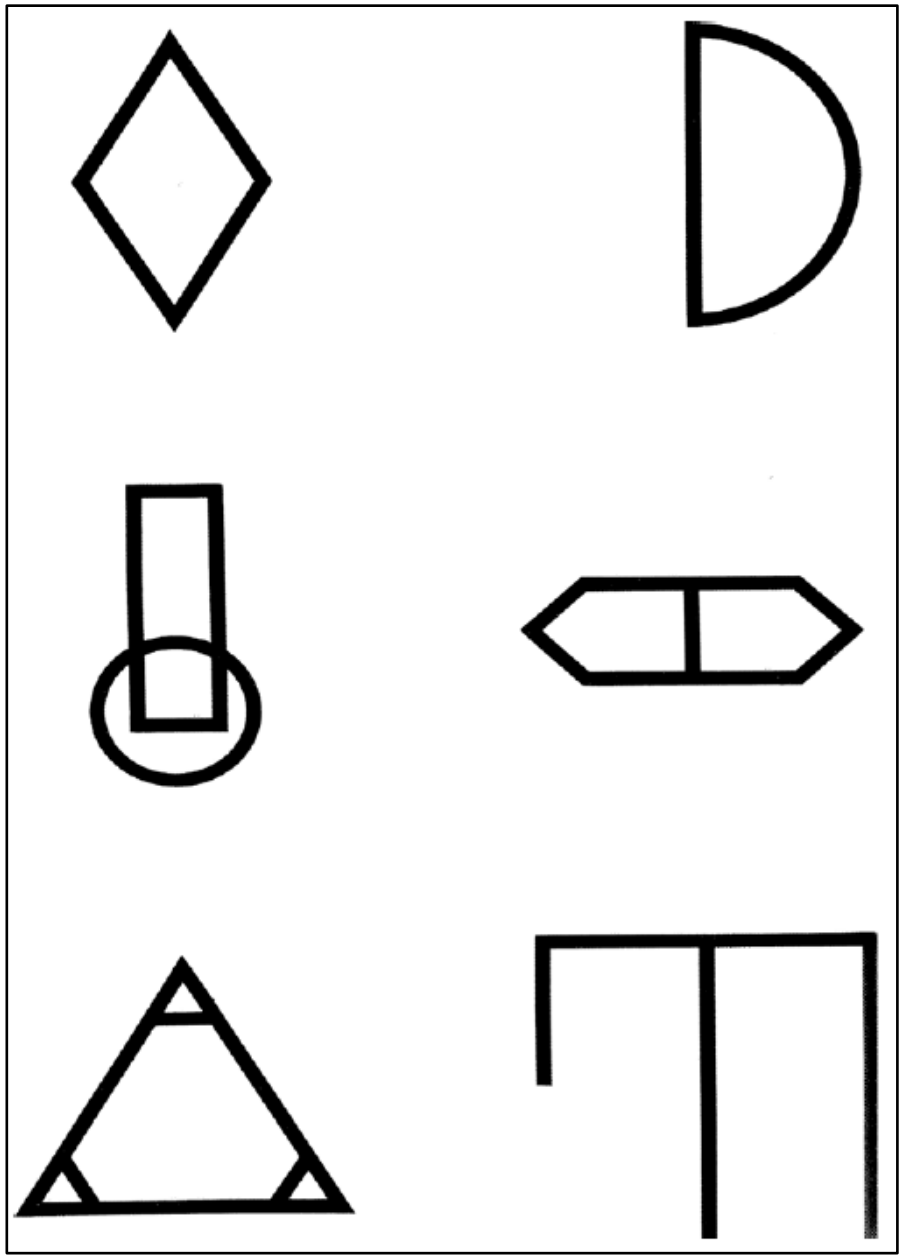
Faux Example

6 / 16	**8 / 16**	**9 / 16**	**8 / 16**	**10 / 16**

Outcome: Number of correct responses across five learning trials

BVMT-R

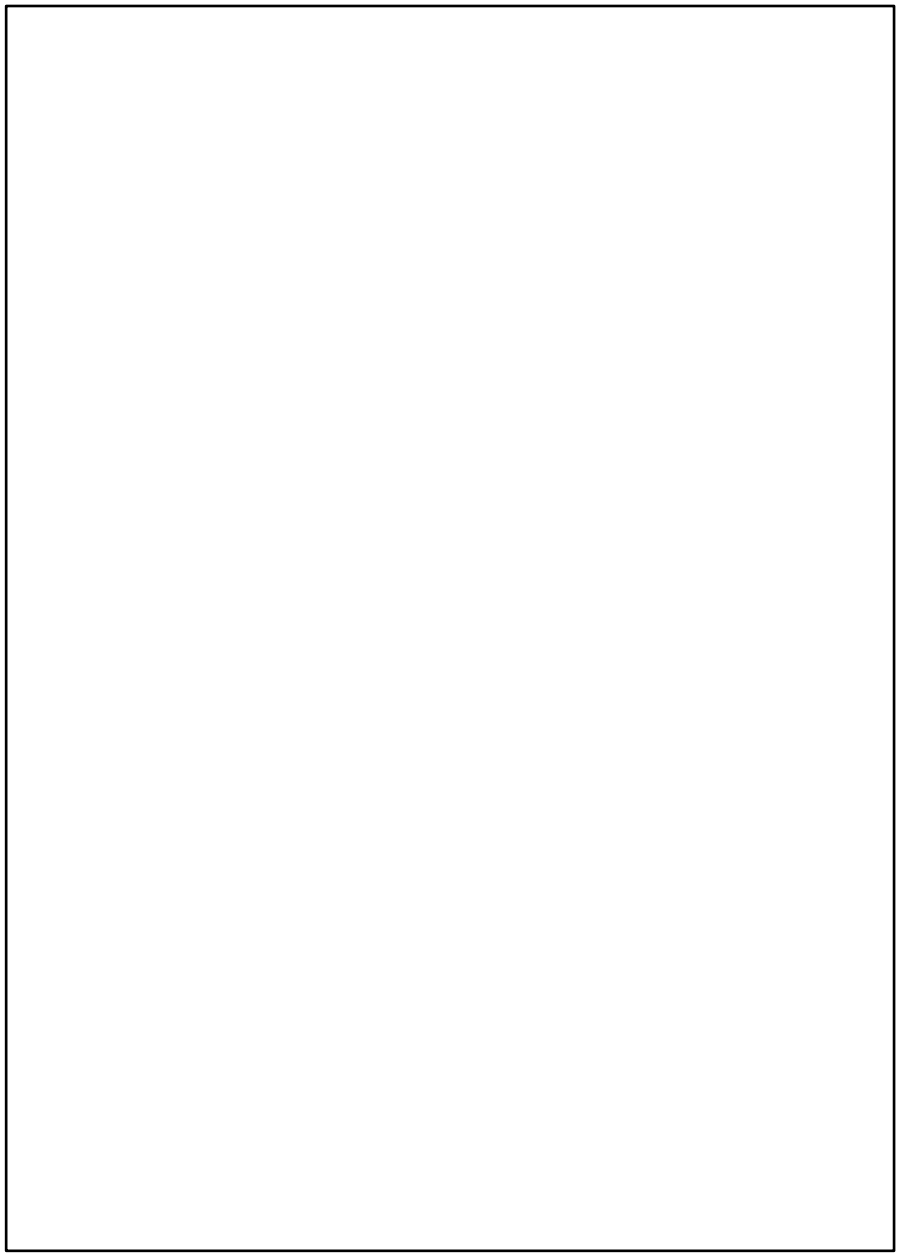
Faux Example



Benedict et al. BMC Neurology 2012, 12:55

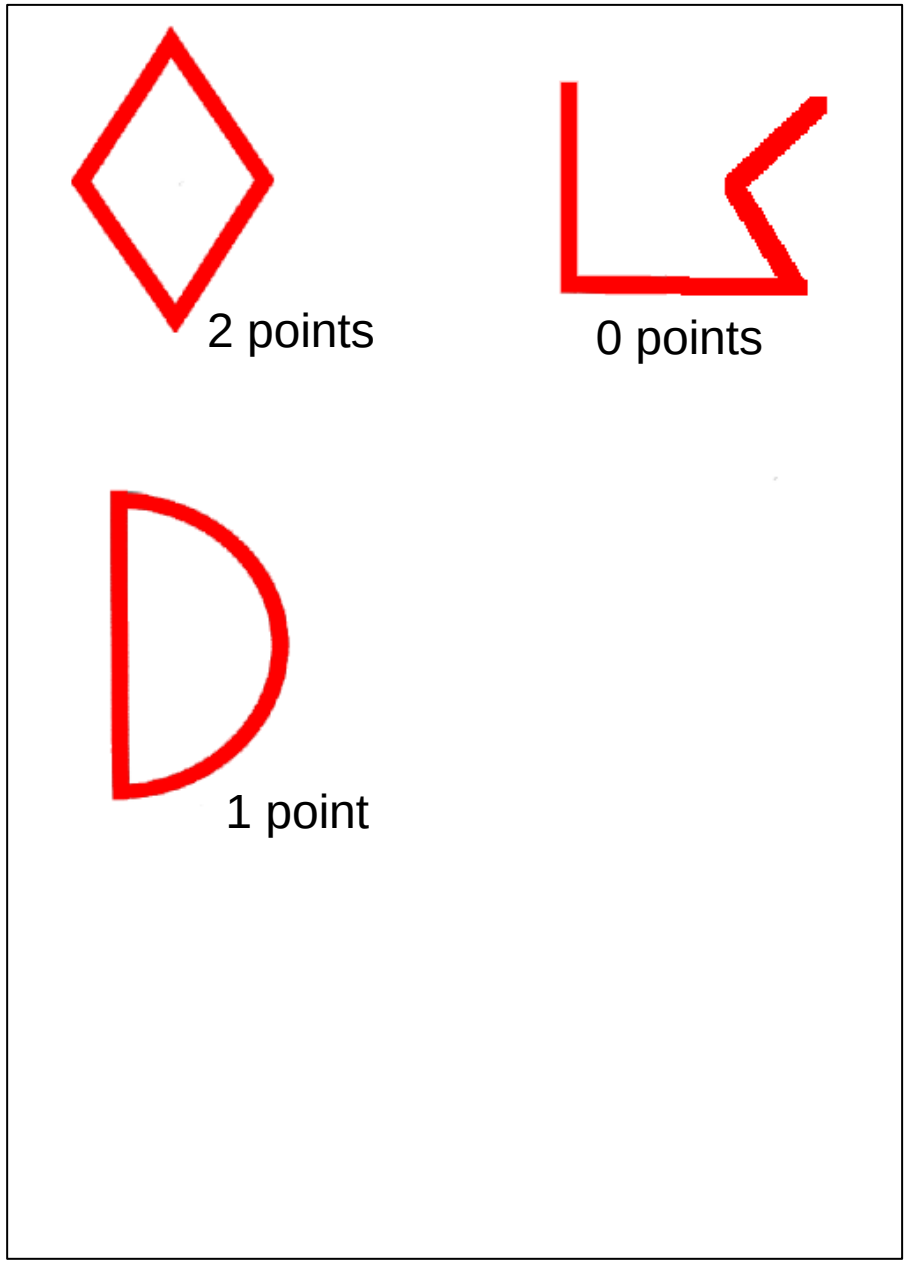
BVMT-R

Faux Example



BVMT-R

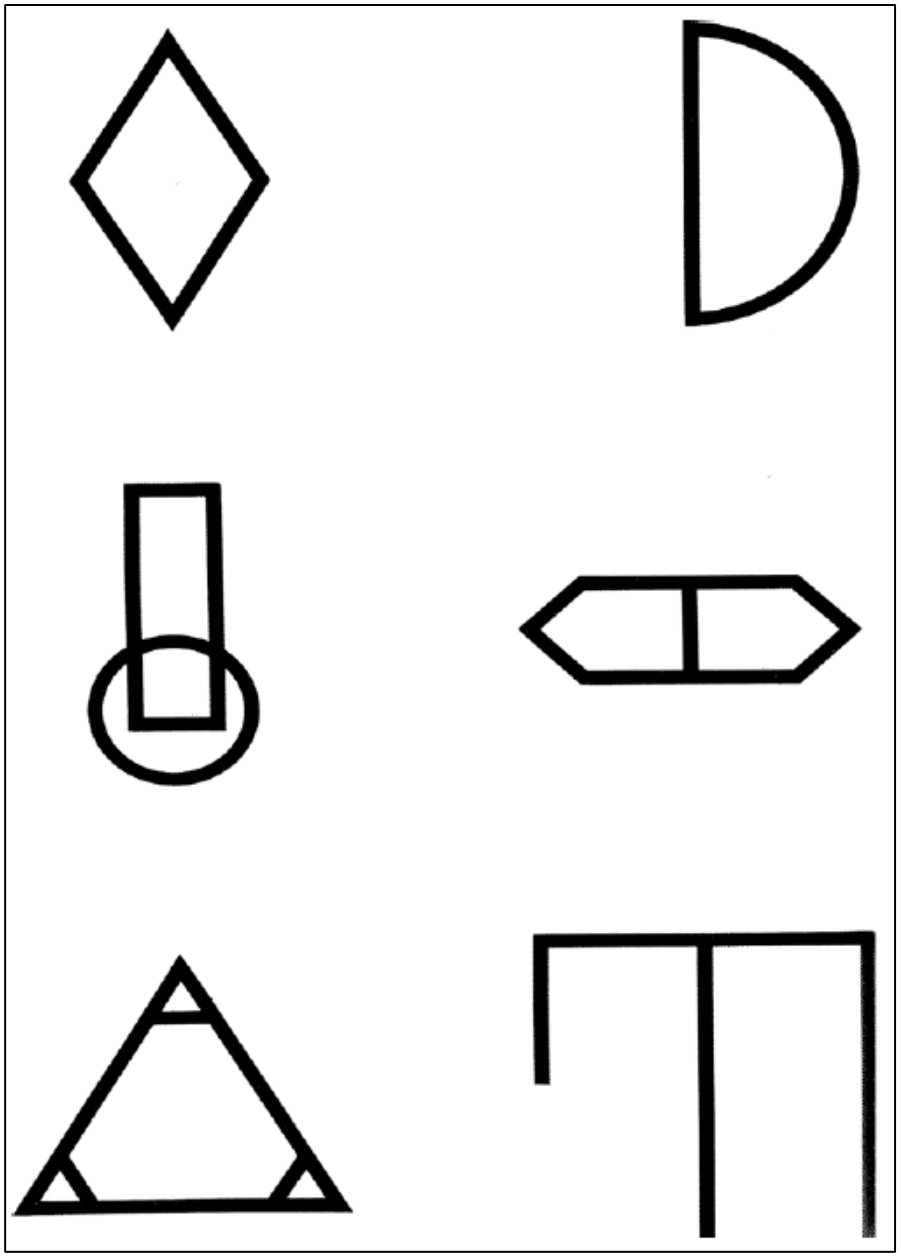
Faux Example



Benedict et al. BMC Neurology 2012, 12:55

BVMT-R

Faux Example



Outcome: Total score across 3 learning trials

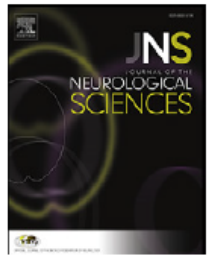
Benedict et al. BMC Neurology 2012, 12:55

Canadian outcomes

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns



Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS): Canadian contribution to the international validation project

Lisa A.S. Walker [a,b,c,d,e,f,*], Leila Osman [a,g], Jason A. Berard [b,d], Laura M. Rees [a,b,d,e], Mark S. Freedman [a,b,c], Heather MacLean [a,b,c], Denis Cousineau [d]

[a] University of Ottawa Brain and Mind Research Institute, Canada
[b] The Ottawa Hospital Research Institute, Canada
[c] University of Ottawa, Faculty of Medicine, Canada
[d] University of Ottawa, School of Psychology, Canada
[e] Carleton University, Department of Psychology, Canada
[f] Carleton University, Institute of Cognitive Science, Canada
[g] St. Paul University, Canada

Main outcomes: BICAMS Canada

- 51 pwMS, 57 healthy controls
- At least 1 test impaired**: 58% of pwMS**
- Most sensitive: SDMT
- Related to employment status: BVMT-R
- Some practice effects → newly emerging impairment meaningful

- Walker et al. (2016): Canadian norms and cut-off scores

Walker et al. (2016). Journal of the Neurological Sciences, 362, 147-152.

Summary 1

- Cognitive challenges are common in MS and related to brain changes.
- Processing speed and learning/memory are most affected.
- MS is not dementia.
- Neuropsychological testing or screening is needed:
  - to know if cognition is compromised
  - to know if cognition changes over time
- The BICAMS is an easy-to administer screening, and now also has data from Canada.

Overview

- Brain & Cognition in MS
- Measuring Cognitive Challenges in MS
- Brain/Cognitive Reserve
- What To Do

Brain Reserve & Cognitive Reserve

- *Hardware* vs. *Software*

- Brain reserve: ‘More brain tissue’ is a buffer to delay the onset of noticeable cognitive problems.

- Cognitive reserve: Having many ways to do a cognitive task makes it more robust to brain damage.

Reserve in MS

- In MS: Ongoing noticeable (e.g., relapses) and less noticeable damage can reduce brain reserve.

- Within limits, the brain adapts to these changes and compensates for lost function → Plasticity.

- If there is no more reserve, compensation becomes impossible.

→ Important to protect reserve.

Brain Plasticity in MS

- How does brain function change under neurological challenges like in MS?

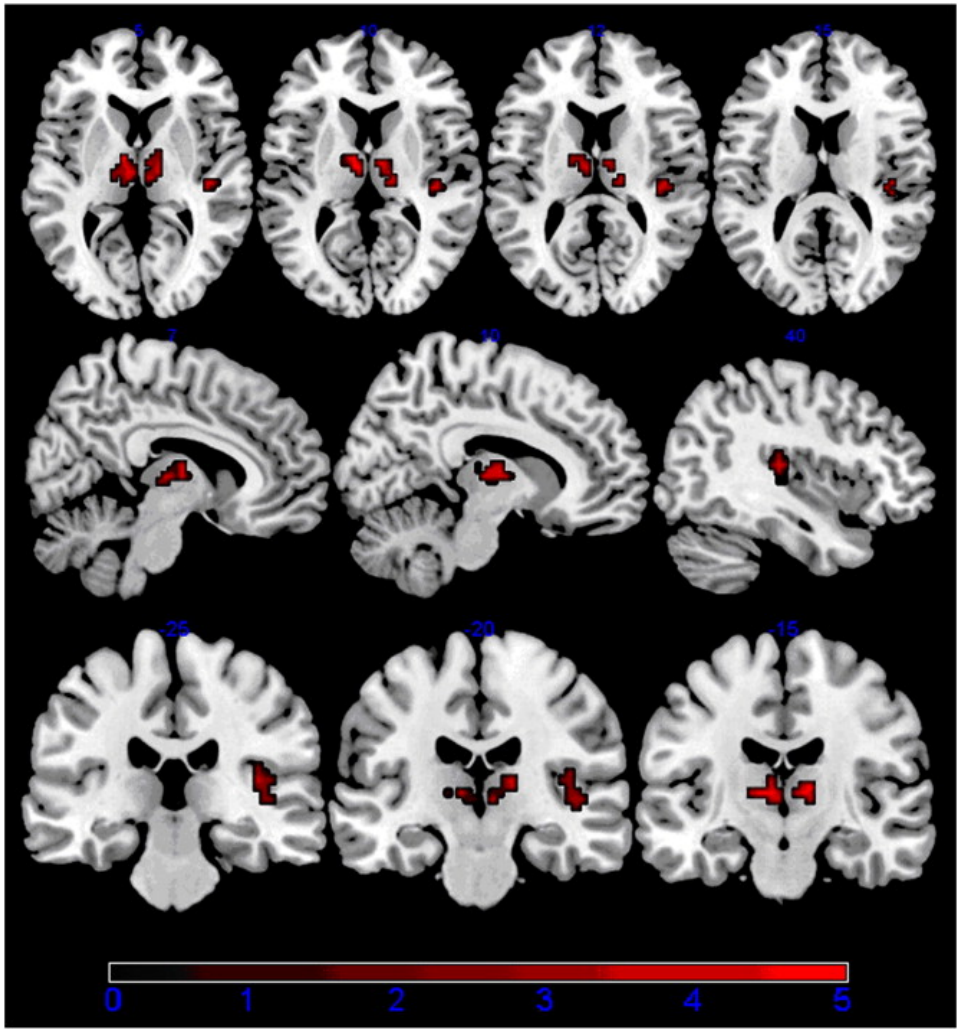
Brain Plasticity in MS

- How does brain function change under neurological challenges like in MS?

  - To compensate, damaged brain structures may have to communicate more to each other

  → Increased “functional connectivity”

Brain Plasticity in MS



Thalamus (and insula): Increased functional connectivity

→ the brain has to "work harder"

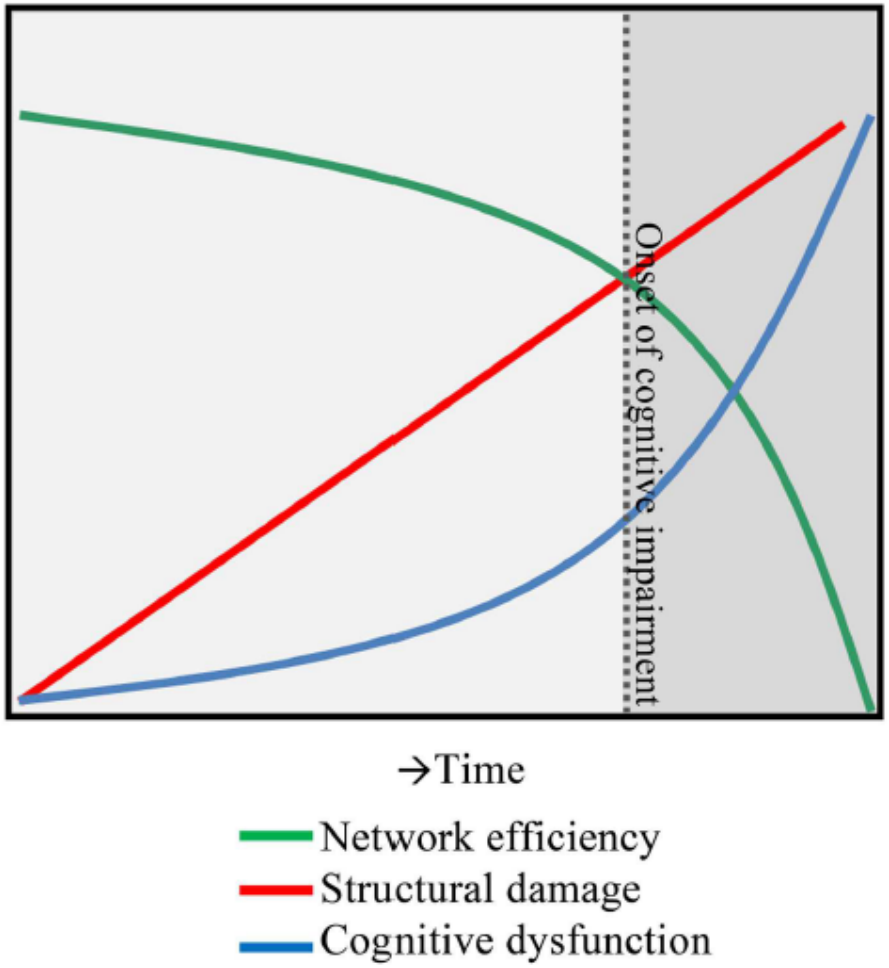
→ fatigue !

Liu et al. (2011). Journal of the Neurological Sciences, Volume 304, Issues 1–2, 2011, 127–131

Brain plasticity in relapsing–remitting multiple sclerosis: Evidence from resting-state fMRI

http://dx.doi.org/10.1016/j.jns.2011.01.023

Brain Structure, Function & Cognition



Hypothetical relationship between the 3 over time

Schoonheim, M. M., Meijer, K. A., & Geurts, J. J. (2015). Frontiers in Neurology, 6.

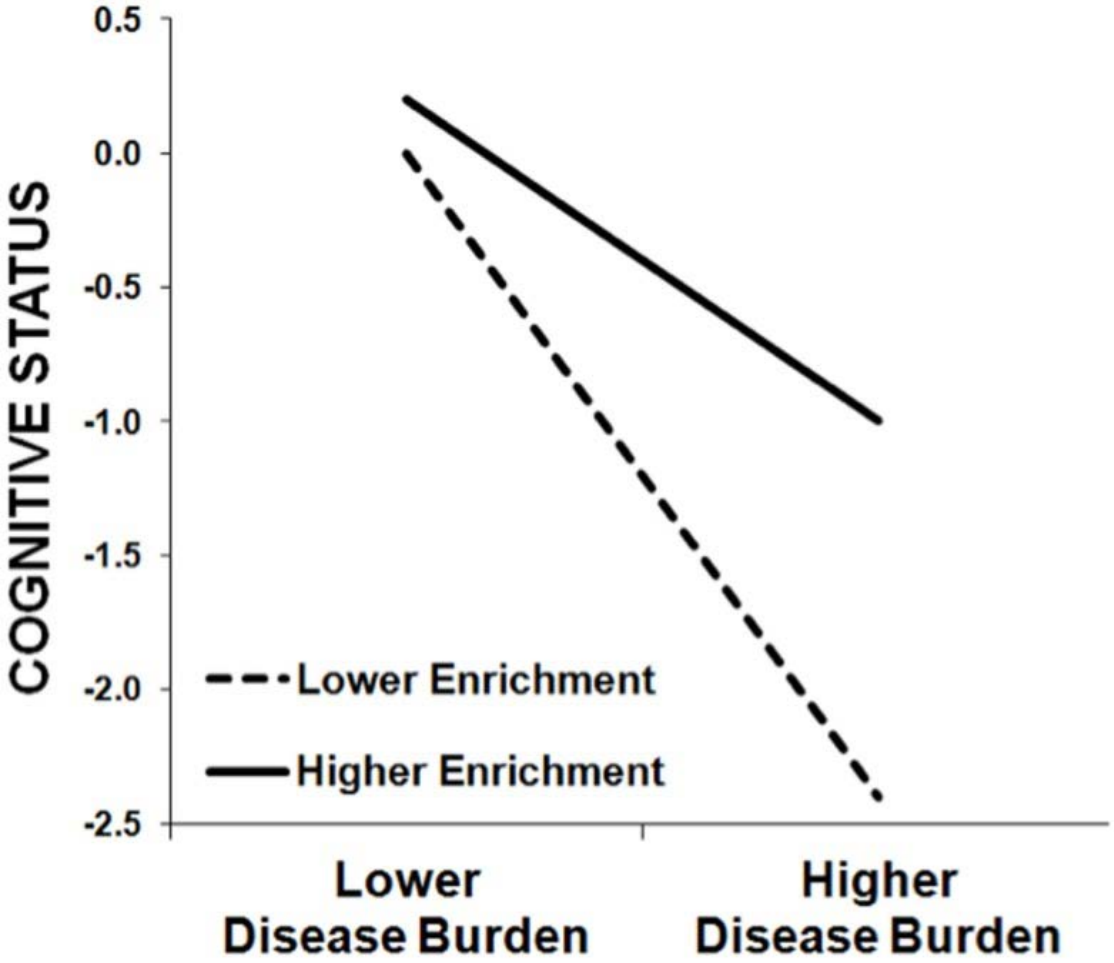
Brain Reserve & Cognitive Reserve

- *Hardware* vs. *Software*

- Brain reserve: ‘More brain tissue’ is a buffer to delay the onset of noticeable cognitive problems.

- Cognitive reserve: Having many ways to do a cognitive task makes it more robust to brain damage.

Cognitive Reserve & MS



"Enrichment" –

Education, but also leisure activities, hobbies, social activities, etc.

Sumowski, J. F. (2015). Frontiers in Neurology, 6, 176. http://doi.org/10.3389/fneur.2015.00176

Summary 2

- Brain and cognitive reserves protect against cognitive decline in MS.
- The brain is ‘neuroplastic’, also in MS.
- Compensates for some of the lost tissue.
- Compensation requires energy.
- Compensation is less likely when reserves are smaller.

Overview

- Brain & Cognition in MS
- Measuring Cognitive Challenges in MS
- Brain/Cognitive Reserve
- What To Do

Keeping and building reserves

Goal

- Keep your brain healthy
- Keep your mind active

- …and your body, too

Treating cognitive challenges in MS

- **Pharmacological**
- Disease-modifying medications in relapsing MS.
- Mixed or null findings for progressive MS and for other drugs.
- Promising: Amphetamine (trials ongoing; Dr. S. Morrow, London, Ont.)
- Alternatives are urgently needed.

Treating cognitive challenges in MS

- **Cognitive Rehabilitation**

- **MEMREHAB trial**

  Intervention: Story Memory Technique

→ Memorizing words by creating visuals and story context.

→ 1 h sessions, 2 x week over 5 weeks

Chiaravalloti et al. (2013). Neurology 81(24), 2066-2072.

Cognitive Rehabilitation

- Learning (CVLT) improved for the intervention group.

Chiaravalloti et al. (2013). Neurology 81(24), 2066-2072.

Cognitive Rehabilitation

- Learning (CVLT) improved for the intervention group.

- The intervention also made everyday memory better → transfer

Chiaravalloti et al. (2013). Neurology 81(24), 2066-2072.

Cognitive rehabilitation

- Learning (CVLT) improved for the intervention group.
- The intervention also made everyday memory better → transfer
- …and the memory boost was still there after 6 months.

Chiaravalloti et al. (2013). Neurology 81(24), 2066-2072.

Cognitive rehabilitation

- But: The intervention was less effective in pwMS with additional processing speed slowing (Chiaravalloti, N. D., & DeLuca, J. (2015). *Multiple Sclerosis Journal*, *21*(12), 1575-1582).
- Other cognitive rehabilitation studies had more mixed findings.

Cognitive rehabilitation

- We need more research to find out:
  - **who** benefits most from
  - which **type** of cognitive rehab, and
  - how much is needed ("**dosage**")

Strategies (http://www.nationalmssociety.org)

Restorative

- Combine modes of learning
- Repeat & verify
- Spaced rehearsal
- Build associations

Combine modes of learning

Combine modes of learning

Hi, Anna.

Combine modes of learning

Combine modes of learning

Build associations

Grandma Anna

Build associations

ANAHEIM

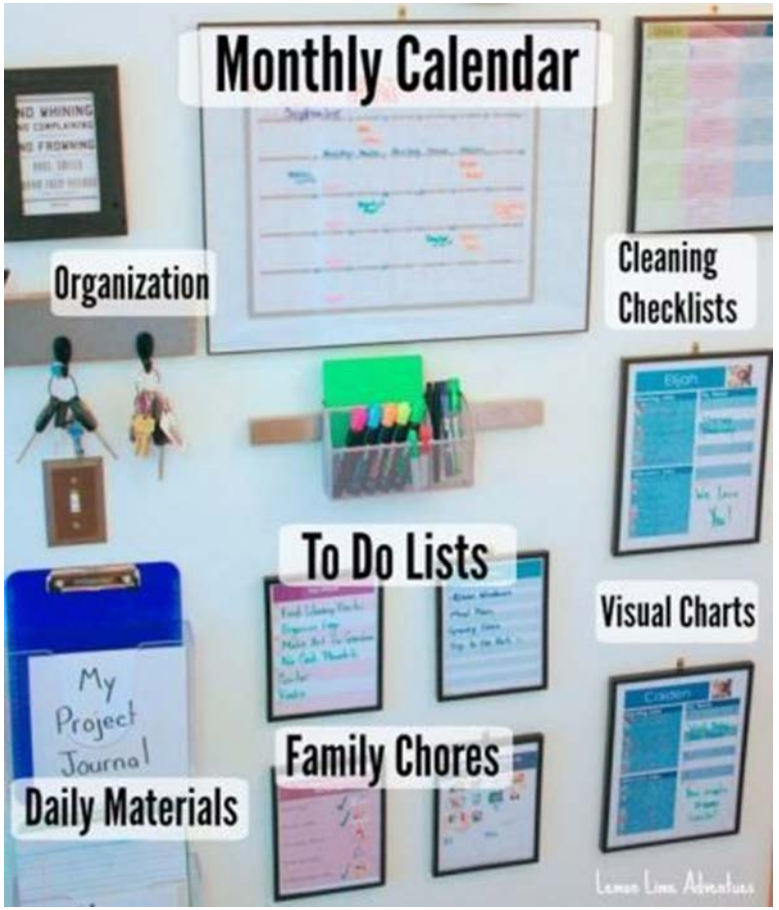
Imagery

A N N A
A N N A
A N N A

Strategies (http://www.nationalmssociety.org)

Compensatory

- Consolidate and centralize
- Plan
- Record
- Remind
- No distractions
- Take a break
- Do one thing at a time



Role of physical activity

- Several studies now suggest physical activity improves cognition (and other symptoms) in MS.

Role of physical activity

- Several studies now suggest physical activity improves cognition (and other symptoms) in MS.
- Aerobic (aka cardio-)exercise in particular.
- Even some recent evidence for brain changes!

Role of physical activity

Neuroradiology (2017) 59:61–67
DOI 10.1007/s00234-016-1767-x

FUNCTIONAL NEURORADIOLOGY

Exercise training effects on memory and hippocampal viscoelasticity in multiple sclerosis: a novel application of magnetic resonance elastography

Brian M. Sandroff[1] · Curtis L. Johnson[2] · Robert W. Motl[3]

Neurocase, 2014
Vol. 20, No. 6, 695–697, http://dx.doi.org/10.1080/13554794.2013.841951

Routledge
Taylor & Francis Group

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

V. M. Leavitt[1,2], C. Cirnigliaro[3,4], A. Cohen[1], A. Farag[3], M. Brooks[3], J. M. Wecht[3], G. R. Wylie[1,2], N. D. Chiaravalloti[1,2], J. DeLuca[1,2], and J. F. Sumowski[1,2]

[1]Kessler Foundation Research Center, West Orange, NJ, USA
[2]Rutgers – New Jersey Medical School, Newark, NJ, USA
[3]James J. Peters VA Medical Center, Bronx, NY, USA
[4]Kessler Institute of Rehabilitation, West Orange, NJ, USA

Key study outcomes

- Small studies, including pw RR-MS.
- Aerobic exercise over 12 weeks of progressive treadmill walking or stationary cycling exercise (3x weekly).

- **Improvement in memory and learning**
- **Increased volume of the hippocampus**
- **Reduced ‘elasticity’ of the hippocampus**

Role of physical activity

Research Paper

MULTIPLE SCLEROSIS JOURNAL | MSJ

Effects of exercise on fitness and cognition in progressive MS: a randomized, controlled pilot trial

Multiple Sclerosis Journal
2014, Vol. 20(3) 382–390
© The Author(s) 2013
Reprints and permissions:
sagepub.co.uk/journalsPermissions.nav
DOI: 10.1177/1352458513507358
msj.sagepub.com
SAGE

S Briken[1,2], SM Gold[1], S Patra[3], E Vettorazzi[4], D Harbs[3], A Tallner[5], G Ketels[6], KH Schulz[3,7] and C Heesen[1,2]

Key study features

Study

- People with progressive MS (EDSS 4–6).
- 3 different aerobic exercise groups
- 8-10 weeks duration

Outcome measures

- Cognition
- Aerobic fitness
- Walking
- Fatigue
- Depression

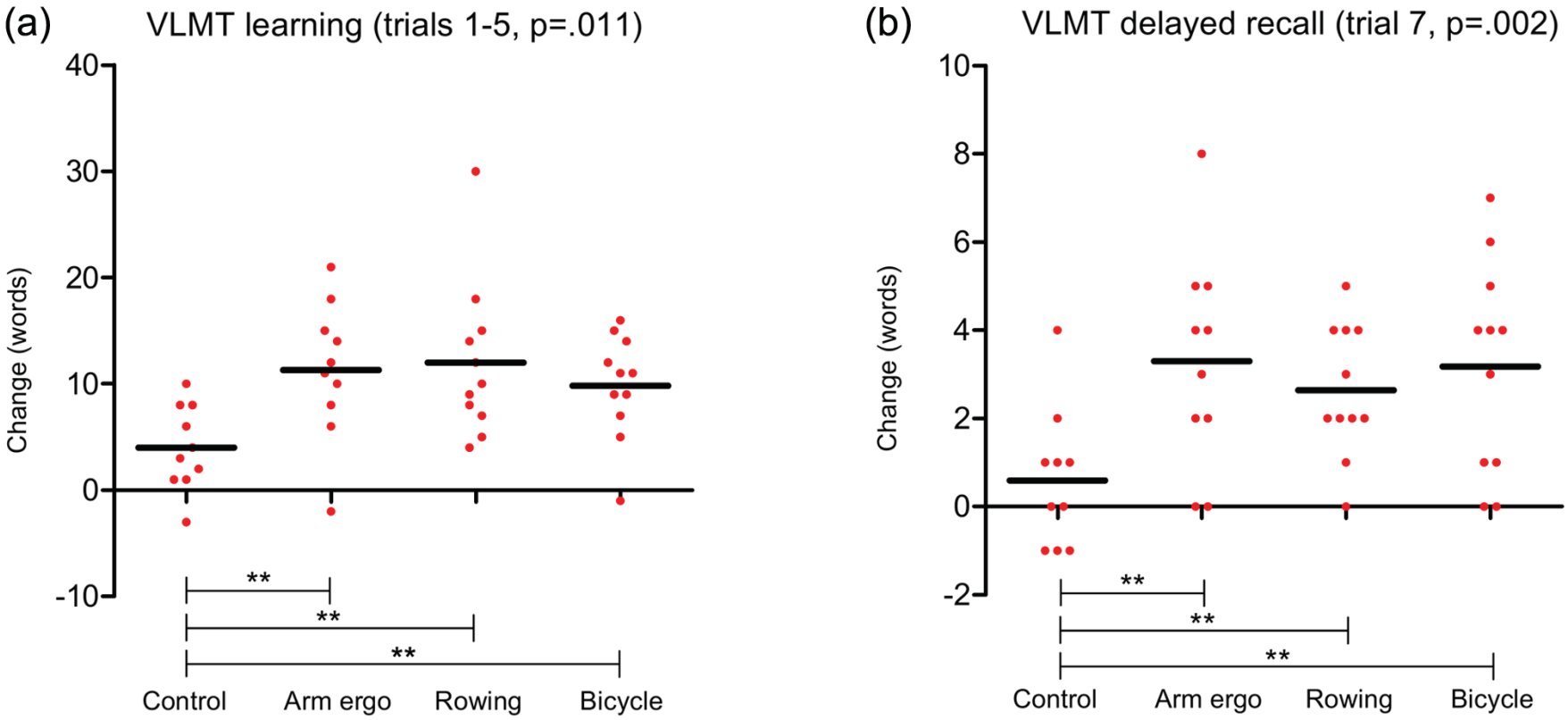
Aerobic exercise interventions

Rowing ergometer

Arm ergometer

Bicycle ergometer

Memory outcome



Better memory in all intervention groups

Briken, S., et al. (2014). Multiple Sclerosis Journal, 20(3), 382-390. reprinted with permission

Summary: What to-do

- Keep mentally active
- Continue leisure activities
- Use strategies to help you focus and remember things
  - “Information central”
  - Enrich your learning (associations, multiple modes)
  - Use reminders
  - etc.
- Try or continue a cardio-exercise

Consensus recommendations

Multiple Sclerosis and Related Disorders 9 (2016) S5–S48

Contents lists available at ScienceDirect

Multiple Sclerosis and Related Disorders

journal homepage: www.elsevier.com/locate/msard

Review article

Brain health: time matters in multiple sclerosis

Gavin Giovannoni [a,*], Helmut Butzkueven [b], Suhayl Dhib-Jalbut [c], Jeremy Hobart [d], Gisela Kobelt [e], George Pepper [f], Maria Pia Sormani [g], Christoph Thalheim [h], Anthony Traboulsee [i], Timothy Vollmer [j]

[a] Queen Mary University London, Blizard Institute, Barts and The London School of Medicine and Dentistry, London, UK
[b] Melbourne Brain Centre, Royal Melbourne Hospital, University of Melbourne, Parkville, Australia
[c] Department of Neurology, RUTGERS-Robert Wood Johnson Medical School, New Brunswick, NJ, USA
[d] Plymouth University Peninsula Schools of Medicine and Dentistry, Plymouth, UK
[e] European Health Economics, Mulhouse, France
[f] Shift.ms, Leeds, UK
[g] Biostatistics Unit, University of Genoa, Genoa, Italy
[h] Patient Advocate in Multiple Sclerosis, Brussels, Belgium
[i] Department of Medicine, University of British Columbia, Vancouver, BC, Canada
[j] Department of Neurology, University of Colorado Denver, Aurora, CO, USA

Thank you