



# Multiple Sclerosis: Depression, Cognition and Fatigue

Hosted by  
Multiple Sclerosis Society of Canada

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# MS Society of Canada

- **Mission Statement:** To be a leader in finding a cure for multiple sclerosis and enabling people affected by MS to enhance their quality of life.

# Multiple Sclerosis: Depression, Cognition and Fatigue

Anthony Feinstein

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University of Toronto and Sunnybrook Health Sciences Centre



# Depression

# Charcot's behavioral observations (1877)

- “marked enfeeblement of memory”
- “slowness of response”

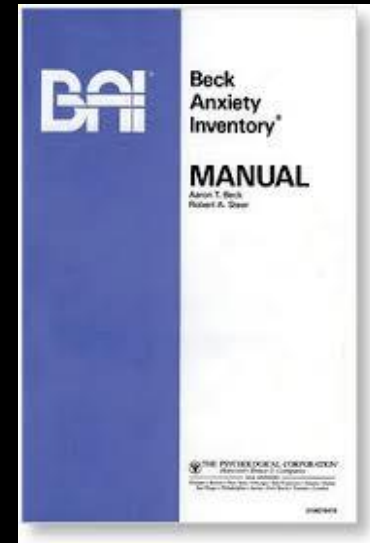
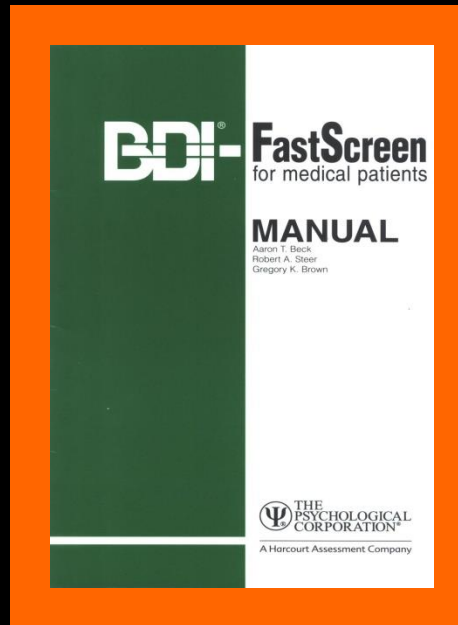
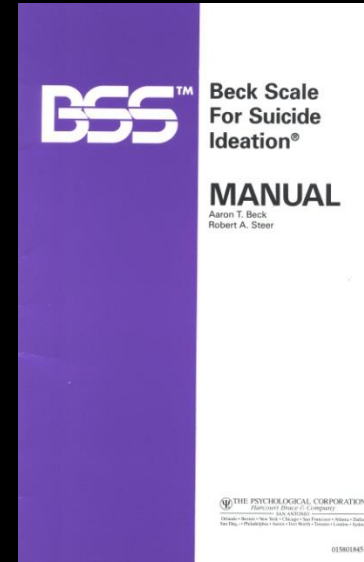
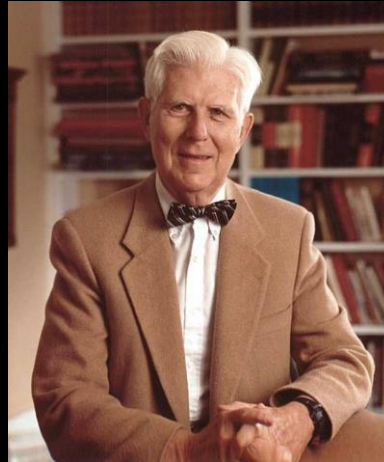
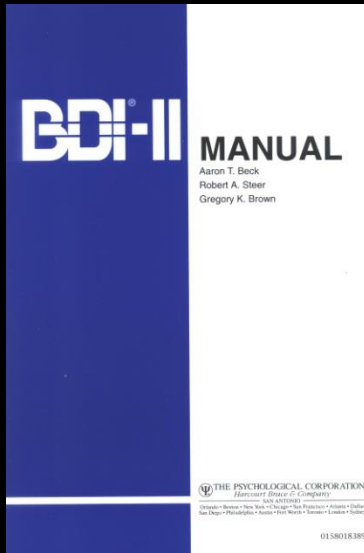


# Major Depression

## Diagnostic criteria

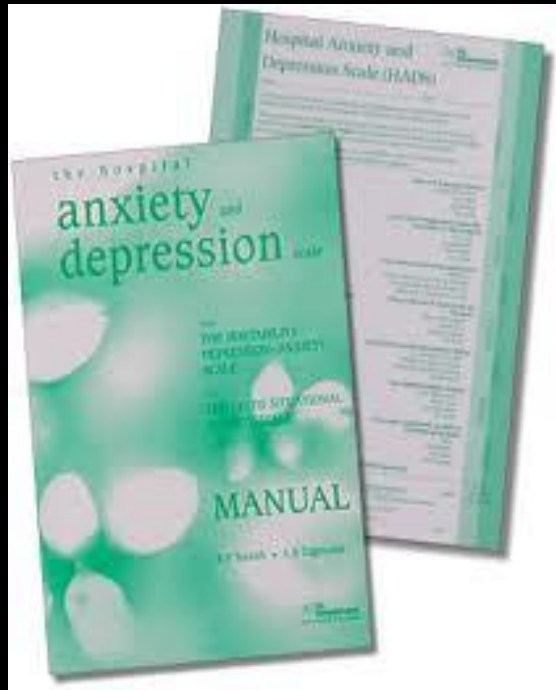
- Five or more of the following during the same two week period:
  - Depressed mood most of the day
  - Markedly diminished interest or pleasure in all activities
  - Appetite change with significant weight loss, or weight gain
  - Insomnia or hypersomnia nearly every day
  - Psychomotor agitation or retardation (observable by others)
  - Fatigue or loss of energy nearly every day
  - Feelings of worthlessness, excessive, inappropriate guilt
  - Diminished ability to think or concentrate
  - Recurrent thoughts of death

# Rating scales





# Rating scales



Research Paper

Multiple  
Sclerosis

Multiple Sclerosis  
15(12) 1518-1524  
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DOI: 10.1177/1352458509347150  
msj.sagepub.com  
SAGE

## Validation of the Hospital Anxiety and Depression Scale for use with multiple sclerosis patients

Kimia Honarmand<sup>1,2</sup> and Anthony Feinstein<sup>1,2</sup>

### Abstract

Detecting clinically significant symptoms of depression and anxiety in medically ill patients using self-report rating scales presents a challenge because of somatic confounders. The Hospital Anxiety and Depression Scale (HADS) was developed with this in mind, but has never been validated for a multiple sclerosis population. Our objective was to validate the HADS for multiple sclerosis patients. Multiple sclerosis patients were interviewed for the presence of major depression ( $n = 180$ ) and anxiety disorders ( $n = 140$ ) with the Structured Clinical Interview for DSM-IV disorders. A receiver operating characteristic (ROC) analysis was undertaken to assess which HADS cut-off scores give the best yield with respect to diagnoses of major depression and all anxiety disorders defined by the Structured Clinical Interview for DSM-IV. A threshold score of 8 or greater on the HADS depression subscale provides a sensitivity of 90% and specificity of 87.3% (ROC area under the curve 0.938). The same cut-off score gives a sensitivity of 88.5% and a specificity of 80.7% on the anxiety subscale (ROC area under the curve 0.913), but for generalized anxiety disorder only. The study confirms the usefulness of the HADS as a marker of major depression and generalized anxiety disorder, but not other anxiety disorders, in multiple sclerosis patients.

### Keywords

multiple sclerosis, major depressive disorder, anxiety disorders, Hospital Anxiety and Depression Scale (HADS)

Date received: 27th March 2009; accepted: 22nd July 2009

# Major Depression

## Prevalence

- lifetime prevalence in patients attending MS clinics approaches 50%
- However, prevalence is also raised in a community based sample.
  - In a study of 115,071 Canadians, the 12 month prevalence of depression in MS patients exceeded that in healthy subjects (odds ratio: 3.4)
  - In subjects ages 18-45 years, the 12 month prevalence was 25.7%.
- Rates increased in relation to other neurological disorders.

# The clinical importance of depression

- Effects on cognition
- Suicidal intent and completion
- Quality of Life
- Depression is treatable

# Suicidal intent and MS



## An examination of suicidal intent in patients with multiple sclerosis

Anthony Feinstein, MD, PhD

**Abstract—Objective:** To examine neurologic and psychiatric correlates of suicidal intent in a community sample of 140 patients with MS. **Methods:** Patients with (28.6%) and without lifetime suicidal intent were compared across MS disease-related and psychiatric variables. All subjects were interviewed with 1) the Structured Clinical Interview for DSM-IV Axis 1 disorders (SCID-IV) to determine lifetime prevalence of major depression and anxiety disorders; and 2) the Social Stress and Support Interview to assess psychological stressors. Suicidal intent was documented with questions from the SCID-IV and Beck Suicide Scale. Patients also completed the Hospital Anxiety and Depression Scale and cognitive testing. **Results:** Suicidal patients were significantly more likely to live alone, have a family history of mental illness, report more social stress, and have lifetime diagnoses of major depression, anxiety disorder, comorbid depression-anxiety disorder, and alcohol abuse disorder. By logistic regression analysis, the severity of major depression, alcohol abuse, and living alone had an 85% predictive accuracy for suicidal intent. A third of suicidal patients had not received psychological help. Two-thirds of subjects with current major depression, all suicidal, had not received antidepressant medication. **Conclusions:** Suicidal intent, a potential harbinger for suicide, is common in MS and is strongly associated with major depression, alcohol abuse, and social isolation. Suicidal intent is a potentially treatable cause of morbidity and mortality in MS.

NEUROLOGY 2002;59:674-678

- Lifetime suicidal intent: 29%
- Lifetime suicide attempt: 6.4%
- 1 Lifetime diagnosis of major depression
- 2 Severity of major depression (↑ HAD scores)
- 3 Living alone
- 4 Alcohol abuse

70% sensitivity, 95% specificity,  
overall 87% predictive ability

- 35% of suicidal patients had received no Rx
- 66% of patients with current major depression not received Rx
- Of the 9 patients who had attempted suicide, 4 had never been given antidepressant Rx
- These data fit with those from Mohr et al (Multiple Sclerosis. 2006;12:204-208) who showed that over half the depressed MS patients in a neurological clinic were not receiving antidepressant medication and of those depressed patients on treatment, a quarter were receiving sub-therapeutic doses.

# Suicide

- 7.5x the general population rate
- 2x the general population rate and increased relative to other neurological disorders (Stenager and Stenager, 1992)
- At risk: males, < 30 yrs, first 5 years of illness

# **Etiology of depression**

# MS, depression and brain imaging

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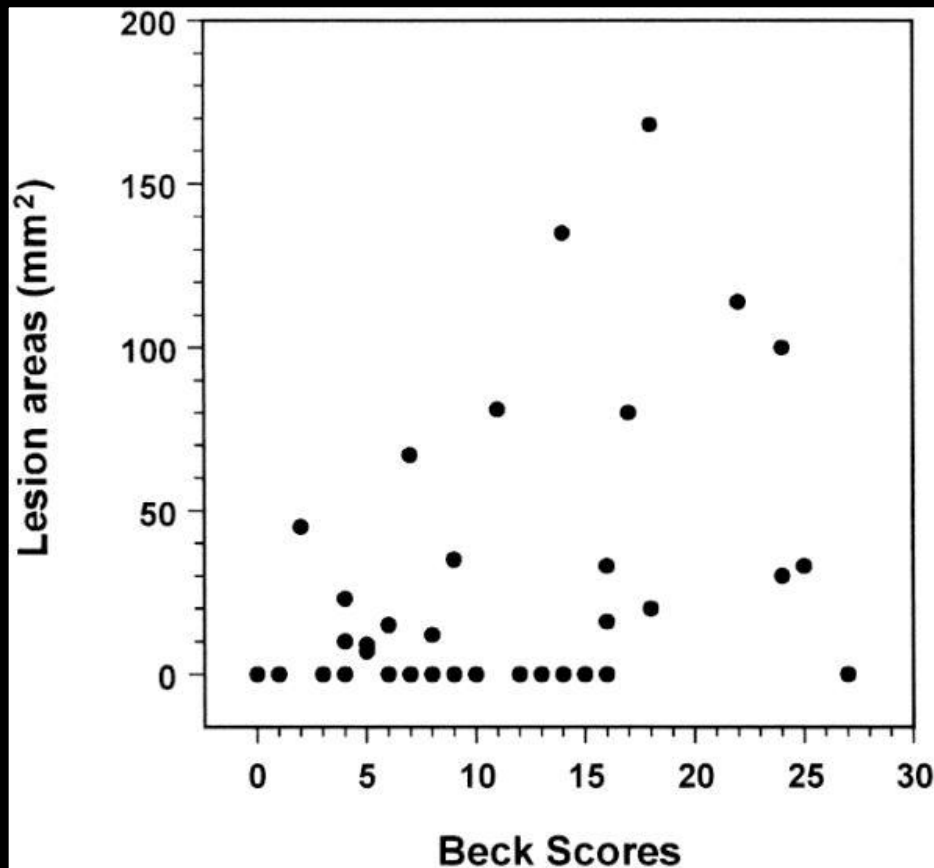
## Lesions in the left arcuate fasciculus region and depressive symptoms in multiple sclerosis

J. Pujol, MD; J. Bello, MD; J. Deus, PhD; J.L. Martí-Vilalta, MD; and A. Capdevila, MD

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**Article abstract**—Depression is a common mood disturbance in multiple sclerosis (MS) patients. Epidemiologic data suggest a causative relationship between depressive symptoms and cerebral demyelination, although a specific lesion site responsible for depressed mood has not been identified. Given that depression in neurologic disease is closely related to frontal and temporal lobe damage, we focused our study on investigating the extent to which lesions in the white matter connecting both cerebral lobes may account for depressive symptoms in MS. Forty-five patients were assessed using the Beck Depression Inventory and an MRI protocol conceived to quantify lesions separately in the basal, medial, and lateral frontotemporal white matter. The presence of lesions in the left suprainular white matter, the region that mainly includes the arcuate fasciculus, was specifically associated with depressive symptoms, accounting for a significant 17% of the depression score variance. Although a multifactorial origin is suspected for depression in MS, this finding gives support to the existence of a direct negative effect of demyelination on mood.

NEUROLOGY 1997;49:1105-1110



**Lesions in the left arcuate fasciculus region and depressive symptoms in multiple sclerosis.**

Pujol, J; Bello, J; Deus, J; Marti-Vilalta, J; Capdevila, A

Neurology. 49(4):1105-1110, October 1997.

Figure 3 . Plot of Beck scores with coronal lesion areas of the left arcuate fasciculus region. Although the relationship was significant ( $r = 0.43$ ,  $p = 0.001$ ), high depression scores were registered in patients with no lesions in this region.



# MS, Depression and MRI changes

- Medial inferior frontal cortex
  - hyper-intense lesion volume
  - hypo-intense lesion volume
- Anterior temporal region
  - Reduced grey matter volume

## Structural brain abnormalities in multiple sclerosis patients with major depression

A. Feinstein, FRCPC; P. Roy, MS; N. Lobaugh, PhD; K. Feinstein, MA; P. O'Connor, FRCPC; and S. Black, FRCPC

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**Abstract—Objective:** To assess the association between major depression and structural brain abnormalities in patients with multiple sclerosis (MS). **Methods:** Two groups of patients with clinically definite MS were studied: 21 with Diagnostic and Statistical Manual of Mental Disorders (4th ed.)-defined major depression and 19 without. The groups did not differ on demographic, disease, or cognitive measures. All subjects underwent brain MRI. Tissue segmentation and regional brain masking were applied to the MRI data. **Results:** Compared with the euthymic subjects, those with major depression had a greater T2-weighted lesion volume ( $p = 0.003$ ) and more extensive T1-weighted lesion volume in the left medial inferior prefrontal cortex ( $p = 0.01$ ) and less gray matter volume ( $p = 0.01$ ) and more CSF volume in the left anterior temporal region ( $p = 0.005$ ). A logistic regression analysis identified two independent predictors of depression: left medial inferior prefrontal cortex T2 lesion volume and left anterior temporal CSF volume. These variables accounted for 42% of the depression variance score. **Conclusion:** Whereas both lesion burden and atrophy are important in the pathogenesis of depression in MS, psychosocial influences should also be considered.

NEUROLOGY 2004;62:586-590

Research Paper

**Multiple  
Sclerosis**

## **Diffusion tensor imaging abnormalities in depressed multiple sclerosis patients**

**A Feinstein<sup>1,2</sup>, P O'Connor<sup>1,3</sup>, N Akbar<sup>1,2</sup>, L Moradzadeh<sup>2</sup>,  
CJM Scott<sup>2</sup> and NJ Lobaugh<sup>1,2</sup>**

*Multiple Sclerosis*

16(2) 189–196

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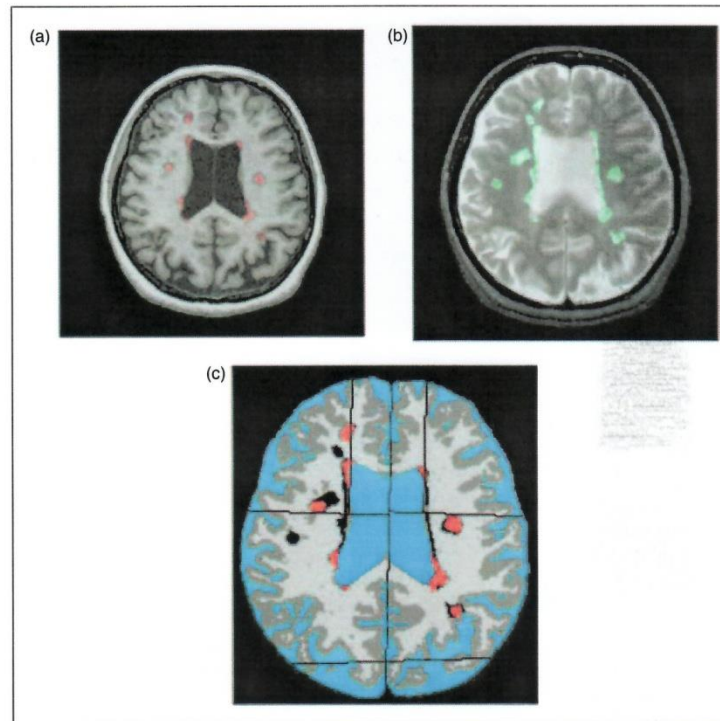
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# MS, Depression, lesion segmentation

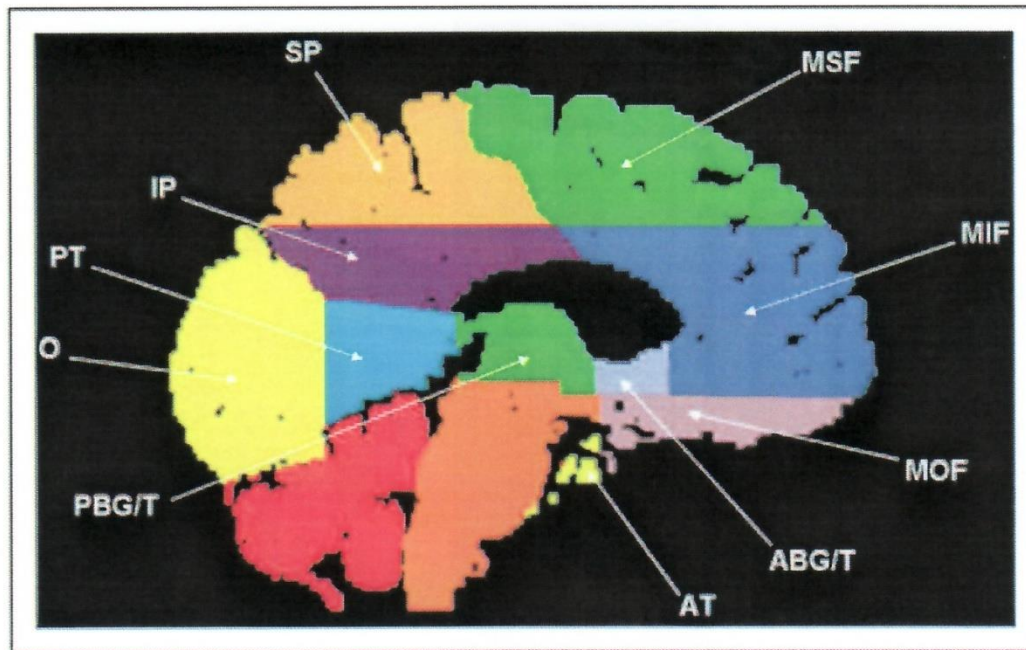
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Multiple Sclerosis 16(2)



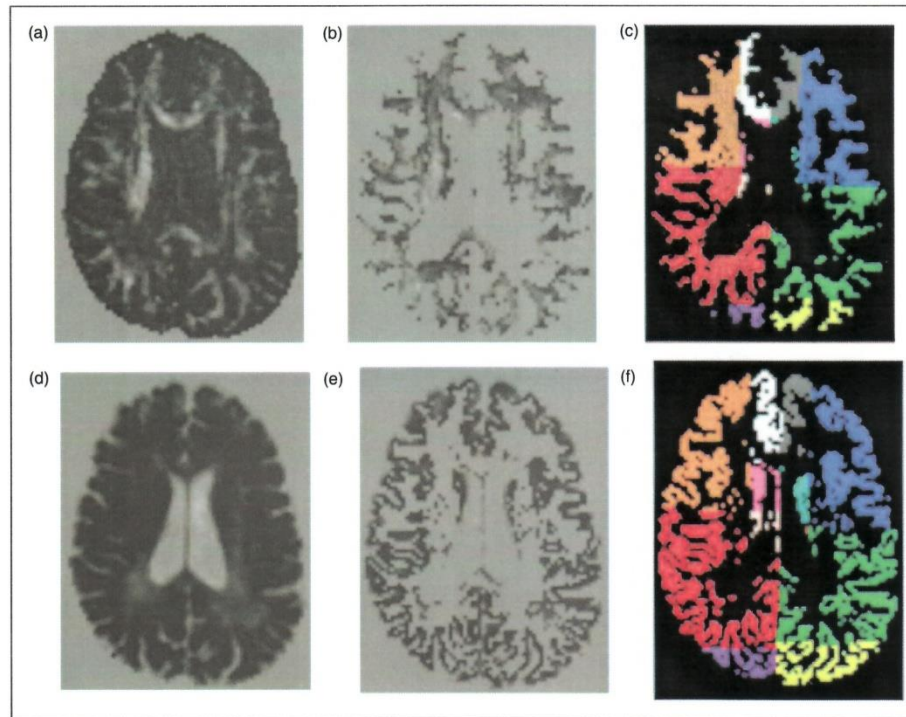
**Figure 2.** Stepwise process to obtain parcellated normal-appearing brain tissue (NABT) segmented according to tissue type. (a) T<sub>1</sub>-weighted image with traced hypointense lesions, (b) T<sub>2</sub>-weighted image with traced hyperintense lesions, (c) NABT and white matter hyperintensity (WMH) segmentations parcellated according to Semi-Automated Brain Region Extraction-defined regions (blue = cerebrospinal fluid (CSF); light gray = white matter; dark grey = grey matter; black = lesions; red = hypointense lesions).

# MS, Depression, brain parcellation



**Figure 1.** Magnetic resonance imaging sagittal view demarcating medial brain regions using Semi-Automated Brain Region Extraction. ABG/T, anterior basal ganglia/thalamus; AT, anterior temporal; IP, inferior parietal; MIF, medial inferior frontal; MOF, medial orbitofrontal; MSF, medial superior frontal; O, occipital; PBG/T, posterior basal ganglia/thalamus; PT, posterior temporal; SP, superior parietal.

# MS, Depression, diffusion tensor imaging



**Figure 3.** Stepwise process to derive fractional anisotropy (FA) and mean diffusivity (MD) from normal-appearing brain tissue parcellated according to Semi-Automated Brain Region Extraction (SABRE)-defined regions. (a) FA image in diffusion tensor imaging (DTI) space; (b) FA normal-appearing white matter (NAWM) image; (c) NAWM mask, parcellated according to SABRE; (d) MD image in DTI space; (e) MD normal-appearing grey matter (NAGM) image; (f) NAGM mask, parcellated according to SABRE.

# MS, Depression, lesions, atrophy, DTI

**Table 2.** Mean regional fractional anisotropy and mean diffusivity differences between depressed ( $n = 30$ ) and non-depressed ( $n = 32$ ) patients with multiple sclerosis

Region	FA	
	BDI $\leq$ 19	BDI $>$ 19
Left anterior temporal normal appearing white matter ( $n = 62$ )	0.209 ( $\pm 0.020$ )	0.197 ( $\pm 0.016$ )*
Region	MD ( $\mu\text{m}^2 \text{ms}^{-1}$ )	
	BDI $\leq$ 19	BDI $>$ 19
Left anterior temporal normal appearing gray matter ( $n = 62$ )	2.99 ( $\pm 0.25$ )	3.14 ( $\pm 0.20$ )*
Right inferior frontal lesion ( $n = 56$ )	2.94 ( $\pm 0.51$ )	3.26 ( $\pm 0.49$ )*

\*Significant difference between groups at  $p = 0.01$ .

BDI, Beck Depression Inventory; FA, fractional anisotropy; MD, mean diffusivity.

# MS, Depression and Diffusion Tensor Imaging

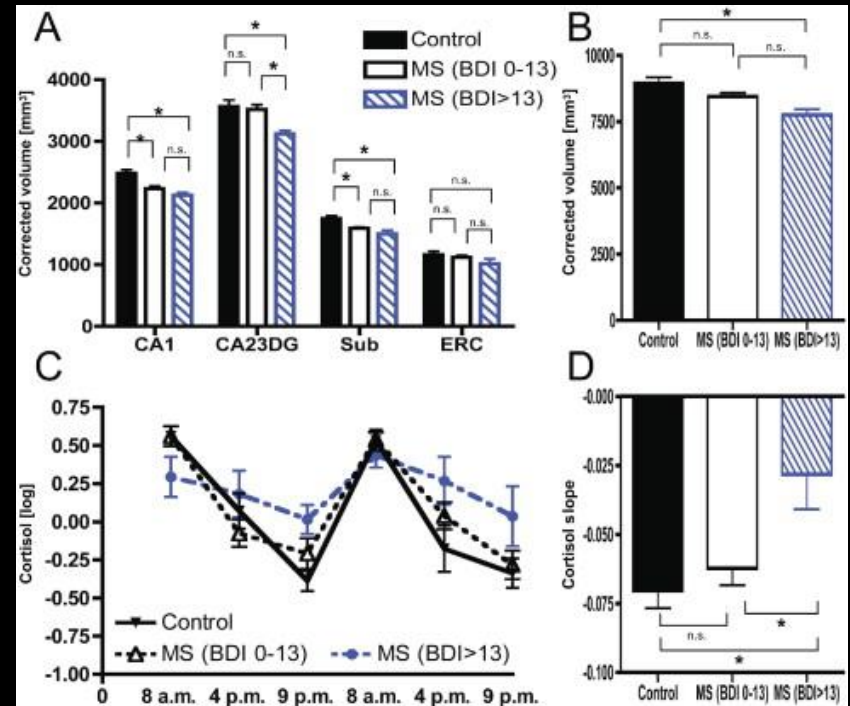
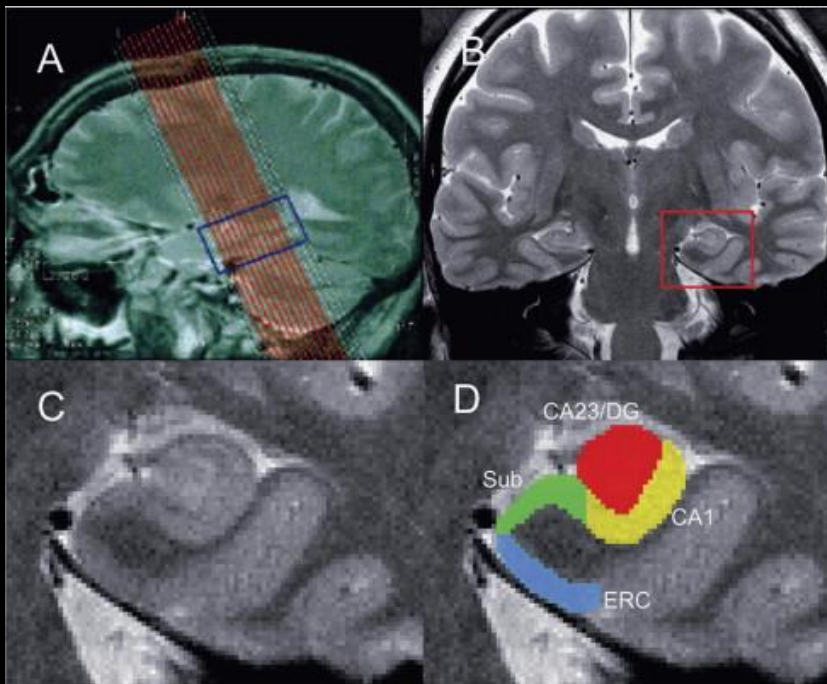
## Imaging predictors of depression

<u>MRI variables</u>	<u>Percentage variance</u>
Lesions + atrophy	23.7%
Lesions + atrophy + regional DTI indices from normal appearing brain tissue	35.1%
Lesions + atrophy + regional DTI indices from normal appearing brain tissue + MD of right inferior frontal lesions.	43.6%



# Smaller Cornu Ammonis 2–3/Dentate Gyrus Volumes and Elevated Cortisol in Multiple Sclerosis Patients with Depressive Symptoms

Gold et al, Biological Psychiatry 2010, 68, 553-9

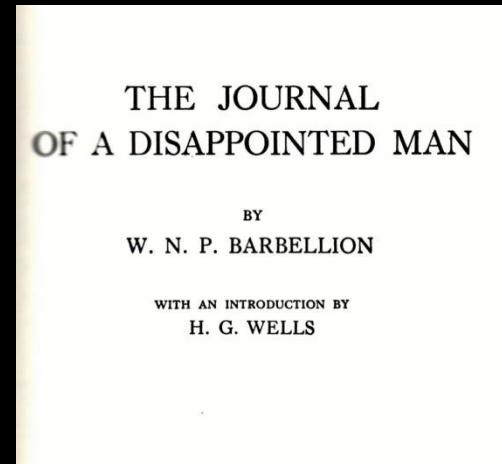




# MS, Depression and brain imaging: summary

Study	Year	Imaging modality	Number of subjects	Rating Scale	Clinical diagnosis	Imaging findings	Laterality
Sabatini, U. <i>et al.</i>	1996	SPECT	N=20 (n=10 depressed & n=10 non-depressed)	DSM-III	Major depression	Increased perfusion in <b>limbic</b> areas.	Left
Pujol, J. <i>et al.</i>	1997, 2000	MRI	N=45	BDI-II	None	Increased T2 lesions in the arcuate fasciculus associated with somatic and affective symptoms	Left
Fassbender, K. <i>et al.</i>	1998	MRI + Gd	N=73 (n=23 RRMS, n=17 healthy control group A, n=33 healthy control group B)	DSM-III-R, HRSD, ZSRDS	Major depression	Increased Gd+ lesions linked to increased cortisol and a positive dexamethasone suppression test	None reported
Bakshi, R. <i>et al.</i>	2000	MRI	N=48 (n=19 depressed & n=29 non-depressed)	DSM-IV criteria for unipolar depression, HRSD, BDI	Major depression	Superior <b>frontal, superior parietal and temporal</b> T1 lesions, lateral and third ventricular enlargement, frontal atrophy.	Left
Berg, D. <i>et al.</i>	2000	MRI	N=78	DSM-IV	Major depression	Increased T2 lesion load in whole brain, parietal and <b>frontal</b> lobes and the cerebellum.	Right
Zorzon, M. <i>et al.</i>	2002	MRI	N=90	HDRS, DSM-IV	Major depression	Atrophy in the left <b>frontal</b> lobe. Severity of depressive symptoms associated with reduced right <b>temporal</b> lobe volume.	Bilateral
Feinstein, A. <i>et al.</i>	2004	MRI	N=40 (n=21 depressed, n=19 non-depressed)	DSM-IV	Major depression	T2 and T1 lesion volume in <b>medial inferior prefrontal</b> cortex, <b>anterior temporal</b> atrophy.	Left
Passa monti, L. <i>et al.</i>	2009	fMRI	N=24 (n=12 MS subjects, n=12 healthy control subjects)		None	Reduced functional connectivity between <b>ventrolateral PFC</b> and <b>amygdala</b> .	Bilateral
Gold, S.M. <i>et al.</i>	2010	MRI	N=49 (n=20 RRMS & n=29 healthy control subjects)	BDI-II	None	<b>Hippocampal</b> atrophy particularly in <b>CA2-3 and dentate</b> gyrus linked to increased cortisol.	Left
Feinstein, A. <i>et al.</i>	2010	MRI plus DTI	N=62 (n=30 depressed, n=32 non-depressed)	BDI-II	None	Increased T1 lesion volume in <b>right medial inferior frontal</b> region, atrophy of left <b>superior frontal</b> region, lower FA, higher MD in <b>left anterior temporal</b> normal-appearing white and grey matter, higher MD in <b>right inferior frontal</b> hyperintense lesions.	Bilateral
Gold, S.M. <i>et al.</i>	2014	MRI	N=109 (females only)	CES-D	None	Reduced <b>hippocampus</b> thickness.	Right

# Psychosocial causes of depression



Bruce Frederick Cummings

- From the journal: *June 15, 1917.*
- *I sit all day in my chair, moving 8 feet to my bed at night, and 8 feet from it to my chair in the morning—and wait. The assignment is certain.*

From the journal: *October 3, 1918.*  
*I am grateful to-day for some happy hours plucked triumphantly from under the very nose of Fate, and spent in the warm sun in the garden . . . A Lark sang . . . I sat by some Michaelmas Daisies and watched the Bees, Flies and Butterflies*

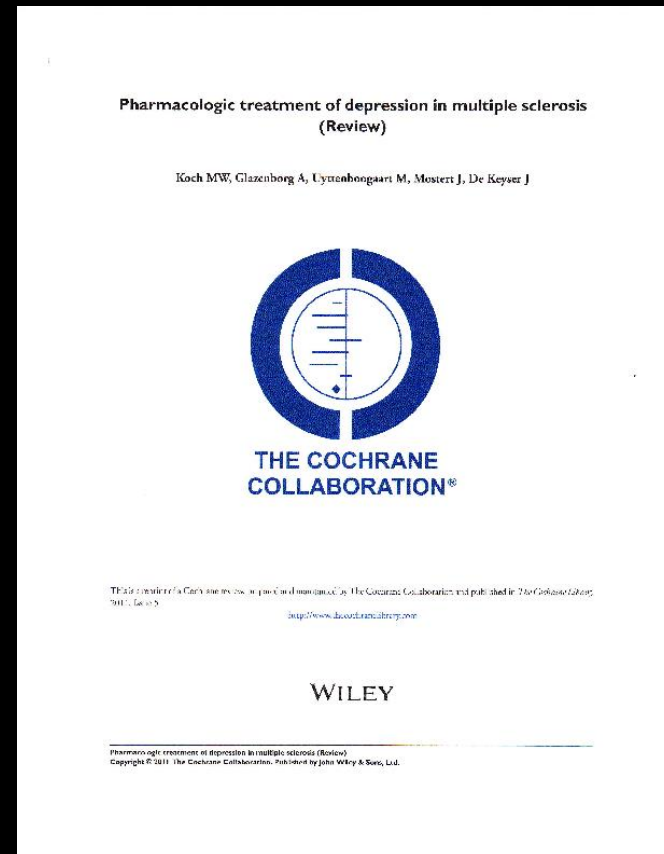
# Depression

## Psychosocial etiology

- Uncertainty (Lynch et al, 2001)
- Inadequate coping strategies (Mohr et al, 1997; Pakenham et al, 1997; Aikens et al, 1997; Jean et al, 1997; Pakenham 1999)
- Helplessness (Shnek et al, 1997; Patten et al, 2002; van der Werf, 2003)
- Poor social relationships (Maybury and Brewin, 1984)
- Loss of recreational activities (Voss et al 2002)
- High levels of stress (Patten et al, 2000)
- Fatigue (Lobentanz et al, 2004)

# Treating Major Depression: Medication

- Only Two RCTs
- Desipramine (tricyclic antidepressant)
- Paroxetine (SSRI)
- Medication effective
- Side effects troubling: anti-cholinergic problems
  - Dry mouth
  - Constipation
  - Sedation
  - Blurred vision
  - Sexual difficulties



# Major Depression: Medication

- Mirtazepine (Remeron):
  - selective noradrenergic and 5HT1 serotonergic action
  - Spares sexual function, no nausea
  - But there is fatigue
  - weight gain
- Bupropriion (Wellbutrin)
  - Selective dopaminergic and noradrenergic action
  - Spares sexual function
  - Contraindicated with seizures

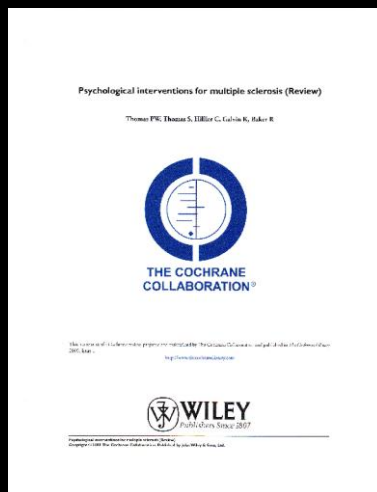
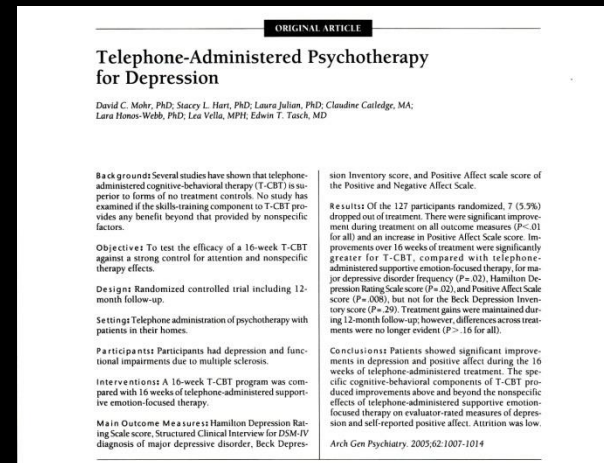


# A new antidepressant

- Vortioxetine
- Antidepressant effects
- Cognitive enhancing effects
- No MS data yet.

# Major Depression: Psychotherapy

- Cognitive-behavior **Rx** vs. Supportive-expressive **Rx** vs. sertraline **Rx** over 16 weeks. (Mohr et al, 2005).
- Can be given effectively over the telephone.
- Mindfulness Based Therapy (Grossman et al, 2010)





# Management of psychiatric disorders in MS

Recommendations from the American Academy of Neurology @014)

SPECIAL ARTICLE



## Evidence-based guideline: Assessment and management of psychiatric disorders in individuals with MS

Report of the Guideline Development Subcommittee of the American Academy of Neurology



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### ABSTRACT

**Objective:** To make evidence-based recommendations for screening, diagnosing, and treating psychiatric disorders in individuals with multiple sclerosis (MS).

**Methods:** We reviewed the literature (1950 to August 2011) and evaluated the available evidence.

**Results and recommendations:** Clinicians may consider using the Center for Neurologic Study Emotional Lability Scale to screen for pseudobulbar affect (Level C). Clinicians may consider the Beck Depression Inventory and a 2-question tool to screen for depressive disorders and the General Health Questionnaire to screen for broadly defined emotional disturbances (Level C). Evidence is insufficient to support/refute the use of other screening tools, the possibility that somatic/neurovegetative symptoms affect these tools' accuracy, or the use of diagnostic instruments or clinical evaluation procedures for identifying psychiatric disorders in MS (Level U). Clinicians may consider a telephone-administered cognitive behavioral therapy program for treating depressive symptoms (Level C). Although pharmacologic and nonpharmacologic therapies are widely used to treat depressive and anxiety disorders in individuals with MS, evidence is insufficient to support/refute the use of the antidepressants and individual and group therapies reviewed herein (Level U). For pseudobulbar affect, a combination of dextromethorphan and quinidine may be considered (Level C). Evidence is insufficient to determine the psychiatric effects in individuals with MS of disease-modifying and symptomatic therapies and corticosteroids; risk factors for suicide; and treatment of psychotic disorders (Level U). Research is needed on the effectiveness in individuals with MS of pharmacologic and nonpharmacologic treatments frequently used in the non-MS population. *Neurology*® 2014;82:174-181



# Stress management

- 24 weeks of treatment
- Less Gd+ lesions
- Less cumulative lesion load
- Effects not sustained beyond 24 weeks
- No clinical benefits, including mood

A randomized trial of stress management for the prevention of new brain lesions in MS

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Jana Lavera, MD  
Ted Brown, MD  
Bruce Cohen, MD  
Thomas Neylan, MD  
Roland Henry, PhD  
Jusaid Siddique, DPH  
Ling Jin, MS  
David Daikh, MD  
Daniel Pelletier, MD

**ABSTRACT**

**Objective:** This trial examined the efficacy of a stress management program in reducing neuroimaging markers of multiple sclerosis (MS) disease activity.

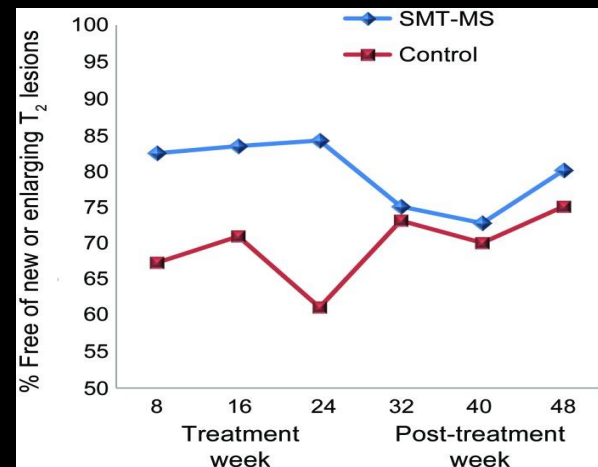
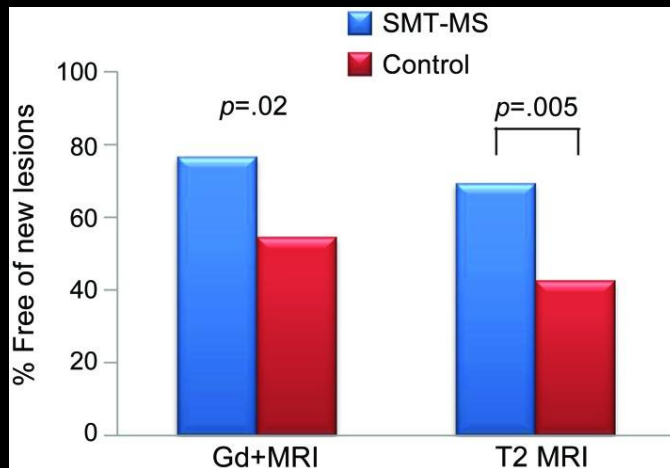
**Methods:** A total of 121 patients with relapsing forms of MS were randomized to receive stress management therapy for MS (SMT-MS) or a wait-list control condition. SMT-MS provided 16 individual treatment sessions over 24 weeks, followed by a 24-week post-treatment follow-up. The primary outcome was the cumulative number of new gadolinium-enhancing (Gd+) brain lesions on MRI at weeks 8, 16, and 24. Secondary outcomes included new or enlarging T2 MRI lesions, brain volume changes, clinical exacerbation, and stress.

**Results:** SMT-MS resulted in a reduction in cumulative Gd+ lesions ( $p = 0.04$ ) and greater numbers of participants remained free of Gd+ lesions during the treatment (76.8% vs 54.7%,  $p = 0.02$ ), compared to participants receiving the control treatment. SMT-MS also resulted in significantly reduced numbers of cumulative new T2 lesions ( $p = 0.005$ ) and a greater number of participants remaining free of new T2 lesions (69.5% vs 42.7%,  $p = 0.006$ ). These effects were no longer detectable during the 24-week post-treatment follow-up period.

**Conclusions:** This trial indicates that SMT-MS may be useful in reducing the development of new MRI brain lesions while patients are in treatment.

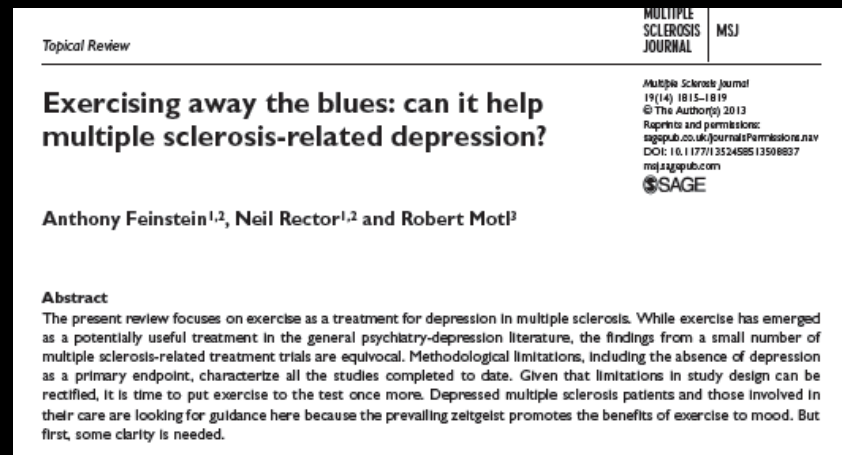
**Classification of evidence:** This study provides Class I evidence that SMT-MS, a manualized stress management therapy program, reduced the number of Gd+ lesions in patients with MS during a 24-week treatment period. This benefit was not sustained beyond 24 weeks, and there were no clinical benefits.

**Trial registration:** ClinicalTrials.gov, number NCT00147446. *Neurology* 2012;79:432-439



# Exercise

- There is, as yet, no exercise study in MS with depression as the primary endpoint
- No study has used a structured interview to define depression
- Data from other studies (n=7) are equivocal
- Hard to draw conclusions from inadequate methodologies, but there is untapped potential that needs to be studied further



# ECT

- Potentially very useful
- Very severe depression
- Failed other treatments
- If you are concerned about high suicide risk
- Risk of MS relapse? Gd enhanced MRI can be predictive here

# Pathological laughing and crying

## THE JOURNAL OF NEUROLOGY AND PSYCHOPATHOLOGY.

Vol. IV.

FEBRUARY, 1924.

No. 16.

### Original Papers.

SOME PROBLEMS IN NEUROLOGY.

By S. A. KINNIER WILSON, LONDON.

No. II.—PATHOLOGICAL LAUGHING AND CRYING.



# Pathological laughing and crying (Pseudobulbar affect)

- Crying without sadness
- Laughter without happiness (mirth)
- Up to 10% of MS patients affected to various degrees

## ORIGINAL CONTRIBUTION

### Prevalence and Neurobehavioral Correlates of Pathological Laughing and Crying in Multiple Sclerosis

*Anthony Feinstein, PhD, MD; Karen Feinstein, MA; Trevor Gray, MD; Paul O'Connor, MD*

**Objectives:** To establish the point prevalence of pathological laughing and crying (PLC) in multiple sclerosis (MS). To define associated neurological, emotional, and cognitive correlates of PLC.

**Design:** A consecutive sample of 152 patients with clinically or laboratory definite MS were screened for PLC, defined as sudden, involuntary displays of laughing or crying or both, without associated subjective feelings of depression or euphoria. Thereafter, a case-control design was followed with patients with PLC matched to patients with MS without PLC on age, gender, physical disability (Expanded Disability Status Scale), duration of MS, and premorbid IQ.

**Setting:** An MS outpatient clinic, the population representative of a large urban catchment area.

**Patients:** Fifteen of 152 patients had PLC, 11 of whom (mean [SD] age, 43.7 [8.3] years, 7 women) agreed to further testing. Thirteen patients with MS without PLC acted as controls.

**Main Outcome Measures:** Neurological examination, Pathological Laughter and Crying Scale, Hospital Anxiety and Depression Scale, 28-item General Health Questionnaire, and the Wechsler Adult Intelligence Scale-Revised.

**Results:** The point prevalence of PLC in MS was 10%. Patients had a mean Expanded Disability Status Scale score of 6.5, had had MS for a mean (SD) of 10 (5.8) years, and had entered a chronic-progressive phase of their illness. Pathological laughing and crying was not associated with disease exacerbations. Compared with controls, patients were not more depressed or anxious, but had a greater decline in IQ.

**Conclusions:** Pathological laughing and crying as distinct from emotional lability affects 1 in 10 patients with MS. It occurs in severely physically disabled patients, generally with long-standing disease. The presence of cognitive deficits relative to controls implies more extensive brain involvement.

*Arch Neurol. 1997;54:1116-1121*

# Major Depression and Pathological Laughing and Crying: Comparison of MRI variance

Major Depression	40%
Pathological laughing and crying	~ 75%

# Pseudobulbar affect

- Rx:
  - low dose amitriptyline
  - SSRI
  - levodopa and amantadine
  - Neudexta (dextromethorphan/quinidine)

**Response to treatment  
in PBA = 48-72 hours**

**Response to treatment  
in major depression =  
10-14 days**

# Cognition



# Cognitive dysfunction in MS

prevalence rates

- Relapsing-remitting MS
  - 40%
- Secondary progressive MS
  - 60-70%

# **Cognitive dysfunction in MS:**

## Clinical significance

- Cognitively impaired MS patients may experience greater difficulties with respect to work, relationships, vocational functions, sexual function and activities of daily living.

# Cognitive dysfunction in MS

- Reduction in cognitive speed
- slowness in information processing
- Working memory
- memory (retrieval >> encoding)
- deficits in abstracting
- attention and vigilance impaired
- language largely spared
- little agnosia and apraxia

# Assessing cognition: the choices

- Self report screening questionnaire
- Brief Screening batteries
- Consensus guidelines for more detailed testing:
  - MACFIMS
- Mini Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA)

# Assessing cognition

## self report

- Multiple sclerosis neuropsychological questionnaire (MSNQ)
- 15 questions for patient
- 15 questions for informant
- Good sensitivity and specificity
- Informant responses more accurate reflection of patient's cognition
- Patient complaints of impaired cognition may better reflect depression.

Benedict et al, 2003

MSNQ Patient

Name: \_\_\_\_\_

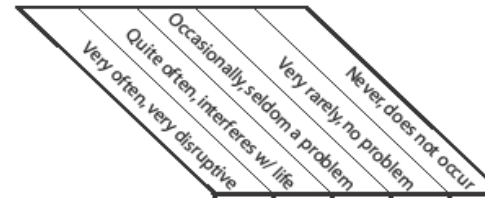
Date: \_\_\_\_\_

Circle one: MALE / FEMALE

**INSTRUCTIONS:**

The following questions ask about problems that you may experience. Rate how often these problems occur **AND** how severe they are. Base your ratings on how you have been over the **last three months**.

Please check the appropriate box.



	4	3	2	1	0
1. Are you easily distracted?					
2. Do you lose your thoughts while listening to somebody speak?					
3. Are you slow when trying to solve problems?					
4. Do you forget appointments?					
5. Do you forget what you read?					
6. Do you have trouble describing shows or programs recently watched?					
7. Do you need to have instructions repeated?					
8. Do you have to be reminded to do tasks?					
9. Do you forget errands that were planned?					
10. Do you have difficulty answering questions?					
11. Do you have difficulty keeping track of two things at once?					
12. Do you miss the point of what someone is trying to say?					
13. Do you have difficulty controlling impulses?					
14. Do you laugh or cry with little cause?					
15. Do you talk excessively or focus too much on your own interests?					

**MSNQ Informant**

Patient's Name: \_\_\_\_\_

Date: \_\_\_\_\_

Your Name: \_\_\_\_\_

How many times do you see the patient per week? \_\_\_\_\_

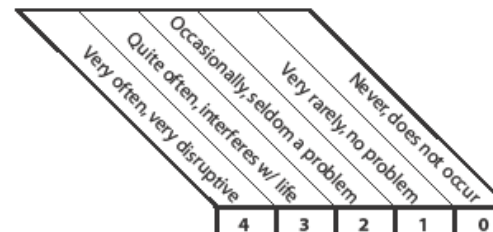
How long have you known the patient? \_\_\_\_\_

Relation to patient:   \_\_\_ SPOUSE   \_\_\_ DOMESTIC PARTNER   \_\_\_ FRIEND   \_\_\_ PARENT  
                                   \_\_\_ CHILD   \_\_\_ OTHER FAMILY   \_\_\_ OTHER FRIEND

**INSTRUCTIONS:**

The following questions ask about problems that the patient may experience. We want you to rate how often these problems occur, **AND** how severe they are. Base your ratings on his/her behavior over the **past three months**.

Please check the appropriate box.



	4	3	2	1	0
1. Does he/she get easily distracted?					
2. Does he/she lose his/her thoughts while listening to somebody speak?					
3. Is he/she slow when trying to solve problems?					
4. Does he/she forget appointments?					
5. Does he/she forget what he/she reads?					
6. Does he/she have trouble describing shows or programs recently watched?					
7. Does he/she need to have instructions repeated?					
8. Does he/she have to be reminded to do tasks?					
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11. Does he/she have difficulty keeping track of two things at once?					
12. Does he/she miss the point of what someone is trying to say?					
13. Does he/she have difficulty controlling his/her impulses?					
14. Does he/she laugh or cry with little cause?					
15. Does he/she talk excessively or focus too much on his/her own interests?					

# Screening batteries

- Brief Repeatable Neuropsychological Battery
  - 15 alternative, equivalent versions
  - Consistent Long Term Retrieval (Selective Reminding Test)
  - 10/36 Spatial Recall Test
  - COWAT (verbal fluency)
  - PASAT (information processing speed and working memory)
  - SDMT (information processing speed)
- 30-40 minutes to complete



# More detailed cognitive batteries

- Many to choose from
- Consensus advice: MACFIMS (Minimal Assessment of Cognitive Function in MS).

PASAT, SDMT (processing speed, working memory)

CVLT, Brief Visuospatial Memory Test (memory)

D-KEFS (Executive Function)

Judgment of Line Orientation Test (visual perception, spatial processing)

COWAT (verbal fluency, language, attention)

90 minutes to complete

# Mini-Mental State Examination

- MMSE not sensitive
- Cognitively impaired MS patients regularly score  $> 27$  on the MMSE.
- MoCA not sensitive too.

# Barriers to Assessment

- Cognitive assessment screening batteries require time and expertise to administer; they are not part of a routine assessment.

# Access to neuropsychological testing

## Impediments

- Shortage of neuropsychologists
- Expensive

## Potential solution

- Computerized batteries
  - ANAM
  - Mindstream
  - Amsterdam Neuropsychological Task
  - Cognitive Stability Index


# SUNSCREEN

## Sunnybrook Computerized Screen for Cognitive Assessment in MS

Research Paper

MULTIPLE  
SCLEROSIS  
JOURNAL | MSJ

### Assessing the validity of a computer-generated cognitive screening instrument for patients with multiple sclerosis

*Multiple Sclerosis Journal*  
19(14) 1905–1912  
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sagepub.co.uk/journalsPermissions.nav  
DOI: 10.1177/1352458513488841  
msj.sagepub.com  


Helen Lapshin<sup>1,2</sup>, Krista L Lanctôt<sup>1,2</sup>, Paul O'Connor<sup>2,3</sup>  
and Anthony Feinstein<sup>1,2</sup>

#### Abstract

**Background:** Neuropsychological testing requires considerable time, expense, and expertise to administer. These factors can limit patient access. Computerized cognitive testing has been proposed as an alternative.

**Objectives:** The objective of this paper is to validate a brief, simple-to-use computer-generated cognitive assessment screening battery for multiple sclerosis (MS) patients that has minimal motor involvement.

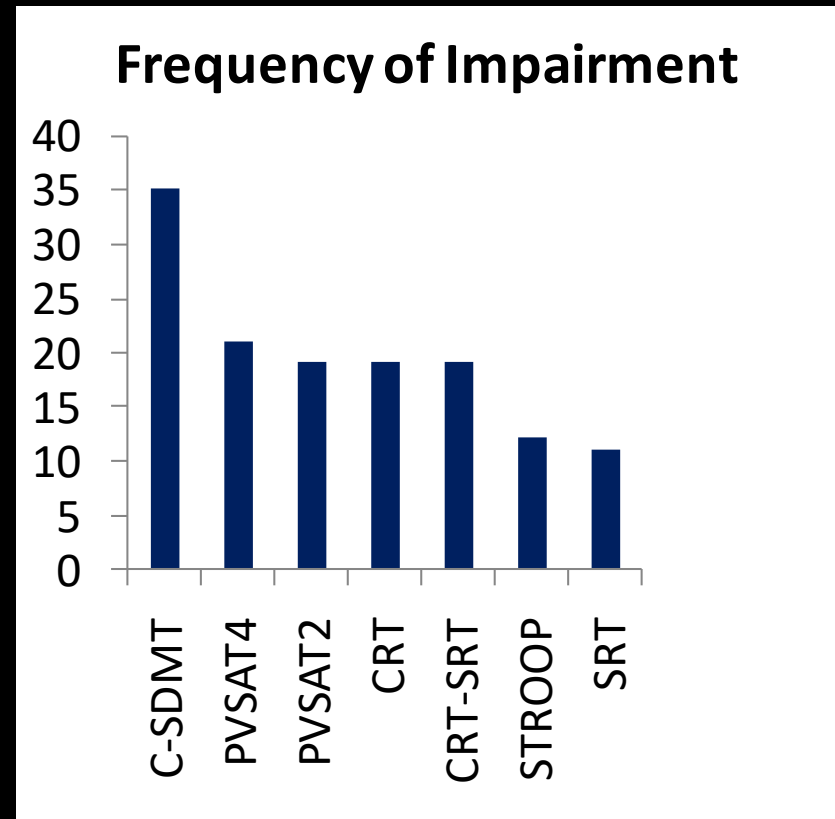
**Methods:** A sample of 96 MS patients and 98 healthy controls completed a computer-generated battery that included the Stroop, Symbol Digit Modalities Test (C-SDMT), a two- and four-second visual analog of the Paced Auditory Serial Addition Test (PVSAT-2, PVSAT-4), and simple and choice reaction time tests. The Minimal Assessment of Cognitive Function in MS was used to define cognitive impairment in the MS sample.

**Results:** Each newly developed test successfully distinguished between cognitively impaired patients and healthy controls as well as cognitively intact patients. A combination of three computerized tests (C-SDMT, PVSAT-2, PVSAT-4) with a mean administration time of 10 minutes had a sensitivity of 82.5% and specificity of 87.5% in detecting cognitive impairment. Good test-retest reliability was obtained for each measure.

**Conclusions:** Good sensitivity and specificity, brevity, ease of administration, and a limited motor component highlight the feasibility of introducing this computer-generated cognitive screening instrument in a busy MS clinic.

# Computerized Tests: Impairment Rate

Test	Impairment rate (score less than 1.5 SD below mean of healthy controls)
C-SDMT	35.4%
PVSAT 4 sec	21.2%
PVSAT 2 sec	19.2%
CRT	19.2%
CRT-SRT	19.2%
STROOP	12.1%
SRT	11.1%



# Sensitivity & specificity compared to MACFIMS

Test(s)	Impairment Threshold	Sensitivity (%)	Specificity (%)
C-SDMT	1/1	66.7	87.7
C-SDMT, PVSAT <sub>4</sub>	1/2	81.0	87.7
C-SDMT, PVSAT <sub>4</sub> , PVSAT <sub>2</sub>	1/3	83.3	87.7
C-SDMT, PVSAT <sub>4</sub> , CRT	1/3	78.4	80.4
C-SDMT, PVSAT <sub>4</sub> , CRT-SRT	1/3	83.8	78.2
C-SDMT, PVSAT <sub>4</sub> , PVSAT <sub>2</sub> , CRT, CRT-SRT	1/5	86.5	74.5

# Final Screen

- C-SDMT, PVSAT 4 sec, PVSAT 2 sec

Threshold - Impaired on at least:	Sensitivity (%)	Specificity (%)
1/3	83.3	87.7
2/3	52.4	94.7
3/3	31.0	98.2

- 10 minute screen.
- No motor ability required.



# Cognition and MR imaging

# Cognitive correlates

brain imaging

- Total lesion volume
  - Modest correlations with computerized volume estimations.

# Cognitive correlates

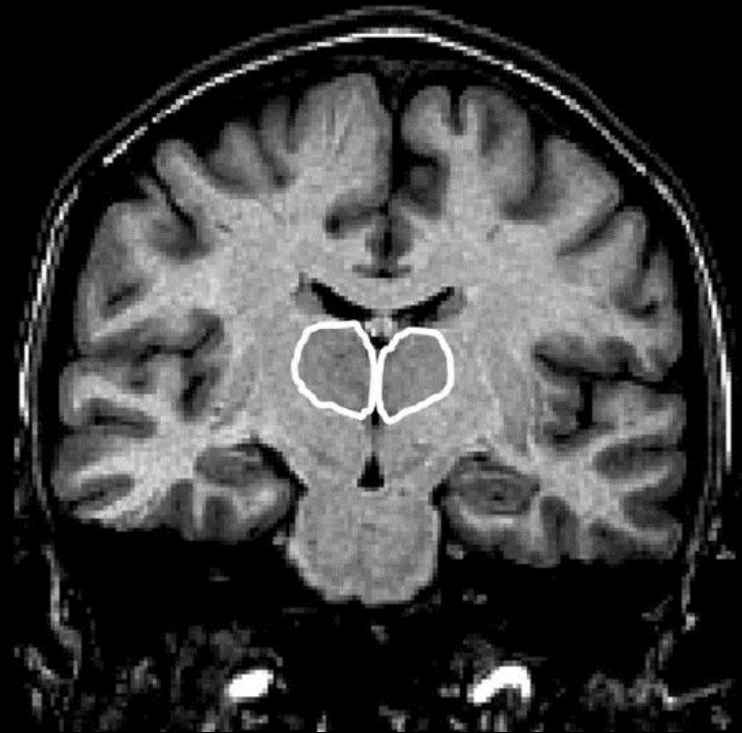
brain imaging: atrophy

- Atrophy has emerged as the most robust correlate of cognitive dysfunction
  - Benedict et al (2004)
    - Hyperintense lesion volume
    - Hypointense lesion volume
    - Third ventricular width
    - Bicaudate ratio
    - Brain parenchymal fraction
    - MACFIMS

# Cognitive correlates

## brain imaging: atrophy

- Atrophy has emerged as the most robust correlate of cognitive dysfunction
  - Houtchens et al (2007)  
Neurology. 69(12):1213-1223
    - thalamic volume

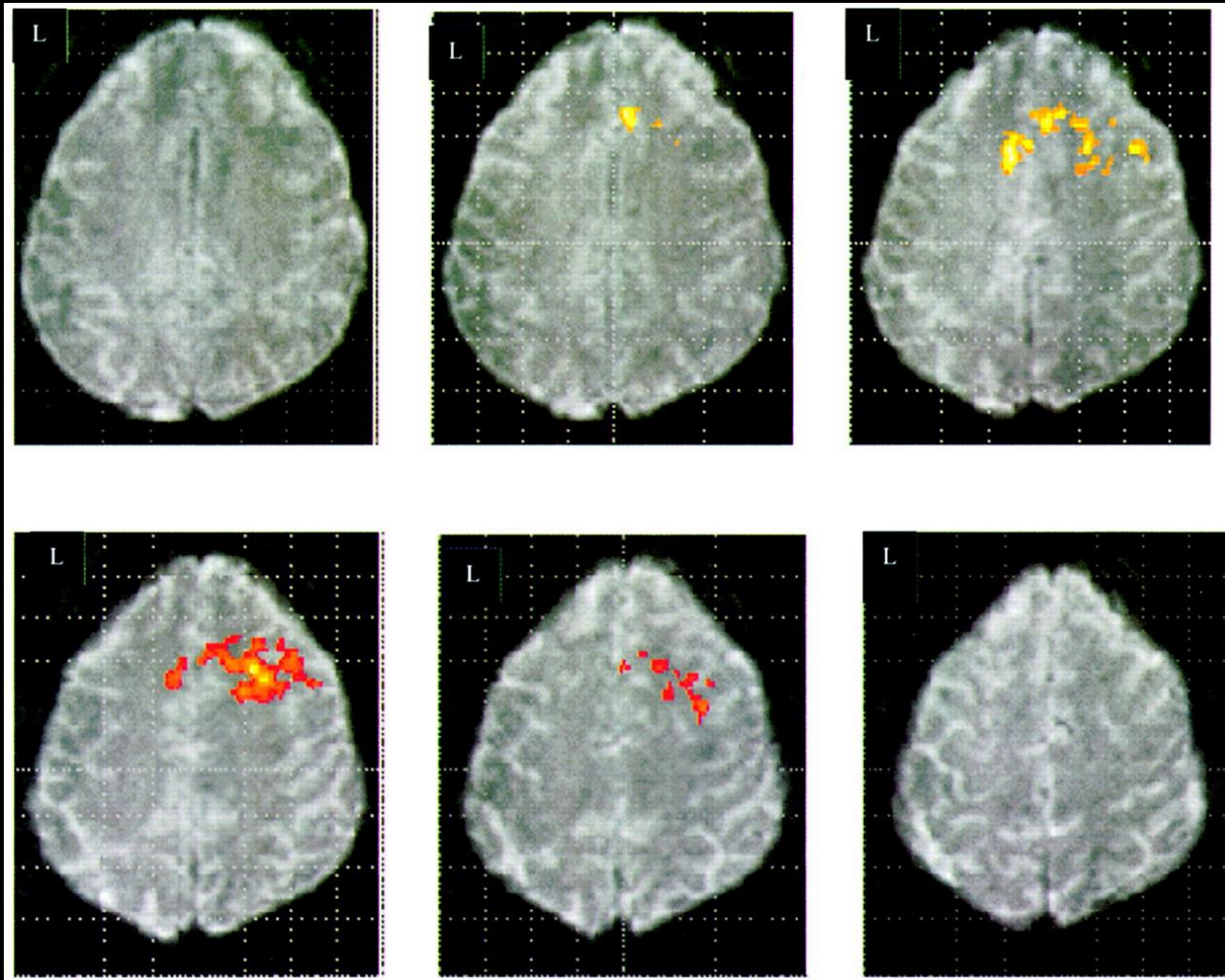


# Cognitive correlates

## fMRI

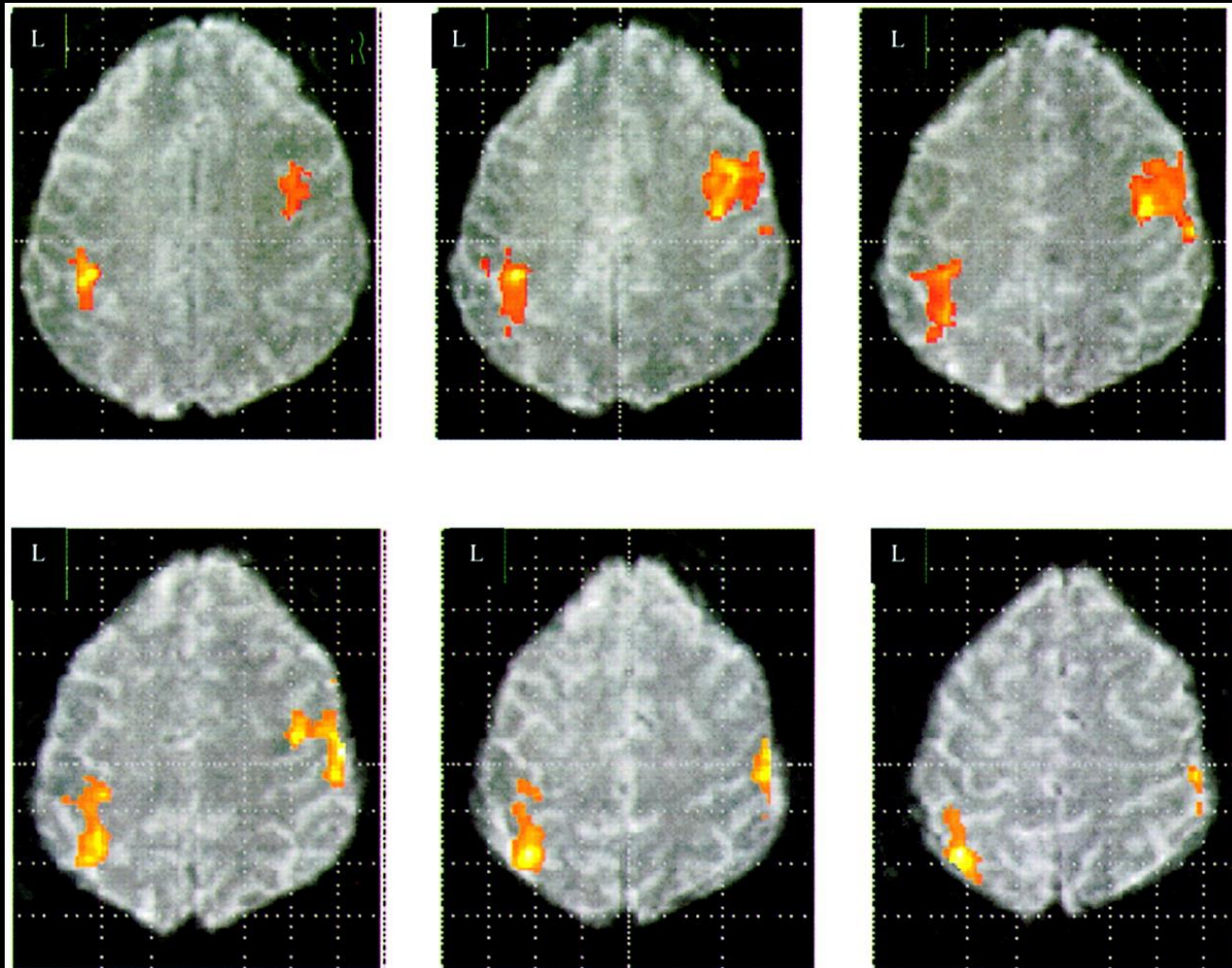
- Growing literature comparing patterns of activation to those seen in healthy subjects
- Similar results: even if MS patients did not do more poorly than healthy controls they required additional cerebral activation to achieve this.
- Imaging reveals the attempts at compensation using ancillary brain regions
- Brain plasticity within a narrower range of milder impairment.
- Threshold effect
- Effects of medication on cerebral activation

## PVSAT activation in healthy controls



Staffen, W. et al. *Brain* 2002 125:1275-1282; doi:10.1093/brain/awf125

## PVSAT activation pattern in the multiple sclerosis patients group



Staffen, W. et al. *Brain* 2002 125:1275-1282; doi:10.1093/brain/awf125



# Intellectual enrichment is linked to cerebral efficiency in multiple sclerosis: functional magnetic resonance imaging evidence for cognitive reserve

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

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# Cognitive reserve

Sumowski et al, 2010

## What is cognitive reserve

- Premorbid IQ
- Lifetime intellectual enrichment
- Education
- Vocabulary
- Lessens the negative cognitive impact of neurological disease

## Brain metrics

- Positive correlations with cerebral activity within the Default Mode Network
- Negatively linked to recruitment of prefrontal regions during cognitive tasks

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

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A. Gonnella, EdM  
N. Chiaravalloti, PhD  
J. DeLuca, PhD

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jsumowski@kesslerfoundation.org

## 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.

**Methods:** Premorbid cognitive leisure was surveyed in 36 patients with MS. Neurologic disease severity was estimated with brain atrophy, measured as third ventricle width on high-resolution MRI. Cognitive status was measured with a composite score of processing speed and memory.

**Results:** Controlling for brain atrophy, premorbid cognitive leisure was positively associated with current cognitive status ( $r_p = 0.49, p < 0.01$ ), even when controlling for vocabulary ( $r_p = 0.39, p < 0.05$ ) and education ( $r_p = 0.47, p < 0.01$ ). Also, premorbid cognitive leisure was unrelated to brain atrophy ( $r = 0.03, p > 0.5$ ), but a positive partial correlation between leisure and atrophy emerged when controlling for cognitive status ( $r_p = 0.37, p < 0.05$ ), which remained when also controlling for vocabulary ( $r_p = 0.34, p < 0.05$ ) and education ( $r_p = 0.35, p < 0.05$ ).

**Conclusions:** Premorbid cognitive leisure contributes to cognitive status in patients with MS independently of vocabulary and education. Also, patients with MS who engaged in more cognitive leisure were able to withstand more severe brain atrophy at a given cognitive status. Premorbid cognitive leisure is supported as an independent source of cognitive reserve in patients with MS.

**Neurology**® 2010;75:1428-1431

# Treatment

- Disease modifying drugs  $\pm$
- Donepezil **x**
- Memantine **x**
- 4-aminopyridine **x**
- Psychostimulants **x**
  - Lisdexamphetamine  $\checkmark$
- Cyclophosphamide **x**
- The importance of cognitive reserve  $\checkmark$ 
  - Premorbid IQ
  - Recreational activities
- Compensatory methods  $\checkmark$
- Cognitive retraining  $\checkmark$

# An RCT to treat learning impairment in multiple sclerosis

The MEMREHAB trial



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John DeLuca, PhD

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org

## 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 with clinically definite MS, 41 in the treatment group and 45 in the placebo control group. Participants completed a baseline neuropsychological assessment, including questionnaires assessing everyday memory, a repeat assessment immediately posttreatment, and a long-term follow-up assessment 6 months after treatment. After completion of the treatment phase, persons in the treatment group were assigned to a booster session or a non-booster session group to examine the efficacy of monthly booster sessions in facilitating the treatment effect over time.

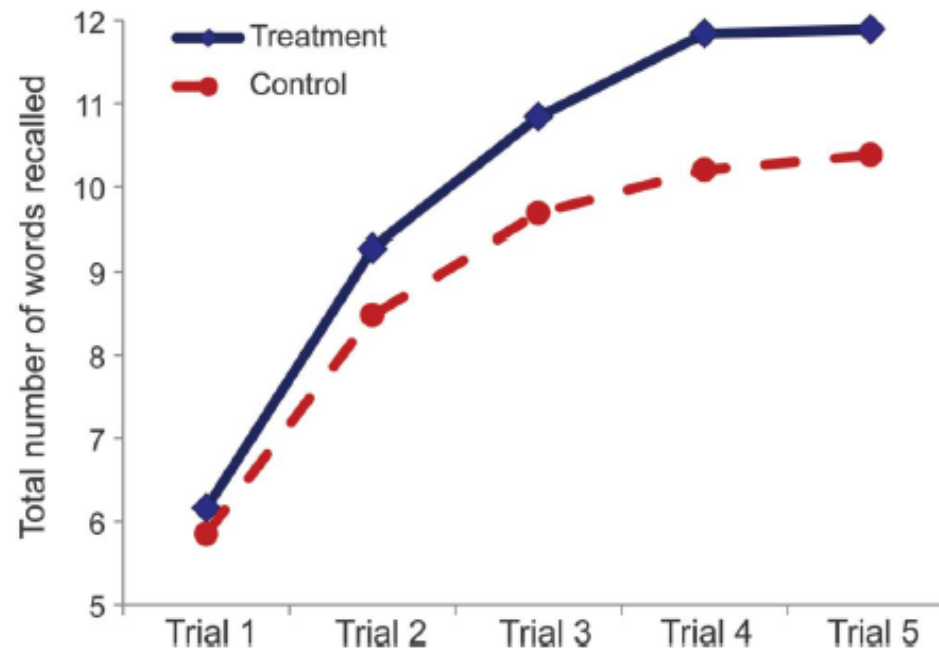
**Results:** The treatment group showed a significantly improved learning slope relative to the placebo group posttreatment. Similar results were noted on objective measures of everyday memory, general contentment, and family report of apathy and executive dysfunction. Long-term follow-up data showed that posttreatment improvement in the treatment group continued to be noted on the list learning and self-report measures. The provision of booster sessions demonstrated little benefit.

**Conclusion:** The mSMT is effective for improving learning and memory in MS.

**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

# A RCT to treat learning impairment in MS

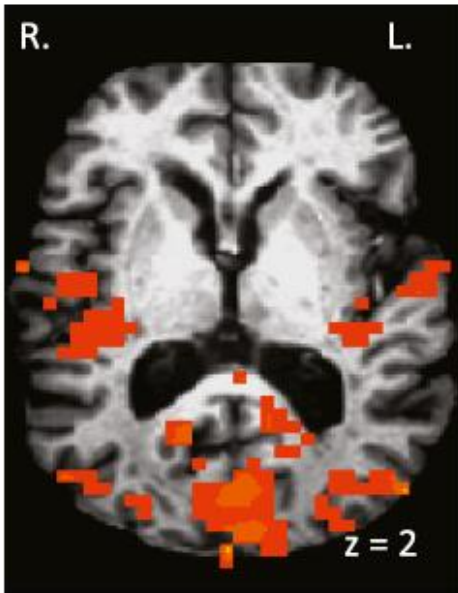
**Figure 2** California Verbal Learning Test (CVLT) learning slope across the 5 learning trials of the CVLT immediately posttreatment, by treatment group ( $p < 0.05$ )



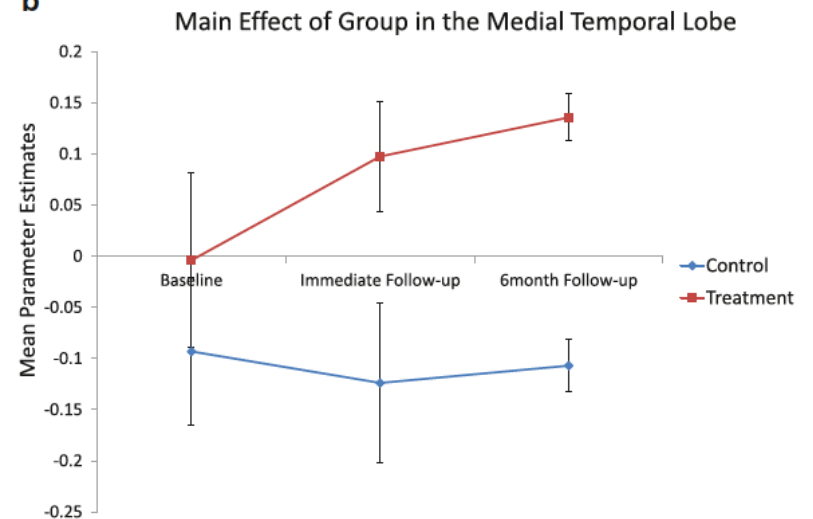
## A pilot study examining functional brain activity 6 months after memory retraining in MS: the MEMREHAB trial

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

a



b



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

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msj.sagepub.com  


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

### Abstract

**Background:** Exercise may have beneficial effects on both well-being and walking ability in multiple sclerosis (MS). Exercise is shown to be neuroprotective in rodents and may also enhance cognitive function in humans. It may, therefore, be particularly useful for MS patients with pronounced neurodegeneration.

**Objective:** To investigate the potential of standardized exercise as a therapeutic intervention for progressive MS, in a randomized-controlled pilot trial.

**Methods:** Patients with progressive MS and moderate disability (Expanded Disability Status Scale (EDSS) of 4–6) were randomized to one of three exercise interventions (arm ergometry, rowing, bicycle ergometry) for 8–10 weeks or a waitlist control group. We analyzed the drop-out rate as a measure of feasibility. The primary endpoint of the study was aerobic fitness. Secondary endpoints were walking ability, cognitive function as measured by a neuropsychological test battery, depression and fatigue.

**Results:** A total of 42 patients completed the trial (10.6% drop-out rate). Significant improvements were seen in aerobic fitness. In addition, exercise improved walking ability, depressive symptoms, fatigue and several domains of cognitive function.

**Conclusion:** This study indicated that aerobic training is feasible and could be beneficial for patients with progressive MS. Larger exercise studies are needed to confirm the effect on cognition.

**Trial Registration:** ISRCTN (trial number 76467492) <http://isrctn.org>

# Fatigue



# Fatigue and MS

- 80 % of people with MS.
- Must be distinguished from the lethargy of depression.
- fMRI: dysfunctional circuit incorporating thalamus, basal ganglia and prefrontal cortex.
- MRI: atrophy of the primary sensorimotor region.
- Assessment scales: with the Fatigue Severity Scale (FSS); the Fatigue Impact Scale (FIS); modified Fatigue Impact Scale (mFIS).

# Fatigue and cognition

- Relationship to cognitive dysfunction equivocal.
- Processing speed deficits equivocal.

# MS Fatigue: treatment

- Medications
  - Modafinil (Provigil)
  - Methylphenidate (Ritalin and Concerta)
  - Amantadine
  - Aminopyridine
  - Natalizumab (one armed, uncontrolled study).
- Exercise
- Behavioral therapies
  - Group therapy (“take control” program).

Thank you.

# Acknowledgments



- MS Society of Canada
- Canadian Institute of Health Research
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