

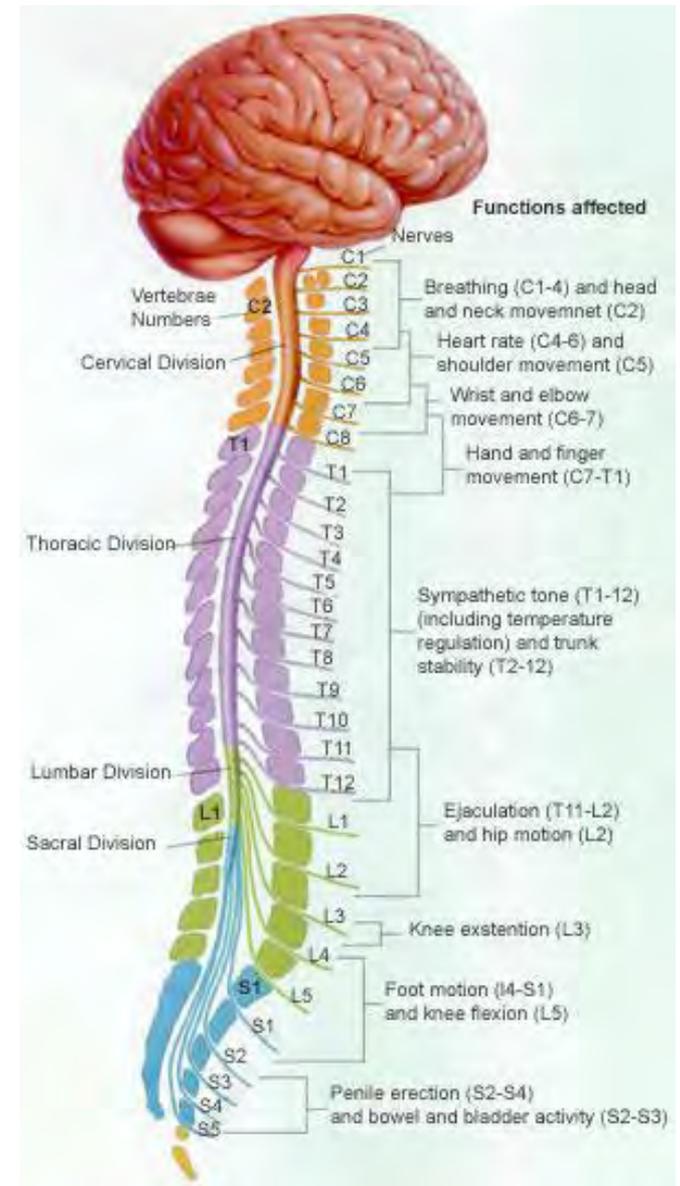
Johns Hopkins TM Regional Symposium: Neuro-Psychiatric Aspects of TM/MS

Adam Kaplin, MD, PhD

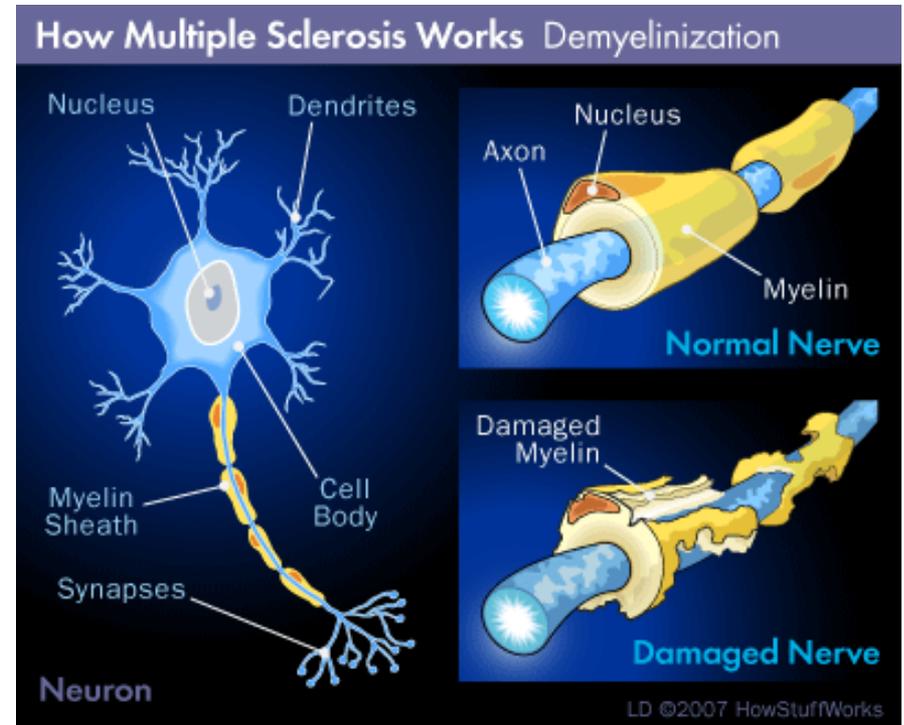
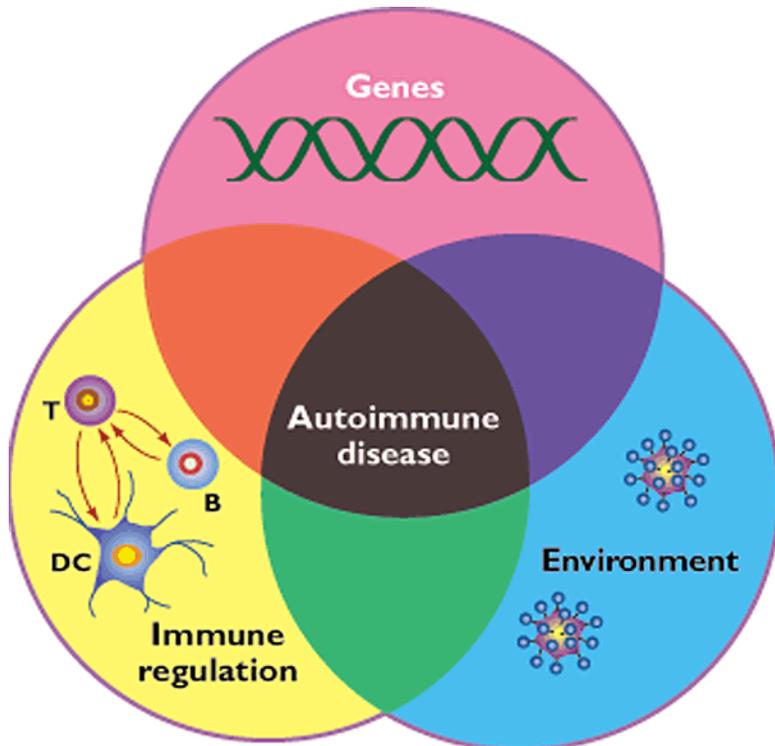
Psychiatric Consultant to the JHTM & JHMS
Centers of Excellence

Introduction to Transverse Myelitis (TM): TM Defined

- **Transverse:**
 - Lying or being across, or in a crosswise direction;
 - often opposed to longitudinal.
- **Myelitis:**
 - An inflammation or infection of the spinal cord.



What is Multiple Sclerosis (MS)?



Psychosocial Impact of Multiple Sclerosis: Exploring the Patient's Perspective

- Phone interviews were used to explore psychosocial functioning, defined as intrapersonal or interpersonal processes, excluding physical symptoms.
- Demographics: 100% RRMS, Northern CA; 75% women; Average: 43 years old, 63% married, 55% employed.
- Psychosocial impact of MS clustered into 3 factors:
 - Deterioration in Relationships: endorsed overall by 20%.
 - Demoralization: endorsed overall by 30%.
 - Benefit-Finding: endorsed overall by 60%.

Benefit-Finding: Percent Endorsing

- **Relationships:**
 - My friends and family have become more helpful (77%); I am closer to my family (70%); I am closer to my significant other (51%); I keep in better touch with my family (44%).
- **Interpersonal Skills:**
 - I have learned to be more compassionate (67%); to be more respectful of others (58%); express more feelings (55%); communicate better (48%); be a better friend (48%).
- **Perspective:**
 - I appreciate the importance of being independent (83%); I appreciate life more (74%); I am more introspective (72%); more conscientious and self-disciplined (60%); more motivated to succeed (59%); more spiritual (45%); more independent in many ways (38%); less inhibited (33%).

Increase in state suicide rates in the USA during economic recession

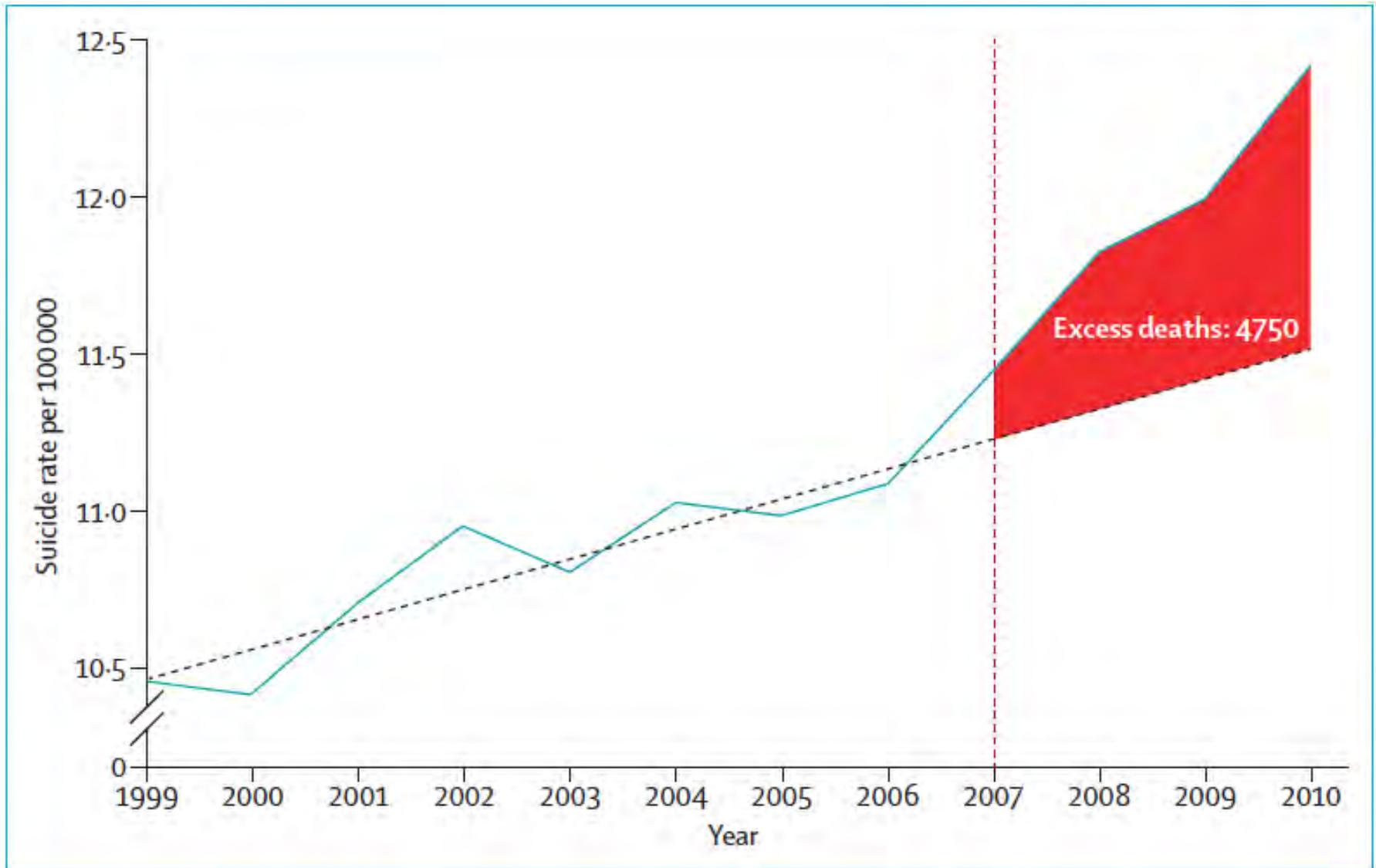


Figure: Time trend analysis of suicide rate in 50 US states and District of Columbia between 1999 and 2010

Vertical line shows onset of recession.

10 Leading Causes of Death by Age Group, United States – 2008

Rank	Age Groups										Total
	<1	1-4	5-9	10-14	15-24	25-34	35-44	45-54	55-64	65+	
1	Congenital Anomalies 5,638	Unintentional Injury 1,469	Unintentional Injury 835	Unintentional Injury 1,024	Unintentional Injury 14,089	Unintentional Injury 14,588	Unintentional Injury 16,065	Malignant Neoplasms 50,403	Malignant Neoplasms 104,091	Heart Disease 495,730	Heart Disease 616,828
2	Short Gestation 4,754	Congenital Anomalies 521	Malignant Neoplasms 457	Malignant Neoplasms 433	Homicide 5,275	Suicide 5,300	Malignant Neoplasms 12,699	Heart Disease 37,892	Heart Disease 66,711	Malignant Neoplasms 391,729	Malignant Neoplasms 565,469
3	SIDS 2,353	Homicide 421	Congenital Anomalies 170	Suicide 2,255	Suicide 4,298	Homicide 4,610	Heart Disease 11,336	Unintentional Injury 20,354	Chronic Low. Respiratory Disease 14,042	Chronic Low. Respiratory Disease 121,223	Chronic Low. Respiratory Disease 141,090
4	Maternal Pregnancy Comp. 1,765	Malignant Neoplasms 394	Homicide 113	Homicide 207	Malignant Neoplasms 1,663	Malignant Neoplasms 3,521	Suicide 6,703	Suicide 8,227	Unintentional Injury 12,782	Cerebrovascular 114,508	Cerebrovascular 134,148
5	Unintentional Injury 1,315	Heart Disease 186	Heart Disease 97	Congenital Anomalies 161	Heart Disease 1,065	Heart Disease 3,254	Homicide 2,906	Liver Disease 8,220	Diabetes Mellitus 11,370	Alzheimer's Disease 81,573	Unintentional Injury 121,902
6	Placenta Cord Membranes 1,080	Influenza & Pneumonia 142	Benign Neoplasms 59	Heart Disease 132	Congenital Anomalies 467	HIV 975	HIV 2,838	Cerebrovascular 6,112	Cerebrovascular 10,459	Diabetes Mellitus 50,883	Alzheimer's Disease 82,435
7	Bacterial Sepsis 700	Septicemia 93	Chronic Low. Respiratory Disease 55	Chronic Low. Respiratory Disease 64	Influenza & Pneumonia 206	Diabetes Mellitus 574	Liver Disease 2,562	Diabetes Mellitus 5,622	Liver Disease 8,526	Influenza & Pneumonia 48,382	Diabetes Mellitus 70,553
8	Respiratory Distress 630	Cerebrovascular 63	Cerebrovascular 41	Cerebrovascular 56	Diabetes Mellitus 204	Cerebrovascular 539	Cerebrovascular 2,035	Chronic Low. Respiratory Disease 4,392	Suicide 5,465	Nephritis 39,921	Influenza & Pneumonia 56,284
9	Circulatory System Disease 594	Chronic Low. Respiratory Disease 54	Influenza & Pneumonia 40	Influenza & Pneumonia 49	Cerebrovascular 189	Liver Disease 423	Diabetes Mellitus 1,854	HIV 3,730	Nephritis 4,803	Unintentional Injury 39,359	Nephritis 48,237
10	Neonatal Hemorrhage 556	Perinatal Period 51	Septicemia 25	Septicemia 36	Complicated Pregnancy 169	Congenital Anomalies 379	Septicemia 892	Viral Hepatitis 2,732	Septicemia 4,552	Septicemia 27,028	Suicide 36,035



Centers for Disease Control and Prevention
National Center for Injury Prevention and Control

Source: National Vital Statistics System, National Center for Health Statistics, CDC.
Produced by: Office of Statistics and Programming, National Center for Injury Prevention and Control, CDC.

Major Depression Versus Sadness

- Major depression is a syndrome.
- It is not just severe sadness.
- Sadness is to major depression what cough is to pneumonia.
 - Cough can be an indicator of pneumonia.
 - Not every cough is the result of pneumonia.
 - Sometimes pneumonia presents without a cough.
 - Consider the company the cough keeps.
 - Productive sputum, tachypnea, fever, consolidation

DSM IV Inventory: SIGEMCAPS

- Sleep (↓ / ↑)
- Interest (or pleasure)
- Guilt (or worthlessness)
- Energy (fatigue)
- Mood
- Concentration
- Appetite (↓ / ↑ or weight loss or gain)
- Psychomotor retardation (or agitation)
- Suicidal ideation (or thoughts of death)
- $\geq 5/9$ Sx for ≥ 2 weeks

Medical Causes of Depression:

- **Neurologic disorders:** CVA (30-50%), subdural hematoma, epilepsy (45-55%), brain tumors (30%), **Multiple Sclerosis (37-62%)**, Parkinson's disease (40-50%), Huntington's disease(40%), syphilis, Alzheimer's disease (15-50%)
- **Autoimmune disorders:** **Multiple Sclerosis (37-62%)**, rheumatoid arthritis (30-50%), DM (30%), SLE (25-44%).
- **Drug induced:** reserpine (15%), **interferon-alpha** (10-57%), β -blockers, corticosteroids, estrogens, benzodiazepines, barbiturates, ranitidine, Ca^{2+} -channel blockers
- **Substance induced** (25%): EtOH, sedative-hypnotic, cocaine & psychostimulant withdrawal
- **Metabolic:** hyper/hypothyroidism, Cushing's syndrome, hypercalcemia, hyponatremia, diabetes mellitus
- **Nutritional:** vitamin B12 deficiency
- **Infections:** HIV, HCV (25%), mononucleosis, influenza
- **Cancer** (20-45%): especially pancreatic CA (40-50%)

Burden of Depression in MS Patients

(Patten & Metz, Psychother Psychosom, 1997, 66:286-92)

- **Lifetime Prevalence:**
 - 37-62% MS
 - 17% General Population (NCS)
- **Current Prevalence:**
 - 14-27% MS
 - 5% General Population (NCS)
- **Cognitive Impairment in MS:**
 - Lifetime prevalence 45-65%

SIGEMCAPS → MS/TM

- Sleep (↓ / ↑) → Insomnia (sedative)
- Interest (or pleasure) → Adjustment to new normal
- Guilt (or worthlessness) → Barrier to rehab and Tx
- Energy (fatigue) → MS Fatigue (stimulant)
- Mood → Sadness
- Concentration → MS memory loss
- Appetite → Weight loss
- Psychomotor retardation → MS memory loss,
- Suicidal ideation → Hopelessness, death

- Magnification of suffering → Chronic Pain (marijuana)

Depression and MS

- Depression is **common** in patients with MS and is associated with considerable **morbidity** and **mortality**.
- The available evidence suggests that depression in MS is **caused by the effects of inflammatory insults to the brain**.
 - No correlation with physical disability.
 - No genetic loading.
 - Periods of immune activation correlate with increased depression and suicides.

Depression and Quality of Life

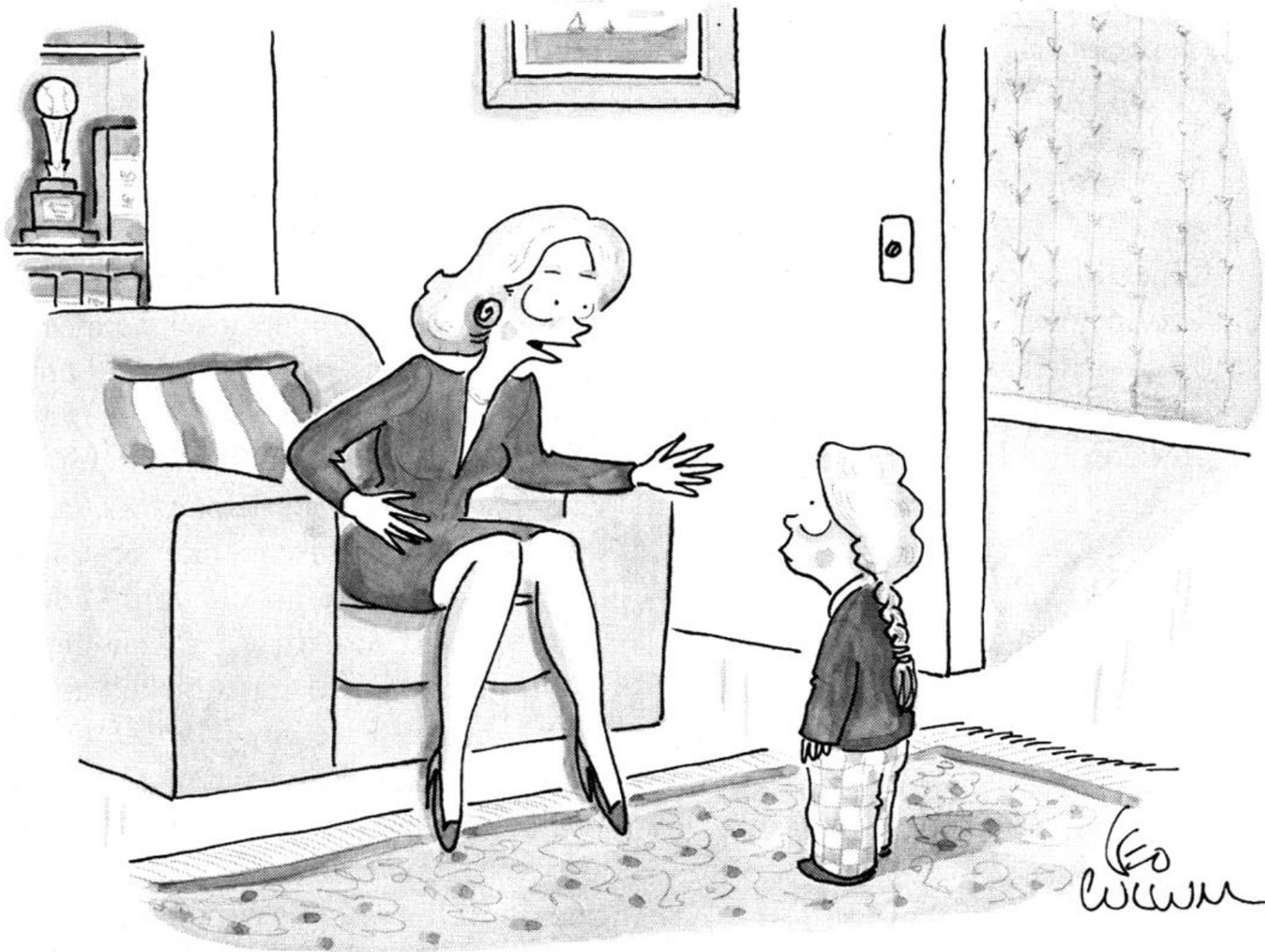
- Multiple studies have shown that depression is the **primary determining factor** in a patient's self reported **quality of life**, with greater impact than other variables investigated, including physical disability, fatigue, and cognitive impairment.
- Also, depression is the number 1 correlate of the **quality of life** of the patient's **caregiver**.

Are you getting enough oxygen?



MS Depression and Suicide: Epidemiology

- 30% lifetime incidence of suicidal intent in patients with MS.
- 6%–12% of patients with MS attempt suicide.
- Suicide in MS patients occurs at 7.5 times the rate of the general population.
- Suicide was the 3rd leading cause (15%) of death of 3000 outpatients in Canadian MS clinics from 1972–1988.
 - MS patients dying from suicide were younger and less disabled than patients dying from pneumonia (23%) and cancer (16%).¹



***“Of course your daddy loves you.
He’s on Prozac--he loves everybody.”***

Treating Depression May Improve MS Disease Severity

- Patients with depression had biological evidence of worse MS disease severity.
- Treatment of depression in MS patients (with either medication or psychotherapy) correlated with improvement in their autoimmune disease status.
- Suggests that treatment of depression may be an important component in the management of patients with MS:
 - “Treatment of depression may provide a novel disease-modifying therapeutic strategy as well as a symptomatic treatment for patients with MS.”¹

Effects of fluoxetine on disease activity in relapsing multiple sclerosis: a double-blind, placebo-controlled, exploratory study

J P Mostert,¹ F Admiraal-Behloul,² J M Hoogduin,³ J Luyendijk,² D J Heersema,¹ M A van Buchem,² J De Keyser¹

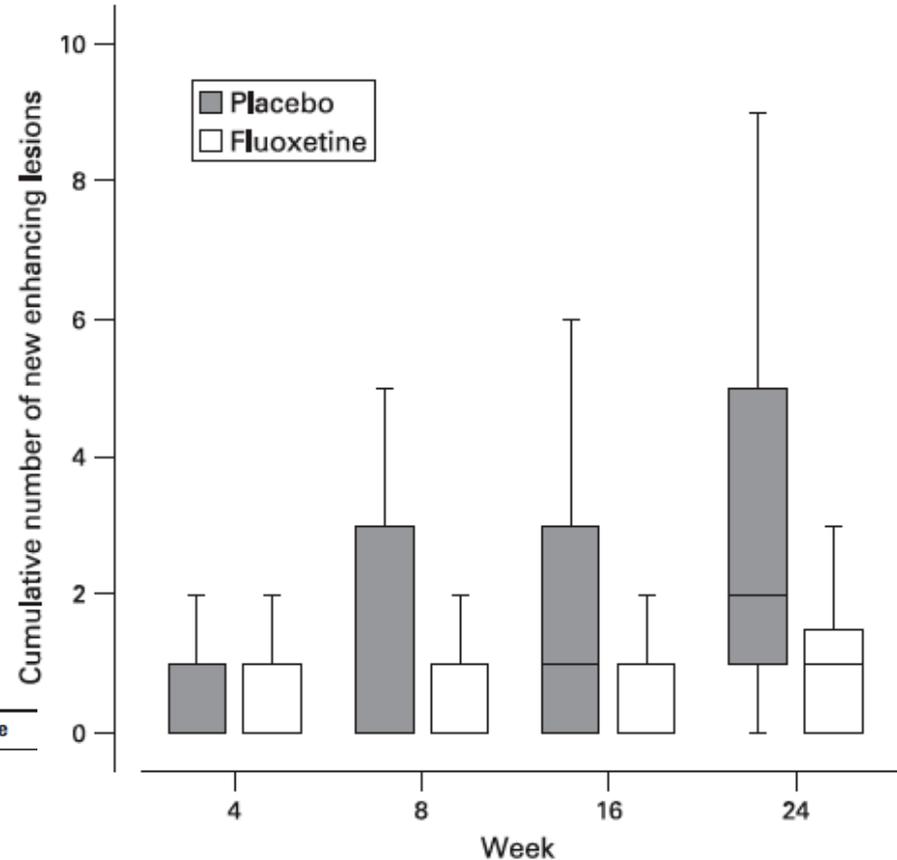
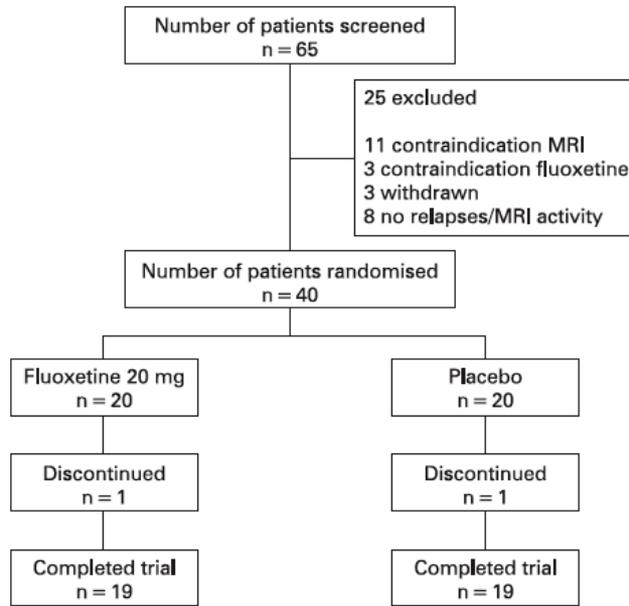
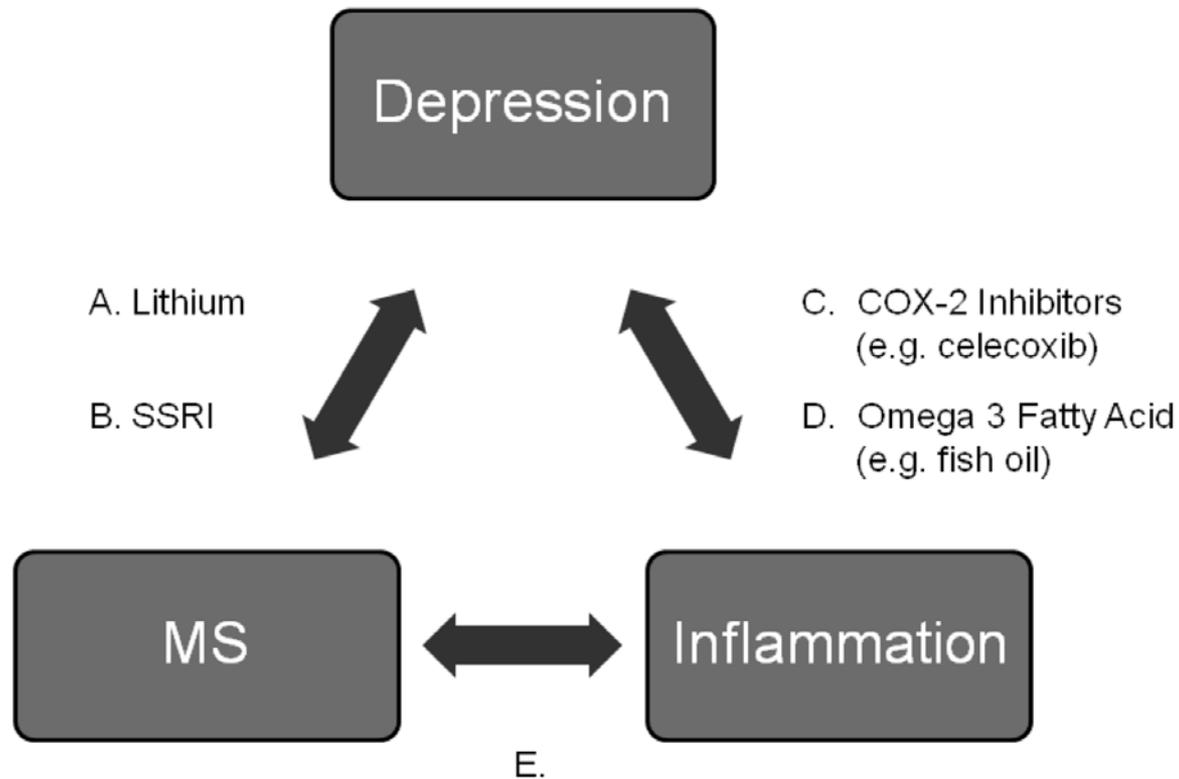


Table 3 MRI outcomes during the past 16 weeks.

	Fluoxetine (n = 19)	Placebo (n = 19)	p Value
Cumulative number of new enhancing lesions			0.05
Mean (SD)	1.21 (2.6)	3.16 (5.3)	
Median (range)	0 (0–11)	1 (0–22)	
Cumulative volume of new enhancing lesions (mm ³)			0.06
Mean (SD)	90 (231)	227 (485)	
Median (range)	0 (0–961)	35 (0–2095)	
Number of patients with no new enhancing lesions	12 (63%)	5 (26%)	0.02
Scans showing new enhancing lesions	9 (24%)	18 (47%)	0.03
Scans showing enhancing lesions	9 (24%)	18 (47%)	0.03

Depression-MS-Inflammation Triad

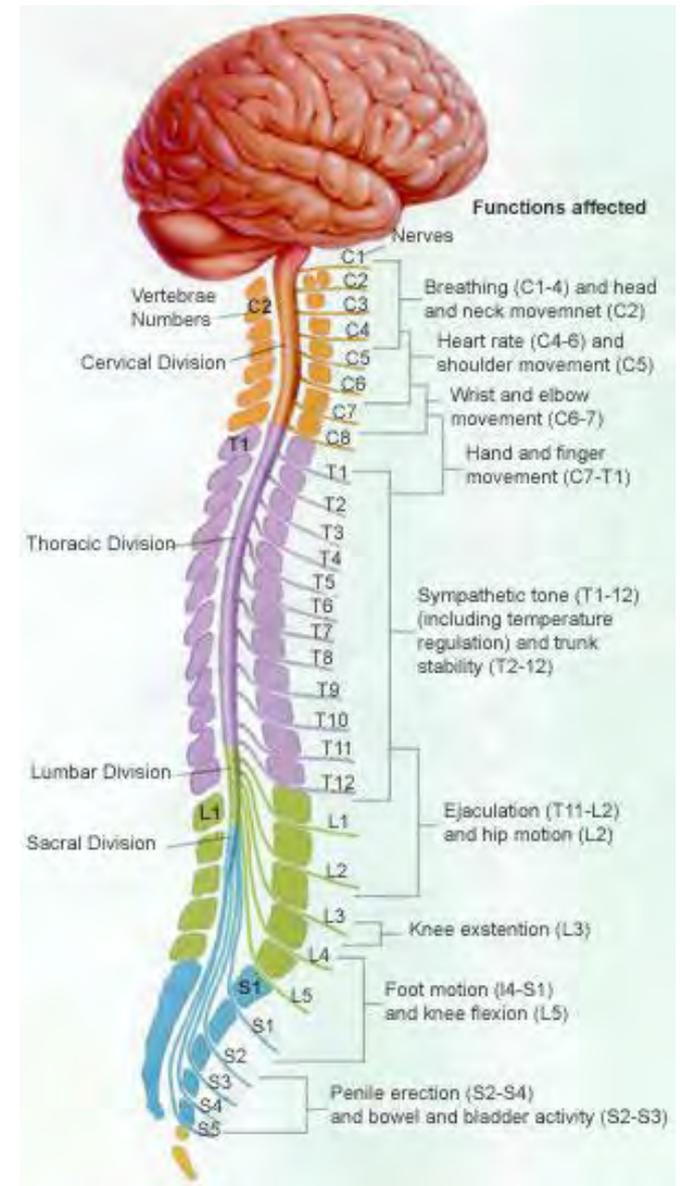


Relationship Between Depression & Autoimmune CNS Diseases

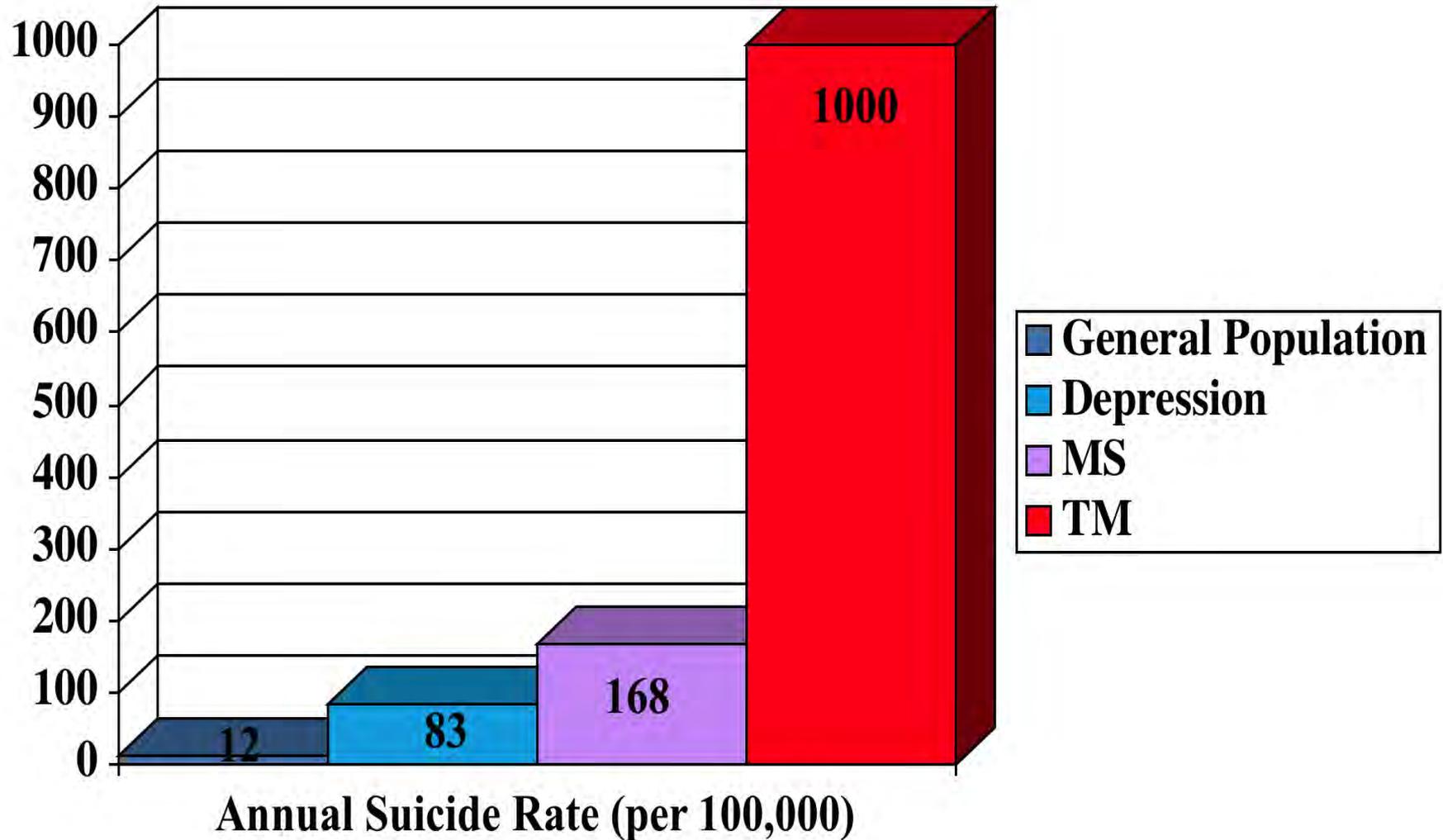
- Depression and MS: A Two-Way Street
 - MS causes depression.
 - Depression worsens MS.
 - Treating depression improves MS.
 - Treating MS improves depression.
 - Autoimmunity and depression are a two-way street.
- Depression is a lethal consequence of MS if left untreated.
- Depression is common and important, caused by the immune system in autoimmune diseases, and treatable.

Introduction to Transverse Myelitis (TM): TM Defined

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Suicide Rate: Depression vs MS vs TM

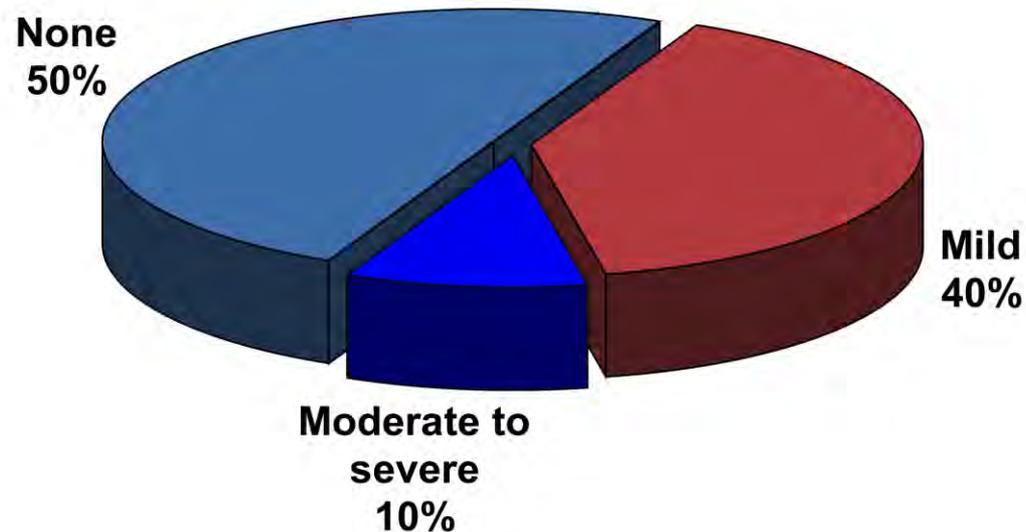


History and Epidemiology of Cognitive Impairment in MS

- Charcot (1877) noted that ‘at a certain stage of the disease’ patients with MS may show ‘marked enfeeblement of the memory; conceptions are formed slowly; the intellectual and emotional faculties are blunted in their entirety.’
- **Thirty years ago**, however, cognitive impairment was thought to be present in only **3% of MS patients**.
 - (Schulz, et al. J Neurol (2006) 253 : 1002–1010)
- Multiple subsequent studies have demonstrated cognitive impairment in **40-70% of MS patients**.
 - (Rao SM, et al. Neurology 41(5):685–691)

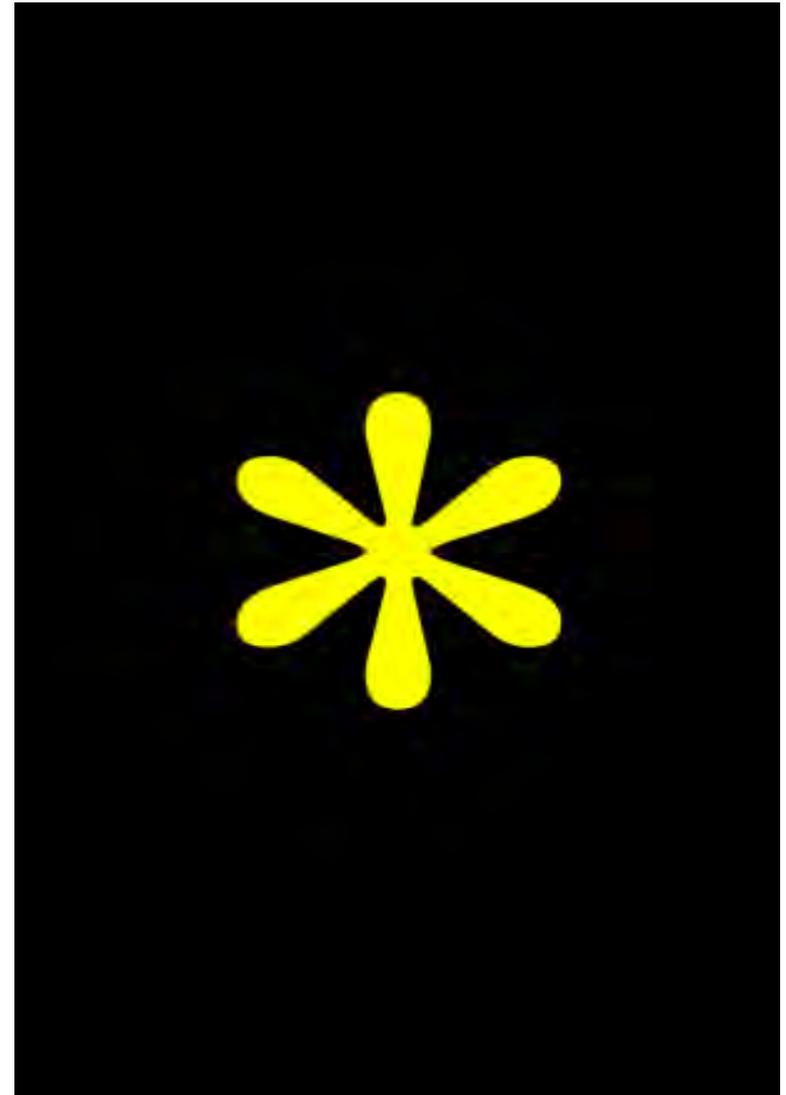
Cognitive Changes in MS

Severity of Cognitive Changes in Multiple Sclerosis

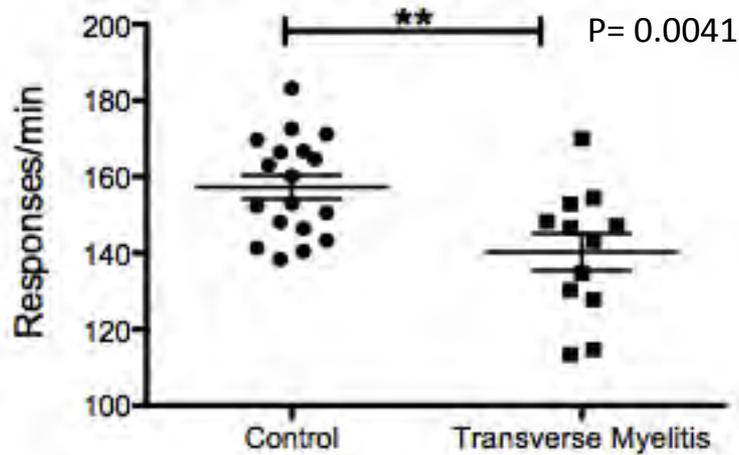


Source: NMSS

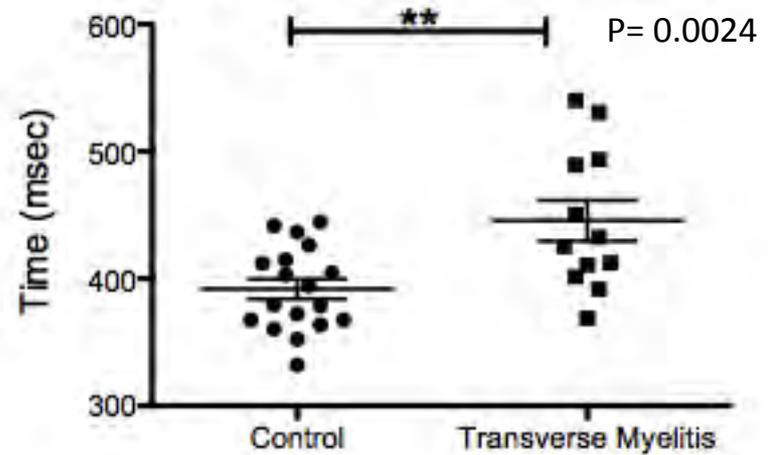
SIMPLE REACTION TIME



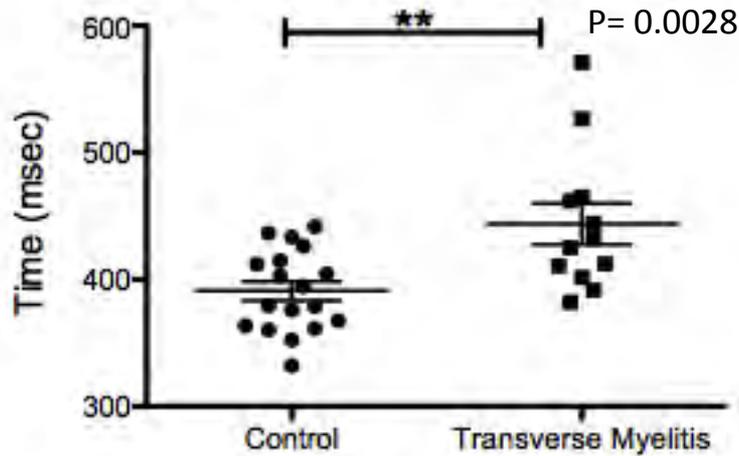
Reaction Time, Responses per Minute



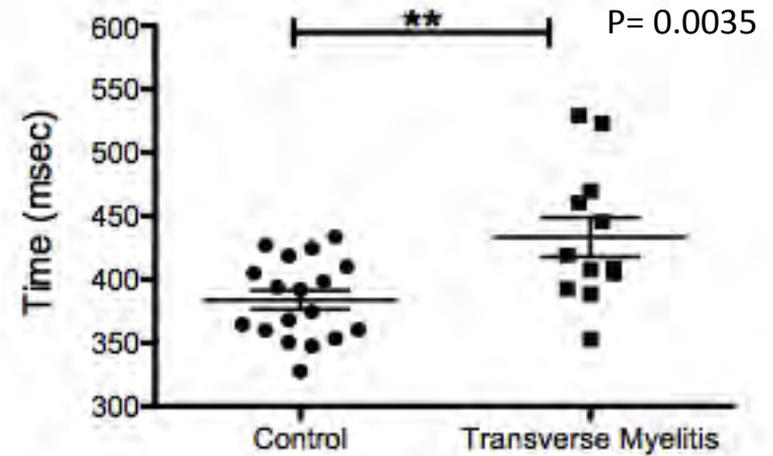
Reaction Time, Mean Correct Response Time



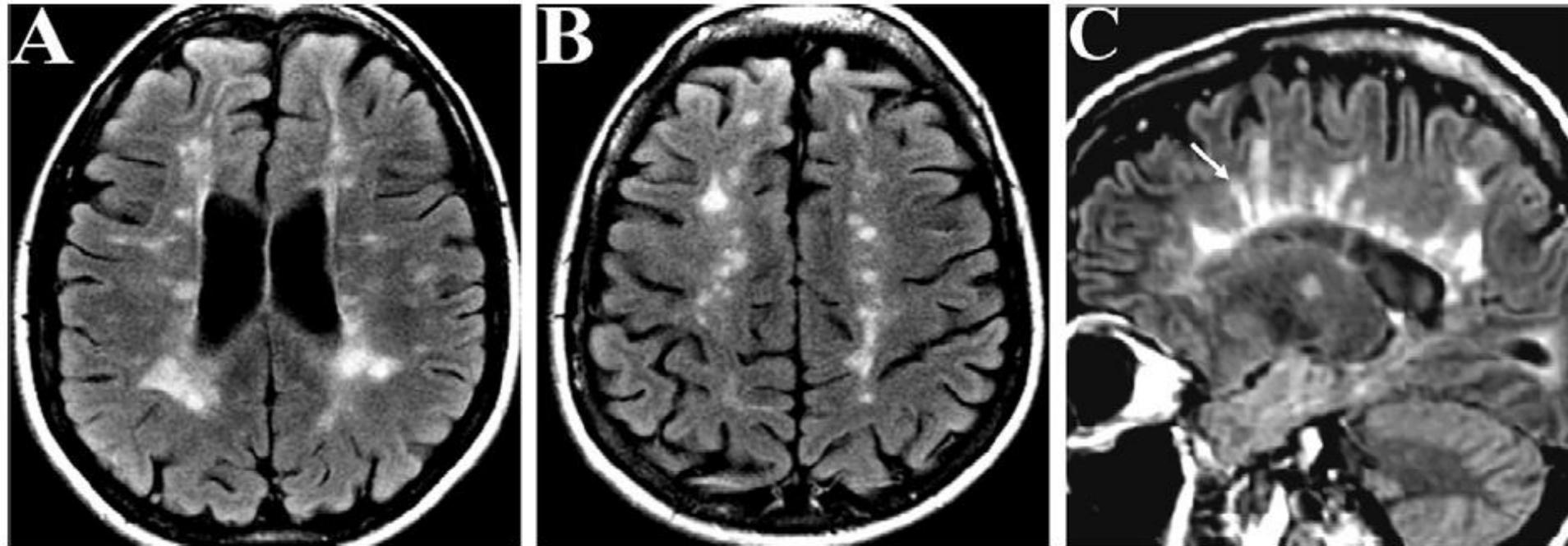
Reaction Time, Mean Response Time



Reaction Time, Median Response Time



MRI in MS: Clinicoradiological Paradox

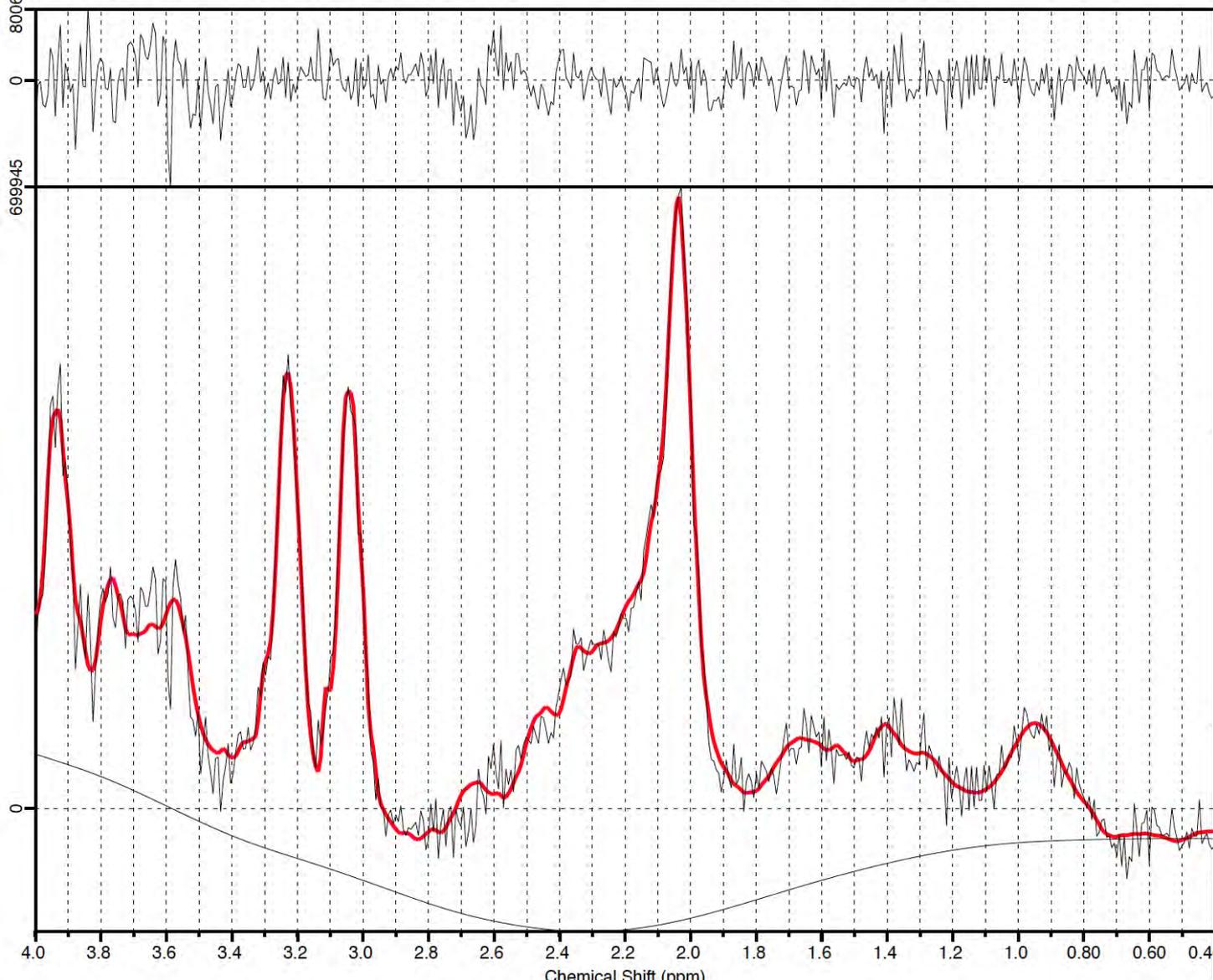


MRS Spectra

LCModel (Version 6.1-0) Copyright: S.W. Provencher.

Ref.: Magn. Reson. Med. 30:672-679 (1993).

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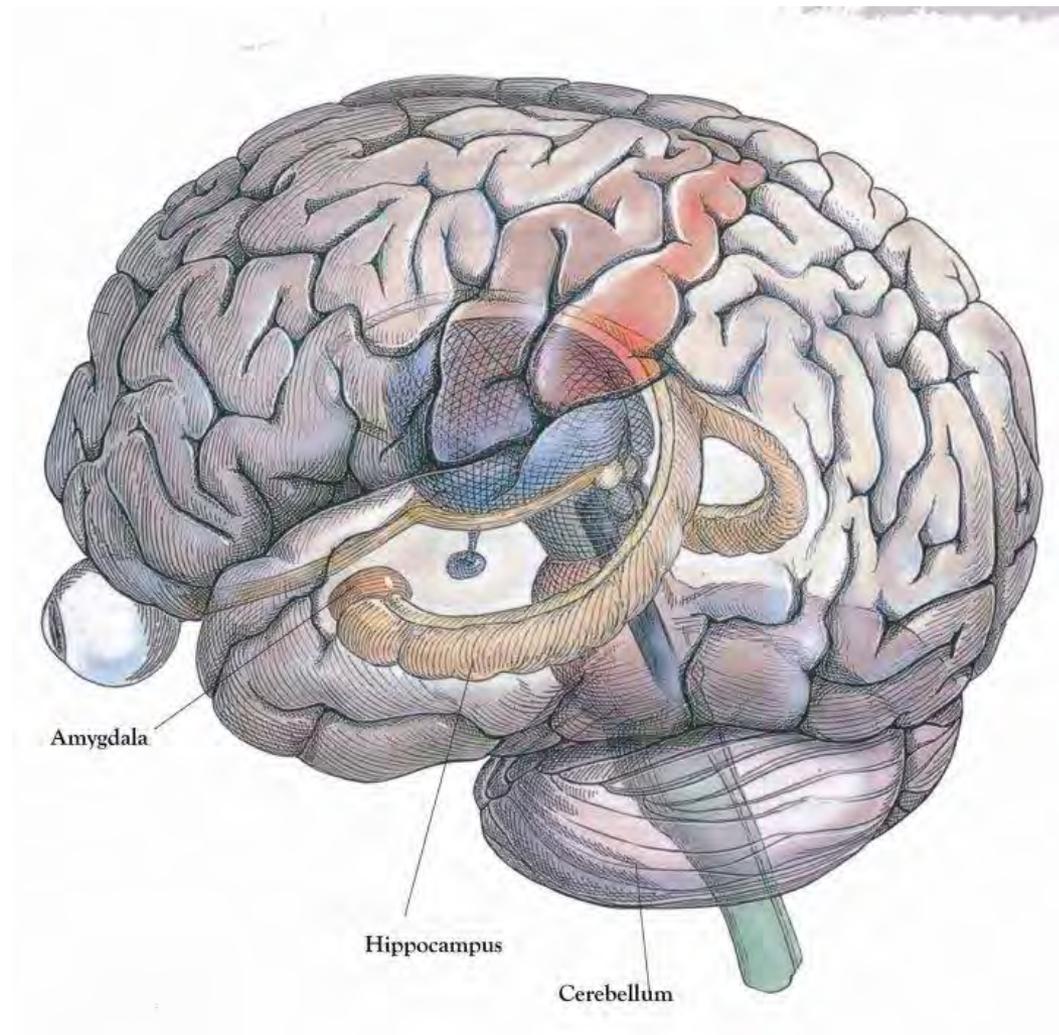


Conc.	%SD	/Cr	Metabolite
1.013	54%	0.144	Ala
1.694	49%	0.241	Asp
2.285	4%	0.325	Cho
7.040	4%	1.000	Cr
0.000	999%	0.000	GABA
0.000	999%	0.000	Glc
7.343	17%	1.043	Gln
6.044	14%	0.859	Glu
3.275	10%	0.465	Ins
0.253	238%	0.036	Lac
2.992	24%	0.425	NAA
5.995	15%	0.852	NAAG
0.335	34%	0.048	Scyllo
0.000	999%	0.000	Tau
0.012	999%	1.6E-03	-CrCH2
1.452	25%	0.206	Gua
8.988	5%	1.277	NAA+NAAG
13.388	8%	1.902	Glu+Gln
1.905	115%	0.271	Lip13a
0.293	155%	0.042	Lip13b
0.486	163%	0.069	Lip09
4.459	21%	0.633	MM09
0.161	325%	0.023	Lip20
3.960	52%	0.563	MM20
1.508	51%	0.214	MM12
4.942	29%	0.702	MM14
4.740	25%	0.673	MM17
2.198	87%	0.312	Lip13a+Lip13b
8.649	24%	1.229	MM14+Lip13a+L
4.946	17%	0.703	MM09+Lip09
4.121	50%	0.585	MM20+Lip20

DIAGNOSTICS	
1 ERROR	MYBASI 10
1 ERROR	MYBASI 9
1 info	MYBASI 2
1 info	FINOUT 9
Doing Water-Scaling	

MISCELLANEOUS OUTPUT	
FWHM = 0.076 ppm	S/N = 14
Data shift = 0.008 ppm	
Ph: -36 deg	-2 deg/ppm

Hippocampus

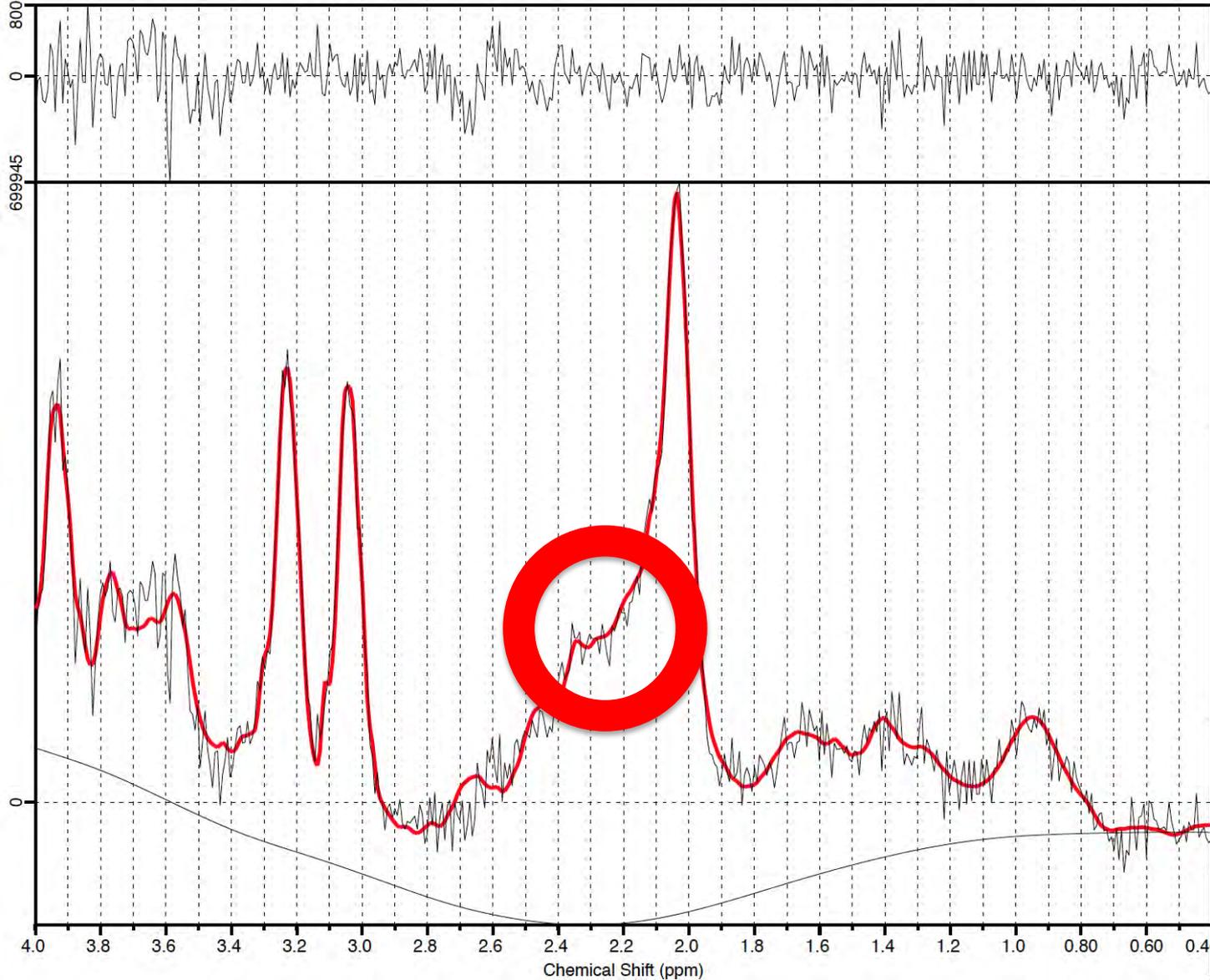


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0.000	999%	0.000	GABA
0.000	999%	0.000	Glc
7.343	17%	1.043	Gln
6.044	14%	0.859	Glu
3.275	10%	0.465	Ins
0.253	238%	0.036	Lac
2.992	24%	0.425	NAA
5.995	15%	0.852	NAAG
0.335	34%	0.048	Scyllo
0.000	999%	0.000	Tau
0.012	999%	1.6E-03	-CrCH2
1.452	25%	0.206	Gua
8.988	5%	1.277	NAA+NAAG
13.388	8%	1.902	Glu+Gln

1.905	115%	0.271	Lip13a
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4.740	25%	0.673	MM17
2.198	87%	0.312	Lip13a+Lip13b
8.649	24%	1.229	MM14+Lip13a+L
4.946	17%	0.703	MM09+Lip09
4.121	50%	0.585	MM20+Lip20

DIAGNOSTICS

1 ERROR MYBASI 10
 1 ERROR MYBASI 9
 1 info MYBASI 2
 1 info FINOUT 9

Doing Water-Scaling

MISCELLANEOUS OUTPUT

FWHM = 0.076 ppm S/N = 14
 Data shift = 0.008 ppm
 Ph: -36 deg -2 deg/ppm

Modified MACFIMS:

Minimal Assessment of Cognitive Function in MS

Symbol Digit Modalities Test

	P value	Pearson r
Written Raw Score	0.0006	0.9129
Oral Raw Score	0.0005	0.9163

Paced Auditory Serial Add. Test

	P value	Pearson r
3-second rate PASAT	0.0025	0.8664
2-second rate PASAT	0.0137	0.7774

Verbal Fluency Tests

	P value	Pearson r
FAS Verbal Fluency Test	0.1258	0.549
Categories	0.0052	0.8342

Judgment of Line Orientation

	P value	Pearson r
Line orientation	0.0589	0.6483

Rey-Osterrieth Complex Fig.

	P value	Pearson r
Copy	0.0313	0.7124
Immediate Recall	0.476	0.2738
Delayed Recall	0.6657	0.168
Recognition Total Correct	0.2382	0.4381

California Verbal Learn. Test-II

	P value	Pearson r
Trial 1 Recall	0.2619	0.4188
Trial 5 Recall	0.0027	0.8631
Trials 1-5 Total	0.0143	0.7744
Trial B	0.0166	0.7639
Short Delay Free Recall	0.0015	0.8843
Short Delay Cued Recall	0.0037	0.8503
Long Delay Free Recall	0.0008	0.9032
Long Delay Cued Recall	0.0008	0.9052
Recognition Hits	0.1466	0.5251
Recognition False- Positives	0.0088	-0.8051
D-Prime	0.0127	0.7826
C	0.0219	0.7425

Brief Visuospatial Mem. Test-R

	P value	Pearson r
Trial 1	0.0651	0.6368
Trial 2	0.0016	0.8837
Trial 3	0.0008	0.903
Delayed Recall	0.0011	0.8955
Hits	0.3735	0.3653
False-Positives	0.1524	-0.5561

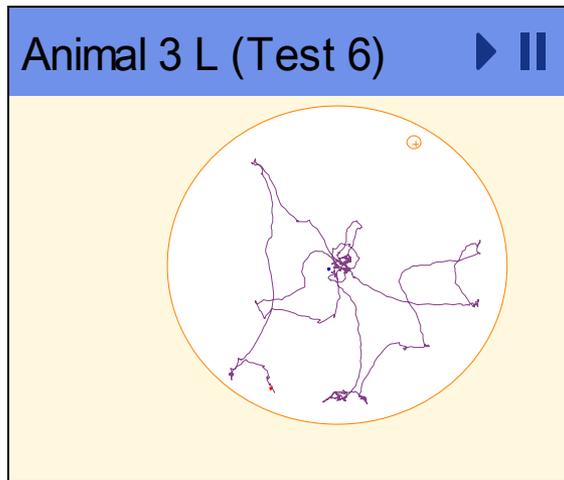
D-KEFS Sorting Test

	P value	Pearson r
Free Sorting Correct Sorts	0.0523	0.6616
Free Sorting Description	0.0216	0.7439
Sort Recognition Description	0.0012	0.8936

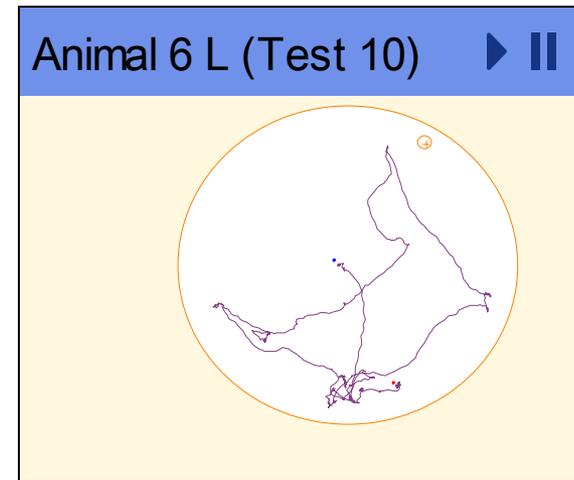
Path Summaries – Trial 1, Day 1

EAE+Vehicle

EAE+2-PMPA



Total Latency = 180 (165.2)
Path Efficiency = 0.072
(0.094)



Total Latency = 180 (173.2)
Path Efficiency = 0.098 (0.096)

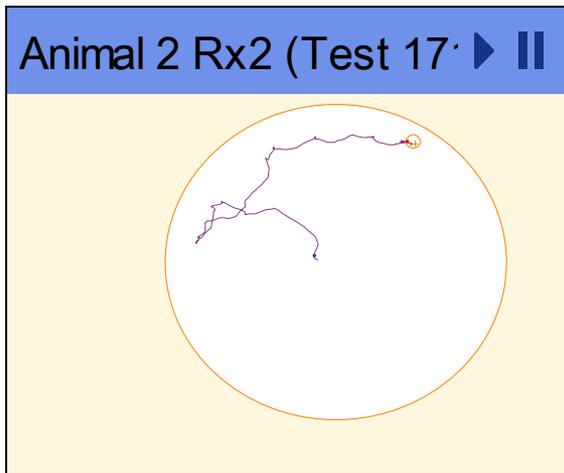
No difference in duration or efficiency
between groups on the first trial of Day 1.

Underlined number = value depicted in graph,
number in parenthesis = group average

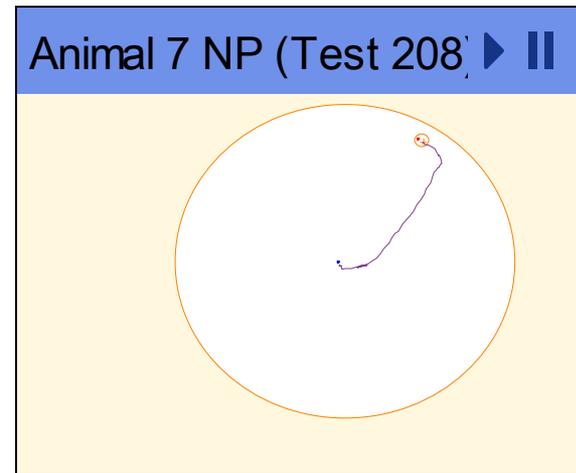
Path Summaries – Trial 1, Day 4

EAE+Vehicle

EAE+2-PMPA



Total Latency = 30.3 (66.82)
Path Efficiency = 0.323 (0.417)

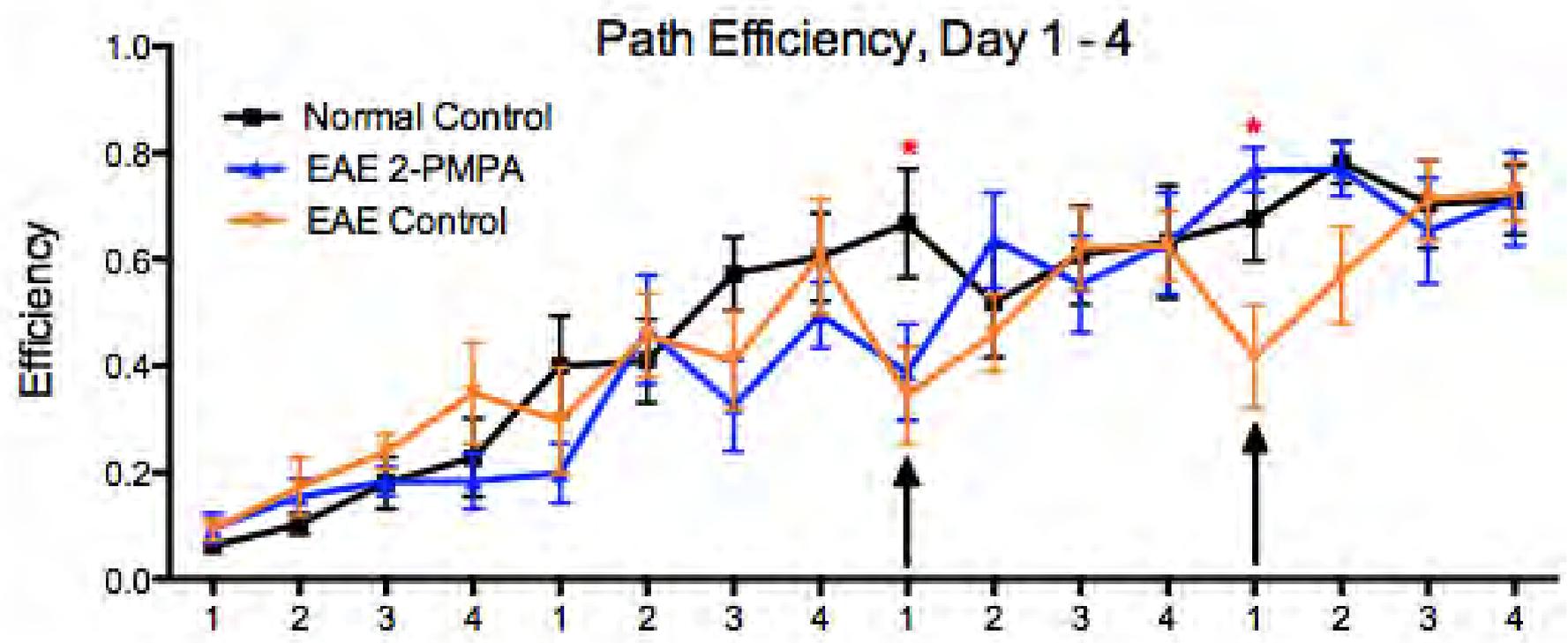


Total Latency = 10.1 (12.32)
Path Efficiency = 0.751 (0.768)

2-PMPA-treated mice have reduced latency and higher efficiency compared to Control mice on the first trial of Day 4.

Underlined number = value depicted in graph,
number in parenthesis = group average

By Day 4 EAE Mice Treated with 2-PMPA Perform Like Control Mice without EAE



What about in Alzheimer's disease?

N-Acetylaspartate and *N*-acetylaspartylglutamate levels in Alzheimer's disease post-mortem brain tissue

Dick Jaarsma ^{b,*}, Lammy Veenma-van der Duin ^a, Jakob Korf ^a

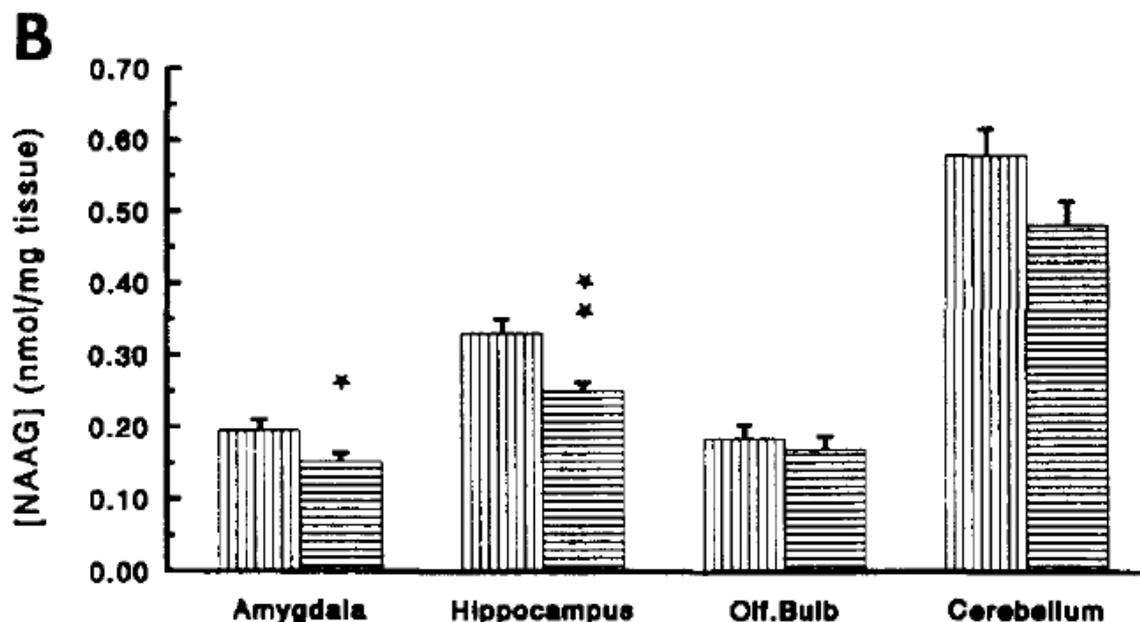


Fig. 1. Mean NAA (A) and NAAG (B) concentrations in brain areas of age-matched controls and Alzheimer's disease patients. Bars represent SEM. * and ** $p < 0.05$ and $p < 0.005$, respectively; AD vs. control, *t*-test.

Healing Waters: Is SCUBA Diving Rehabilitation?

Daniel Becker, MD

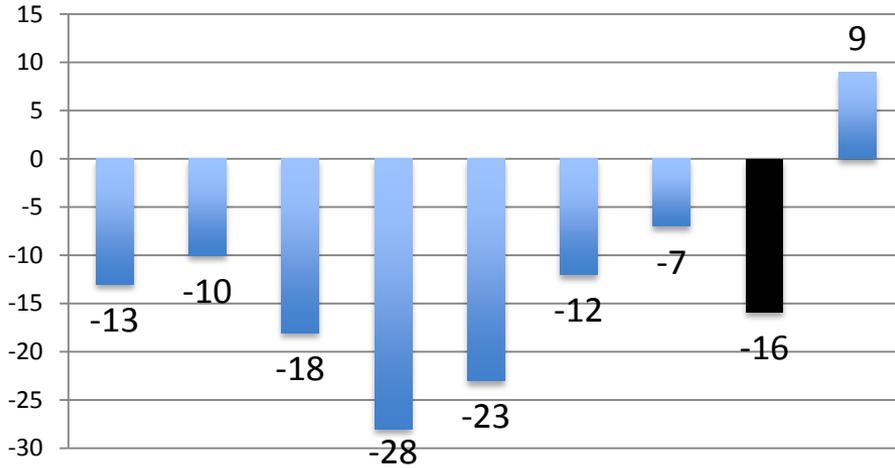
Adam Kaplin, MD, PhD

Cody Unser, BA

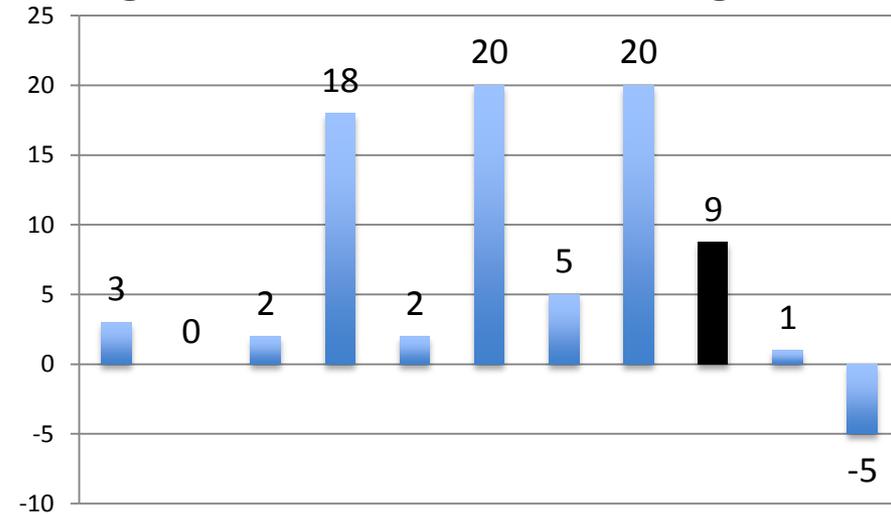
Johns Hopkins University
Kennedy Krieger Institute
Cody Unser First Step Foundation

An Unanticipated Result

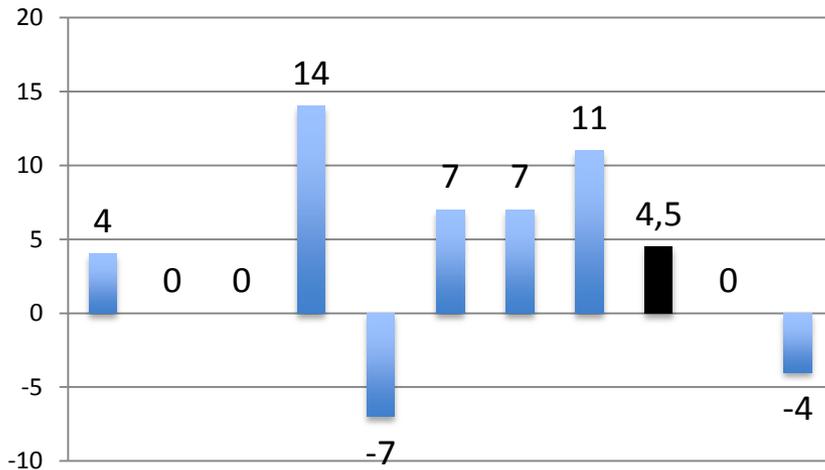
Spasticity Lower Extremities Percent Change



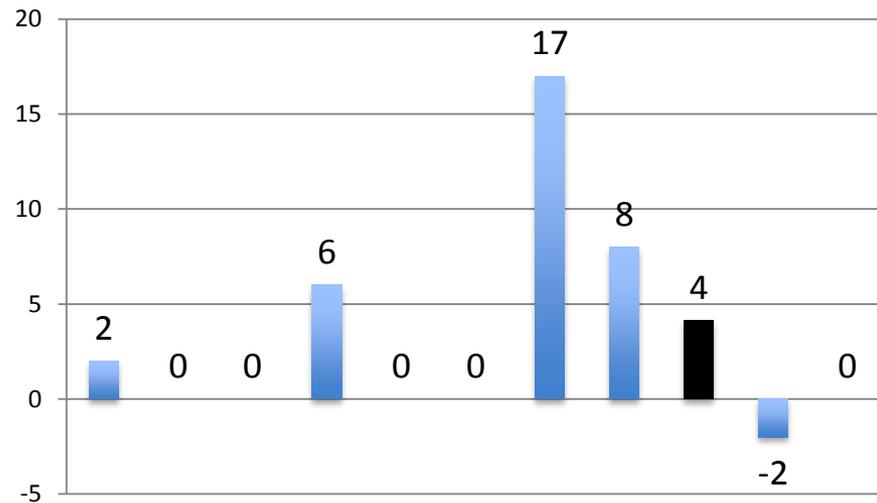
Light Touch Score Percent Change



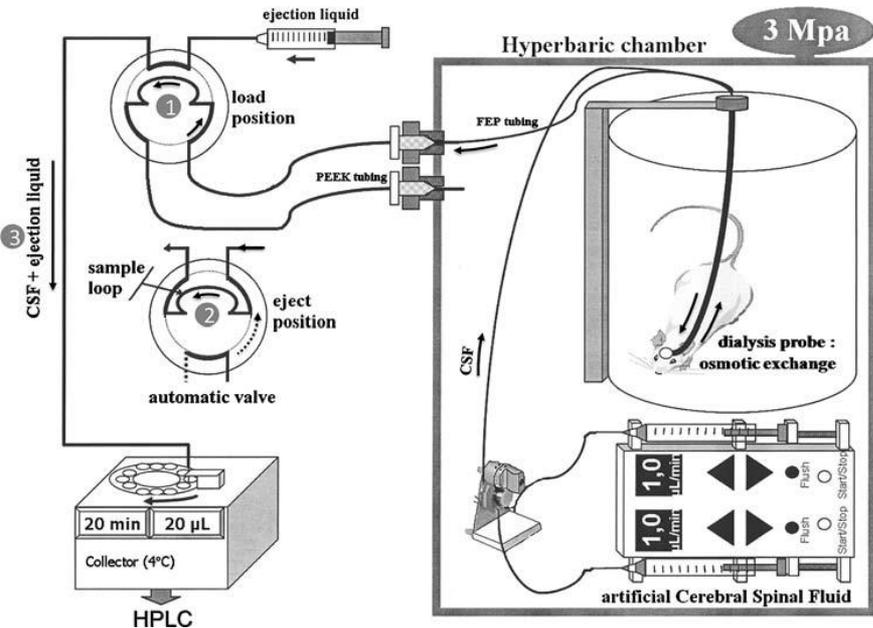
Pin Prick Score Percent Change



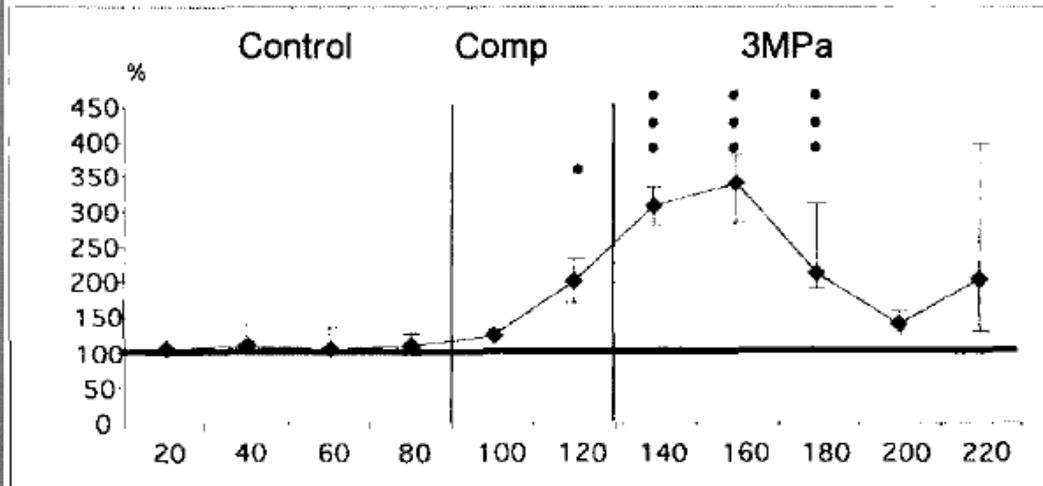
Motor Score Percent Change



I am personally quite receptive to nitrogen rapture. I like it and fear it like doom. It destroys the instinct of life... Intellectuals get drunk early and suffer acute attacks on all the senses, which demand hard fighting to overcome. When they have beaten the foe, they recover quickly. The agreeable glow of depth rapture resembles the giggle-party jags of the nineteen-twenties when flappers and sheiks convened to sniff nitrogen protoxide.



Serotonin



Central Pattern Generator

Modulation of State Dependence

MLR Stimulation

Epidural Stimulation

Afferent Stimulation

Pharmacological Facilitation

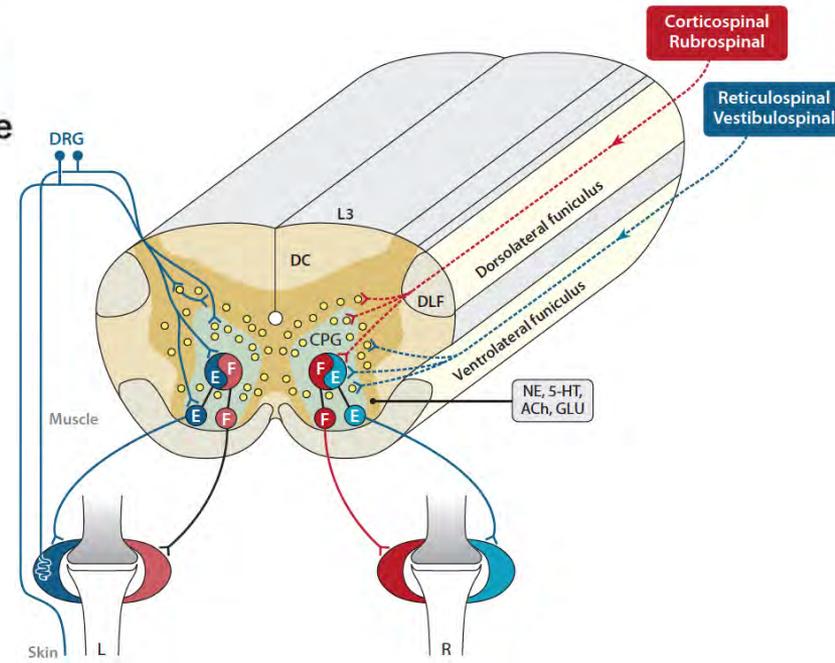
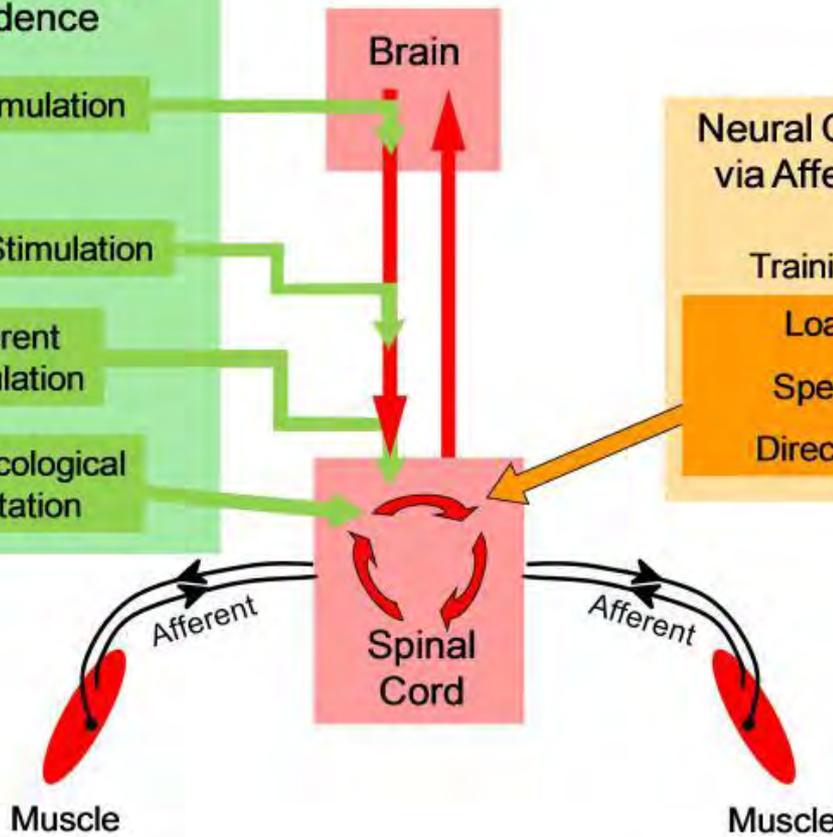
Neural Control via Afferents

Training

Load

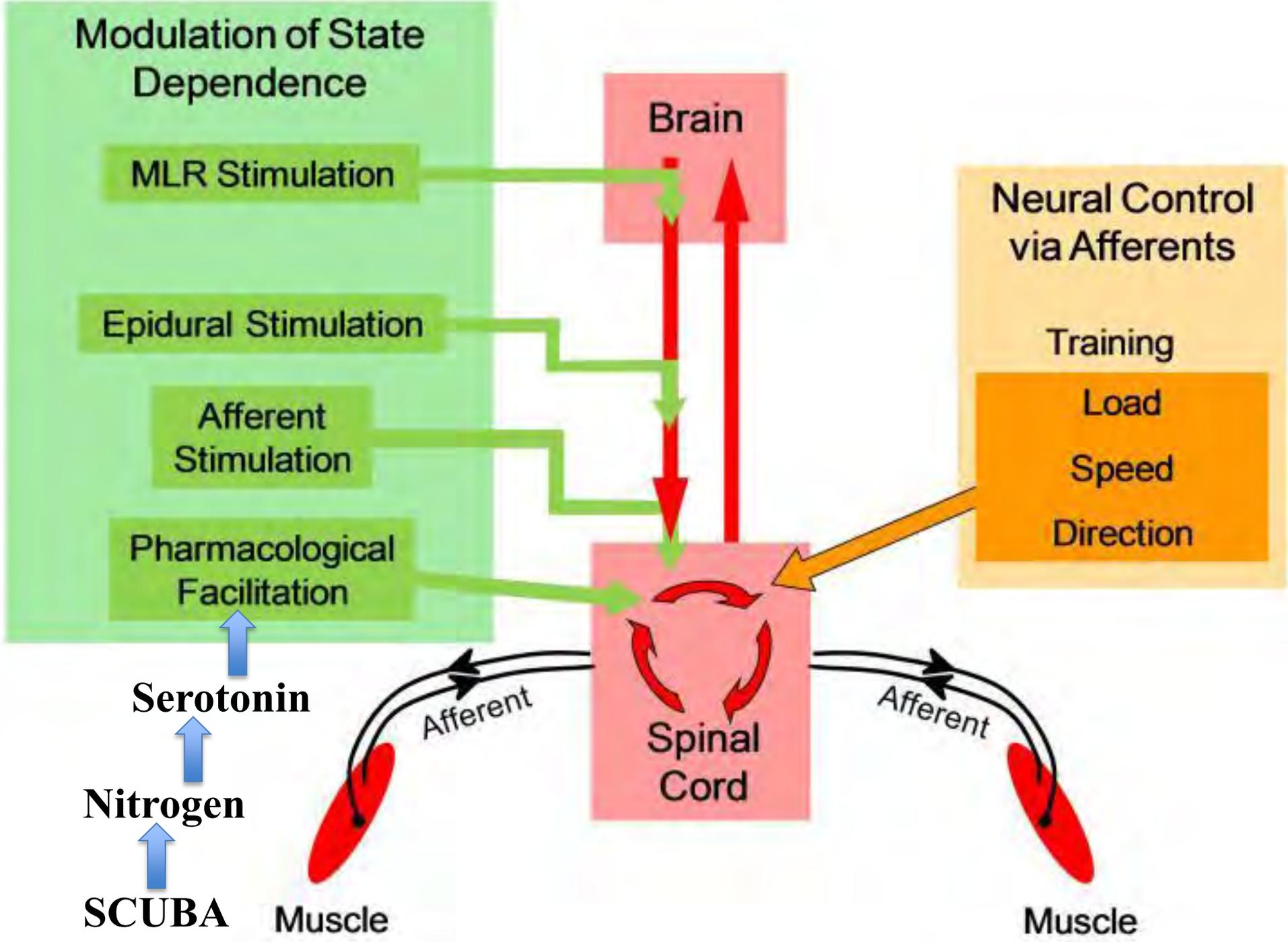
Speed

Direction



Serotonin in the Spinal Cord

- 5-HT is central to the core development of the Spinal Cord Central Pattern Generator (CPG).
- Serotonergic neurons are selectively preserved in the CNS after injury.
- Correlating with the improvement in locomotion following SCI is the increased release in the Ventral Horn of 5-HT by 300%.
- Repeated stimulation of 5-HT receptors results in the rehabilitation of locomotion and following SCI.

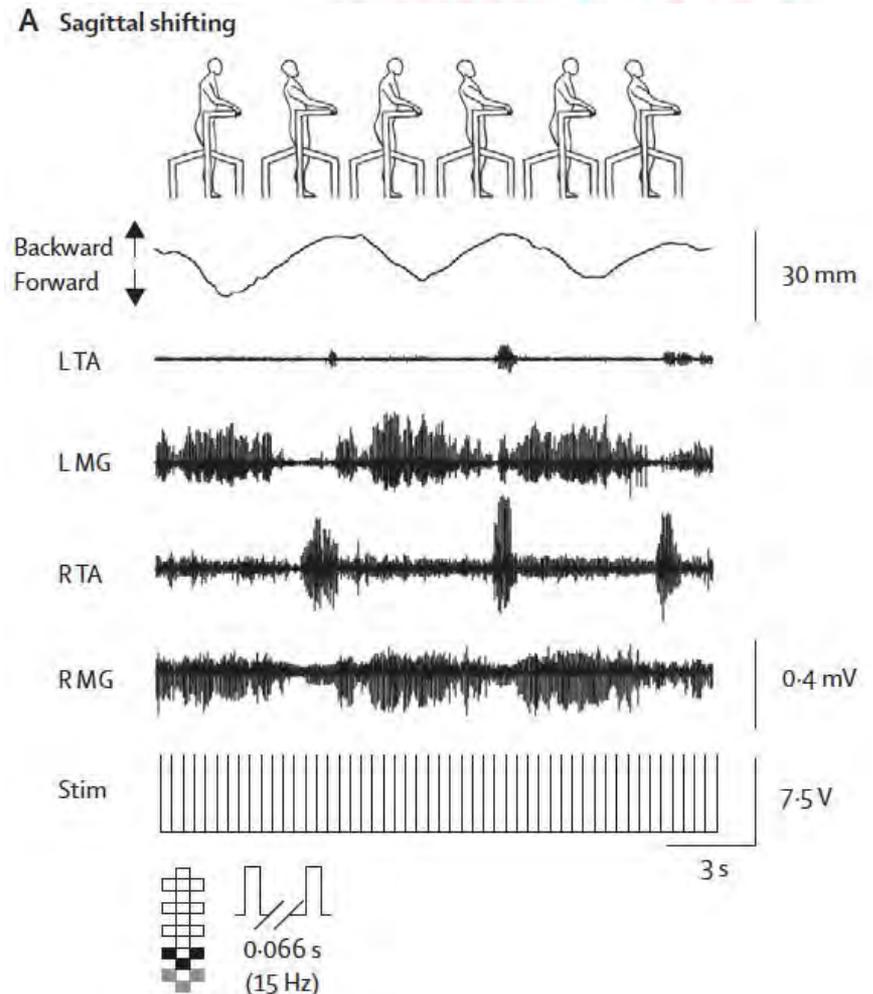


Effect of epidural stimulation of the lumbosacral spinal cord on voluntary movement, standing, and assisted stepping after motor complete paraplegia: a case study

Susan Harkema, Yury Gerasimenko, Jonathan Hodes, Joel Burdick, Claudia Angeli, Yangsheng Chen, Christie Ferreira, Andrea Willhite, Enrico Rejc, Robert G Grossman, V Reggie Edgerton

Lancet 2011; 377: 1938-47

- 23 year old who suffered C7-T1 SCI by MVA.
- Epidural spinal stimulator placed over L1-S1.
- Report after 80 standing sessions over 7 months with stimulation lasting 40-120 min.
- Patient was able to stand with full weight bearing with assistance for balance while stimulation was on.



Conclusions

- There is a need for restorative treatments for chronic spinal cord injured (SCI) individuals.
- No systematic studies have been done of SCUBA in SCI.
- We saw unprecedented improvement in motor and sensory function in paraplegic war veterans after undergoing four days of 9 successive SCUBA dives.
- SCUBA diving is known to increase CNS nitrogen levels, which in turn generate large increases in serotonin (5-HT) release within the central nervous system.
- Though never tested in humans, serotonin has been shown in animals to stimulate motor and sensory recovery in the context of spinal cord injury in animals.
- This pilot study suggests a back door mechanism to awaken function in the chronically injured spinal cord.
- There are novel ways of testing this hypothesis that could lead to new therapies for SCI from many causes.