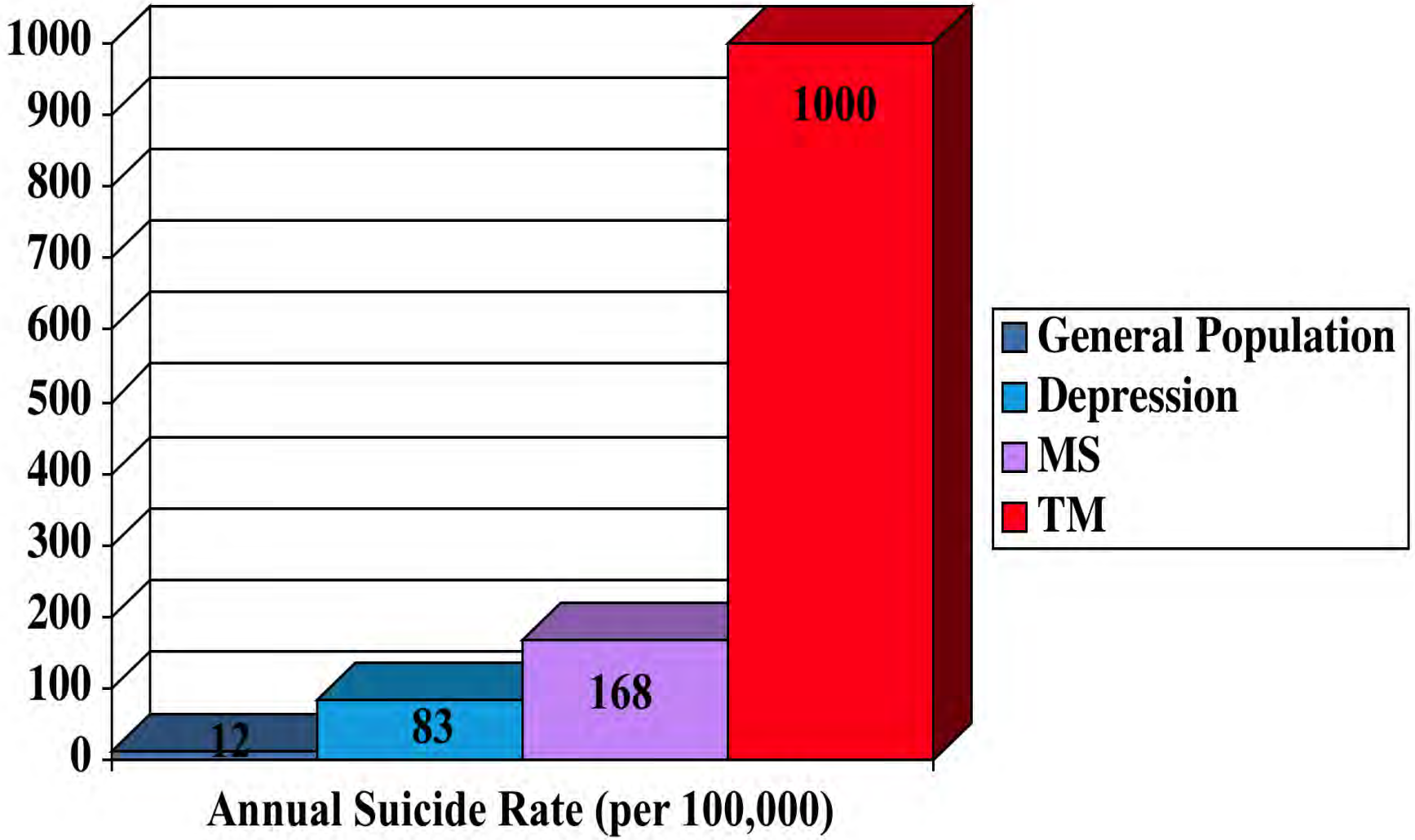
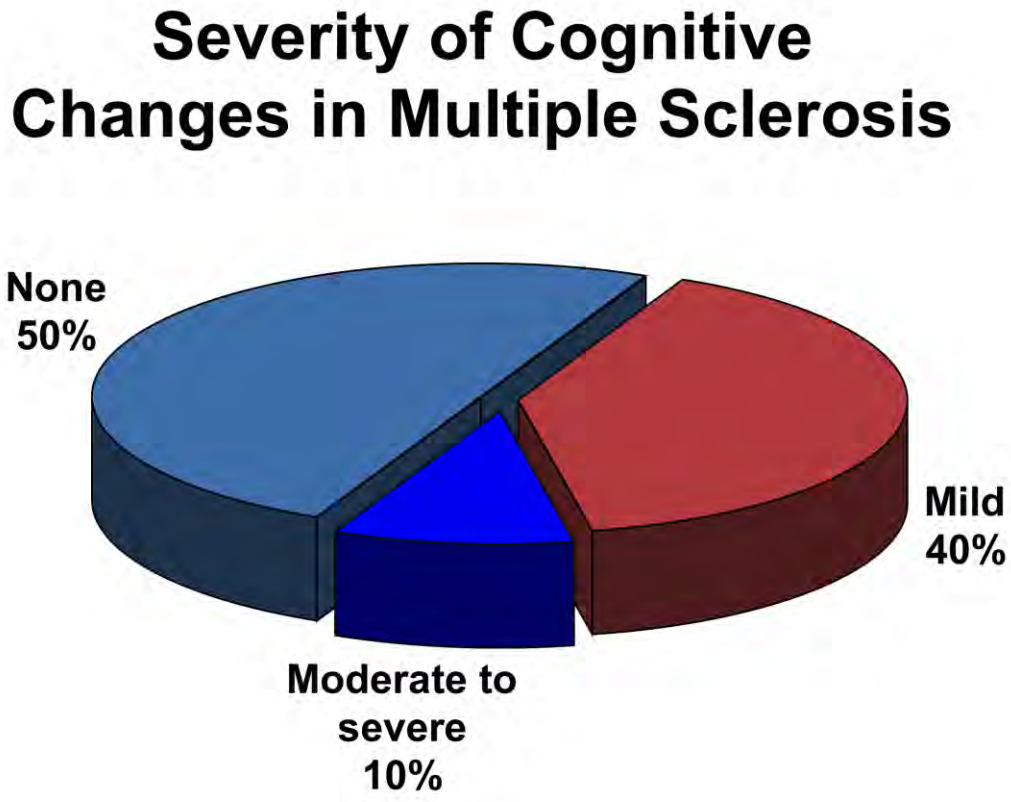
Suicide Rate: Depression vs MS vs TM



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)

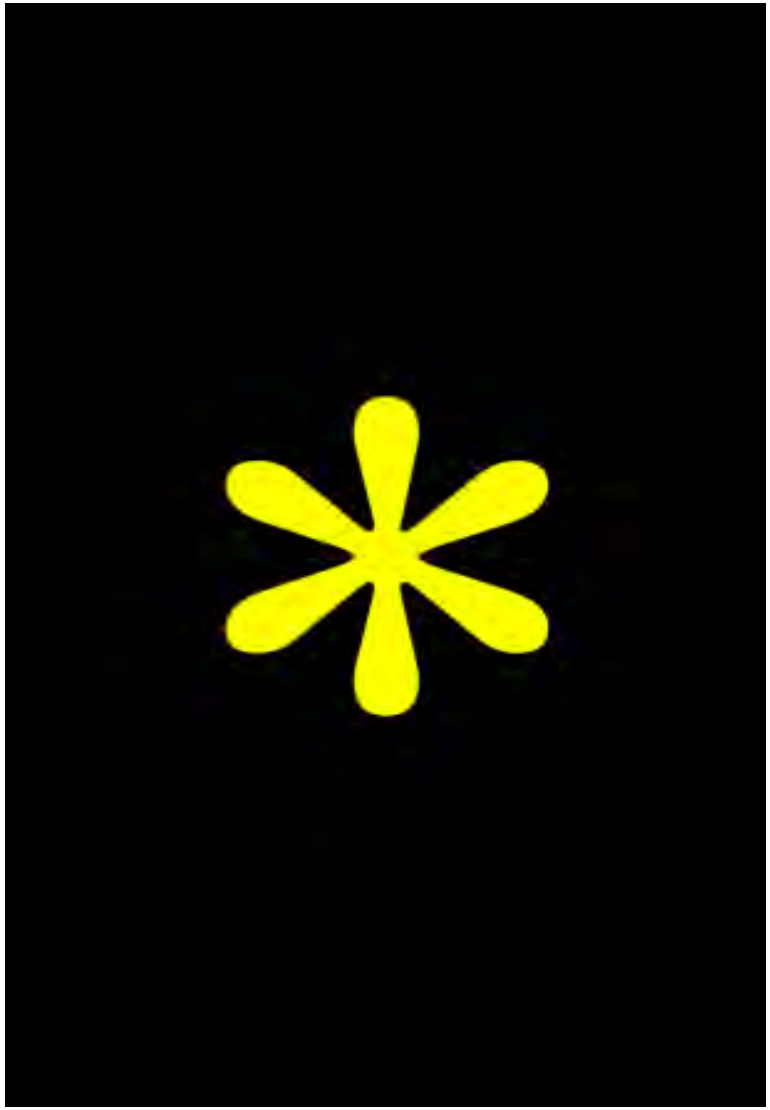
Cognitive Changes in MS

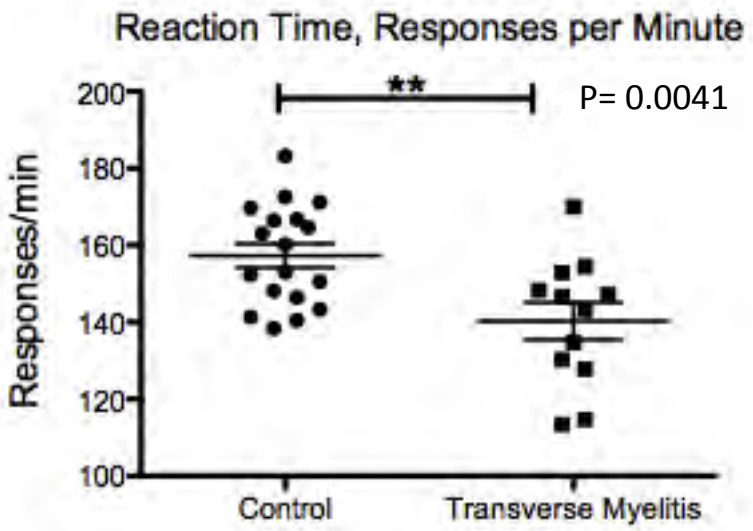


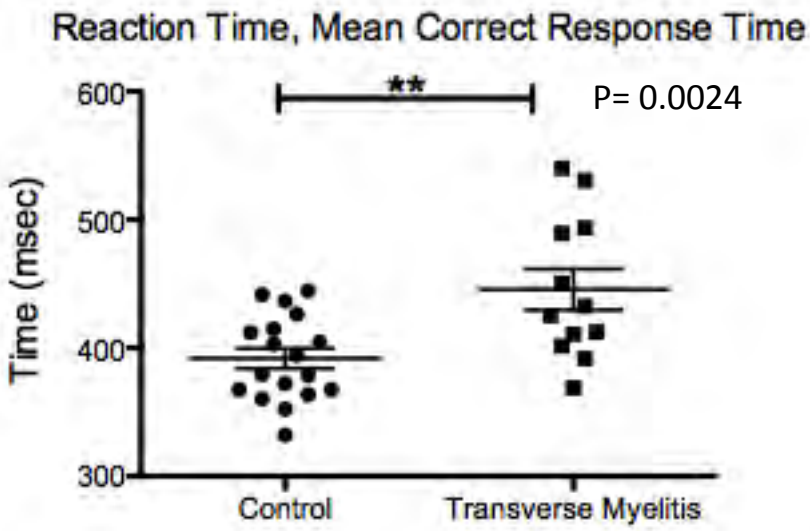
Source: NMSS

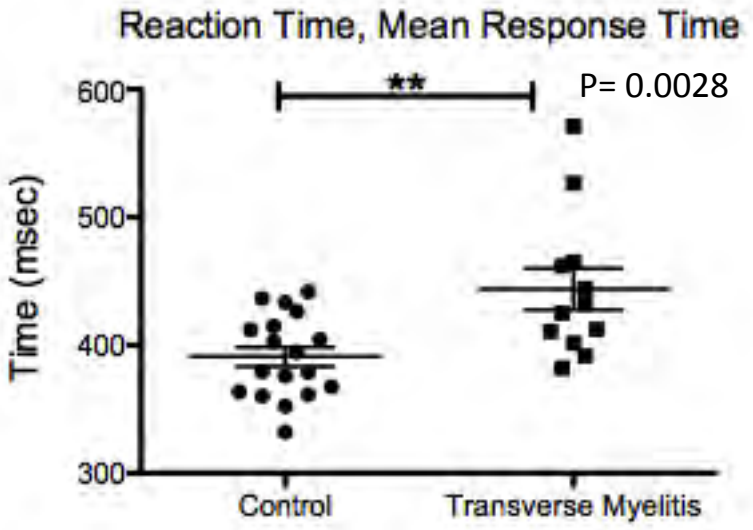
AnthroTronix

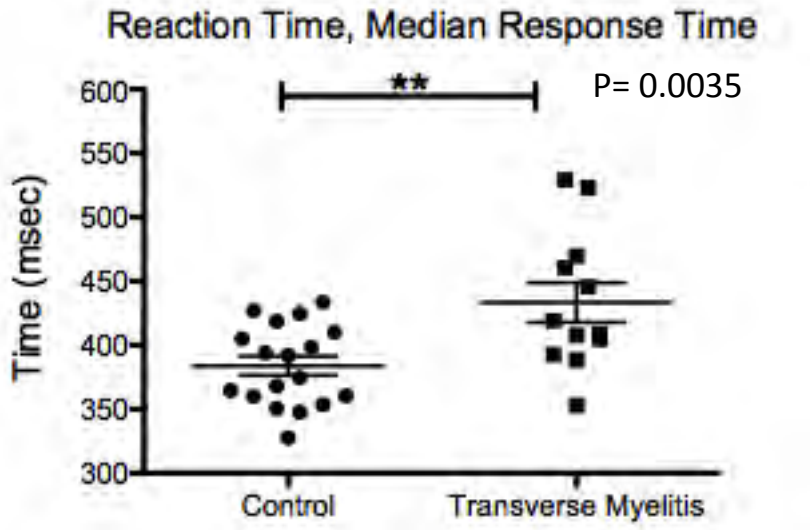
SIMPLE REACTION TIME



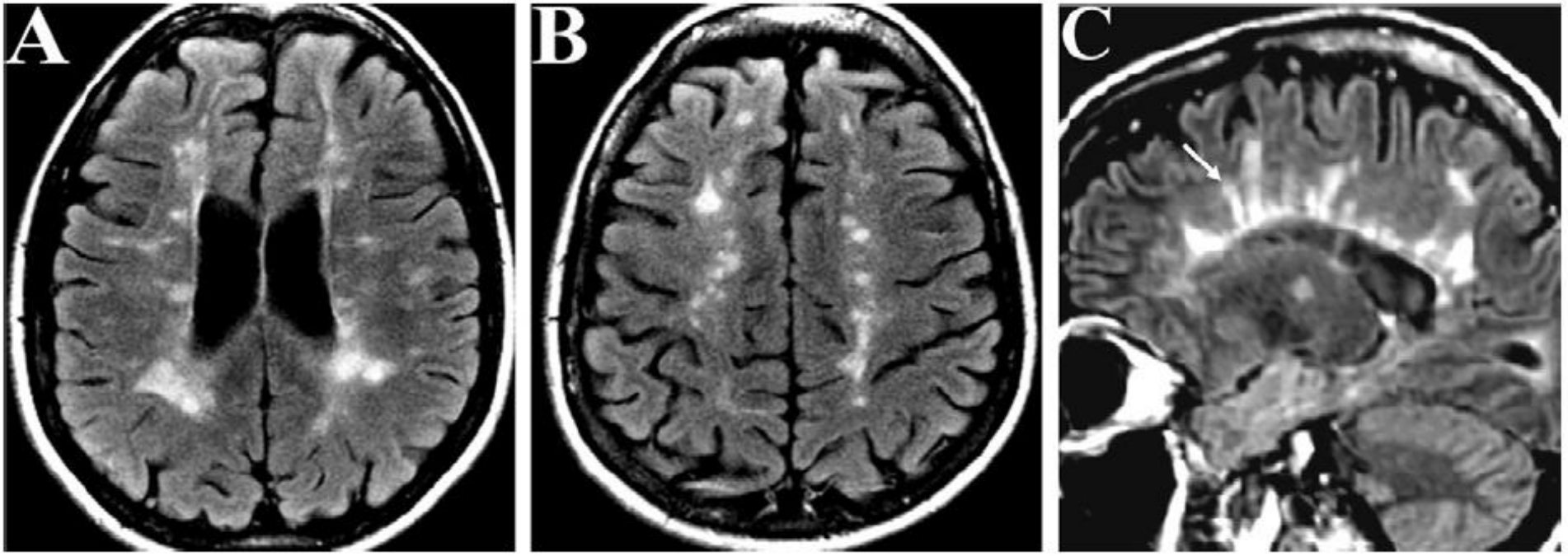

Reaction Time, Responses per Minute
**
P= 0.0041
Responses/min
200
180
160
140
120
100
Control
Transverse Myelitis


Reaction Time, Mean Correct Response Time
**
P= 0.0024
Time (msec)
600
500
400
300
Control
Transverse Myelitis

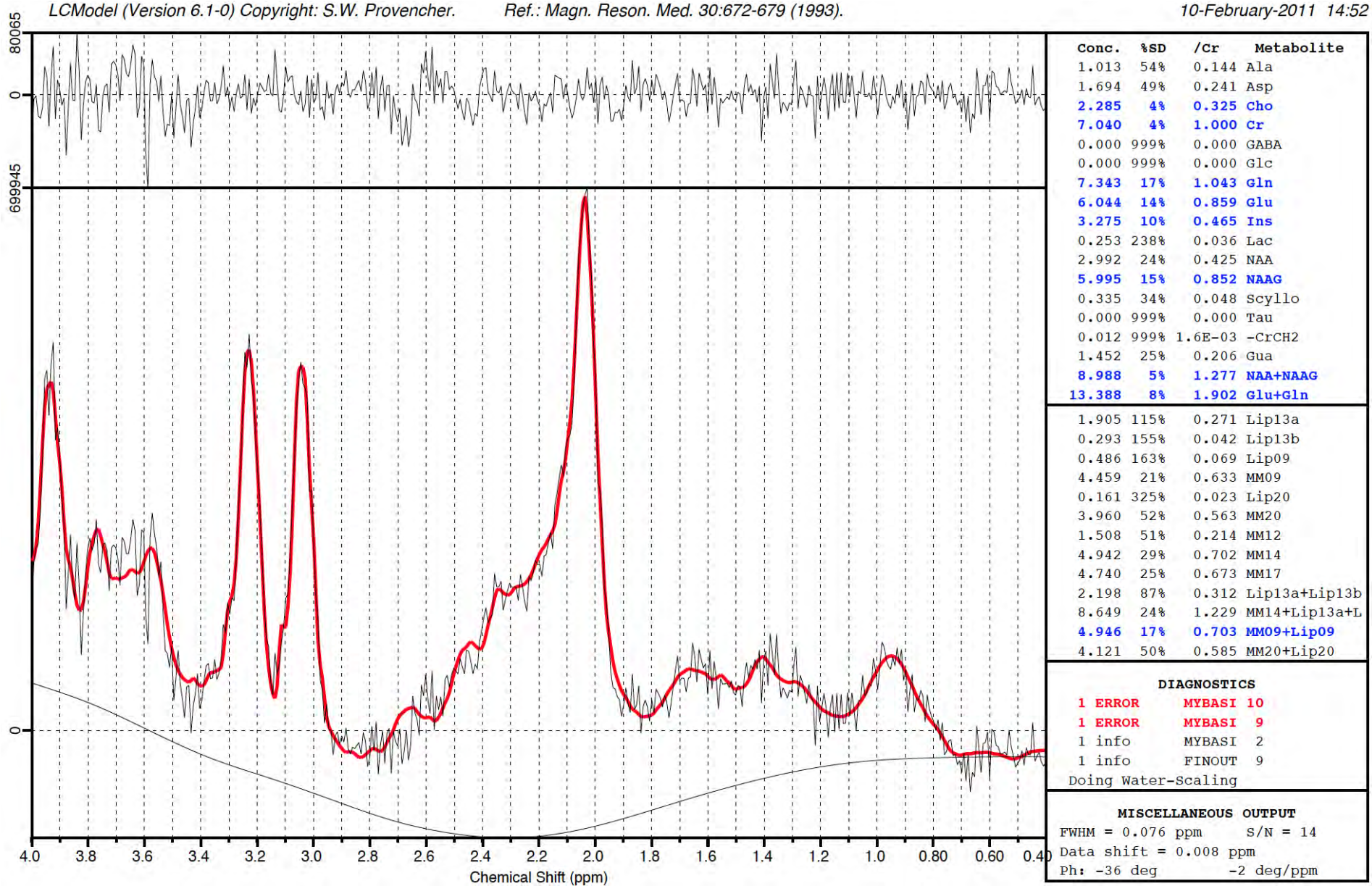

Reaction Time, Mean Response Time
**
P= 0.0028
Time (msec)
600
500
400
300
Control
Transverse Myelitis


Reaction Time, Median Response Time
**
P= 0.0035
Time (msec)
600
550
500
450
400
350
300
Control
Transverse Myelitis

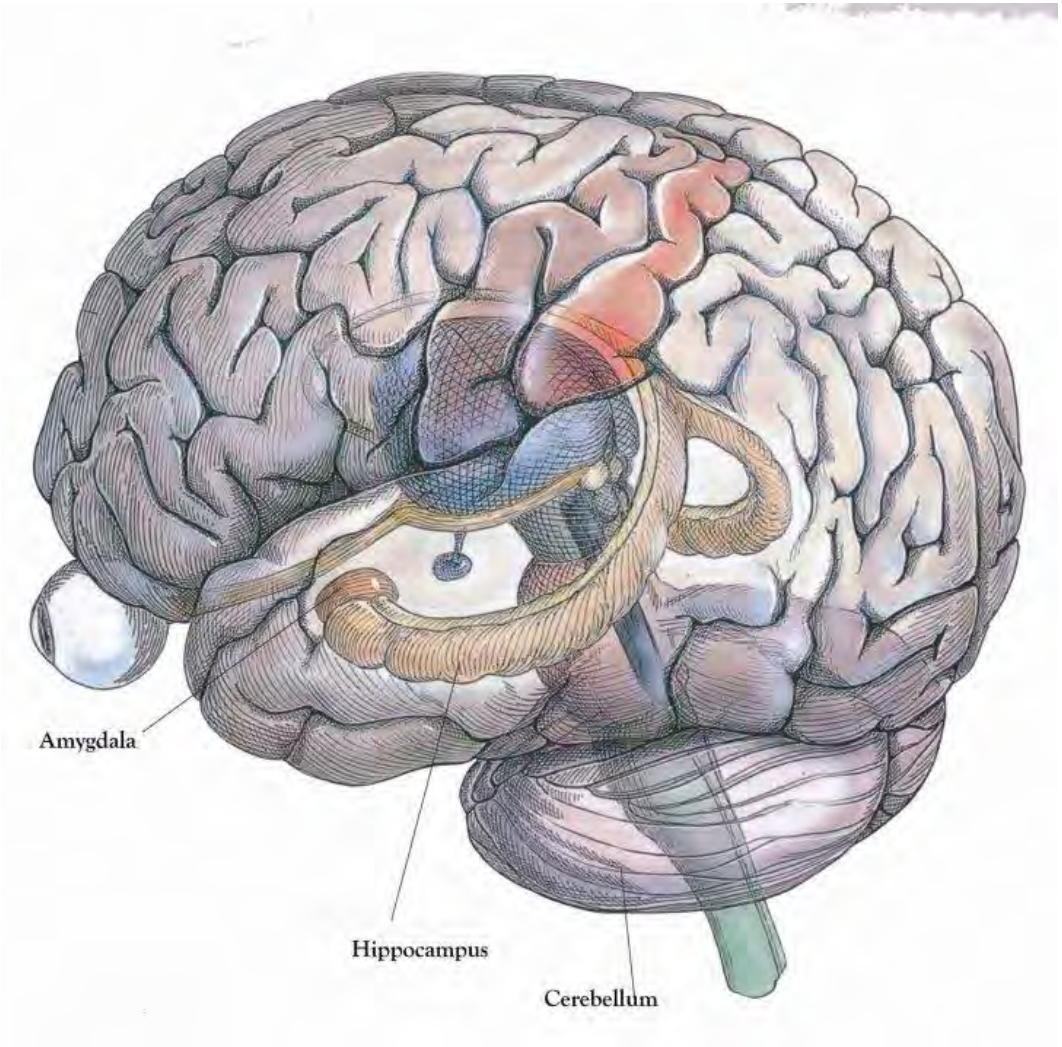
MRI in MS: Clinicoradiological Paradox



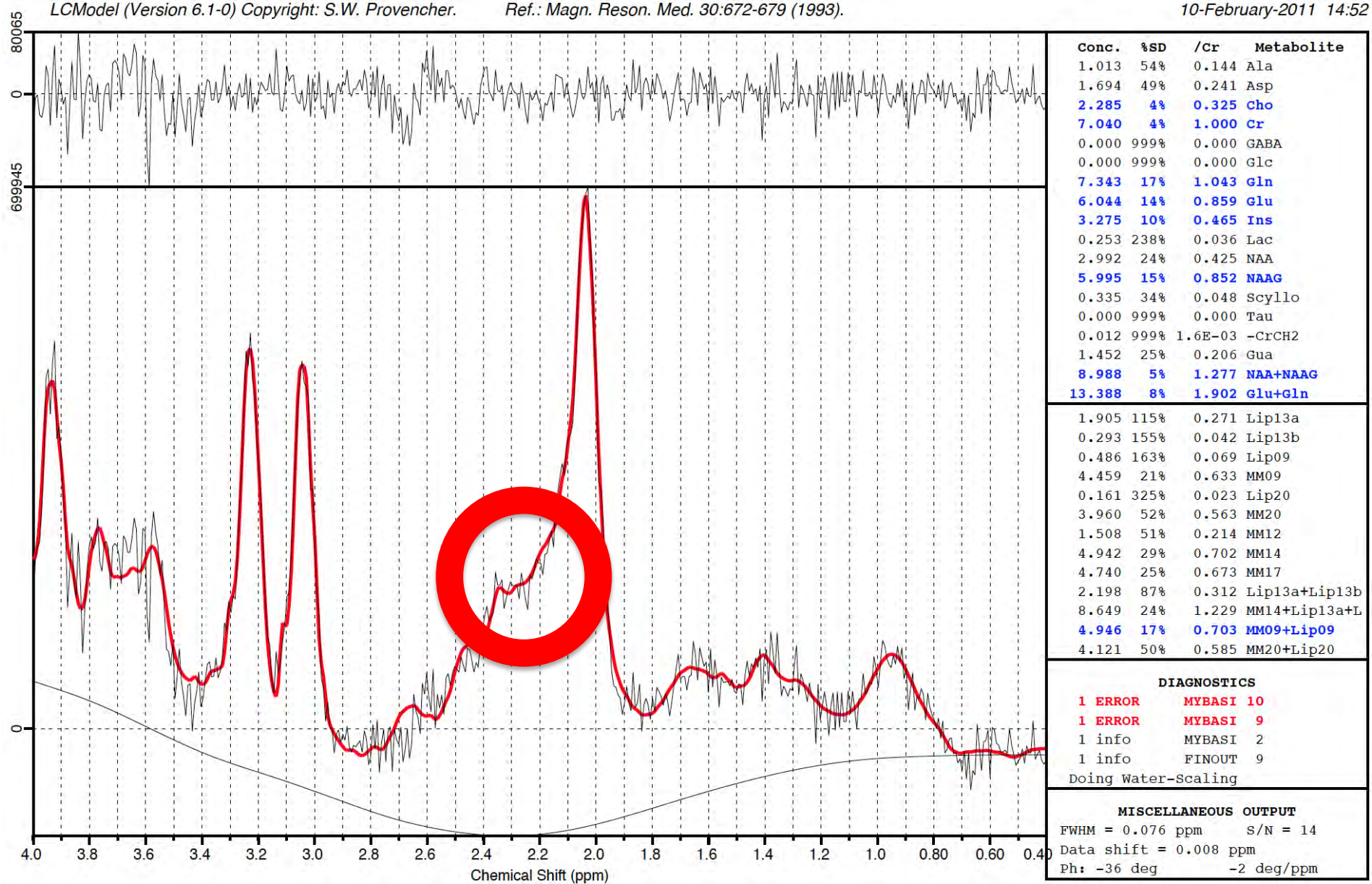
MRS Spectra


LCModel (Version 6.1-0) Copyright: S.W. Provencher.
Ref.: Magn. Reson. Med. 30:672-679 (1993).
10-February-2011 14:52
80065
0
699945
0
4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4 1.2 1.0 0.80 0.60 0.40
Chemical Shift (ppm)
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



MRS Spectra


LCModel (Version 6.1-0) Copyright: S.W. Provencher.
Ref.: Magn. Reson. Med. 30:672-679 (1993).
10-February-2011 14:52
80065
0
699945
0
4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4 1.2 1.0 0.80 0.60 0.40
Chemical Shift (ppm)
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

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

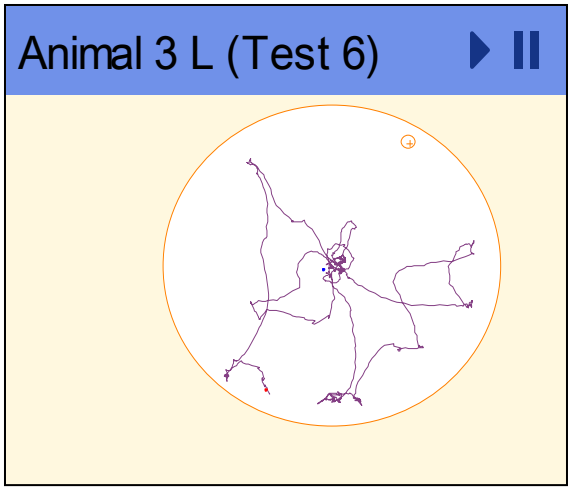
California Verbal Learn. Test-II	P value	Pearson r
Trial 1 Recall	0.2619	0.4188
Trial 5 Recall	0.0027	0.8631
Trials 1-5 Total	0.0143	0.7744
Trial B	0.0166	0.7639
Short Delay Free Recall	0.0015	0.8843
Short Delay Cued Recall	0.0037	0.8503
Long Delay Free Recall	0.0008	0.9032
Long Delay Cued Recall	0.0008	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

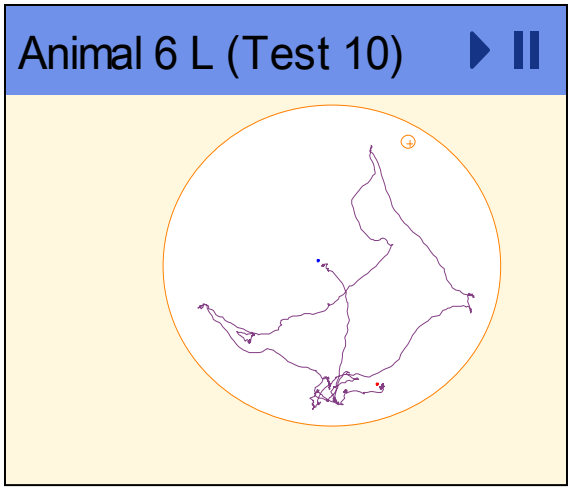
Path Summaries – Trial 1, Day 1

EAE+Vehicle



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

EAE+2-PMPA



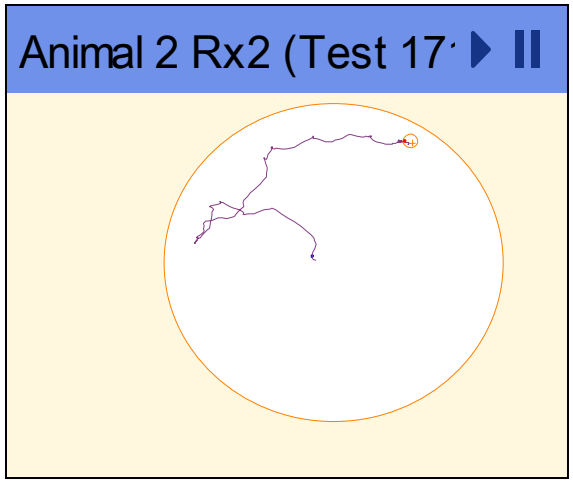
Total Latency = 180 (173.2)
Path Efficiency =0.098 (0.096)

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

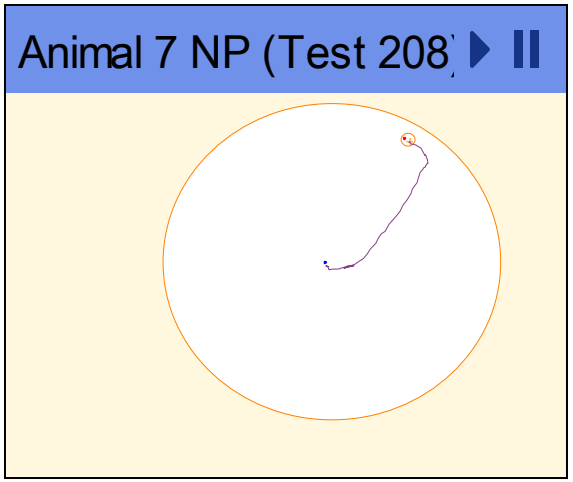
Path Summaries – Trial 1, Day 4

EAE+Vehicle



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

EAE+2-PMPA

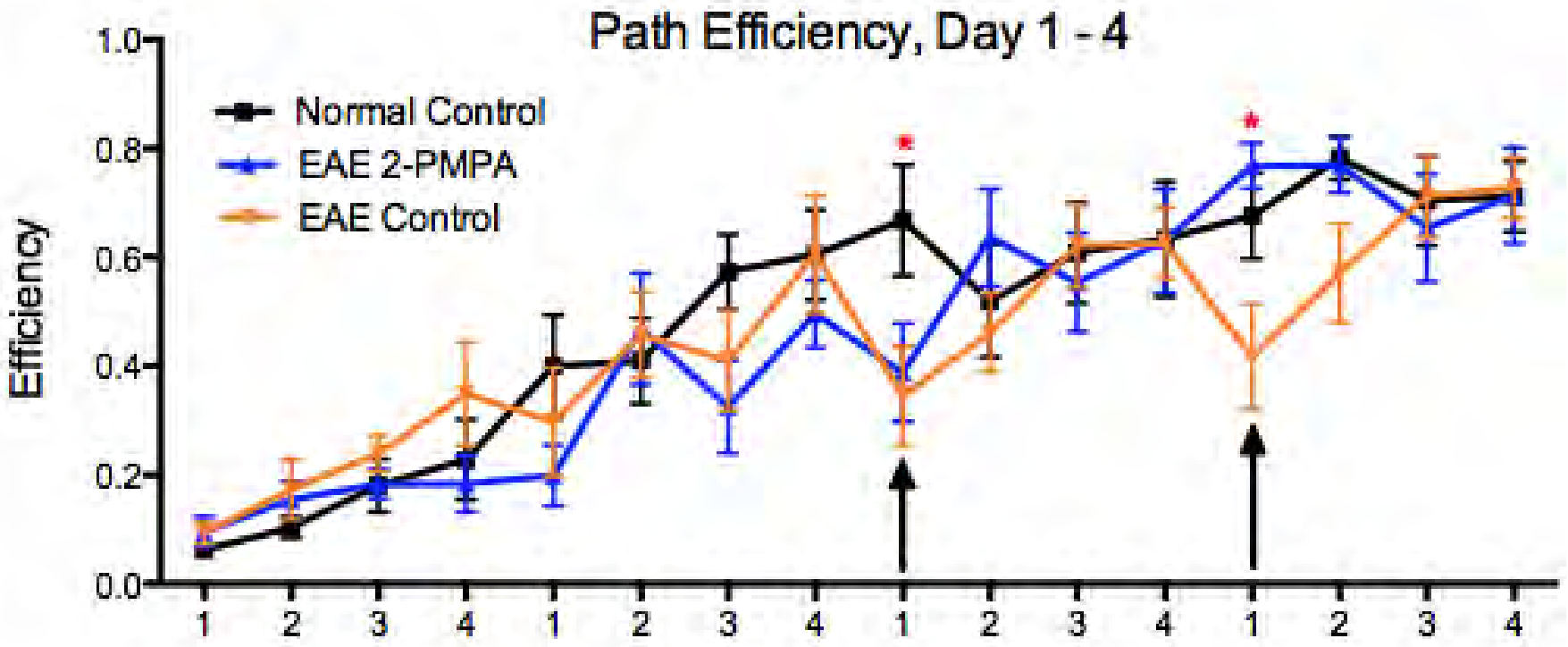


Total Latency = 10.1 (12.32)
Path Efficiency = 0.751 (0.768)

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]

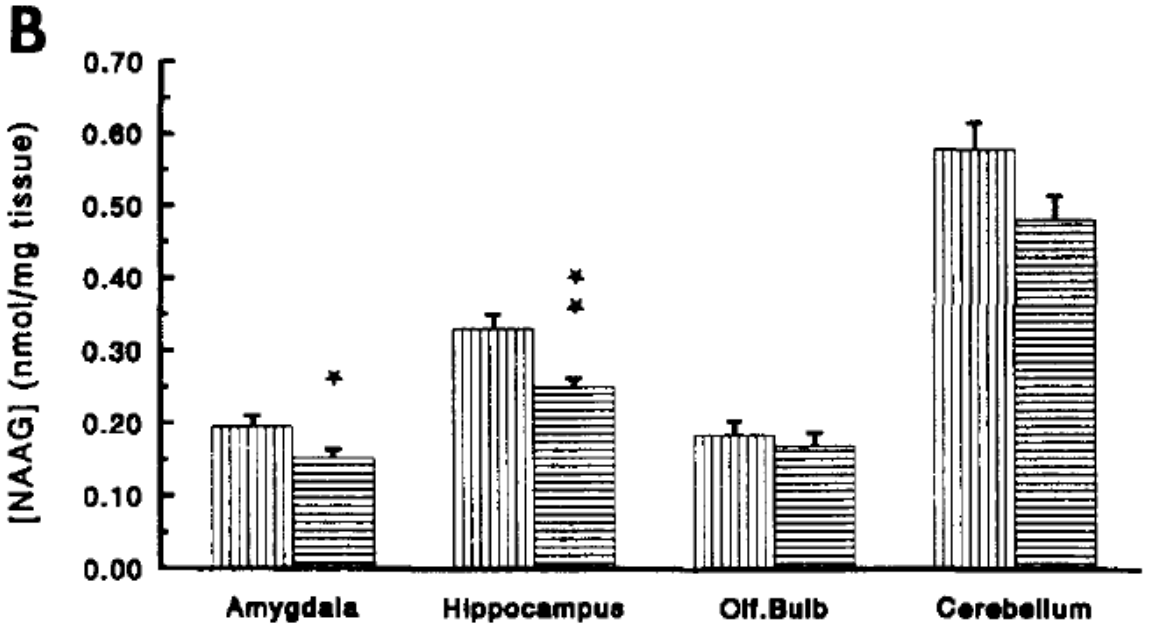


Fig. 1. Mean NAA (A) and NAAG (B) concentrations in brain areas of age-matched controls and Alzheimer's disease patients. Bars represent SEM. * and ** $p < 0.05$ and $p < 0.005$, respectively; AD vs. control, *t*-test.

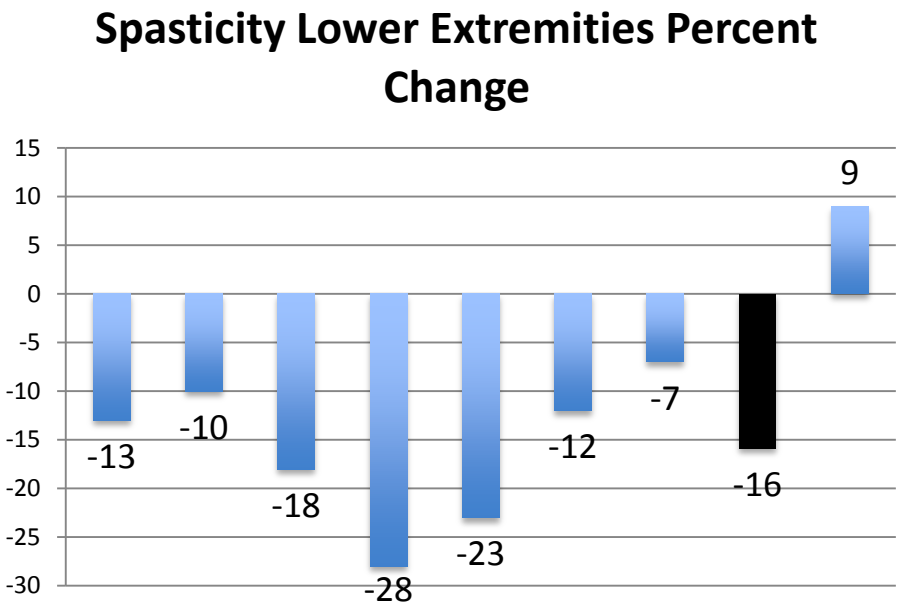
Journal of the Neurological Sciences 127 (1994) 230–233

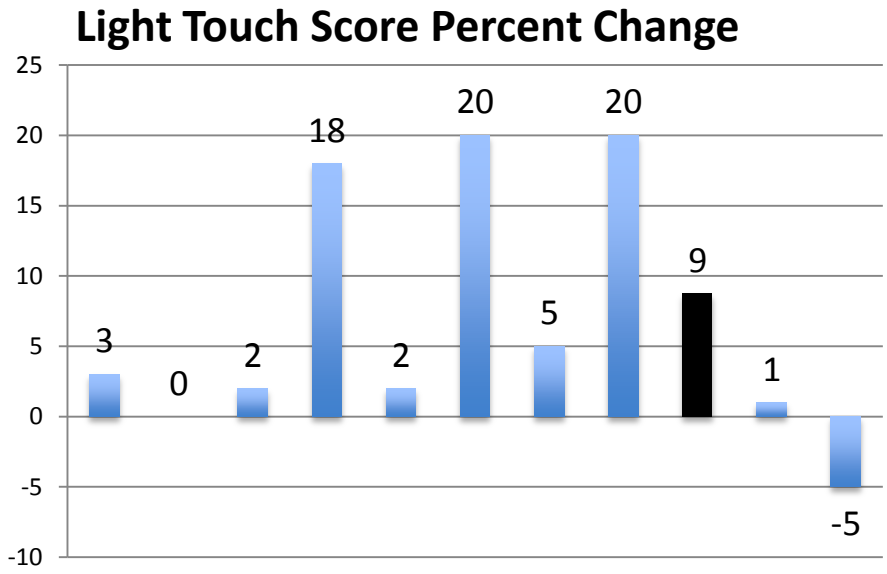
Healing Waters:
Is SCUBA Diving Rehabilitation?

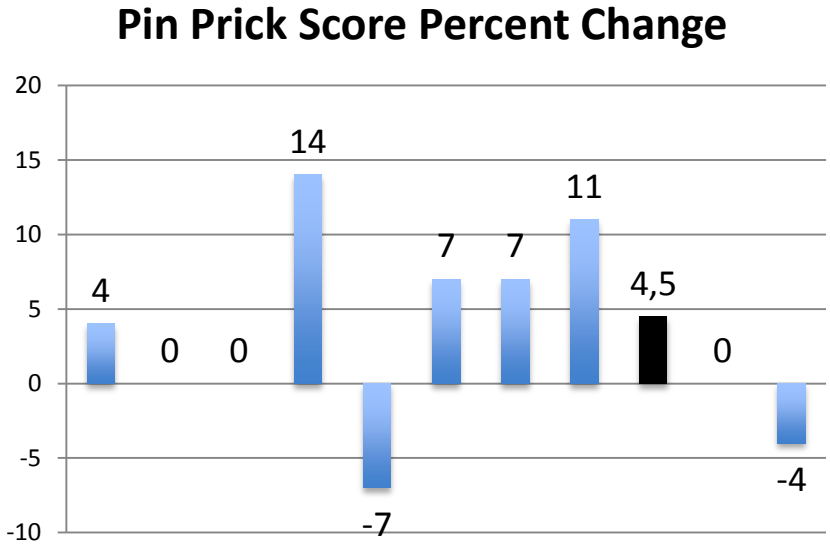
Daniel Becker, MD
Adam Kaplin, MD, PhD
Cody Unser, BA

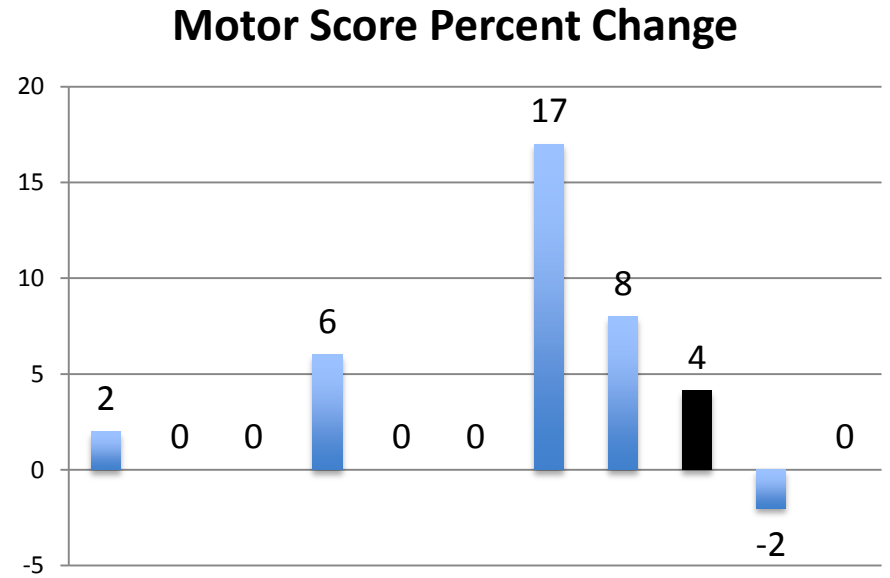
Johns Hopkins University
Kennedy Krieger Institute
Cody Unser First Step Foundation

An Unanticipated Result

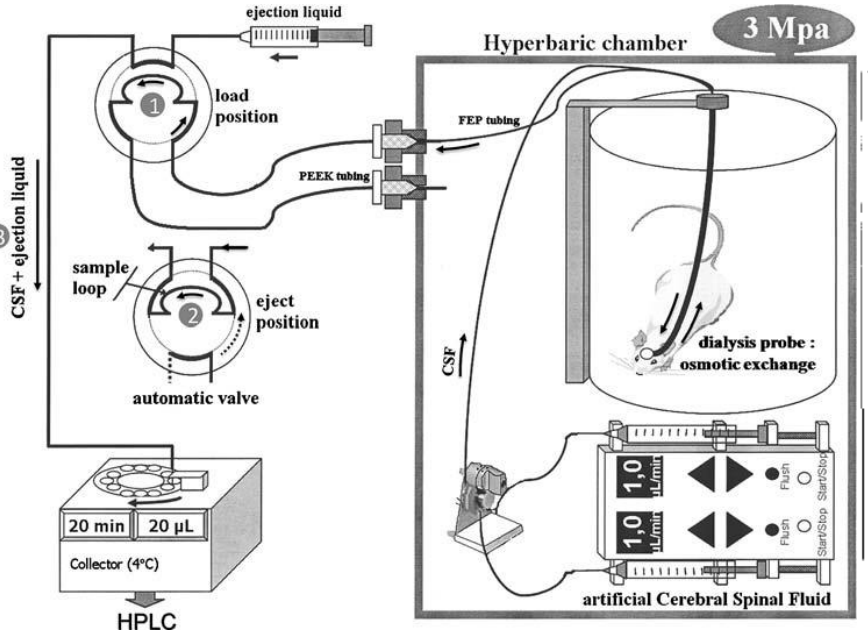


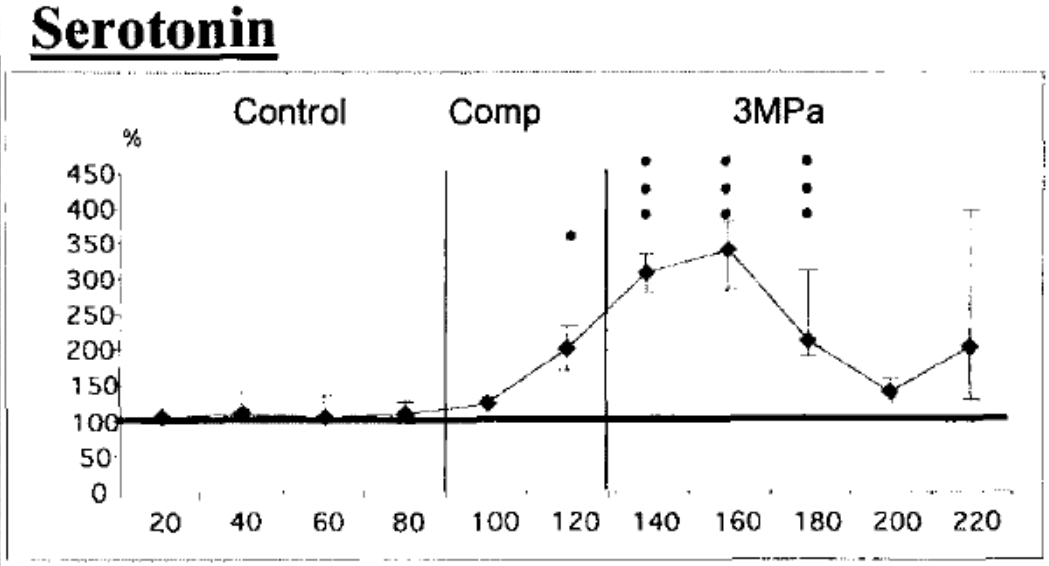




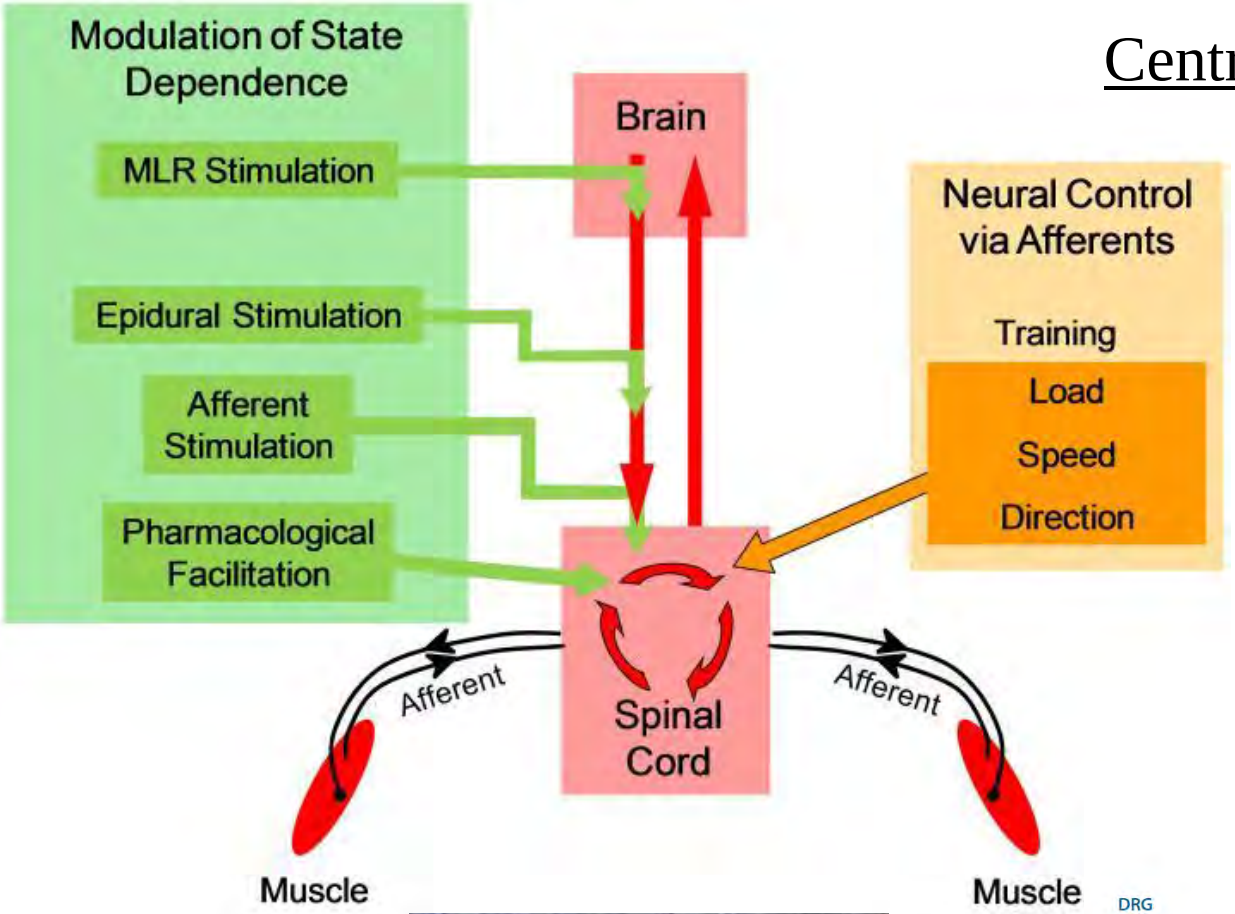


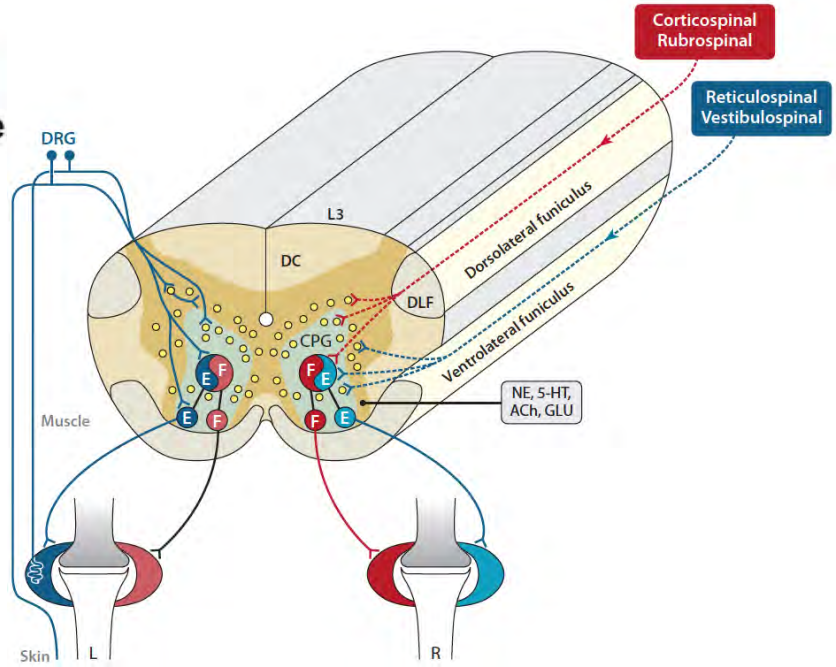
I am personally quite receptive to **nitrogen rapture**. **I like it and fear it like doom.** It destroys the instinct of life… **Intellectuals get drunk early and suffer acute attacks on all the senses, which demand hard fighting to overcome. When they have beaten the foe, they recover quickly.** The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





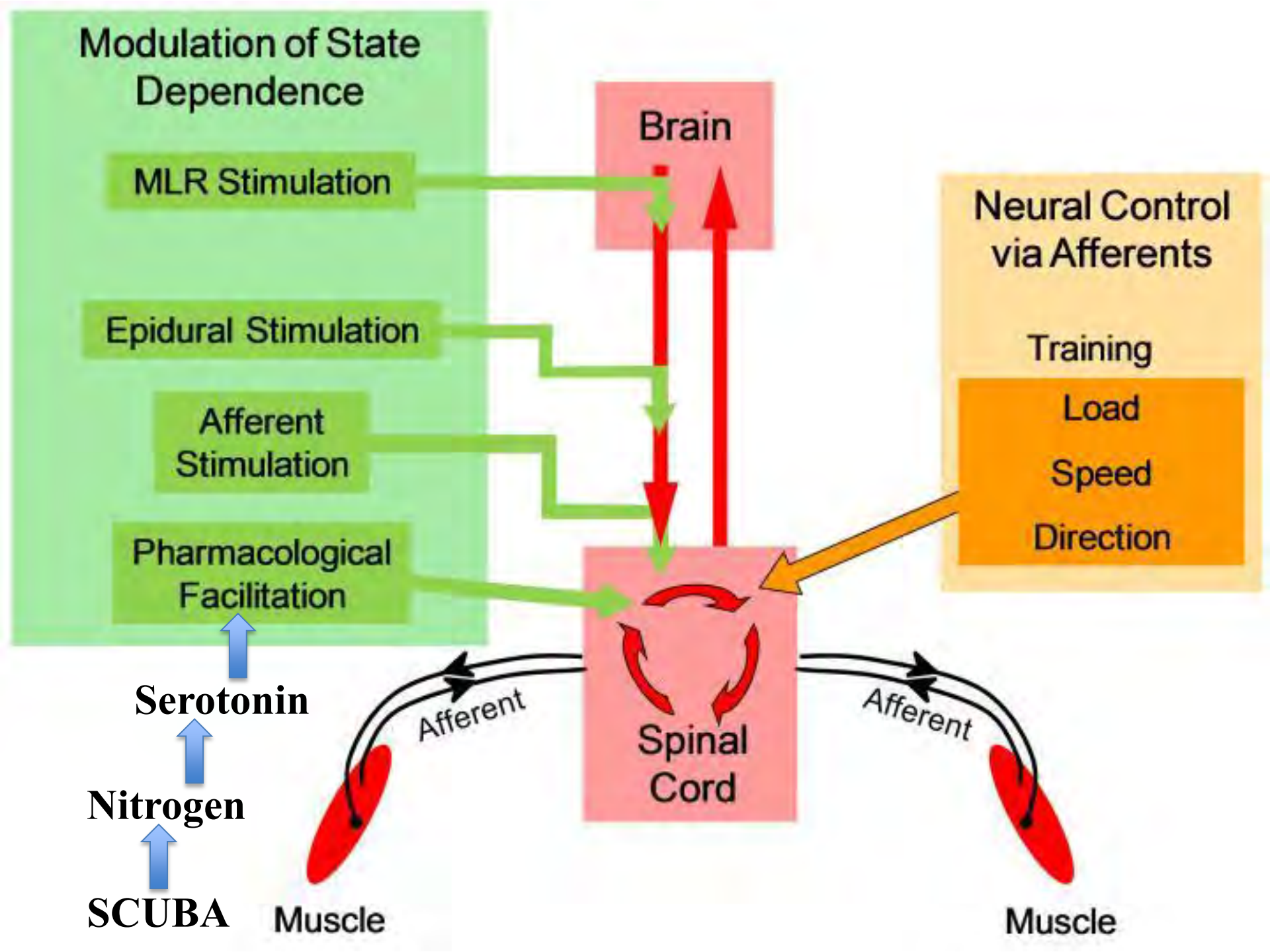
Central Pattern Generator





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.

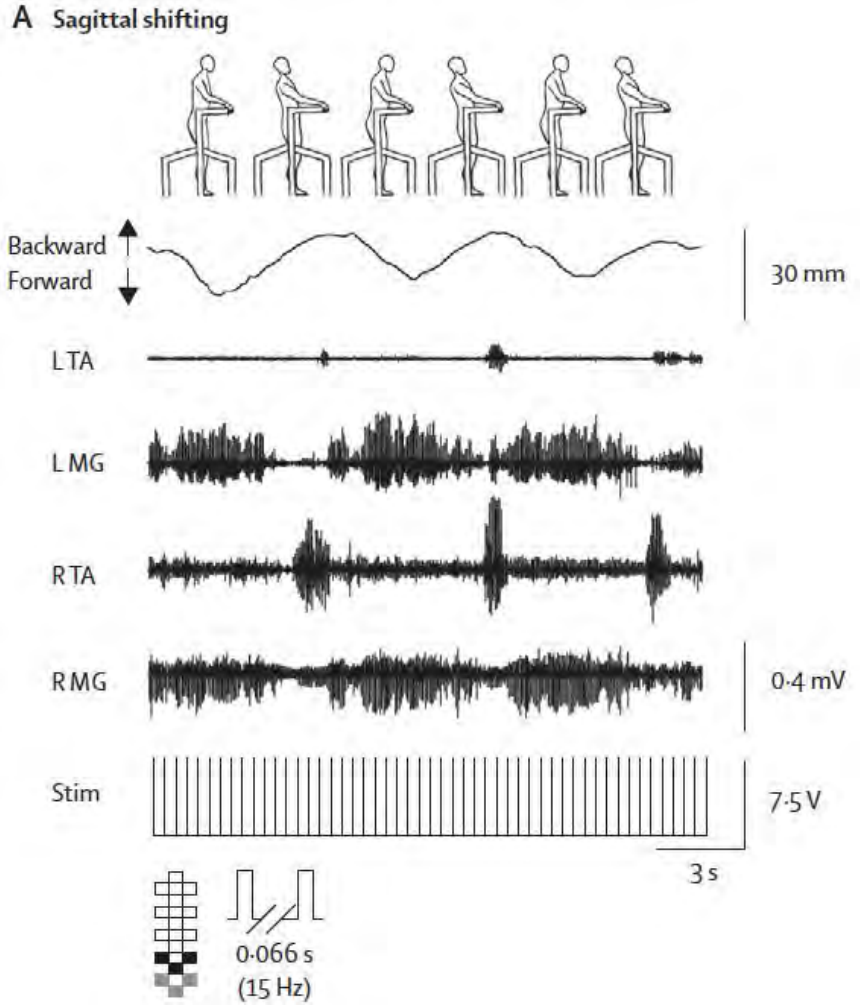

Modulation of State Dependence
MLR Stimulation
Epidural Stimulation
Afferent Stimulation
Pharmacological Facilitation
Serotonin
Nitrogen
SCUBA
Brain
Neural Control via Afferents
Training
Load
Speed
Direction
Afferent
Afferent
Spinal Cord
Muscle
Muscle

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.