

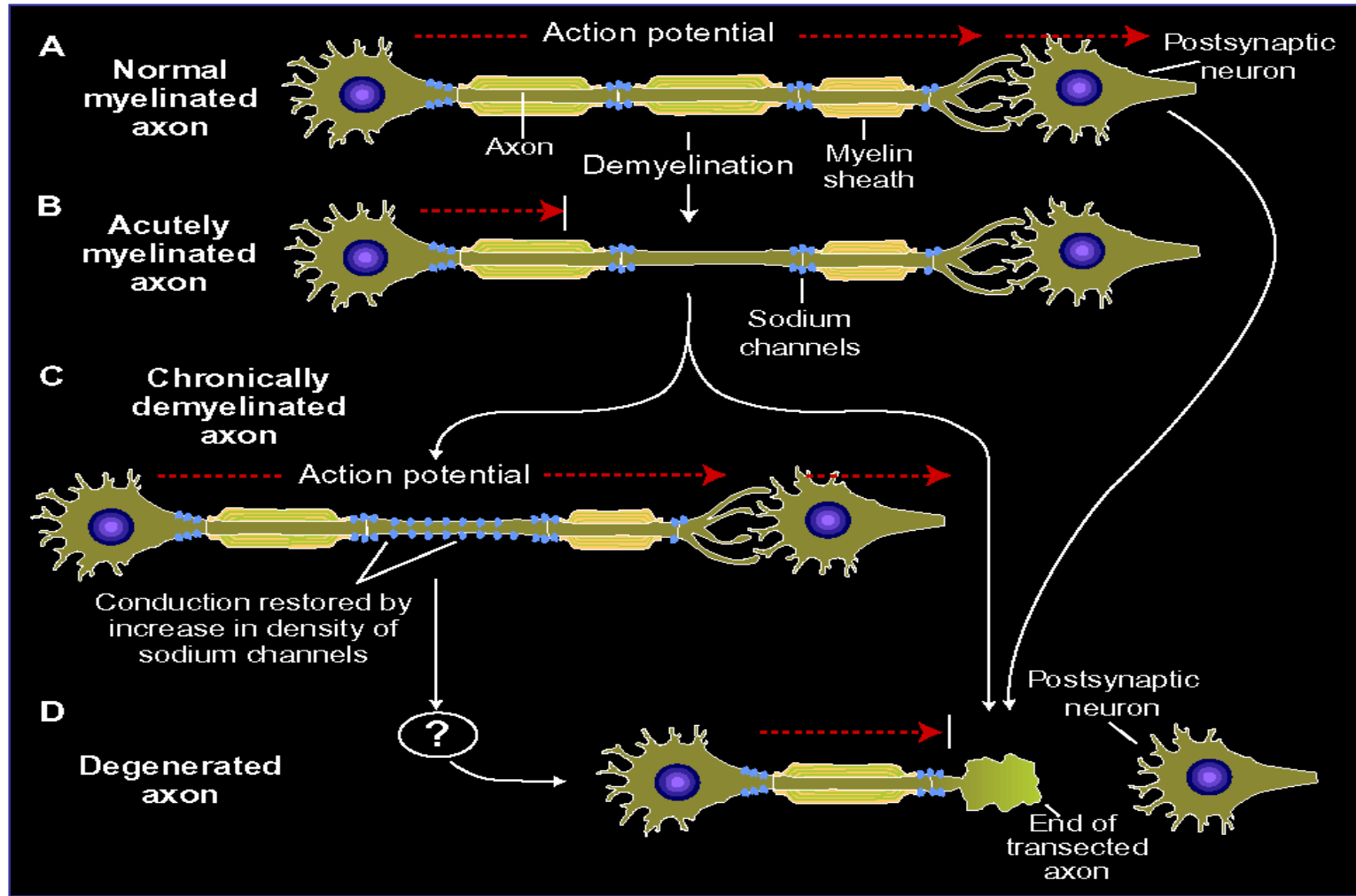
Psychometric considerations and consensus standards for cognitive testing in MS

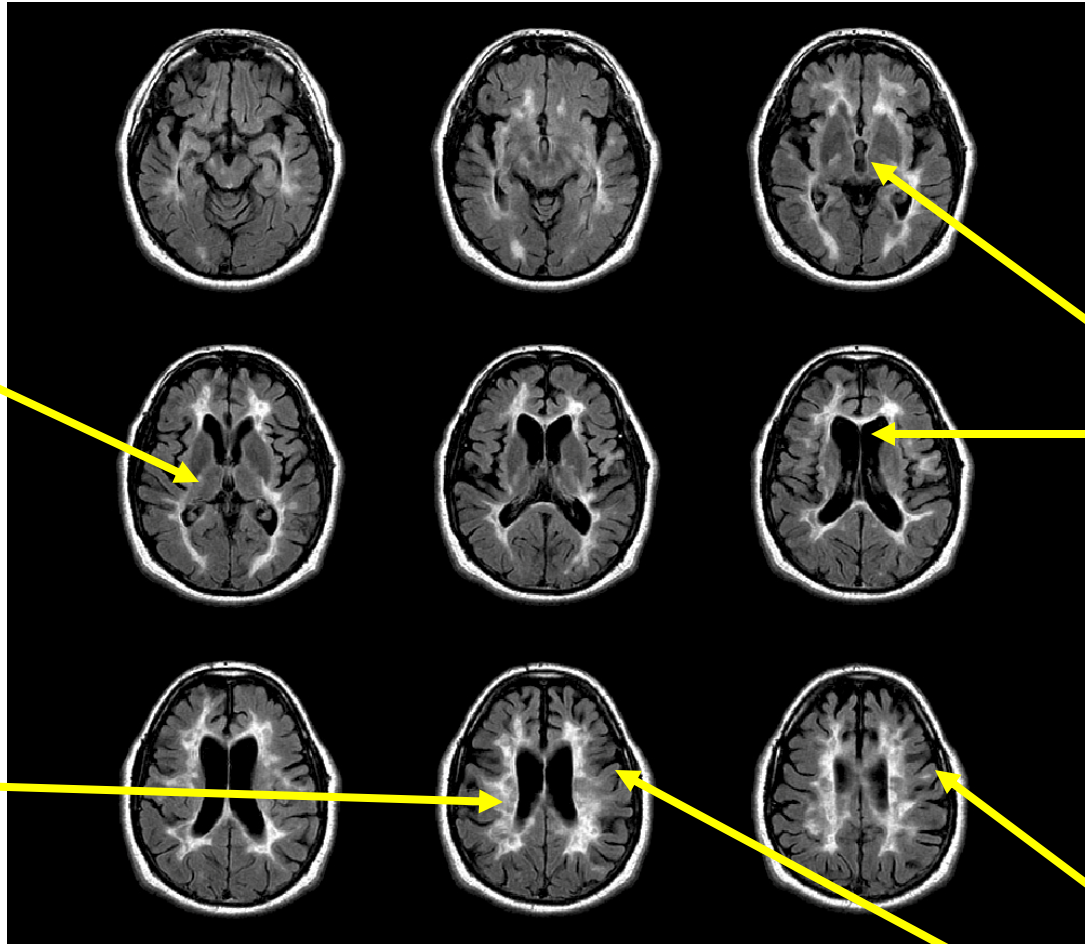
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Thal atrophy corr robustly eg $r = 0.75$

Ventricle Enlargement corr robustly eg $r = 0.71$

Demyelination and axonopathy corr w processing speed

Regional Cort atrophy corr after control for ventricle volume

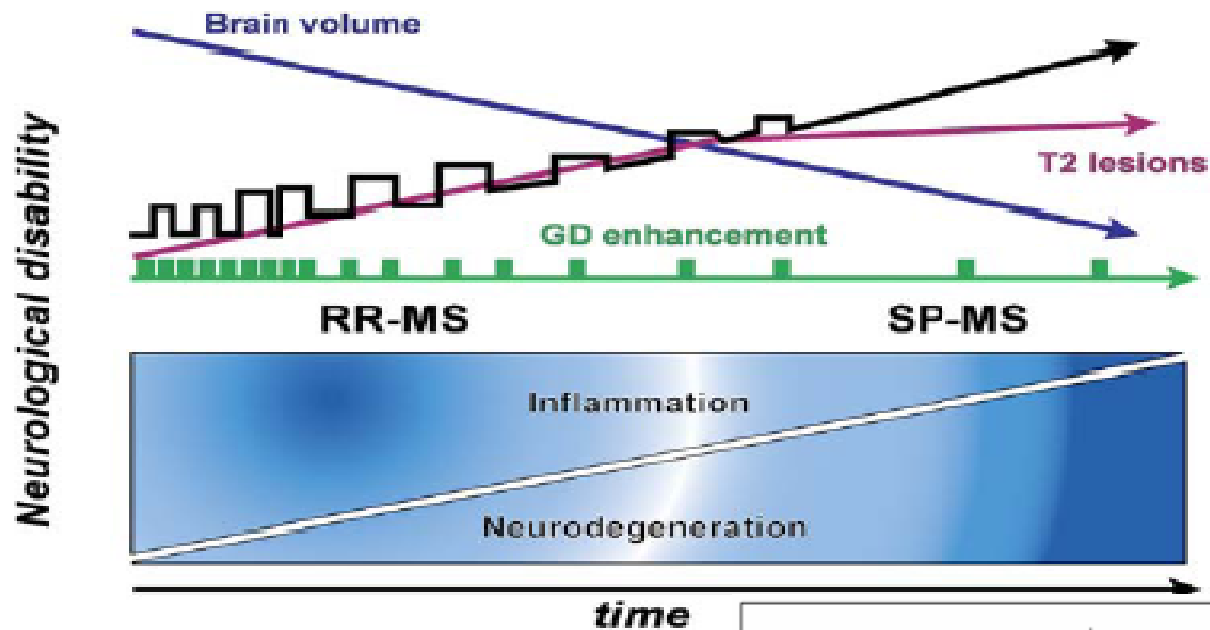
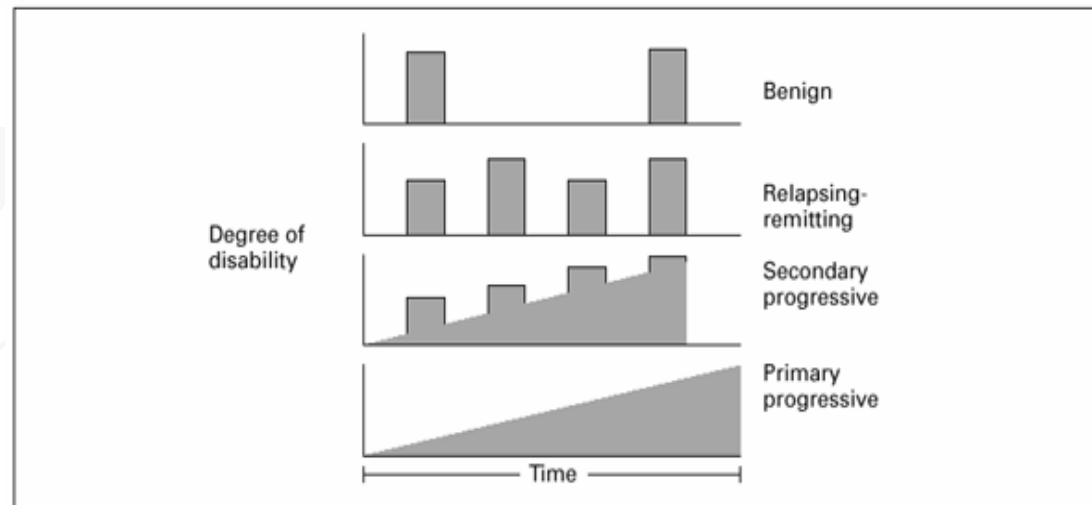
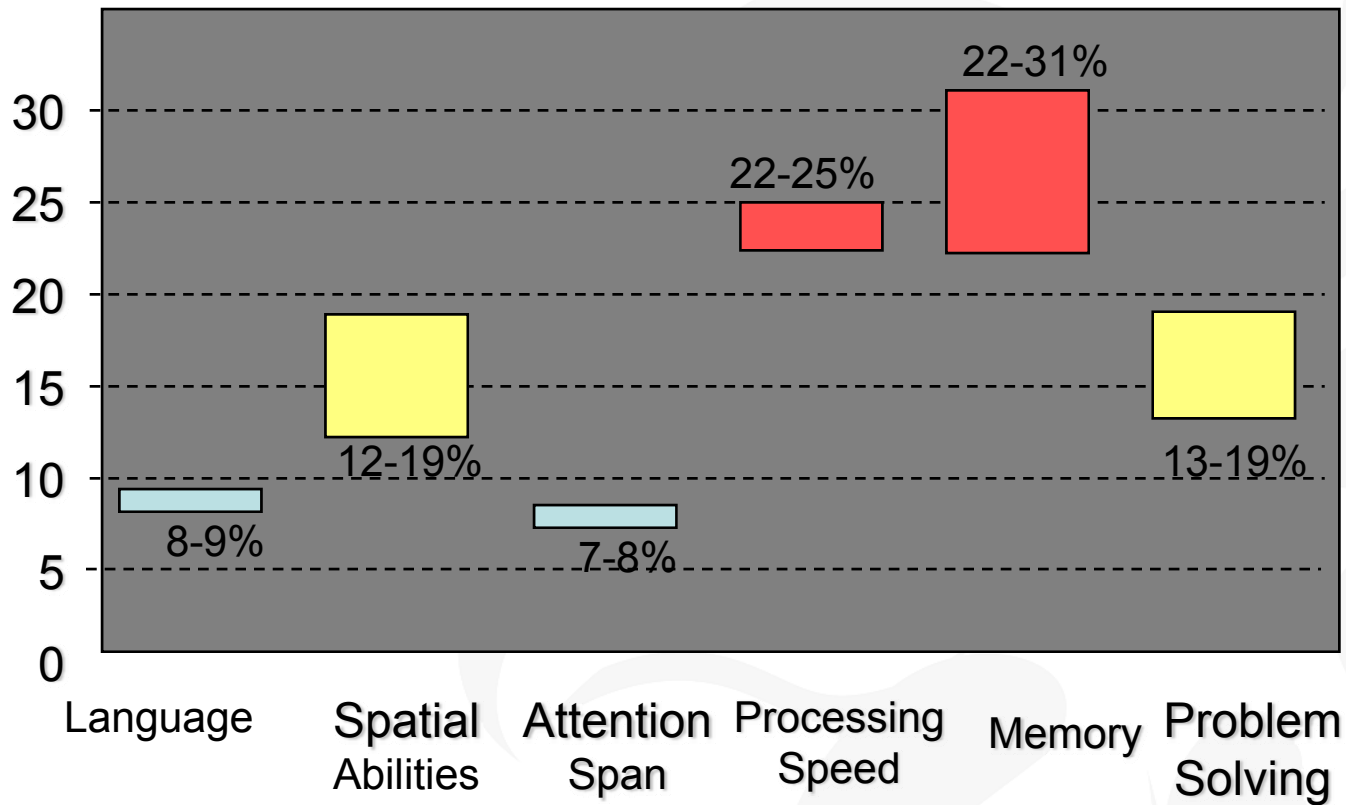


Figure 2. Natural History of MS



- Freq 43% (Rao et al 1991) to 60% (Benedict et al 2006).
- Most common in SP course (Benedict et al 2004a; Comi et al 1995; Foong et al 2000) but is common in RR, and is found in so-called benign MS (Rovaris et al 2008).
- Correlation with disease duration is insignificant (Lynch et al 2005; Rao et al 1984) or small, and CI is seen early disease (Achiron & Barak 2006; Deloire et al 2005b; Jonsson et al 2006; Schulz et al 2006).
- Progresses slowly and the breadth of CI increases over time (Amato et al 2001; Kujala et al 1997).
- NP testing associated with ADLs, employment and social function (Rao et al 1991; Benedict et al 2006).

S Rao et al. 1991. Neurol, 41:685-691

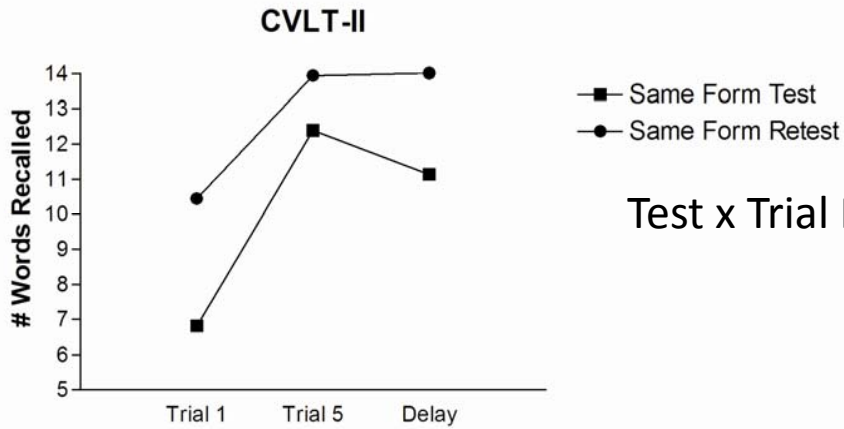


<u>Domain</u>	<u>Rao BRNB</u>	<u>MACFIMS</u>
Processing Speed and Working Memory	SDMT	SDMT
Processing Speed and Working Memory	PASAT	PASAT
Auditory/Verbal Memory	SRT	CVLT-II
Visual/Spatial Memory	7/24 or 10/36	BVMT-R
Language	COWAT	COWAT
Spatial Processing		JLO
Executive Function		D-KEFS Sorting

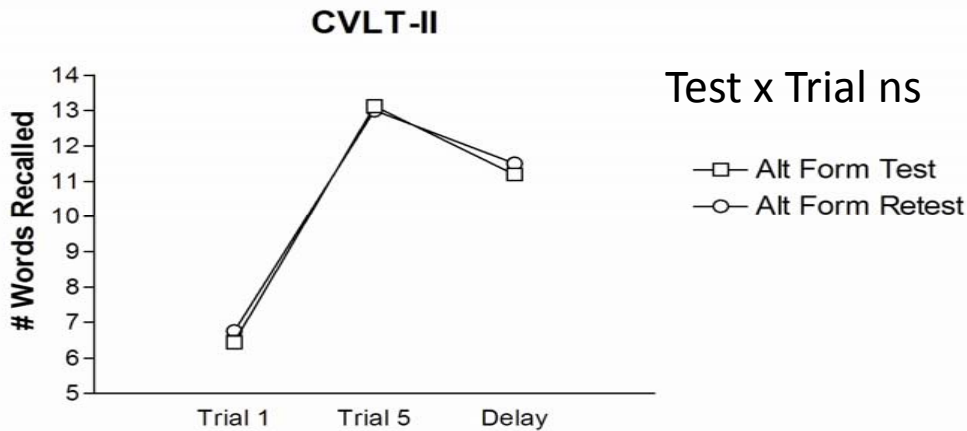
	% z < -1.5
COWAT	13.1
JLO	22.3
CVLT-II Learning	29.6
CVLT-II Delayed Recall	34.4
BVMT-R Learning	54.3
BVMT-R Delayed Recall	56.0
PASAT 3.0 ISI	27.4
Symbol Digit Modalities Test	51.9
DKEFS Sorting Test Categories	15.8
DKEFS Sorting Test Description	25.8

N: 291 MS, 56 NC

If Cog Impairment = defect on
2 or more measures, freq =
59.5%



Test x Trial $F=9.5$ $p<.01$

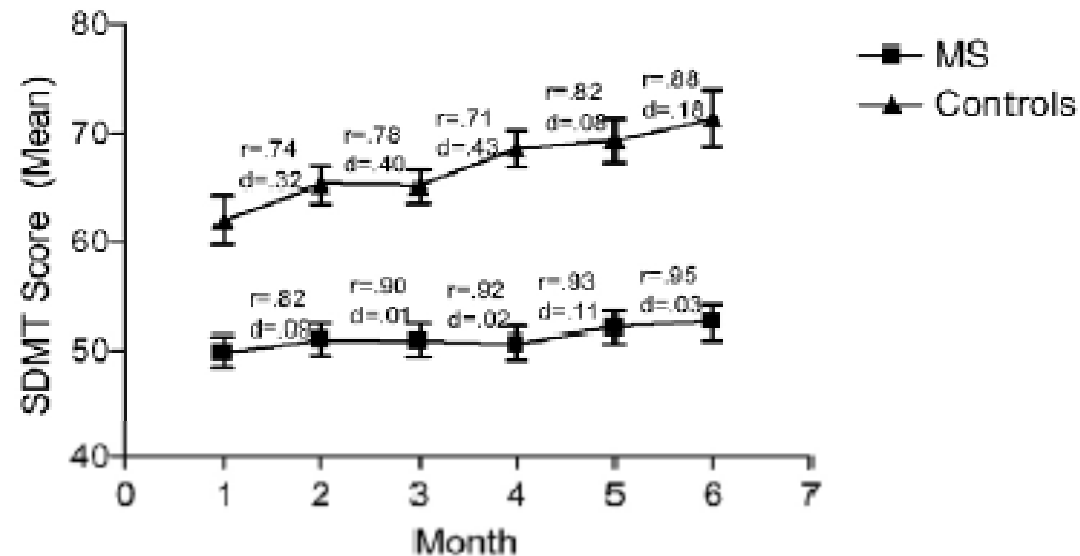


Test x Trial ns

	Test-Retest r
CVLT2 Total Learning	0.78
CVLT2 Delayed Recall	0.89
BVMTR Total Learning	0.91
BVMTR Delayed Recall	0.85
PASAT Total Score	0.94
SDMT	0.97
COWAT	0.84

Symbol Digit Modalities Test (SDMT)

- most reliable NP test in MS
- most sensitive to MS Dx
- strongest correlate of multiple brain MRI measures
- predicts functional outcomes



Expanded Disability Status Scale (EDSS)

- Visual system
 - Brainstem
 - Pyramidal
 - Cerebellar
 - Sensory
 - Bowel/Bladder
 - Ambulation
 - Cerebral
-

Disease Modifying Therapy (DMT)

- medications intended to suppress immunological activity at site of lesion, may have short- and long-term effects
- cognition never primary outcome
- majority of trials do not include secondary cognitive outcomes
- general assumption that what is good for relapses, brain lesions & EDSS is good for cognition

Improving Cognitive Symptoms

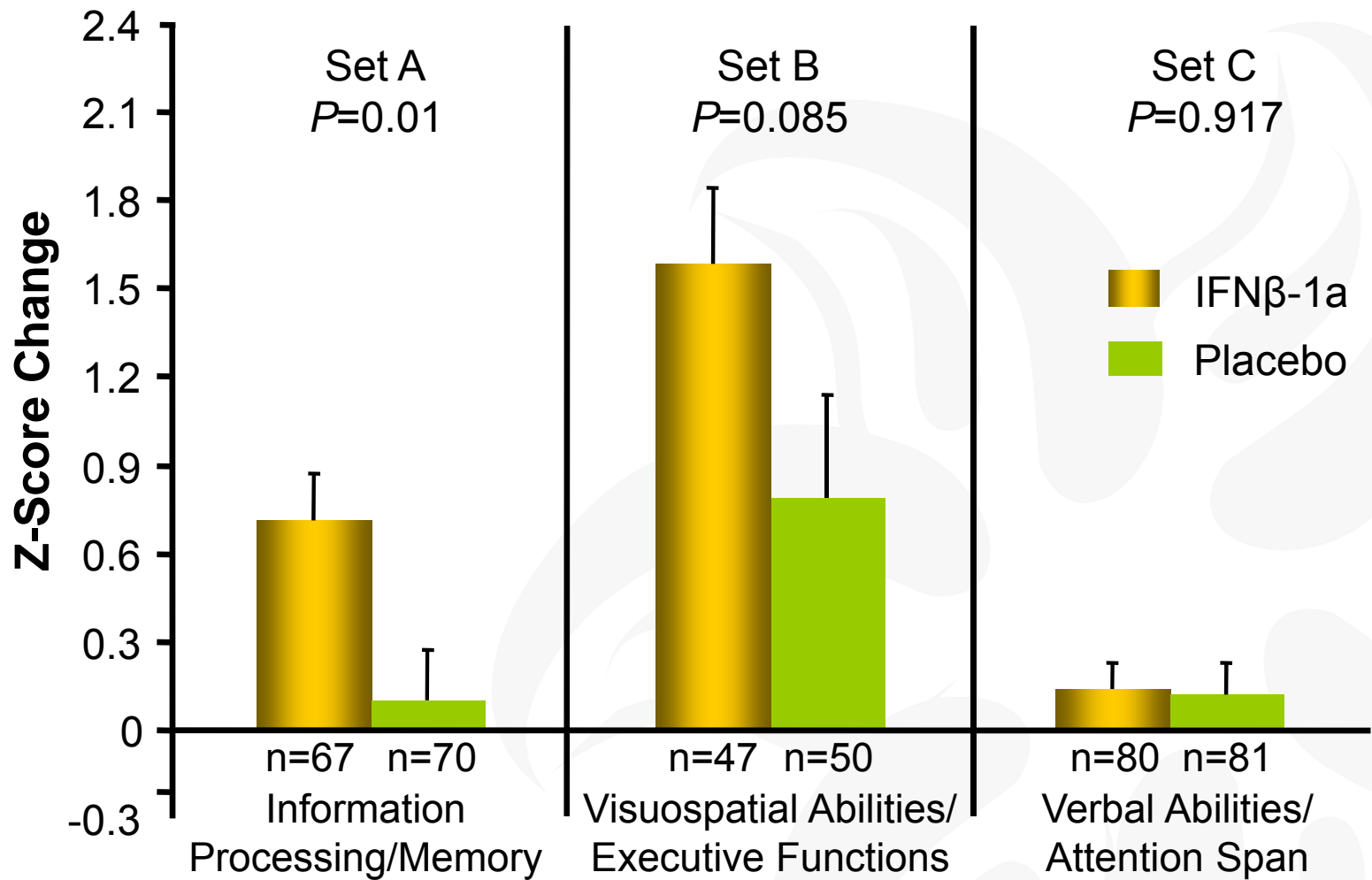
- mainly short-term effects
- cholinomemetic drugs for memory impairment
- stimulants for bradyphrenia
- concordant w DMT
- very few trials because: (a) MS is progressive; (b) only ½ of pts are affected, (c) very complicated disease, (d) liberal use of medications indicated for same symptoms in other diseases

Neuropsychological Effects of Interferon β -1a in Relapsing Multiple Sclerosis

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Richard A. Rudick, MD,* Robert M. Herndon, MD,§ John R. Richert, MD,|| Andres M. Salazar, MD,¶
Donald E. Goodkin, MD,# Carl V. Granger, MD,** Jack H. Simon, MD,†† Jordan H. Grafman, PhD,‡‡
Muriel D. Lezak, PhD,§§ Kathleen M. O'Reilly Hovey, MS,† Katherine Kawczak Perkins, BA,*
Danielle Barilla-Clark, MA,* Mark Schacter, PhD,‡ David W. Shucard, PhD,‡ Anna L. Davidson, MPH,†
Karl E. Wende, PhD,† Dennis N. Bourdette, MD,§§ Mariska F. Kooijmans-Coutinho, MD, PhD,|||
and the Multiple Sclerosis Collaborative Research Group

Ann Neurol 2000;48:885–892

- n = 166
- Interferon beta-1a vs placebo
- Comprehensive NP battery requiring 6 hrs of administration
- Set A measures = processing speed and memory
- Set B measures = spatial abilities, executive functions
- Set C measures = language, general intelligence, immed memory



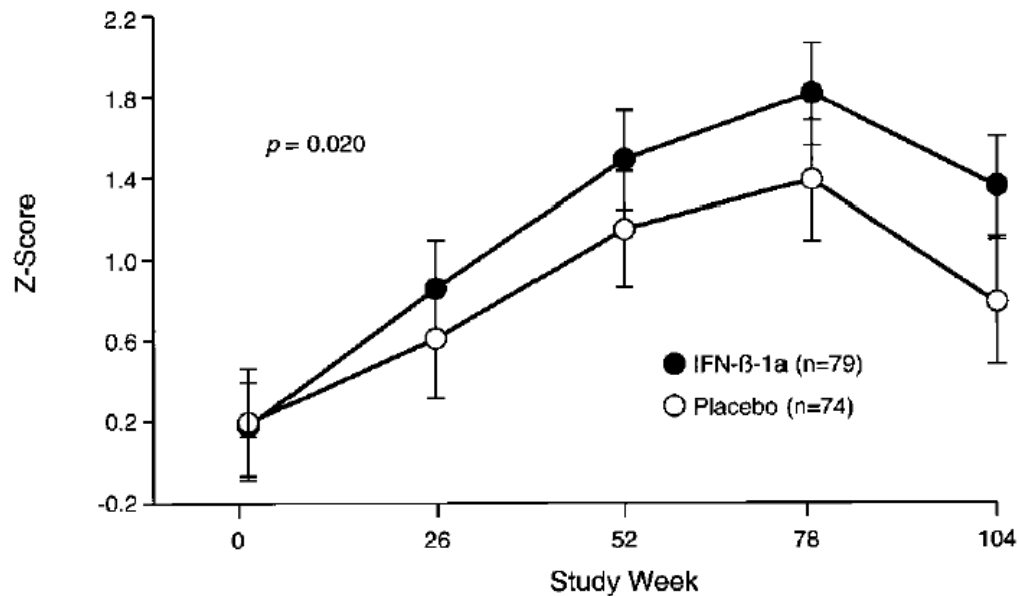


Fig 3. Brief Neuropsychological Battery composite performance (mean z score \pm SEM) at each study visit by treatment group.

Donepezil improved memory in multiple sclerosis in a randomized clinical trial

NEUROLOGY 2004;63:1579-1585

L.B. Krupp, MD; C. Christodoulou, PhD; P. Melville, RN; W.F. Scherl, MS;
W.S. MacAllister, PhD; and L.E. Elkins, PhD

- 24 week
- Placebo-controlled
- MS diagnosis, all subtypes, on all DMTs
- EDSS \leq 6.5
- Absence of severe depressive symptoms (MADRS < 15).
- At least mild verbal memory difficulties
 - RAVLT at least $\frac{1}{2}$ SD below norms
 - Sample Mean (SD) RAVLT = 1.52 (1.35) below

Table 2 Mean \pm SD performance of the donepezil and placebo groups on the SRT primary outcome and other neuropsychological tasks at week 0, week 24, and week 24–0

	Week 0		Week 24		Week 24–0	
	Placebo	Donepezil	Placebo	Donepezil	Placebo	Donepezil
SRT total	42.7 \pm 8.8	42.3 \pm 9.0	43.2 \pm 9.2	46.8 \pm 9.3	0.7 \pm 6.3	4.6 \pm 9.1*
10/36 total	18.9 \pm 4.5	20.6 \pm 5.2	20.2 \pm 5.4	22.1 \pm 4.7	1.2 \pm 4.2	1.5 \pm 4.6
SDMT total	42.4 \pm 14.9	47.0 \pm 11.8	44.5 \pm 14.1	48.3 \pm 14.1	2.0 \pm 6.5	1.0 \pm 7.5
PASAT 2 + 3 sec total	66.6 \pm 23.1	67.9 \pm 21.0	66.3 \pm 26.4	72.8 \pm 16.8	0.8 \pm 11.1	5.3 \pm 9.9†
COWA mean	17.7 \pm 4.4	18.4 \pm 3.7	17.8 \pm 4.6	18.3 \pm 5.1	0.2 \pm 3.6	-0.2 \pm 3.1
TOH mean	12.1 \pm 7.9	17.3 \pm 7.0	12.7 \pm 7.2	17.8 \pm 7.6	0.7 \pm 5.7	0.3 \pm 7.3

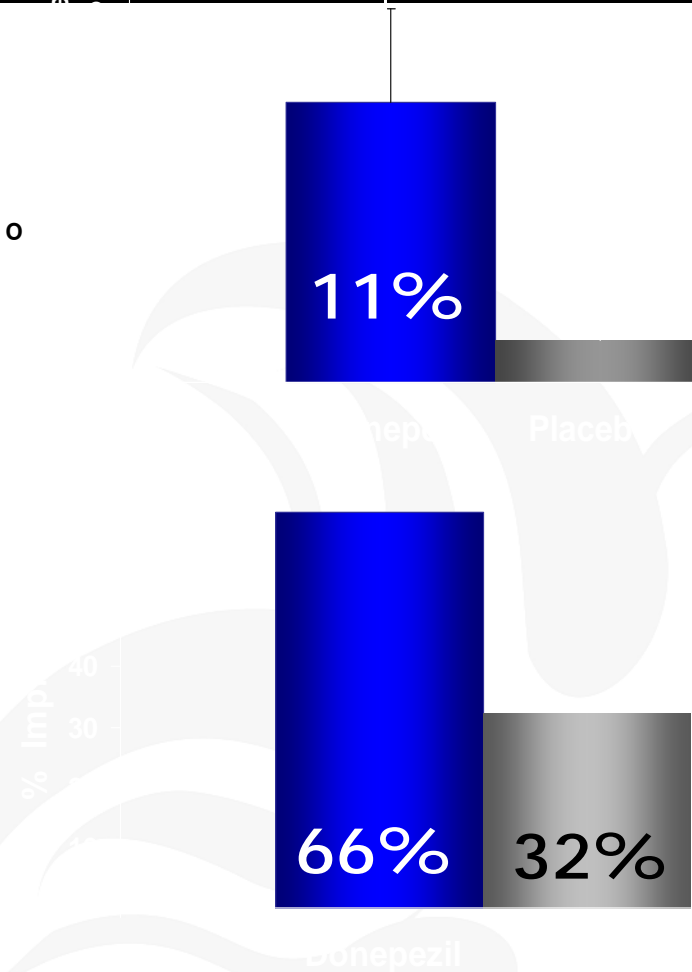
* $p < 0.05$.

† $p < 0.10$.

SRT = Selective Reminding Test; 10/36 = 10/36 Spatial Recall Test; SDMT = Symbol Digit Modalities Test; PASAT = Paced Auditory Serial Addition Test; COWA = Controlled Oral Word Association semantic fluency; TOH = Tower of Hanoi.

Improve verbal memory performance, ($P=0.043$), the 1^o outcome

Increase likelihood of self-reported memory improvement ($P=0.006$), a 2^o outcome



The Effects of l-Amphetamine Sulfate on Cognition in MS patients: Results of a Randomized Controlled Trial

Morrow et al, Journal of Neurology, in press

- 151 MS Pts, randomized 2:1 l-amphetamine vs placebo
- $z = <-1.5$ on SDMT, or, <-1.0 and <-1.0 on CVLT2 or PASAT
- no benzodiazepines, anticonvulsants, corticosteroids, narcotics, or antipsychotics
- no current major depression
- EDSS < 7.0
- Dosing: 5mg qd \rightarrow 15mg \rightarrow 30mg
- Primary Outcomes: SDMT, Subject Global Assessment of Change
- Secondary Outcomes: CVLT2, BVMTR, PASAT
- ANCOVA with baseline as covariate

Neuropsychological Test	Mean \pm SD Day 0 (baseline)	Mean \pm SD Day 29	d (effect size)	p-value (ANCOVA)
SDMT l-amphetamine sulfate placebo	38.0 \pm 13.1 36.5 \pm 10.5	42.2 \pm 11.2 41.7 \pm 11.9	0.04	0.506
CVLT2-TR l-amphetamine sulfate placebo	43.9 \pm 12.3 41.9 \pm 12.1	46.7 \pm 11.7 44.8 \pm 14.2	0.15	0.912
CVLT2-DR l-amphetamine sulfate placebo	8.0 \pm 3.8 8.0 \pm 3.8	9.7 \pm 3.4 8.4 \pm 4.4	0.33	0.012
BVMTR-TR l-amphetamine sulfate placebo	16.8 \pm 7.5 15.9 \pm 8.4	19.4 \pm 7.0 16.9 \pm 9.2	0.31	0.041
BVMTR-DR l-amphetamine sulfate placebo	6.4 \pm 3.2 6.2 \pm 3.6	7.5 \pm 3.0 6.3 \pm 3.7	0.37	<0.01
PASAT l-amphetamine sulfate placebo	32.1 \pm 12.7 30.4 \pm 13.1	40.6 \pm 14.1 38.1 \pm 12.7	0.19	0.205

Limitations

- Generalizability: NP testing battery too cumbersome [Fischer 2000], low participation rate [Krupp 2004], high drop out rate [Morrow 2009]
 - Single study site [Krupp 2004]
 - Groups not matched on disease course w RR over-represented in treatment group [Krupp 2004]
 - Outcome measures determined post-hoc [Fischer 2000]
 - Alternate forms not available for many tests [Fischer 2000]
 - Patients were all RR pts with unknown impairment [Fischer 2000]
 - Little information on concomitant medications [Fischer 2000]
 - No collateral impression of change [Fischer 2000; Krupp 2004]
 - Risk of over-interpreting medium effects on outcomes not designated as primary a priori [Fischer 2000; Morrow 2009]
-

Challenges and Uncertainties in Carrying Out Cognition Clinical Trials in MS

- Difficult balance between proper medication exclusion, and successful enrollment and generalizability of results
- RR disease? SP disease? Both?
- Cognitively impaired or all levels of ability?
- Psychiatric factors: Depression has 90% lifetime prev in MS
- Practice effects on outcome measures, run in to stability?
- What is the best non-performance valid measure?
- Difficulties conducting NP testing in neurology clinic milieu