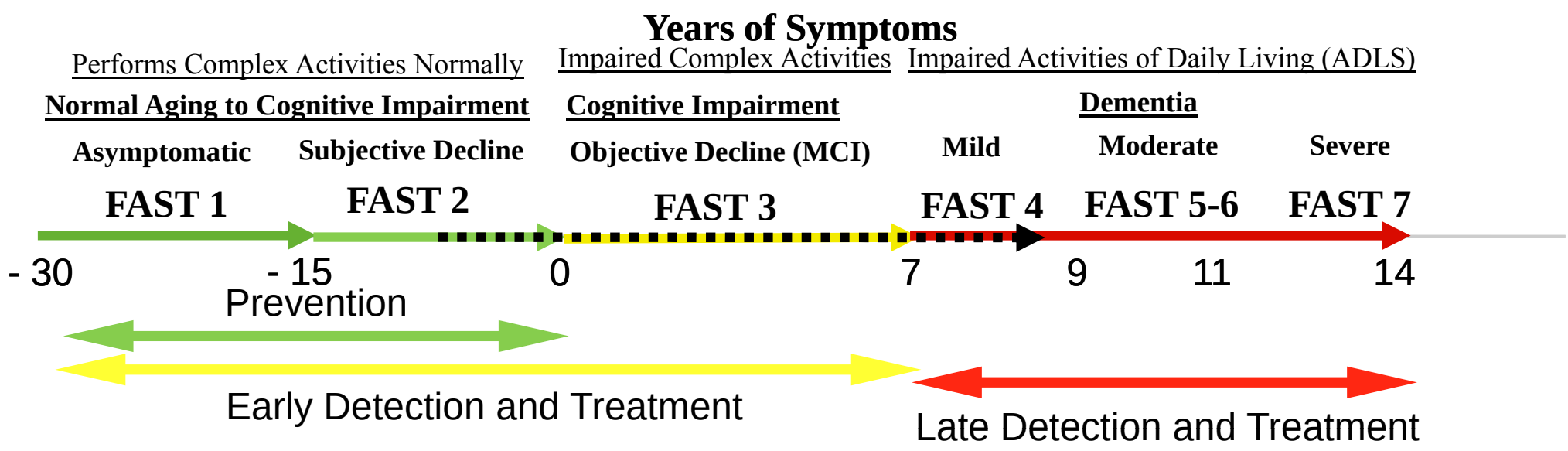
The current state of healthcare for Normal Aging, Mild Cognitive Impairment, & Alzheimer's Disease

William Rodman Shankle, MS MD FACP

Director, Alzheimer's Program, Hoag Neurosciences Institute
Neurologist, Shankle Memory & Cognitive Disorders Clinic
Research Fellow, UC Irvine Cognitive Science Department
Chief Medical Officer, Medical Care Corporation

The Spectrum of Cognitive Impairment [CI] & Dementia due to Alzheimer's Disease

Functional Assessment Staging Test (FAST)[1]



- In an unselected Primary Care Sample of Patients > 65 years old, The Prevalence of Cognitive Impairment During FAST Stage 1 was 14-20%, and During FAST Stages 1-3 Was 23-28%[5].
- The Iowa EPESE Population study showed that 2/3 of Non-Demented Subjects with CI Reported No Memory loss[6]

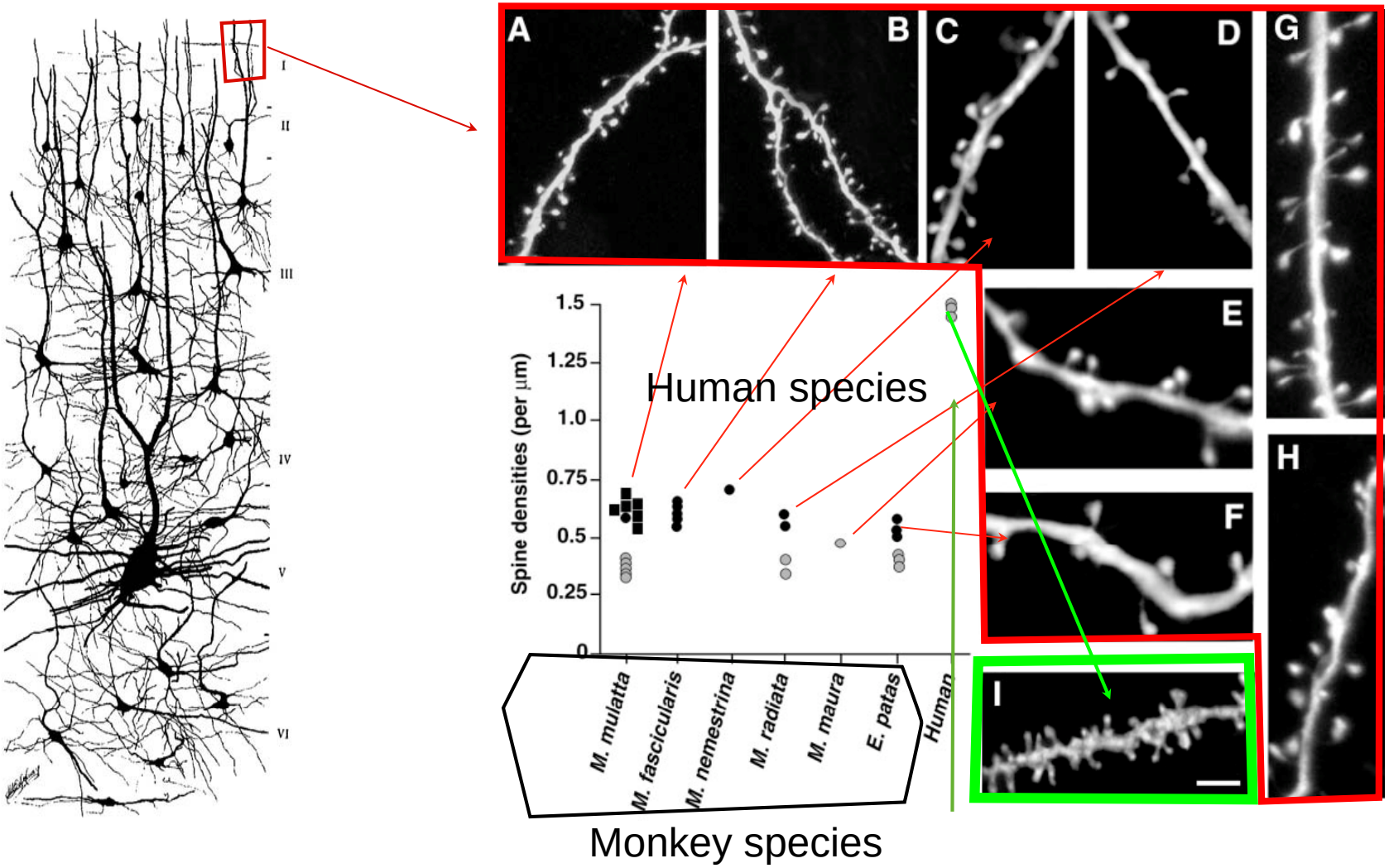
- AD Progression Can Be Delayed During the MCI & Dementia Stages by 25-33% & 50-60% respectively, Which delays progression by 5 to 11 years[3,4], and can Eliminate Institutionalization.

Reisberg, Geriatrics. 1986. 41(4):30-46
Rozzini et al. J Am Geriatr Soc 44: 1025-9, 1996.
Ferris et al. Gender Medicine. 2009. 6(2): 345-355
Atri et al., Alzheimer Dis Assoc Disord 2008;22:209–221
Trenkle et al. Journal of Alzheimer's Disease 11 (2007) 323–335
J.L. Purser, G.G. et al. J Am Geriatr Soc. 2006:54;335–338.

Brain Function Depends On Connectivity

Number of Brain Cell Connections: Constant Across Monkeys.

In Humans, Number of Connections Per Brain Cell Triples



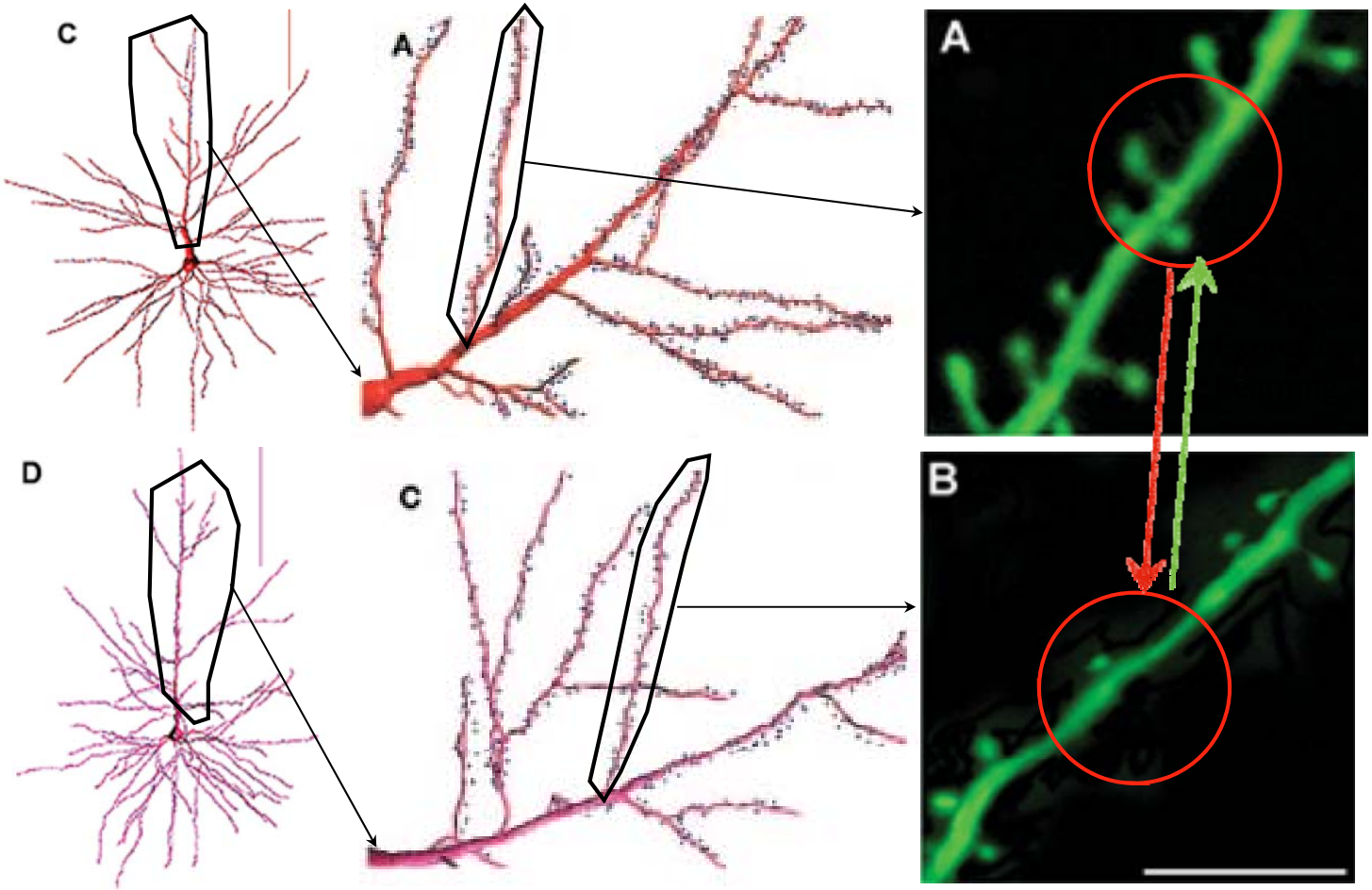
Aging Reduces Brain Connectivity Which Affects Brain Function

The Number of Brain Connections Declines with Age.
Physical Exercise and Continued Learning Can Forestall This Decline

Brain Cell (Neuron) **Neuron** **Connections**

Young

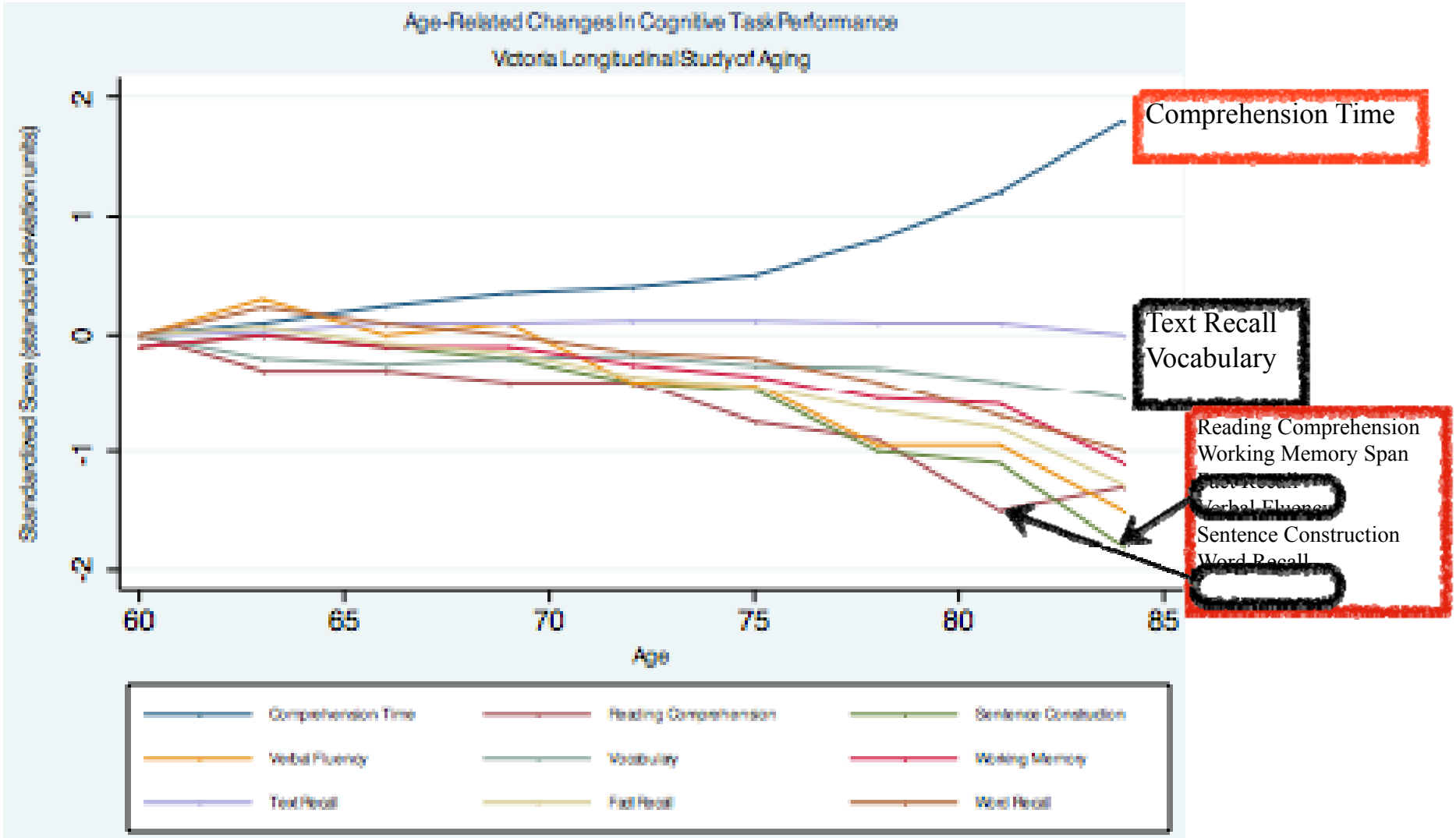
Old



Duan et al. Cerebral Cortex. 2003:13(9)

Many Cognitive Functions Decline With Age

List Learning (Word Recall) & Fact Recall Are Tests of Episodic memory Strongly Affected By Aging

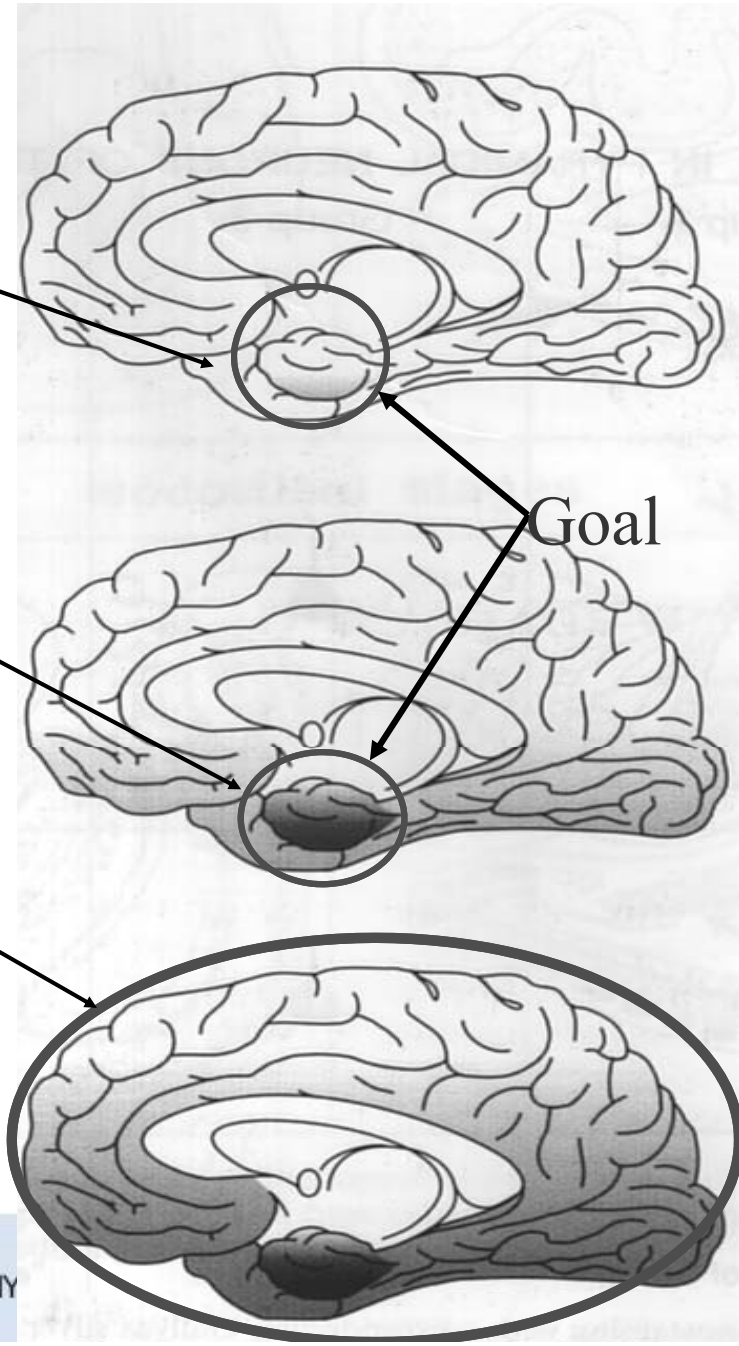


Hippocampal Pathology in AD
First Affects Episodic Memory

Pathological Stages I-II (10-50 years):
Hippocampal Damage can be compensated for.
No functional impairment. Possible Cognitive Impairment

Pathological Stages III-IV(7 years):
Hippocampal Damage can no longer be compensated for.
Objective Functional and Cognitive Impairment (**MCI**).
Episodic Memory loss impairs complex task performance[2].

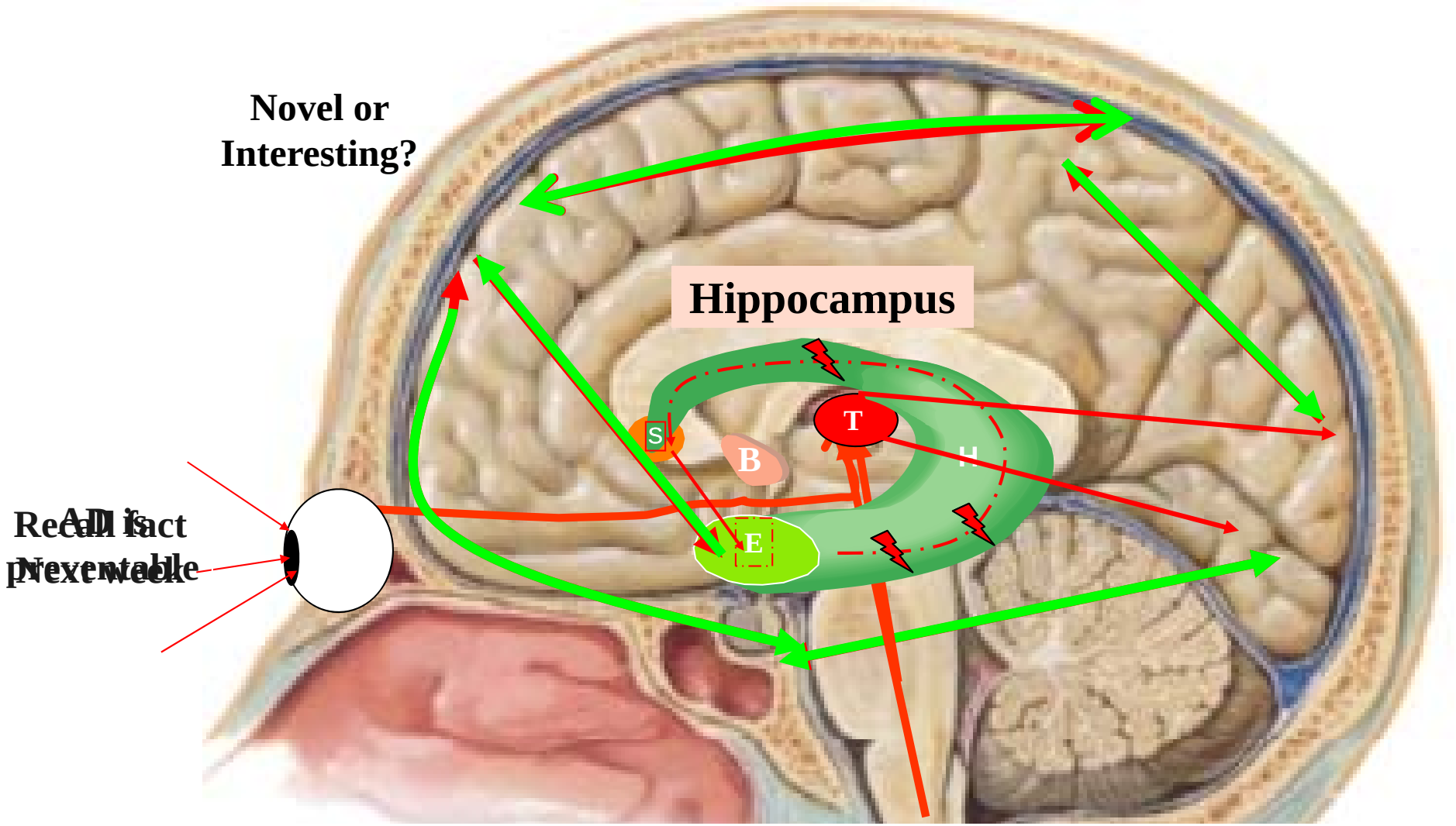
Pathological Stages V-VI (5-11 years):
Widespread hippocampal and cerebral cortical damage.
Dementia. Impaired Routine Activities of Daily Living.



[1]Braak & Braak, Acta Neurol. Scand Supp., 1996, 165:3-12
[2]Convit A et al. Neurobiol Aging 18: 131-8, 1997.

Episodic Memory Recalls Information Over the Period of 2 Minutes to 2 Weeks

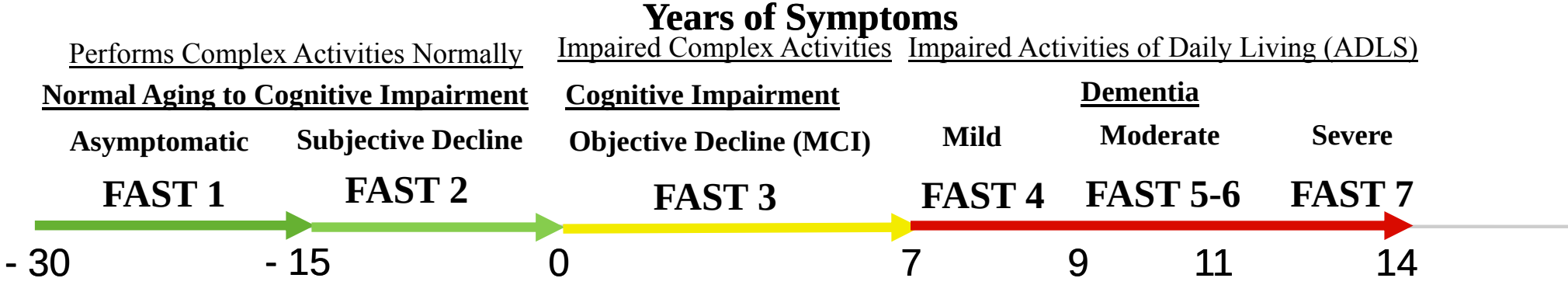
- Episodic Memory declines by 10%-20% With Aging[1].
- The Hippocampus Is Affected First in AD Because It's A Traffic Cop: It Condenses 6 Channels of Information Down Into 1 Channel.



[1]Memory Change in the Aged. Hultsch, Hertzog, Dixon & Small. Cambridge Univ Press, 1998: 34, 279

How Early Can We Detect Cognitive Impairment?

Functional Assessment Staging Test (FAST)[1]



Diagnostic Validity* OF MCIS By FAST Staging		
FAST Stages	Level of Cognitive Impairment	Kappa ± std. error[1]
FAST Stage 1	Asymptomatic (ACI)	0.87 ± 0.11
FAST Stages 1-3	ACI, SCI, MCI	0.91 ± 0.09
FAST Stages 1-4	ACI, SCI, MCI, Mild Dementia	0.92 ± 0.09

*Validity was determined by measuring agreement (kappa coefficient) between each screening test and clinical diagnosis group after removing chance agreements.

[1]Trenkle et al. Journal of Alzheimer's Disease 11 (2007) 323–335

What Are Clinicians Doing When Presented With Memory Concerns?

Clinician's Action	Sensitivity for MCI[1]	Specificity for Normal	Accuracy[1]
Attribute To Aging	0%	100%	?
Prescribe Aricept (No effect)	80%	20%	?
AD8 Questionnaire[5]	68%	90%	88%
MMSE[1]	22–27%	95%	51-72%
Clock Drawing[1]	9–14%	95%	43-64%
MOCA[3,4]	64-89%	50-84%	79-94%
MRI Hippocampal Volume[2]	70%	100%	66-72%
FDG PET Hippocampal Activity[2]	69%	100%	78%
Neuropsychology Referral	?	?	?
MCI Screen (EMST)[1,2]	86–96%	95-100%	96-97%

1 Frenkle et al. Journal of Alzheimer's Disease 11 (2007) 323–335
2 Cho et al. American Journal of Alzheimer's Disease & Other Dementias. 2008. 23(2): 162-6.
3 Hoops S et al. Neurology. 2009;73(21):1738-45.
4 Lee JY et al. J Geriatr Psychiatry Neurol. 2008;21(2):104-10.
5 Ryu et al. Alzheimer Dis Assoc Disord. 2009;23(4):371-6.

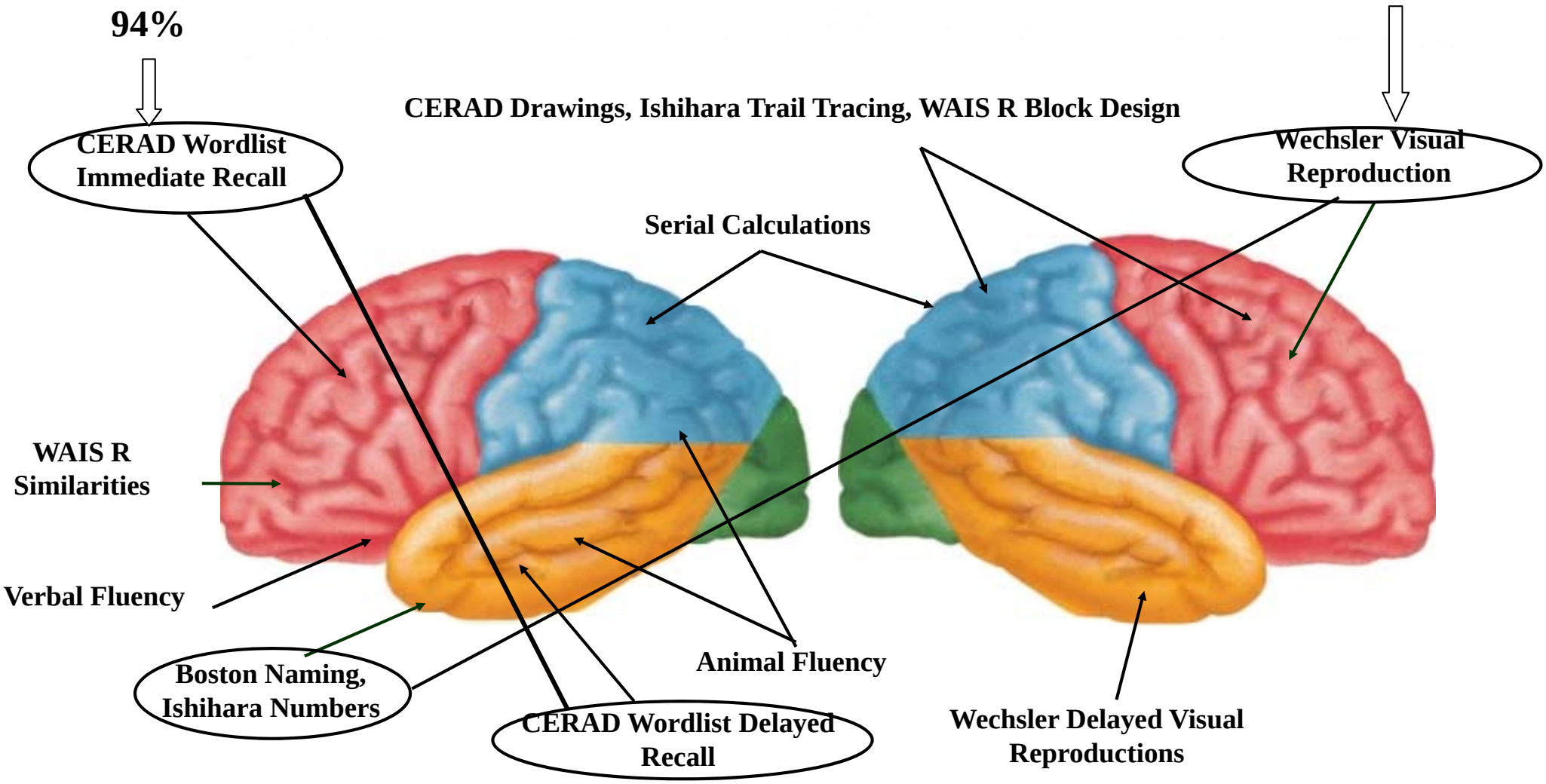
Identifying The Most Sensitive Early Detection Tests:
The CERAD Wordlist Best Discriminates Normal Aging from Mild Cognitive Impairment (N=100).
No Other CERAD Test Statistically Improves This Discrimination

MMSE, Full Scale IQ, Premorbid Verbal IQ

6% N.S.

94%

CERAD Drawings, Ishihara Trail Tracing, WAIS R Block Design



Developing The EMST (MCIS) Measurement Technology: Memory Patterns

Raw CWL Data Matrix of Recalled and Forgotten Words (eg: 0010101101)

Correspondence Analysis[1] (Multivariate Gaussian-Distributed Optimal Patient & Word Score Vectors)

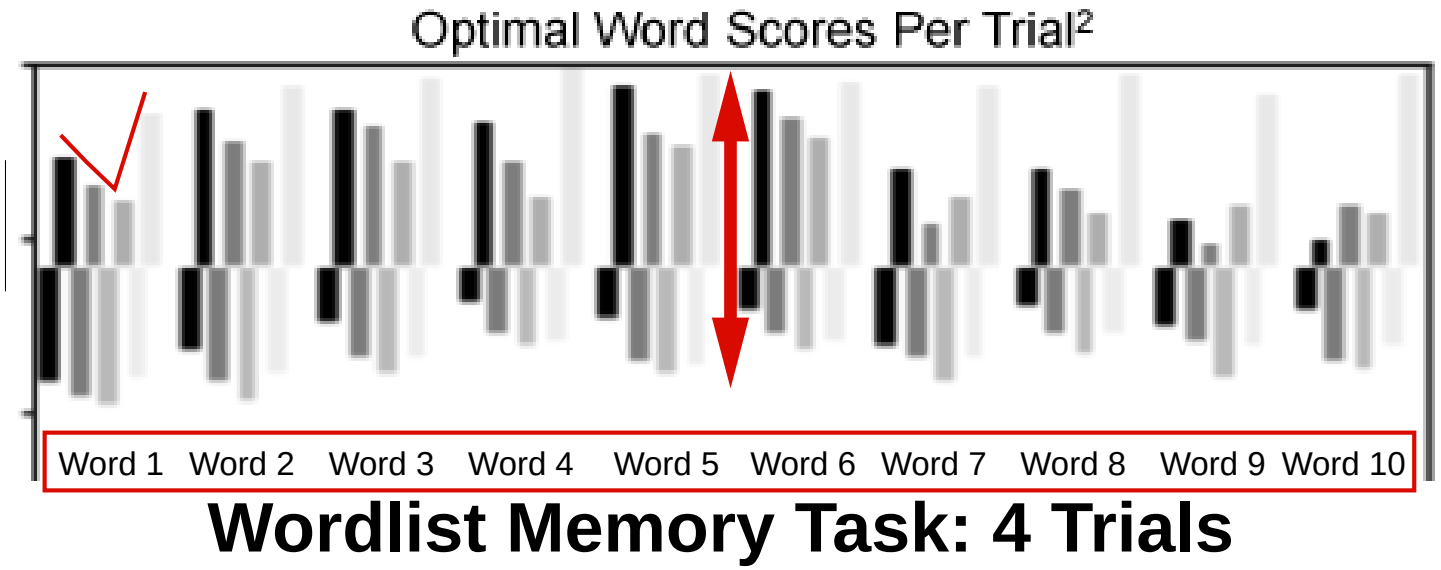
- Logistic Regression
- ROC Curve Analysis
- Age-Specific Prevalence

Classification algorithm & Memory Performance Index **(MPI)** scaling

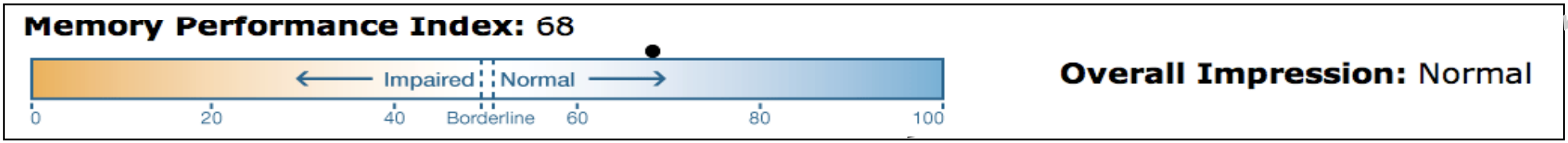
[1]This method explains the maximum possible amount of the raw data's variance for the class of linear methods. In contrast to FA & PCA, Correspondence analysis accounts for differences due to heterogeneous samples.

Optimal Scores Vary By:

- List Position
- Exposure Frequency
- Delay
- Being Recalled or Not

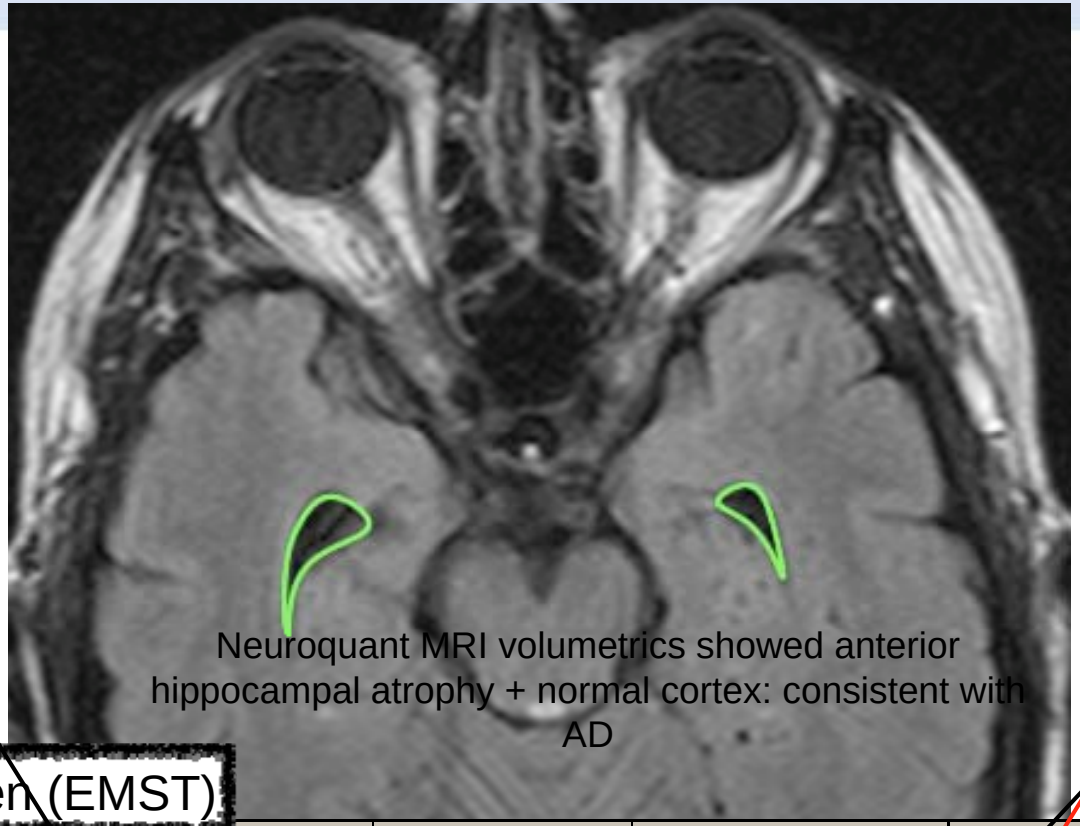


Wordlist Memory Task: 4 Trials



[1]Kendall & Stuart, The Advanced Theory of Statistics. 1961.
[2]Shankle et al. PNAS 2005.

MCI, Hippocampal Atrophy And Episodic Memory Loss In AD



Neuroquant MRI volumetrics showed anterior hippocampal atrophy + normal cortex: consistent with AD

Cognitive Impairment

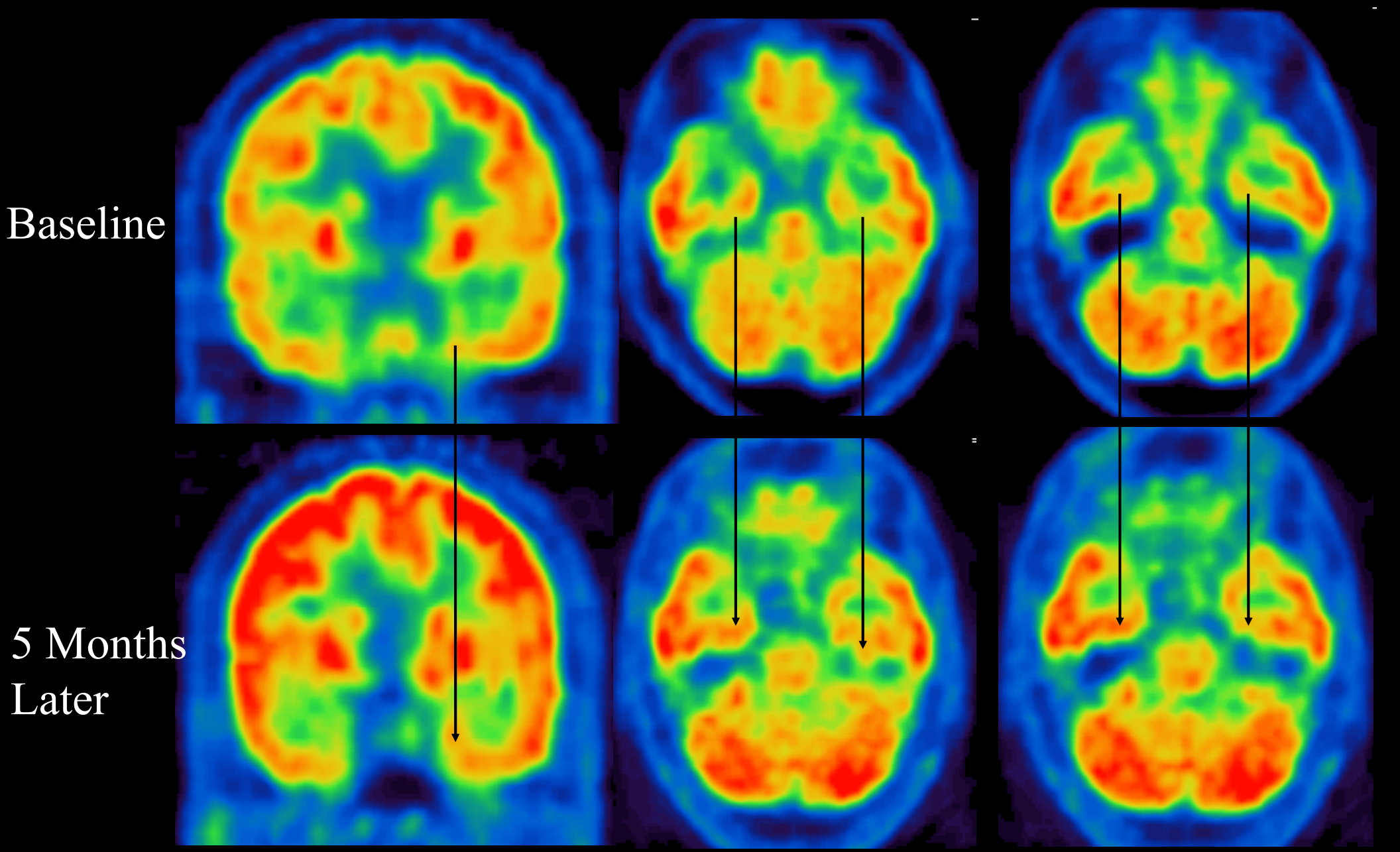
Overestimating memory ability is consistent with Alzheimer's disease

Impaired Delayed Retrieval & Storage is consistent with Alzheimer's disease

MCI Screen (EMST)

Date and Time	Overall Impression	Memory Performance Index [?]	Immediate Recall Trials [?]				Delayed Free Recall			Delayed Cued Recall [?]			Animal Recall [?]
			1	2	3	Σ	Est. [?]	Act. [?]	Δ [?]	Yes	No	Σ	
1/14/09 11:30 AM	Impaired	46	5	7	5	17	5	1	4.0	9	6	15	5

Pt MS: FDG PET Before vs. on Exelon



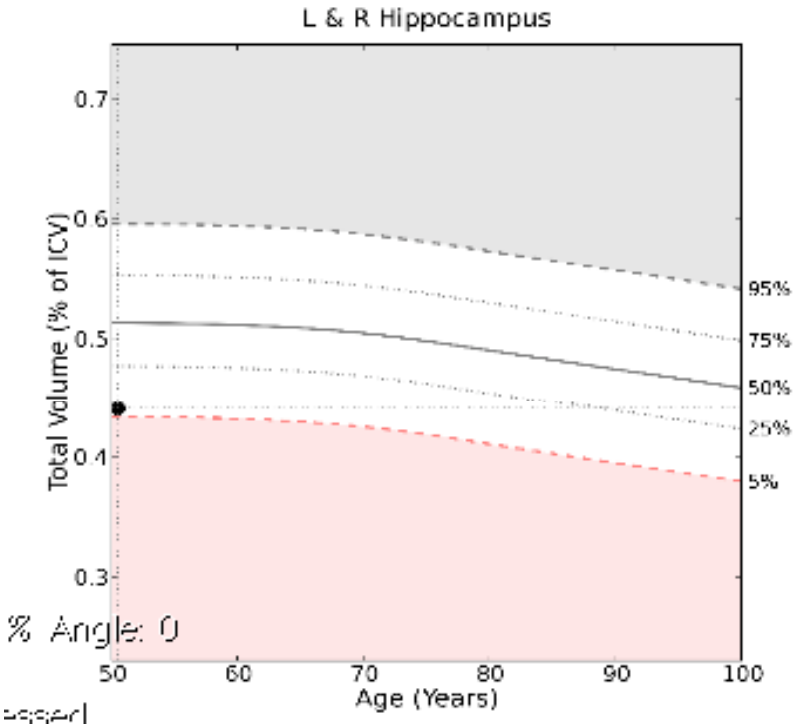
OC Vital Aging Program Impaired Case

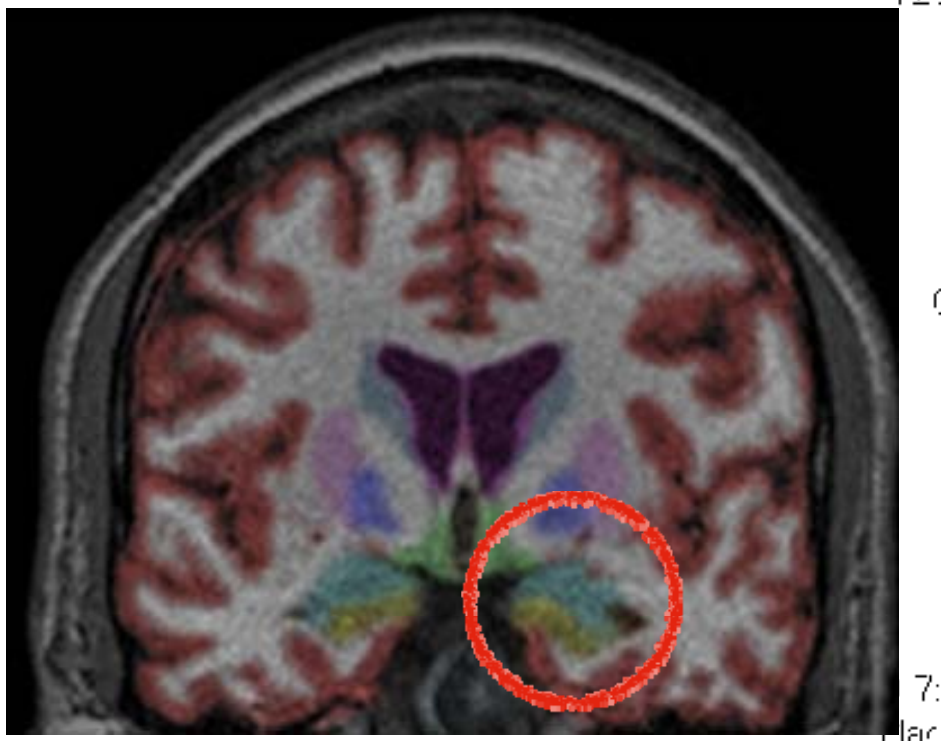
- 50 year old male having memory related difficulty at work.
- Had strong family history (4 members) of Alzheimer's Disease
- Took In-Person MCI Screen Test. Borderline, Suggestive.
- Lab workup identified an e2/e2 apoE genotype
- Hippocampal Volume was 2 std. dev. below age-adjusted mean.

Quantitative MRI Assessment

Very Mild Left Anterior Hippocampal Atrophy with Normal Temporal Horn Ventricles

Brain Structure	Volume (cm^3)	% of ICV (5%-95% Normative Percentile*)	Normative Percentile*
Hippocampi	8.10	0.44 (0.43-0.60)	7
Lateral Ventricles	37.14	2.02 (-0.13-2.95)	82
Inferior Lateral Ventricles	1.87	0.10 (0.05-0.23)	43
AGE-MATCHED REFERENCE CHARTS*			

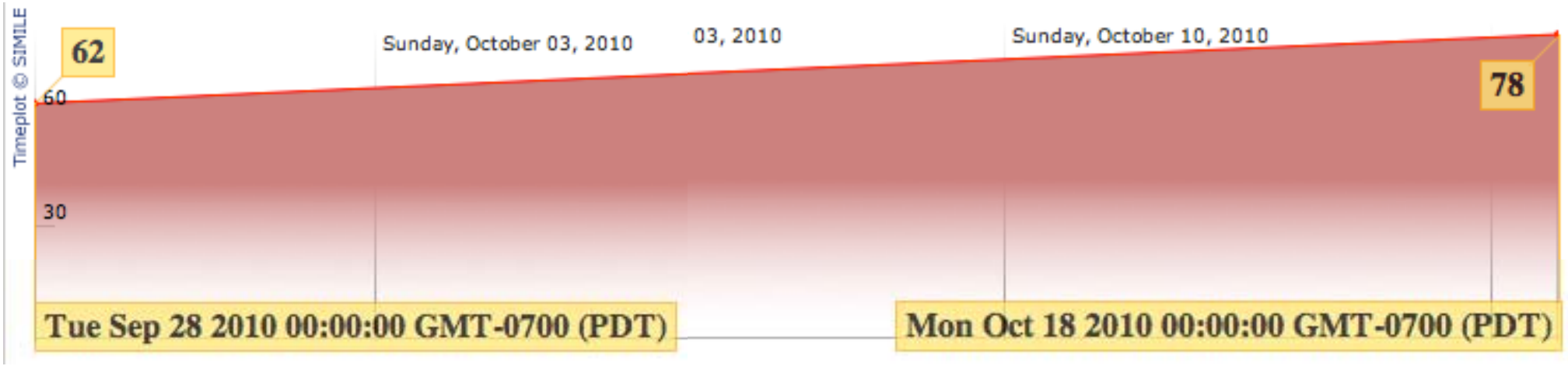




OC Vital Aging Program Impaired Case

- CSF study was done:
- p-tau181 = 23.5, <61 pg/ml (non-diagnostic for AD)
- Abeta42 was 468, low (supportive of AD).
- Abeta42/Total Tau Index = 1.14, borderline for AD
- Started on Treatment (Exelon, then Namenda).
- Spouse counseled at Alzheimer's Family Services Center
- Repeat MCI Screen showed marked improvement.
- Functioning Much Better at Work

MCI Screen Results at OCVAP Baseline Testing & On Treatment



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			1	2	3	Σ	Est. [?]	Act. [?]	Δ [?]	Yes	No	Σ	
9/28/10 12:54 PM	Normal	62	5	5	6	16	4.5	3	1.5	8	9	17	8
10/18/10 4:20 PM	Normal	78	7	8	9	24	8	8	0.0	10	10	20	9

On Exelon Patch, 9.5 mg

What Happens To Persons with MCI?

Published Rates of MCI In Persons >65 Years Old Range From 5%-15% Per Year

- At 5% per year, all patients will be demented in 20 years
- At 15% per year, all patients will be demented in 7 years
- Virtually everyone who develops MCI of a progressive nature will become demented if not detected early and effectively treated

DELAYING ALZHEIMER'S PROGRESSION

Combined Therapy Delays Functional Decline at Every Clinical Stage of AD

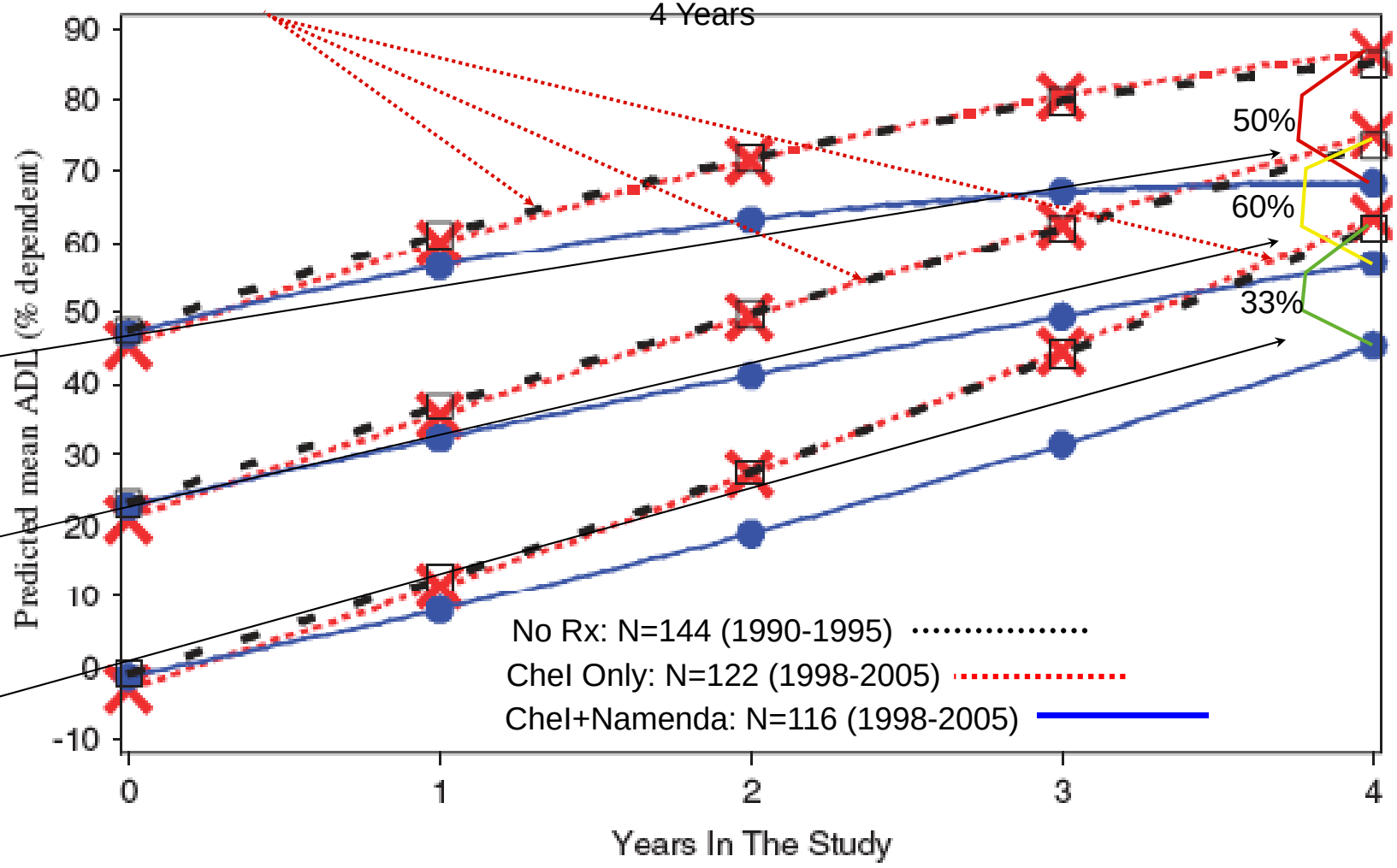
Cholinesterase Inhibitors Alone (Predominantly Effect of Aricept) Do Not Delay AD Progression Over 4 Years

Starting At:

50% Impairment = Moderate Dementia

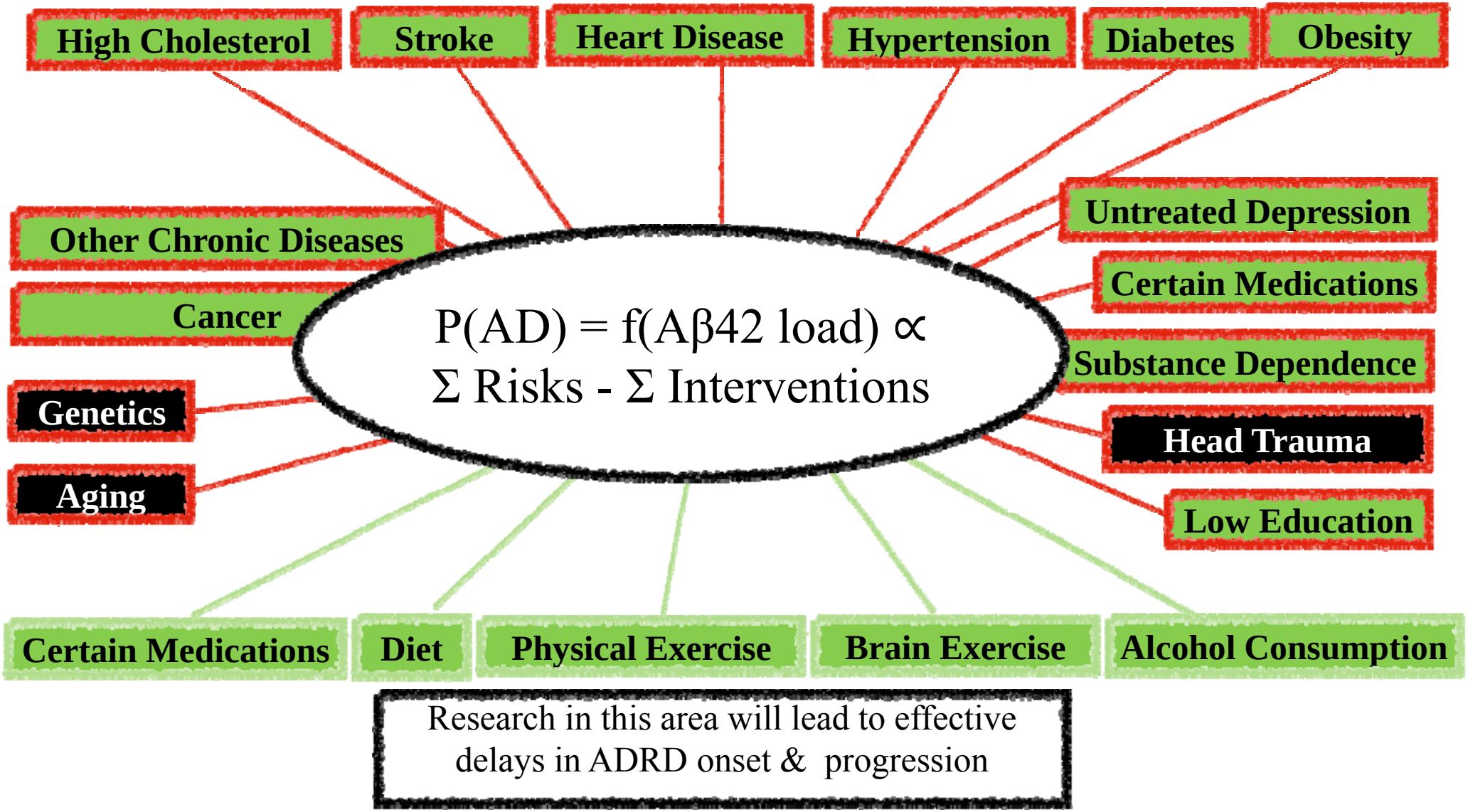
25% Impairment = Mild Dementia

No Impairment = MCI



Atri et al. Alzheimer Dis Assoc Disord 2008;22:209–221

Interventions The May Delay Onset & Progression of AD & Related Disorders (ADRD)



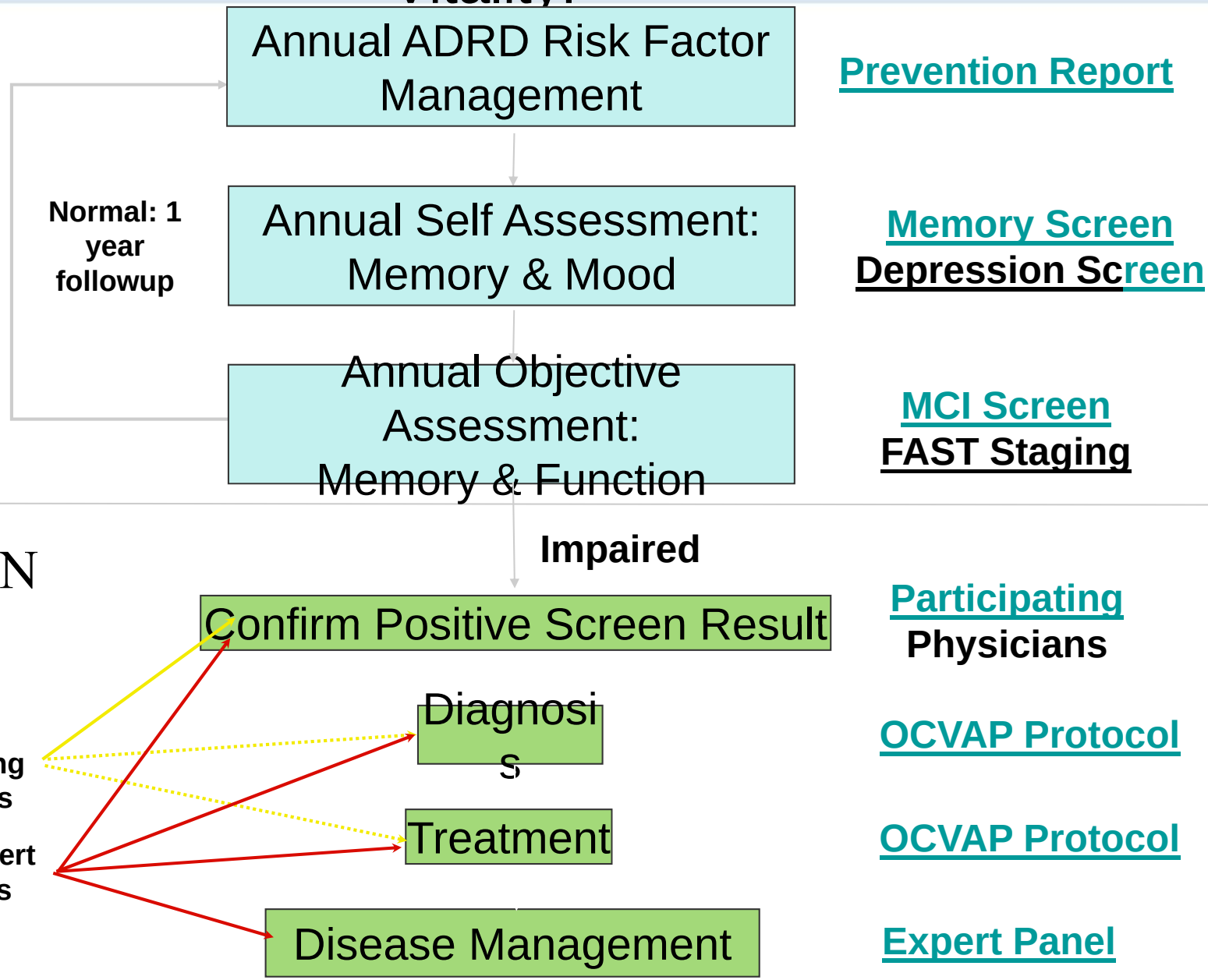
Research in this area will lead to effective delays in ADRD onset & progression

Maintaining Cognitive Vitality:

The Orange County Vital Aging Program

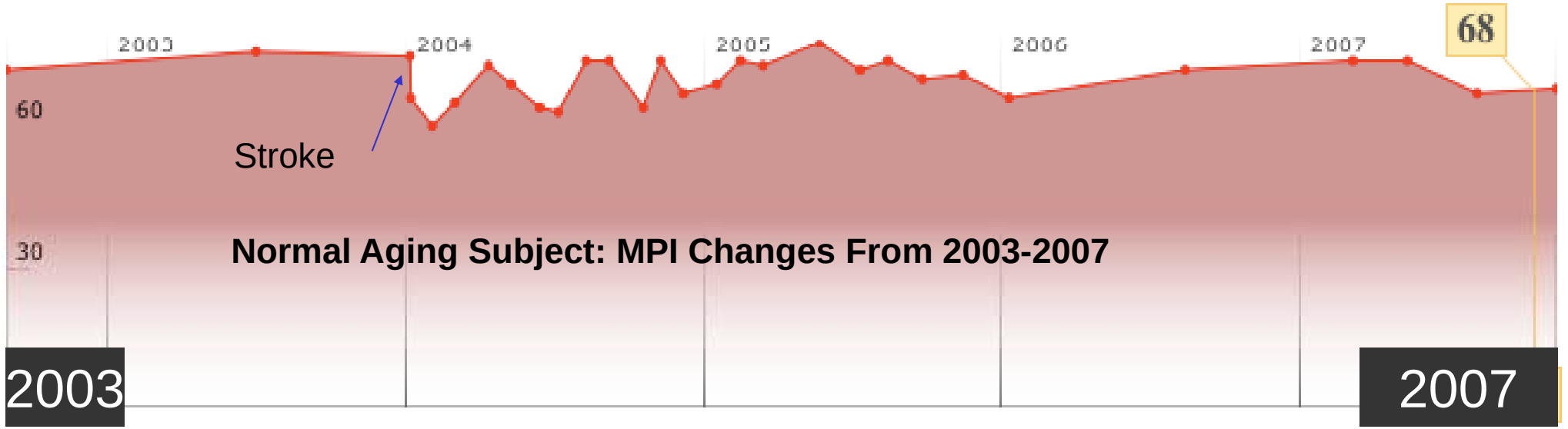
PUBLIC

PHYSICIAN



Early detection & Monitoring of Cognitive impairment due to lacunar infarction

Longitudinal Monitoring With MCI Screen



- This patient's only symptom of a stroke was a sudden onset of memory decline.
- Objective testing showed a sharp decline in cognition after this small stroke.
- Objective testing showed that cognitive recovery took place over 2 to 3 years.
- None of this would have been known without objective testing.

OC Vital Aging Program Goal: Individualized ADRD Prevention

Subjects

Risk Factors

Interventions

Biomarkers

Integrative Methods Research

Funding a 7 Year Study at $2 million/year can identify individualized ADRD Prevention

Commentary on "Developing a national strategy to prevent dementia: Leon Thal Symposium 2009." Methodologic considerations for preventing Alzheimer's disease by 2020

William R. Shankle* Alzheimer's & Dementia 2010:6;145-146