
Cognitive and Brain Aging: Using Imaging to Distinguish Potential Risks and Benefits of Estrogen

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CONTEXT: Estrogen-Containing HT Effects on Specific Cognitive Functions

- ◆ Age-related changes are observed in some but not all cognitive functions.
- ◆ Estrogens and other hormones may have different effects on specific aspects of cognitive functions.

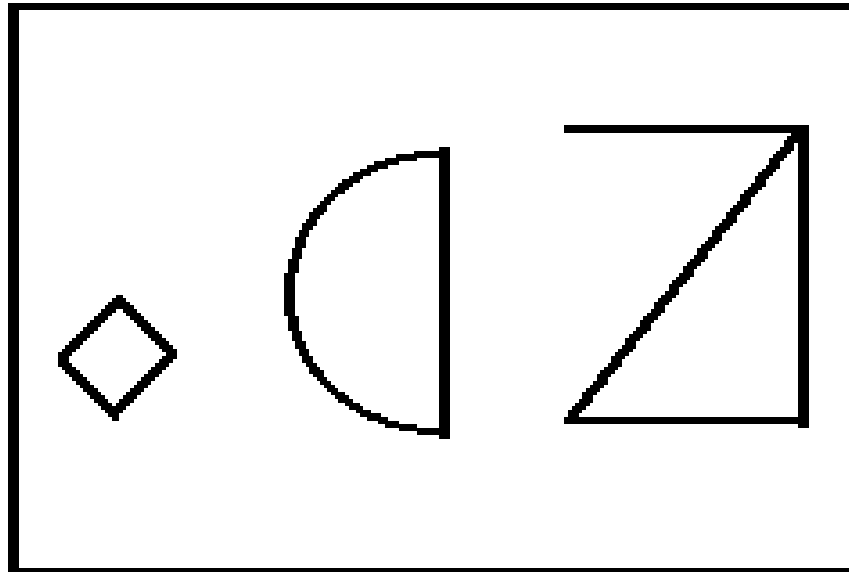
Baltimore Longitudinal Study of Aging

BLSA

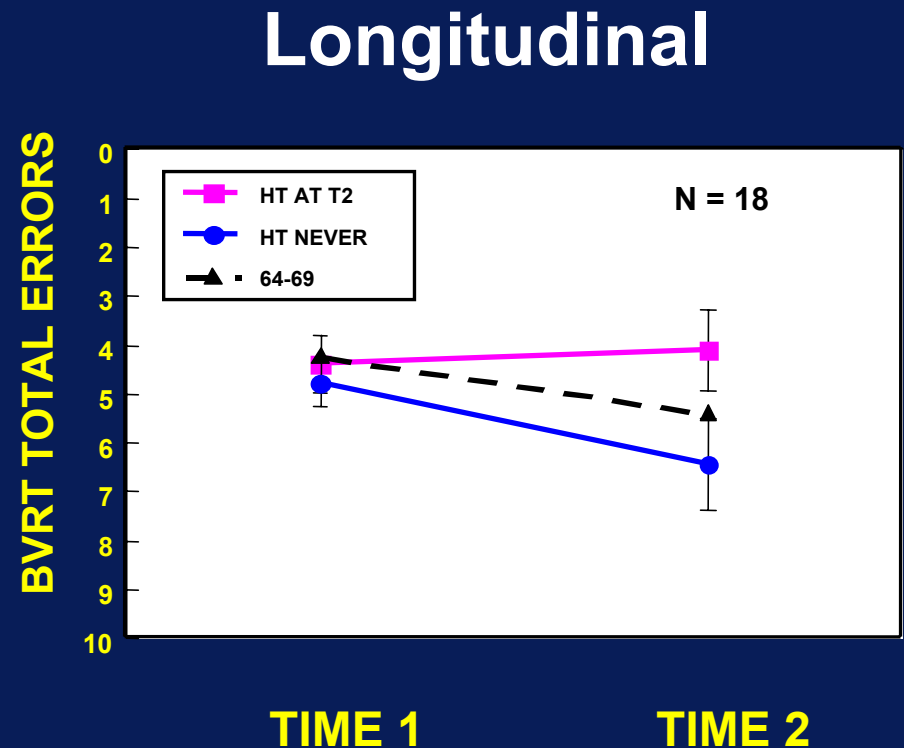
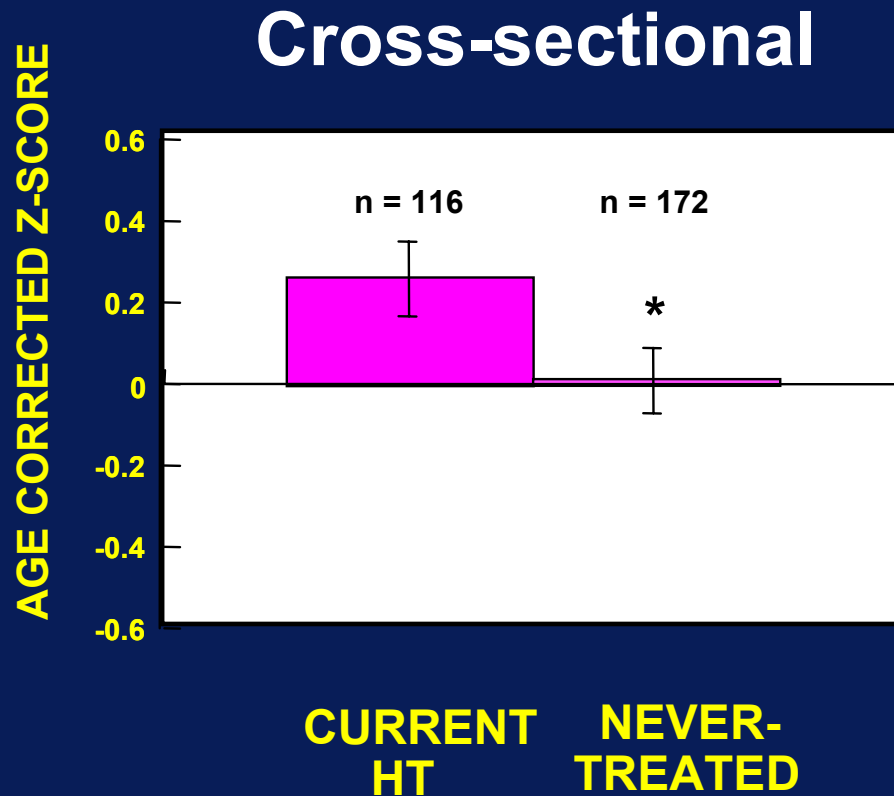
- ◆ Study initiated in 1958
- ◆ Women studied since 1978
- ◆ Highly educated community-dwelling sample
- ◆ NIA-IRP visits every 2 years for 2 1/2 days
- ◆ Behavioral and physical assessments
- ◆ Prospective diagnoses of dementia

Benton Visual Retention Test

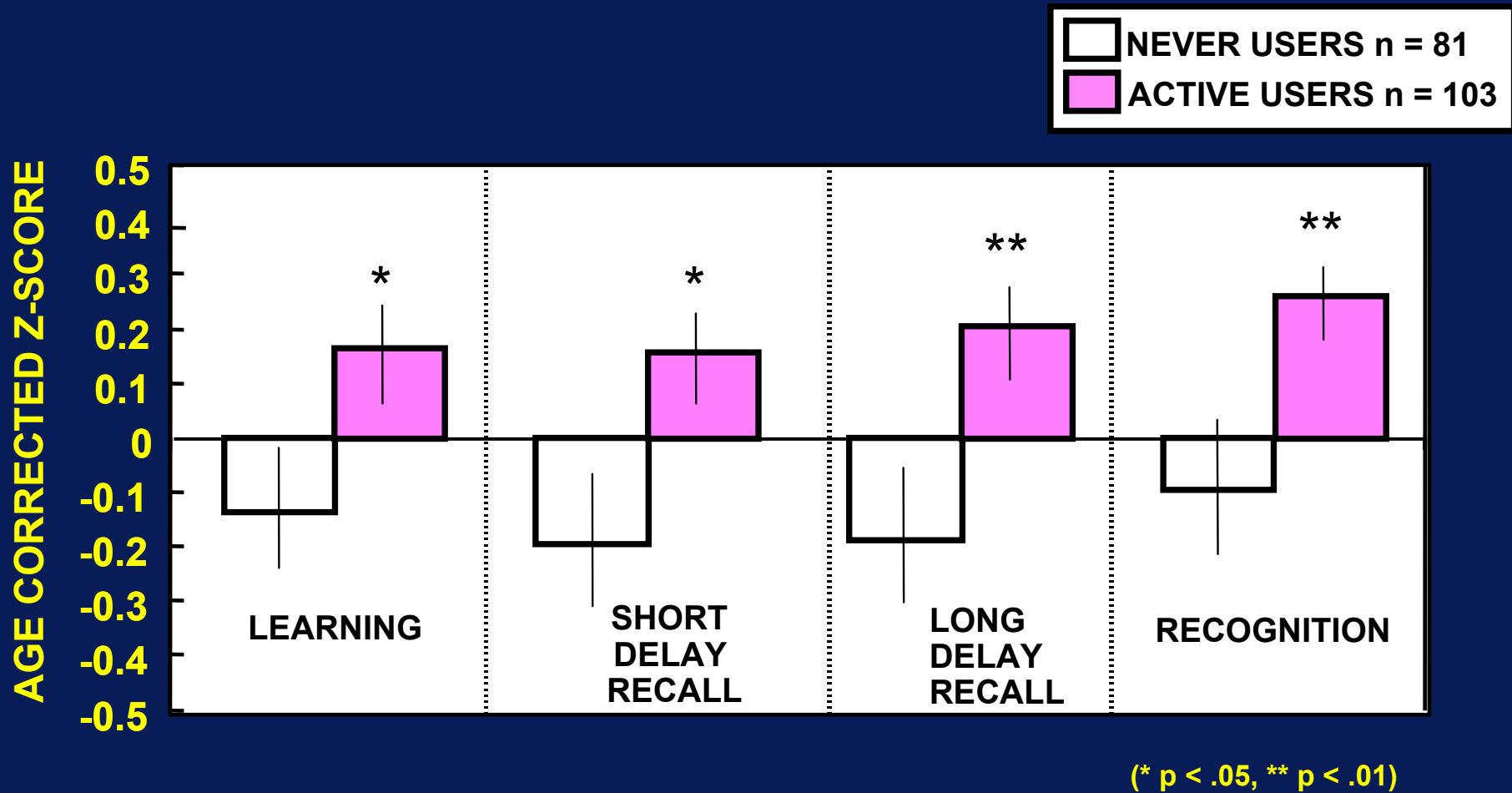
SAMPLE BVRT DESIGN



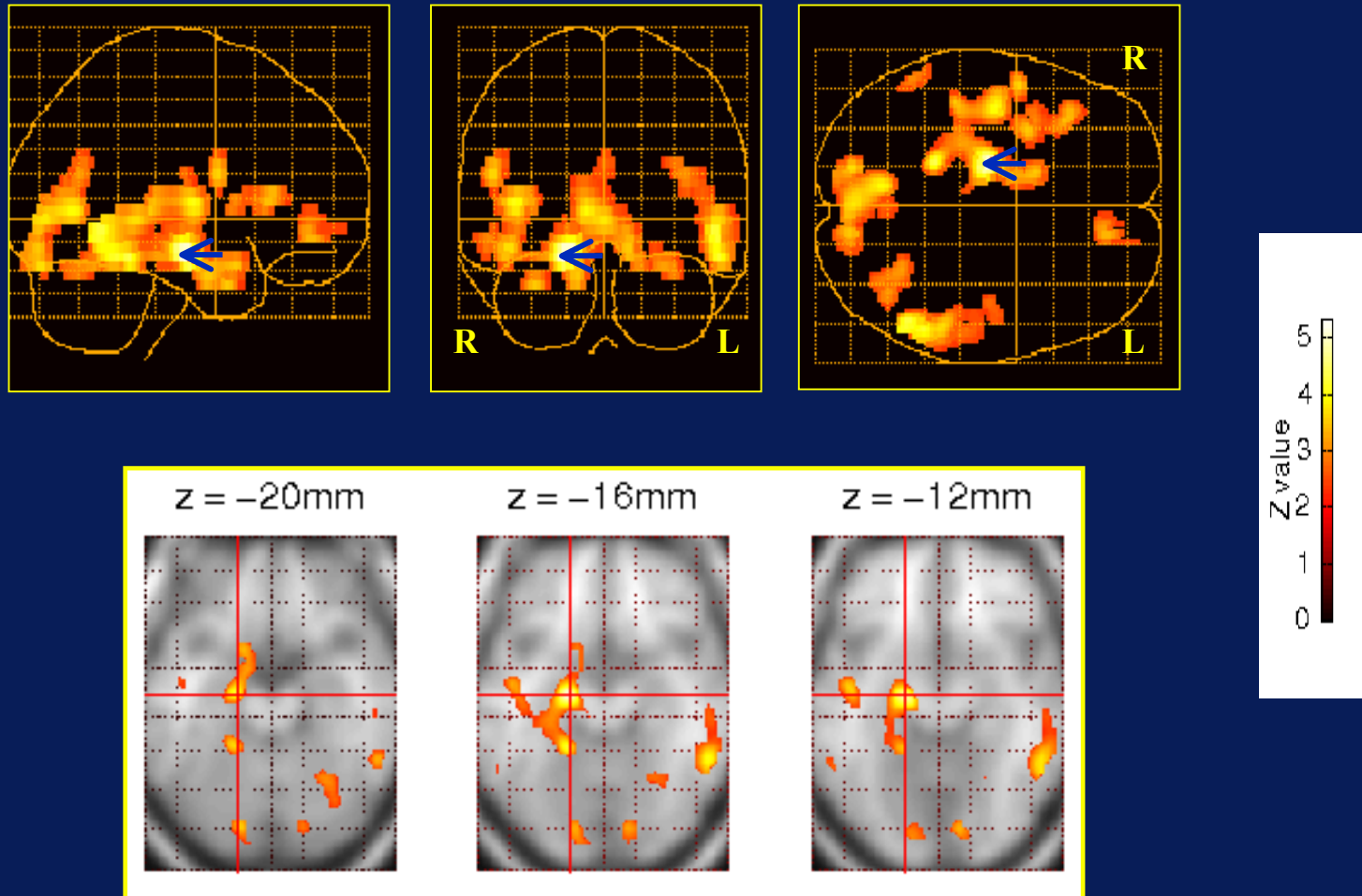
HT Users Have Better Figural Memory and Fewer Errors Over Time



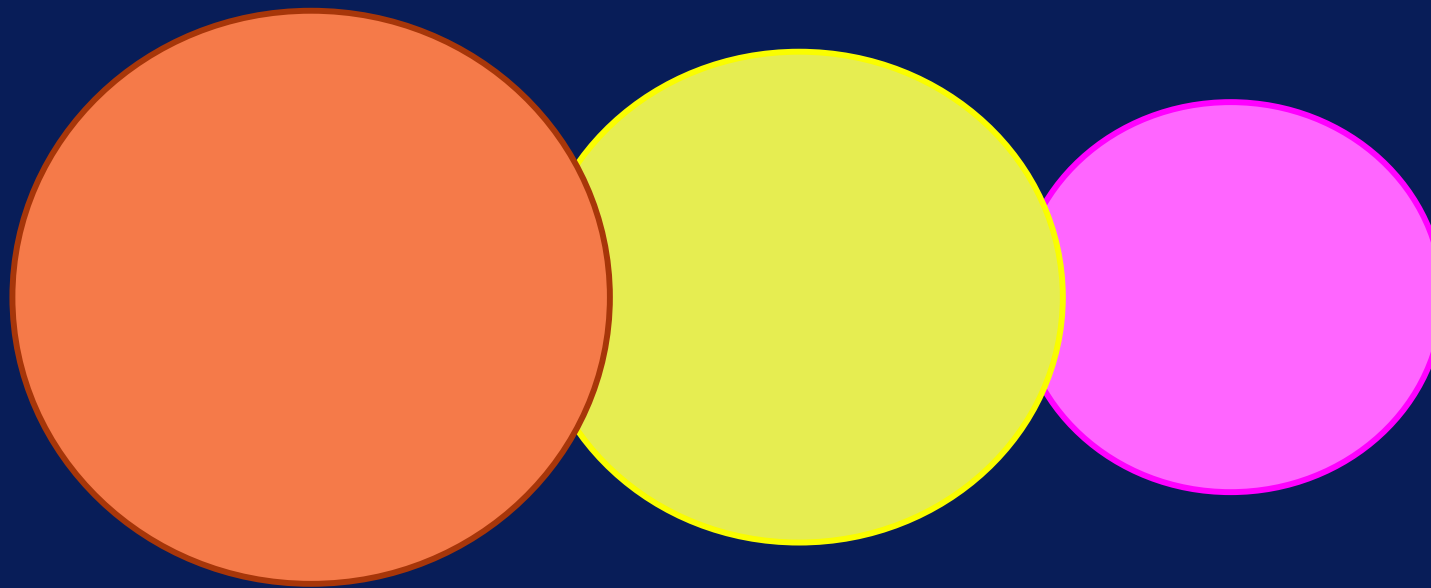
HT is Associated with Better Verbal Learning and Memory



HT Users Have Greater Longitudinal Increases in Hippocampal CBF over a 2-Year Interval



Randomized Trials in the WHI: Estrogen (CEE) Alone and Combination CEE + MPA



WHI
40 sites
N = 27,348

WHIMS
39 sites
N = 7480

WHISCA
14 sites
N = 2302

WHISCA: Women's Health Initiative Study of Cognitive Aging

- ◆ Effects of CEE alone and combination CEE + MPA assessed within the framework of a large-scale clinical trial
- ◆ Longitudinal assessments to evaluate within-individual change
- ◆ Emphasis on tests with demonstrated sensitivity to:
 - Age effects
 - Hormone effects
 - A broad range of performance

WHISCA Test Battery

Cognitive Function

Word Knowledge

Verbal Fluency

Figural Memory

Verbal Memory

Attention and

Working Memory

Spatial Ability

Motor Speed

Affect

Test

PMA Vocabulary

Letter and Category Fluency

Benton Visual Retention Test BVRT

California Verbal Learning Test CVLT

Digits Forward and Backward

Card Rotations

Finger Tapping

PANAS Positive and Negative Affect

Geriatric Depression Scale GDS

CEE + MPA Subtrial (N = 1416)

Sample Characteristics of WHISCA

	Placebo (726)	E + P (690)
Age at WHISCA Enrollment (yrs)	73.86 (3.8)	73.69 (3.6)
Time from WHI Randomization	3.0 (0.7)	3.0 (0.7)
Follow-up period (yrs)	1.36 (0.6)	1.33 (0.6)
Education (% \geq college grad)	34.5	36.0
Race (n, %white)	673 (93.0)	632 (91.6)
WHI baseline 3MS	96.15 (3.6)	96.24 (3.5)
% of Eligible Women	68	68

WHISCA assessments completed prior to termination of study medications on July 8, 2002

	Placebo	CEE + MPA
	N	N
Initial Assessment	726	690
One-year follow-up	673 (92.7%)	636 (92.2%)
Two-year follow-up	320 (44.1%)	291 (42.2%)

WHISCA Initial Assessment: CEE + MPA Effects on Specific Cognitive Functions

Tapping Nondom

Tapping Dom

Card Rotations

Digits Backward

Digits Forward

CVLT Delay

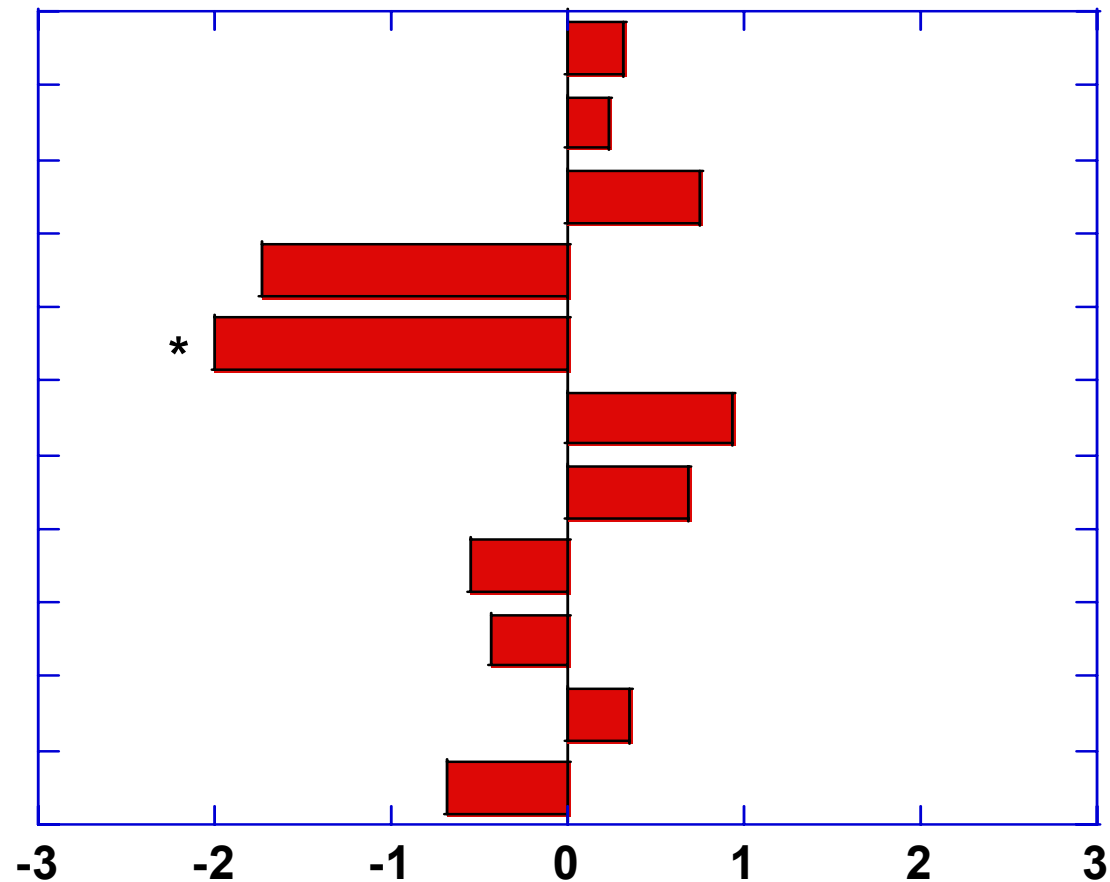
CVLT Imm

BVRT

Category Fluency

Letter Fluency

Vocabulary

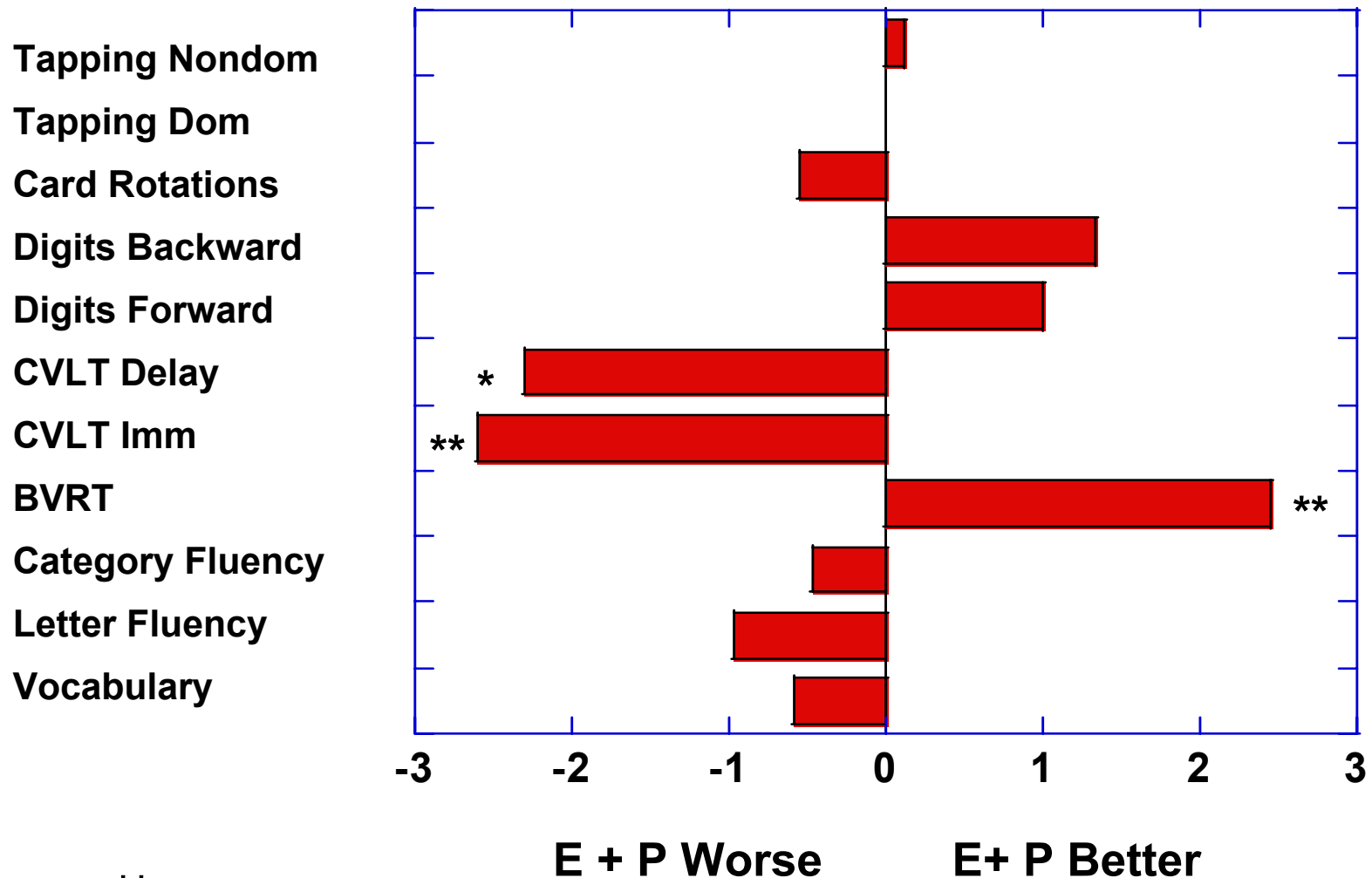


* $p \leq 0.05$

E + P Worse

E+ P Better

Annual Rates of Change: CEE + MPA Effects on Specific Cognitive Functions



* $p \leq 0.05$; ** $p \leq 0.01$

WHISCA CONCLUSIONS

- ◆ Combination HT may have different effects on different cognitive functions.
- ◆ These effects are modest and are seen only after 4 to 5 years of treatment.
- ◆ Our understanding of the effects of HT on cognitive function is still evolving.

WHIMS/WHISCA vs. BLSA Studies

- ◆ **Age:** WHISCA women 7-10 years older than BLSA women
- ◆ **Timing of Initiation of HT:** Most BLSA women began HT during or shortly after menopause
- ◆ **Duration of treatment:** More than 40% of BLSA women used HT for 5 or more years
- ◆ **Regimen:** Variety of treatments in BLSA, with higher likelihood of E alone and cyclical E/P treatments

Reconciling WHIMS and WHISCA E + P Findings: Competing Risks and Cognition



Increased Risk for
Stroke and
Thromboembolic Events

Protect Against
Development of AD
Pathology in Healthy
Women

MPA Antagonizes
Beneficial Effects of E
on CNS

Directions

- ◆ WHISCA CEE alone analysis continuing
- ◆ Continued follow-ups to assess long-term effects of HT in older women
- ◆ WHIMS MRI substudy to investigate joint effects of infarcts and atrophy on cognitive change
- ◆ Imaging to distinguish potential risks from benefits
 - Atrophy, vascular, and inflammatory changes with MRI
 - Blood flow and metabolism with PET and MRI
 - *In vivo* amyloid burden with PET

WHISCA – NIA R & D Contract N01-AG-1-2106

NIA

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Pauline Maki, PhD

Alan Zonderman, PhD

Wake Forest University

Sally Shumaker, PhD

Stephen Rapp, PhD

Mark Espeland, PhD

Laura Coker, PhD

WHISCA Sites

Gainesville

Milwaukee

Minneapolis

New York City

Rush Presbyterian-St. Lukes MC

Ohio State University

Stanford University

State University of New York-Stony Brook

University of California-Davis

University of California-LA

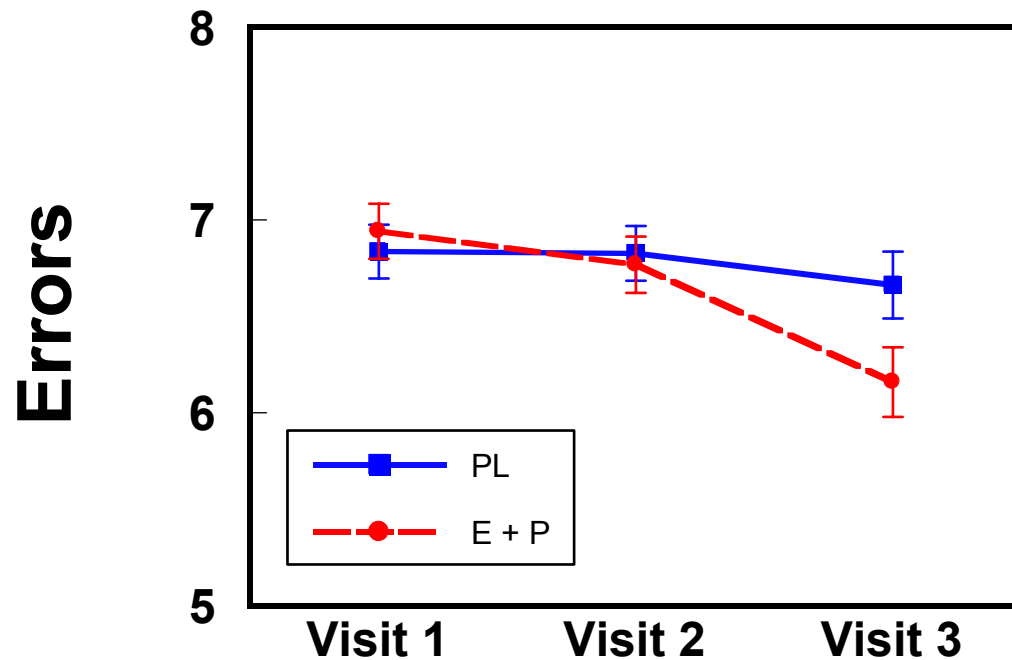
University of Iowa College of Medicine

University of Massachusetts-Worcester

University of Nevada

University of North Carolina

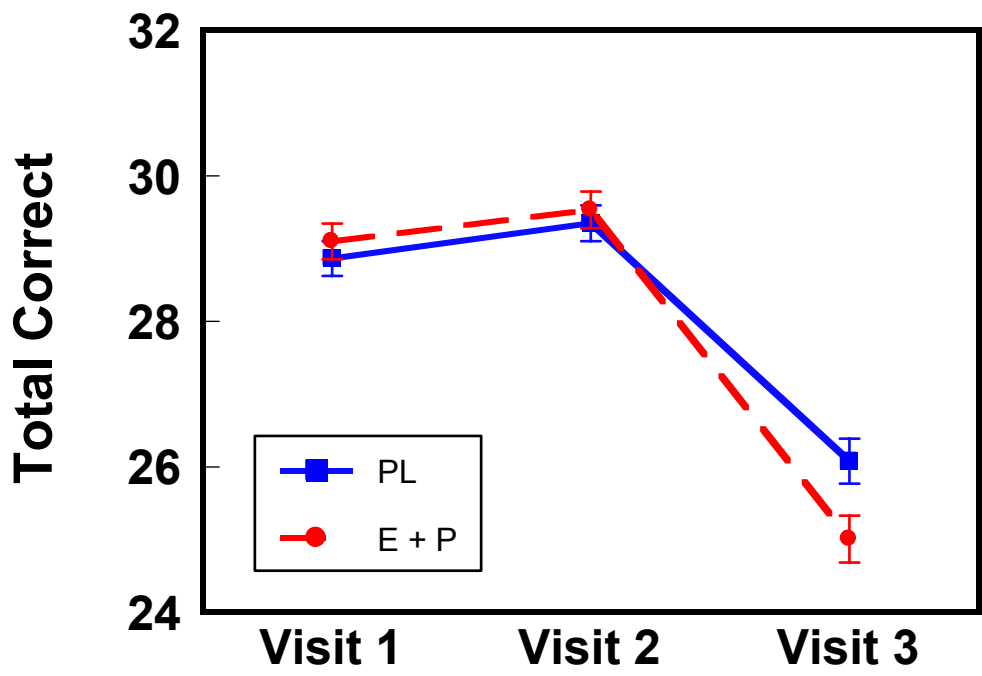
E + P is Associated with Decreases in BVRT Errors over Time



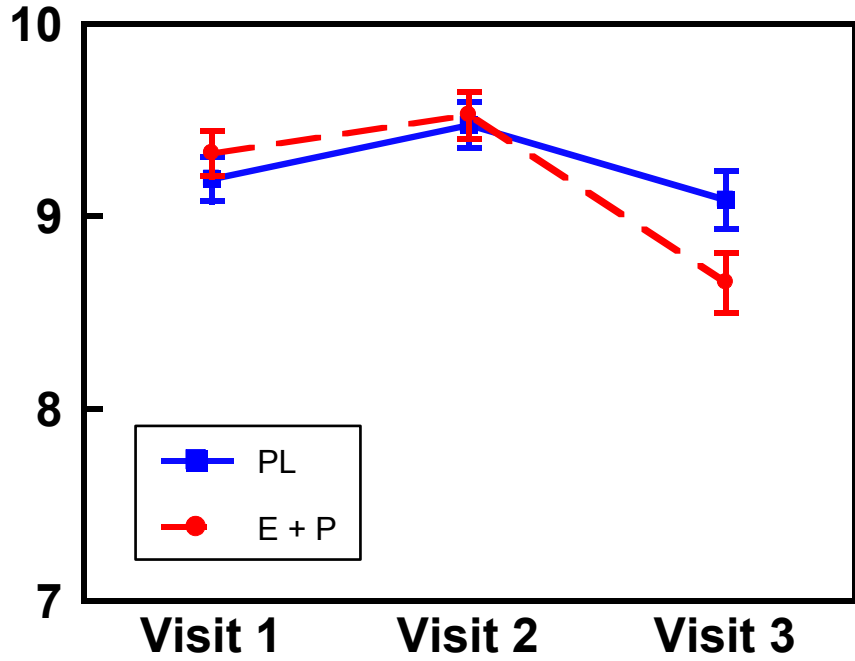
- Observed treatment effect of 0.27 errors per year vs. predicted treatment effect of 0.23 errors per year
- BVRT errors predict AD years prior to diagnosis

E + P is Associated with Greater Declines in CVLT Verbal Memory at Visit 3

Free Recall Imm Sum



Free Recall Delay



Visit	1	2	3	4	5
CVLT Form	a	a	b	b	a

WHISCA Diagnoses During Follow-up

- 11 cases of probable dementia (5 E + P, 6 Placebo)
- 19 cases of mild cognitive impairment (6 E + P, 13 Placebo)
- 14 incident strokes (9 E + P, 5 Placebo)

No Effect of E + P on Affect at WHISCA Enrollment or Rates of Change

Measure

Differences (E+P – PL)
at WHISCA Enrollment

Differences (E+P – PL)
in Rates of Change

Affect

PANAS Positive

0.02 (0.03)

0.01 (0.02)

PANAS Negative

0.01 (0.03)

-0.02 (0.02)

GDS

-0.03 (0.11)

0.04 (0.07)

Group Differences at WHISCA Enrollment and in Rates of Change (Intention-to-treat)

Measure	Differences (E+P – PL) at WHISCA Enrollment	Differences (E+P – PL) in Rates of Change
<i>Verbal Knowledge</i>		
PMA Vocabulary	-0.35 (0.51)	-0.10 (0.17)
<i>Verbal Fluency</i>		
Letter Fluency	0.23 (0.66)	-0.28 (0.29)
Category Fluency	-0.14 (0.33)	-0.09 (0.19)
<i>Figural Memory</i>		
BVRT	0.11 (0.20)	-0.27 (0.11)**
<i>Verbal Memory</i>		
CVLT Free	0.23 (0.34)	-0.52 (0.20)**
CVLT Delay	0.15 (0.16)	-0.23 (0.10)*

**p ≤ 0.01; * p ≤ 0.05

Group Differences at WHISCA Enrollment and in Rates of Change

Measure	Differences (E+P – PL) at WHISCA Enrollment	Differences (E+P – PL) in Rates of Change
<i>Attention and Working Memory</i>		
Digits Forward	-0.22 (0.11)*	0.06 (0.06)
Digits Backward	-0.19 (0.11)	0.08 (0.06)
<i>Spatial Ability</i>		
Card Rotations	1.07 (1.44)	-0.39 (0.70)
<i>Motor Speed</i>		
Finger Tapping – Dom	0.10 (0.42)	0.00 (0.21)
Finger Tapping – Non	0.11 (0.35)	0.02 (0.17)
<i>Affect</i>		
PANAS Positive	0.02 (0.03)	0.01 (0.02)
PANAS Negative	0.01 (0.03)	-0.02 (0.02)
GDS	-0.03 (0.11)	0.04 (0.07)