Combined Effects of Estradiol & Cortisol on Cognition

Laura Baker

Assistant Professor, Psychiatry & Behavioral Sciences
University of Washington School of Health Sciences

Geriatric Research, Education & Clinical Center
The Veterans Affairs Puget Sound Health Care System

Estrogen & the Brain

- Basic science literature continues to support numerous neuroprotective actions of estrogen (estradiol)
  - Actions that should theoretically protect against the development of Alzheimer's disease by
    - increasing neurotransmission & CBF
    - modulating various growth proteins
    - ameliorating of beta-amyloid neurotoxicity
- However, the benefits of estradiol for postmenopausal women are not consistently reported in clinical studies
  - Disparate results may relate to a number of factors
    - timing of HRT relative to menopause
    - type of estrogen administered & estradiol levels achieved
    - co-administration with a progestin

Estrogen & HPA Axis

- **Gonadal hormones influence reactivity of the hypothalamic-pituitary-adrenal axis to stress** (Lund et al. 2004; Shors 2006; Bowman et al. 2002)
  - **Stressed-induced impairments on cognition are ameliorated by estradiol administration in animal studies** (Bowman et al. 2002)
  - **Stress-induced hormonal response is exacerbated for estradiol-treated animals** (Lund et al. 2004; Burgess & Handa 1992)

Cortisol & Brain Function

- **Elevated cortisol is linked to impaired declarative memory, & impaired executive function** (Li et al., 2005; Birnbaum 2004)
- **Increased HPA axis activity may contribute to neurodegeneration & AD pathology in particular** (Peskind, Wilkinson, Petrie, Schellenberg, Raskind, 2001)

Cortisol …*PLUS* Estradiol

- **Acute stress & elevated cortisol IMPROVES associative learning in male rats but IMPAIRS performance in female rats** (Shors et al. 1998; Wood et al. 2001)
- **Sex differences in rat hippocampal spine density formation & opposite stress-induced consequences** (Shors et al. 2004)
- **Estradiol-treated ovariectomized rats vs. controls have lingering HPA axis sensitivity after a period of repeated stress** (Lunga & Herbert, 2004)
- **Cortisol levels climb with age** (van Cauter et al. 1996; Laughlin & Barrett-Connor, 2000)**; and in response to a cognitive challenge, levels rise MORE for older women than for older men** (Seeman et al. 2001)

EsCort Study: The Intent

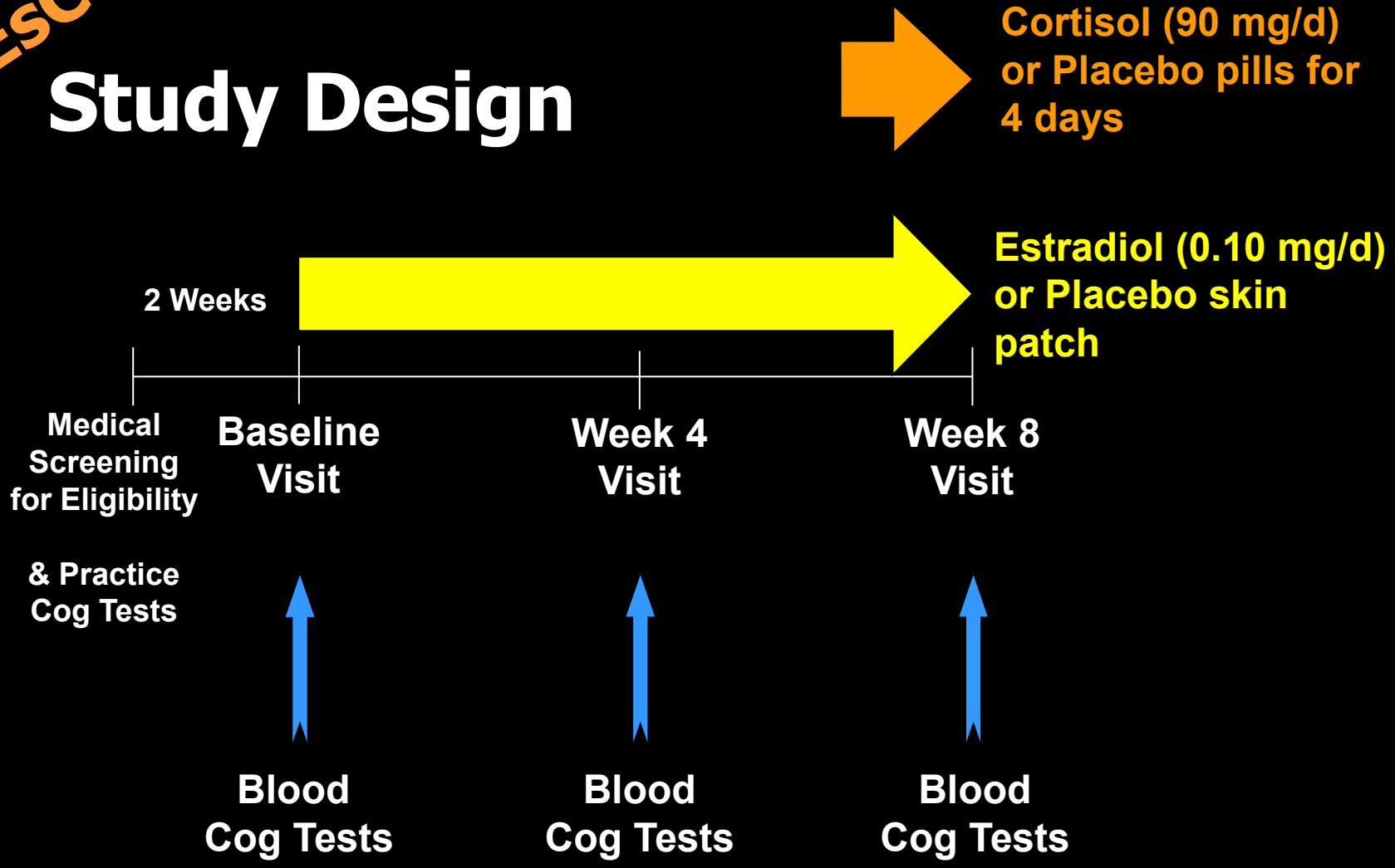
- To examine whether increased cortisol mediates cognitive response to estradiol for healthy postmenopausal women
- To examine the independent & combined effects of estradiol & cortisol on insulin-like growth factor (IGF) activity; an important growth factor not only for aging in general, but also for *aging* cognition
- To examine the influence of estradiol+cortisol on a peptide linked to the development of Alzheimer's disease

EsCort Study: Hypotheses

- Estradiol administration will have a beneficial effect on cognition
- Elevated cortisol will detrimentally affect cognitive performance
- Combined estradiol + cortisol administration will
  - attenuate estrogen-induced cognitive benefits
  - but … ameliorate cortisol-induced impairments

EsCort

Study Design



Cognitive Tests

Executive Function

- Stroop Color-Word Interference Test
- Self-ordered Pointing Test (SOPT)

Declarative Memory

- Story Recall
- Hopkins Verbal Learning Test
- Delayed Match-to-Sample
- Verbal Fluency

Blood Assays

- Cortisol (total, free, cbg)
- Estradiol
- IGF (total IGF-1, free IGF-1, IGFBP-3)
- Aβ40, Aβ42

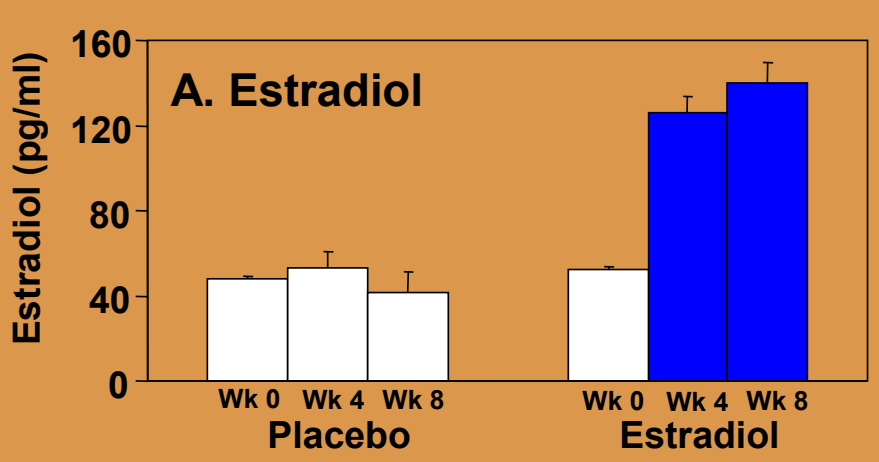
Estradiol lowers & cortisol raises IGF-1

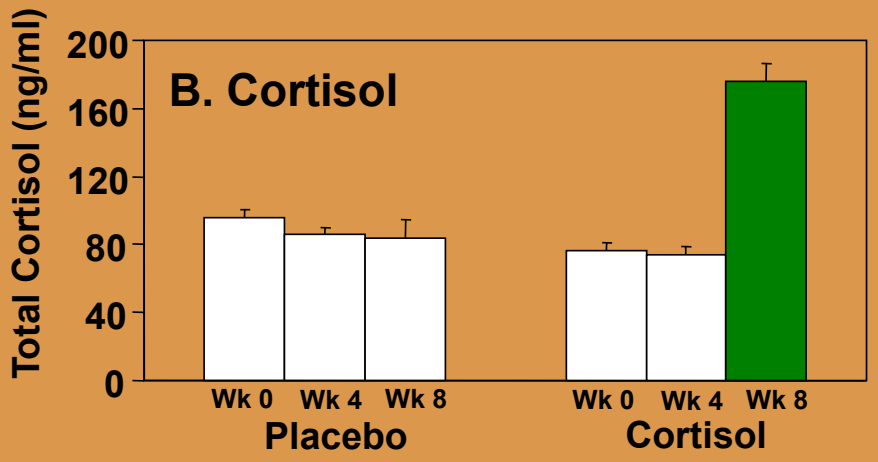
Increased IGF linked to reduced Aβ clearance

Subjects

	Placebo	Cortisol Only	Estradiol Only	Estradiol +Cortisol
N	10	10	10	9
Mean Age (sd)	70 (8)	72 (8)	74 (9)	71 (5)
Mean DRS (sd)	139 (2)	140 (2)	141 (2)	140 (2)
Mean BMI (sd)	28 (3)	29 (8)	27 (3)	29 (6)

Results


A. Estradiol
Estradiol (pg/ml)
160
120
80
40
0
Wk 0
Wk 4
Wk 8
Placebo
Wk 0
Wk 4
Wk 8
Estradiol


B. Cortisol
Total Cortisol (ng/ml)
200
160
120
80
40
0
Wk 0
Wk 4
Wk 8
Placebo
Wk 0
Wk 4
Wk 8
Cortisol

Cognitive Effects

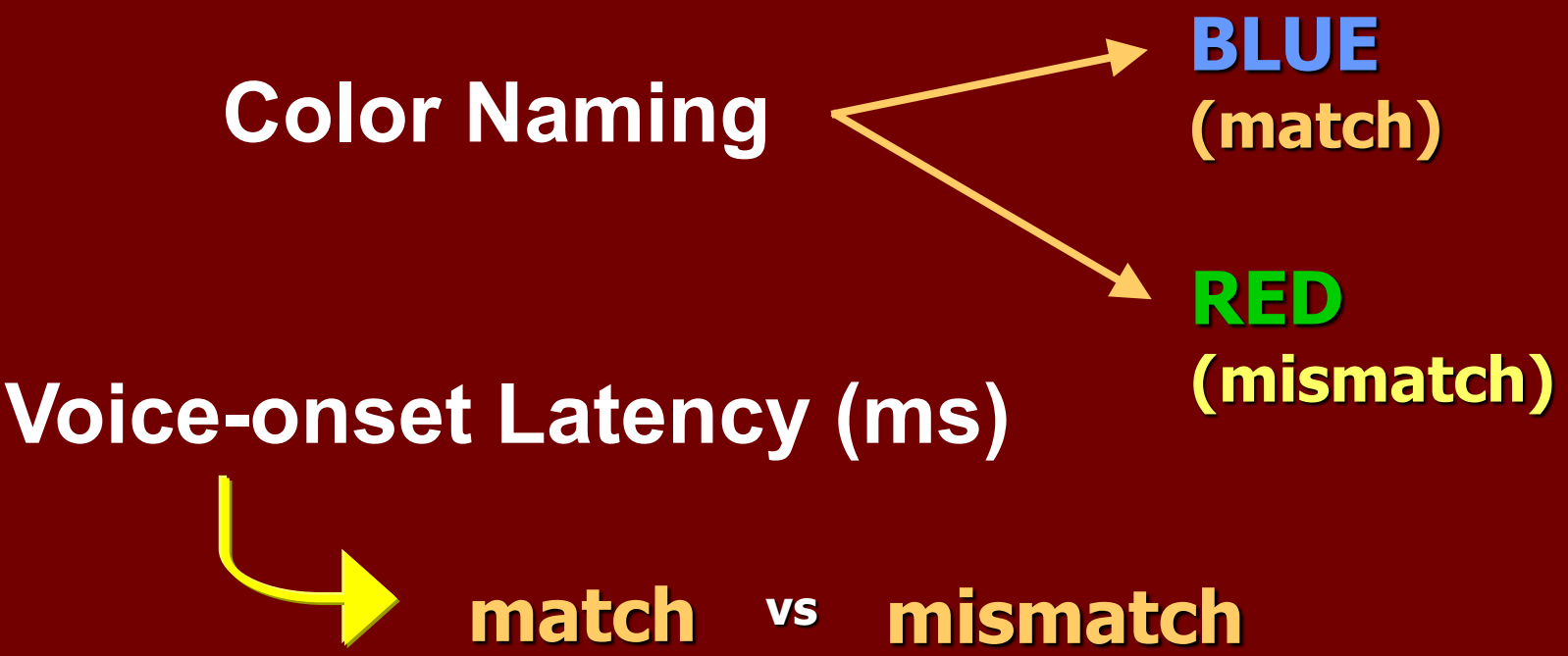
Stroop Color-Word Interference

GREEN	BLUE	RED	BLUE
BLUE	RED	GREEN	GREEN
YELLOW	GREEN	BLUE	RED
RED	BLUE	YELLOW	BLUE
BLUE	YELLOW	RED	YELLOW
YELLOW	RED	GREEN	YELLOW
RED	GREEN	YELLOW	BLUE
GREEN	BLUE	RED	GREEN
BLUE	YELLOW	GREEN	RED

Stroop Color-Word Interference

Stroop Color-Word Interference

~ Computer Administration ~



Name the Ink Color

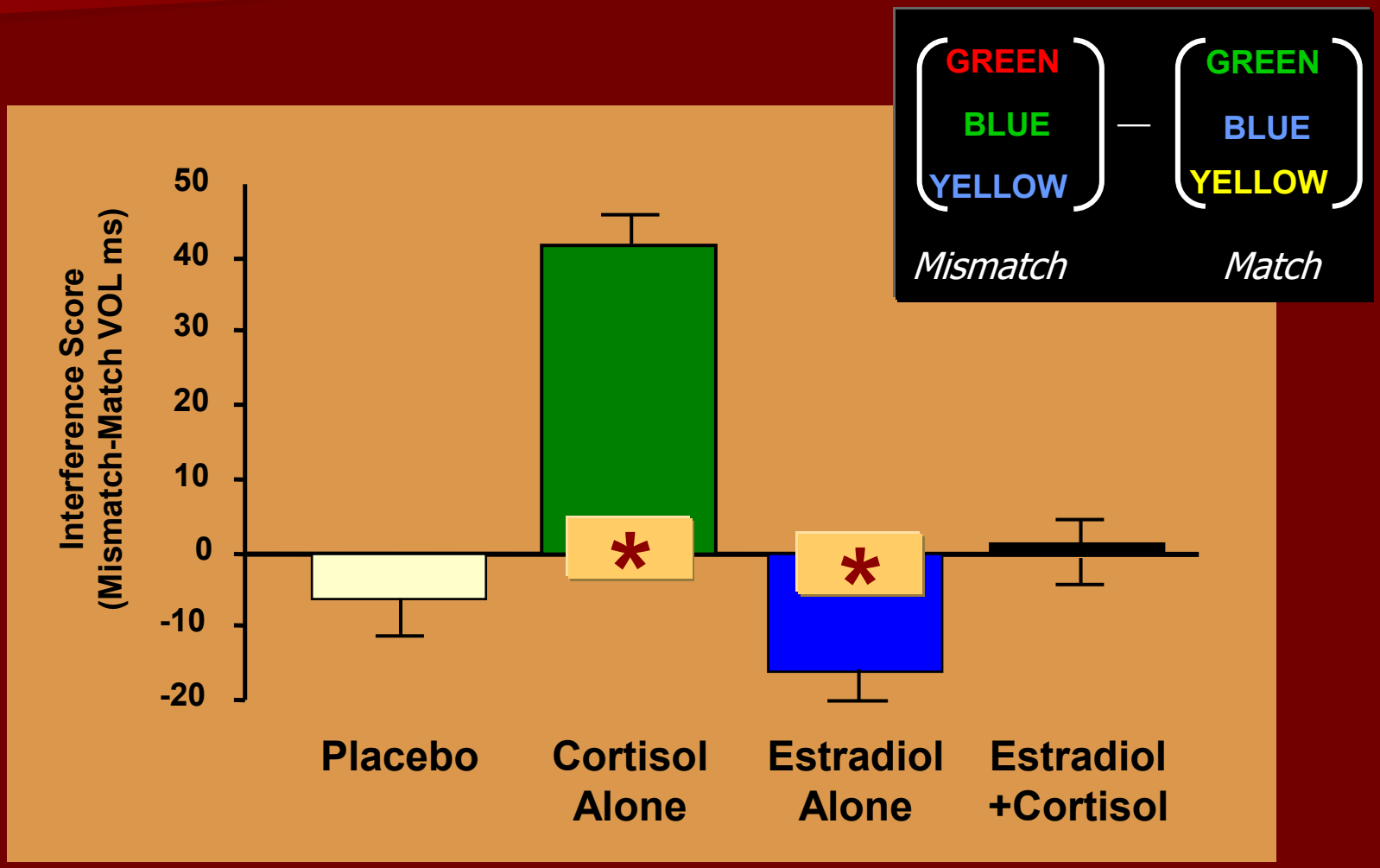
BLUE

Name the Ink Color

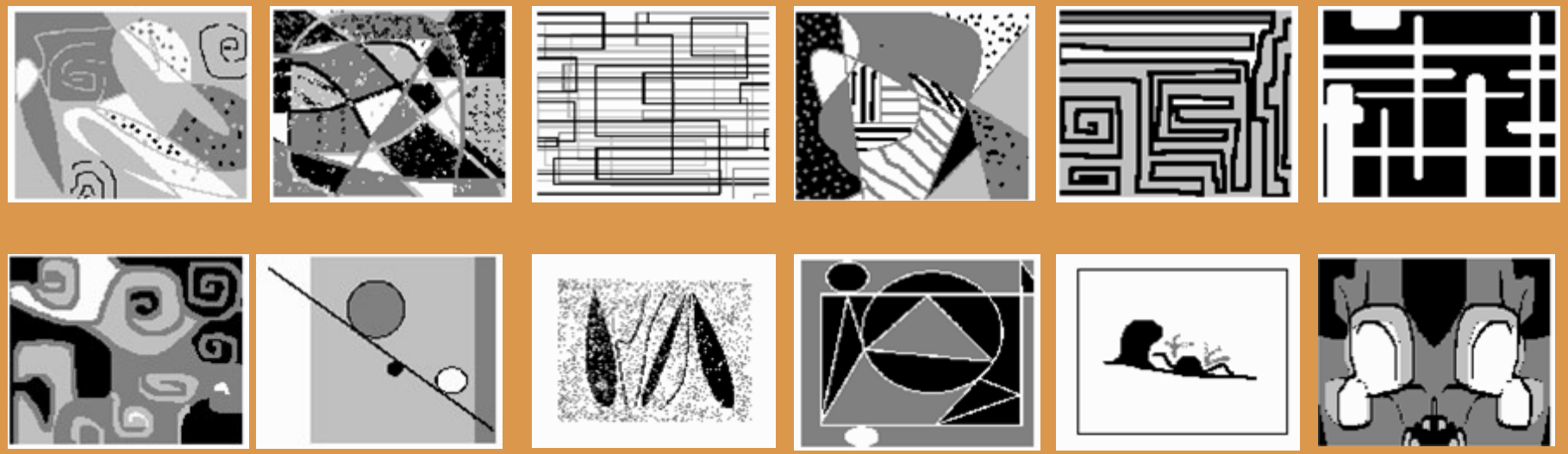
RED

Stroop Color-Word Interference

Color Naming : Change from Baseline

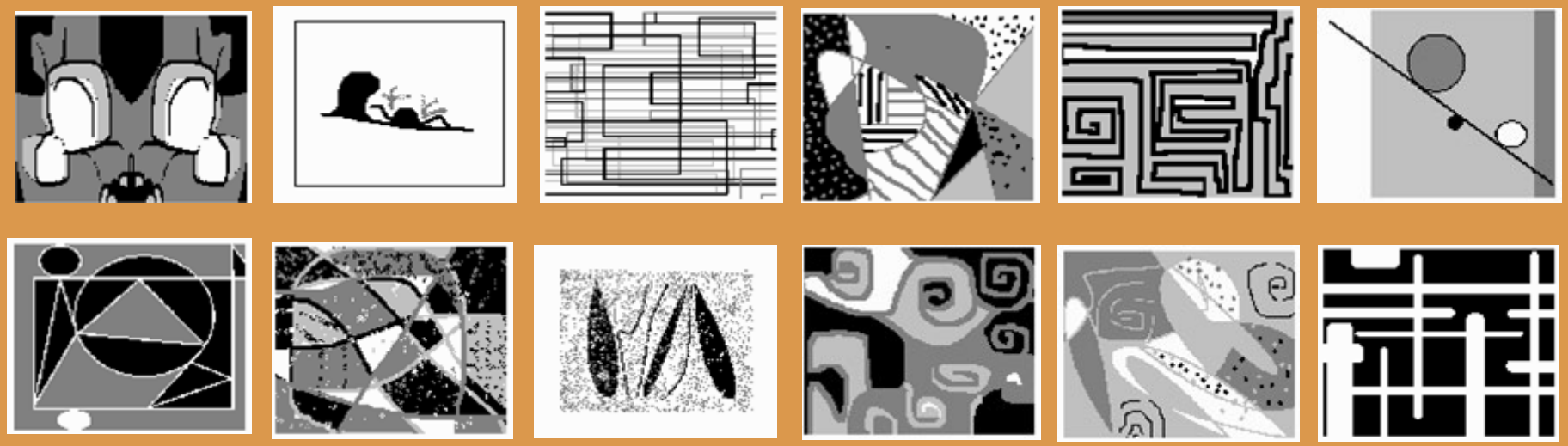


Self-Ordered Pointing Test

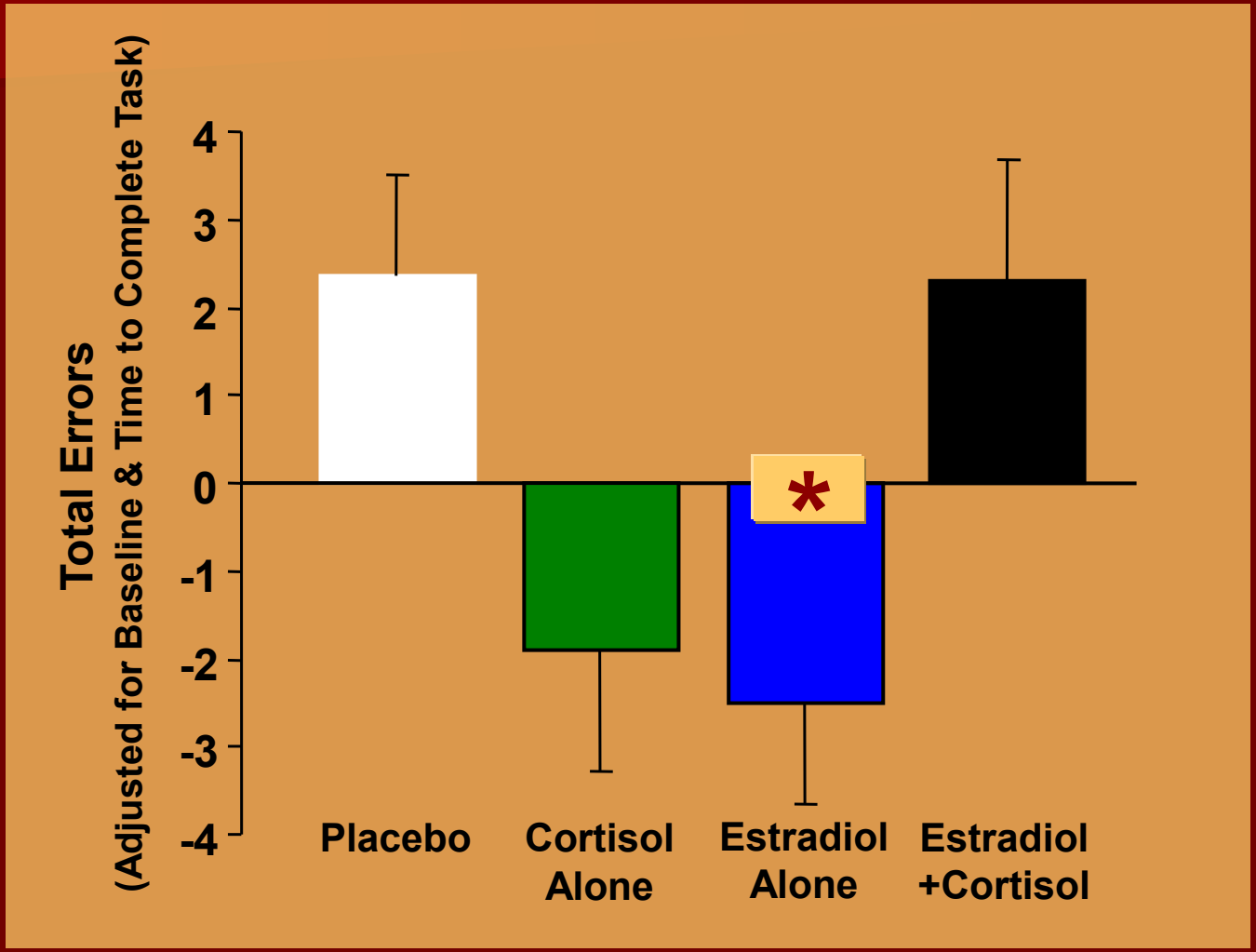


Self-Ordered Pointing Test

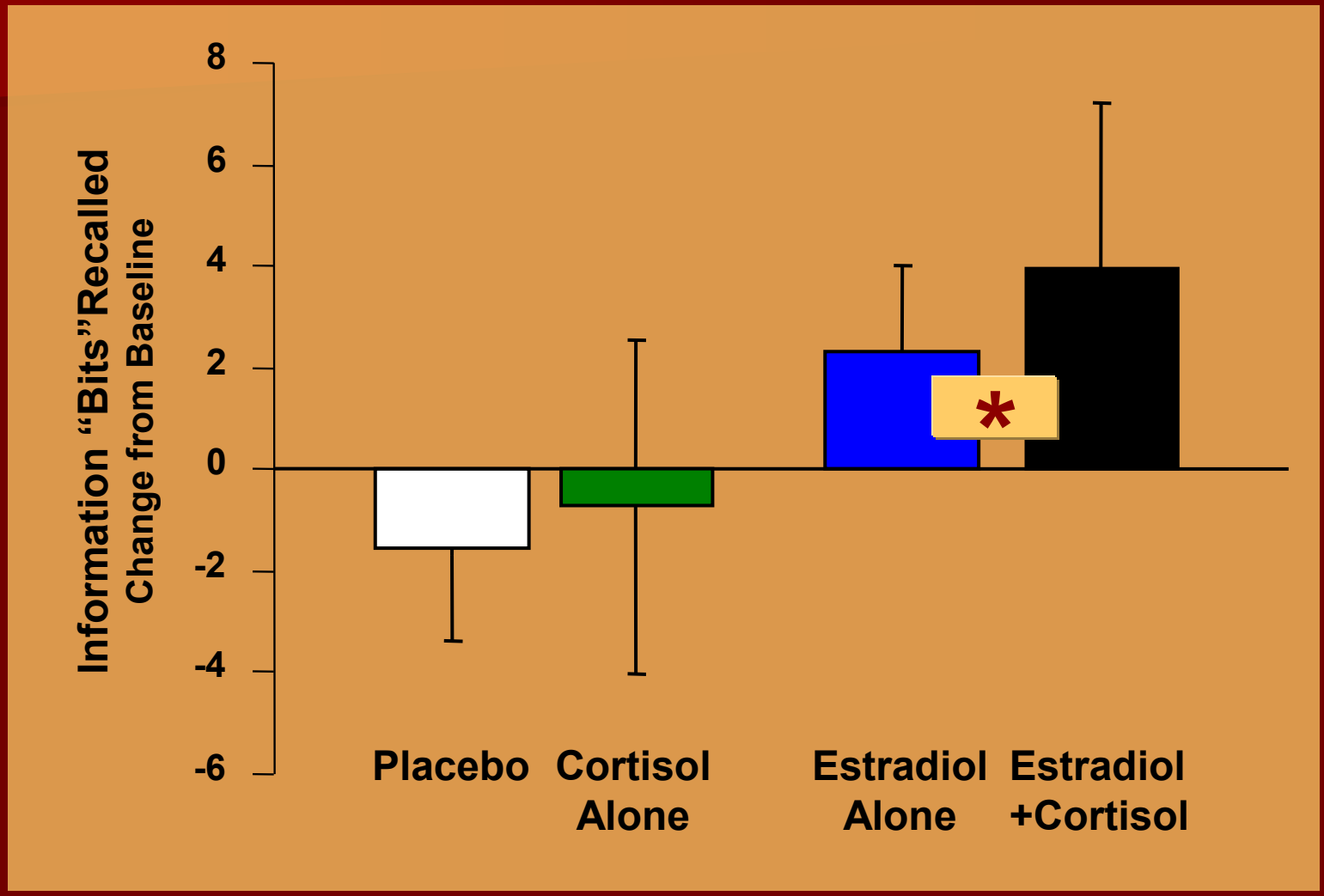
Self-Ordered Pointing Test



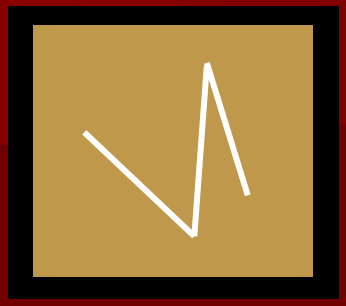
Self-Ordered Pointing Test



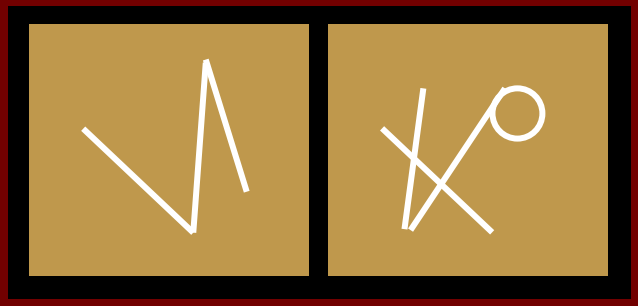
Story Recall



Delayed Match-to-Sample



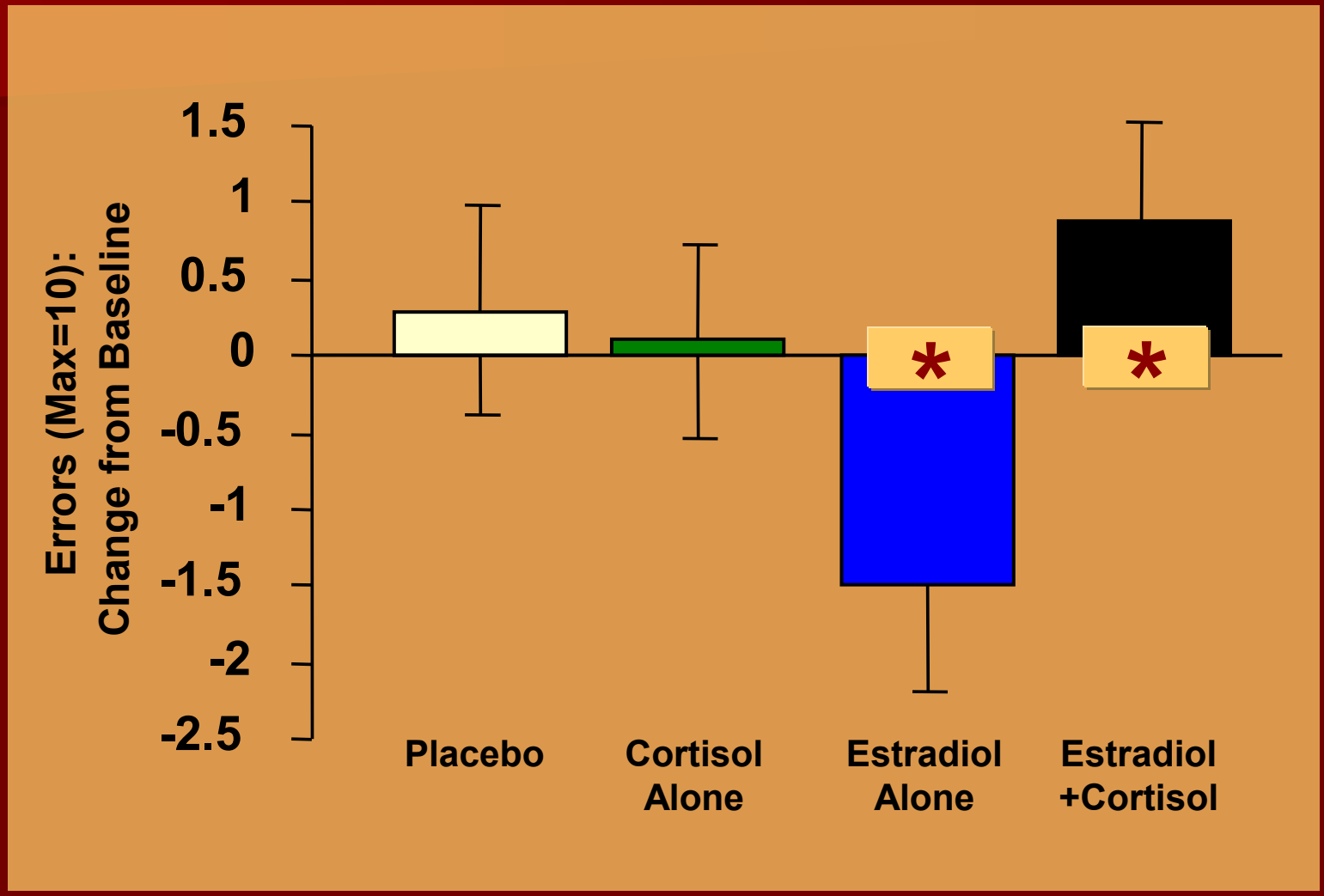
Study



Immediate Recall

Delayed Recall

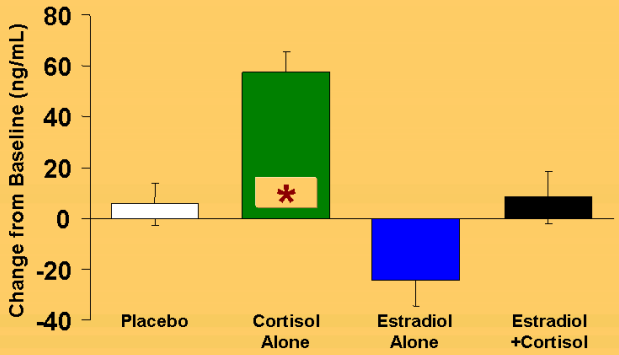
Delayed Match-to-Sample



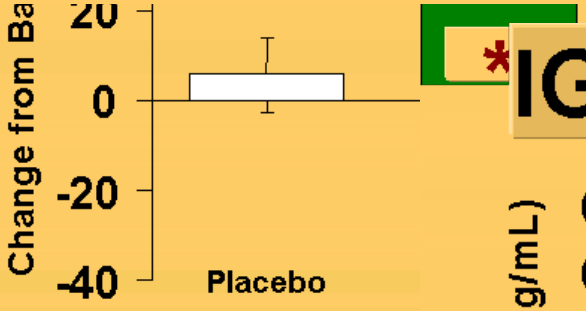
IGF & Aβ

IGF-1

Total IGF-I

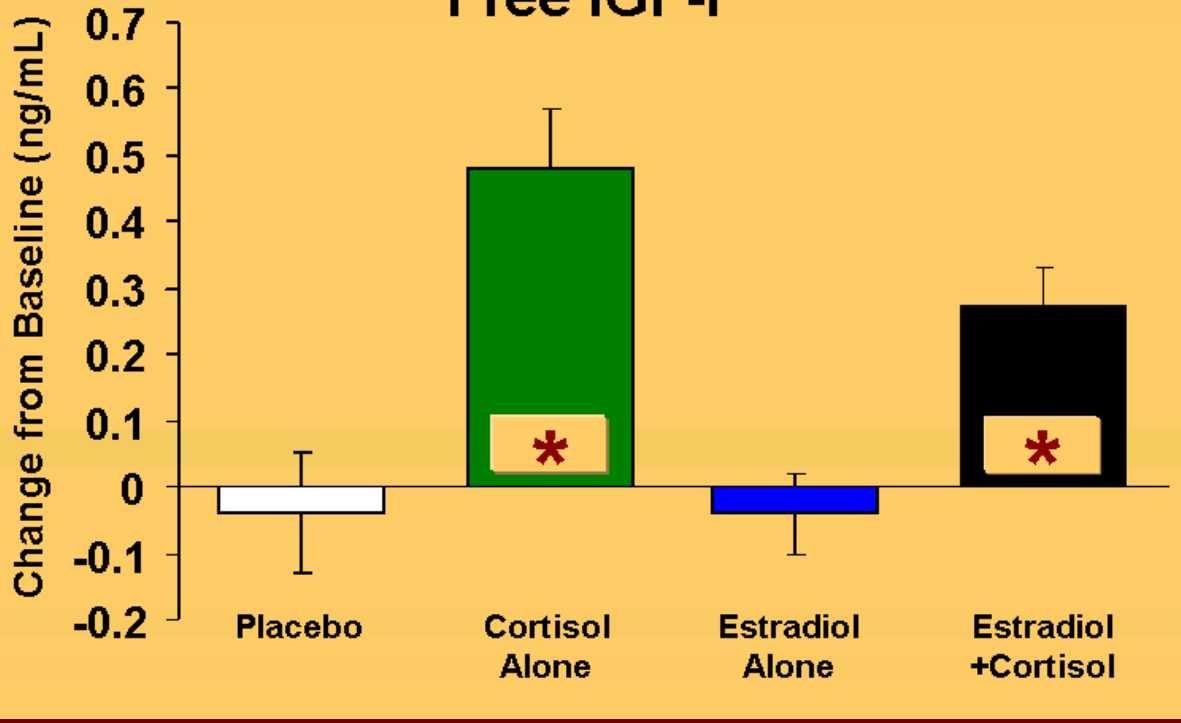


GF-I



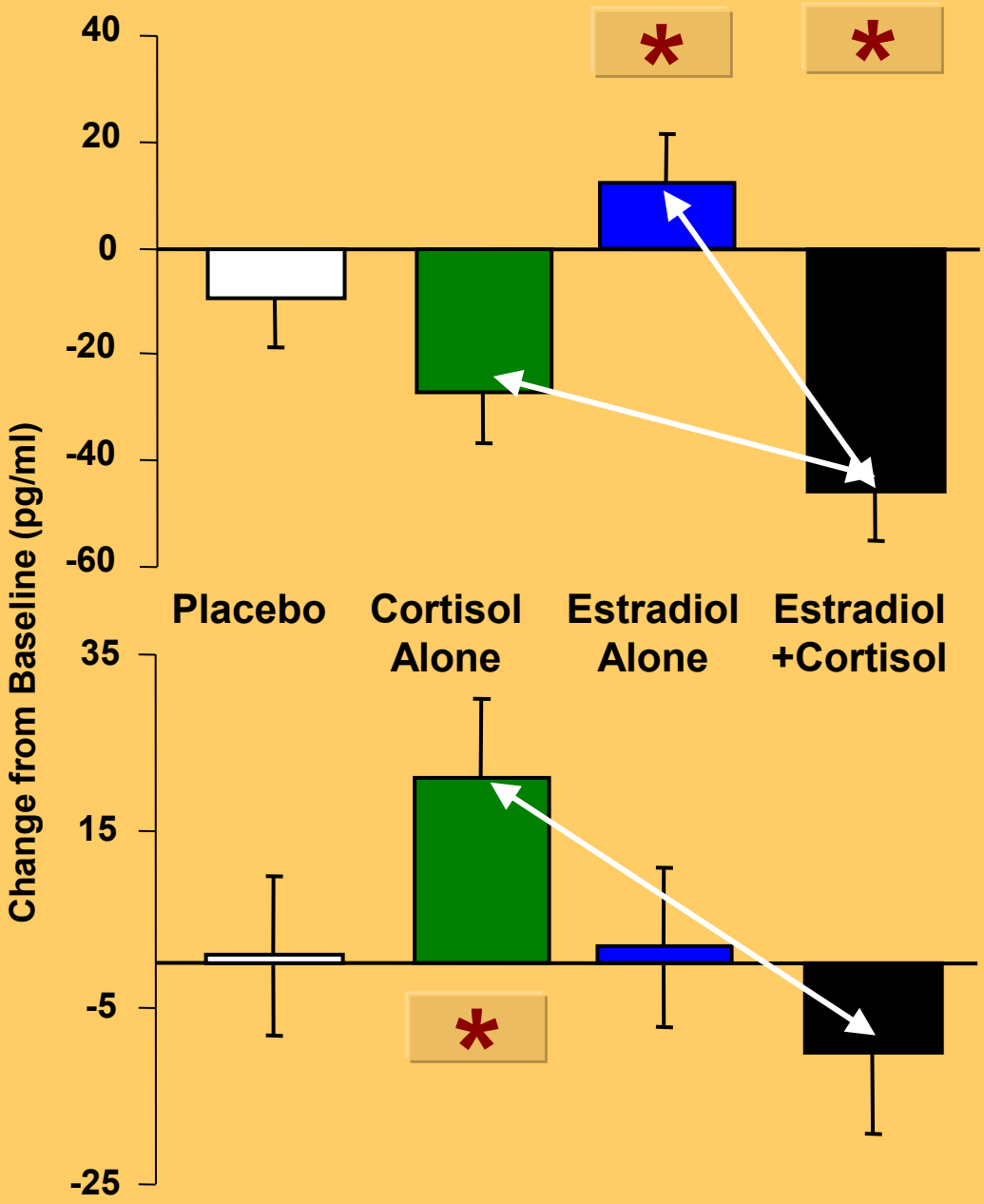
IGF-1

Free IGF-I



Aβ40

Aβ42


40
20
0
-20
-40
-60
*
*
Placebo
Cortisol Alone
Estradiol Alone
Estradiol +Cortisol
Change from Baseline (pg/ml)
35
15
-5
-25
*

Summary : Cognitive Effects

- 2 months of estradiol, without elevated cortisol, has a beneficial effect on executive function for healthy postmenopausal women
- Estradiol appears to benefit verbal memory independent of cortisol levels
- 4 days of cortisol use impairs performance on select executive function tasks
- Clear evidence for an interactive effect of estradiol & elevated cortisol on cognition … combined regimen <> effects of cortisol & <> effects of estradiol

Summary : IGF & Aβ Effects

- As expected, 4 days of cortisol increases IGF-1; trend indicating decreased levels for estradiol-treated subjects; combine regimen appears to mimic effects of cortisol administration
- 8 weeks of estradiol increases aβ40; 4 days of cortisol alters both aβ40 & aβ42 levels; again, the combined regimen appears to mimic effects associated with cortisol administration

Future Directions

- Take a closer look at the parameters of "stress" that may interact with estradiol use
- Examine specific task demands that may be differentially affected by estradiol and cortisol
- Assess interactive effects for older adults who are beginning to manifest symptoms of cognitive impairment
- Continue to explore the aβ-IGF-cortisol relationship as a potential contributor to cognitive response to estradiol

Collaborators

Suzanne Craft, PhD
Charles Wilkinson, PhD
Stephen Plymate, MD
Pattie Green, PhD

SANJAY ASTHANA, MD
George Merriam, MD
Mark Fishel, MD

Pamela Asberry, RN
Darla Chapman, RN, BS
Tracia Clark
Karen Enstrom, RN, BS
Karen Hyde, RN
Amy Morgan
Kristopher Rhoads, PhD

Dana Belongia
Brenna Cholerton, PhD
Donna Davis, RN, BS
Margaret Grout
Jaime Iliff
Mark Reger, PhD
Stennis Watson, PhD