

# Low Dose Estrogen, fMRI, and Cognitive Function

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# Goals

To examine the effects of low-dose 17  $\beta$ -estradiol on behavioral performance and brain function during a sustained visual attention task.

## Questions:

1. What are the effects of low-dose estradiol on behavioral performance during a simple visual attention task?
2. What are the effects of low-dose estradiol on brain function during performance of this task?

# Background

- Some studies and meta-analyses support the positive effects of estrogen compounds on neural and cognitive function, and some do not.
- Anderer et al. *Electroencephalography & Clinical Neurophysiology: Evoked Potentials* (1998)
  - Estrogen shortens the P300 ERP response
    - P300 lengthens with age
    - Results suggests a more “youthful” P300 with estrogen

# Participants

- Recruited from a larger study to evaluate the effects of ultra-low dose micronized estradiol on bone density
  - Prestwood, K. M., Kenny, A. M., Kleppinger, A., Kulldorff, M., (2003). Ultralow-dose micronized 17  $\beta$ -estradiol and bone density and bone metabolism in older women: A randomized controlled trial. *JAMA*, 290, 1042-1048.
- 112 women completed full  $\beta$ -estradiol study
  - Approximately 60 of these women completed full neuropsychological evaluation
  - Of these 60, 16 women agreed to do the fMRI portion
- Studied after 3 years of randomized double blinded administration of 25 mg/d 17  $\beta$ -estradiol
  - progesterone 100 mg per day for 2 weeks every 6 months
  - calcium citrate 1300 mg and 1000 IU vitamin D per day

# Participant Characteristics

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	Mean (SD) or %	
	E	Placebo
Age	76.9 (3.94)	79.0 (3.93)
Handedness		
Right	87.5%	100.0%
Education		
High school grad	12.5%	0.0%
Some college or grad	87.5%	62.5%
Post grad work	0.0%	37.5%

# Effects of $\beta$ -Estradiol Hormone Levels

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	Mean (SD) or %	
	E <sub>2</sub>	Placebo
Estradiol level (pg/ml)		
Baseline	8.4 (4.32)	9.3 (3.52)
3-year	21.0 (14.23)	7.6 (2.25)
Estrone level (pg/ml)		
Baseline	13.4 (5.33)	14.7 (6.01)
3-year	50.9 (50.73)	13.2 (4.17)

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# Effects of $\beta$ -Estradiol Depression & Anxiety

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	Mean (SD) or %	
	E	Placebo
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Geriatric Depression Scale		
Baseline	3.0 (4.28)	3.9 (2.70)
3-year	3.8 (5.70)	4.6 (5.26)
Beck Anxiety Scale		
Baseline	2.0 (2.98)	3.8 (3.65)
3-year	5.5 (5.73)	4.3 (2.87)

# Effects of $\beta$ -Estradiol Personality & Behavior

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	Mean (SD) or %	
	E <sub>2</sub>	Placebo
<hr/>		
Folstein MMSE score		
Baseline	28.8 (1.39)	29.5 (0.53)
3-year	28.8 (1.04)	29.4 (0.53)
PASE		
Baseline	134.7 (52.27)	122.0 (87.09)
3-year	102.2 (50.50)	84.5 (32.86)



# fMRI Methods

- 1.5 Tesla Siemens Vision MRI
- Visual stimuli displayed using virtual reality goggles (Resonance Technologies)
- Eight 3-minute runs of the three-stimulus oddball task

# Three Stimulus Oddball Task

QuickTime™ and a  
Motion JPEG OpenDML decompressor  
are needed to see this picture.

200 msec duration, ISI averages 1 per sec (550-2050 msec)

Rare Target - “X” - 8% - Requires button press response

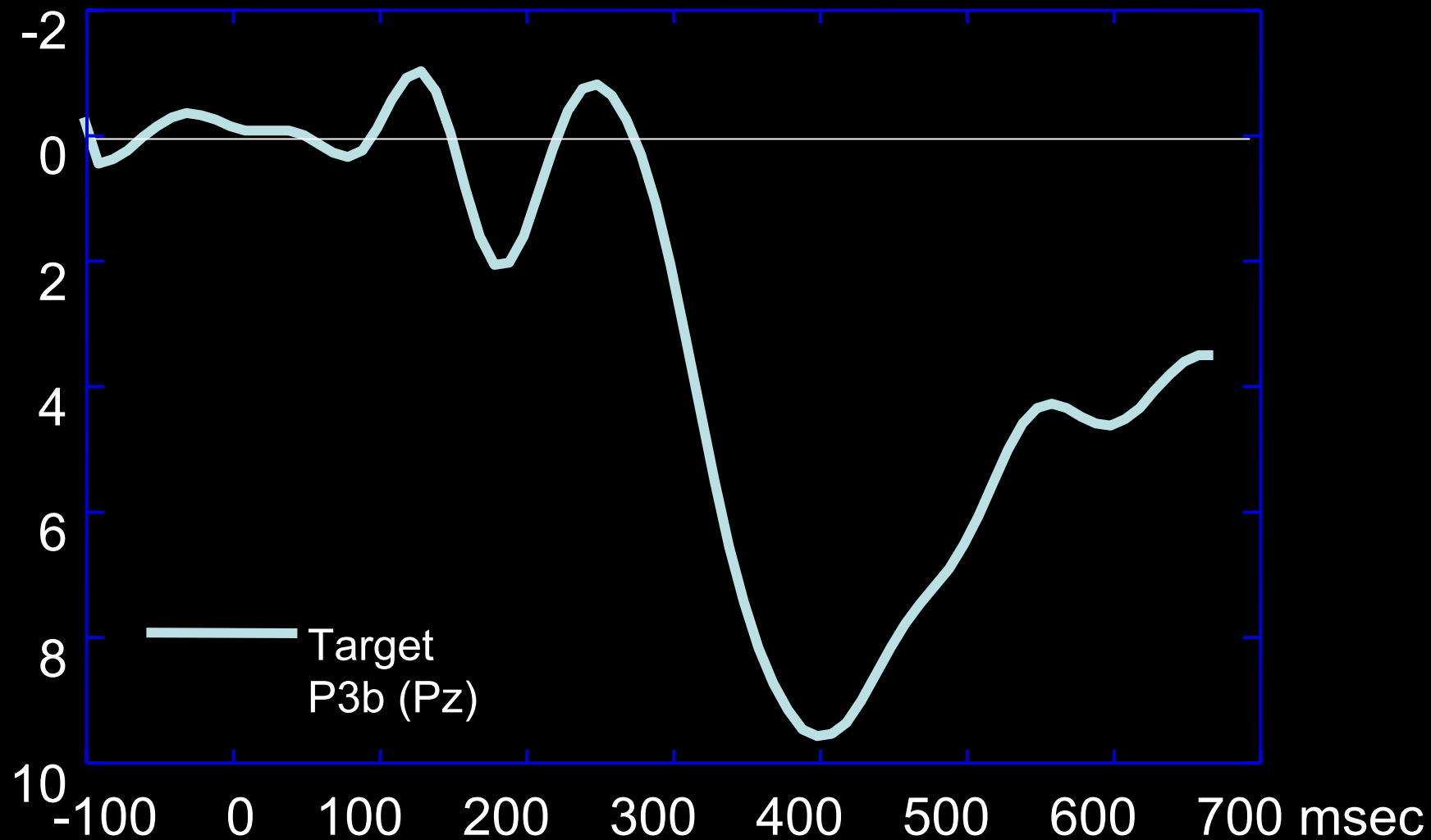
Rare Distractor - “C” - 8% - No response

Standard - “T” - 82% - No response

Robustly sensitive to CNS function:

- Clark et al. (2000; 2001; 2002), Stevens et al. (2001)
- R01 DA12852 “Neural Function in Cocaine Dependence and Relapse”

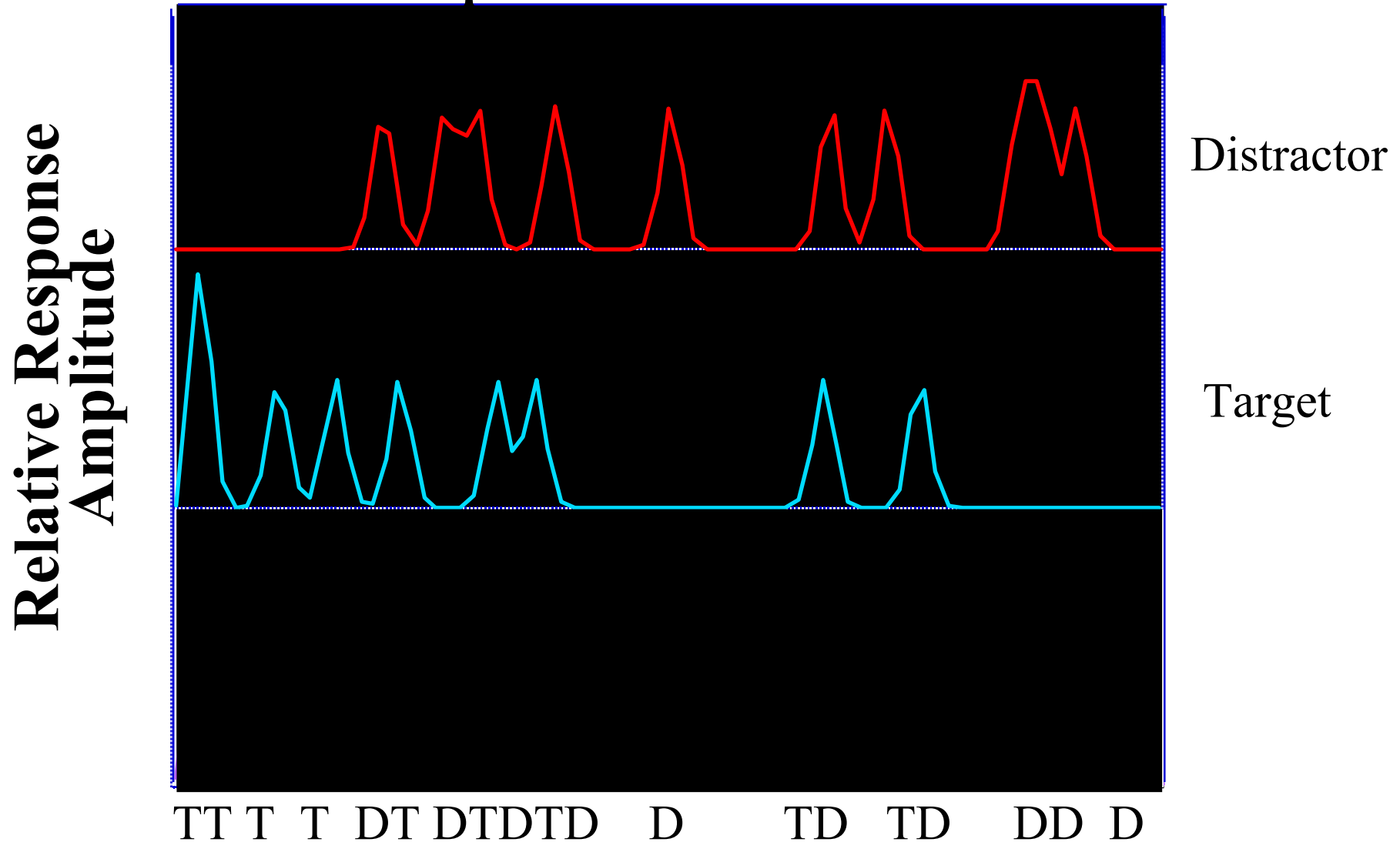
# P300 Evoked by the Three Stimulus Oddball Task



# Analyses

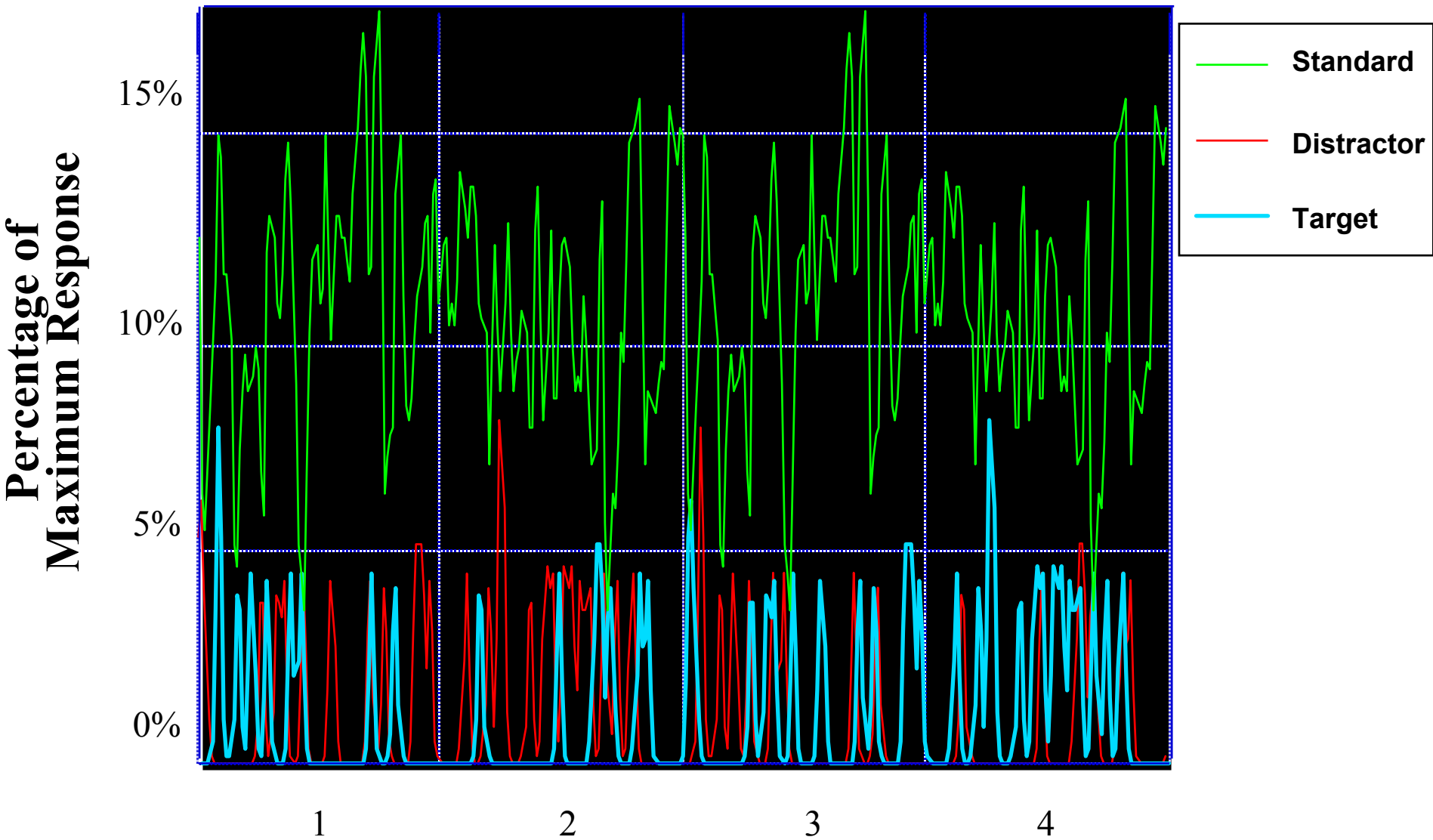
- Behavioral analyses
  - Accuracy, reaction time, false alarms
- fMRI analyses
  - Used SPM99 to examine amplitude of event-related responses to target, distractor and standard stimuli
  - Examined differences between groups in these measures

# Stimulus Sequences & Predicted HRFs



Orthogonality allows independent testing of each stimulus type.

# Predicted HRFs



# Behavioral Results

- No significant differences were found in behavioral performance.

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	Mean (SD)	
	E	Placebo
Target Reaction Time ( <i>ms</i> )	530.4 (47.52)	518.9 (53.61)
Distractor False Positives	0.03 (0.06)	0.00 (0.00)
Standard False Positives	0.61 (0.45)	0.93 (0.60)
Accuracy	98.7	99.6

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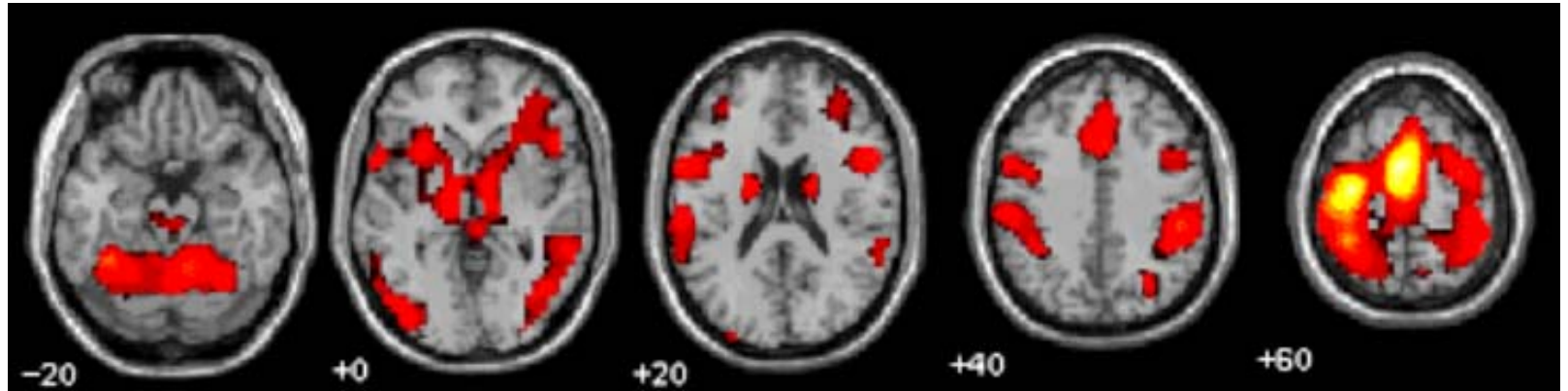
# fMRI Results

- Altered hemodynamic responses to stimuli
  - Target stimuli
    - increased hemodynamic activity in visual and motor areas
    - less activation in parietal areas
  - Distractor stimuli
    - greater activity in anterior cingulate and other prefrontal cortical and adjacent subcortical areas
    - reduced parietal activity

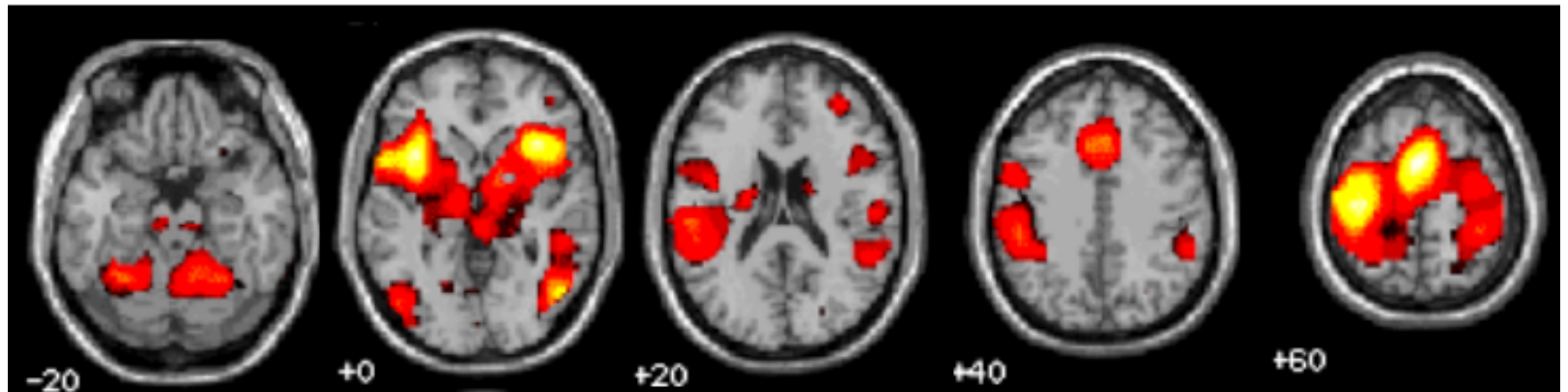


# $\beta$ -estradiol and Placebo Target Response

Placebo

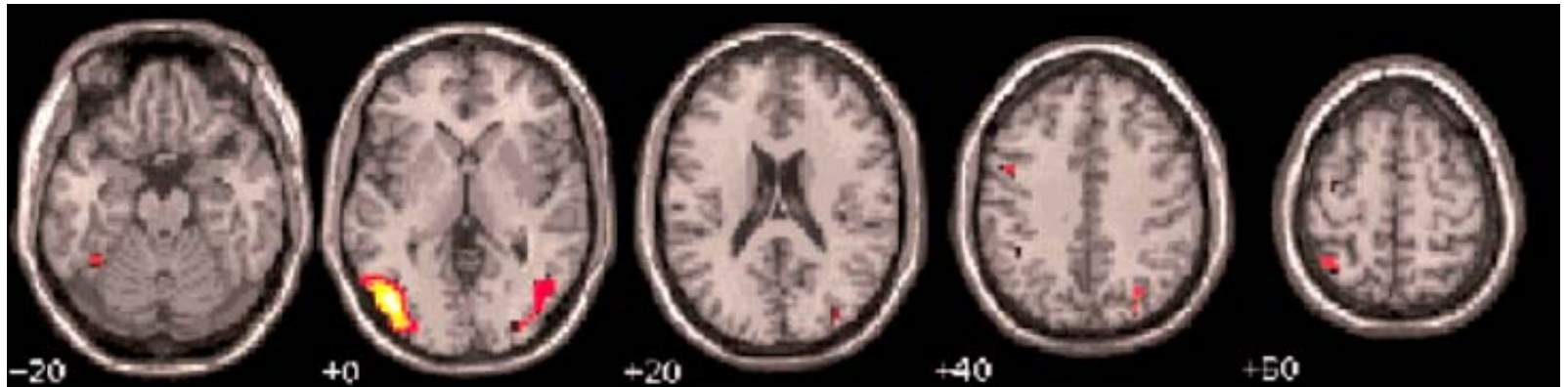


Estrogen

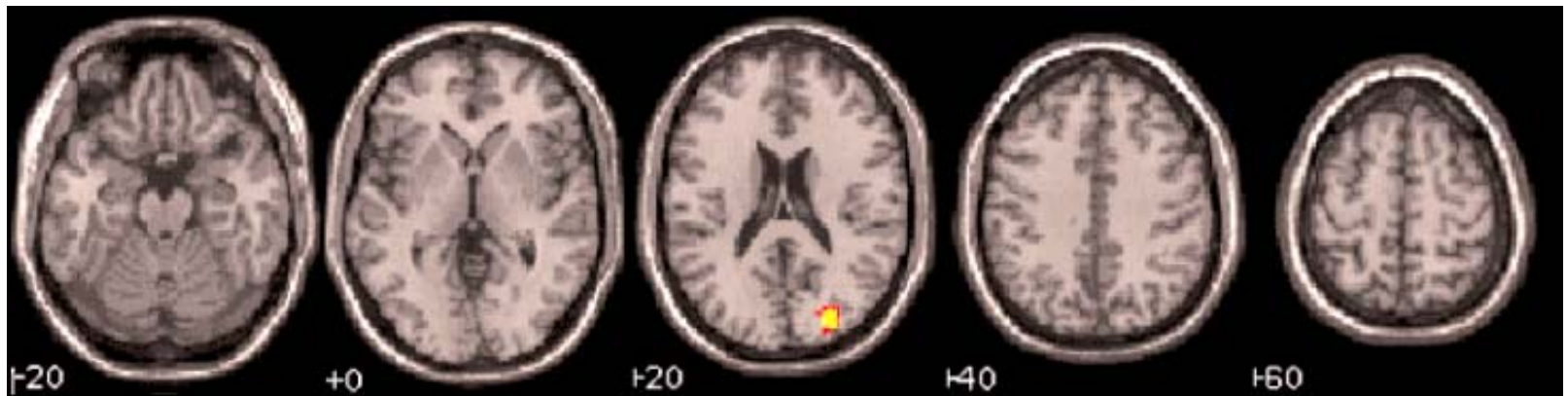


# $\beta$ -estradiol and Placebo Distractor Response

Placebo

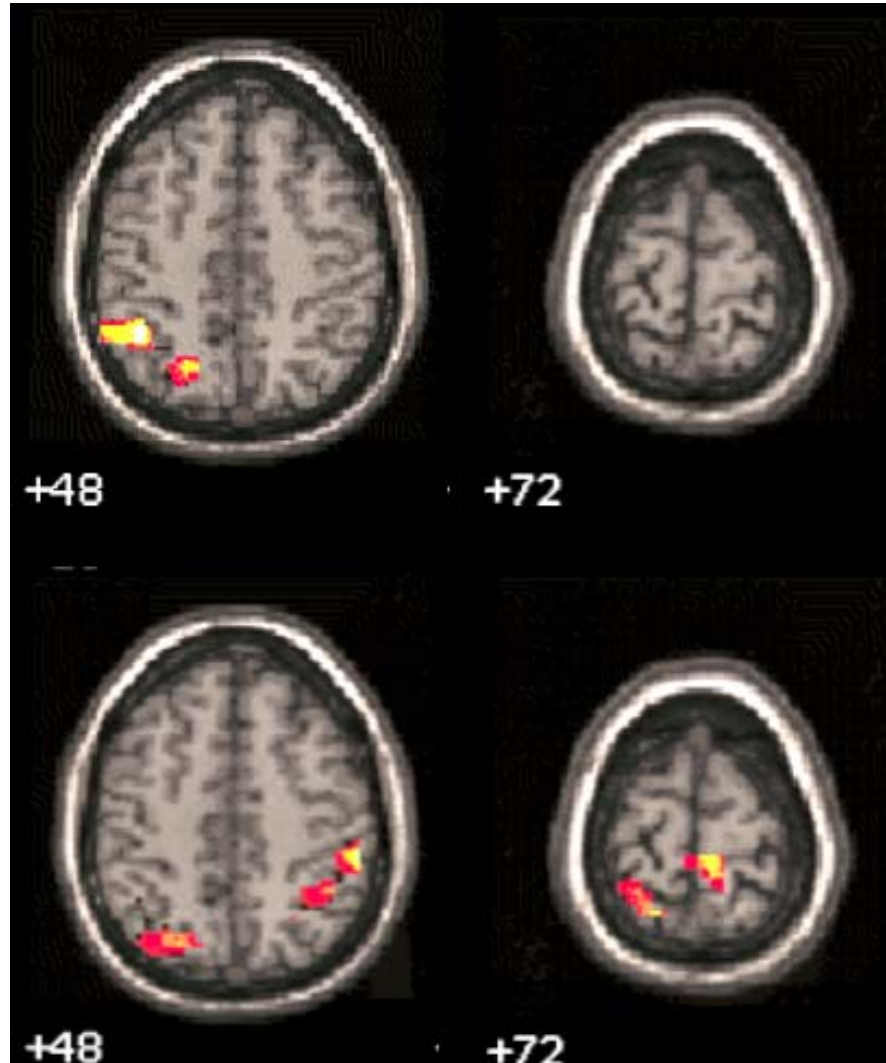


Estrogen



# Placebo > $\beta$ -estradiol

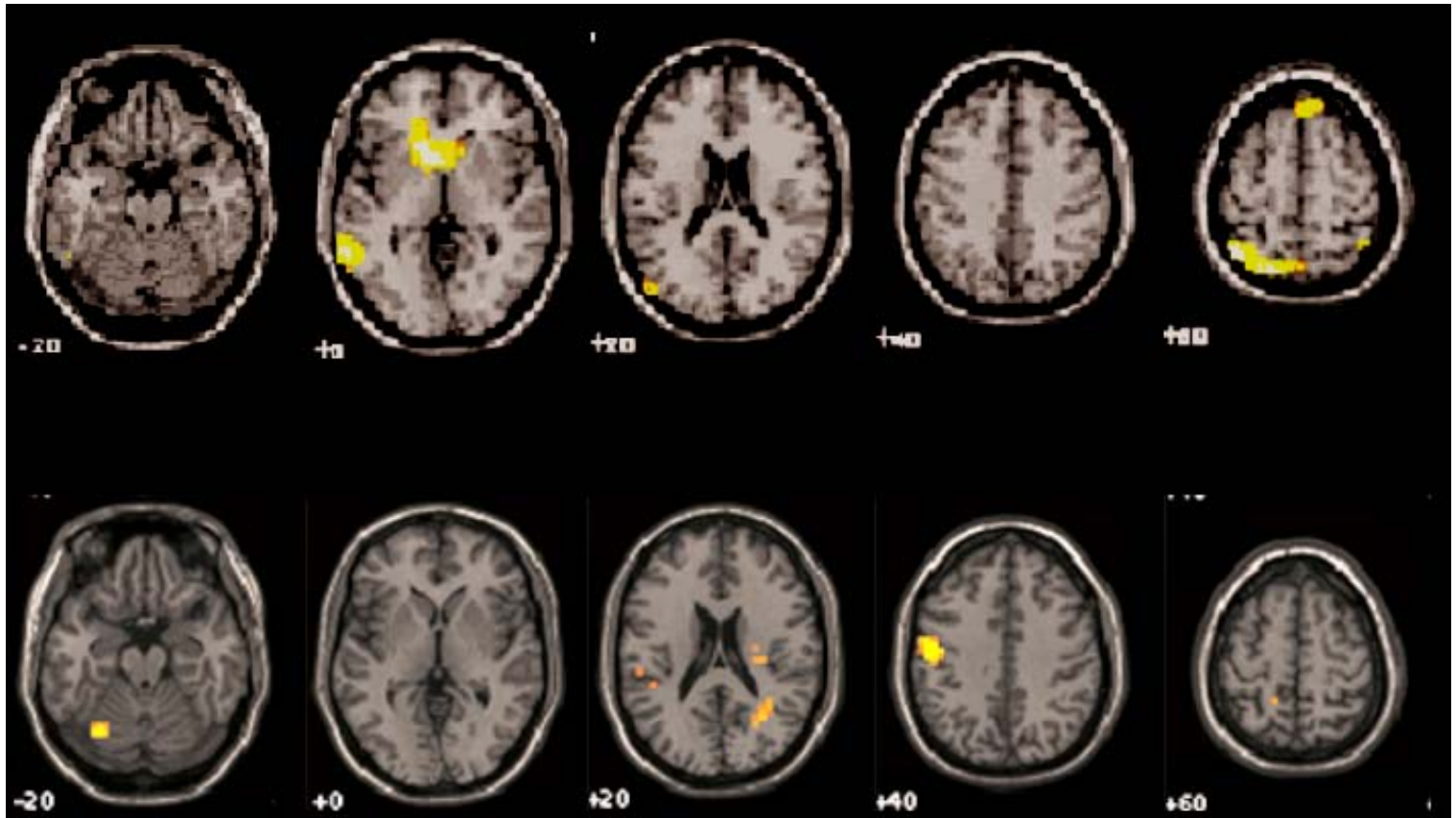
Novels



Targets

# $\beta$ -estradiol > Placebo

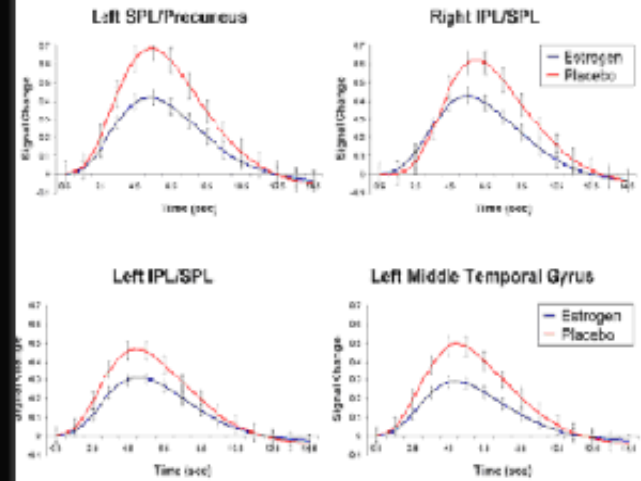
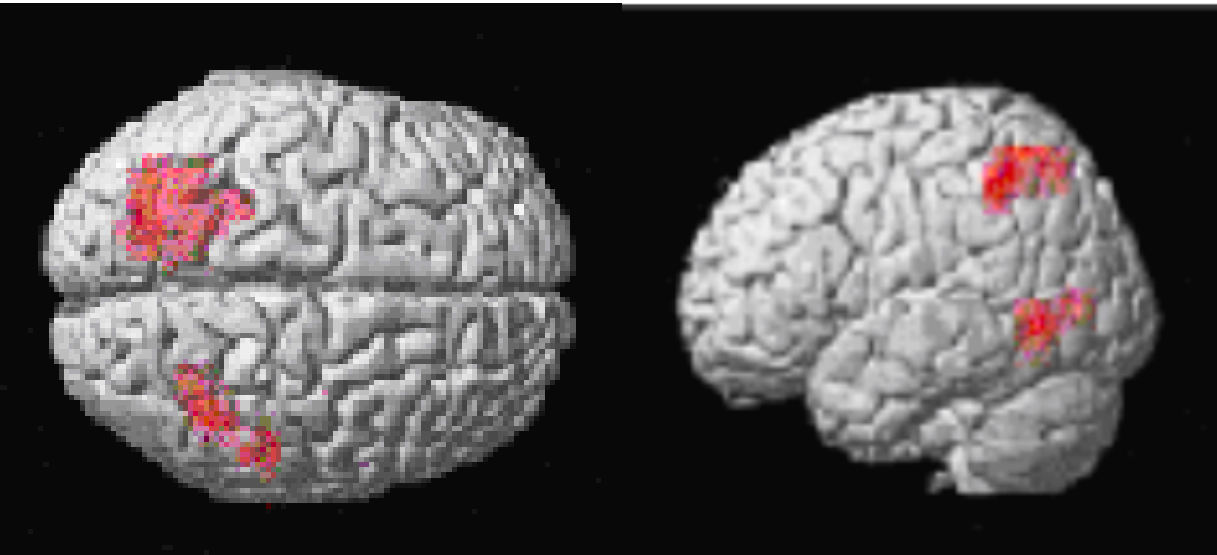
Novel



Target



# Random Effects Analysis and Evoked Response



# Conclusions

- Low-dose 17  $\beta$ -estradiol does not greatly alter behavioral responses in a simple reaction time task.
- Brain activation patterns are consistent with our findings in younger persons.
- BOLD responses in posterior brain areas were reduced.
- Responses in anterior subcortical and cortical regions were enhanced, but to a lesser degree.
- Because fMRI is an indirect measure of neural activity, these results may be due to either the neural or hemodynamic effects of 17  $\beta$ -estradiol.

# Collaborators

- Michael C. Stevens
  - Thomas Shepherd
- Karen M. Prestwood
  - Allison Kleppinger