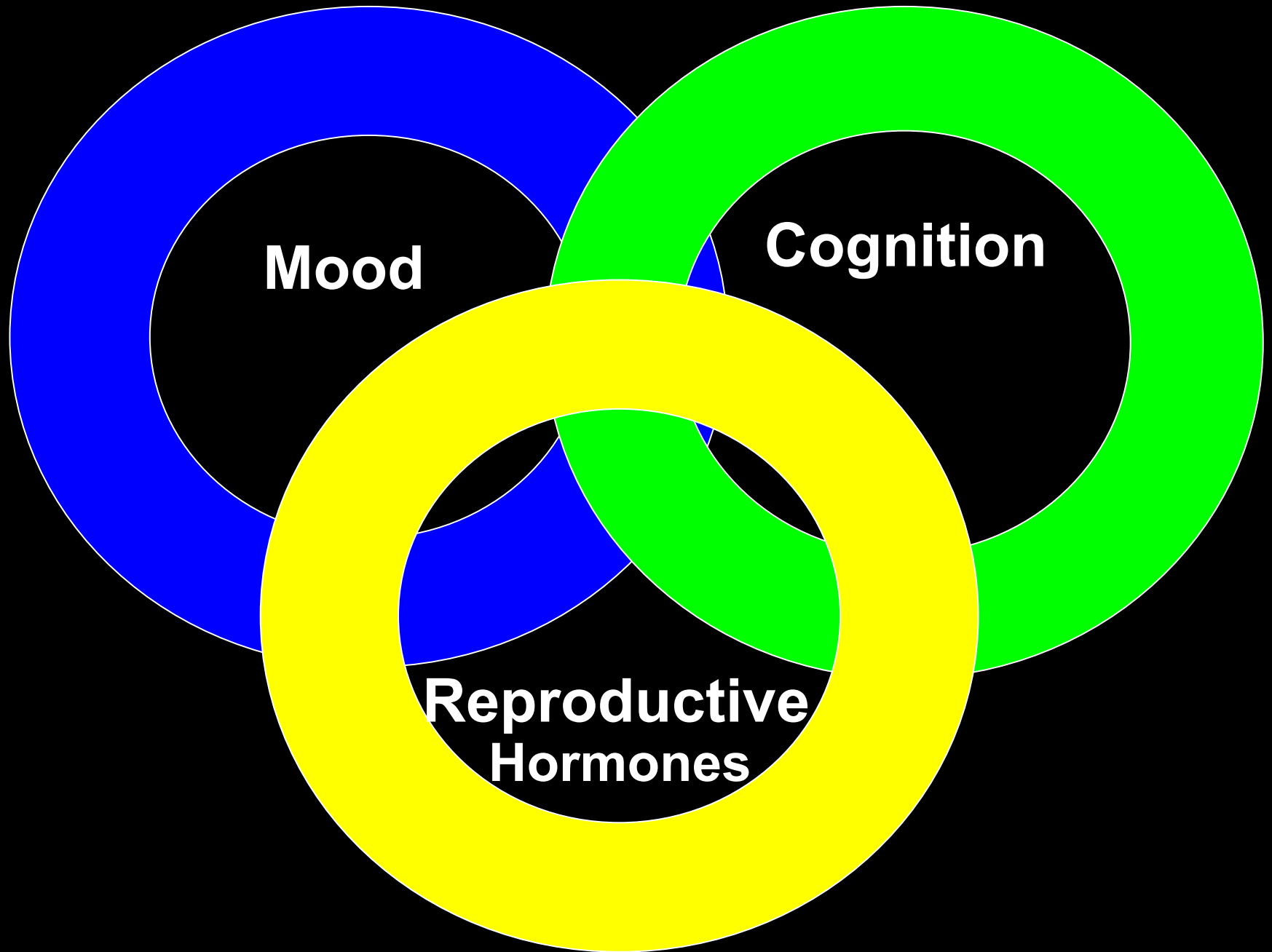


# **CNS Effects of Hypogonadism and Estrogen Therapy in Humans: Mood the “Other” White Meat**

**Peter J. Schmidt  
David R. Rubinow  
Khursheed Khine  
Pedro E. Martinez  
BEB, NIMH**

**Lynnette K. Nieman  
PREB, NICHD  
Karen F. Berman  
CBDB, NIMH**



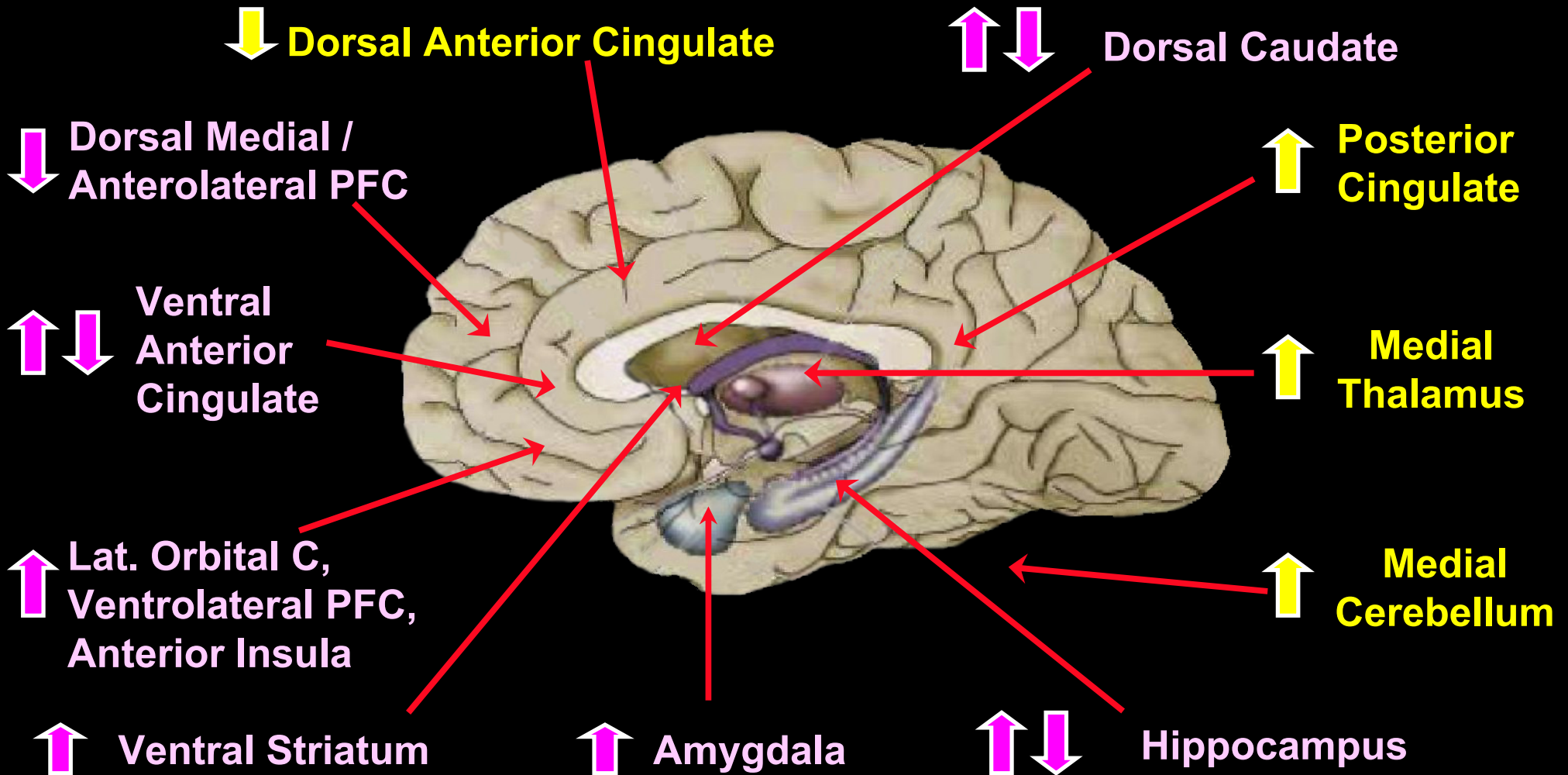


**Mood**

**Cognition**

**Reproductive  
Hormones**

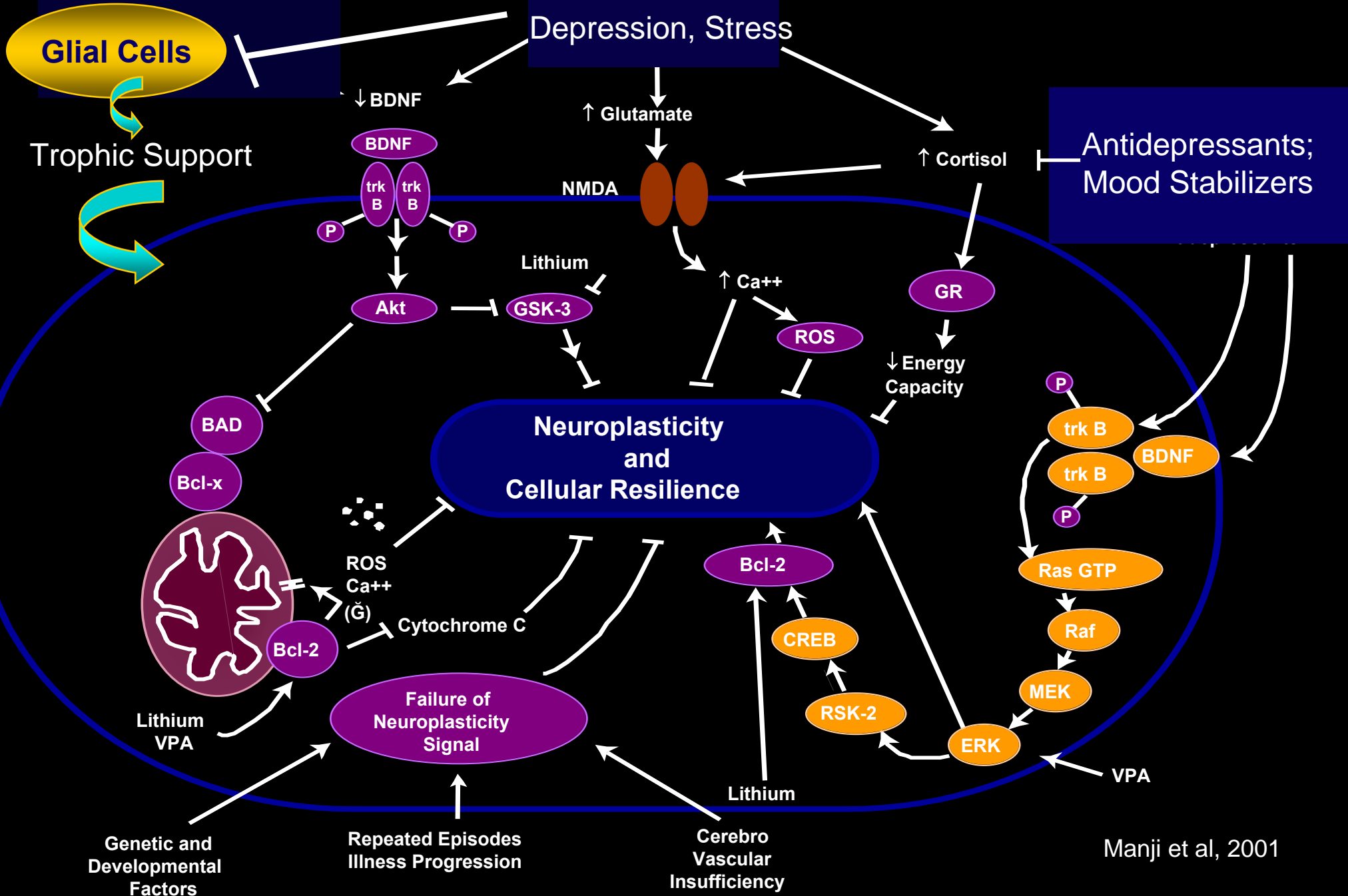
# ABNORMALITIES OF CBF, METABOLISM IN MDD

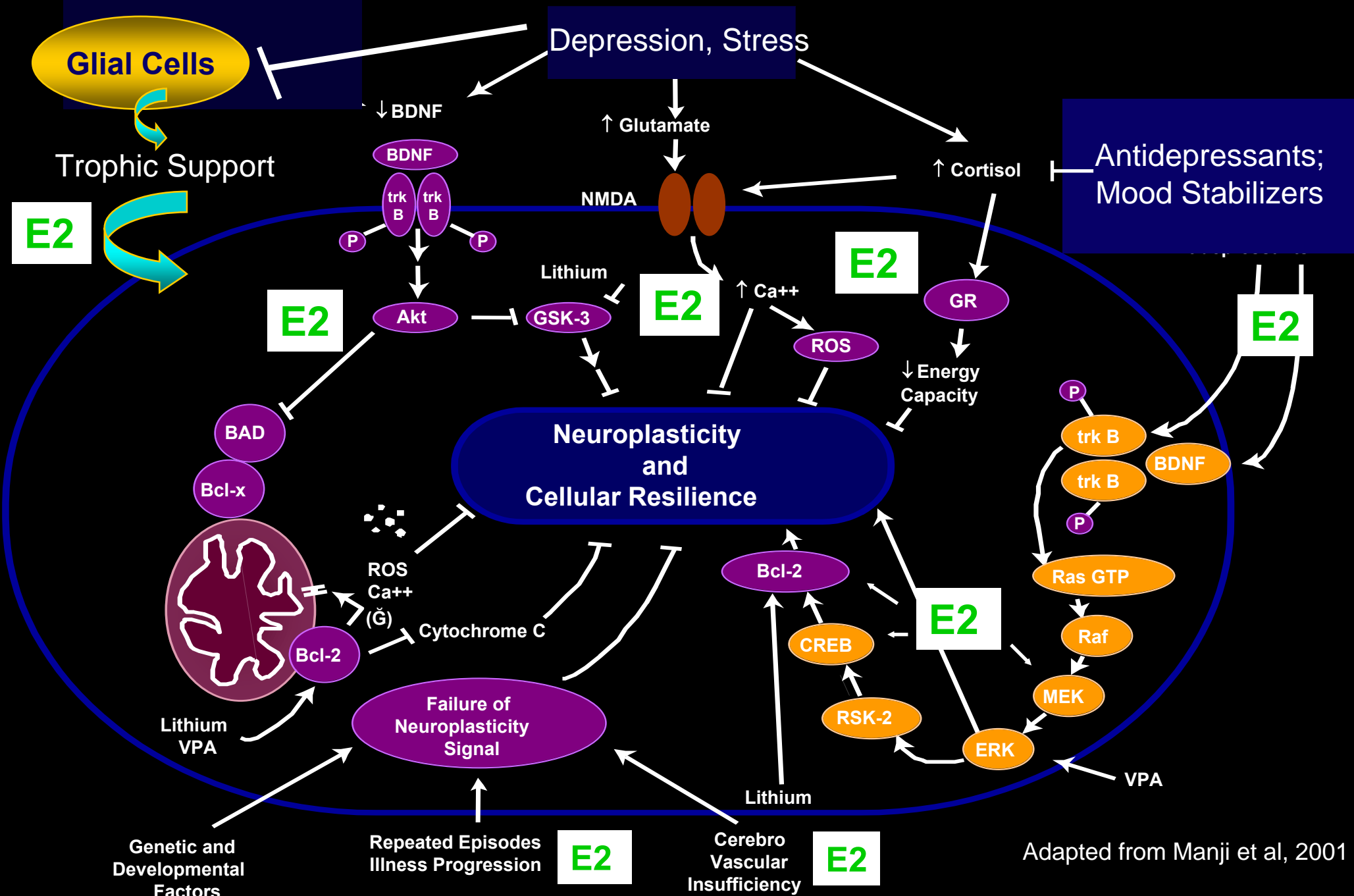


Areas where neuropathological / morphometric changes reported



Indicates direction of metabolic abnormality relative to control





Adapted from Manji et al, 2001

# Study Designs

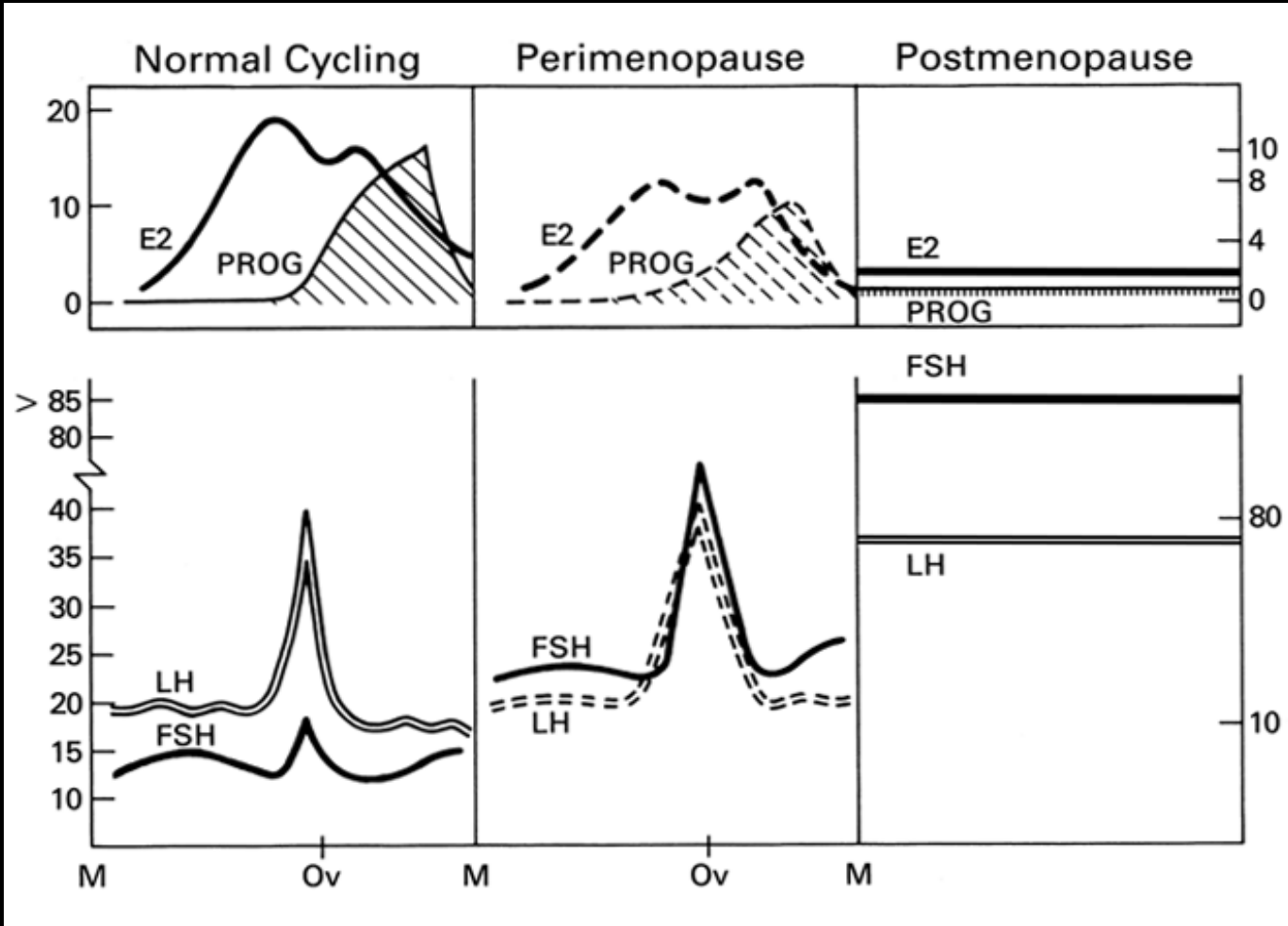
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1. Hormonal Treatments
2. Naturalistic
3. Experimentally-induced hypogonadism

Is the **Perimenopause** associated with an increased susceptibility to develop **Depression**?

**Estradiol (E2)  
(ng/dL)**

**Progesterone  
(ng/mL)**



**FSH  
(IU/L)**

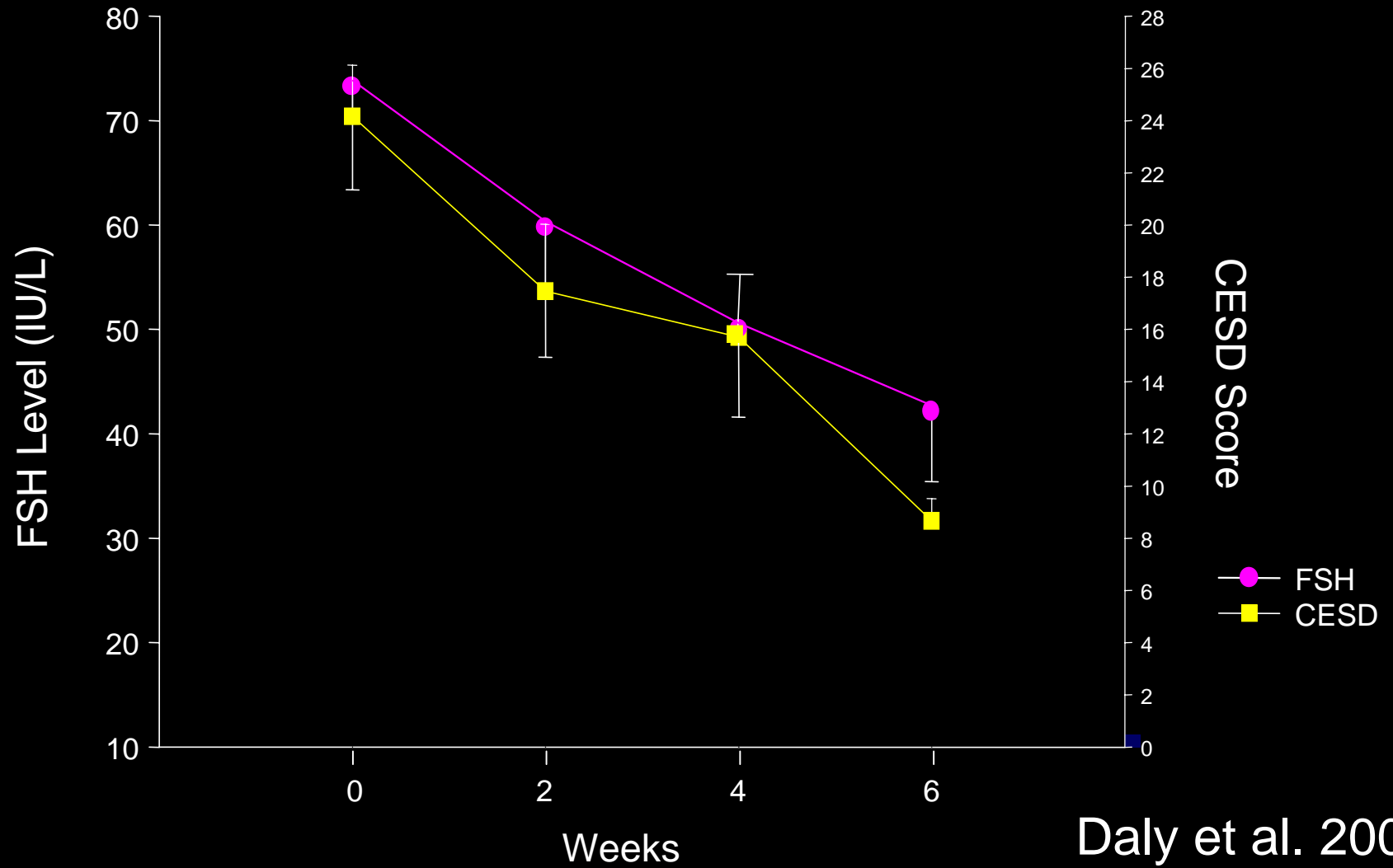
**LH  
(IU/L)**



**Perimenopause-related depressions are NOT secondary to:**

- increased number of personal losses/exit events**
- hotflush-induced sleep disturbances**
- excessive deficiency of ovarian estrogens or androgens**

# Concordant restoration of ovarian function and mood in perimenopausal depression (n=18)



Daly et al. 2003

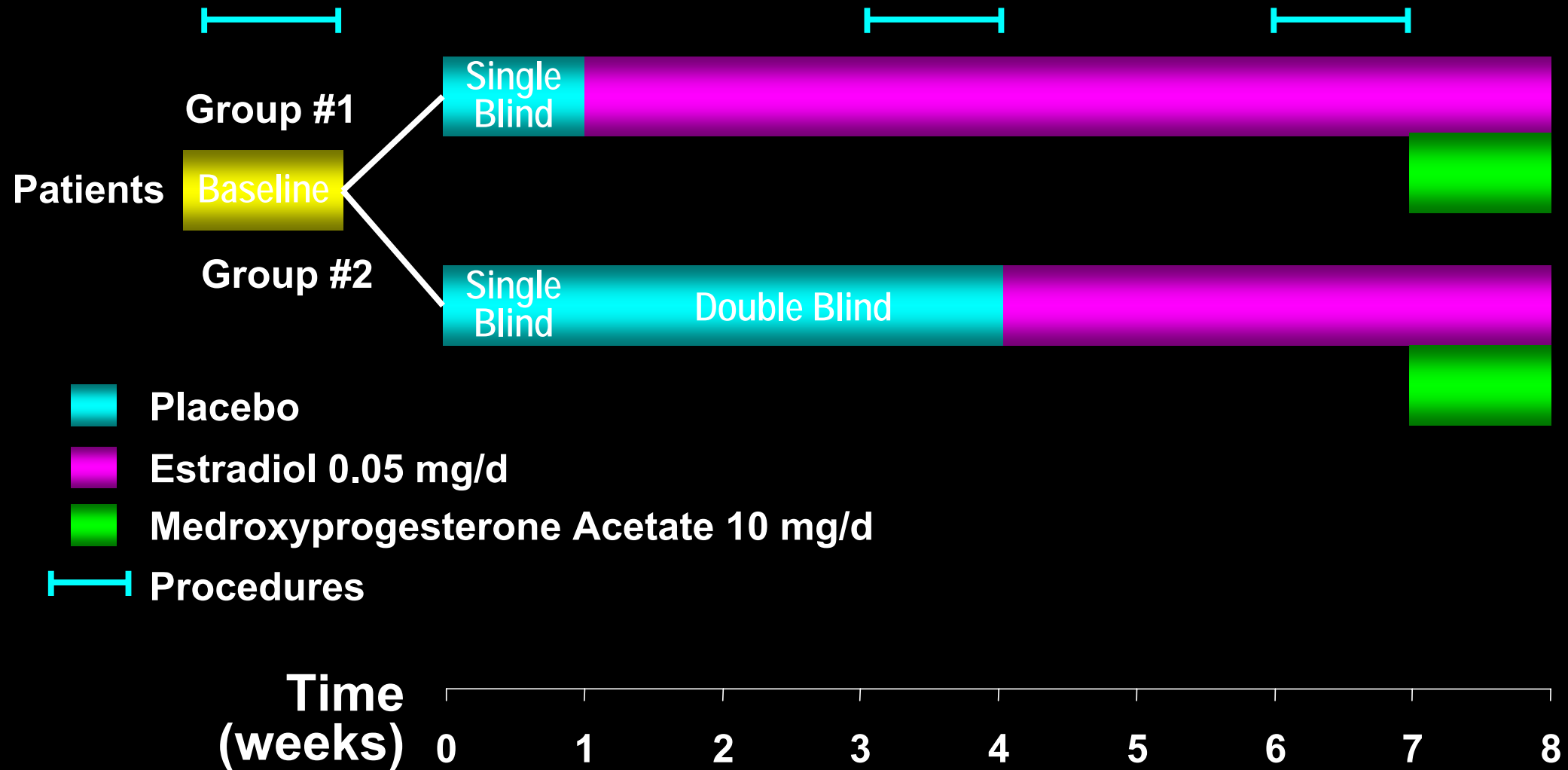
**Does the reversal of hypoestrogenism eliminate the symptoms of perimenopausal depression?**

## Study Entry Criteria

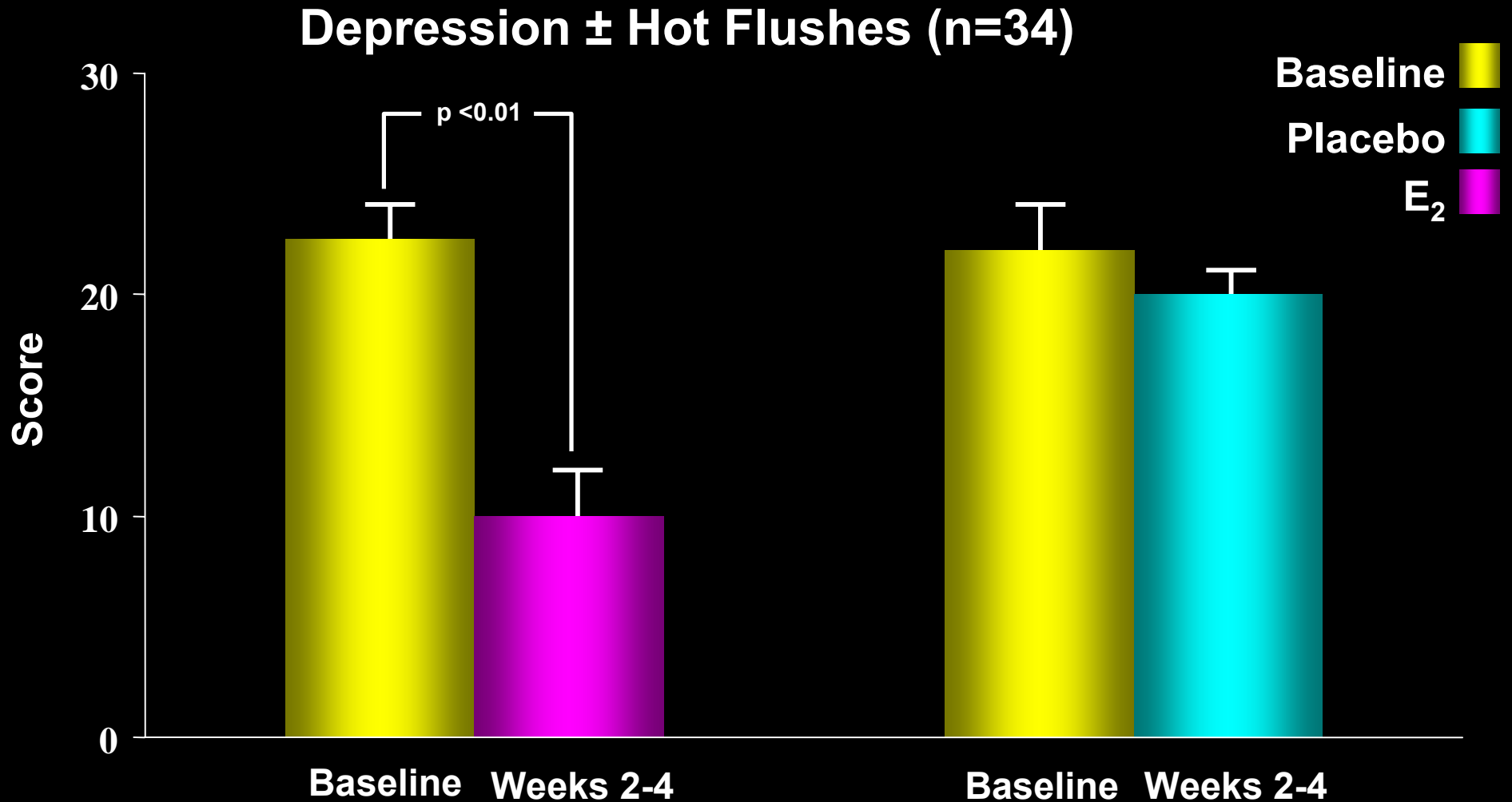
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- Serial elevated plasma gonadotropin levels
- Depression: minor (modified SADS) or major (SCID)
- Absence or presence of **hot flushes** confirmed by daily ratings over 2 months prior to study entry

# Therapeutic Trial of Estradiol in Perimenopause-Related Mood Disorders

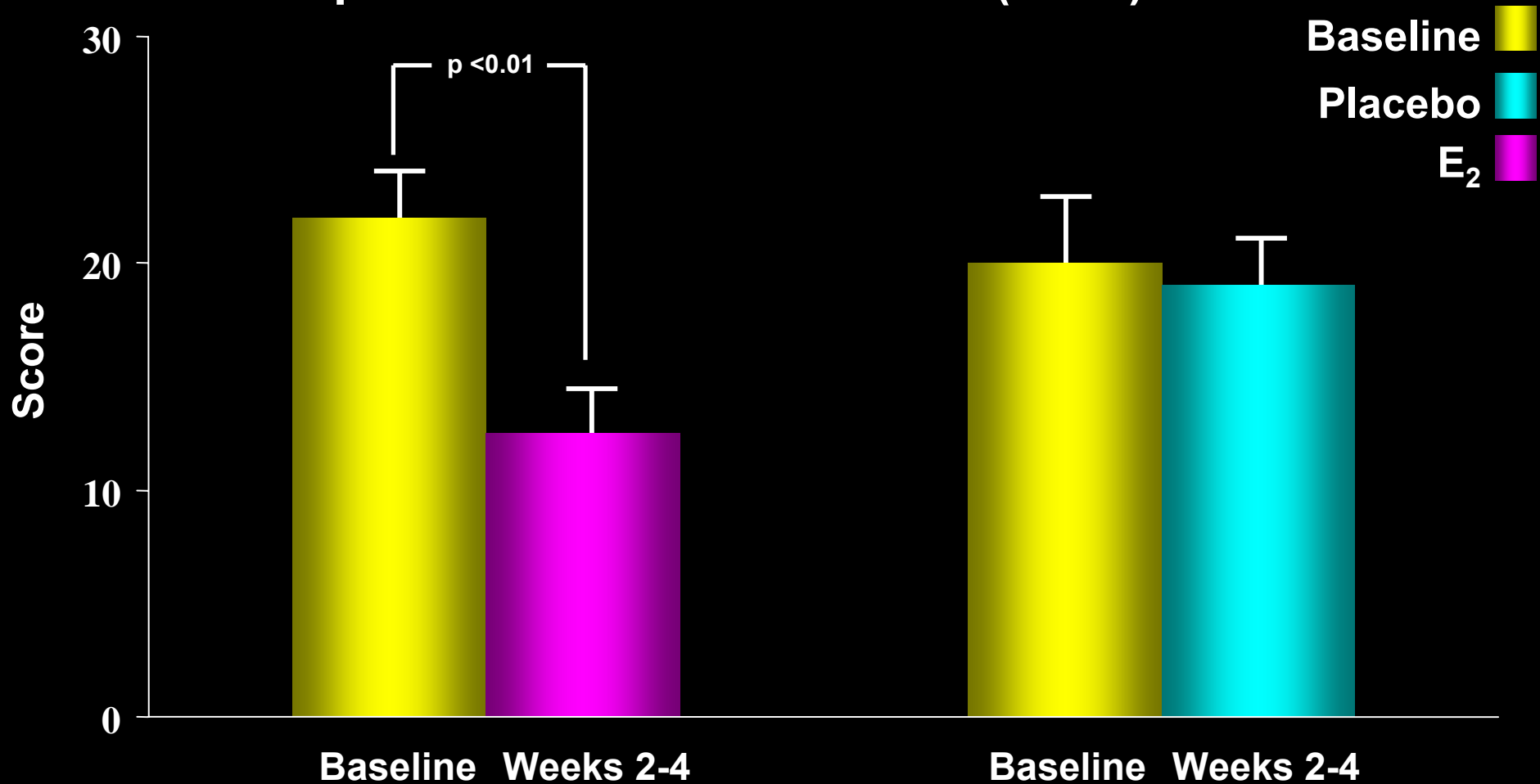


# Effect of E<sub>2</sub> on Perimenopausal Depression



# Effect of E<sub>2</sub> on Perimenopausal Depression

## Depression – No Hot Flashes (n=18)



Center for Epidemiological Studies of Depression

Schmidt et al, 2000

# Estradiol Therapy in Perimenopausal Depression:

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- Demonstrated acute efficacy
- Efficacy in post-menopause unlikely
- Predictors of response unknown
- Duration of efficacy unknown
- Mechanism of efficacy unknown
- Role of estradiol **withdrawal** in depression unknown



# Study Designs

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## 1. Hormonal Treatments

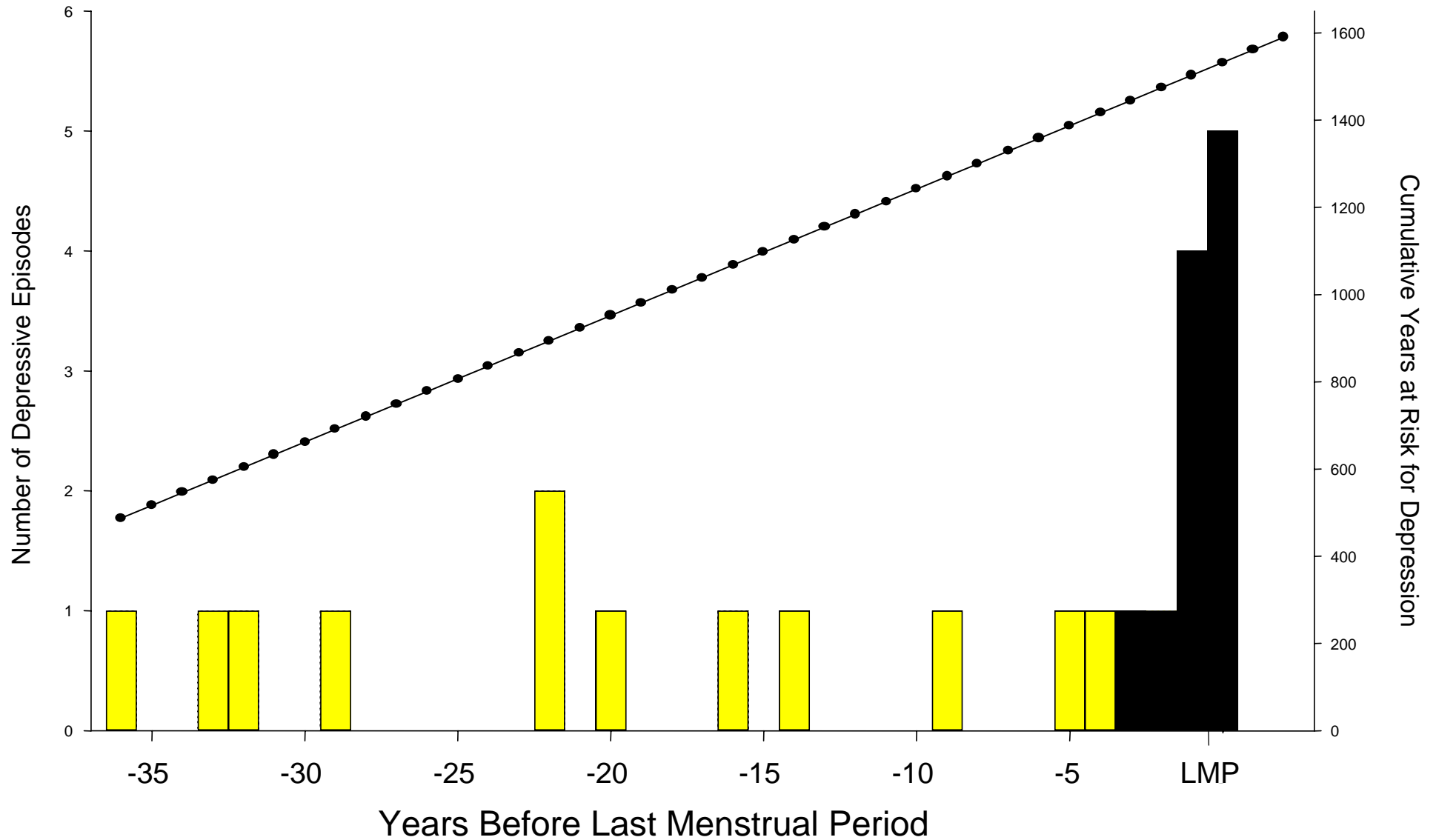
**Estradiol in perimenopausal depression**

## 2. Naturalistic

**Prospective evaluation of menopausal transition**

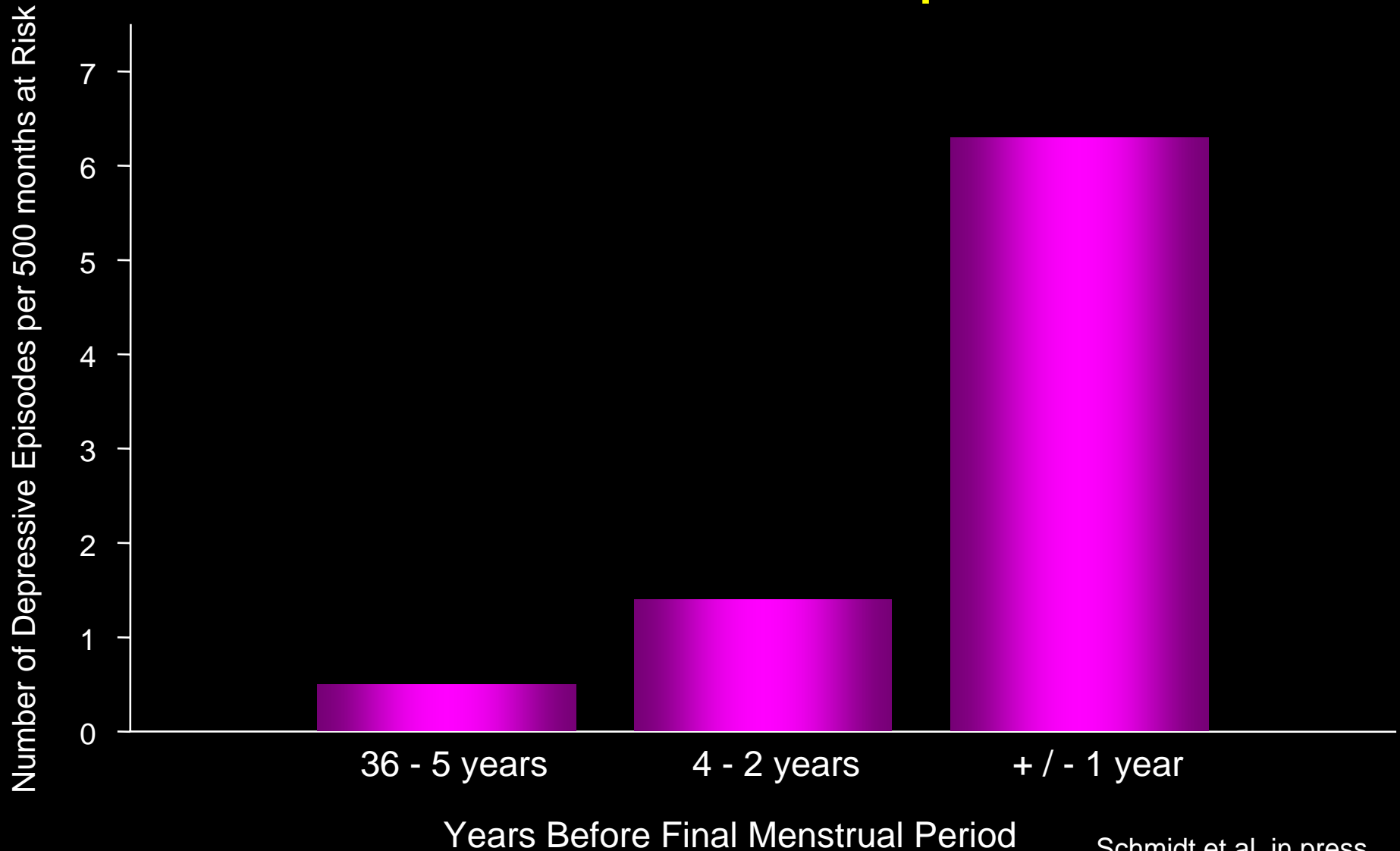
## 3. Experimentally-induced hypogonadism

# Longitudinal Study: Increased Risk of Depression Proximate to the Menopause



Schmidt et al, in press

# Longitudinal Study: Increased Risk of Depression Proximate to the Menopause



# Study Designs

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## 1. Hormonal Treatments

**Estradiol in perimenopausal depression**

## 2. Naturalistic

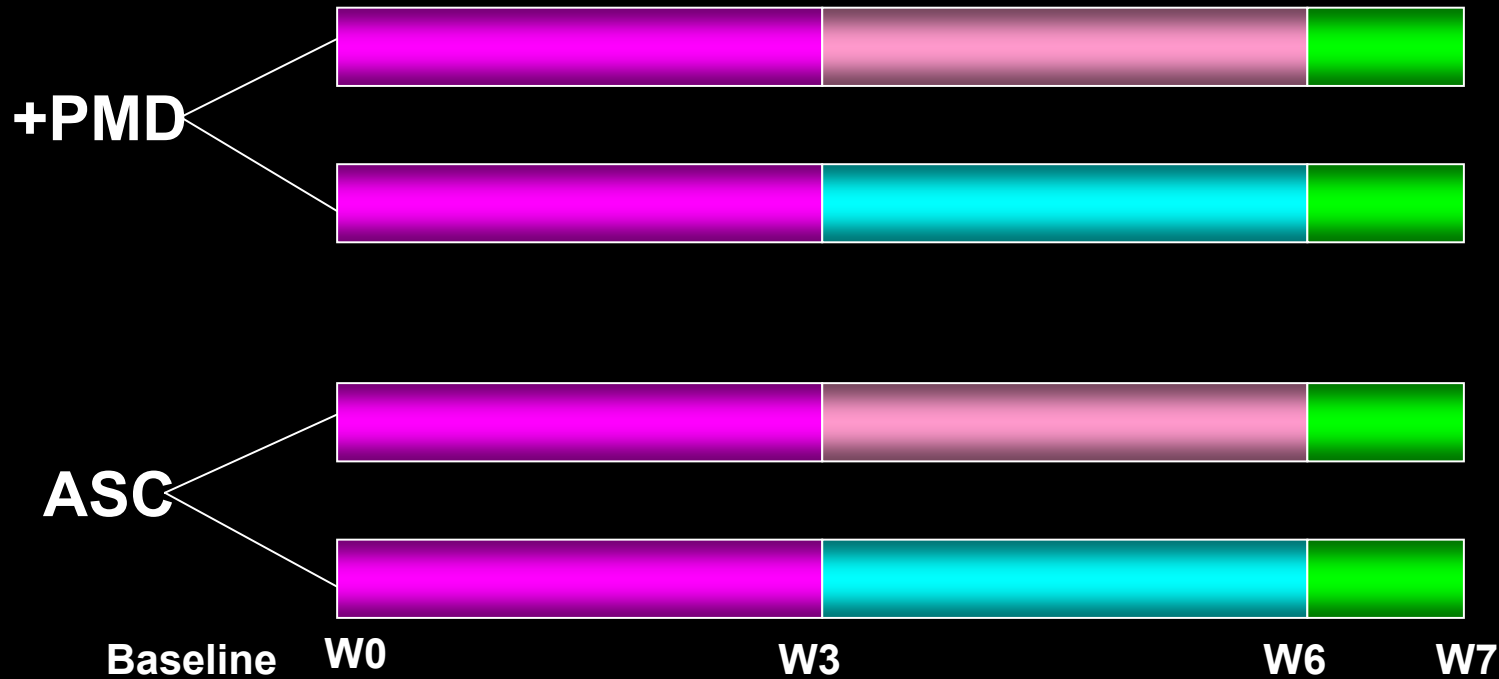
**Prospective evaluation of menopausal transition**

## 3. Experimentally-induced hypogonadism

**Estradiol withdrawal in perimenopausal depression**





**GnRH agonist in normal volunteers**

# E2 Withdrawal Schematic

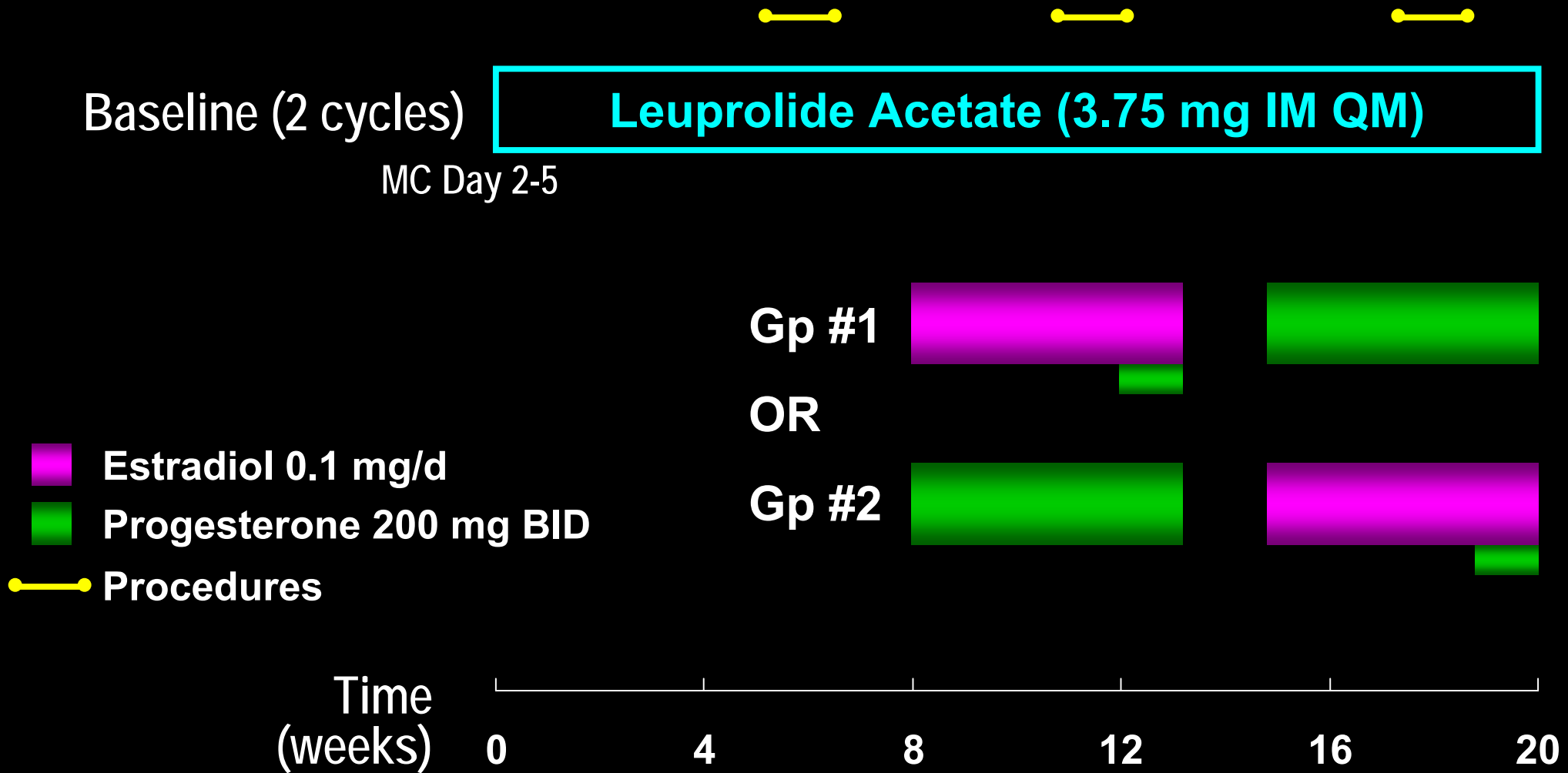


**+PMD = Past history of perimenopause- related depression responsive to Estrogen**

**ASC = Asymptomatic controls**

-  -Estradiol 100 µg/day (open label)
-  -Estradiol 100 µg/day (double-blind)
-  -Placebo (skin patch)
-  -Provera 10 mg daily (PO)

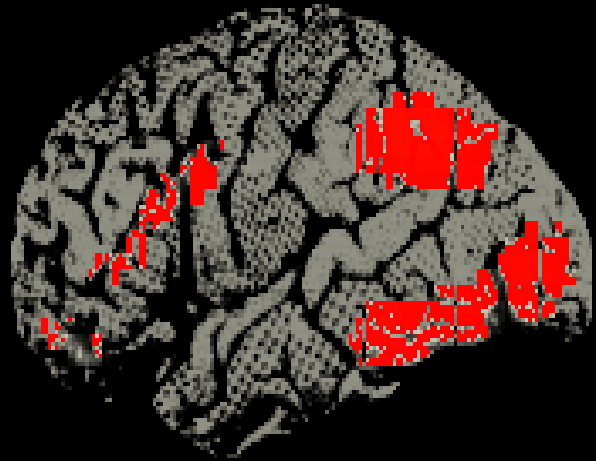
# Central Nervous System Effects of GnRH Agonist & Gonadal Steroid Replacement in Asymptomatic Controls—Schematic



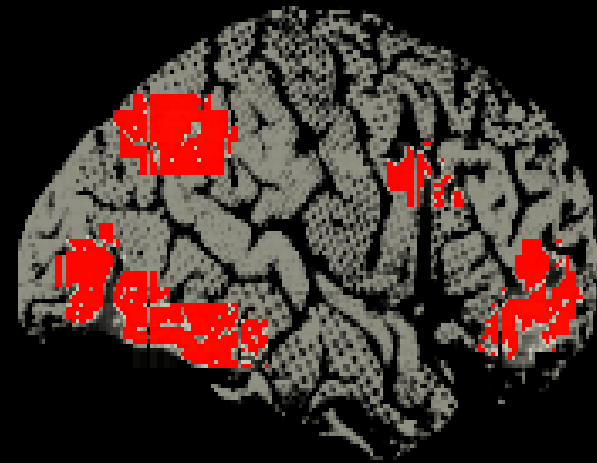
# WISCONSIN CARD SORTING TEST - ACTIVATION

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CONTROLS (n=24)



Left



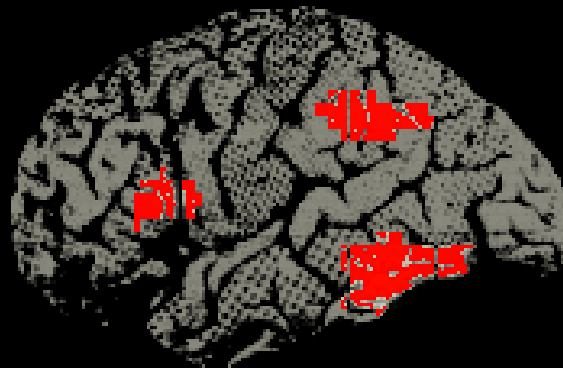
Right

# ALTERED WORKING MEMORY ACTIVATION WITH HORMONAL MANIPULATION

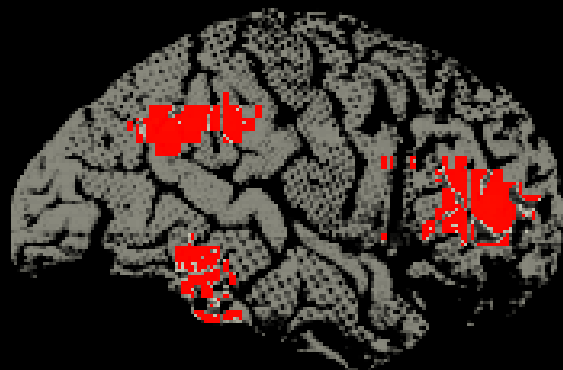
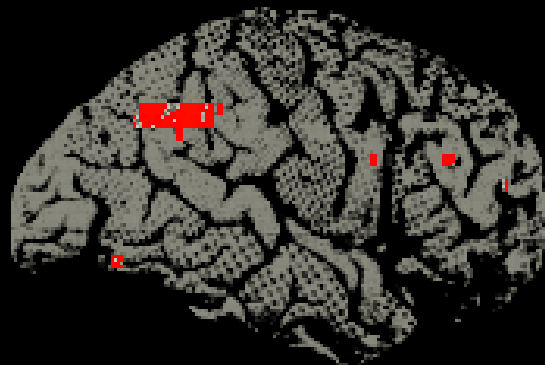
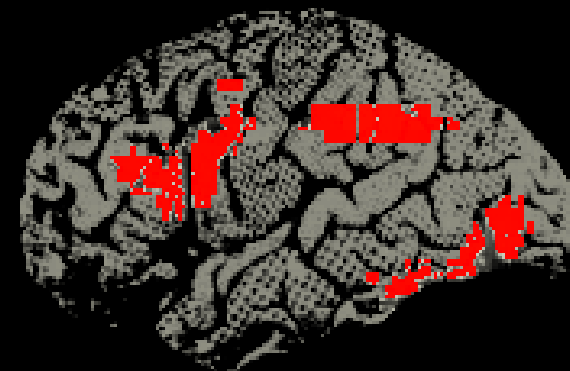
Lupron Alone



Lupron + Estrogen



Lupron + Progesterone



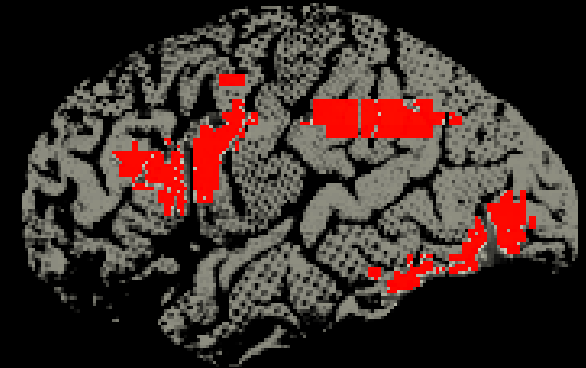
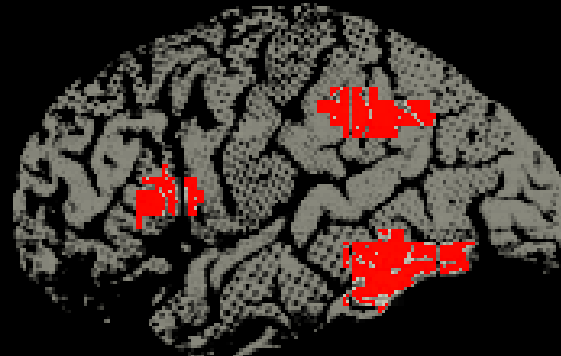
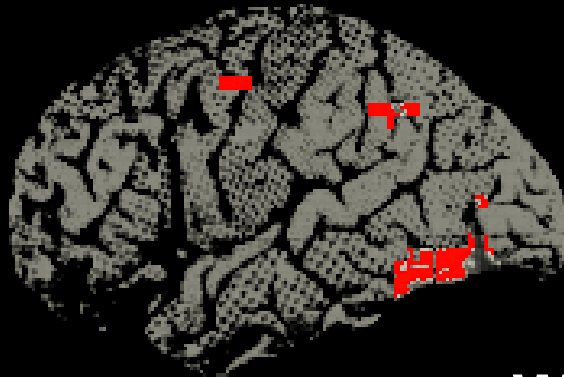


# rCBF ACTIVATION DURING HORMONAL MANIPULATION

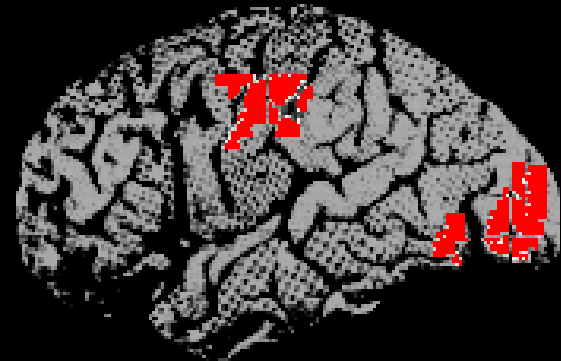
Lupron Alone

Lupron + Estrogen

Lupron + Progesterone



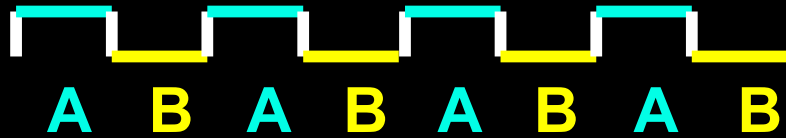
WORKING MEMORY ACTIVATION



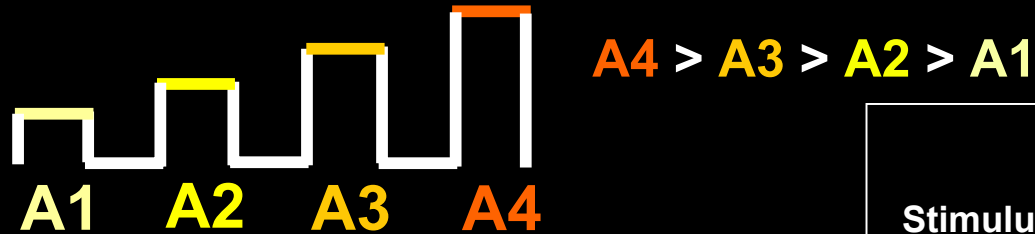
PRIMARY MOTOR & VISUAL ACTIVATION

# FUNCTIONAL NEUROIMAGING: RESEARCH DESIGN & ANALYSIS

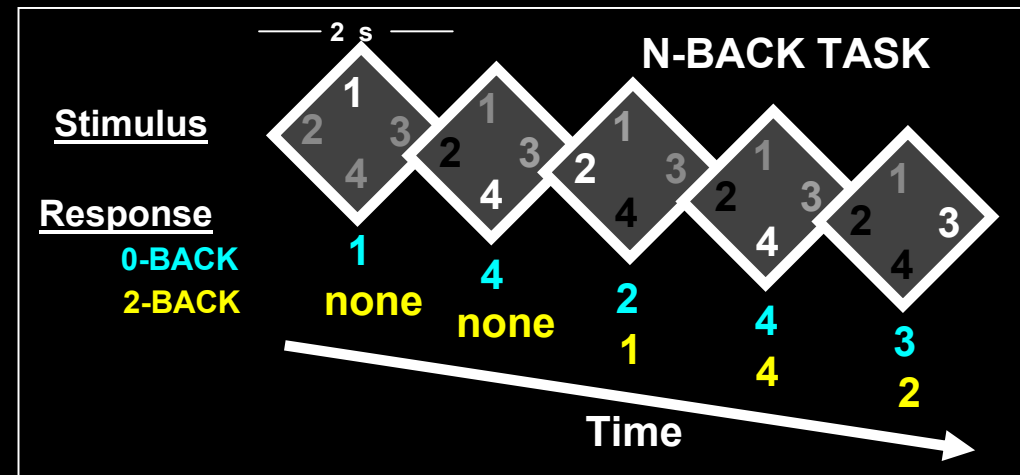
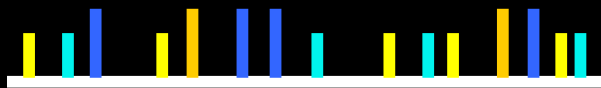
- COGNITIVE SUBTRACTION: A - B



- PARAMETRICALLY GRADED TASKS:



- EVENT-RELATED fMRI:



# Objectives:

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- 1) Discrepancies**
- 2) Effects**
- 3) Need to know**
- 4) Lessons learned**