

# Women & Dementia: Estrogens, Memory, & Alzheimer's Disease

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# Plan:

- i. Conditions more common in women than men:  
Alzheimer's disease: **Might it be due to estrogen loss?**
- ii. Discuss estrogens and their effects on brain & their importance in establishing sex differences
- iii. Discuss the role of estrogen withdrawal on memory decline in older women
- iv. **What is the pathway from ovarian removal in younger women to an increased risk of AD?**

# Introduction:

## Sex & Gender effect the brain

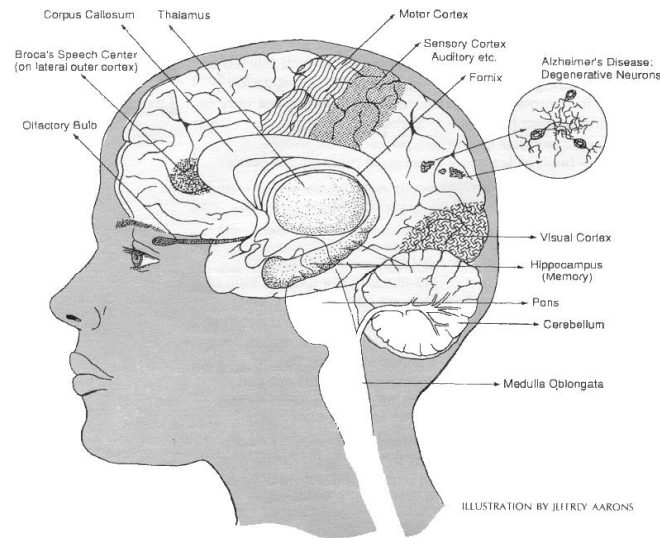
- Biological Factors = Sex
- Social Factors = Gender

Rigour in Science and  
Medicine!



Canadian Institutes of Health Research Institute of Gender & Health, established 2000

# Conditions More Common in Women



# Conditions More Common in Women: Chronic Pain

- Women are more sensitive to experimentally induced pain & tend to have lower pain thresholds than men (Paller, Campbell et al., 2009; Riley et al. 1998; Wiesenfeld-Hallin, 2005)
- Many chronic non-cancer pain (CNCP) conditions occur more frequently in women (Berkley, 1997; LeResche, et al., 2003; Unruh, 1996)
- CNCP displays a significant increase in prevalence between puberty and menopause, i.e., in the reproductive years (Martin, 2009)
- Pain thresholds highest when estrogen is highest (Hassan et al., 2014)

# Conditions More Common in Women: Catamenial Epilepsy

- Recurrent seizures correlated with estrogen level/ratios
- Sub-classified by timing during menstrual cycle
- 1/3 of women with inadequately controlled seizures meet criteria for catamenial epilepsy (Herzog, 2008)
- Catamenial epilepsy is an uncommon condition. Patient claims about frequency of seizures in relation to menstruation are not always accurate (Duncan et al., 1993)

# Conditions More Common in Women: Depression

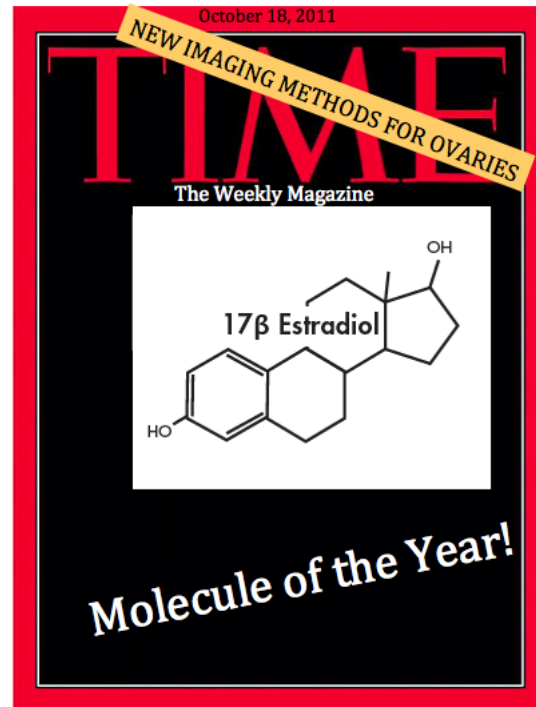
- PMDD: 3-9% adult females
  - Disinterest in daily activities and relationships
  - Fatigue or low energy
  - Feeling of sadness or hopelessness, possible suicidal thoughts
  - Feelings of tension or anxiety
  - Feeling out of control
  - Food cravings or binge eating
  - Mood swings marked by periods of teariness
  - Panic attack
  - Persistent irritability or anger that affects other people
  - Physical symptoms, such as bloating, breast tenderness, headaches, & joint or muscle pain
  - Problems sleeping
  - Trouble concentrating
- (Rubinow & Schmidt, 2006)

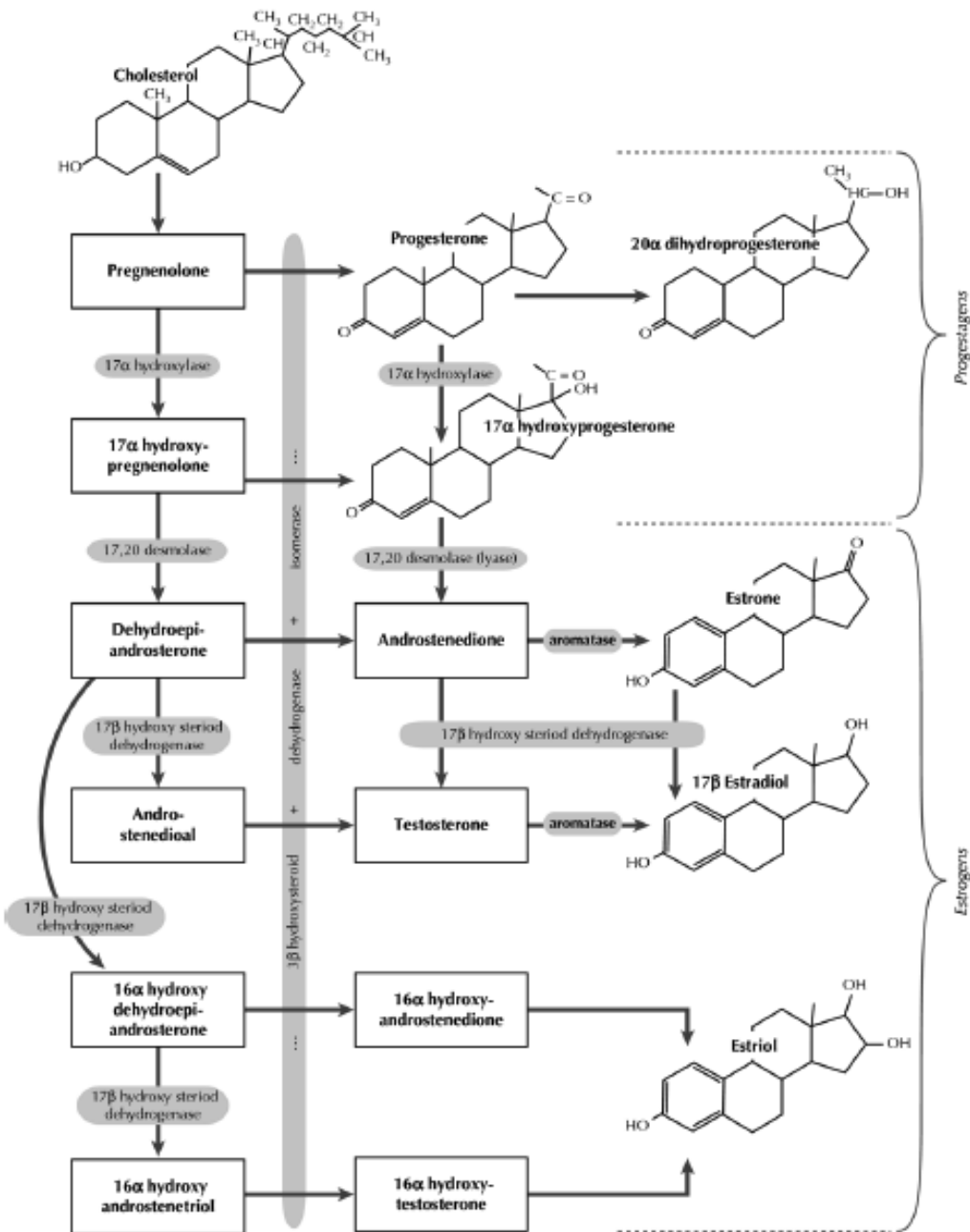
# Conditions More Common in Women: AD

- Prevalence of AD is higher in women 2:1 (Hebert et al. 2013; Association As. Alzheimer's disease facts and figures, 2014)
- Female advantage in verbal memory maintained at prodromal stages of AD (Sundermann et al., 2016)
- Women have faster atrophy rates (Hua et al., 2010; Ardenkani et al., 2016; Holland et al., 2013)
- APOE  $\epsilon$ 4 allele confers higher risk of AD onset & conversion in women (Farrer et al., 1997; Altmann et al., 2014; Neu et al., 2017)
- Greater hippocampal atrophy and faster rate of cognitive decline in the presence of CSF A $\beta$ 42 and total tau (Koran et al., 2016)



# Estrogens & the Brain



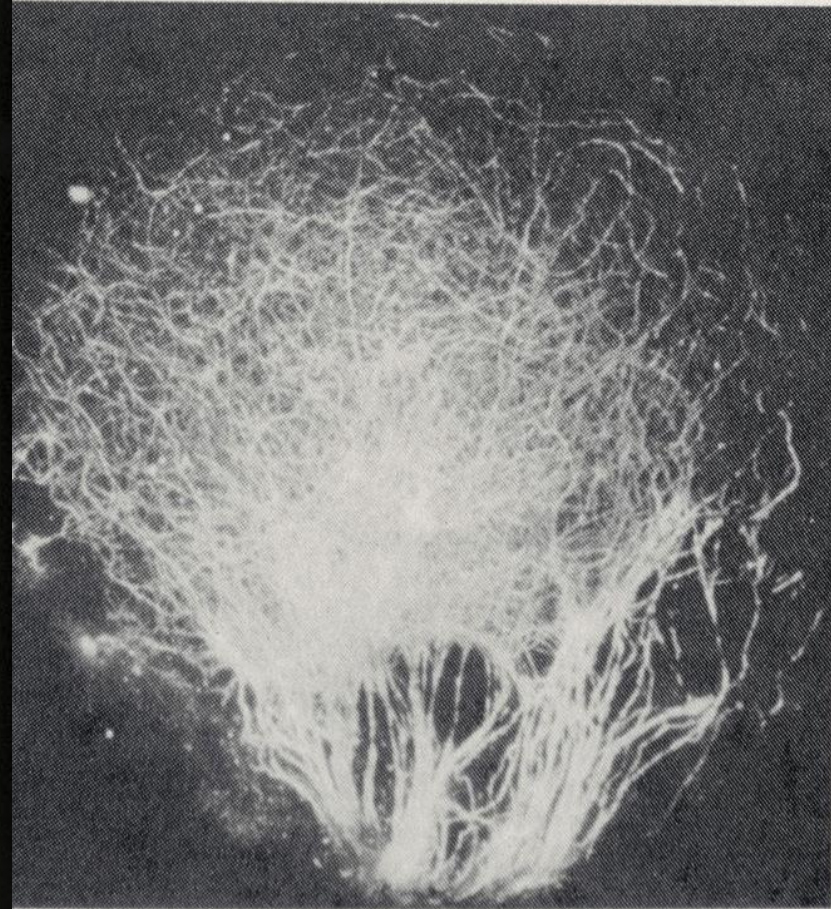
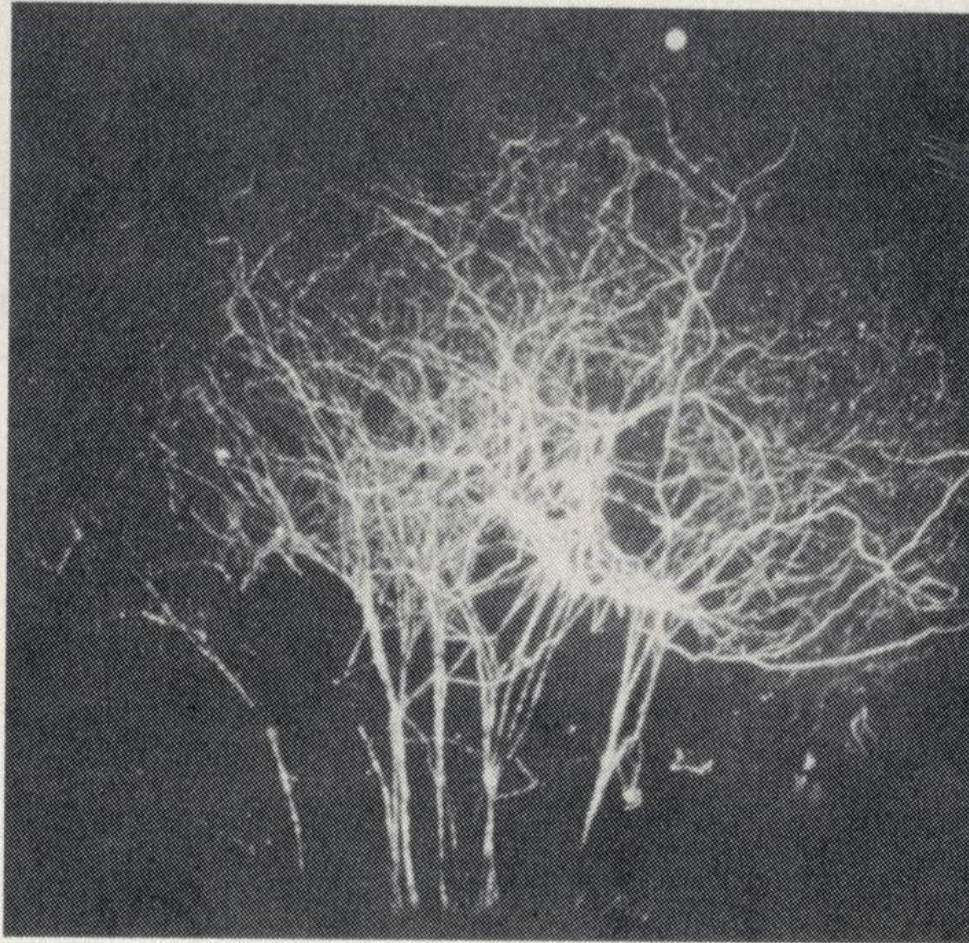


# Estrogens are synthesized from cholesterol

Bellem et al., 2011

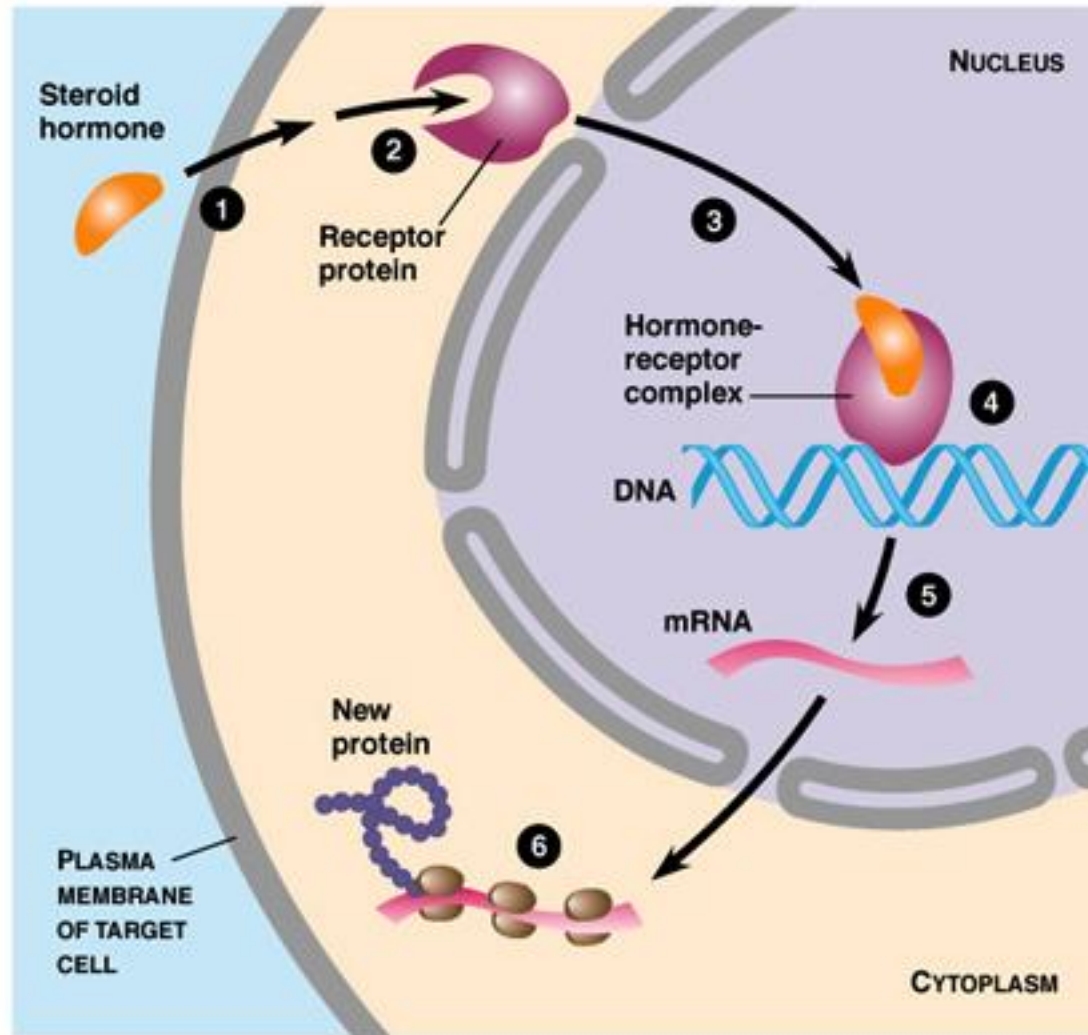
# Estrogens are growth factors

(A)



Toran-Allerand, 1976

# Estrogens effect gene transcription



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# Estrogens may lead to sex differences during development

## rodent:

- medial preoptic area (hypothalamus)
  - SDN
  - VMN
- VTA
- SNB
- BNST

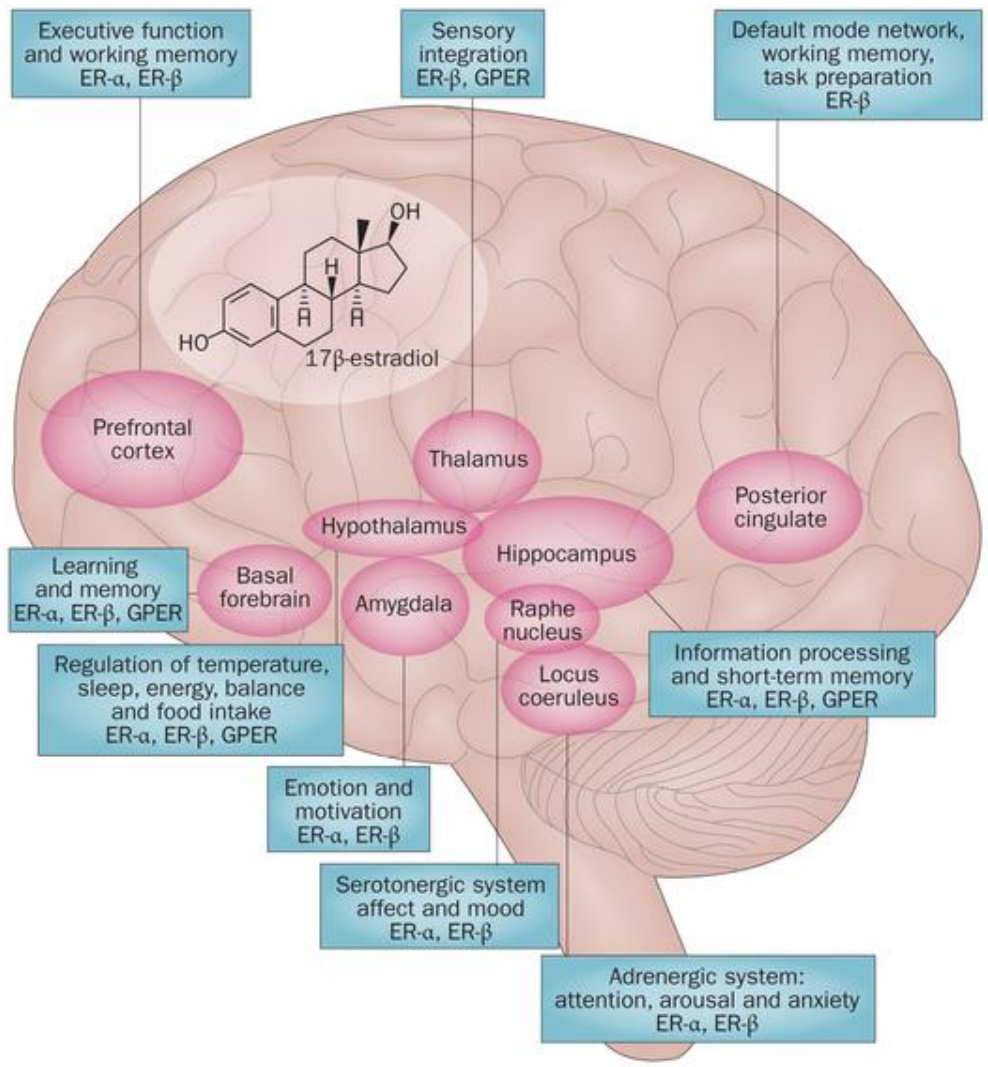
## human

- INAH nuclei
- Onuf's nucleus (ventrolateral group)
- activation of left and right hemispheres
  - cerebral cortical areas
  - amygdala

## behaviour:

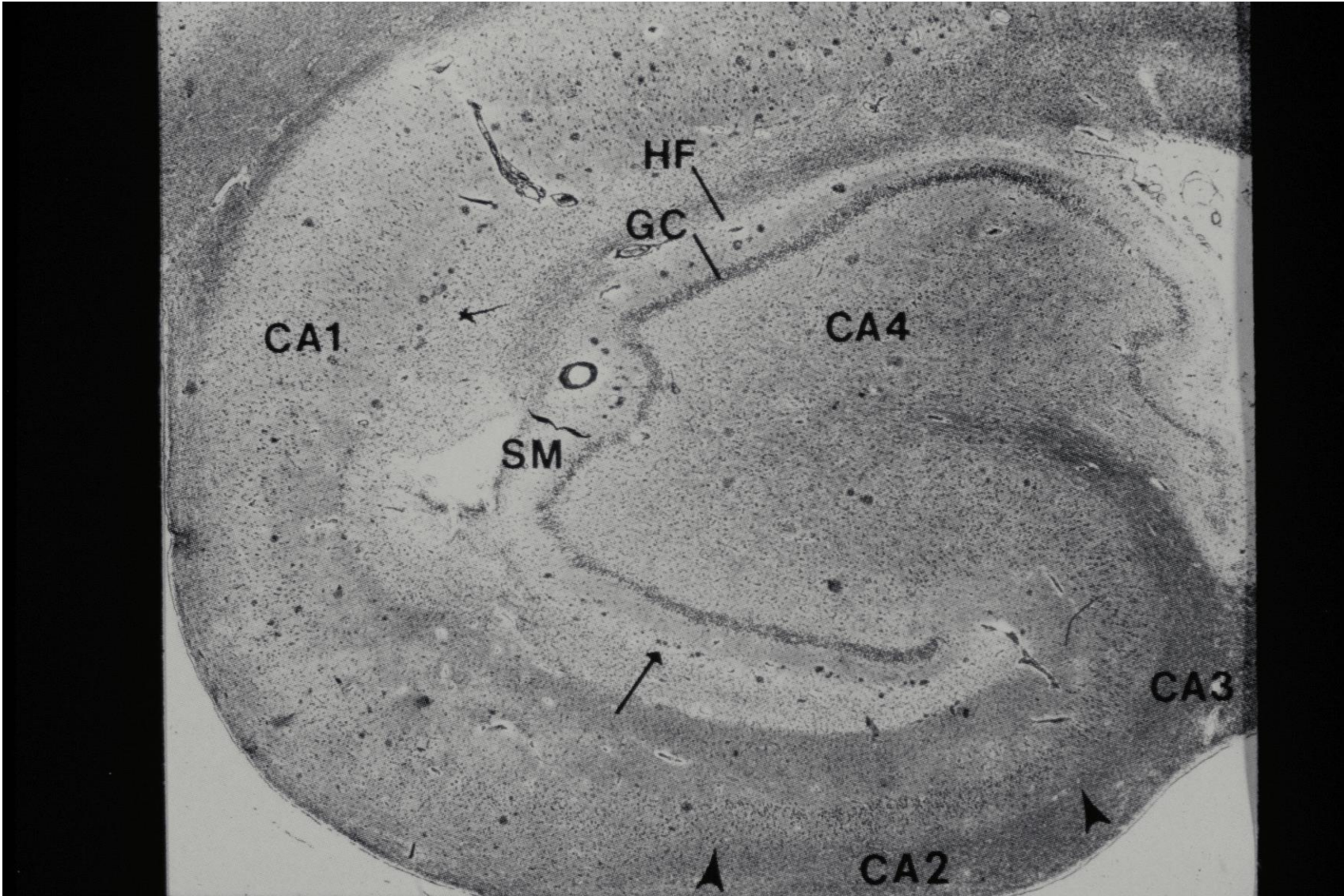
- women outperform men in verbal tasks
- verbal memory declines at slower rate, even in the elderly.
- men perform better in visuospatial and motor coordination tasks

# Estrogen Receptors in the Brain

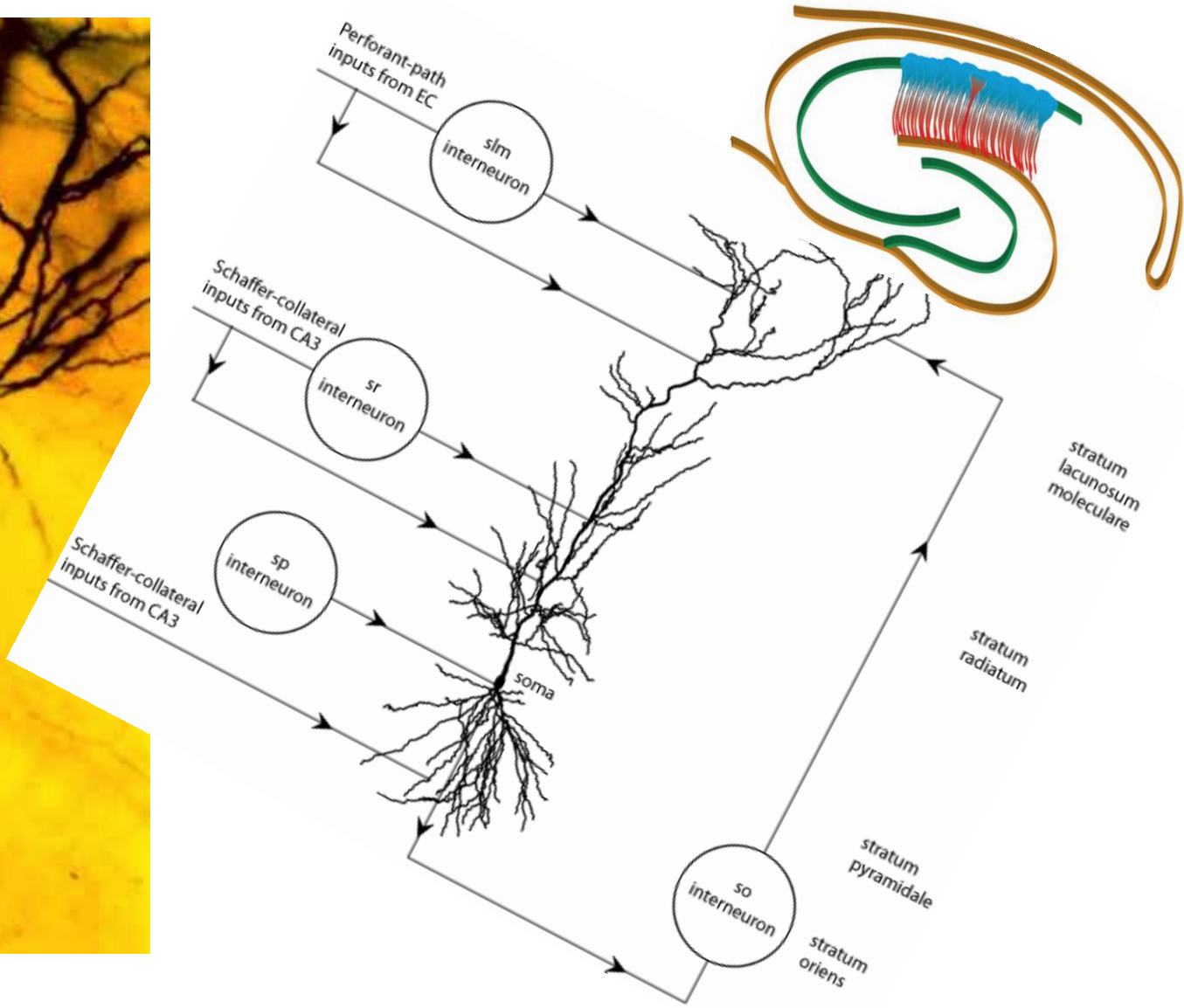


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# Estrogen Receptors in the Brain

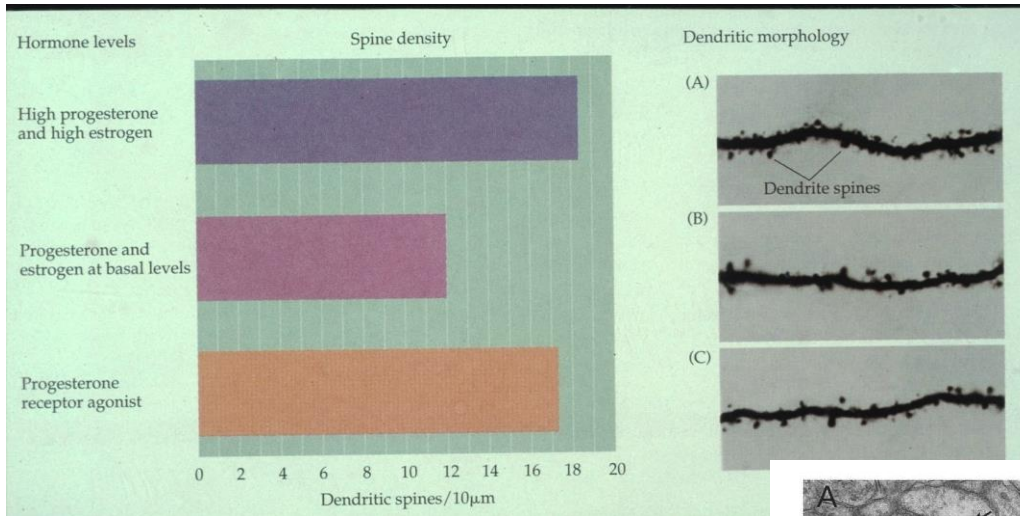


# Estrogen Receptors in the Brain



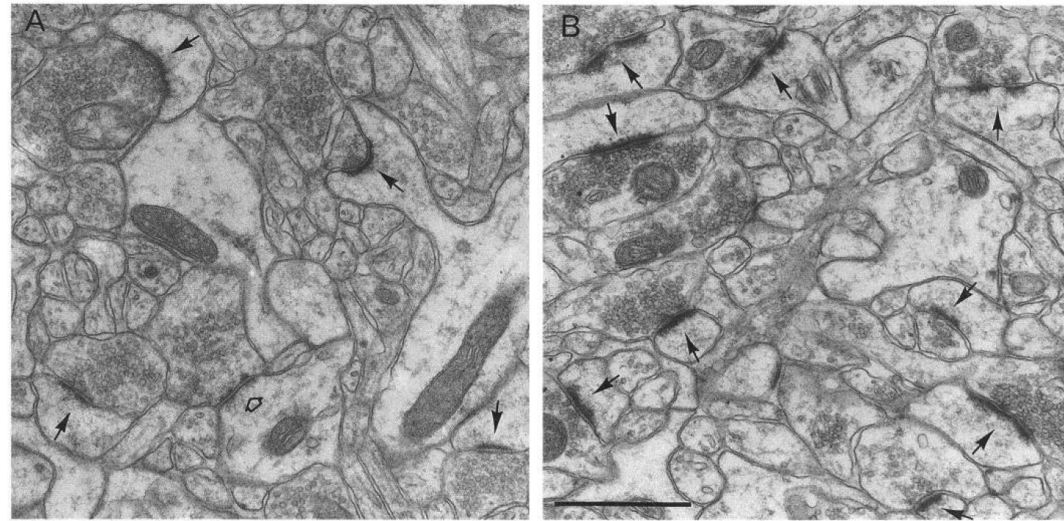


# Estrogens & CA1 Synaptic Density



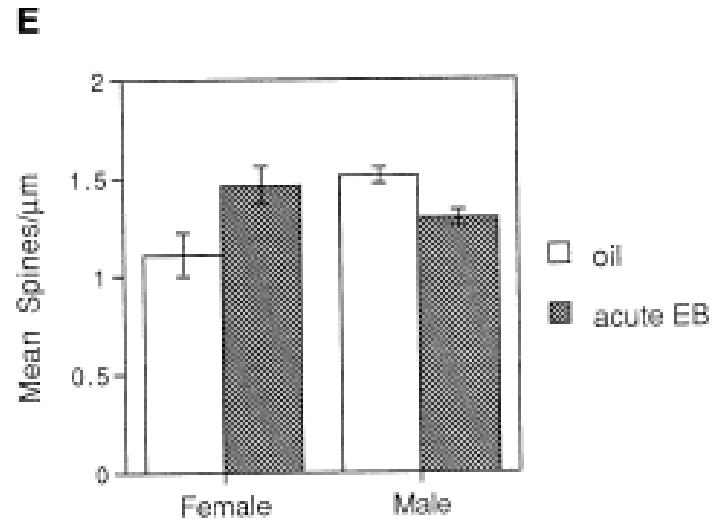
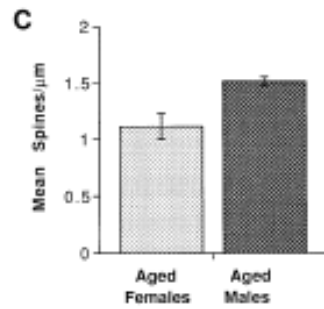
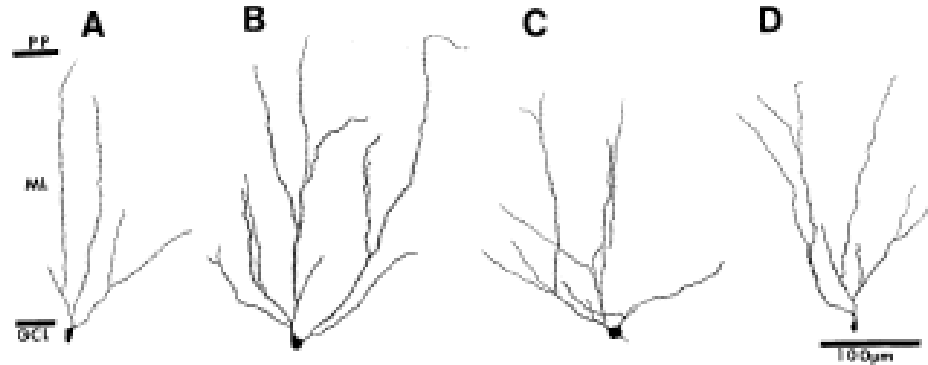
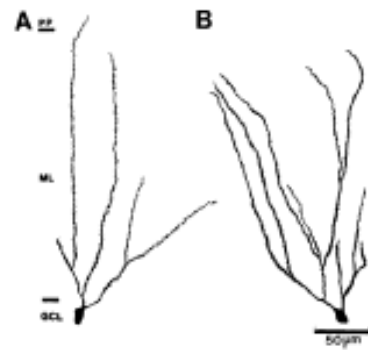
Young rodents  
estrous cycle

Woolley & McEwen, 1992



**Figure 2.** Electron micrographs of the stratum radiatum in the hippocampal CA1 region of an ovariectomized adult female rat that received oil (A) or estradiol (B). Synapses on dendritic spines are marked by *solid arrows*, whereas the *open arrow* in A marks a synapse on a dendritic shaft. Scale bar, 1  $\mu$ m.

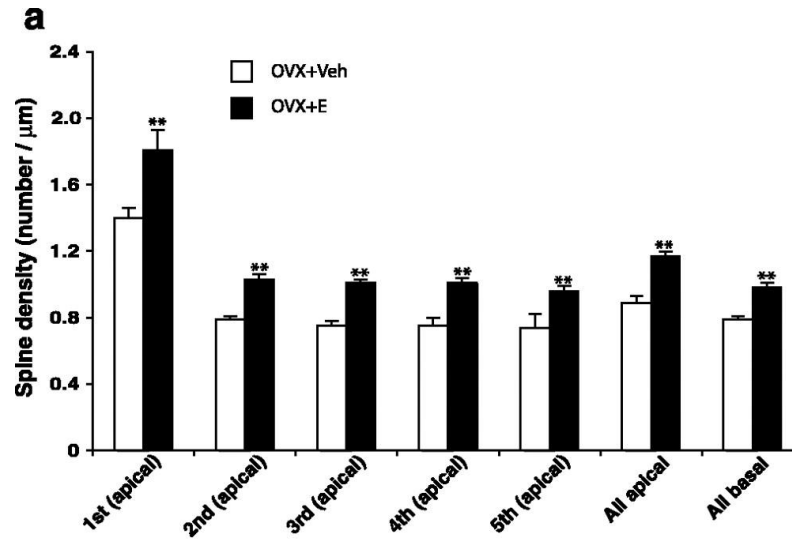
# Dentate Granule Cell Spine Density



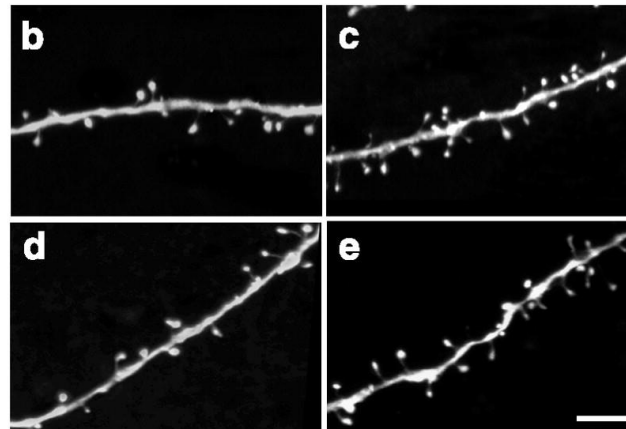
Miranda et al, 1999

Ovx rodents  
E2 administration

# Estrogens & PFC Spine Density



Ovx old Rhesus  
E2 administered

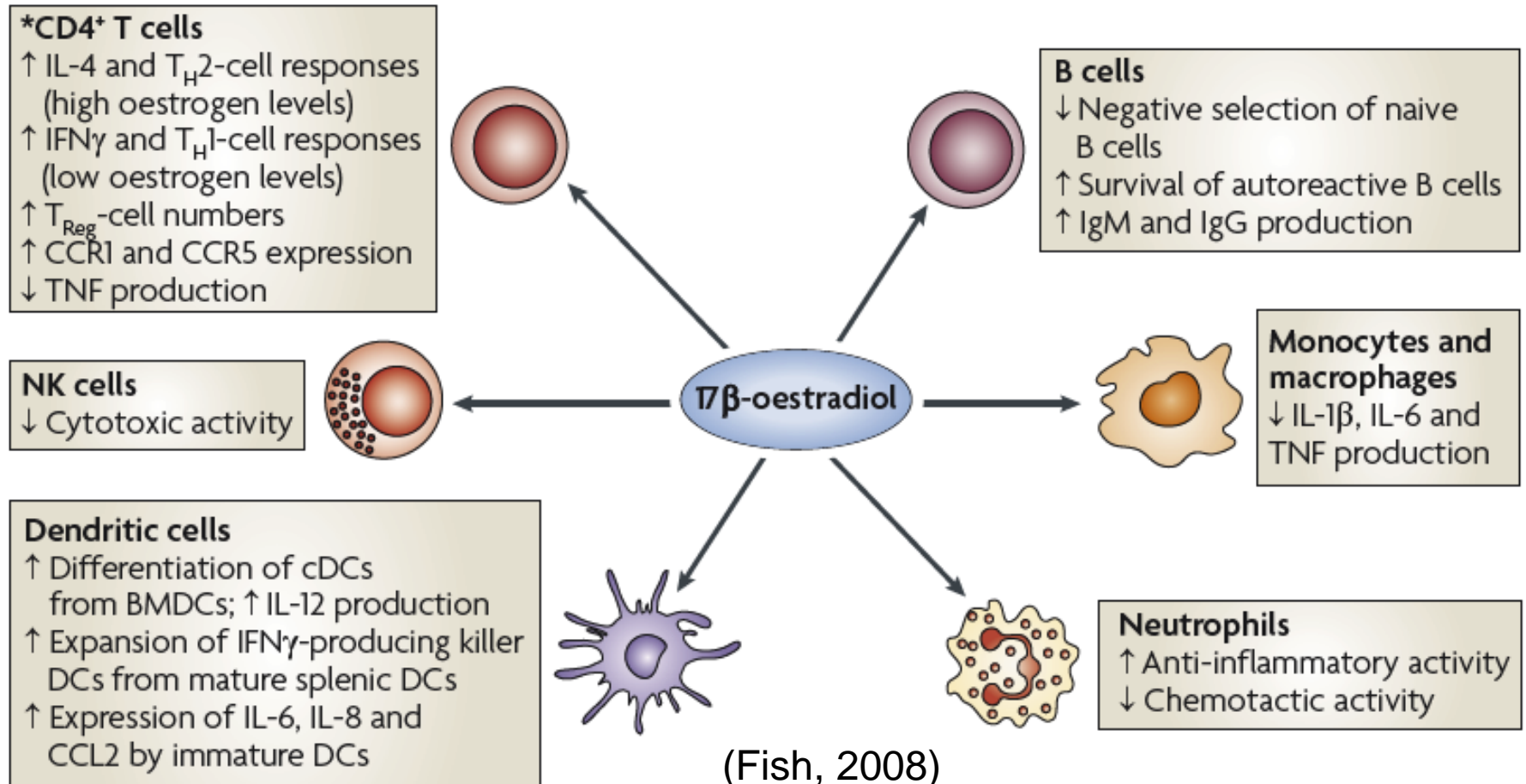


Hao et al, 2004

# Estrogens & Other Body Systems (that could effect the brain)

- Women without ovaries 2.62X more likely than premenopausal women to get CVD (Shuster et al., 2008)
- Women with menopause before the 40 were at an increased risk of ischemic heart disease; significant risk was only found in women who were not treated with estrogens by age 45 (Lokkegaard et al., 2006)
- Changes in immune system response and regulation—changes to T-lymphocytes correlated with changes in the E2 receptors (Zhang et al., 2009)
- Women without ovaries due to BRCA1/2m revealed that most of these women who had BSO prior to 55 developed a different type of cancer within a decade (excepting lung cancer, which developed at a later average age) (Cohen et al., 2012)

# Estrogens & the Immune System



# Summary so far

- Some brain conditions are more common in women than in men
- Estrogens during development make a difference in shaping neural circuits of the brain
- During adulthood, these changes in hormonal levels might make a difference to neuronal connectivity & activity
- This will affect some domains of cognition and across the life span
- Estrogens' effects on other body systems may also have an effect on the brain

# Estrogens & Memory:

## Older Women

# Estrogen Withdrawal & AD

- Prevalence of AD is higher in women 2:1 (Hebert et al. 2013; Association As. Alzheimer's disease facts and figures, 2014)
- Performance on short delay recall is a significant predictor of AD (Tierney et al., 2005)
- Age of oophorectomy is correlated with dementia risk (Rocca et al., 2007)



# Estrogens, Cognition, & Aging

- Estrogen/HRT improves verbal and non-verbal (spatial, visual and attentional) memory in surgically and aging menopausal women (Kimura, 1995; Phillips & Sherwin, 1992; Resnick et al, 1997; Jacobs et al., 1998; Maki et al., 2001; Smith et al., 2001; Tierney et al., 2009)
- 2-year, randomized, double-blind, placebo-controlled trial of 142 women aged 61-87—women with hormone replacement who scored at or above the average showed significantly less decline than the placebo group in short-delay verbal recall after 1 year,  $p = 0.007$  and 2 years,  $p = 0.01$ . no treatment effects were found in women below the average in either year (Tierney et al., 2009)
- E2 replacement improves DR & D(N)MS task in Rhesus and is accompanied by increased spine density in PFC (Rapp et al., 2013; Baxter et al., 2018)

# Estrogens, Cognition, & Aging

- **Negative relationship** between HRT use and cognitive scores (Espeland et al., 2004, File et al., 2002)
- COGENT p-menopausal; randomized, 2x blind, placebo-controlled; **no differences** between groups on any cognitive or QoL measures, except for an increase in sexual interest and thoughts with HT. Modest negative effects on short- and long-term verbal memory approached significance; baseline vasomotor symptoms (VMS) showed a decrease in VMS and improvement in general QOL, but no cognitive benefit vs placebo (Maki et al., 2007)
  - **No relationship at all** (Binder et al., 2001; Dumas et al., 2006; Joffe et al., 2006)
  - Women's health initiative Memory Study (WHIMS) a corollary to the women's health initiative (WHI): HRT has an **adverse effect** on cognition in postmenopausal women (Espeland et al., 2004; Shumaker et al., 2003)

# But...Confounders

- **Type of hormone given**  
—best results observed with 17-beta estradiol (animal studies (Tierney et al., 2009))
- **Timing of administration**  
—there may be a critical period for which the effectiveness of estrogen replacement is substantially reduced as time post menopause (natural or surgical) is increased (Daniel et al., 2006; Markowaska & Savonenko, 2002)
- **Administration pattern** (Miranda et al., 1997; Baxter et al., 2018)

# Estrogens & Memory:

## Young Women & Surgical Menopause

# Estrogens & Memory

changes w/ menstrual cycle

- Performance on spatial memory tasks vary across the menstrual cycle in and are associated with estradiol levels (Duff & Hampson, 2001)
- Working memory improves in the late follicular phase (Schöning et al., 2007)

# Estrogen Withdrawal in Young Women

## (Prior to natural menopause)

- Estrogen withdrawal prior to natural menopause is correlated with decreased memory function if not replaced for 3 months post-oophorectomy (Sherwin, 1988)
- E2 replacement improves verbal word recall after two months treatment post-oophorectomy (Phillips & Sherwin, 1992)

# Estrogen Withdrawal in Young Women

## (Prior to natural menopause)

- Estrogen withdrawal prior to natural menopause is correlated with decreased verbal memory (Farrag et al., 2002)

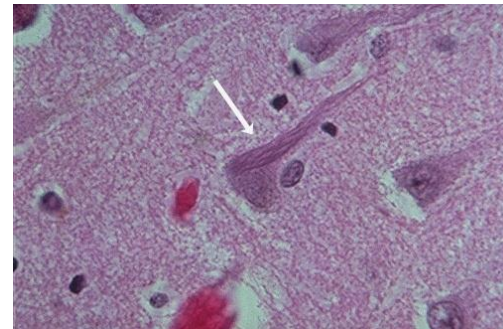
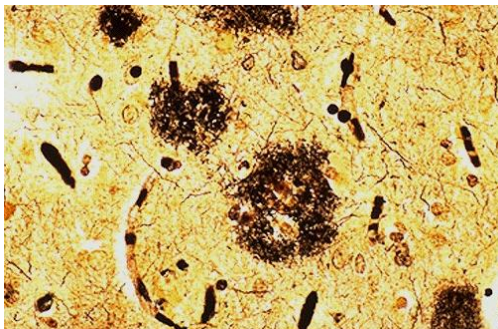
	Preoperatively	3 months postoperatively	6 months postoperatively
MMSE	23.54 ± 3.2	22.86 ± 3.0**	21.23 ± 2.9***
<i>WMS</i>			
Digit span	8.17 ± 1.7	7.86 ± 1.7	6.11 ± 1.9***
Mental control	2.19 ± 1.5	1.67 ± 1.3	1.21 ± 1.1***
Logical memory	9.19 ± 2.1	8.76 ± 1.7	7.99 ± 1.5**
Associate learning	10.94 ± 4.9	9.96 ± 4.4*	9.89 ± 4.6*
Visual reproduction	1.92 ± 1.3	1.63 ± 1.1	1.46 ± 1.2*
<i>ERPs</i>			
N100 latency	126.9 ± 26.9	128.2 ± 27.4	135.00 ± 29.5
P200 latency	227.96 ± 41.9	240.82 ± 34.3	236.91 ± 36.5
P300 latency	338.71 ± 37.9	360.09 ± 40.4*	367.82 ± 51.3**

\* p < 0.05; \*\* p < 0.001; \*\*\* p < 0.0001 (comparison with the preoperative data).

# Estrogen Withdrawal in Young Women

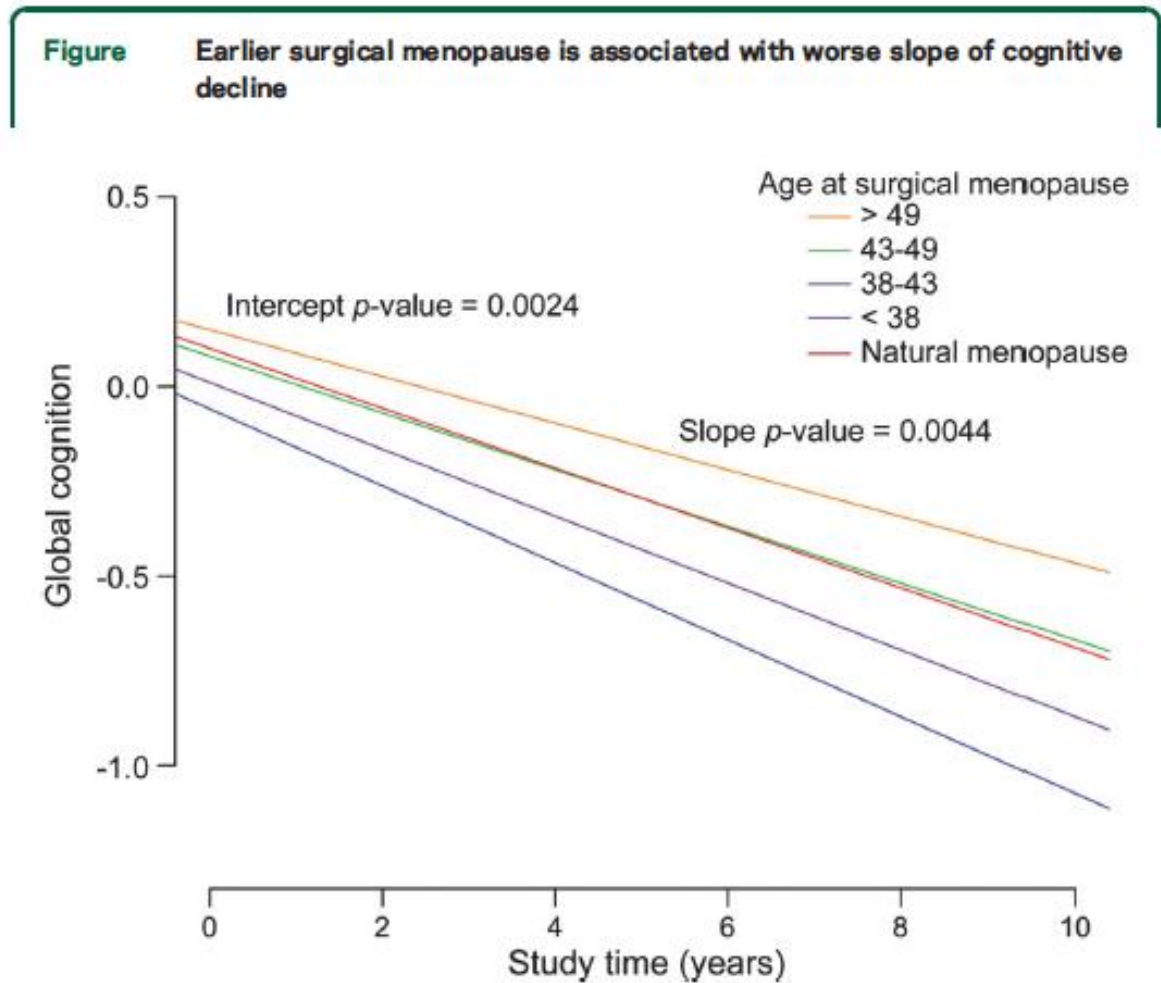
## (Prior to Menopause due to Aging)

- Age of oophorectomy is correlated with increased all causes of death and dementia risk (Rocca et al., 2007)
- age at surgical menopause related to decline in a global cognition score.
- decline in 5 cognitive subdomains
- Increase in a global measure of the burden of AD pathology. (Bove et al., 2014)



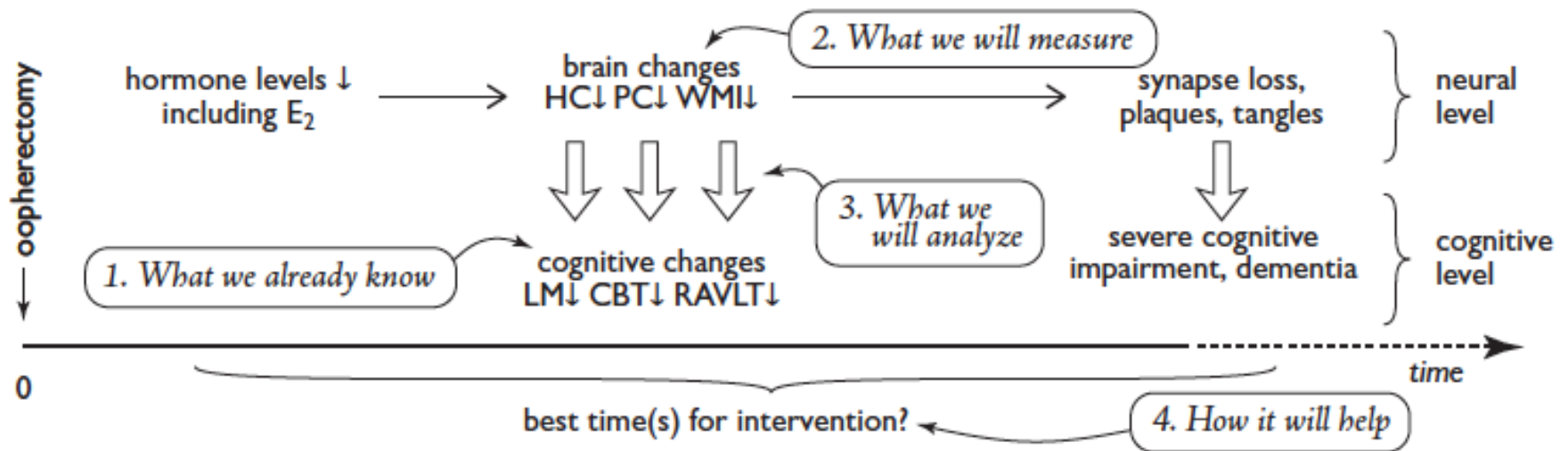


# Estrogen Withdrawal in Young Women (Prior to Menopause due to Aging)



(Bove et al., 2014)

# Our Project in the Large: In women with the BRCA1/2 mutation



**Estrogen withdrawal may establish important sex differences in aging and dementia**

# Ovarian removal in young women

Our Population: Women with BRCA1/2 mutations

Recommended Prophylaxis: Bilateral Salpingo-oophorectomy (BSO)

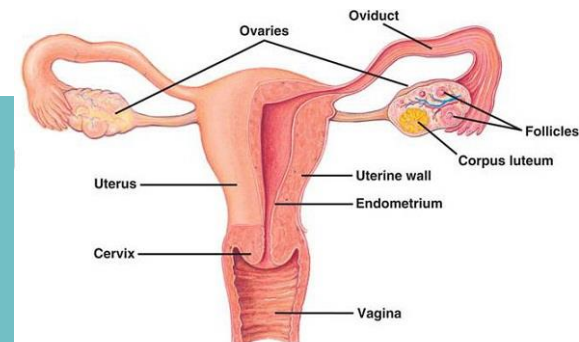
- Recommended before age 40
- 80% reduction in risk of dying from ovarian cancer
- 56% reduction in risk of dying from breast cancer
- 77% reduction in risk of dying from any cause

NCI

• Because it's prophylaxis, most women are healthy

## Oophorectomies

- In US—600,000 oophorectomies performed annually
- 50% are BSO



# Ovarian removal in young women

## Experimental Design

- Women with BRCA1/2 Mutation
- Tested 1 – 10 years post-oophorectomy
- Each women tested once a year for 3 years
- Provides information from 1 – 13 years post oophorectomy
- Neuropsychological measures
- Imaging
- Measure E2, P4, APOE genotype

**Toronto, Linköping, Sweden & Montreal**

# Ovarian removal in young women: Cognitive Tasks

## Verbal Memory

- Logical Memory (Wechsler Memory Scale)
- Digit Span Forward
- Rey Auditory Verbal Learning Task (RAVLT)

## Verbal Fluency

- Phonemic and Semantic fluency (cluster and switching)

## Recollection/Familiarity

- Remember/know

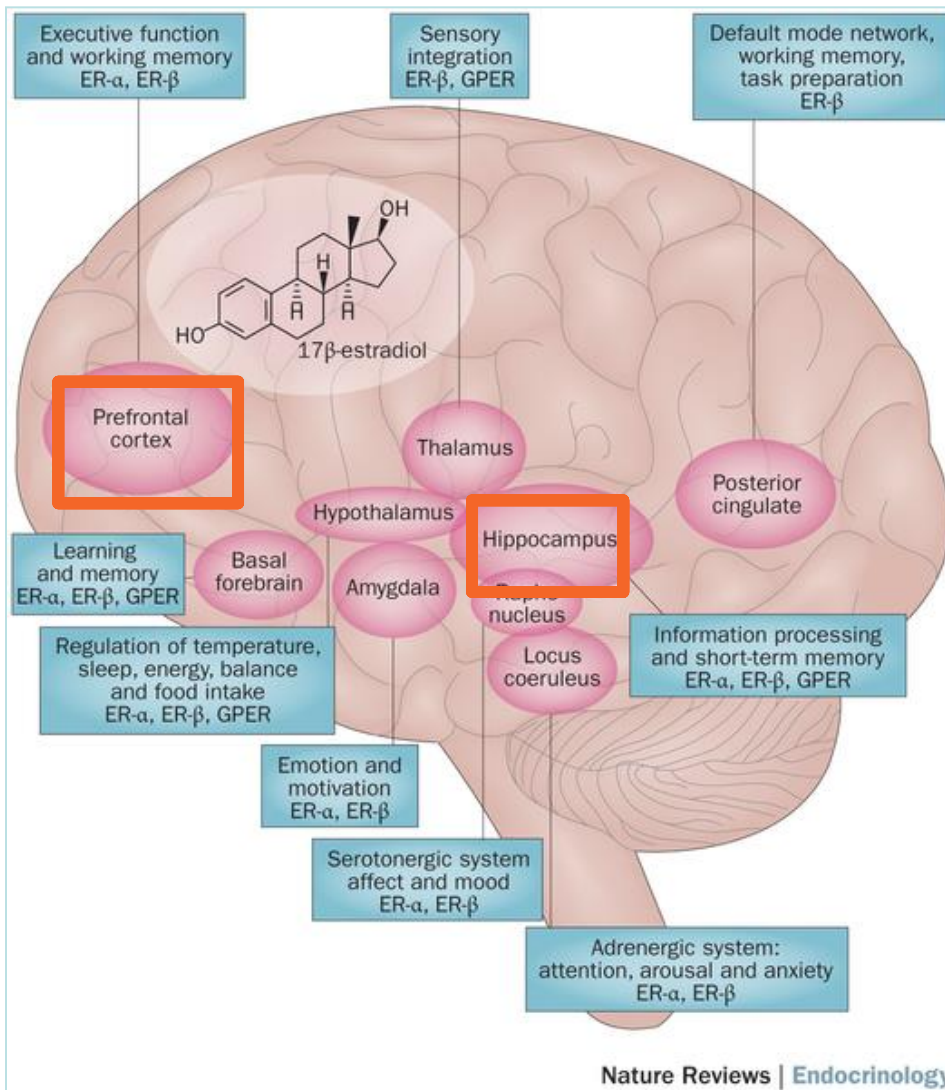
## Spatial Memory

- Corsi Block Tapping Task
- Object Placement Task

## Working Memory

- Spatial Working Memory Task
- Digit Span Backward
- Digit Ordering Task

# Ovarian removal in young women



## Predictions

- i. Decrements in PFC & HC task performance
- ii. E2 replacement will mitigate these decrements
- iii. apoE4 will increase decrement
- iv. Decrements will worsen with time since BSO

# Ovarian removal in young women

## Demographics – T 1

	AMC	BSO+E2	BSO
n	26	20	26
Age*	44.66 (3.85)	42.45 (3.63)	45.85 (5.46)
Urinary E1G, ng/mL*	33.24 (20.08)	38.96 (23.43)	19.03 (13.58)
Urinary PdG, ug/mL*	2.57 (2.85)	10.47 (2.70)	0.64 (0.58)
Age at BSO*	n/a	39.00 (3.10)	41.92 (4.37)
Time since BSO (years)	n/a	3.78 (3.05)	3.4 (2.56)
Years of Education*	19.19 (3.56)	17.58 (1.87)	16.42 (2.97)
Estimated IQ (NAART)	114.16 (7.43)	111.75 (8.31)	111.84 (5.89)
Body Mass Index, kg/m <sup>2</sup>	25.17 (4.85)	27.25 (5.03)	27.03 (6.55)
CES-D	8.42 (7.19)	7.55 (5.44)	9.89 (8.32)
Perceived Stress Scale	14.05 (5.84)	13.20 (5.72)	16.09 (8.47)
Married/Common law	50.0 %	100.0 %	80.77 %
With children	38.46 %	90.0 %	76.92 %
Non-Hispanic Caucasian	78.26 %	90.91 %	80.0 %
Smoke cigarettes	7.14 %	8.33 %	15.0 %
e4	17.4%	16.7%	26.1%
BRCA1 +	n/a	63.2%	52%
BRCA2 +	n/a	36.8%	48%
<b>Past history of</b>			
Breast Cancer	0.0 %	5.0 %	50.0 %
Other Cancer	0.0 %	0.0 %	7.69 %



Nicole Gervais



April Au

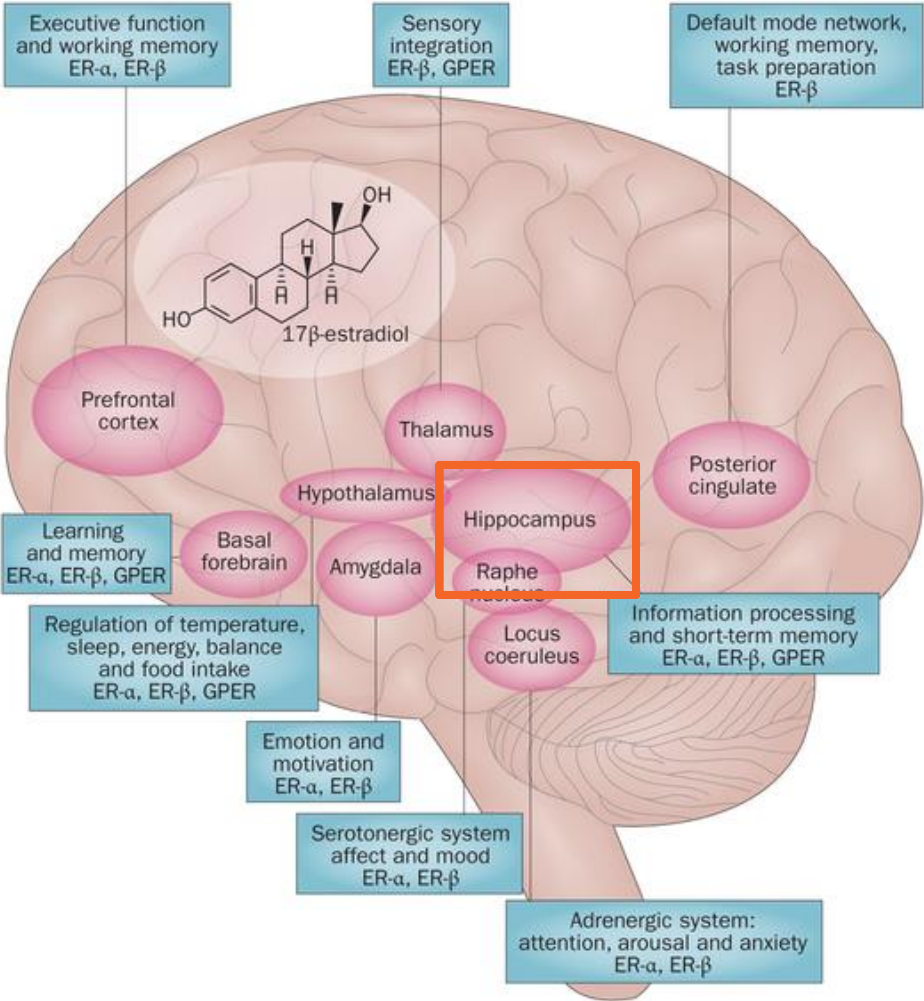
**Table 1.** Characteristics of participants by group. Standard deviations are presented in parentheses. Group differences were found at \*p < .05. CES-D = Centre of Studies for Epidemiology – Depression

# Ovarian removal in young women: Summary so far

- Performance decrements in PFC tasks
- HC tasks starting to corroborate Sherwin and Phillips findings (1992) who reported the worst performance in the LM task in women post BSO, no HRT replacement
- Women without E2 do worse on all tasks though not yet significantly worse



# Effects of ovarian removal over time



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# Effects of ovarian removal over time

## Demographics T1-T3

### BSO Group

# of Participants	59
# of Observations	112
Age	44.71 (4.50)
E1G, ng/mL	22.49 (13.96)
PdG, ug/mL	2.20 (5.77)
CESD	10.25 (8.01)
PSS	16.11 (6.36)
Years Since BSO	3.70 (3.06)
Range of Years since BSO	.5-14



Rebekah Reuben

### Model Predictors:

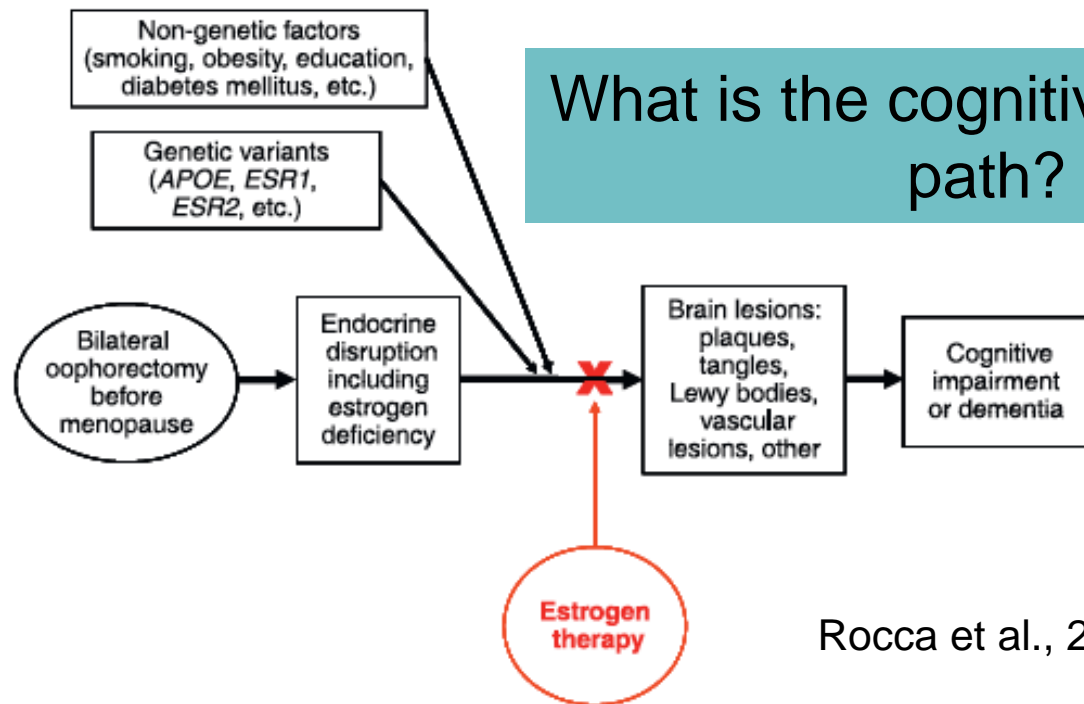
- Main effect of time post-oophorectomy
- Main effect of e4 status
- Interaction effect of time post-oophorectomy and e4 status

### Controlling for:

- Age
- Years of education
- E1G levels

# Ovarian Removal in Young Women

Results suggest that deprivation of E2 by prophylactic BSO may lead to cognition and memory changes that eventually lead to AD



Rocca et al., 2014

# Time post-oophorectomy: Summary so far

- HC seems to be the region most affected by time since oophorectomy
- Apoe4 modulates the performance of some tasks, worsening outcome

# Sex Differences in the Brain: Estrogens, Memory, & Alzheimer's Disease: Summary

- There are sex differences in brain conditions
- Estrogens effect the brain from womb to tomb
- Estrogen withdrawal may be an important factor in young women's brain health
- The trajectory of brain changes after BSO may start with the PFC
- However, to date, the HC is most affected with time since oophorectomy
- The ovaries are important for all over body health, including the brain!
- Estrogen loss may be implicated in Women and Dementia

# Students & Collaborators

- Nicole Gervais
- Rebekah Reuben
- April Au, MA
- Elizabeth Hampson, PhD
- Mary Tierney, PhD

## Referring MDs

- Andrea Eisen, MD
- Wendy Meschino, MD
- Marcus Bernadini, MD
- Steven Narod, MD

# Funders

The Posluns Family Foundation

