



**Karolinska  
Institutet**

# Effects of estrogen and testosterone treatment on serotonin transporter binding in the brain of surgically postmenopausal women – A PET study

**Ljiljana Kocoska-Maras, M.D. 1**, Hristina Jovanovic, M.D.,Ph.D. 2, Angelique Flöter Rådestad, M.D., Ph.D. 1 , Anna-Lena Nordström, M.D., Ph.D.2, Angelica Lindén Hirschberg, M.D., Ph.D.1

1 Department of Women's and Children's Health, Division of Obstetrics and Gynecology, Karolinska Institutet/Hospital, Stockholm, Sweden

2 Department of Clinical Neuroscience, Psychiatry Section, Karolinska Institutet/Hospital, Stockholm, Sweden

## Specific aim:

To explore the effects of estrogen treatment alone or in combination with testosterone on serotonin transporter binding potentials (5-HTT BPs) in specific brain areas of surgically postmenopausal women.

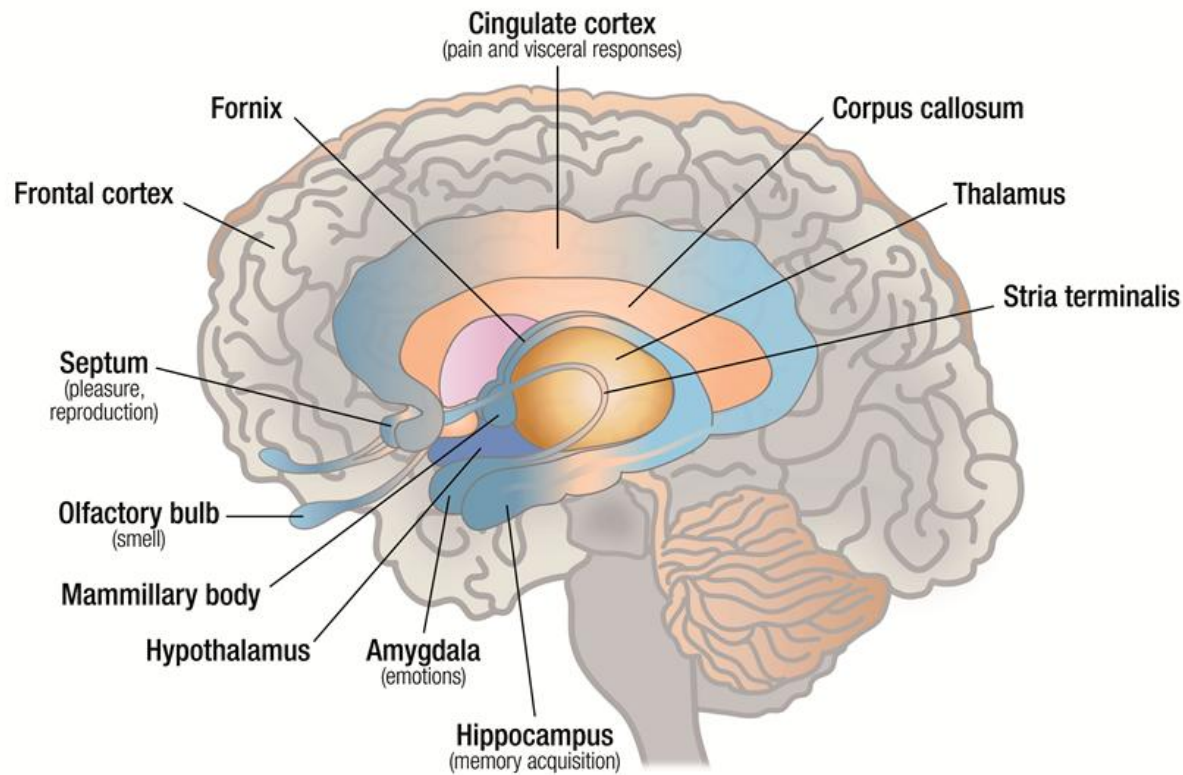
## Hypothesis:

Sex hormone treatment influences 5-HTT BPs in cortical and limbic areas of the human brain.

# PET, sex steroids and serotonergic system

- Using positron emission tomography (PET), direct measurements of serotonin biomarkers in the human brain in vivo can be obtained and related to molecular changes in the central nervous system
- To our knowledge this is the first study to show in vivo changes of 5-HTT after estrogen and testosterone administration in humans

# The brain - a target organ for sex steroids



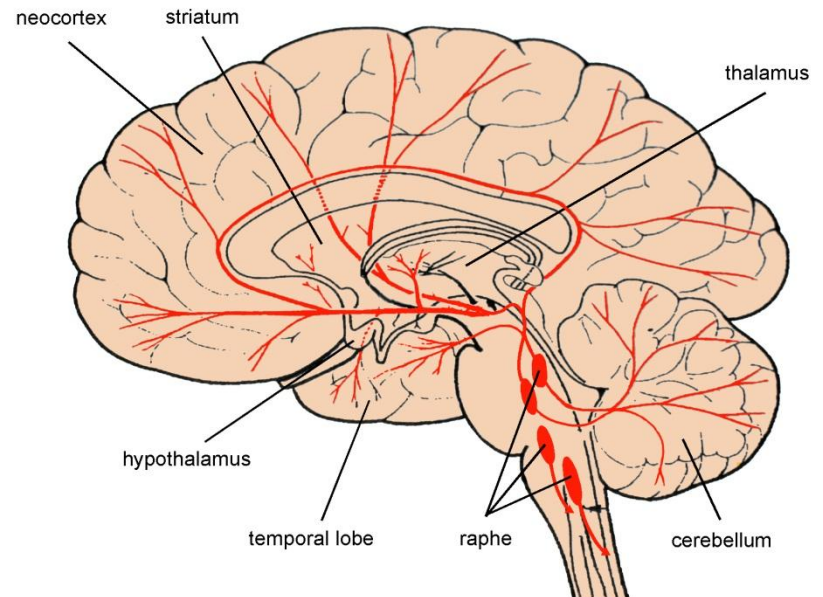
# Sex steroids and serotonin system

- The activities of the ovarian hormones and the central serotonergic system **have been linked in a variety of ways:** both systems involved in the regulation of mood and behavioural functions:
  - affect,
  - learning,
  - memory,
  - sexual behavior
  - aggression (Rubinow et al 1998, Birzniece et al 2006).

# Sex steroids and serotonin neurotransmitter system

Serotonin-producing neurons in the raphe nuclei are targets of ovarian steroids (Sheng et al 2004)

Ovarian steroids facilitate serotonin neurotransmission (Bethea et al 2002)



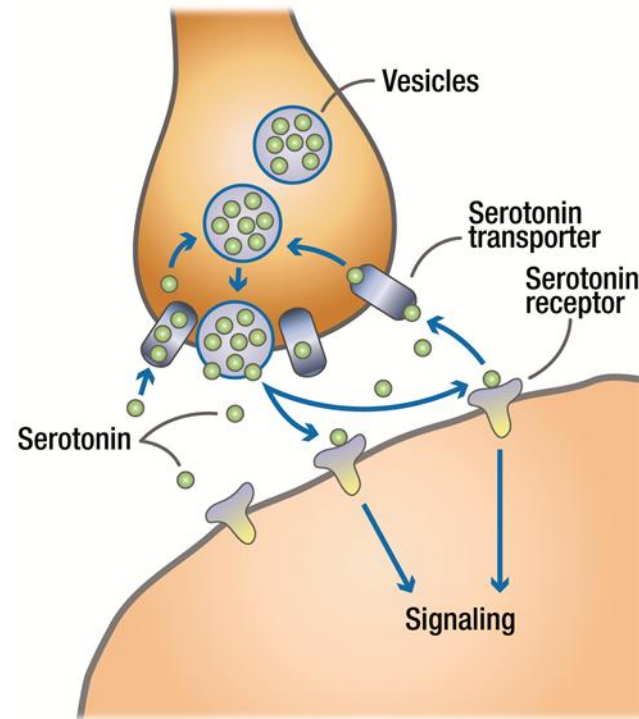
---

## **Note**

Gender differences in the serotonin system (Jovanović et al 2008)

# The serotonergic neuron

- Serotonin concentrations are regulated by serotonin reuptake system (5-HTT)



---

## **Note**

Few studies have investigated the influence of sex hormones on the serotonin system in humans

# Sex steroids and the serotonergic system

- Dysfunction of serotonin neurotransmission associated with depression, anxiety and suicidal behavior ( Arango et al 2002).
- 5-HTT is a primary target for the action of SSRIs (Parsey et al 2006).
- SSRIs (selective serotonin re-uptake inhibitors) bind to the transporter, block the reuptake of serotonin, increase the synaptic serotonin concentration (Blier and de Montigny 1999).



# Sex steroids and the serotonergic system

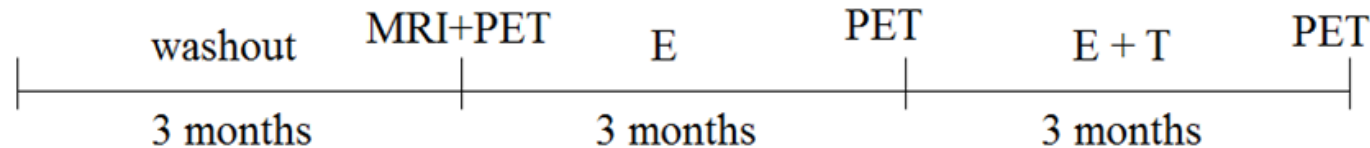
- Ovarian steroids inhibit serotonin re-uptake by binding to 5-HTT via non-genomic mechanism (Chang & Chang 1999).
- Estrogen treatment may have important permissive effects on the actions of serotonergic antidepressants in postmenopausal women (Schneider et al 2001, Rasgon et al 2007).
- Gender differences in brain structure and function - suggesting higher biological susceptibility to depression in females (Cogrove et al 2007).

## Sex steroid treatment and mood

- HRT - positive effect on depression in peri- and postmenopausal women (Zweifel and O'Brien 1997, Soares et al 2001, Frey et al 2008)
- Results contradicted by Morrisson et al 2004.
- Estrogen and SSRI in combination improve postmenopausal depression (Schneider et al 2001, Rasgon et al 2007).
- Not confirmed in other studies (Huttner and Shepard 2003).
- Testosterone and estrogen replacement therapy in combination better effect on psychological wellbeing than compared to estrogen treatment alone (Shifren et al 2000, Nathorst-Boos et al 2006).

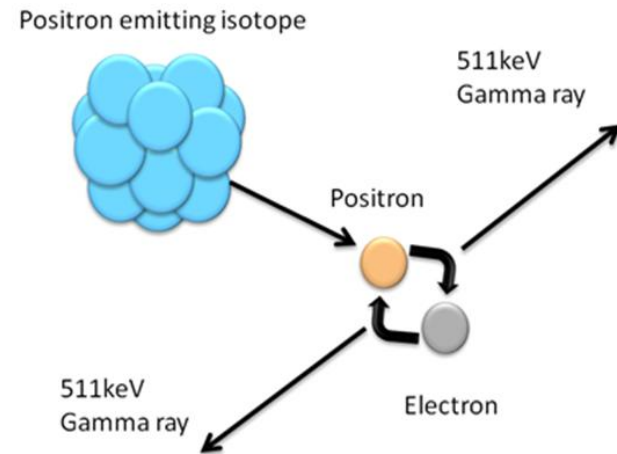
## Materials and methods

- Prospective study
- 10 healthy surgically postmenopausal women, age 50-65 years
- Three months treatment with transdermal estradiol 100 µg/24 hours (E) followed by three months of oral testosterone addition with testosterone undecanoate 40 mg daily (E + T)



- At baseline, after three and six months of treatment women underwent PET and serum levels of sex hormones, mood and cognitive test were measured.

# PET camera and principles of PET



Specific radioligand is used:  
[<sup>11</sup>C]MADAM, N,N-dimethyl-2-(2-amino-4-methylphenylthio) benzyl  
amine

# Mood and cognitive function

- **Symptoms of depression** - Beck Depression Inventory (BDI) (Beck et al 1996)
- **Anxiety** - Beck Anxiety Inventory (BAI) (Beck et al 1993)
- **Verbal and category fluency** (Lezak 1995)
- **Speed of processing** - Trail Making Test part A (TMT-A) (Lezak 1995)
- **Executive functions** - Trail Making Test part B (TMT-B) (Lezak 1995)
- **Social cognition** - The test reading the mind of the eyes (Baron-Cohen et al 2005)

## Baseline characteristics

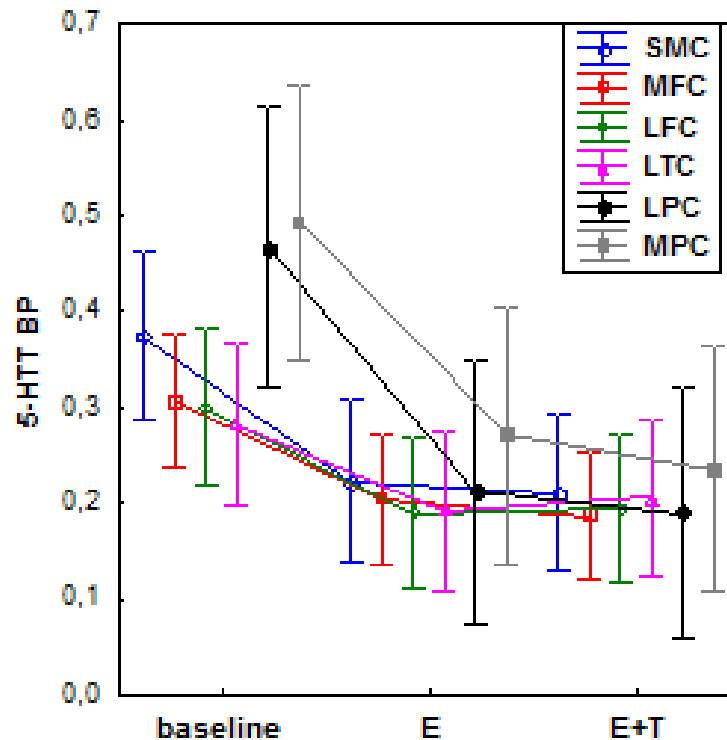
	n = 10
Age, years	58.4 ± 4.7
BMI, kg/m <sup>2</sup>	25.9 (24.0-27.7)
Time since oophorectomy, years	7.6 ± 4.0
Previous HRT, %	60
Duration of HRT after surgery, years	1 (0-3.3)
Higher education, %	40

# Serum hormone levels

Hormones	Baseline	E2	E2 + T
E2 pmol/l	23 ± 8	228 ± 138 <sup>a***</sup>	280 ± 151 <sup>b***</sup>
T nmol/l	1.07 ± 0.43	0.90 ± 0.35	1.71 ± 1.06 <sup>b*c*</sup>
fT pmol/l	15.4 ± 6.6	10.6 ± 5.0 <sup>a**</sup>	23.8 ± 15.4 <sup>b*c**</sup>

- E2 = estradiol-17β; SHBG = sex hormone-binding globulin; T = testosterone; fT = free testosterone.
- Significant differences after treatment are denoted by \* = p<0.05; \*\* = p<0.01; \*\*\* = p<0.001, respectively.
- a = E2 versus baseline; b = E2 + T versus baseline; c = E2 + T versus E2

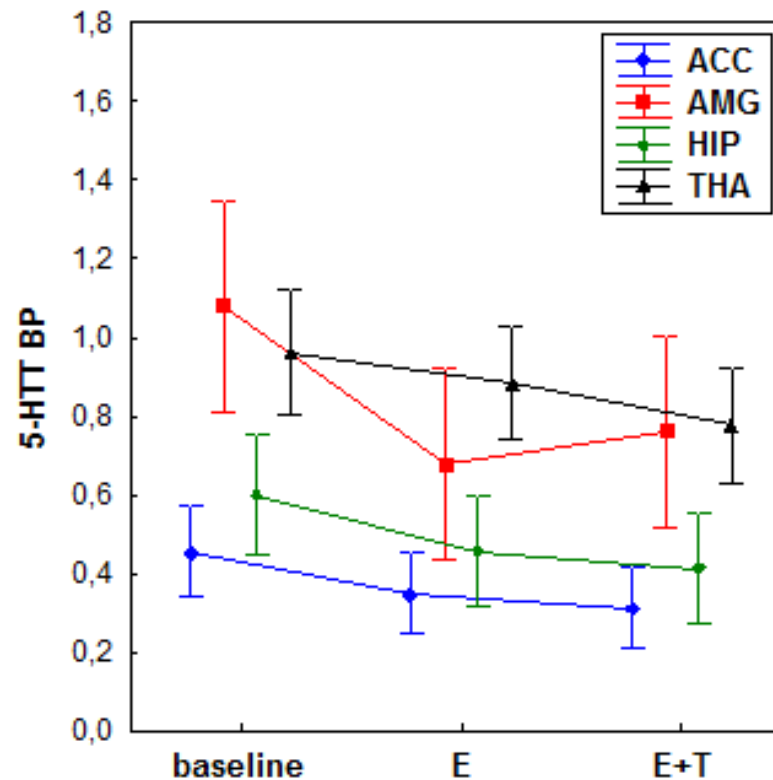
## 5-HTT BP in cortical areas



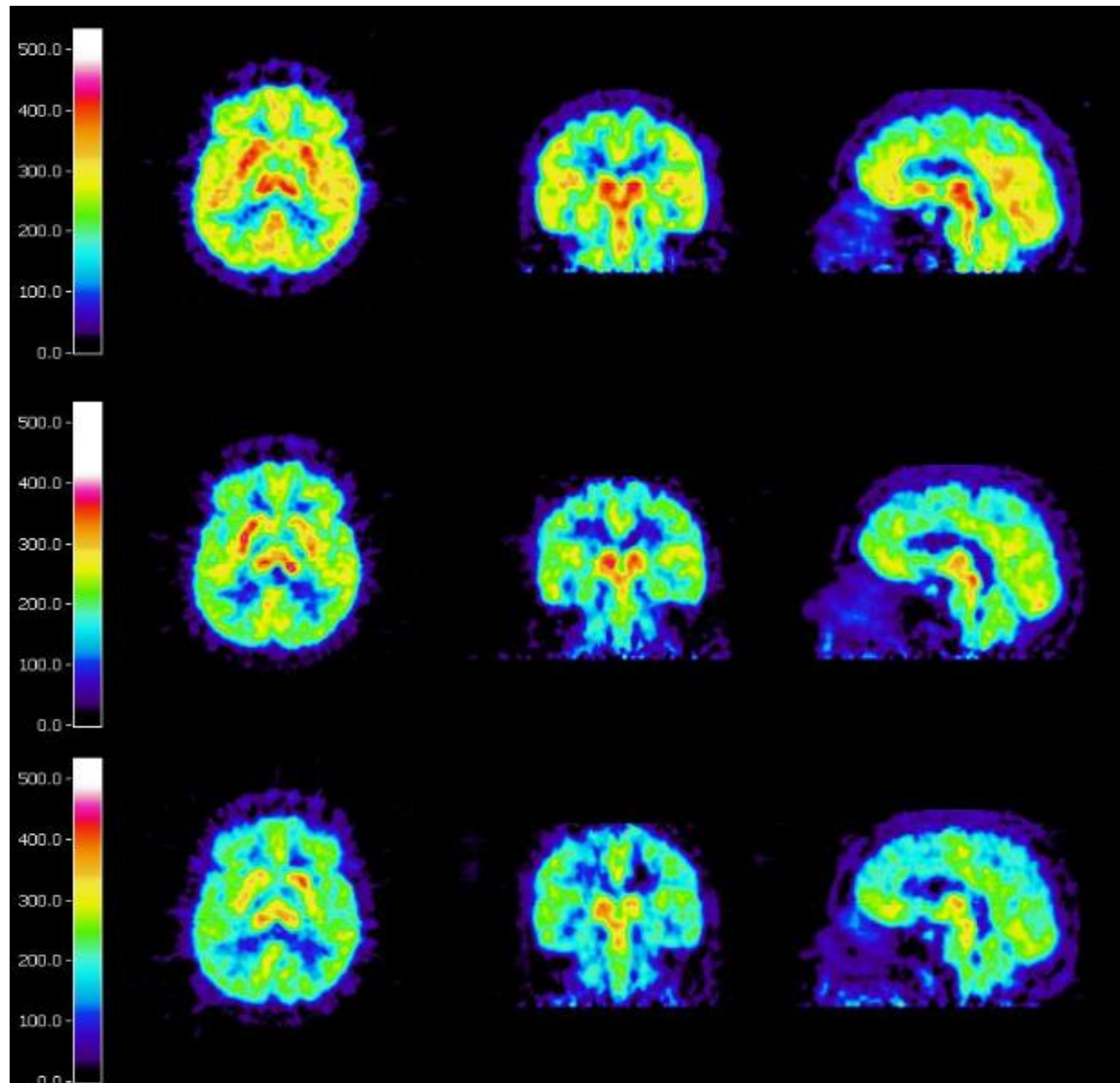
SMC = sensory motor cortex, MFC = medial frontal cortex, LFC = lateral frontal cortex, LTC = lateral temporal cortex, LPC = lateral parietal cortex, MPC = medial parietal cortex



## 5-HTT BPs in limbic areas



ACC = anterior cingulate cortex, AMG = amygdala, HIP = hippocampus,  
THA = thalamus



# Mood and cognitive function

Assessment	Baseline	E2	E2 + T
BDI	6.8 ± 5.9	<b>6.0 ± 6.0<sup>a*</sup></b>	4.7 ± 6.4
BAI	3.9 ± 3.5	5.8 ± 5.9	10.3 ± 13.1
TMT-A	35.1 ± 9.2	28.5 ± 6.9	34.4 ± 14.6
TMT-B	77.0 ± 27.1	77.0 ± 26.4	86.4 ± 24.1
Social cognition	26.0 ± 5.3	26.7 ± 4.5	28.0 ± 3.9
Letter fluency	44.6 ± 10.2	48.5 ± 8.3	<b>54.0 ± 13.1<sup>b*</sup></b>
Category fluency	54.2 ± 9.1	54.3 ± 4.5	<b>69.8 ± 9.8<sup>b**, c**</sup></b>

## Conclusion

- The results suggest that treatment with estrogen alone or in combination with testosterone reduces serotonin reuptake in the brain of postmenopausal women, and thereby increases the synaptic serotonin concentration, which could lead to improvement of depressed mood and cognition.

## Conclusion

- The positive effects of sex hormones on mood and verbal cognitive ability in the small group of women in our PET study indicate important effects of sex hormones and especially for surgically postmenopausal women's well-being and health.

# Tack



**Karolinska  
Institutet**

Prof Angelica Lindén Hirschberg

Med dr Angelique Flöter Rådestad

Birgitta Byström, FRH labb

Lotta Blomberg, Siw Rödin Andersson och Berit Lagerstam, Kvinnohälsan

Department of Women's and Children's Health, Division of Obstetrics and Gynecology,  
Karolinska Institutet/Hospital, Stockholm, Sweden

Ass Prof Anna-Lena Nordström

Med dr Hristina Jovanovic

PET centrtrum

Department of Clinical Neuroscience, Psychiatry Section, Karolinska Institutet/Hospital,  
Stockholm, Sweden

**Tack  
Thank You  
Благодарам**



# Sex steroids and serotonergic system

- Women are more likely than men to suffer from depression and anxiety disorders (Kessler 2003).
- Occurrence of depression is similar in young boys and girls.
- Change to 2:1 female to male ratio after puberty (Kessler & Walters 1998)



# Sex steroids and serotonergic system

- Women: more depressive and dysphoric symptoms during times of large hormonal changes e.g. premenstrual period, postpartum and perimenopause (Soares&Zitek 2008).
- PMDD – severe cyclic mood changes during luteal phase of menstrual cycle (Sundström et al 1999).
- Gender differences in brain structure and function
  - suggesting higher biological susceptibility to depression in females (Cogrove et al 2007).

# Sex hormones and cognition – gender differences

- Men tend to excel women in spatial ability tests (Lewin et al 2001)
- Women outperform men in verbal fluency and episodic memory (Lewin et al 2001, Kimura 2002, Kimura & Clarke 2002)
- Menstrual cycle studies:
  - Improvement in visuospatial skills in follicular phase
  - Enhanced verbal fluency during luteal phase with high estradiol level (Kimura 2002, Sherwin 2009)

---

## — **Note**

Inconsistent results in cognitive ability: reports of no differences in cognitive performance during the phases of the menstrual cycle (Rosenberg & Park 2002), or between the groups of premenopausal, perimenopausal and postmenopausal women (Herlitz et al 2007)

# Sex hormones and cognition – gender differences

- Men tend to excel women in spatial ability tests (Lewin et al 2001)
- Women outperform men in verbal fluency and episodic memory (Lewin et al 2001, Kimura 2002, Kimura & Clarke 2002)
- Menstrual cycle studies:
  - Improvement in visuospatial skills in follicular phase
- Enhanced verbal fluency during luteal phase with high estradiol level (Kimura 2002, Sherwin 2009)

---

## == **Note**

Inconsistent results in cognitive ability: reports of no differences in cognitive performance during the phases of the menstrual cycle (Rosenberg & Park 2002), or between the groups of premenopausal, perimenopausal and postmenopausal women (Herlitz et al 2007)

# Sex hormones and cognition– inconsistent results

- The discrepancies in the literature probably due to several factors e.g.
  - individuals of varying age and hormonal levels
  - differences in hormonal assays and tests used for cognitive assessment (Thilers et al 2006).
  - the balance between estrogen and testosterone and thus the estradiol/testosterone ratio has been suggested to be more important than the absolute hormone levels (Sherwin 2009).

# Sex hormones and cognition– inconsistent results

- The association between sex steroid hormone levels and some aspects of brain function - not dose dependent in a straight linear fashion.
- Several GABA receptor agonists, including the progesterone metabolite allopregnanolone, have a biphasic dose response curve (Srinivasan et al 1999).
  - a low dose may induce negative reactions, such as dysphoria, anxiety and aggression
  - a high doses of GABA-A agonists have anxiolytic, antiepileptic and sedative effects (Backstrom et al 2011).

# Sex hormones and cognition

- Data suggest positive effects of estrogen treatment on cognitive function in healthy postmenopausal women of younger age (Sherwin 1988, Shaywitz et al 2003, Joffe et al 2006).
- However - in the large prospective Women's Health Initiative Memory Study (WHIMS):
  - rather an adverse effect was found of estrogen treatment alone (Espeland et al 2004).
  - whereas estrogen in combination with progestin did not improve global cognitive function in postmenopausal women 65 years and older (Rapp et al 2003).

# Sex hormones and cognition

- A curvilinear relationship and an optimal level have also been suggested for the effects of testosterone on visuospatial ability in both women and men (Moffat and Hampson 1996, Muller et al 2005).

# Sex hormones and cognition

- Protective effect of estrogen on cognition when the therapy is initiated early after menopause.
- An adverse effect in older women (Sherwin and Henry 2008, Maki and Sundermann 2009).