Winners rome 2017

Ovariectomy

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www.gynsurgery.org www.mondoginecologico.it

Winners rome 2017

Ovariectomy

during hysterectomy

Philippe R. Koninckx *,***

Anastasia Ussia **,***

50 years = No no

60 years = No

70 years = ?

WOMEN WITH OVARIES LIVE LONGER

Removal of Androgens =

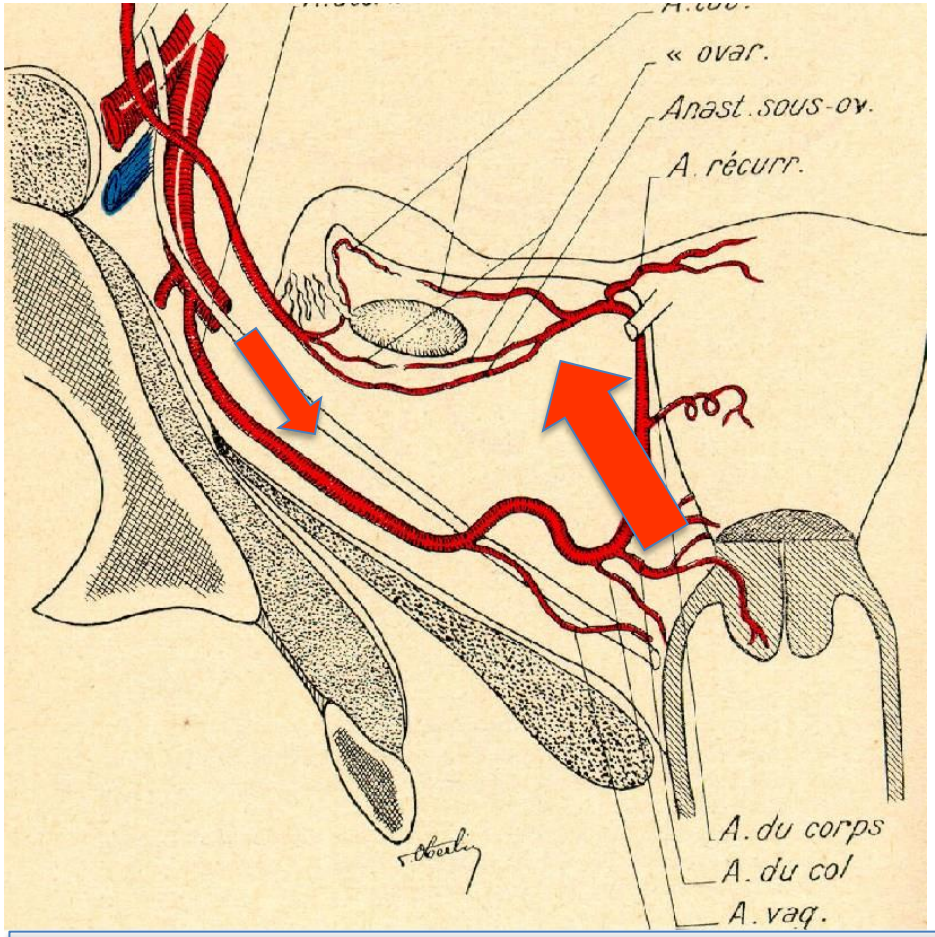
- **less estrogens & beneficial effects**
- **thin skin and wrinkels**
- **brain effects and sexuality**

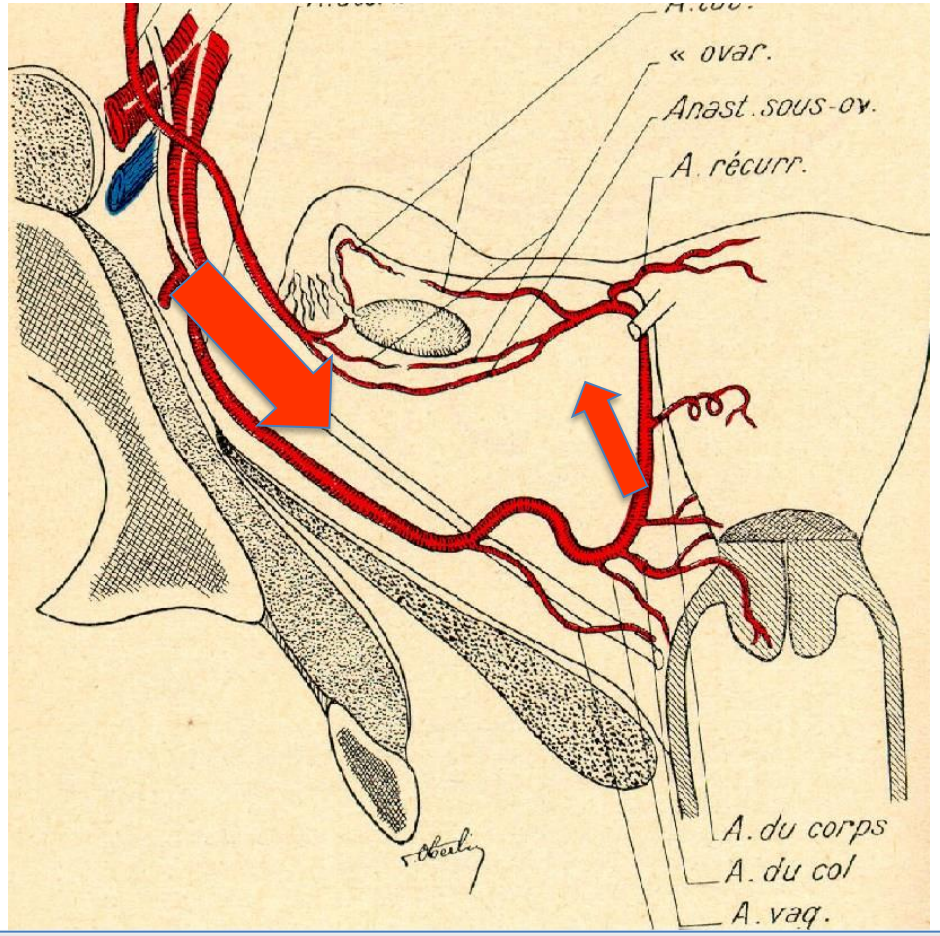
Versus risk of ovarian cancer

www.gynsurgery.org/presentations-gruppo-italo-belga/

www.mondoginecologico.it

Anatomy for surgeons





ovarian vascularisation can be predominantly from uterine ovary or from infundibulo-pelvic ligament

Therefore hysterectomy can a (temporary) ovarian devascularization

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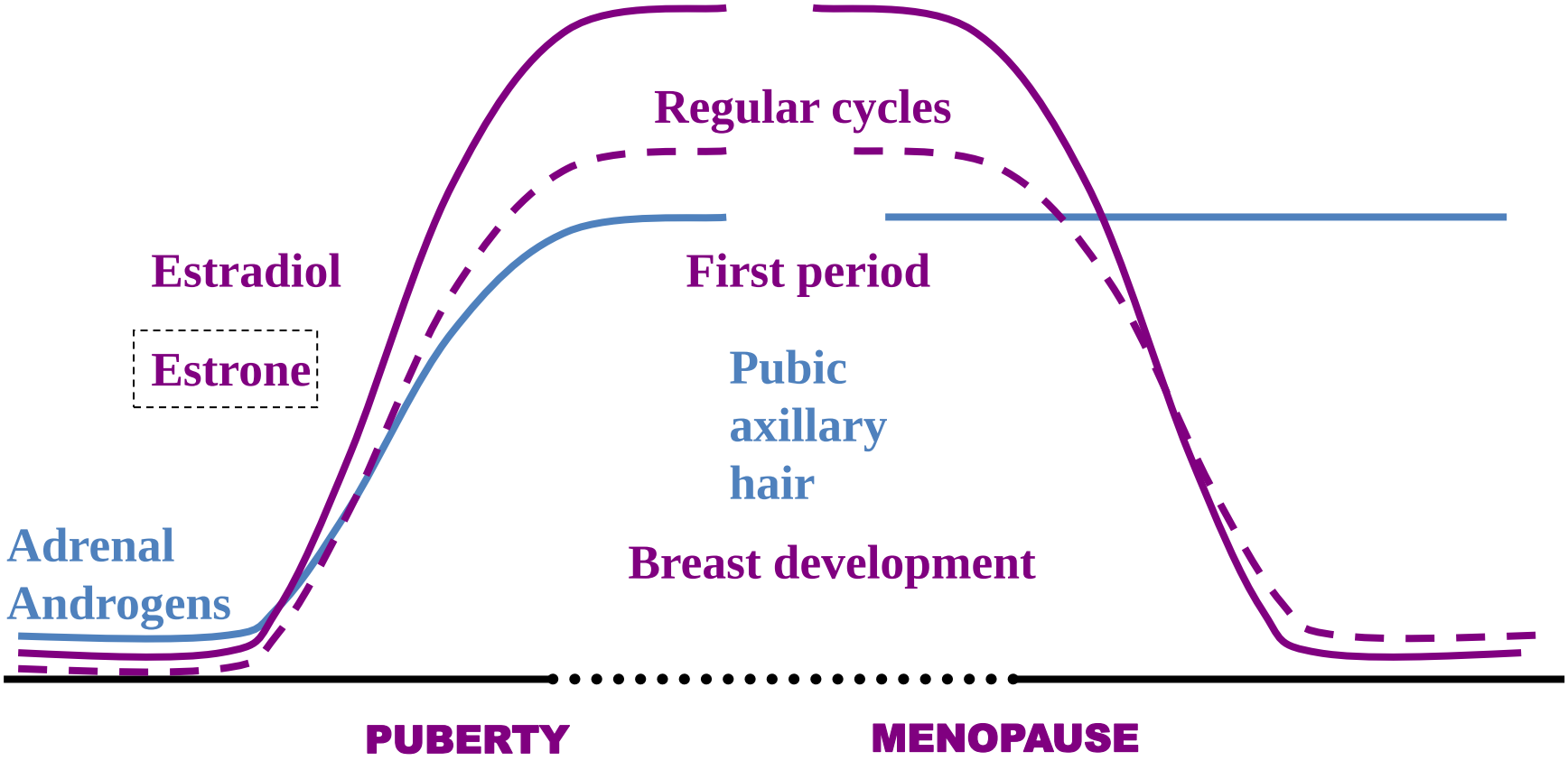
Puberty & Menopause

relative concentrations



Puberty = androgens and slightly later oestrogens

Menopause = estrogens decrease

Menopause : a relative androgen dominance

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What is an Androgen

5α- reduced

androsterone ↔ *5α-a-dione*

androstanediol ↔ DHT

5α reductase

Δ 4 3 keto

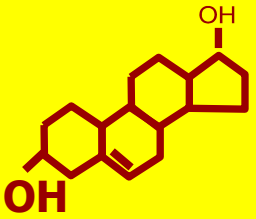
Androstenedione

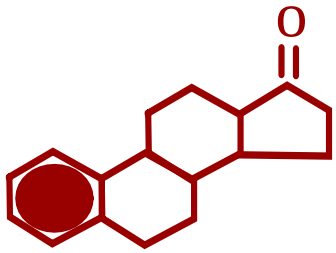
testosterone

3B hydroxy isomerase

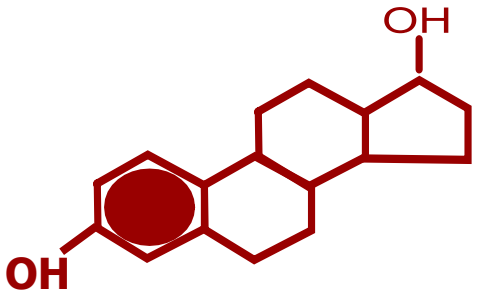
Δ5 3 OH

DHEA





estrone



estradiol

17β-estradiol

estrone

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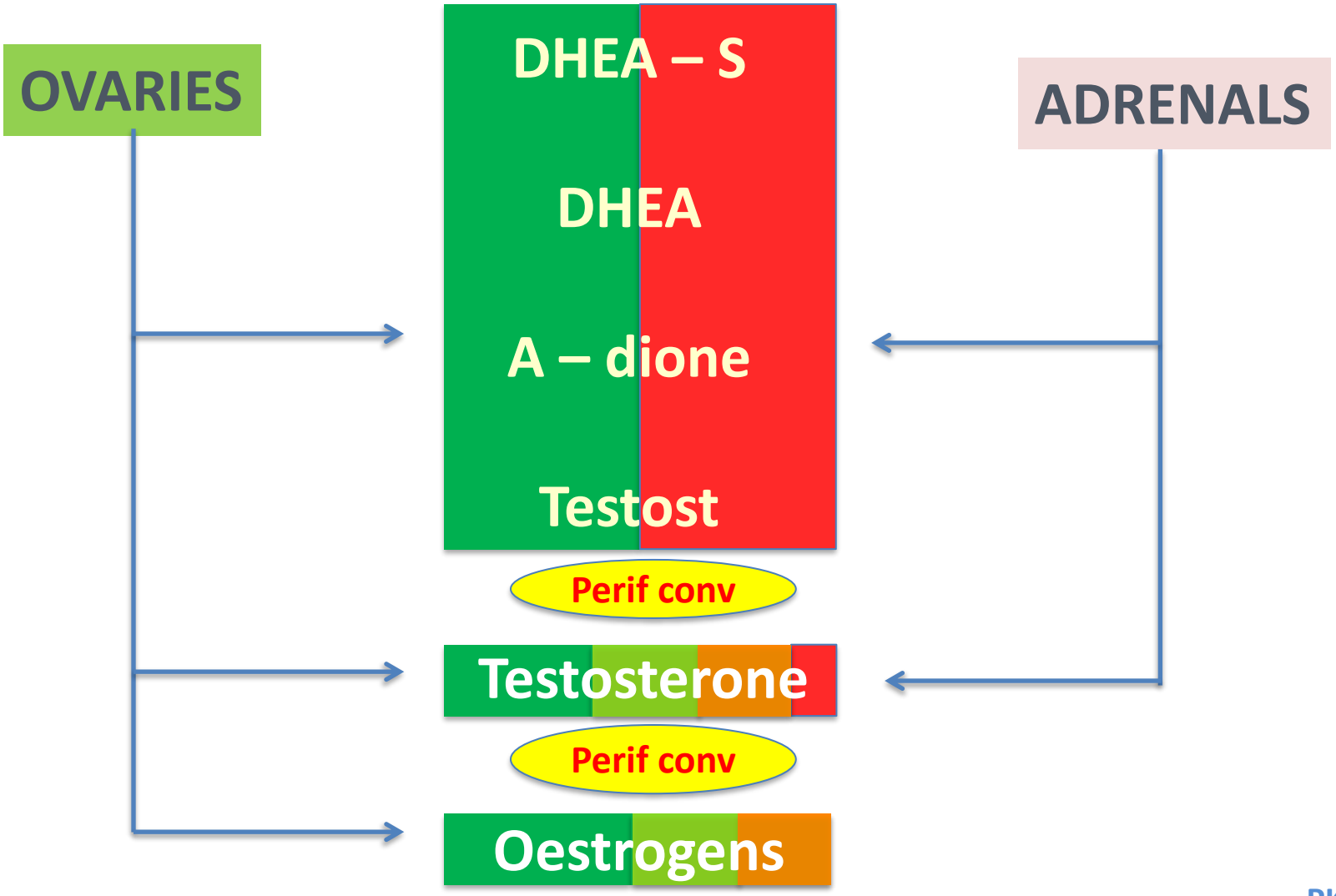
Androgens after menopause



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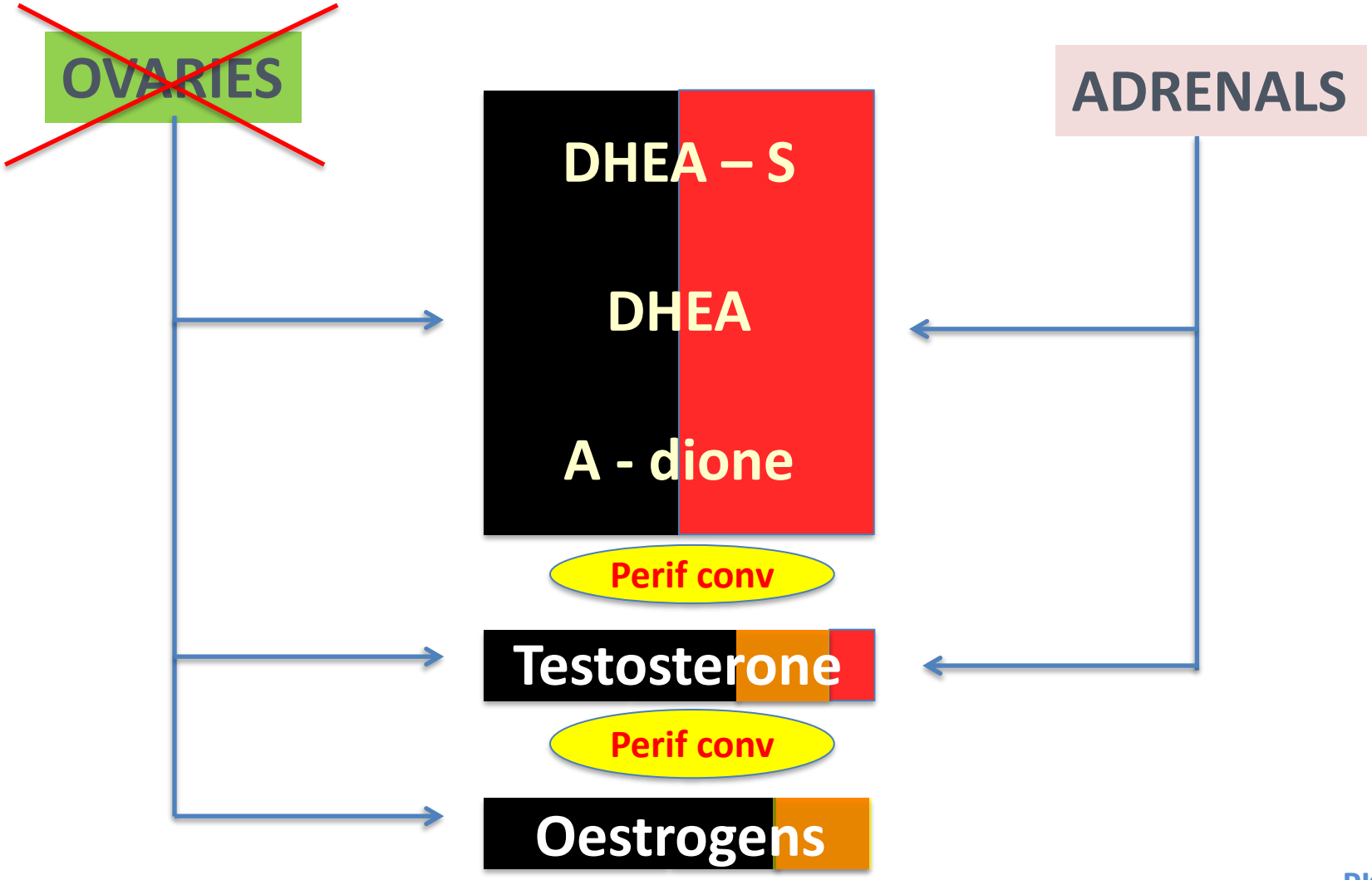
Androgens after ovariectomy



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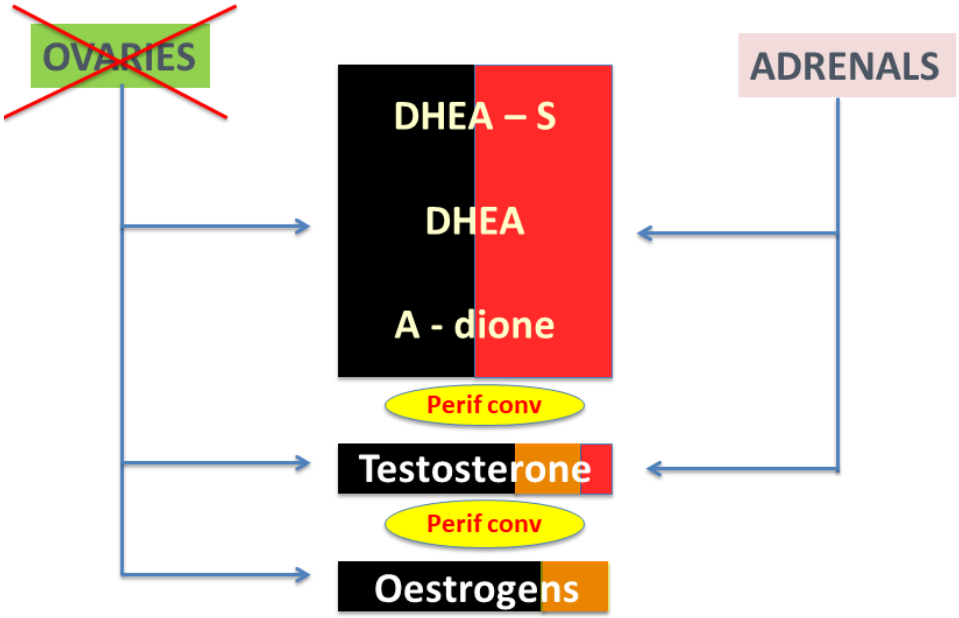
Conclusions

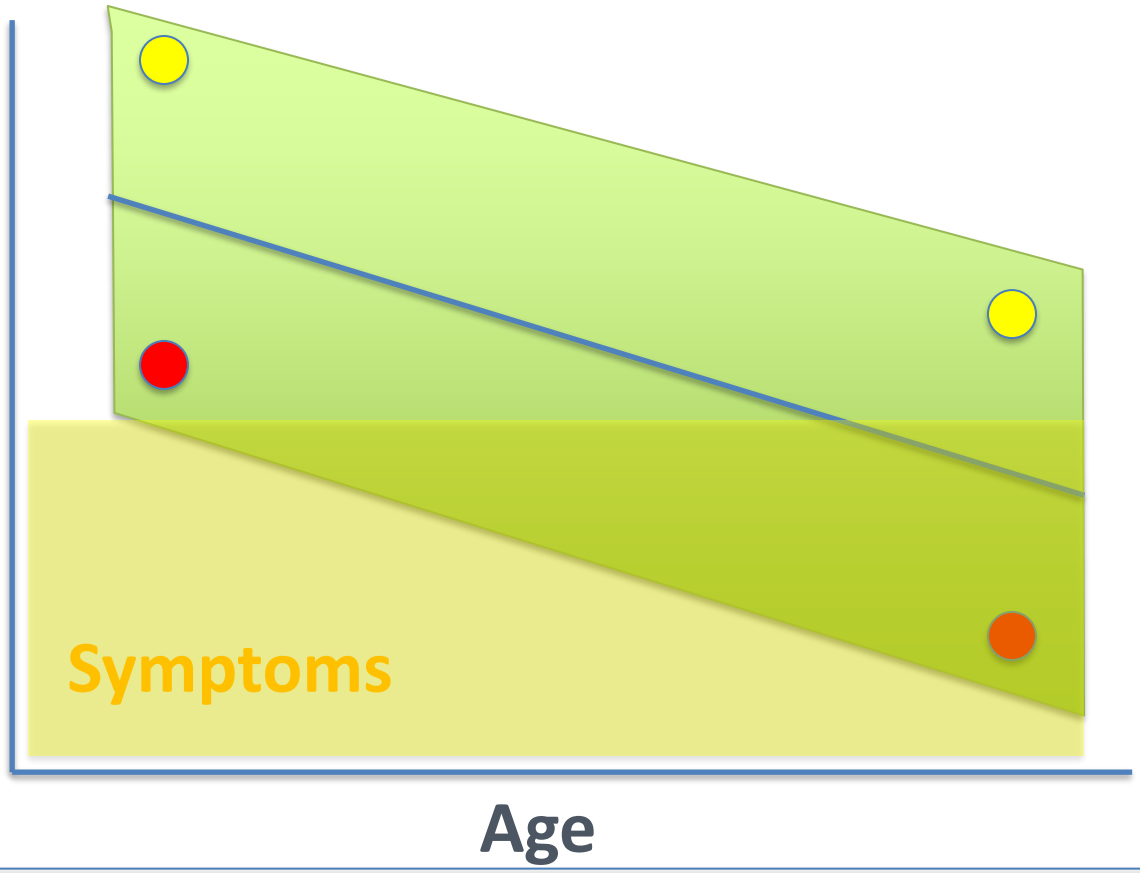
- Menopause = progressive decline of estrogens
  - estrogens below 100 pg = amenorrhoea
  - 10 years later : below 50 pg
  - Androgens remain normal
- Ovariectomy
  - Abrupt
  - severe



Age - normal range

- individualize

DHEA



A normal range means : some have high others lower concentrations

After a decrease the high normal have less symptoms

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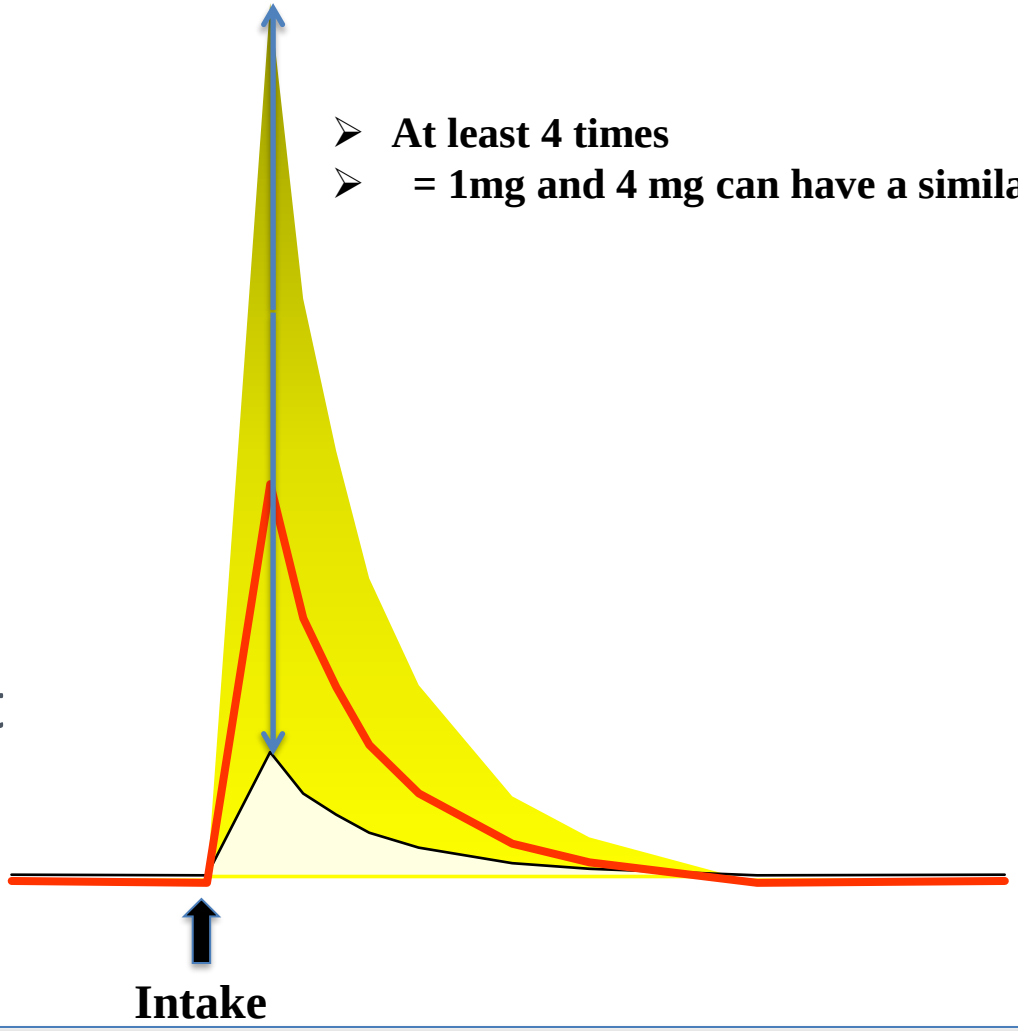
Hormone replacement therapy

- Oestrogens
  - Oral micronized soluble oestrone
  - Transdermal limited dose
- Progestagens
  - Either bleeding or 10% spotting
  - Many types
- Androgens
  - DHEA
  - Testosterone
- Bioavailability : at least 4x

Bioavailability ??

- Only Clinical

- Variable
  - Patient
  - Product
  - Oesto -progest

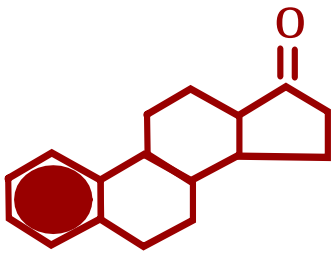


- **At least 4 times**
- **= 1mg and 4 mg can have a similar effect**

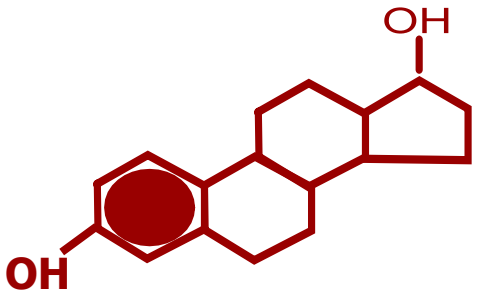
= 1mg and 4 mg can have a similar effect Therefore clinical judgment is necessary

Steroid Hormones : Farmacology

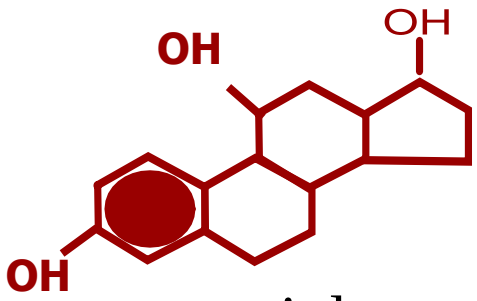
1. Solubility in water



estrone



estradiol

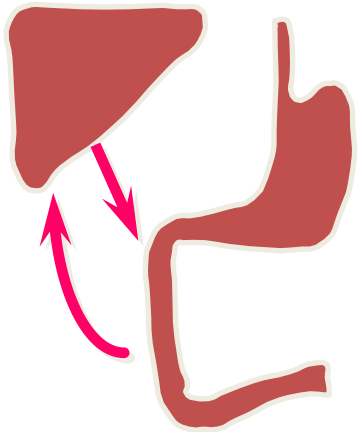


estriol

progesterone

conjugated

2. The enterohepatic cycle



3. First pass effect in the liver

* metabolisation E2-E1
* concentrations and effects

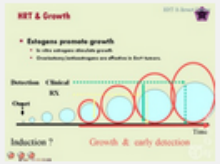
high liver concentrations
One intake a day is sufficient

Advantages of Hormone replacement

No atrophy

- **of the vagina**
- **of breasts**
- less **dry eyes**

Breast Cancer



- **Estrogens increase growth rate** and thus :
  - the diagnosis is made 8 years earlier
  - a less aggressive cancer with lower mortality
- **Not more breast cancers**
  - There are no data demonstrating that estrogens induce breast cancers
  - important is that the intervan between the onset and the diagnosis is generally some 20 years
  - accelerated growth means that the incidence of cancer diagnosis will be higher in woepmn taking hormone replacement therapy (odds ratio : 1.25)

Positive brain effects

- less **hot flushes and night sweats**.
- less **depressions**
- less **sexual problems**
- better **sleep**
- Positief effect op de **cognitieve functie** bv geheugen
- Minder kans op **Alzheimer**

Less cancers

- 50% less **bowel cancers**
- 50% less **adenocarcinoma of the uterus ;** (*unless estrogen only therapy)*
- no effect upon **cervical cancer**
- no effect upon **ovarian cancer**

Women taking hormones live longer

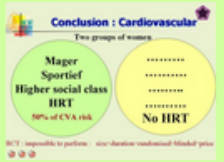
- Women with ovaries live longer

Better support tissues

- no **osteoporosis**
- less **wrinkles**
- less **pelvic floor descent and urinary incontinence ,**
- less **pain in muscles and joints**
- less **thin skin**

Positive caradiovascular effects

- 50% less **cardiovascular problems**



if HRT is taken from the onset of menopause. After a delay of 5 years this effect disappears. This should be compared to flowers without water

see http://www.gynsurgery.org/menopause/

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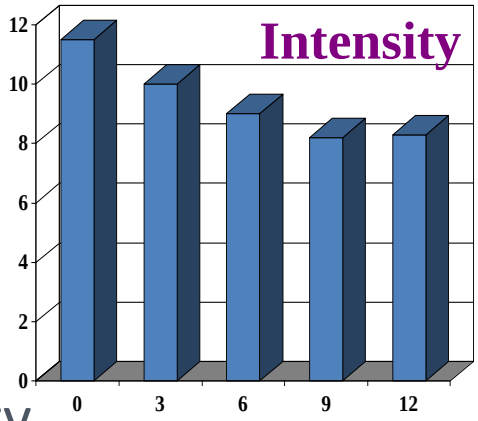
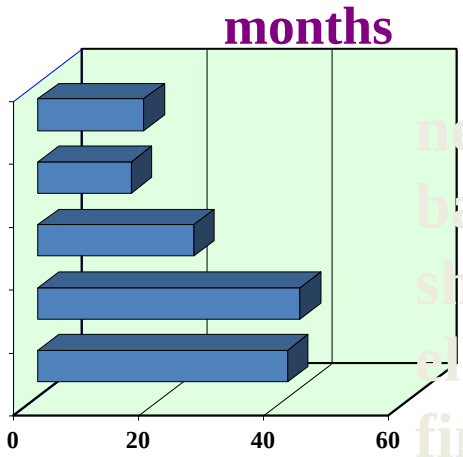
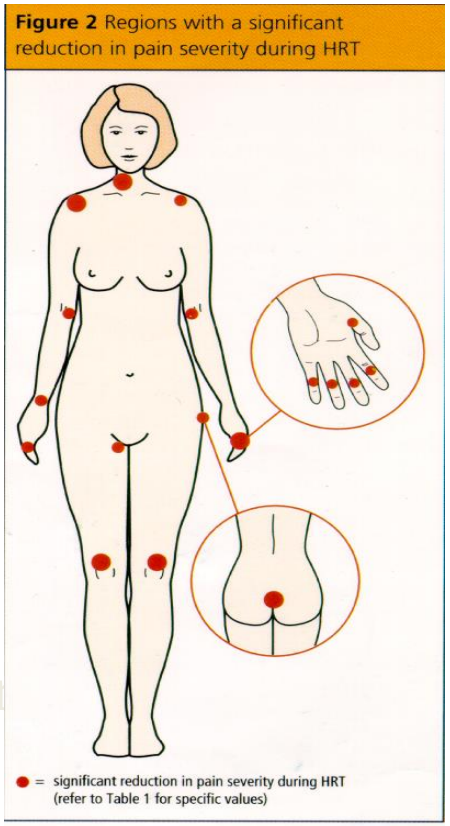
Muscle & Joint pain

- n=168
- pain severity 0-4 at 20 locations
- effect of 2 mg E2
- incidence & intensity
- localisations





neck
back
shoulder
elbow
finger



Oldenhave, Schoten, Euser Boon : Sydney 97

Androgen effect unknown – but likely

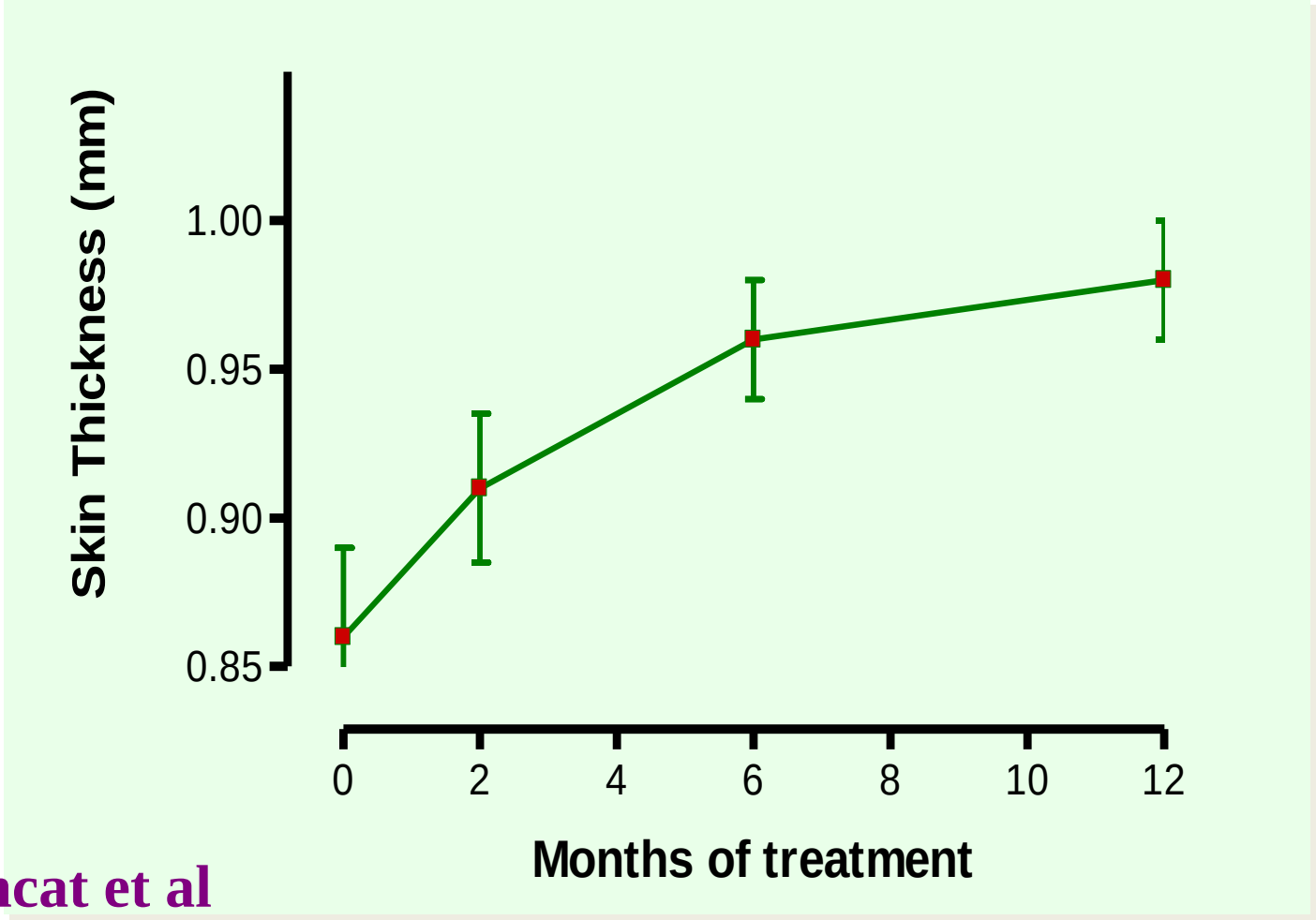
Androgens

- Skin thickness
- Sexuality
- Wellbeing

Little data of efficacy - dose – type + estrogens

After ovariectomy : clinically more difficult

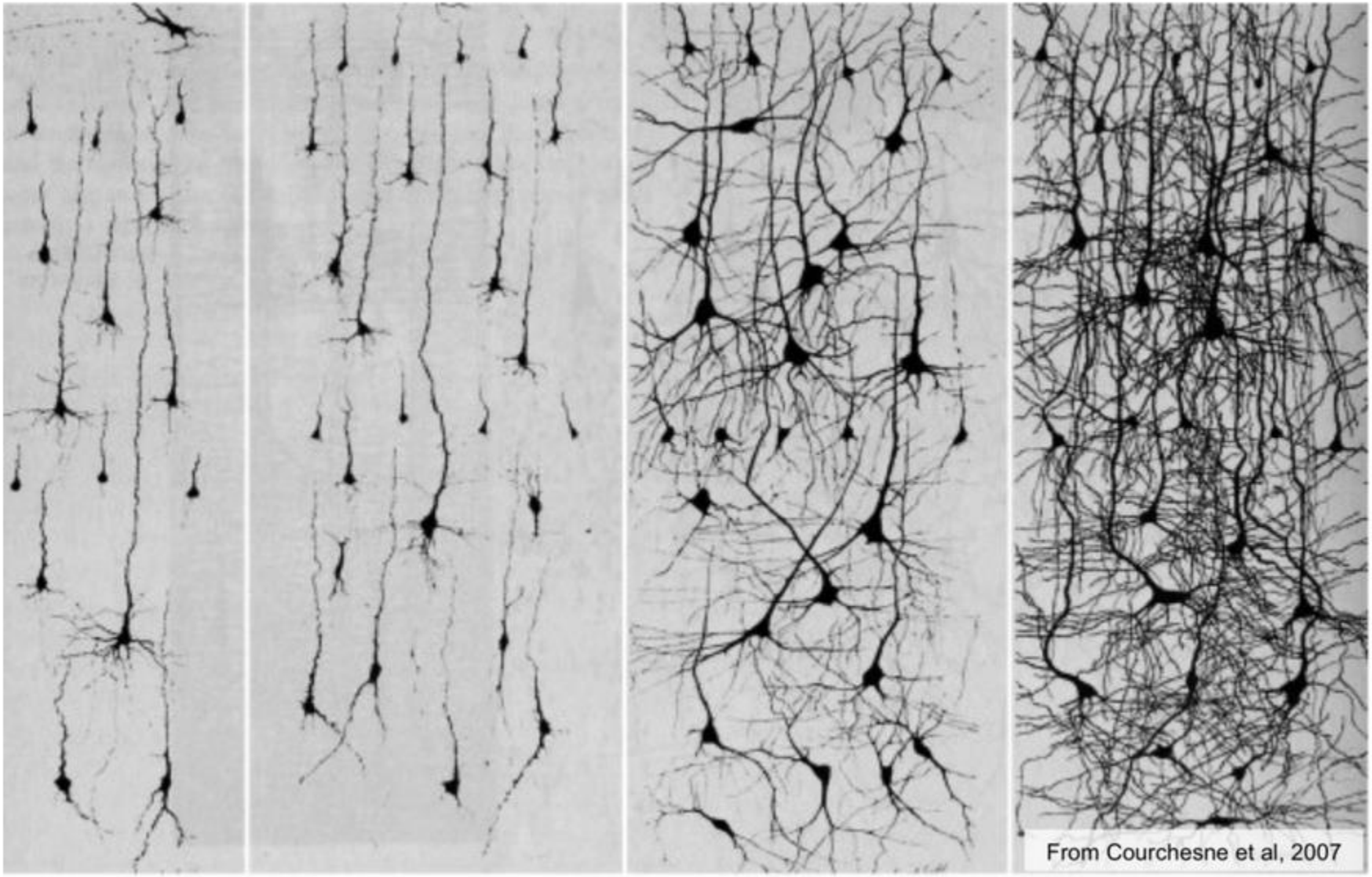
Skin & Collagen



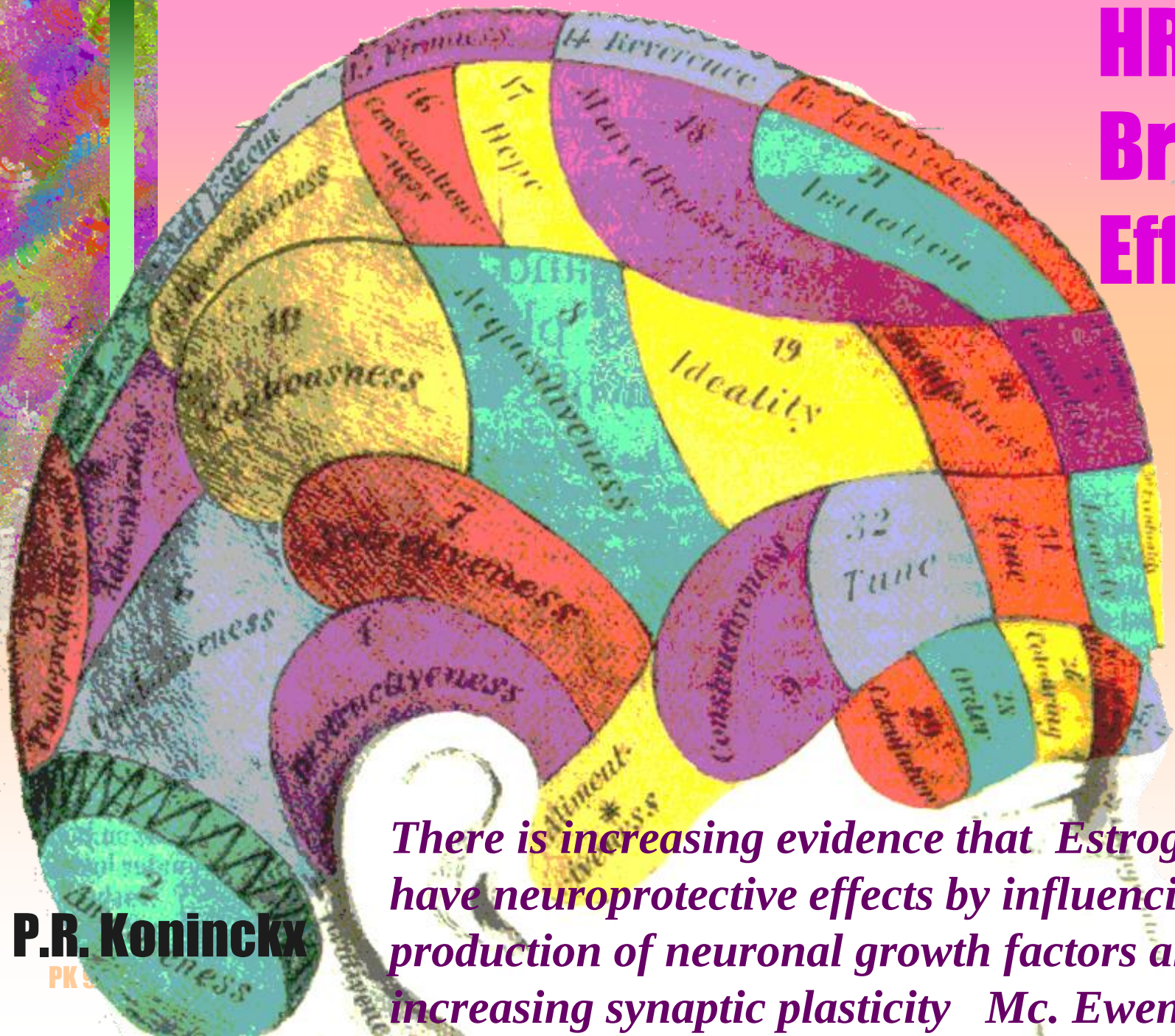
Brincat et al

skin gets thicker – less wrinkles - look younger : **Androgen are important**
For all collagen and for bone !! Also trabecular bone and mandibula

Dendritic density



HRT : Brain Effects



15/4/99

There is increasing evidence that Estrogens may have neuroprotective effects by influencing the production of neuronal growth factors and increasing synaptic plasticity Mc. Ewen 97

P.R. Koninckx

PK 9

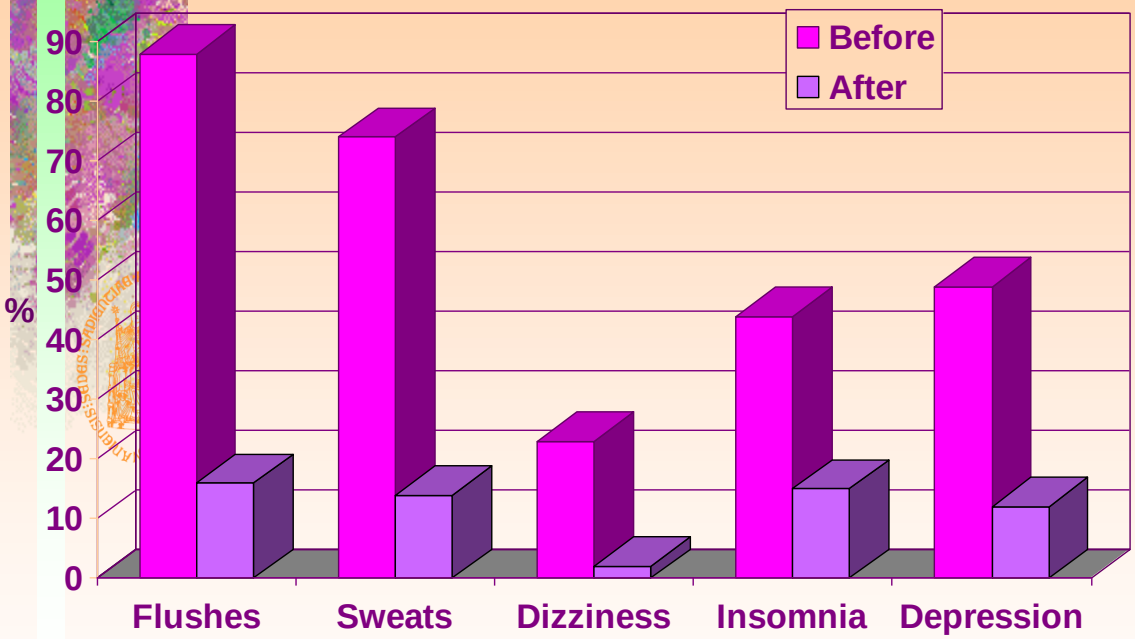
Differences between Men & women

Hypothesis : Hormonal milieu might influence cognitive function

- Differential aptitudes in certain cognitive domains
- Age related decline in complex visuospatial and motor function : more in postmenopausal women *(Halbreich 95)*
- 3D
- Verbal activities
- fine motor skills

Climen Review
Eur Menop J 97

Brain effects



transmission speed
synaptic density

n=173

De Aloysio
Koninckx
Hirvonen

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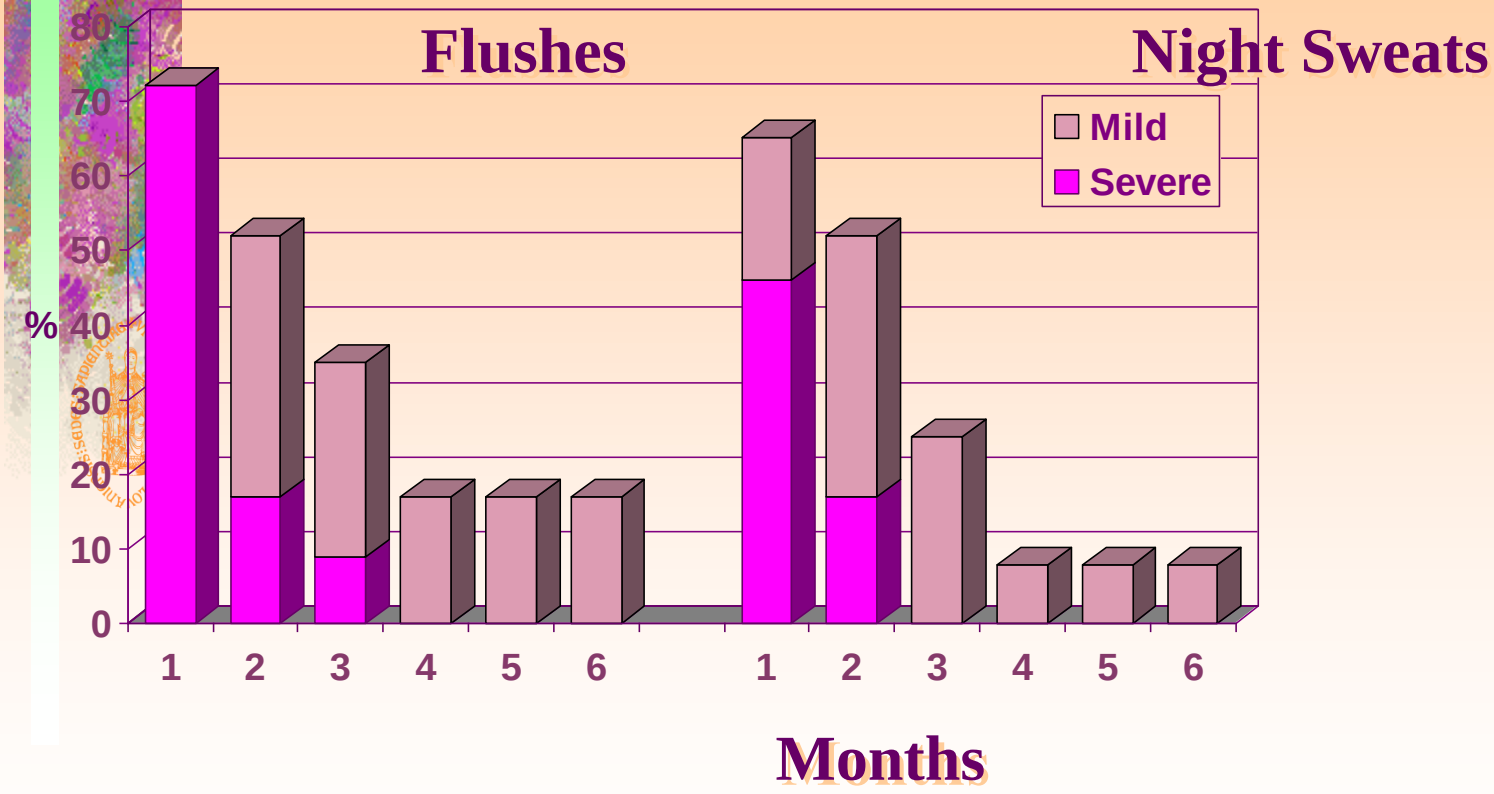
Climen Review
Eur Menop J 97

Brain effects



it takes 3 months to decrease flushes and sweats = brain effects

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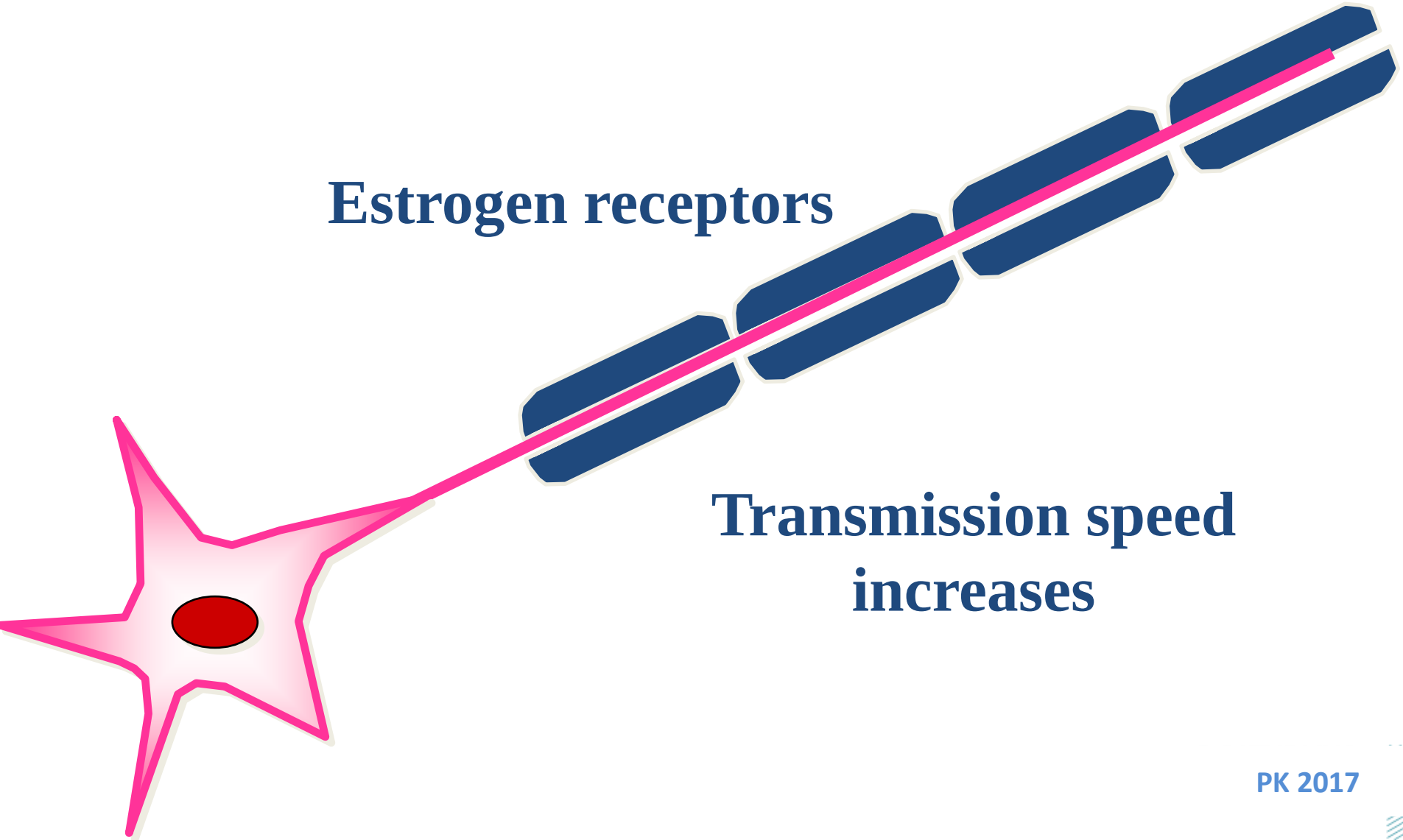
Estrogens and the Brain



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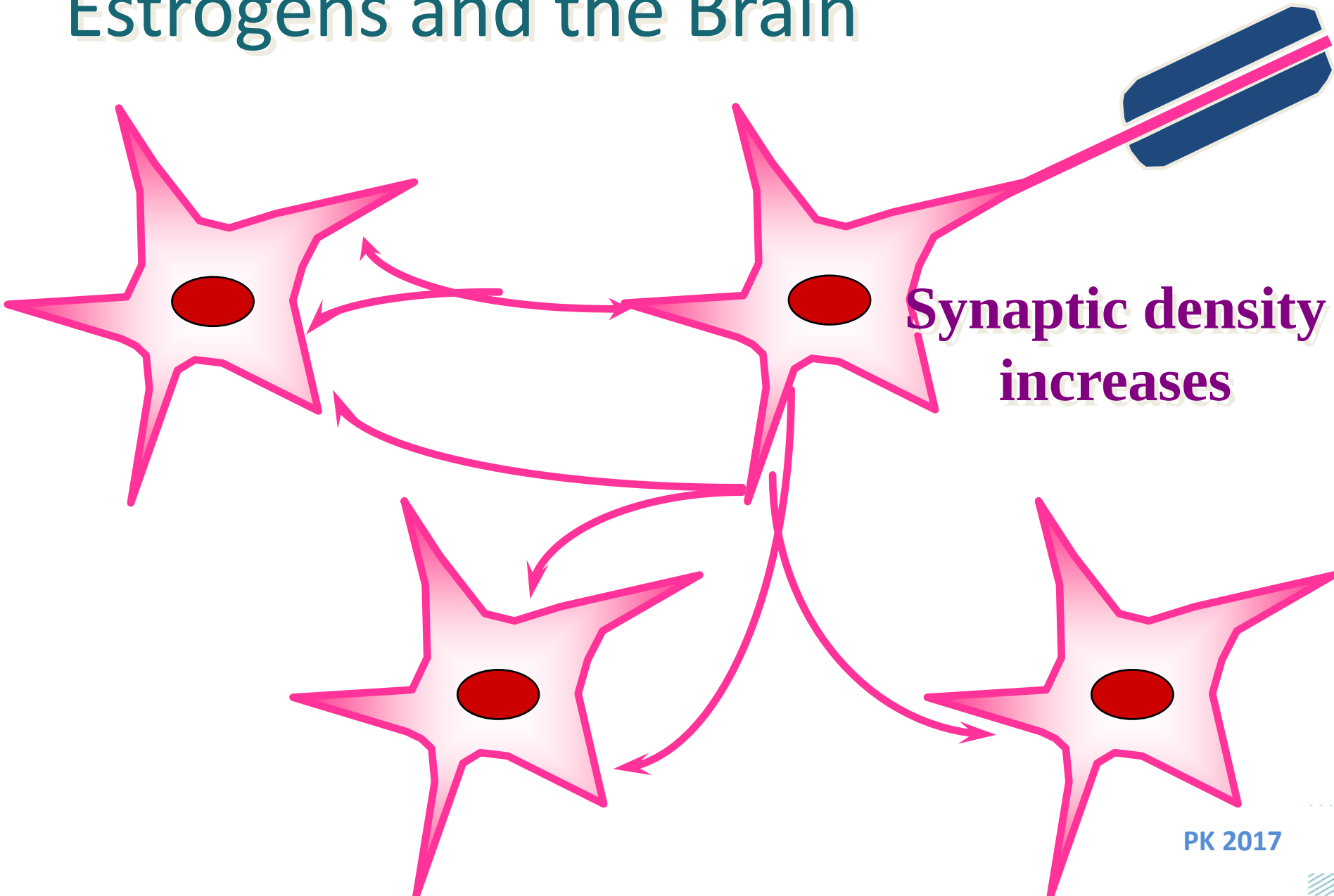
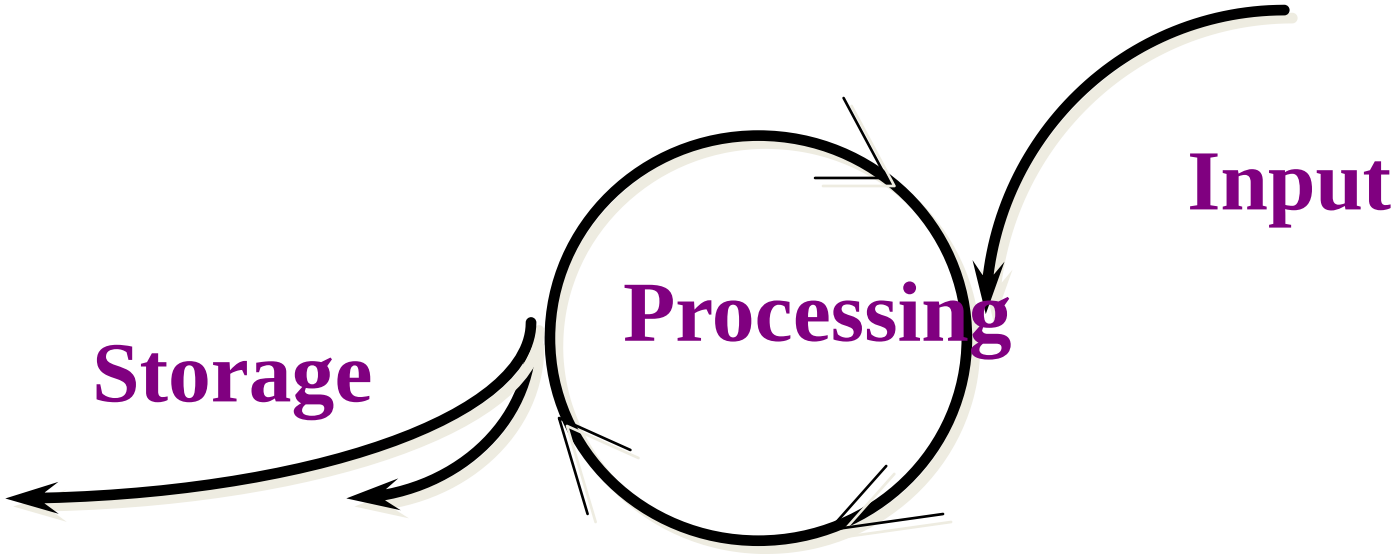
Estrogens and the Brain



Estrogens and the Brain



Short & long term memory

Transmission speed cell-cell contacts

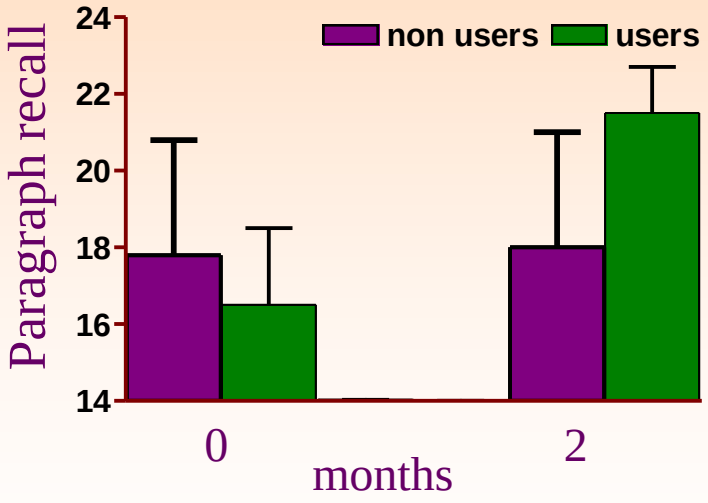
Cerebral blood flow

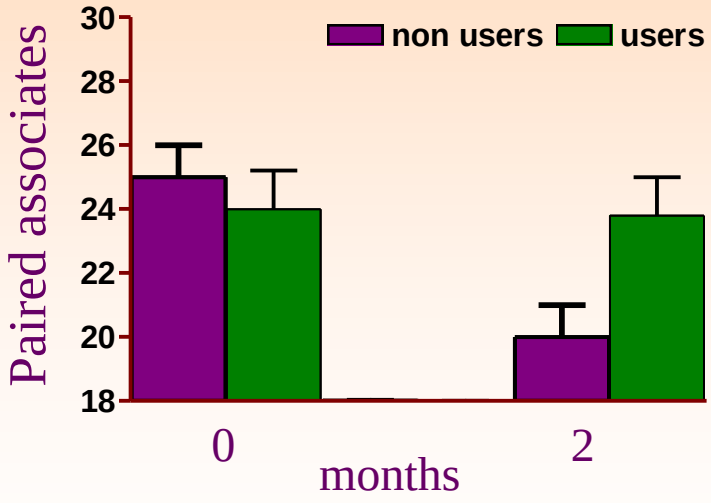
- 0, 4, 6, 9, 22 weeks ; n=12
- transdermal 50 µgr
- pulsatility index ; internal carotid artery
- duration of menopause // PI
- increase in PI // duration of menop
- Conclusion : the decrease in pulsatility index (= distal impedance) in the brain and the uterus suggest a generalized effect.

Gangar, K. F., Vyas, S., Whitehead, M., Crook, D., Meire, H., and Campbell, S.Gangar, K. F., Vyas, S., Whitehead, M., Crook, D., Meire, H., and Campbell, S. Pulsatility index in internal carotid artery in relation to transdermal oestradiol and time since menopause. Lancet 338(8771), 839-842. 10-5-1991.

Auditive memory**

- PRT post hysterectomy + BSO
- Treatment 2 months
- Paired associate (retention of new material)
- Immediate paragraph recall
- no effect : visual recall





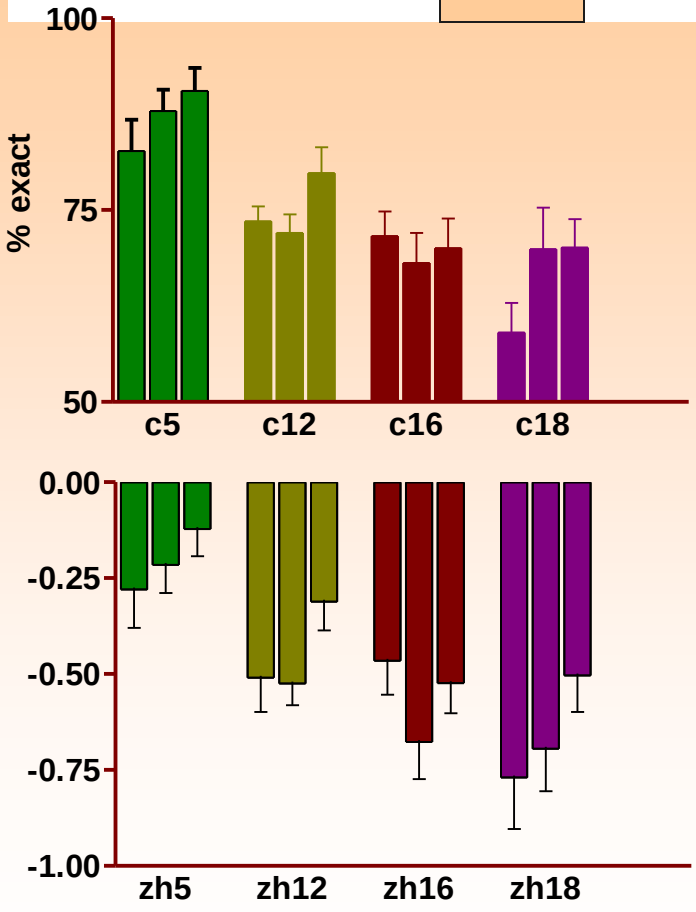
Sherwin, B. B. Estrogenic effects on memory in women. Ann.N.Y.Acad.Sci. 1991,743, 213-30;

estrogens increase auditive memory

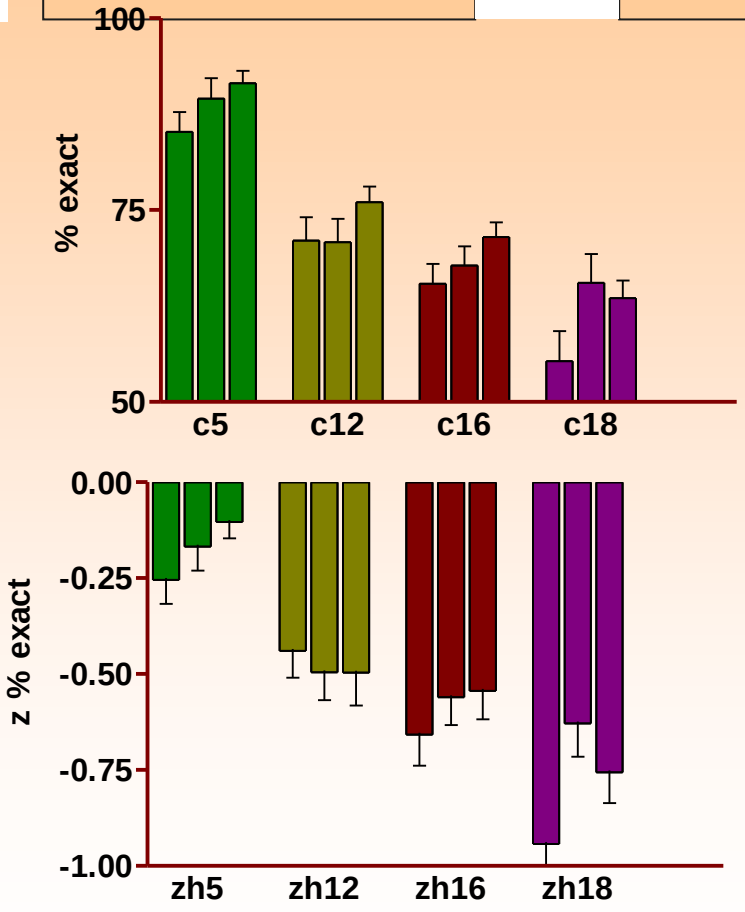
Visual memory

- + - + - +

evaluation 1 2 3



evaluation 1 2 3



Koninckx P.R. , Rosiers AM, Craessaerts M., Orban. G.

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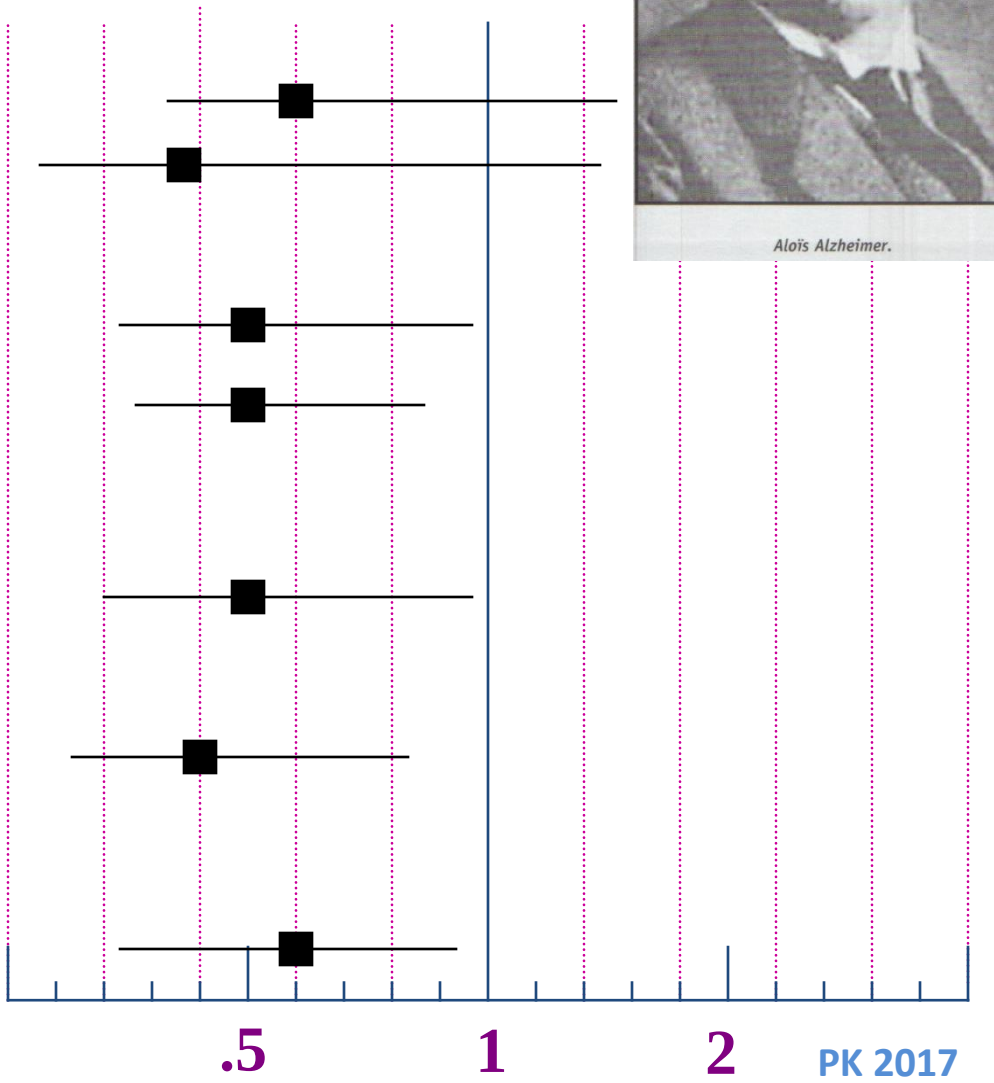
estrogens : no effect on visual memory

Alzheimer disease

- Brenner et al 1994
  - Ever-never
  - Current –never
- Paganini-Hill et all 1996
  - >15y – never
  - >1.25 – never
- Kawas et al 1997
  - Ever – never
- Tang et al 1996
  - Ever-never
- Lerner et al 1996
  - Ever-never

Aloïs Alzheimer.



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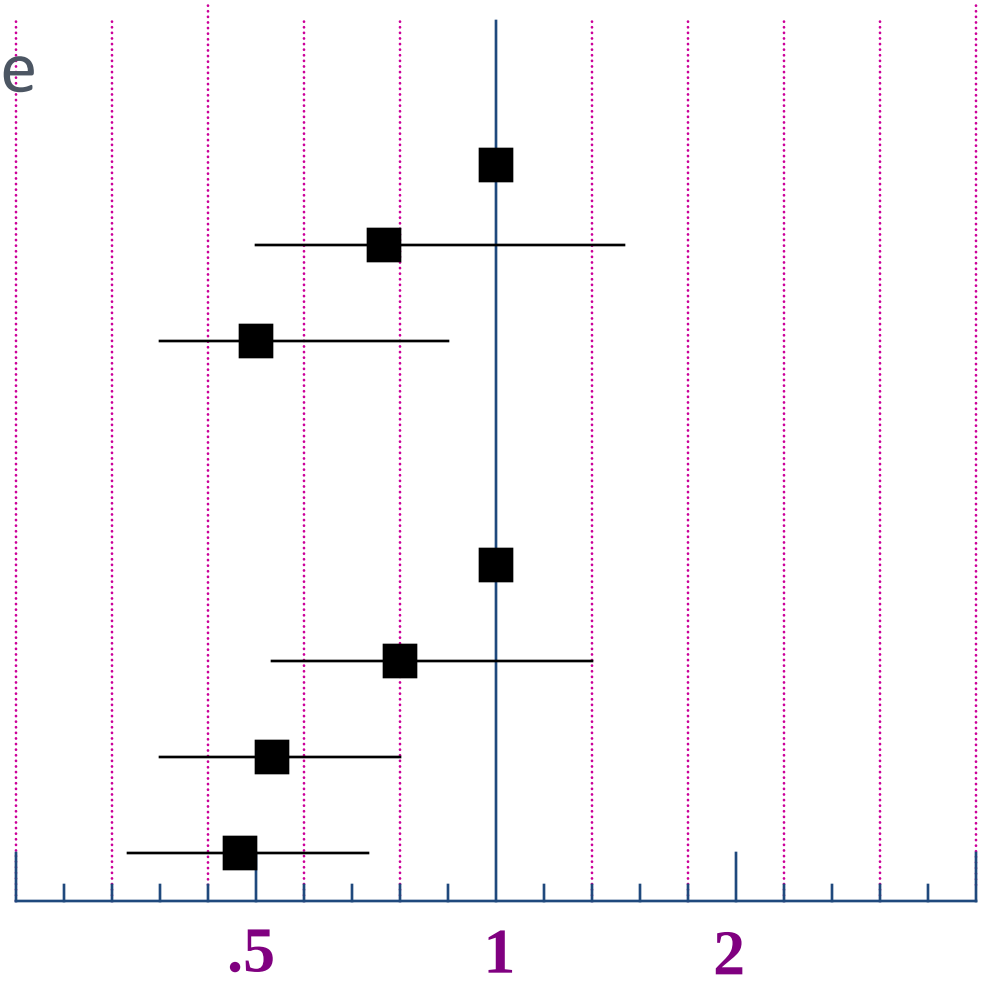
Alzheimer Disease

- Estrogen dose
  - None
  - .625
  - 1.25
- Duration
  - None
  - <3
  - 4-14
  - >15 years



Paganinin-Hill 1996

DHEA ?

- …….. do not support the idea of strong beneficial effects of a physiological DHEA substitution on well-being or cognitive performance in healthy elderly individuals

Wolf, O. T., Neumann, O., Hellhammer, D. H., Geiben, A. C., Strasburger, C. J., Dressendorfer, R. A., Pirke, K. M., and Kirschbaum, C.Wolf, O. T., Neumann, O., Hellhammer, D. H., Geiben, A. C., Strasburger, C. J., Dressendorfer, R. A., Pirke, K. M., and Kirschbaum, C. Effects of a two-week physiological dehydroepiandrosterone substitution on cognitive performance and well-being in healthy elderly women and men. JOURNAL OF CLINICAL ENDOCRINOLOGY AND METABOLISM 82(7), 2363-2367. 7-1997.

Androgens after menopause

RCTs of women with surgical menopause demonstrated increased sexual desire and frequency of satisfying sexual activity in women using 300mcg daily testosterone patches (Braunstein et al 2000; Buster et al 2005).

It has been suggested that to be effective, androgen levels must be increased above normal (Cameron and Braunstein 2004).

However, the question of whether there is a syndrome of female androgen insufficiency and whether supplementary androgens have a beneficial effect on libido, energy or sense of wellbeing in pre and postmenopausal women remains unresolved. In the absence of high quality evidence expert opinion is divided. Whilst some high quality RCTs have

Garefalakis, M. and M. Hickey (2008). "Role of androgens, progestins and tibolone in the treatment of menopausal symptoms: a review of the clinical evidence." Clin Interv Aging 3(1): 1-8.

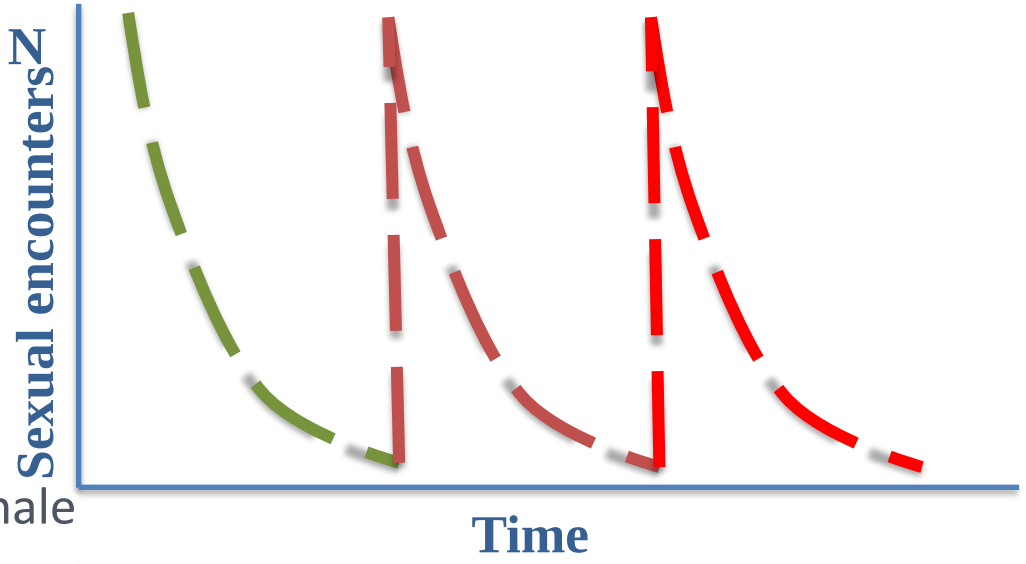
Garefalakis, M. and M. Hickey (2008). "Role of androgens, progestins and tibolone in the treatment of menopausal symptoms: a review of the clinical evidence." Clin Interv Aging 3(1): 1-8.

- symptoms, including depression, nervousness, agitation, insomnia, arthralgia, and poor concentration are associated with the menopause (Bachmann 1998), but the relationship between these symptoms and low estrogen is more difficult to determine
- There is little evidence of the beneficial effects of testosterone on mood or sense of well-being

Lack of good data since not industry driven : testosterone and DHEA are cheap without a patent

Sexuality and hormones

- Primates
  - Partner effect
  - Androgens =libido in male and female
  - Estrogens = attractivity in females
  - Progesterone …….
- Human trials : not feasible
  - Randomised
  - controlled
  - crossover



Very well performed primate experiments to investigate partner effect , libido , atractivity etc.

No solid data in the human for obvious reasons

Ovarian cancer risk

Life time risk 1/200 - high mortality

Effect of

- Age
- Heredity
- Ampulla
- Oral contraception
- Tubal ligation

Unclear

- Effect of yearly ultrasound

Clinical consequences : remove ampulla at hysterectomy
effect insufficient for systematic ampullectomy, tubal ligation in all women

To remove both ovaries during hysterectomy

- Cancer risk
  - <0.5%/year = low frequency

- Oestrogens
  - Variable secretion for 5-10 years
  - Can be replaced but ……

- Androgens
  - Mental tonic effect
  - Estrogen precursor
  - Difficult to replace