

Sex Steroids and Brain



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Gender Brain Differentiation

Biological
Factors

Genetic
Factors

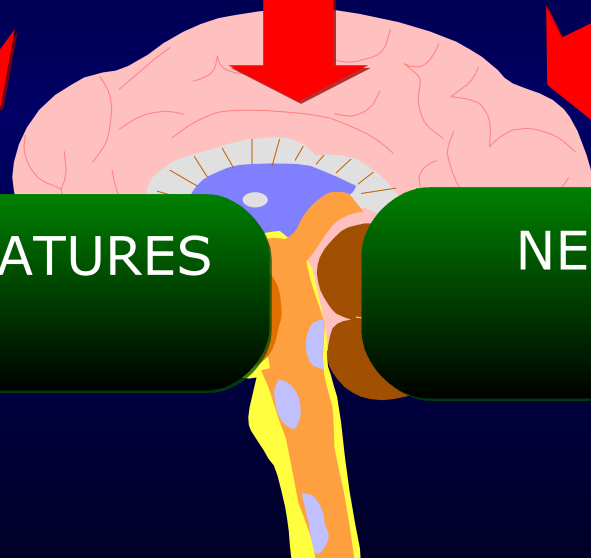
Development
Factors

- Behavioural
- Socio-cultural norms

ANATOMICAL FEATURES

NEUROCHEMICAL
ACTIVITIES

BRAIN FUNCTION
THROUGHOUT ALL LIFE

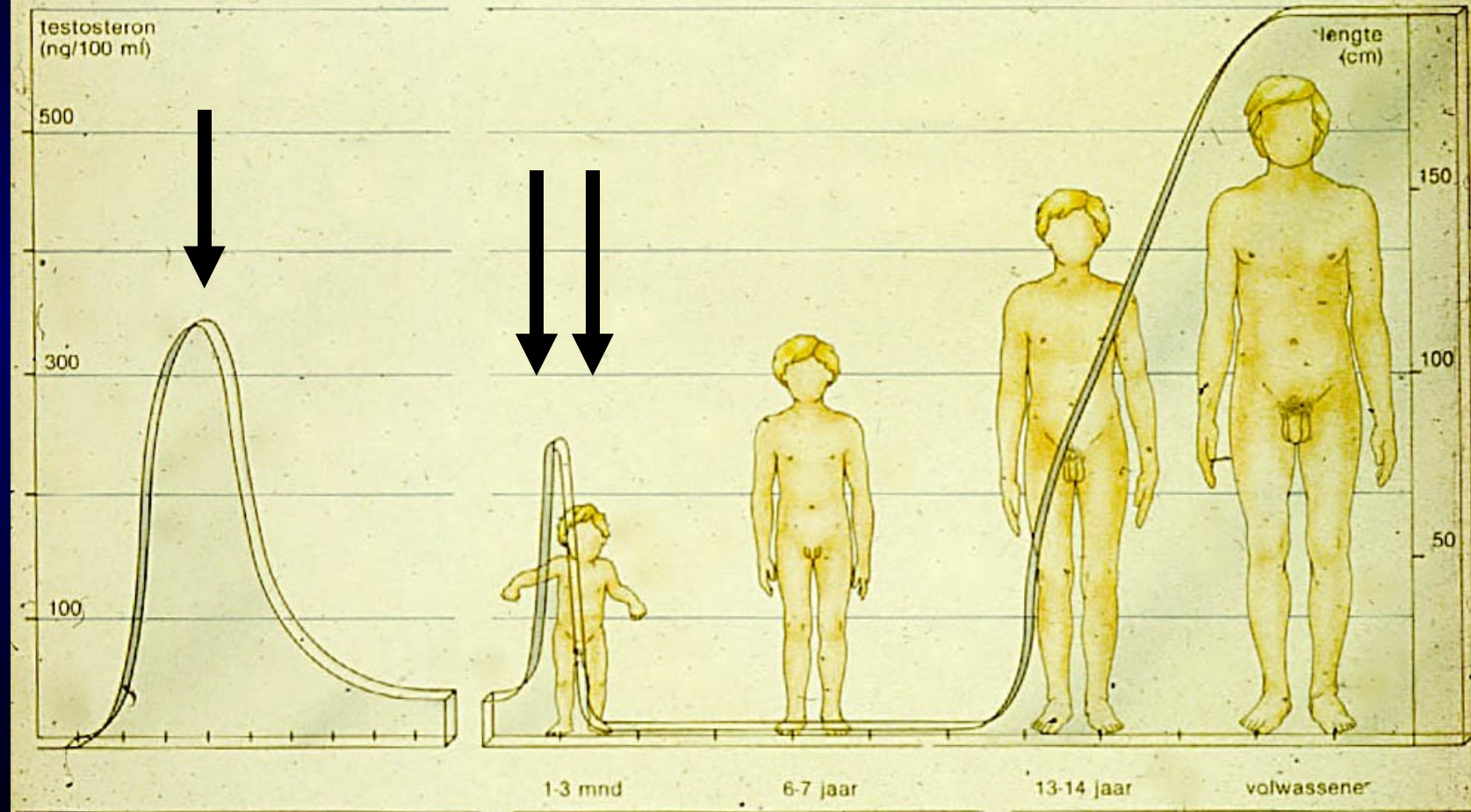


Mechanisms by which sex steroids impact the CNS

- Organizational (largely prenatal in humans)
- Activational (adolescence and beyond)
- Genomic vs membrane effects
- Neurotransmitter and neuropeptide function
- Cerebral blood flow and metabolism
- Receptor subtype cross-talk
- Induction of receptors

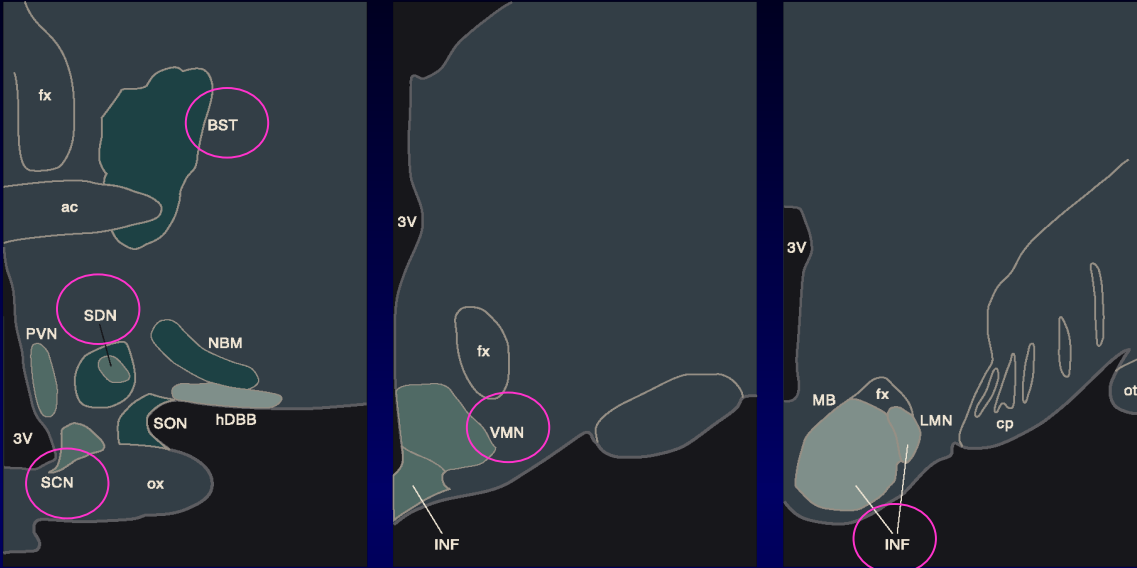
Testosterone Plasma Levels in Men

Testosteronconcentraties in het plasma op verschillende leeftijden (naar Butt en London, *Clinics in Endocrinology and Metabolism* 1975; 4, 3: 585).



Sex differences in the distribution of androgen receptors in the human hypothalamus.

Males



SDN: Sexual Dimorphic Nucleus

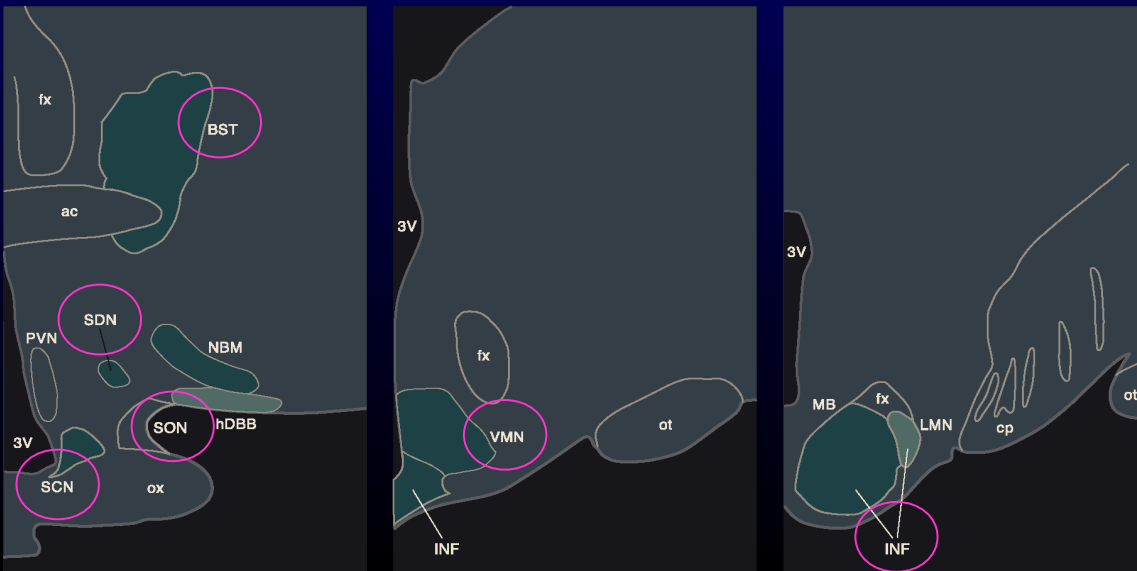
- Sexual Behaviour
- Copulatory behaviour
- Integration of sexual motivation with copulatory program

BST: Bed Nucleus of Stria Terminalis

- Sexual Behaviour
- Anxiety and stress response
- A major aromatization center

Fernandez-Guasti, et al., JCN, 2000

Females

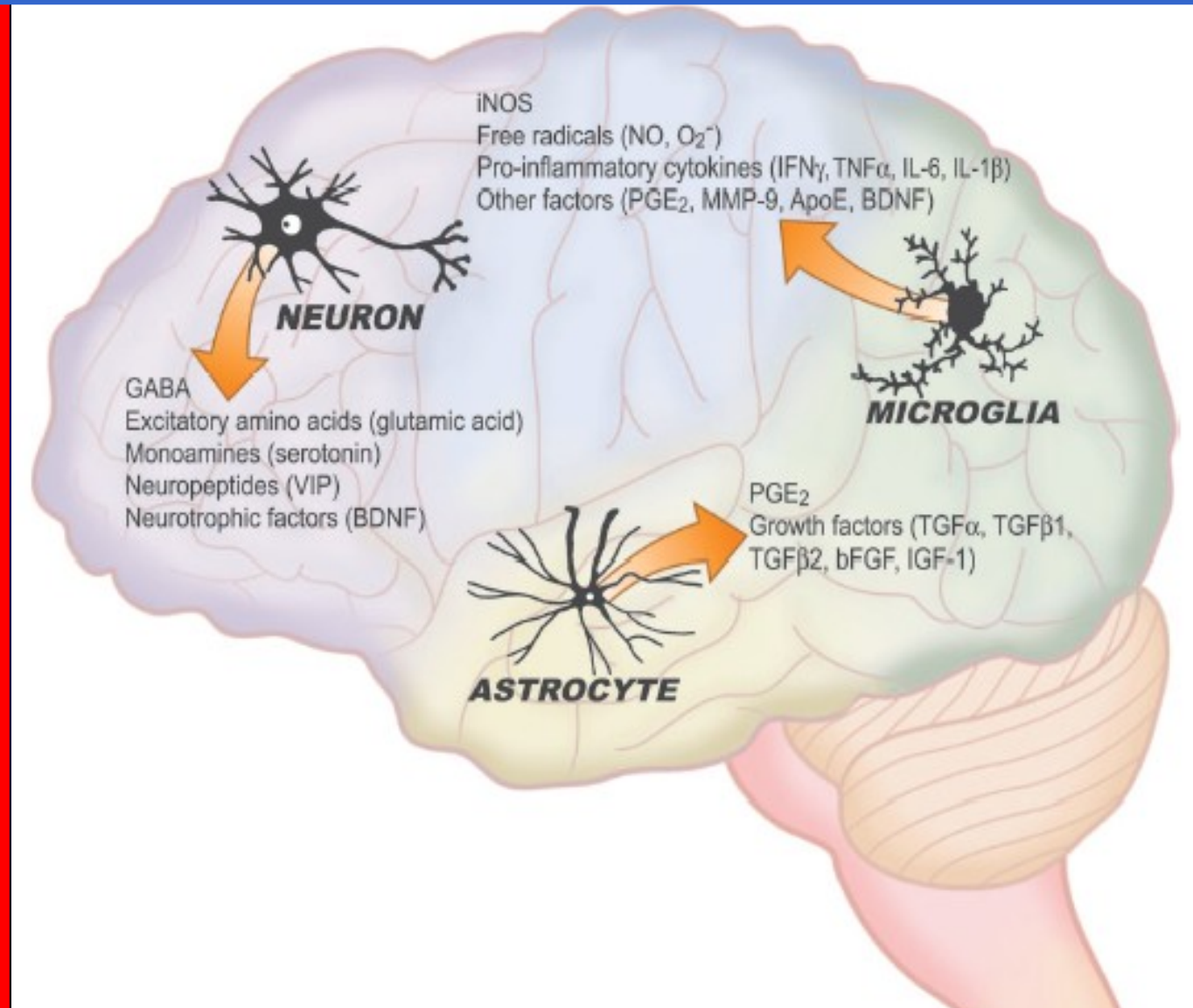


INF: infundibular Nucleus

VMN: Ventromedial hypothalamic nucleus

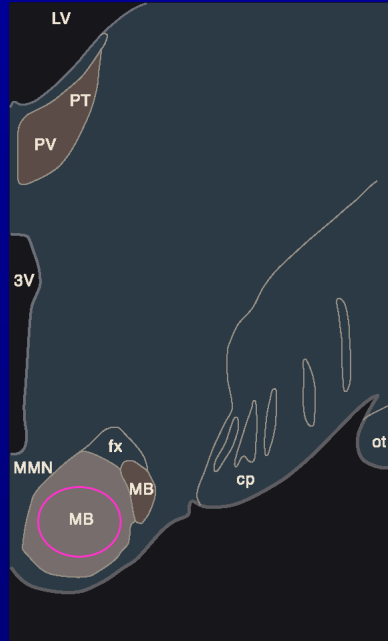
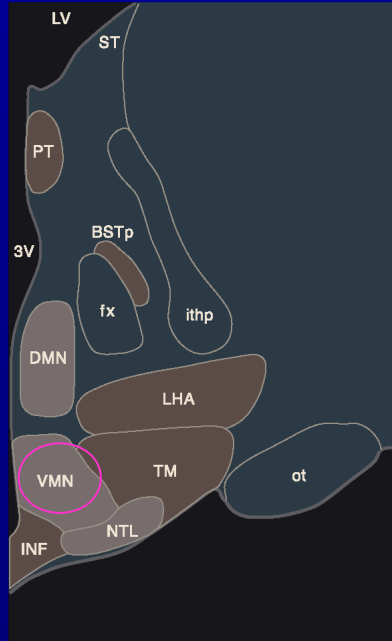
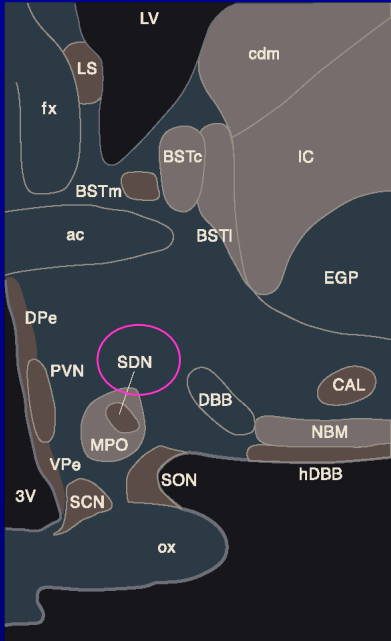
SCN: Suprachiasmatic nucleus

Cellular and Subcellular Estrogen Effects



Males

ER α Nuclear



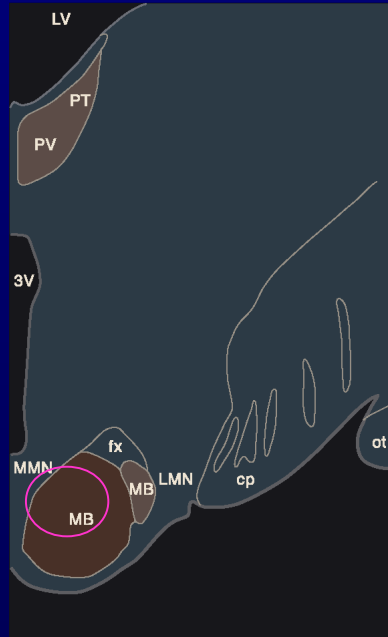
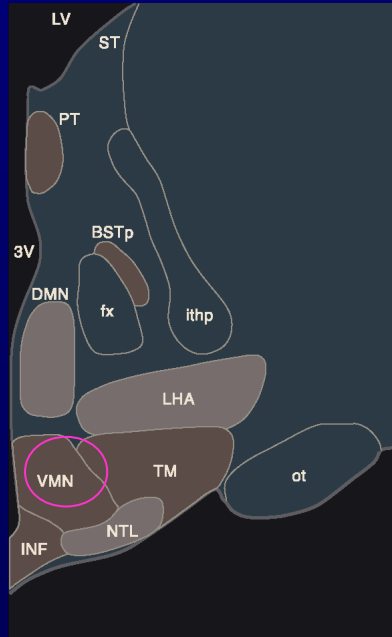
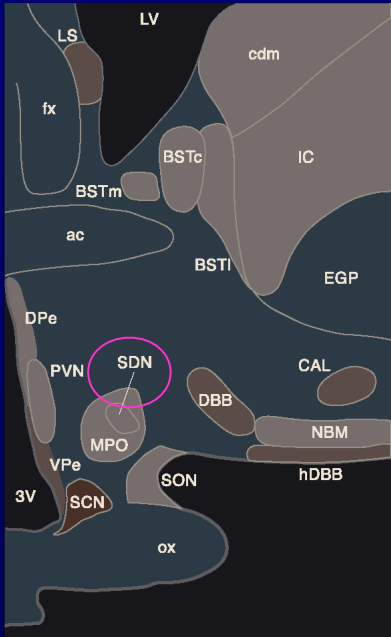
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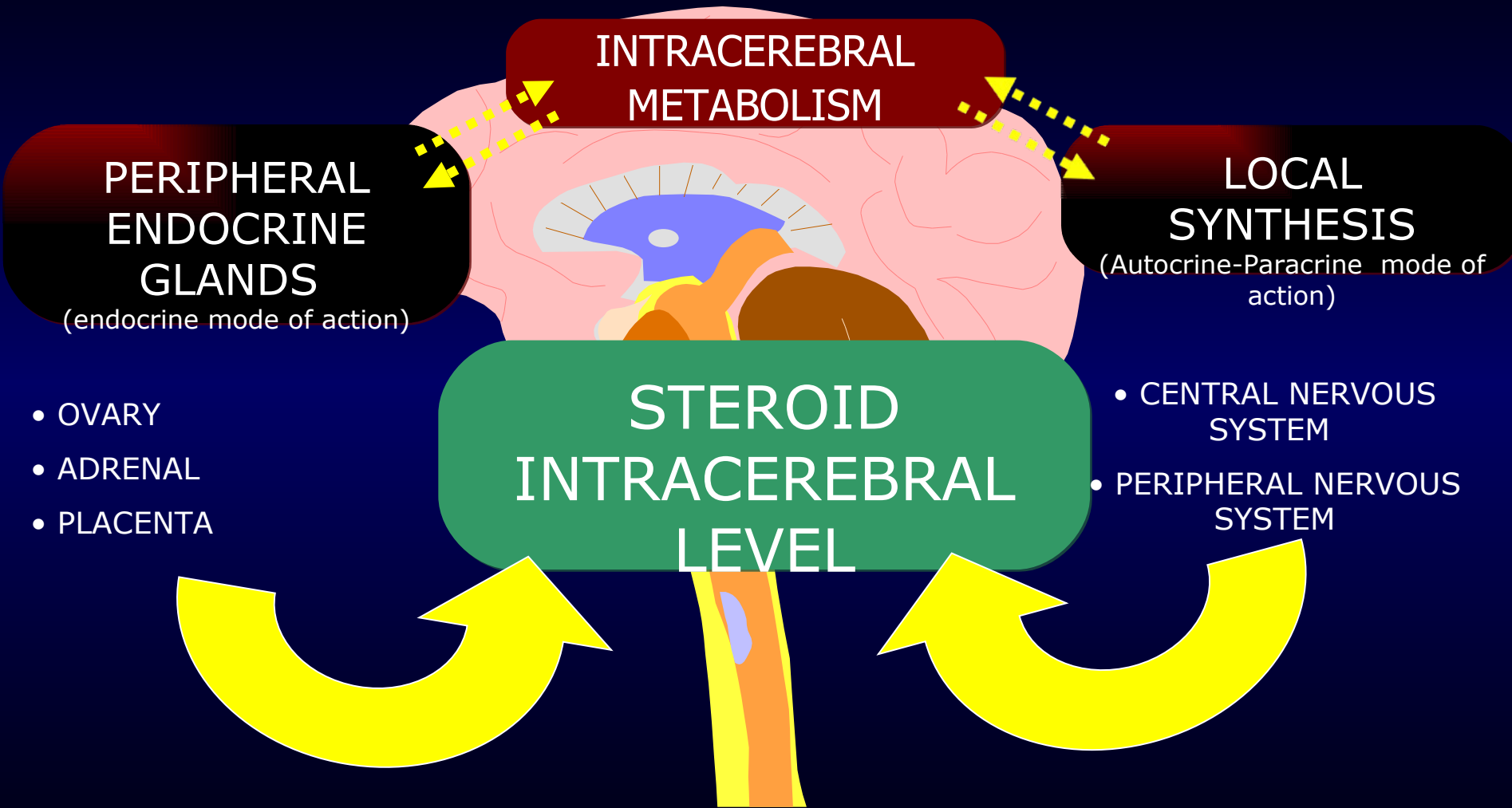


INF: infundibular Nucleus

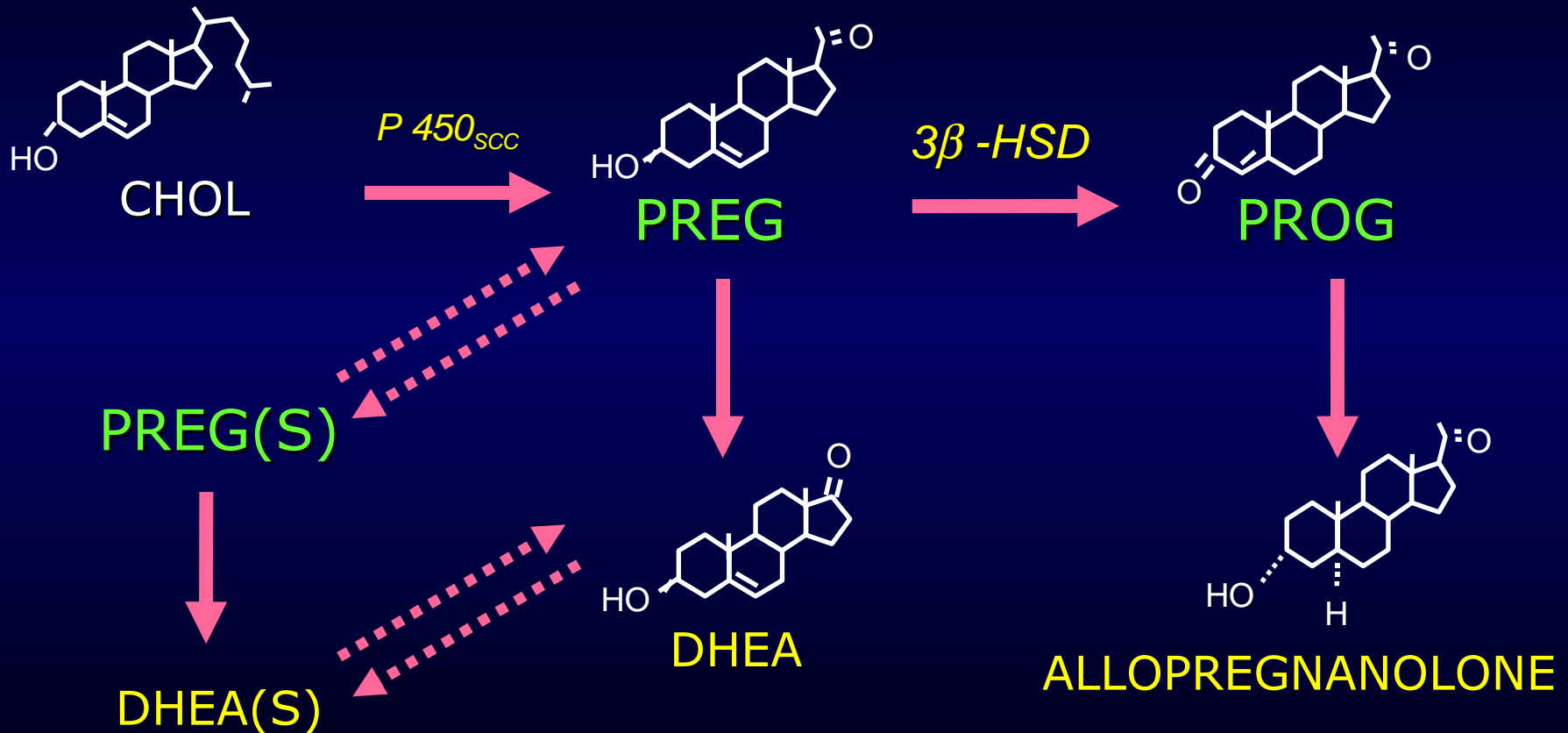
VMN: Ventromedial hypothalamic nucleus

SCN: Soprachiamatic nucleus

Steroids and Neurosteroids

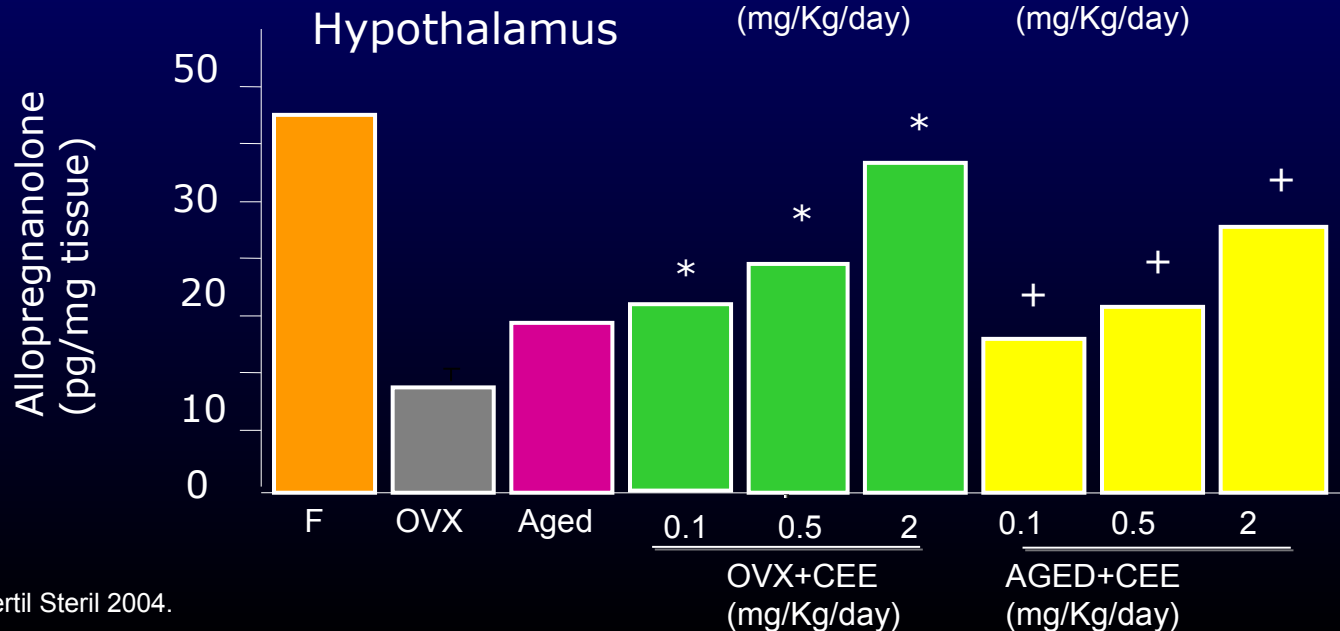
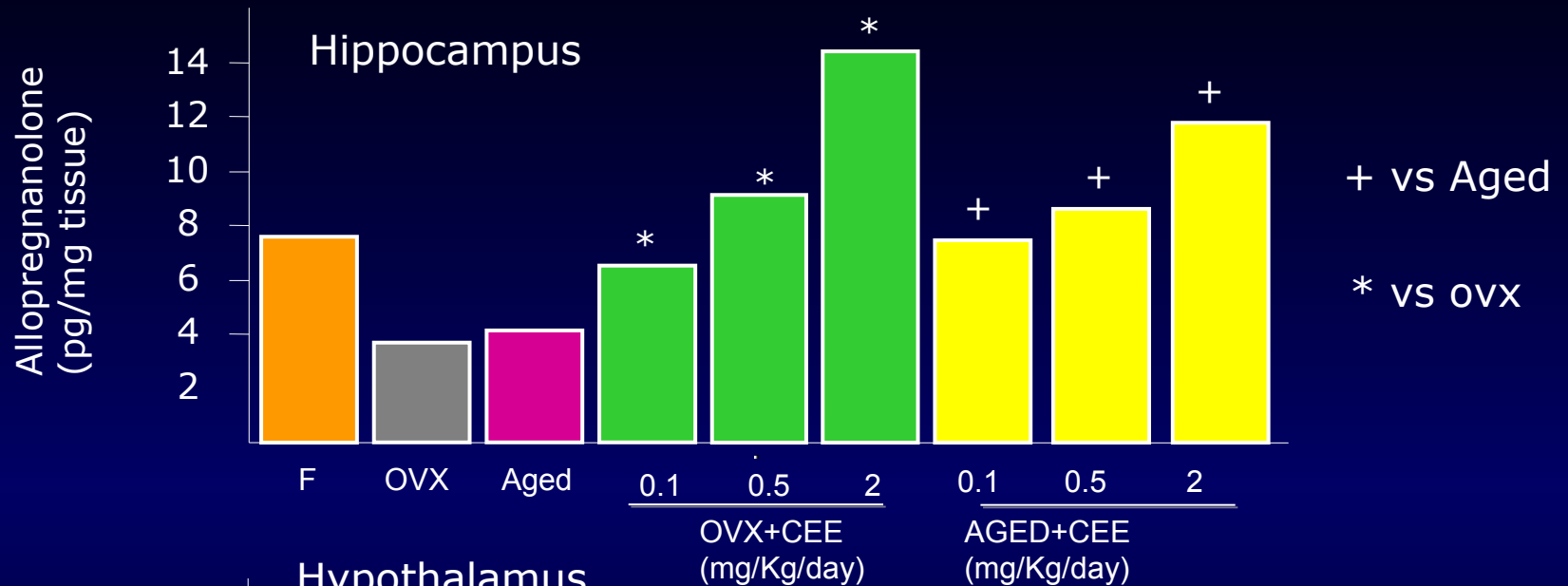


Biosynthesis of Progesterone and Androgens in CNS



Neurosteroids are steroids synthesized in the brain, de-novo from cholesterol or by metabolism of blood-born precursors

Estrogens effects on Allopregnanolone in OVX and aged rats



Progestins and Allopregnanolone

	MP 2-4-8	MPA 0.05-0.1-0.2	DYG 0.2-0.6-1	DRSP 0.1-0.5-1	NOM Ac 0.05-0.1-0.2-0.5-1
Frontal cortex	↑ 4-8 mg/kg/d	↑ 0.2 mg/kg/d	↑ 1 mg/kg/d	=	=
Parietal cortex	↑ 2-4-8 mg/kg/d	↑ 0.2 mg/kg/d	=	=	=
Hippocampus	↑ 8 mg/kg/d	↑ 0.2 mg/kg/d	↑ 1mg/kg/d	=	↑ 0.5-1mg/kg/d
Hypothalamus	↑ 4-8mg/kg/d	↑ 0.2mg/kg/d	↑ 1mg/kg/d	=	=
Anterior Pituitary	↑ 8 mg/kg/d	↑ 0.2mg/kg/d	=	=	=
Adrenal cortex	=	=	=	=	↓ 1mg/kg/d
Serum	↑ 2-4-8 mg/kg/d	=	=	=	=

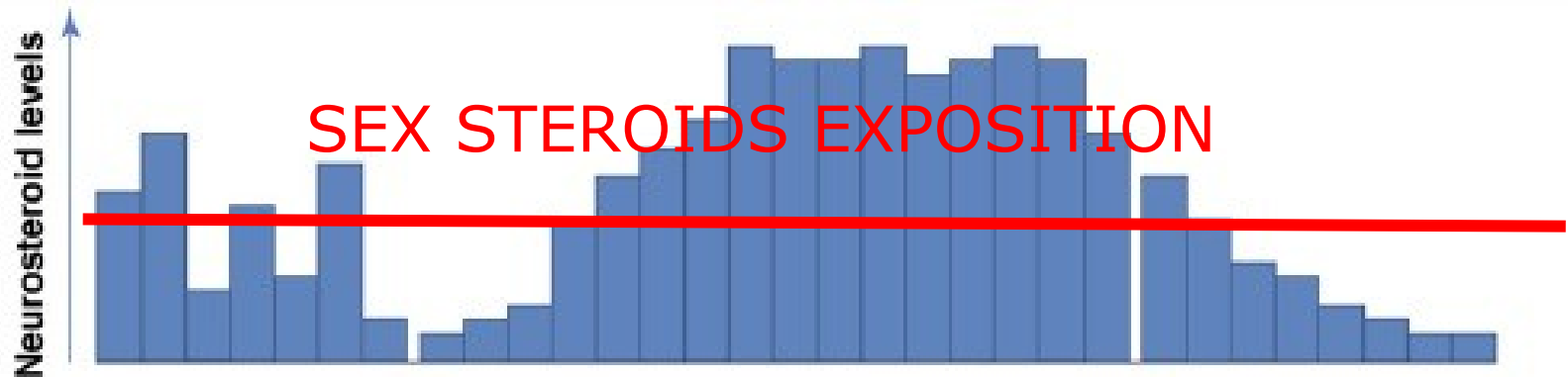
=: no differences vs ovx; ↑: increase vs ovx; ↓: decrease vs ovx.

Progestins and Allopregnanolone

	E2V 0,05	MP+ E2V 2-4-8	MPA+ E2V 0.05-0.1-0.2	DYG+ E2V 0.2-0.6-1	DRSP+ E2 0.1-0.5-1	NOM Ac+ E2V 0.05-0.1-0.2-0.5-1
Frontal cortex	↑	▲ 8 mg/kg/d	▲ 0.2 mg/kg/d	▲ 1mg/kg/d	—	—
Parietal cortex	↑	▲ 4-8 mg/kg/d	▲ 0.2mg/kg/d	—	—	—
Hippocampus	↑	▲ 8 mg/kg/d	—	▲ 1mg/kg/d	—	▲ 1 mg/kg/d
Hypothalamus	↑	▲ 8 mg/kg/d	▲ 0.2mg/kg/d	▲ 1mg/kg/d	—	▲ 1 mg/kg/d
Anterior pituitary	↑	▲ 8 mg/kg/d	▲ 0.2mg/kg/d	—	—	▲ 1 mg/kg/d
Adrenal cortex	=	—	▲ 0.2mg/kg/d	—	—	▼ 1 mg/kg/d
Serum	↑	▲ 2-4-8mg/kg/d	—	▲ 1mg/kg/d	—	—

↑: vs ovx; ▲: increase vs E2V; ▼: decrease vs E2V; —: no differences E2V.

Neurosteroidogenesis throughout the lifespan



Development

Temporalspatial fluctuations of neurosteroids participate in the control of neuronal survival and apoptosis and of neural stem cell self-renewal and differentiation

Early life

Elevated concentrations of neurosteroids protect the brain from endogenous and environmental neurotoxic factors and induce neurogenesis.

Adulthood

Aging

The decline of neurosteroid levels leaves the brain unprotected against endogenous and environmental neurotoxic factors

Brain DHEA Function

DHEA(S) ON NEUROTRANSMISSION

↓ GABA_A-R

↓ glycine-R

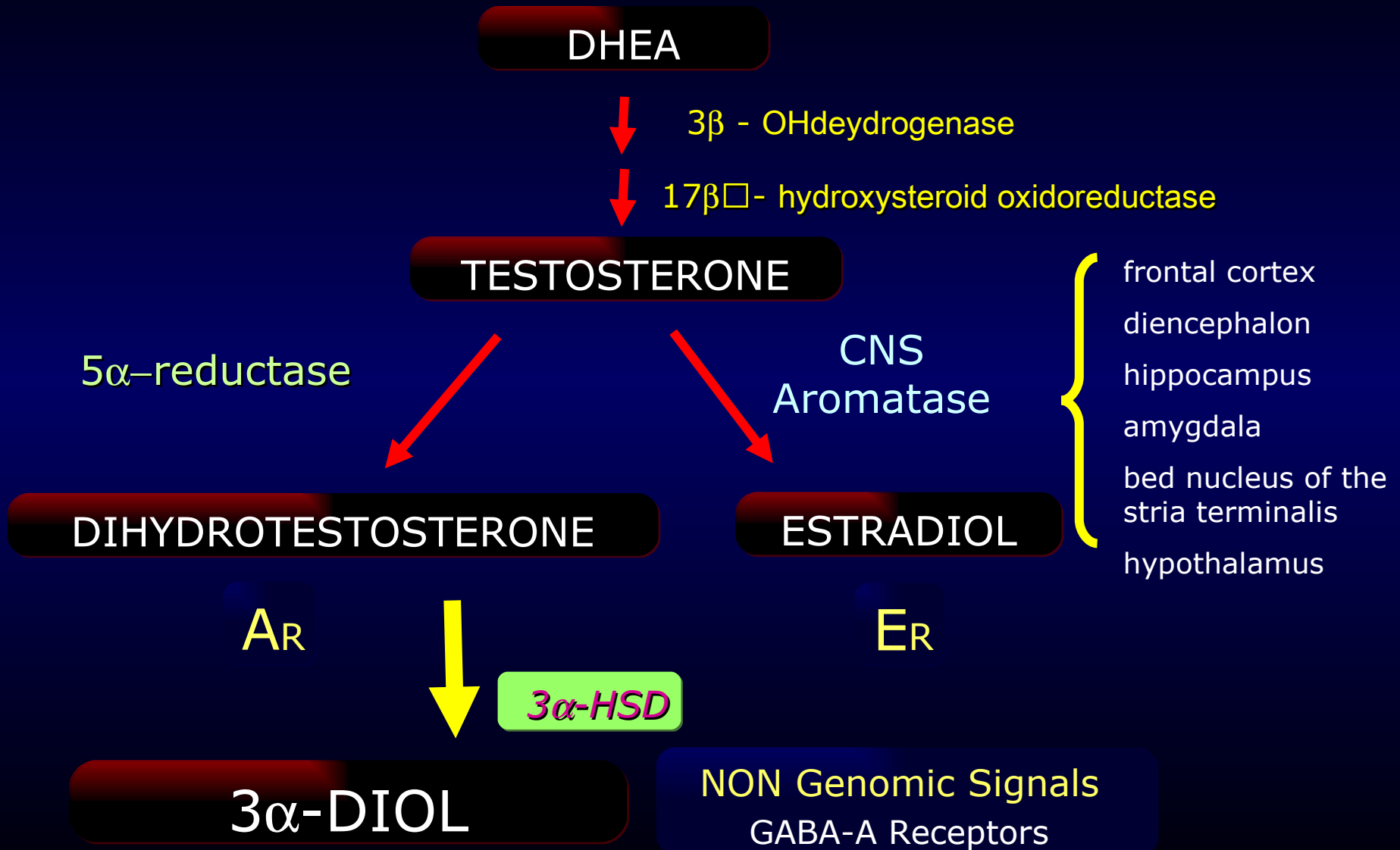
↑ NMDA-R

↓ voltage gated Ca²⁺ current

↑ σ -R

Majewska, Schwartz, Gibbs, Mienville, Young,
Wu, Farb, Monnet, French-Müllen, Gruol.

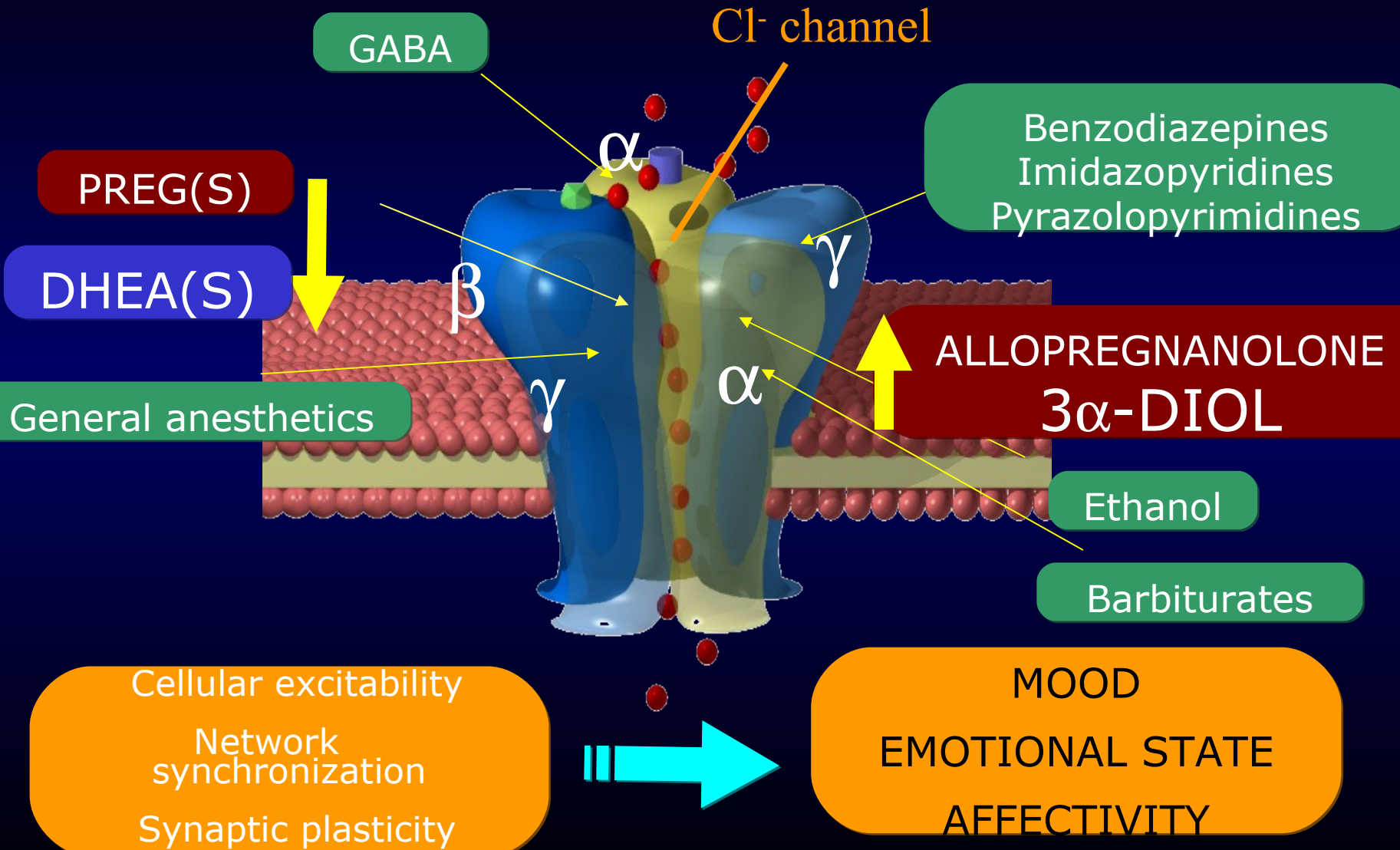
Central Metabolism of Androgens



Simpson ER. *et al*, 1997

MacLusky NJ, *J Neuroscience*, 2004

Neurosteroids and GABA-A



Brain Sexual Differentiation

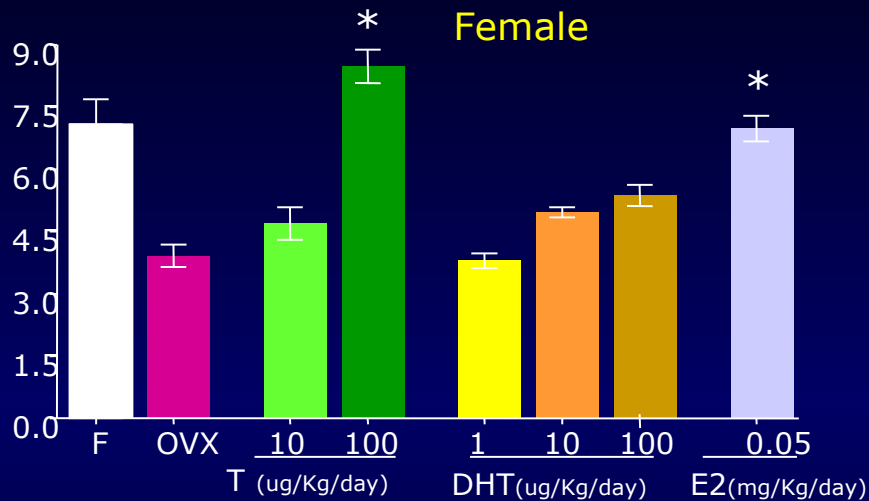
Multisignaling process

“THE HORMONAL FACTOR”

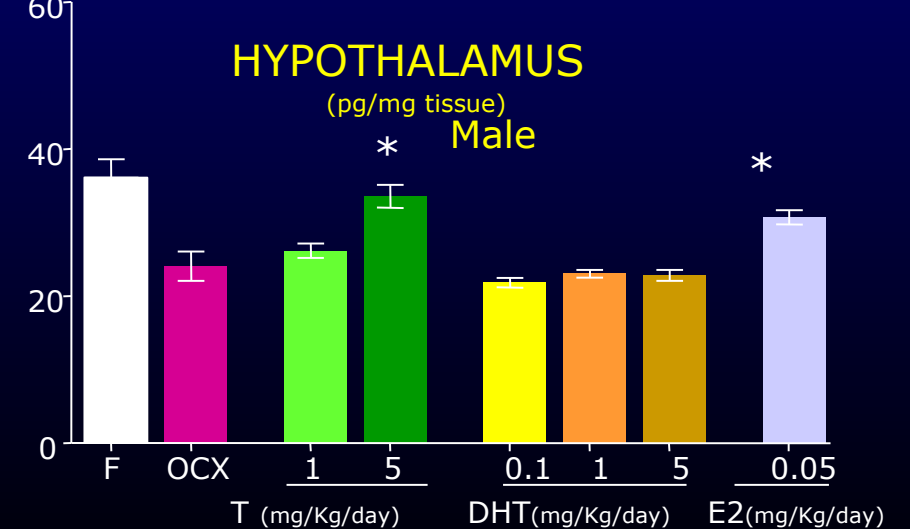
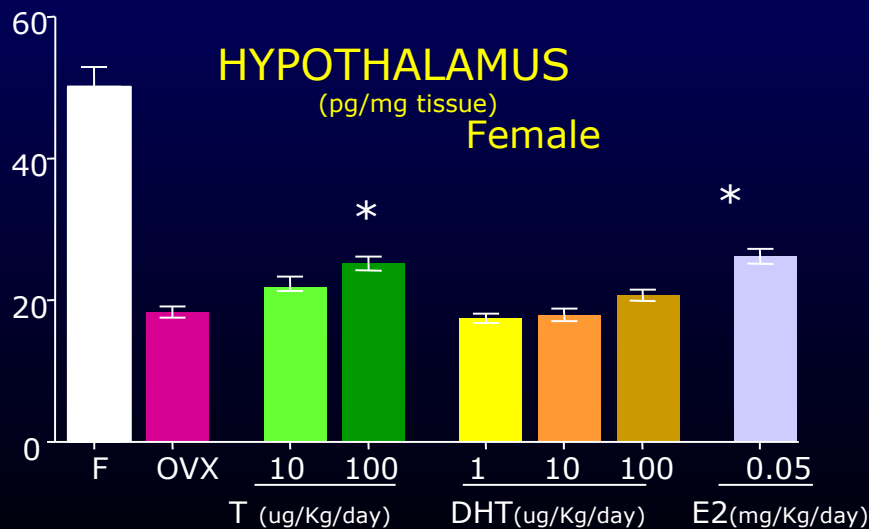
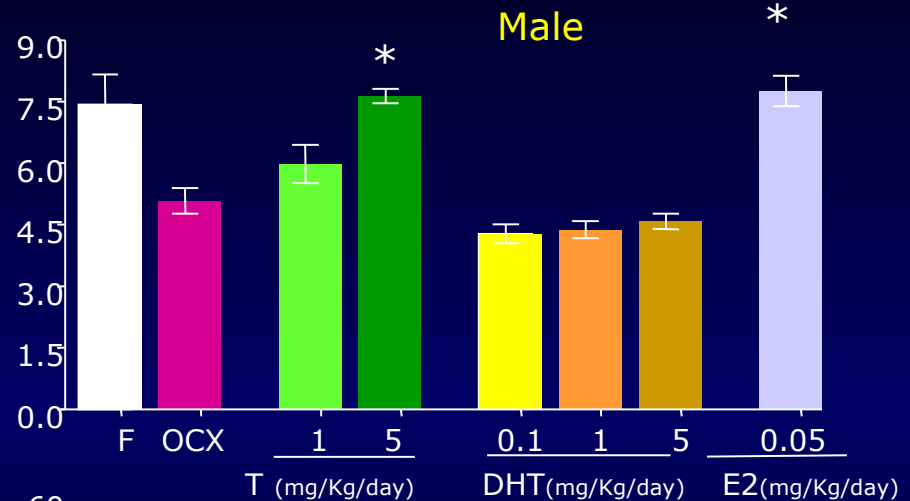
- BRAIN Aromatase
- BRAIN 5 α -Reductase type 1 and type 2

Gender Differential Response of Allopregnanolone to Sex Steroids

HIPPOCAMPUS *vs OVX
(pg/mg tissue)

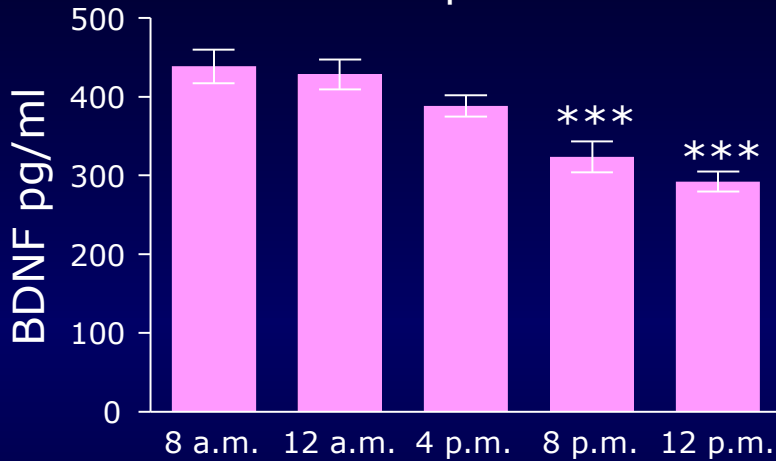


HIPPOCAMPUS *vs OCX
(pg/mg tissue)

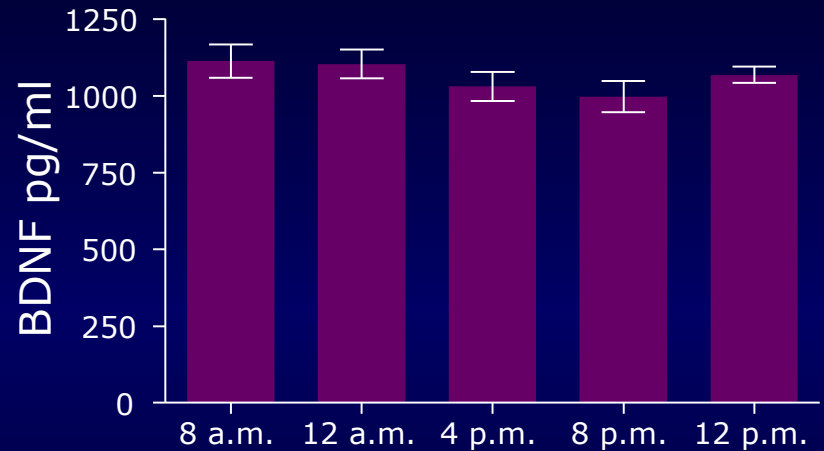


Gender Differential levels of Brain-derived neurotrophic factor (BDNF)

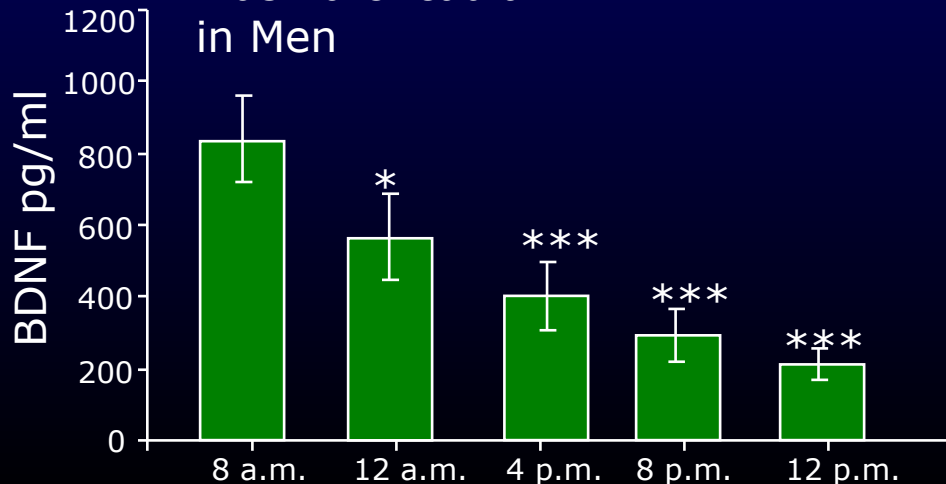
Plasma circadian BDNF in follicular phase



Plasma circadian BDNF in luteal phase



Plasma circadian BDNF in Men

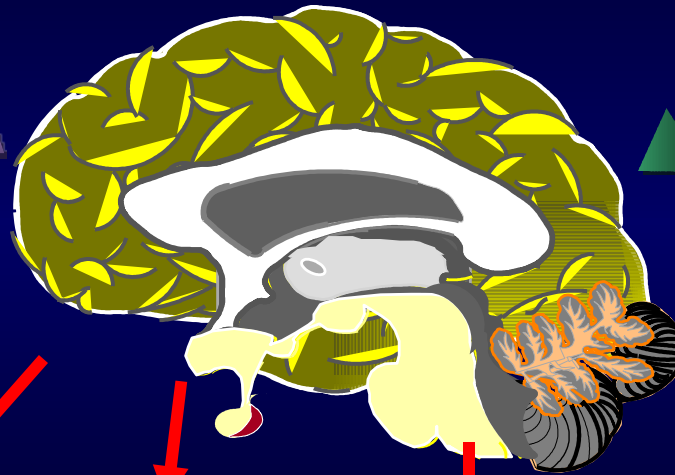


The Brain as a target tissue for Sex Steroids

CNS Sexual Dimorphism

FUNCTIONAL SEX DIFFERENCES

- ERs PRs ARs different expression in brain areas
- ER polymorphisms
- Enzymes induction



STRUCTURAL SEX DIFFERENCES

- Different neuronal subpopulations in brain areas

SEXUAL ORIENTATION

GENDER IDENTITY

COGNITIVE DIMORPHISM

PREVALENCE OF NEUROLOGICAL AND PSYCHIATRIC DISEASES

Ratios for Females over Males Suffering from Particular Neurological And Psychiatric Diseases

% FEMALE : MALE

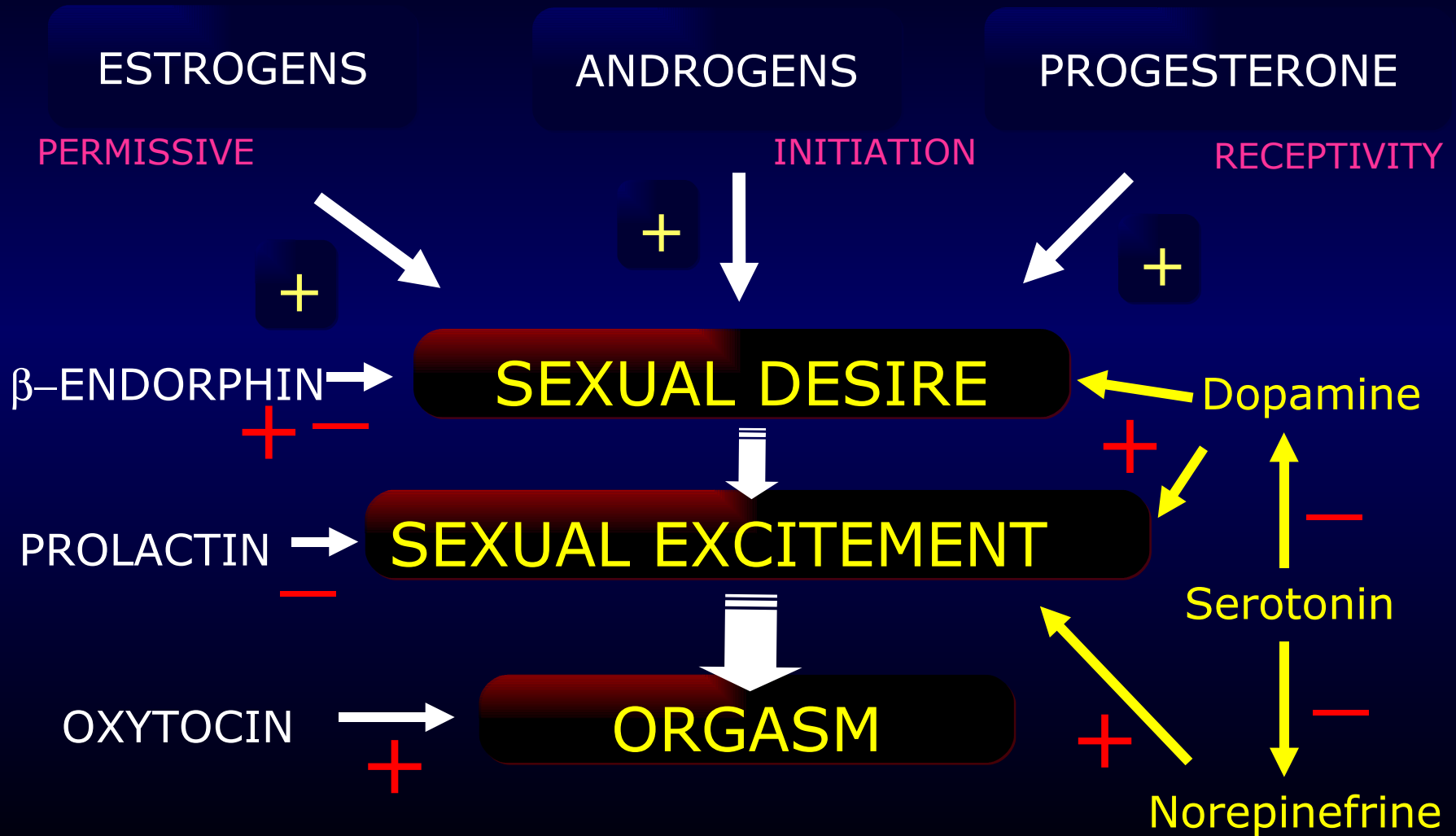
Female > Male

- Anorexia nervosa 93 : 7
- True (central) precocious puberty 90:10
- Hypnotic headache syndrome 84 : 16
- Bulimia 75 : 25
- Senile dementia of the Alzheimer type 74 : 26
- Post-traumatic stress disorders 70 : 30
- Multiple sclerosis 67 : 33
- Anxiety disorder 67 : 33
- Post traumatic stress disorder 66:34
- Dementia 64: 36
- Unipolar depression, dysthymia 63 : 37

Female < Male

- Severe mental retardation 38 : 62
- Substance abuse 34 : 66
- Schizophrenia 27 : 73
- REM sleep behavioral disorder 24 : 76
- Dyslexia 23 : 77
- Autism 20 : 80
- Sleep apnoea 18 : 82
- Kallmann syndrome 17 : 83
- Gilles de la Tourette 10 : 90

Brain Function and Sexual Response



Estradiol, gender and age balances

Estradiol : in > 60 y men : higher than in younger men
in > 60 y men : higher than in untreated > 60 y women

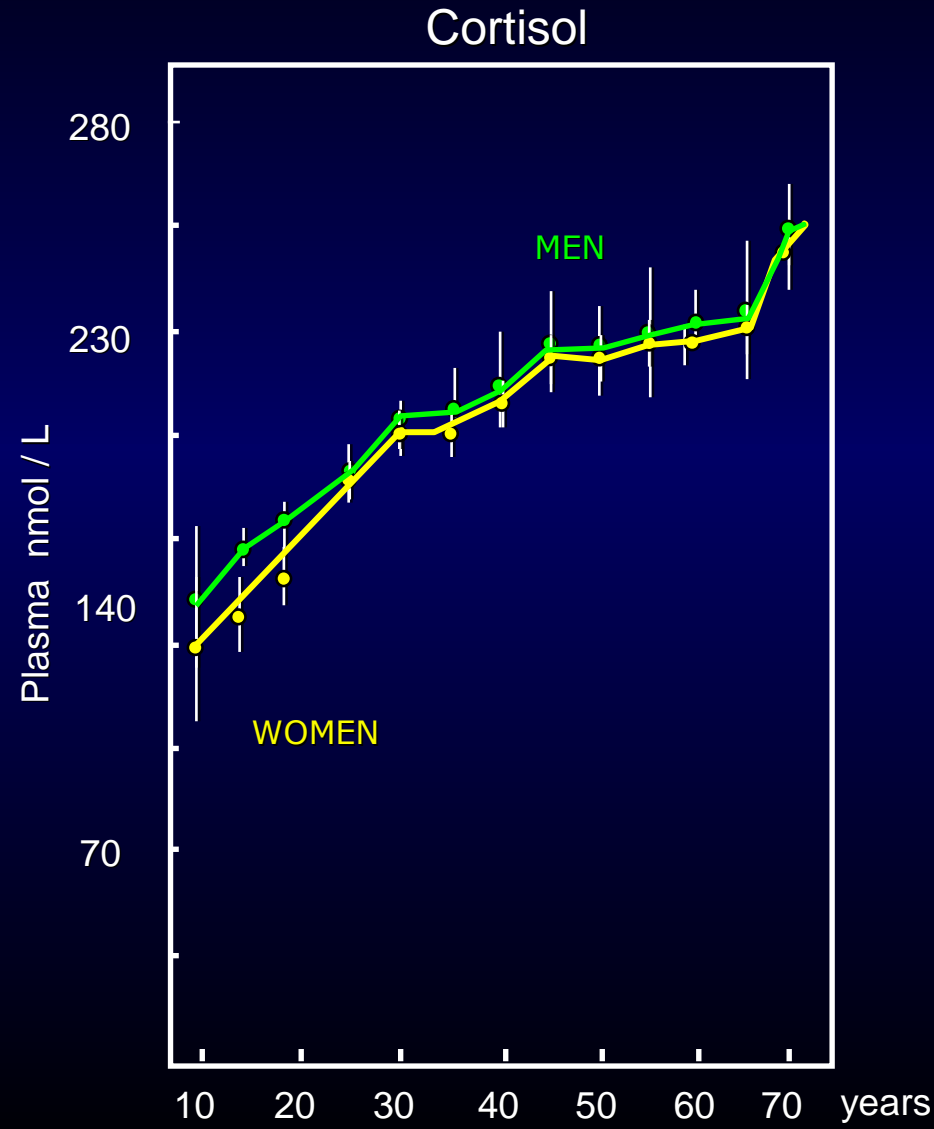
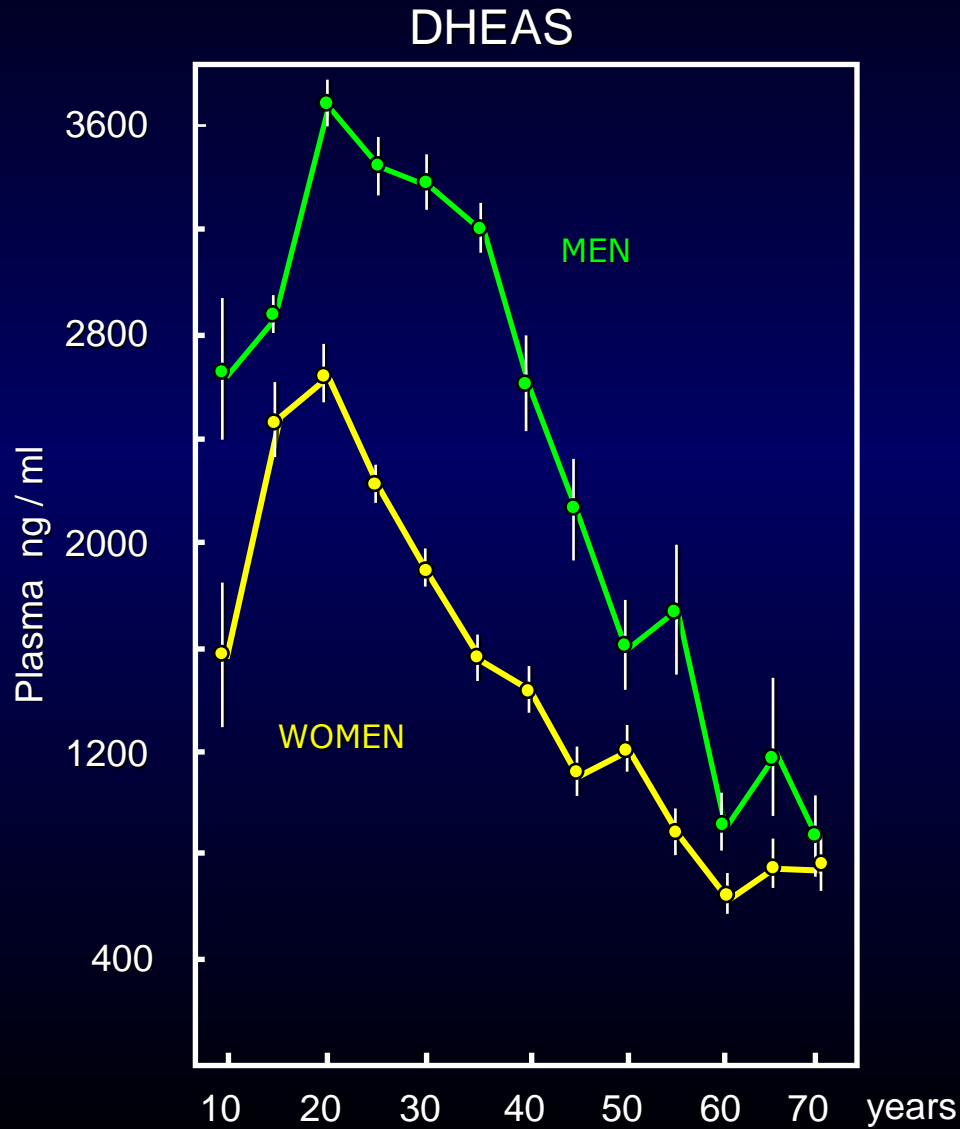
Vermeulen A, van Pottelberg I, 2002

Yaffe et al, 2002

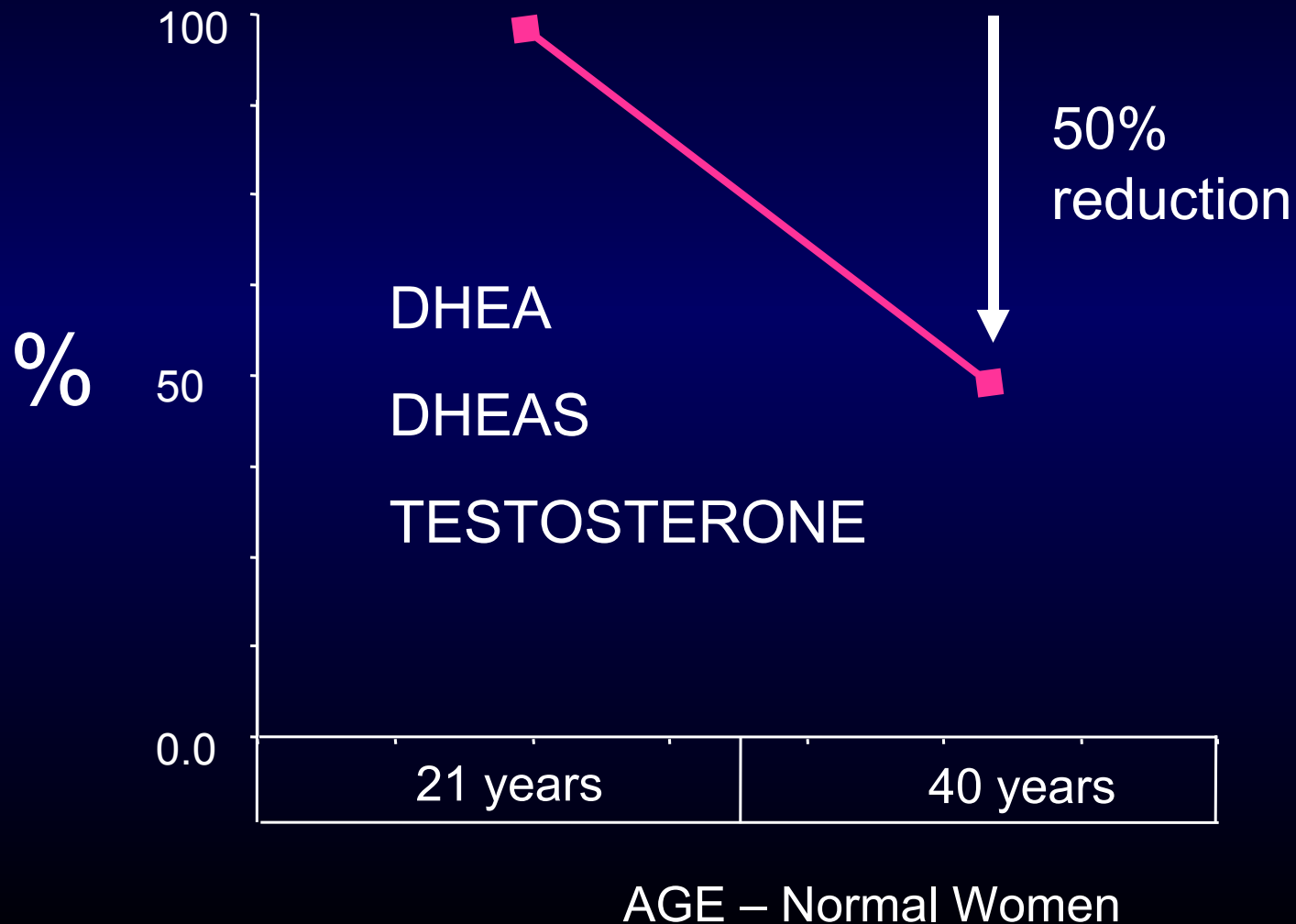
Muller M, et al, 2003

M. Roger, N. Lahlou and E.E. Baulieu, 2003

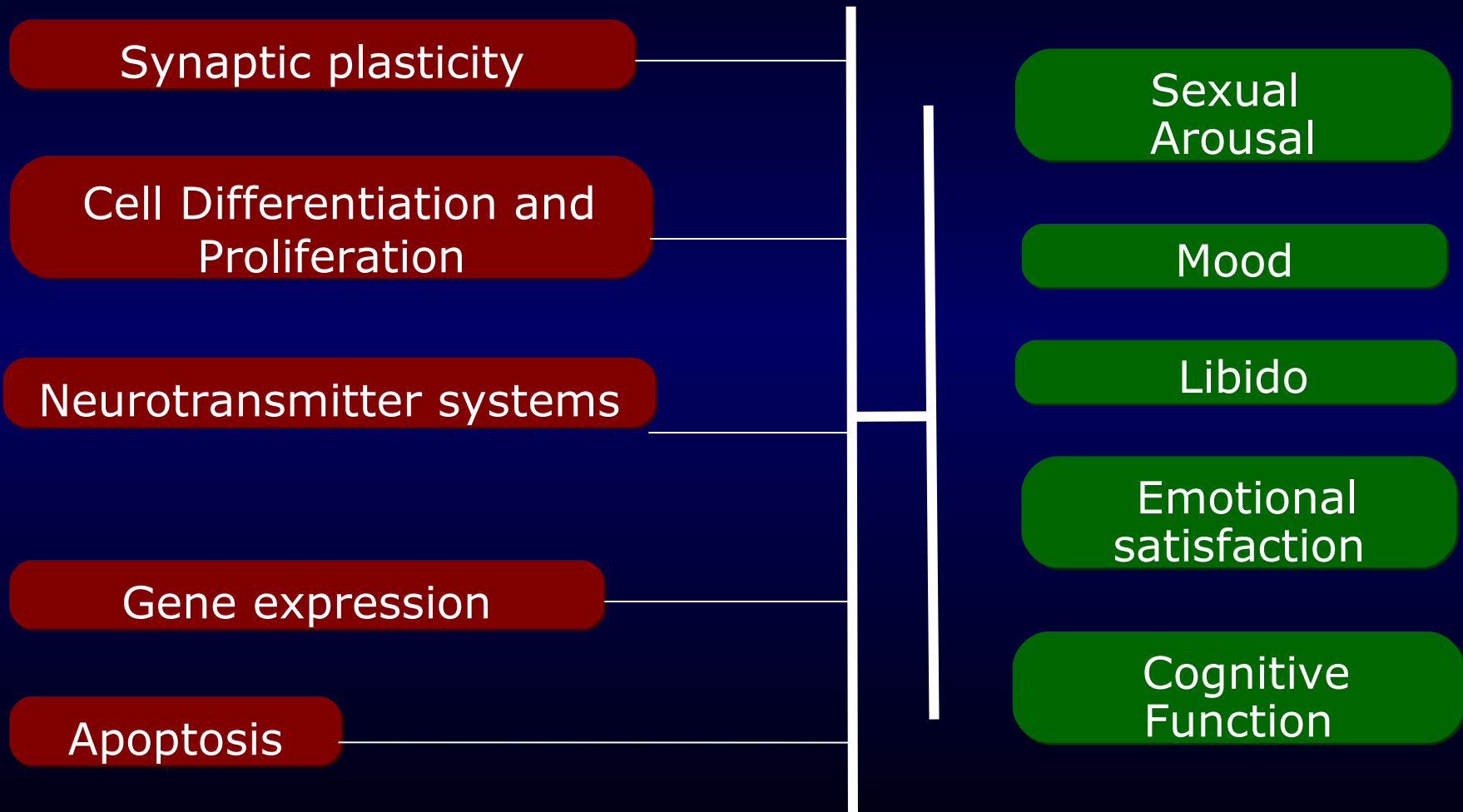
Age-related changes in DHEAS and Cortisol



Androgens and Ageing



Roles of Androgens in the Brain



Profile of Female Sexual Function Domain Scores and androgen levels

	Desire	Arousal	Responsiveness	Pleasure	Orgasm	Self-image
No./Total (%) of participants with 0 domain score	55/637 (8.6)	113/638 (17.7)	24/589 (4.1)	103/623 (16.5)	78/609 (12.8)	26/646 (4.0)
DHEAS AUROC	0.51	0.62	0.66	0.58	0.57	0.47
<i>P</i> value	.90	.001	.007	.008	.04	.65
Androstenedione AUROC	0.57	0.56	0.57	0.59	0.55	0.41
<i>P</i> value	.10	.06	.24	.004	.13	.12
Testosterone AUROC						
Total	0.54	0.56	0.57	0.52	0.54	0.41
<i>P</i> value	.38	.06	.23	.60	.22	.12
Free	0.54	0.56	0.59	0.50	0.56	0.43
<i>P</i> value	.34	.04	.13	.96	.08	.21

18-44 y

	Desire†	Arousal†	Responsiveness‡	Pleasure	Orgasm	Self-Image¶
No./Total (%) of participants with low domain score	17/335 (5.1)	18/338 (5.3)	18/336 (5.4)	16/336 (4.8)	16/334 (4.8)	14/339 (4.1)
DHEAS AUROC	0.68	0.68	0.72	0.54	0.56	0.62
<i>P</i> value	.01	.01	.002	.61	.42	.13
Androstenedione AUROC	0.58	0.61	0.66	0.58	0.56	0.60
<i>P</i> value	.25	.12	.02	.28	.41	.19
Testosterone AUROC						
Total	0.58	0.56	0.64	0.54	0.55	0.60
<i>P</i> value	.30	.36	.05	.58	.47	.23
Free	0.59	0.56	0.61	0.50	0.53	0.44
<i>P</i> value	.22	.37	.12	.99	.70	.48

> 45 y

Brain Vulnerability

SEX STEROIDS WITHDRAWAL

MECHANISMS



SIGNS AND SYMPTOMS

- ↓ CRH
- ↓ POMC-related peptides
↓ VASOPRESSIN
- ↓ Central noradrenergic system
↓ Central dopaminergic system
↓ Central serotonergic system
- ↓ GABA

- Irritability
- Anxiety
- Fear
- Depression
- Fatigue
- Psychosis
- Decreased Seizure Threshold
- Hot Flashes, Autonomic Hyperactivity

Symptoms that Underline Brain Susceptibility to Estrogen-Androgen Deprivation

- Hot Flashes
- Sleep problems
- Climacteric Depression
- Decreased Sexual interest/activity



INCREASED RISK OF COGNITIVE IMPAIRMENT IN ELDERLY?

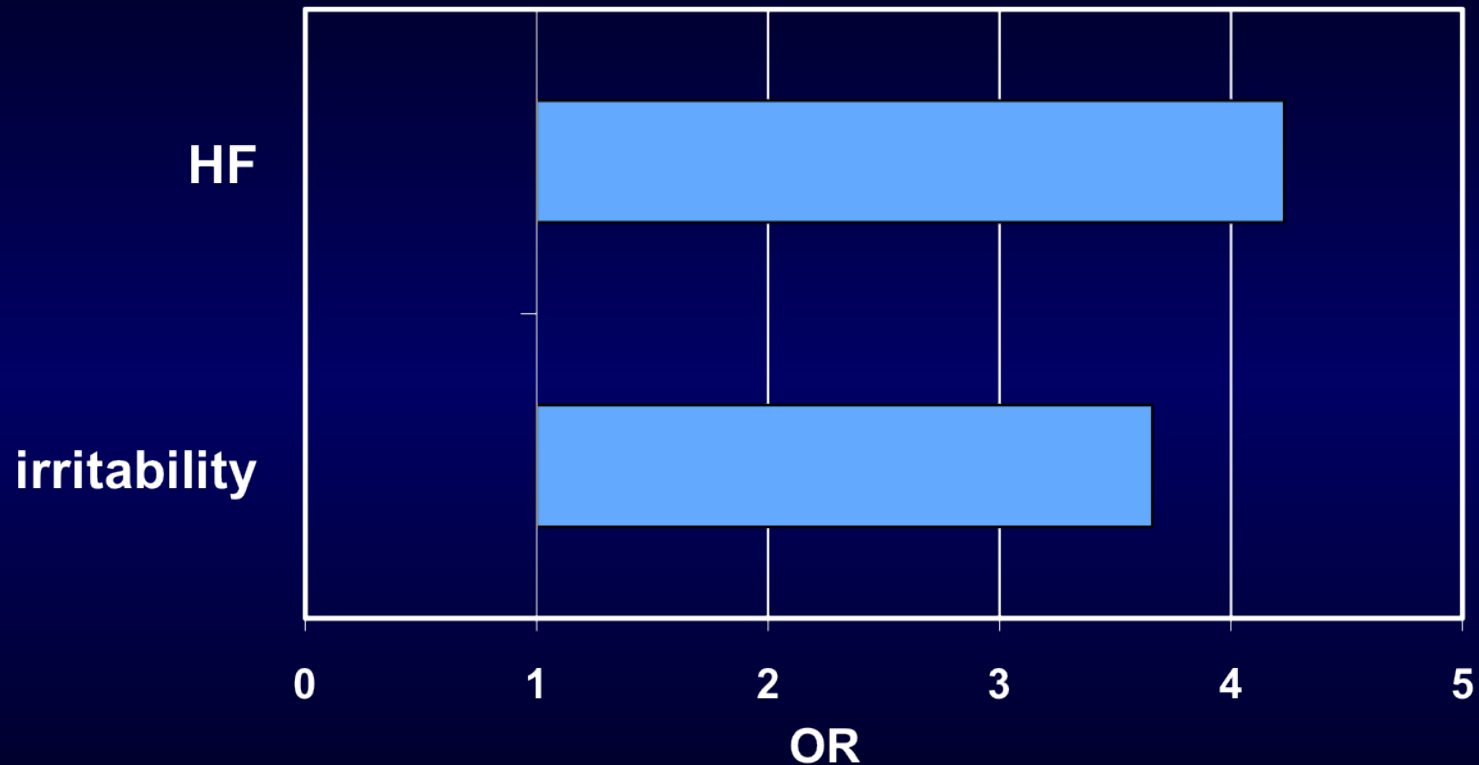


Estrogen deprivation and HF

- HF are not just a symptom
- HF underline the female brain susceptibility to estrogen deprivation

Disturbed sleep in PMW with menopause symptoms links to depression

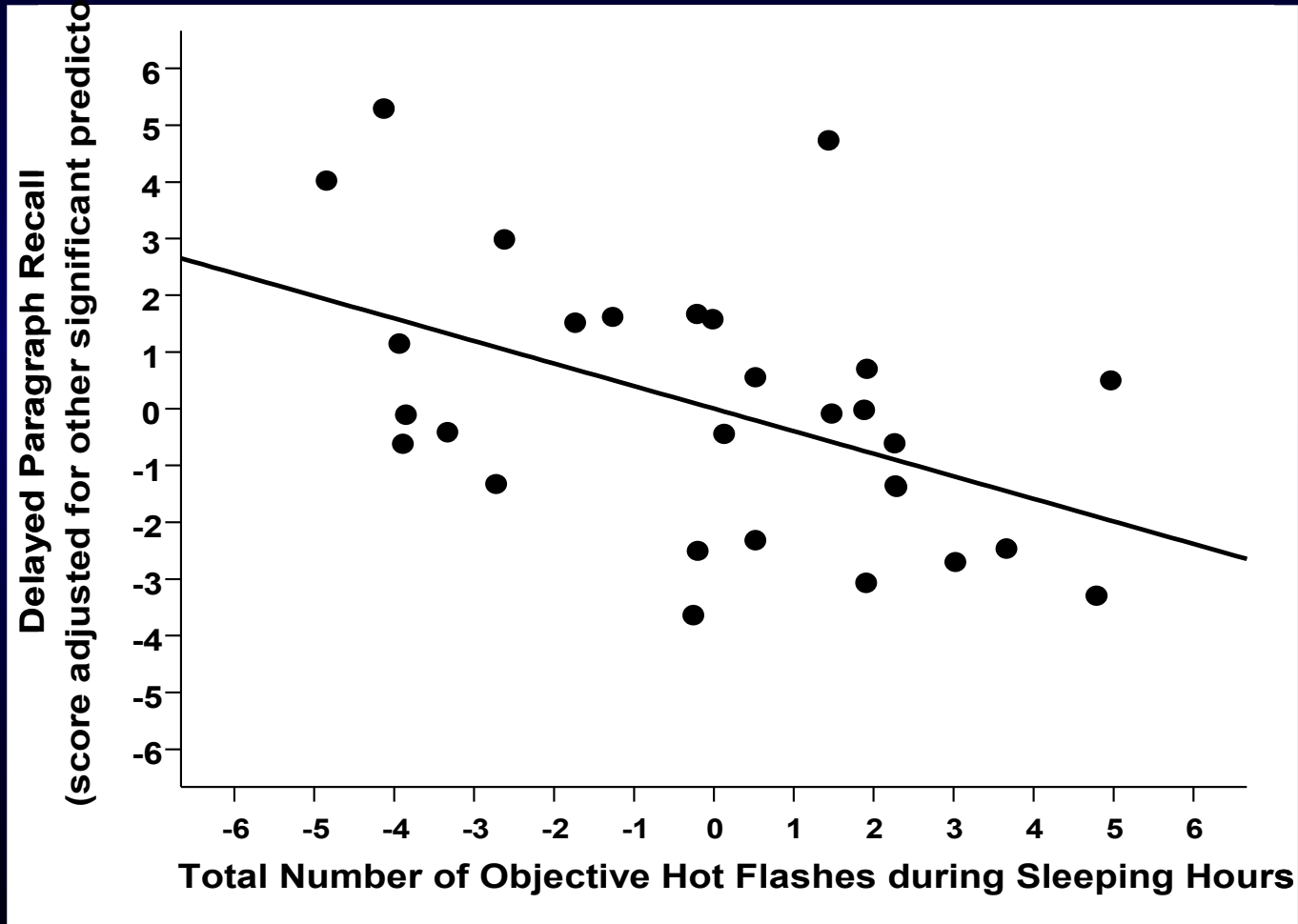
Risk for depression vs asymptomatic PMW women



The experience of perimenopause depressive symptoms may be explained by vasomotor and other menopausal symptoms, such as irritability and anxiety.

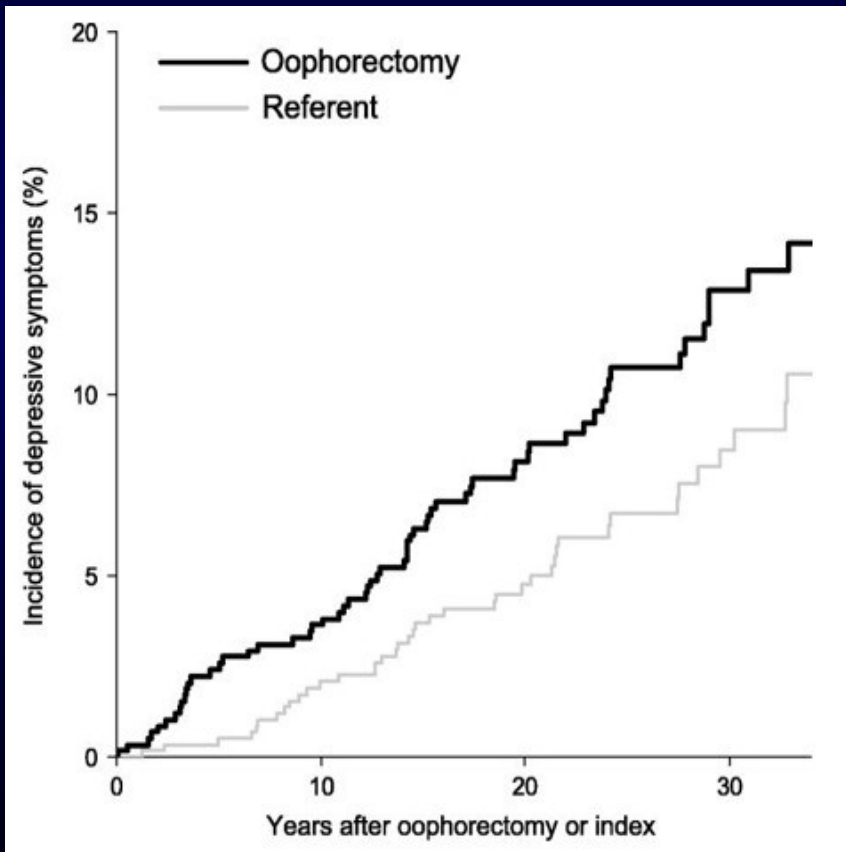
HF and Cognitive Function

Objective hot flashes are negatively related to verbal memory performance in midlife women.

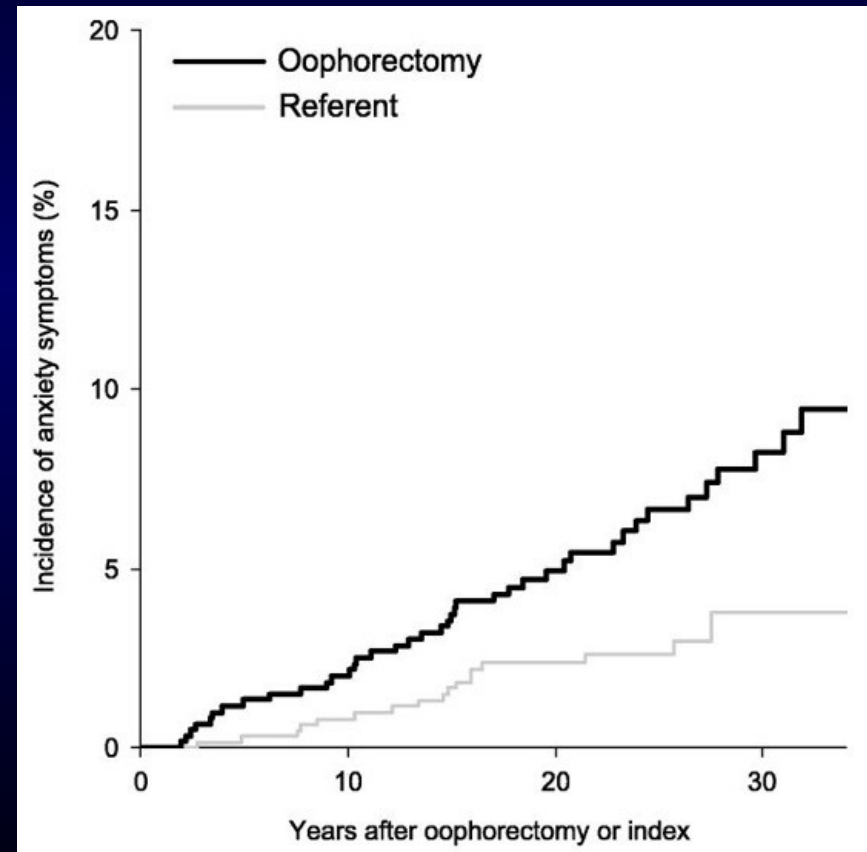


Sex Steroids and Mood Decline

Long-term risk of depressive and anxiety symptoms after early bilateral oophorectomy



hazard ratio = 1.54 CI: 1.04-2.26



hazard ratio = 2.29, CI: 1.33-3.95

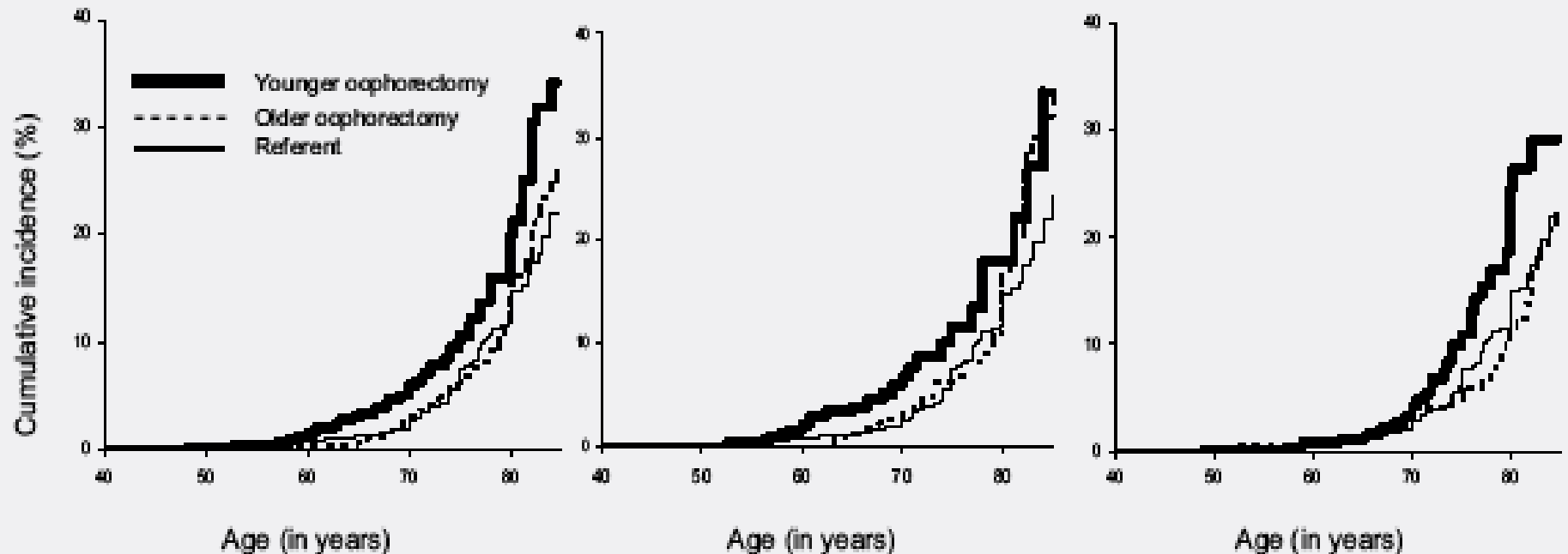
Sex Steroids and Cognitive Decline

The Mayo Clinic Cohort Study of Oophorectomy and Aging

A Any oophorectomy

B Unilateral oophorectomy

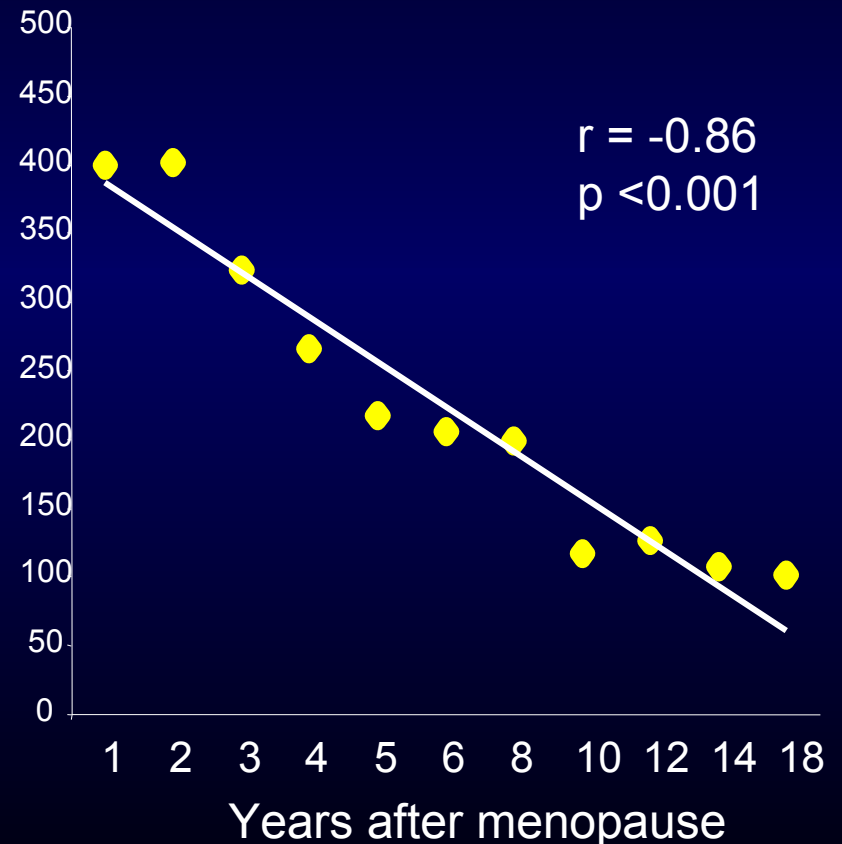
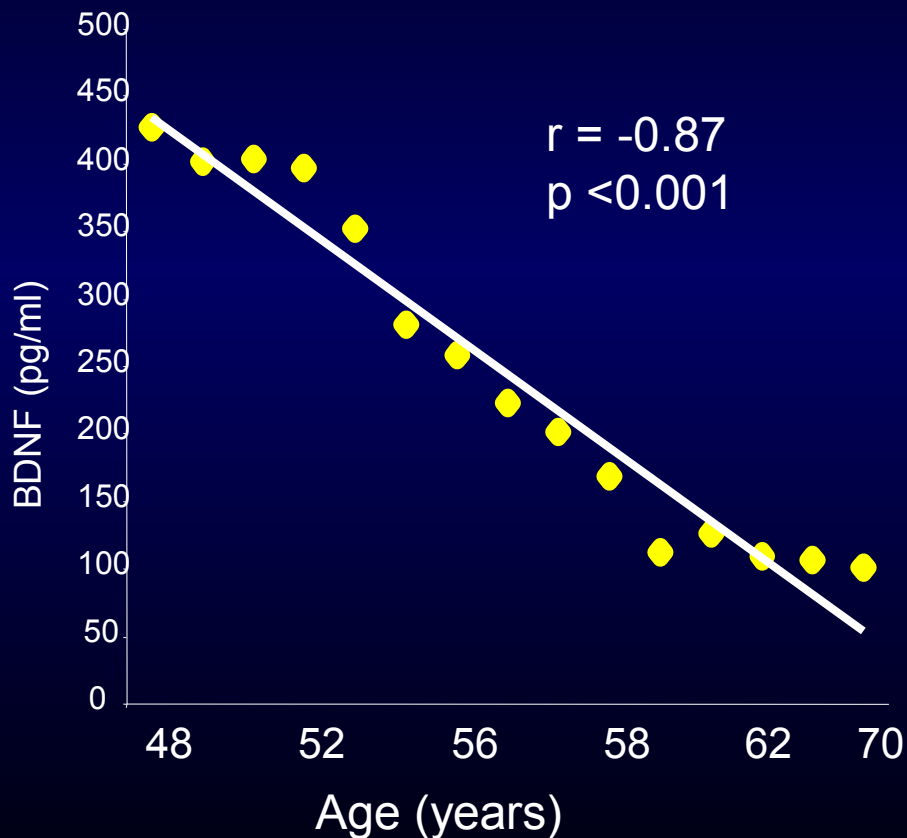
C Bilateral oophorectomy



Unilateral and bilateral oophorectomy preceding the onset of menopause are associated with an increased risk of cognitive impairment or dementia.

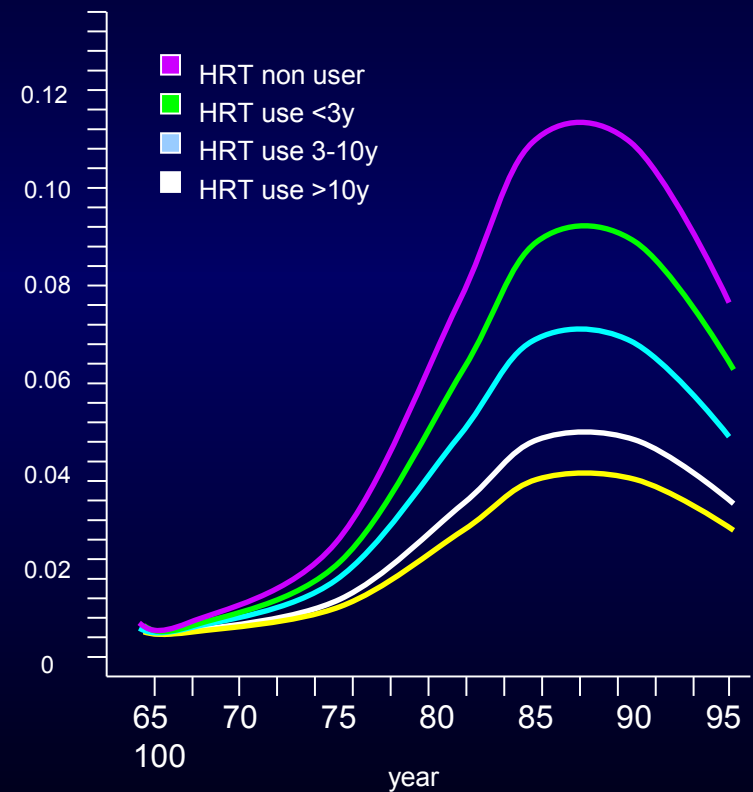
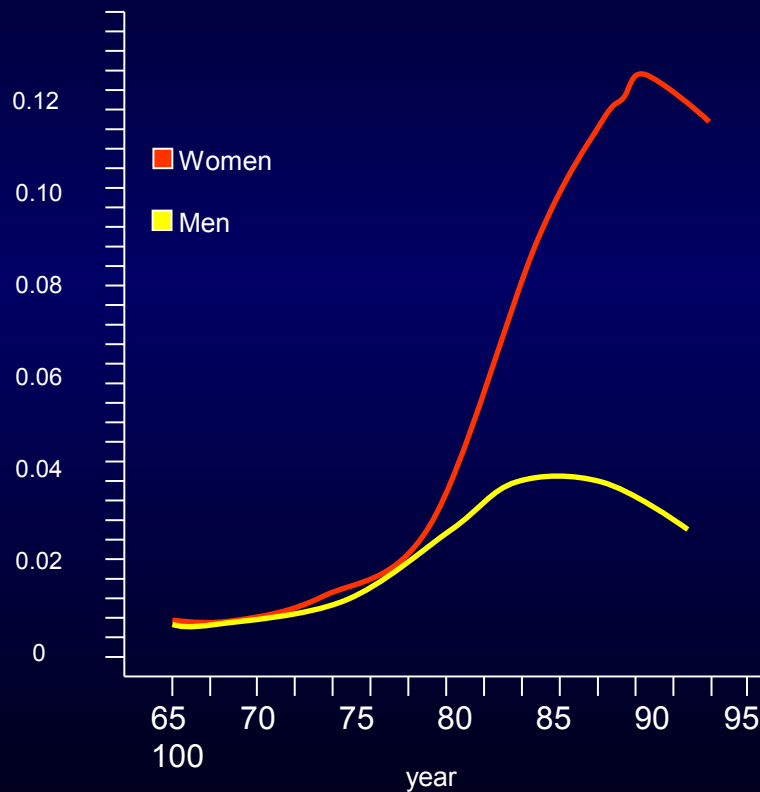
Hazard ratio 1.46; [1.13 to 1.9]

BDNF in Postmenopausal Healthy Women

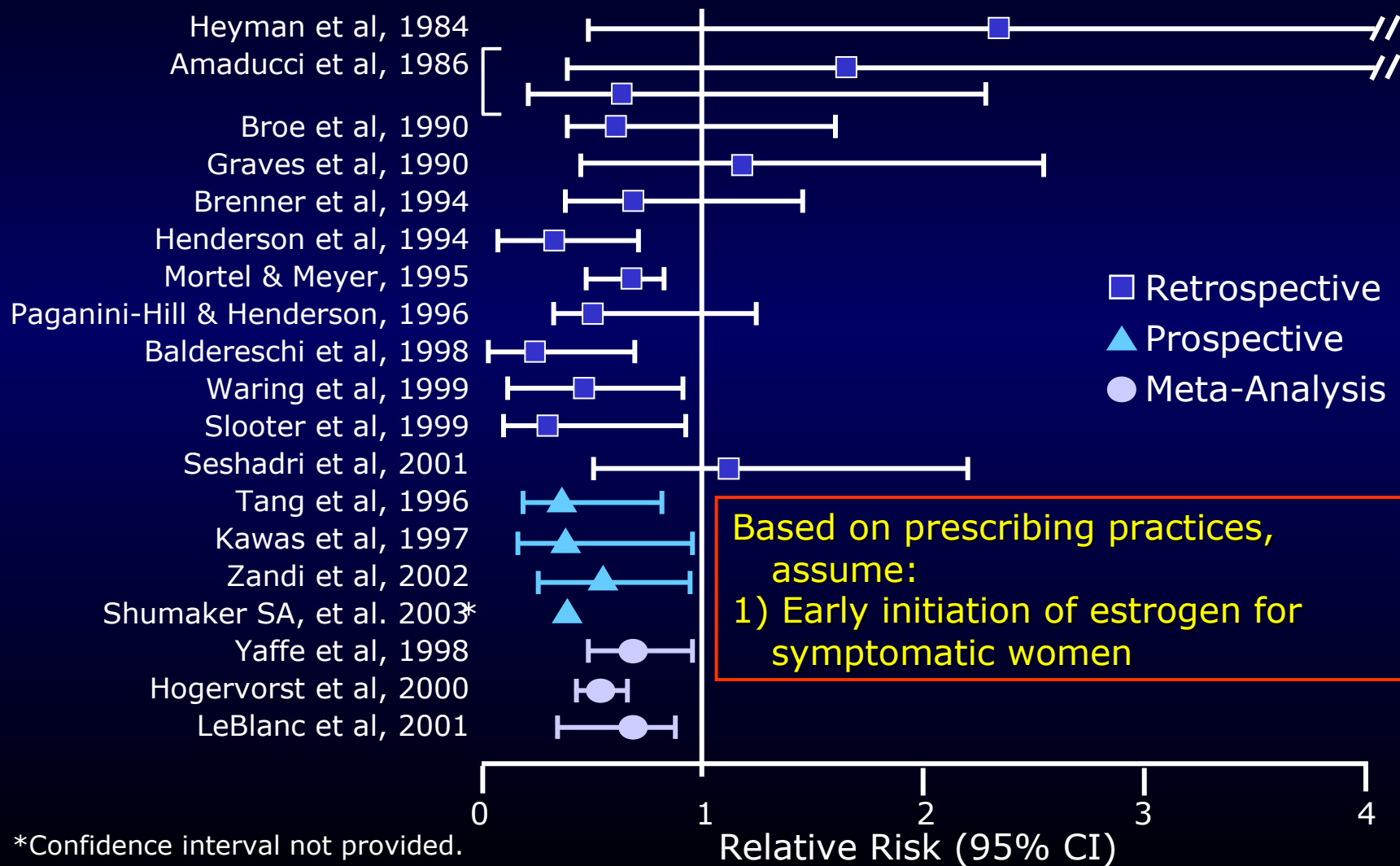


Hormone Replacement Therapy and Incidence of Alzheimer Disease in Older Women

The Cache County Study



Observational Studies Show a Decreased Risk of AD in Hormone Therapy Users



Based on prescribing practices, assume:
1) Early initiation of estrogen for symptomatic women

*Confidence interval not provided.
Adapted from LeBlanc ES, et al. *JAMA*. 2001;285:1489-1499.

HRT and Brain: ADDITIONAL CLUES AND NEW DIRECTIONS

- TYPE OF ESTROGEN
- DOSE (low dose HRT and neuroprotection)
- ROUTE OF ADMINISTRATION
- THE PROGESTIN "STORY"
- GENETIC POLYMORPHISM

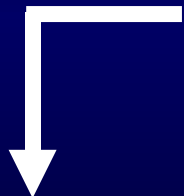
Δ -5 and \square Δ -4 Androgens therapy in Postmenopausal Women: 'Uncharted Territory'

THE GREAT CHALLENGE



BRAIN

FUNCTION



BIOLOGICAL
EFFECTS

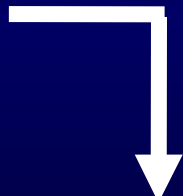
NEUROACTIVE STEROIDS

Neurotrophic Factors

Neurotransmitters

ENDOGENOUS OPIOIDS

Cellular and subcellular Networks



CLINICAL
EFFECTS

Cognitive Function

Mood

Libido and Sexual Arousal

Neuroendocrine Activity

Sex Steroids and Lifelong Brain Function

