



Stress e infertilità

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L'infertilità può dipendere dallo stress?

- Teoricamente si e con diversi meccanismi
- ma...
- ...studiare il fattore stress e quantizzarne l'effetto nel singolo caso è difficile, trattare questa causa lo è ancor più



PubMed search: ("Stress, Physiological"[Mesh] OR "Stress, Psychological"[Mesh]) AND ("Infertility"[Mesh] OR "Ovulation"[Mesh] OR "Ovulation Induction"[Mesh] OR "Reproductive Techniques, Assisted"[Mesh]) and **Trip database search for EBM**

Ridurre lo stress prima di concepire non è un consiglio basato su evidenze, *ma nemmeno gli altri consigli preconcezionali che diamo!*



Preconception lifestyle advice for people with subfertility

AUTHORS' CONCLUSIONS: No RCTs were located that assessed the effects of preconception advice on the chance of a live birth or other fertility outcomes in people who perceived that they may be infertile and were investigating the possibility of medical treatment to address subfertility. Given the lack of RCTs evaluating the effectiveness of preconception lifestyle advice for people in the aforementioned population, this review cannot provide guidance for clinical practice in this area. However, it does highlight the need for further research into this important subject.

Anderson K. Preconception lifestyle advice for people with subfertility. *Cochrane Database of Systematic Reviews* 2010, Issue 4. Art. No.: CD008189. DOI: 10.1002/14651858.CD008189.pub2

Vale la pena ridurre lo stress per migliorare la fertilità?



It is still unclear whether reducing stress improves pregnancy rates.

Two reviews of intervention studies did not find the impact of reducing distress affected reproductive outcomes

Boivin Soc Sci Med. 2003 Dec;57(12):2325-41

Wishmann J Psychosom Obstet Gynaecol 2008; 29: 83–90.

Others suggested a possible increase in conception rates with reduced anxiety

Cousineau Best Pract Res Clin Obstet Gynaecol 2007; 21: 293–308

De Liz Hum Reprod 2005; 20: 1324–1332.

Given the methodological pitfalls that limit an interpretation of the identified studies and insufficient understanding of the mechanism of stress-relieving therapy on reproduction, further research in this area is warranted.

Anderson Aust N Z J Obstet Gynaecol. 2010

Nonostante
siano passati
molti anni dalla
pubblicazione...

..le conoscenze di
base restano le
stesse e la
soluzione appare
lontana anche
facendo una
revisione in
Pubmed e Trip
database

Lino Del Pup

STRESS

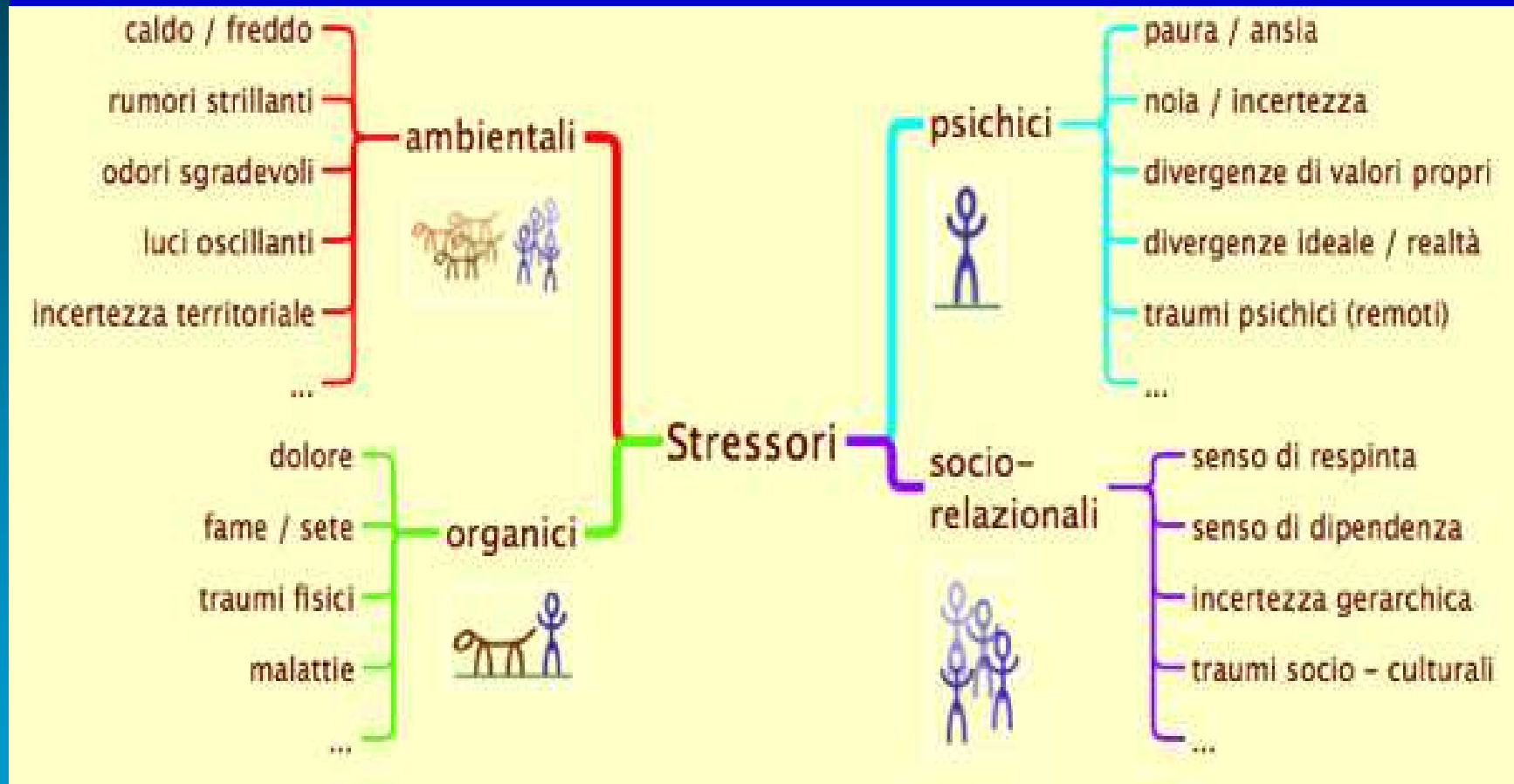
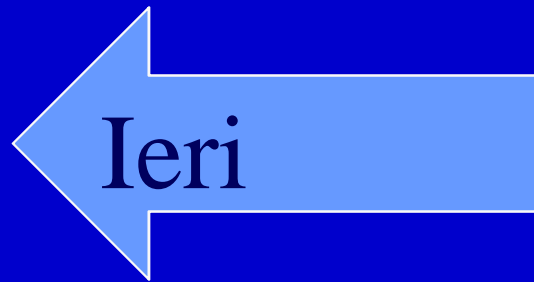
dai problemi
sessuali
all'infertilità

presentazione di
Jole Baldaro Verde

Città Nuova

Stressor

- Azione



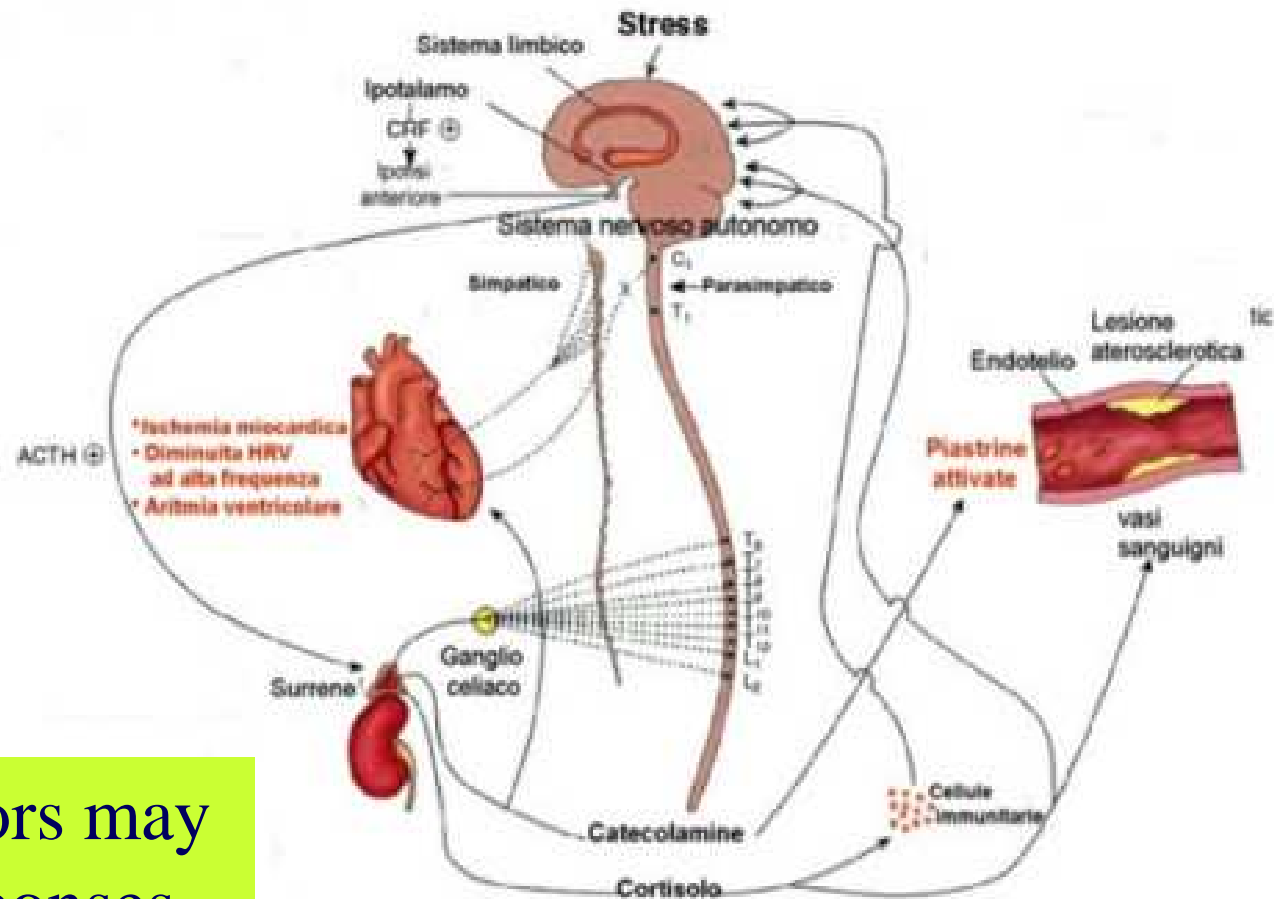
Coping Reazione

ieri

=

oggi

Today's stressors may trigger old responses leading to harmful rather than helpful bodily reactions



I programmi di reazione agli stress acquisiti nell'evoluzione sono poco utili o dannosi oggi

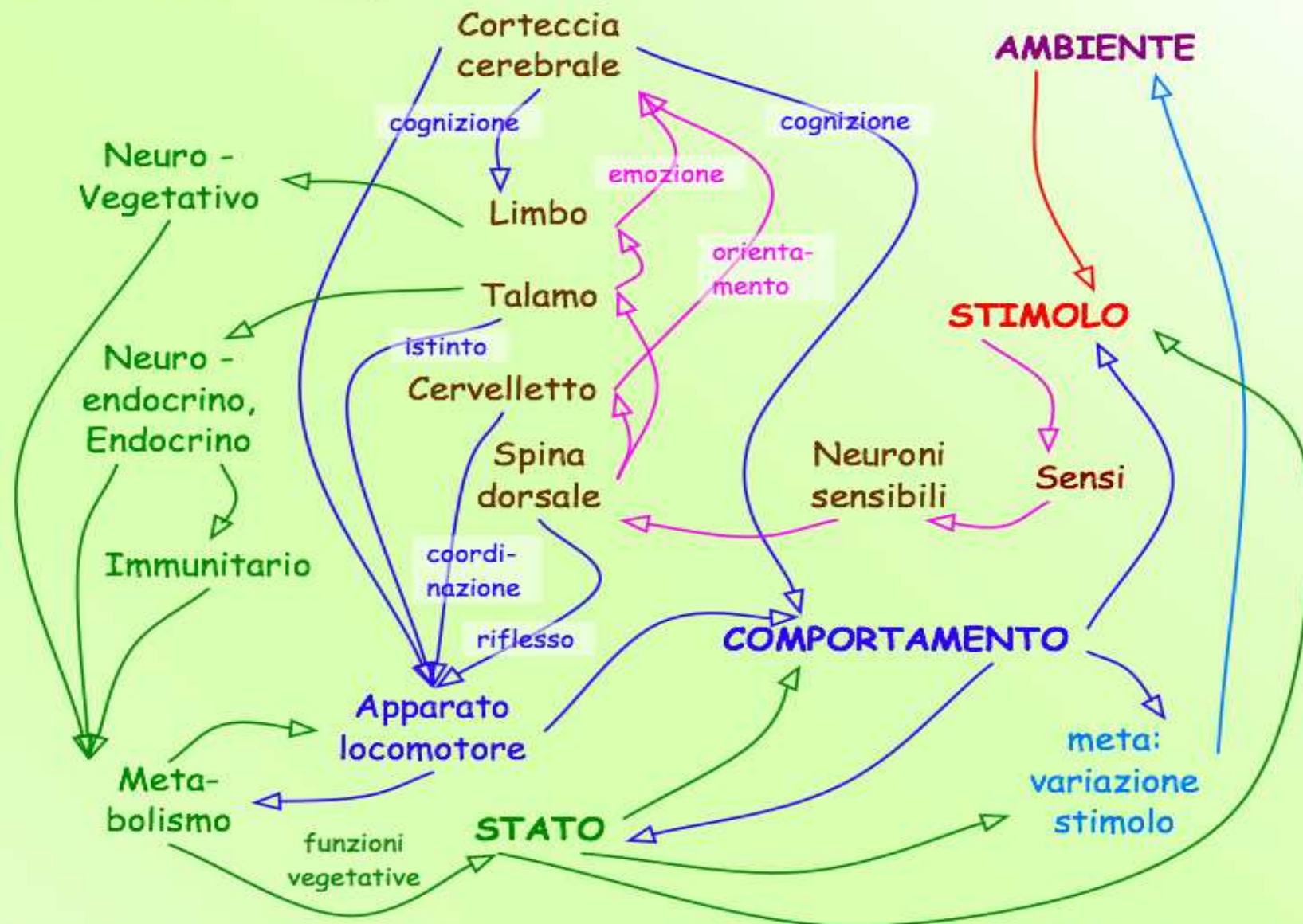


Ieri utile per difendersi

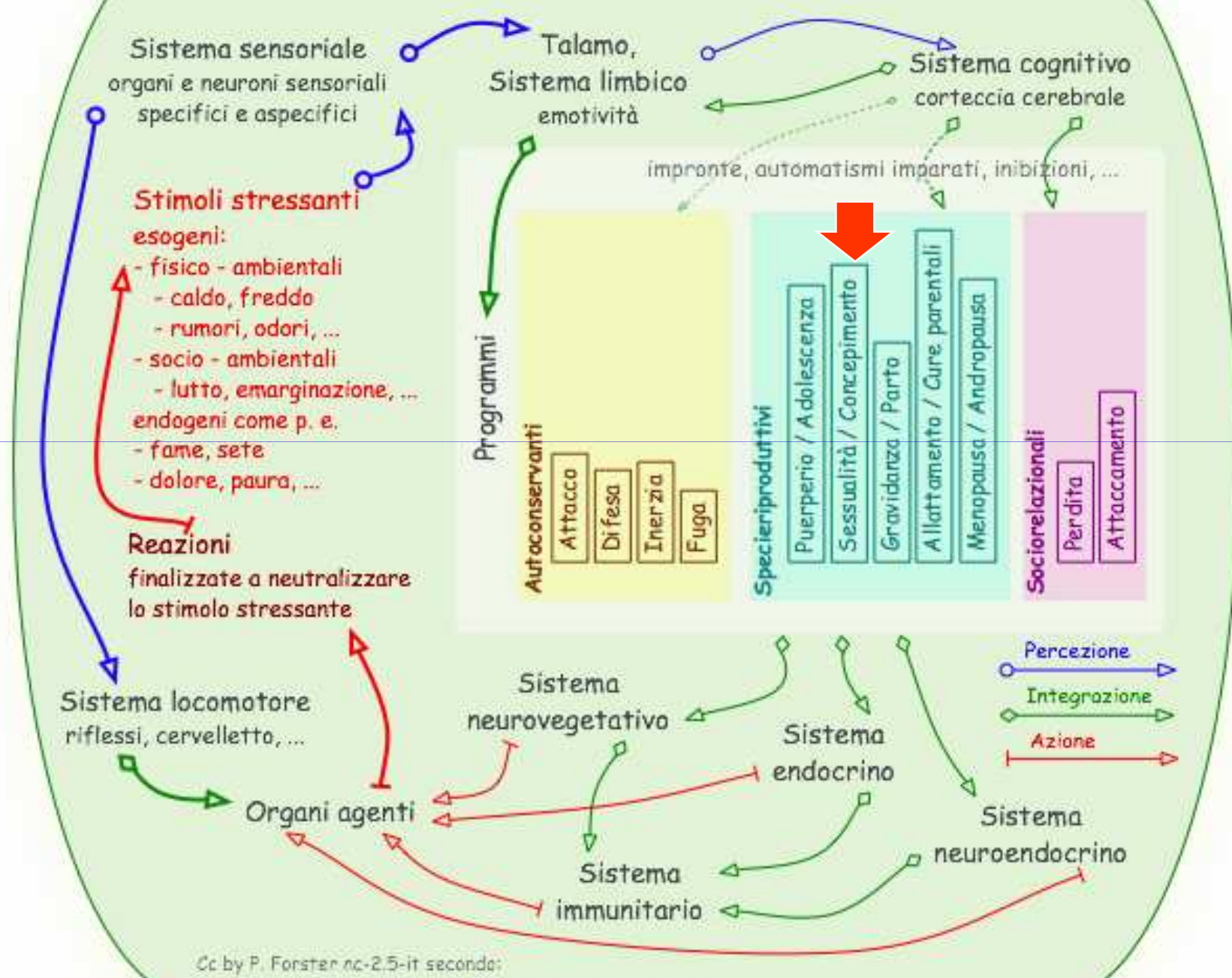
Oggi causa di patologie



Elaborazione organica di stimoli



Programmi biologici per la regolazione di stress umano

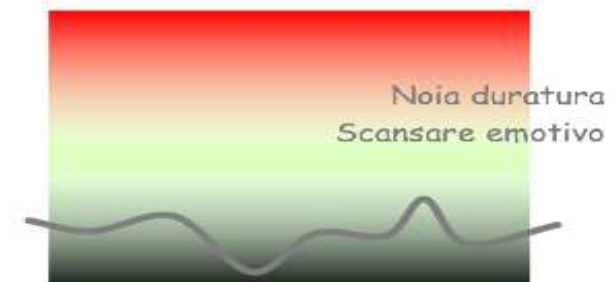
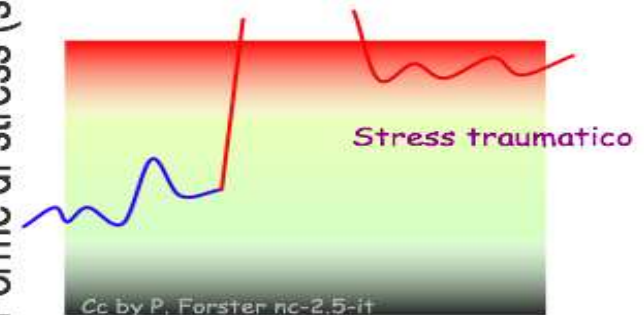
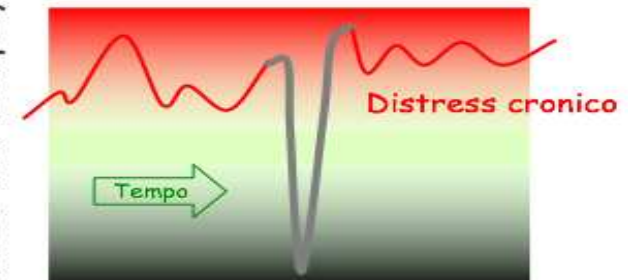
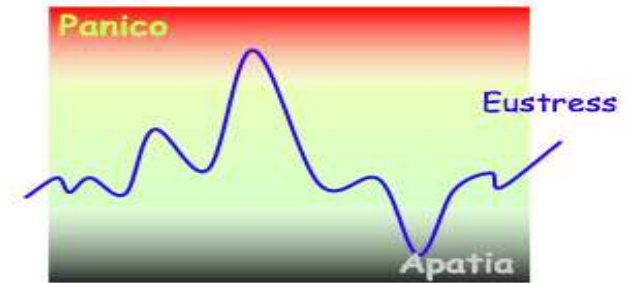


Intensità e durata

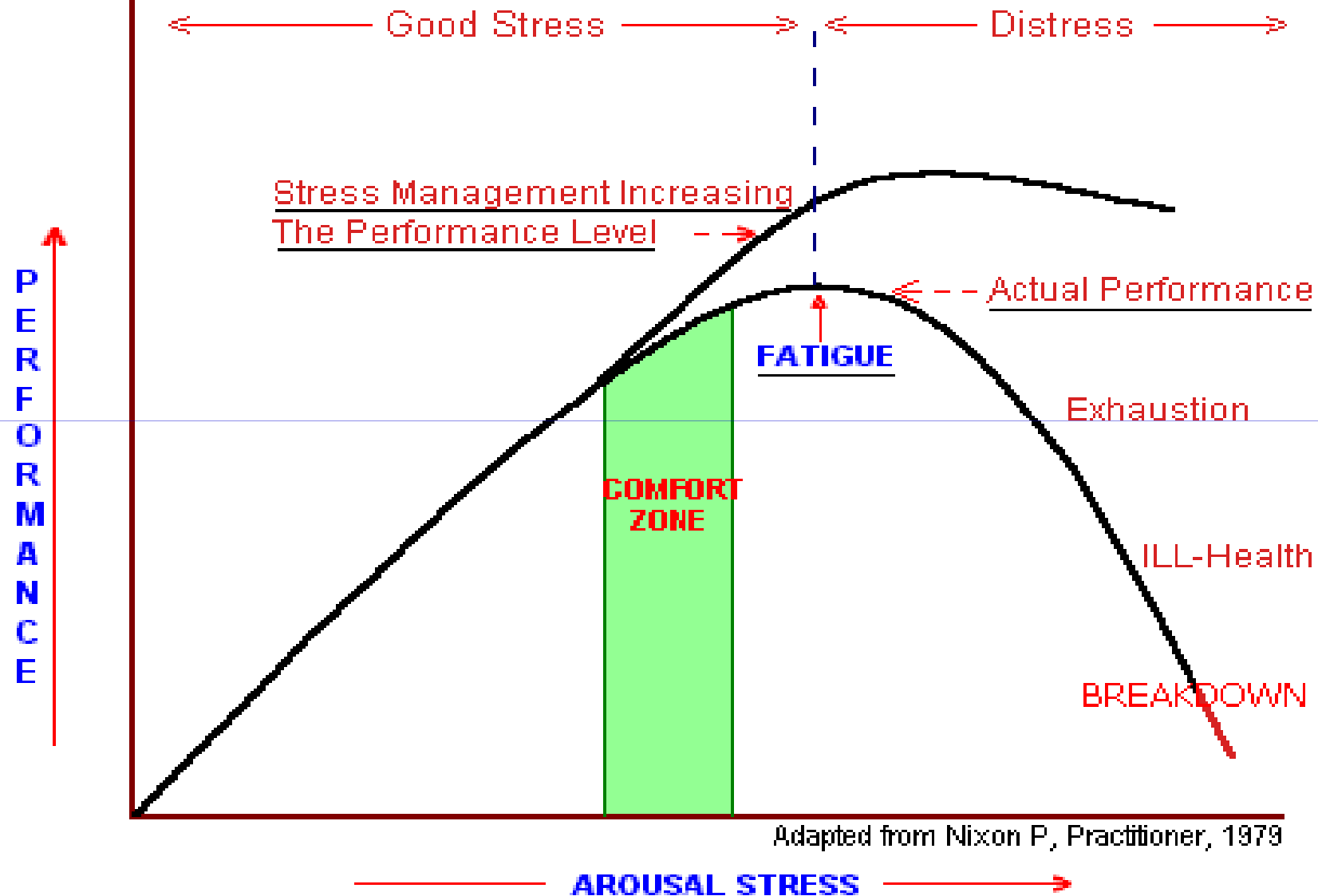


- Eustress
- Distress

Forme di stress (stimoli nel tempo)



THE STRESS RESPONSE CURVE



Adapted from Nixon P, Practitioner, 1979

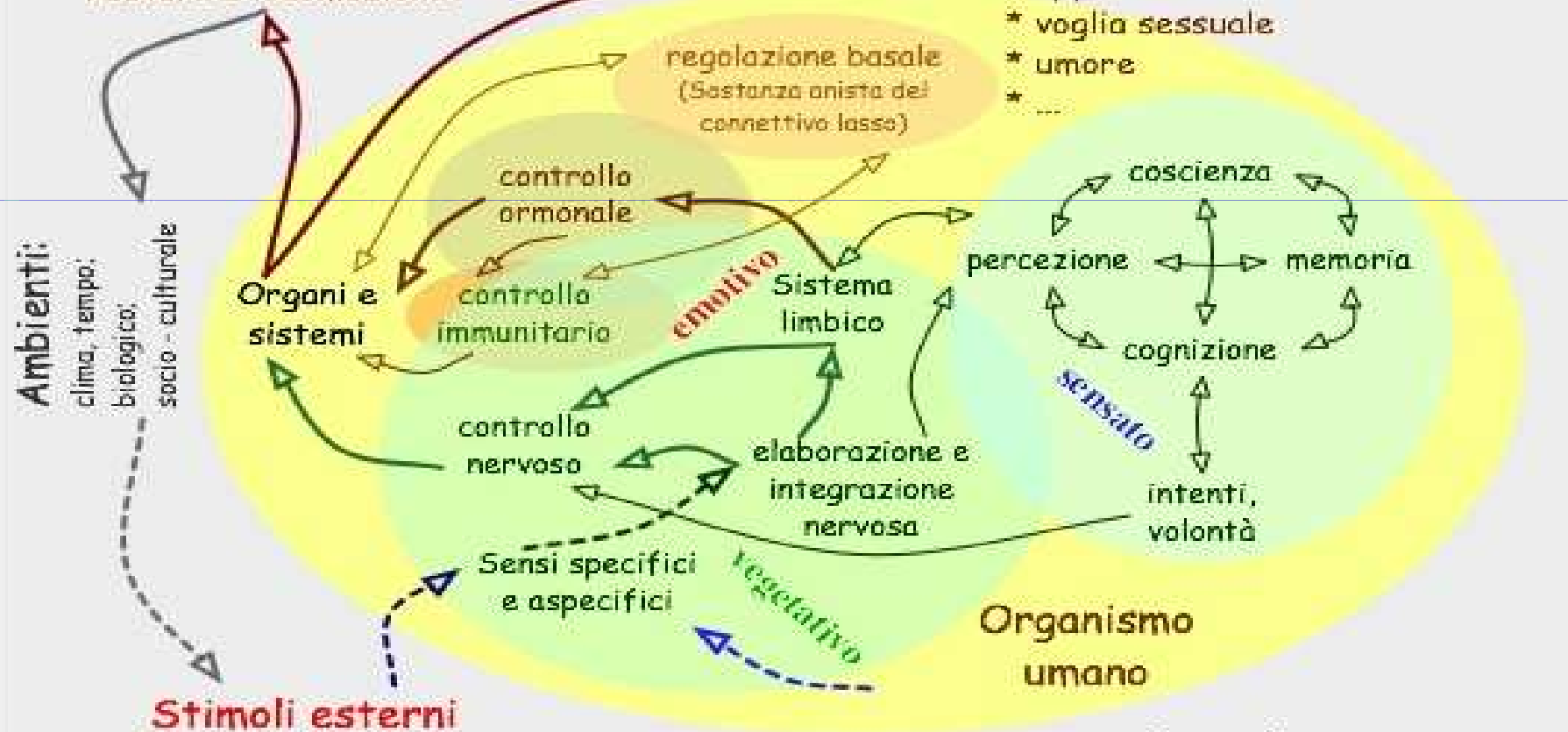
Reazioni umane

esteriorizzate:

- * Reazione specifica: inerzia, fuga, difesa, attacco
- * Espressioni spontanee: mimica, gestualità, voce, ...
- * Comportamento sociale
- * Espressioni sensate: lingua, movimenti
- * Uso di attrezzi e strumenti
- * Postura e locomozione

interiorizzate (vegetative):

- * attenzione (vista, udito, ...)
- * respirazione
- * polso
- * pressione sanguigna
- * transpirazione
- * appetito
- * voglia sessuale
- * umore
- * ...



Reazione umana
a stimoli

Reazioni interne allo stress

Here are ways in which some key body systems react.

1 NERVOUS SYSTEM

When stressed — physically or psychologically — the body suddenly shifts its energy resources to fighting off the perceived threat. In what is known as the “fight or flight” response, the sympathetic nervous system signals the adrenal glands to release adrenaline and cortisol. These hormones make the heart beat faster, raise blood pressure, change the digestive process and boost glucose levels in the bloodstream. Once the crisis passes, body systems usually return to normal.

2 MUSCULOSKELETAL SYSTEM

Under stress, muscles tense up. The contraction of muscles for extended periods can trigger tension headaches, migraines and various musculoskeletal conditions.

3 RESPIRATORY SYSTEM

Stress can make you breathe harder and cause rapid breathing — or hyperventilation — which can bring on panic attacks in some people.

4 CARDIOVASCULAR SYSTEM

Acute stress — stress that is momentary, such as being stuck in traffic — causes an increase in heart rate and stronger contractions of the heart muscle. Blood vessels that direct blood to the large muscles and to the heart dilate, increasing the amount of blood pumped to these parts of the body. Repeated episodes of acute stress can cause inflammation in the coronary arteries, thought to lead to heart attack.

5 ENDOCRINE SYSTEM

Adrenal glands
When the body is stressed, the brain sends signals from the hypothalamus, causing the adrenal cortex to produce cortisol and the adrenal medulla to produce epinephrine — sometimes called the “stress hormones.”

Liver

When cortisol and epinephrine are released, the liver produces more glucose, a blood sugar that would give you the energy for “fight or flight” in an emergency.

6 GASTROINTESTINAL SYSTEM

Esophagus

Stress may prompt you to eat much more or much less than you usually do. If you eat more or different foods or increase your use of tobacco or alcohol, you may experience heartburn, or acid reflux.

Stomach

Your stomach can react with “butterflies” or even nausea or pain. You may vomit if the stress is severe enough.

Bowels

Stress can affect digestion and which nutrients your intestines absorb. It can also affect how quickly food moves through your body. You may find that you have either diarrhea or constipation.



7 REPRODUCTIVE SYSTEM

In men, excess amounts of cortisol, produced under stress, can affect the normal functioning of the reproductive system. Chronic stress can impair testosterone and sperm production and cause impotence.

In women, stress can cause absent or irregular menstrual cycles or more-painful periods. It can also reduce sexual desire.

Lavoro = stressor sempre più diffuso può ridurre la fertilità?

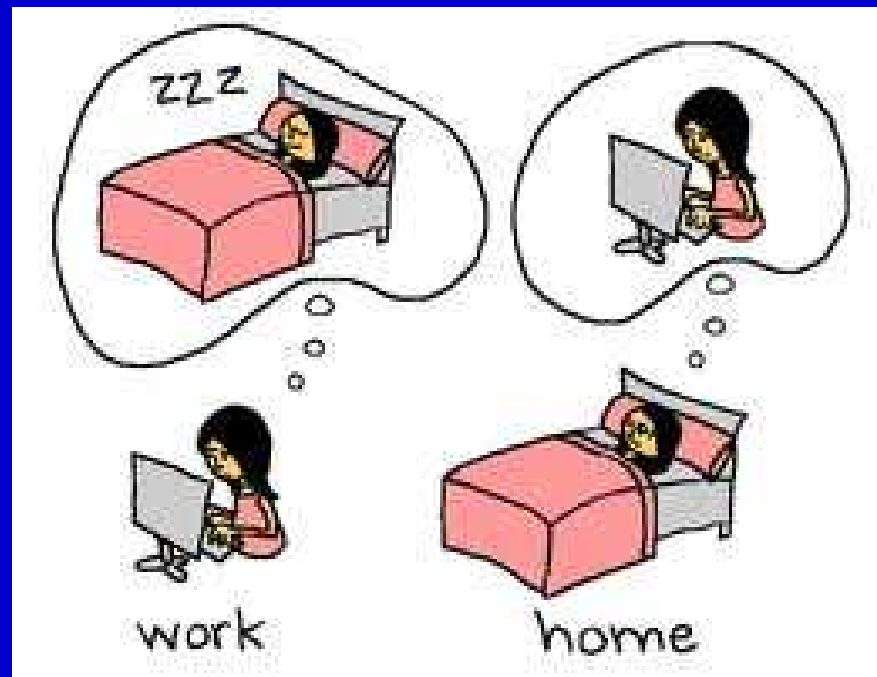


Table 3.2 Occupational agents and their effects on female fertility

Occupational agents	Occupational groups	Effects on female fertility
<i>Physical</i> Shift work/intense physical work load/long working hours	Hospital workers	Reduced fecundability, ^{143,144} prolonged time to pregnancy, ^{110,111} no association ¹¹¹
Ionising radiation Visual display units	Nuclear industry workers Office workers	Non-significant association ¹⁴⁵ No association, ¹⁴⁶ increased risk of infertility ¹⁴⁷
<i>Chemical</i> Pesticides Lead	Agricultural workers Smelters	Inconsistent time to pregnancy ¹⁴⁸ No association at low levels, ¹⁴⁹ prolonged time to pregnancy ¹⁵⁰
Mercury, cadmium Anti-neoplastics (chemotherapy drugs) Antibiotics	Nurses, pharmacists	prolonged time to pregnancy ¹⁵⁰ Increased self-reported infertility ¹⁵¹ Small risk of prolonged time to pregnancy ¹⁵²
Nitrous oxide	Anaesthetists, theatre nurses dental assistants	Reduced fecundability ^{143,153,154}
Chloroform, benzene Mercury vapour	Lamp factory workers	No association ¹⁴¹ No clear association, ¹⁵⁵ reduced fecundability ¹⁵⁶
Solvents Formaldehyde	Wood workers	Infertility ¹⁴⁷ Reduced fecundability ¹⁵⁷

Table 3.1 Occupational agents and their effects on male fertility

Occupational agents	Occupational groups	Effects on male fertility
<i>Physical</i>		
Shift work/long working hours	Shift workers	No association ^{110,111}
Heat (increase in scrotal temperature)	Welders, bakers, drivers	Abnormal sperm parameters ⁹⁹
X-ray	Radiotherapists	Azoospermia, reduced sperm count, may be reversible ^{112,113}
Non-ionising radiation: electromagnetic fields	Metal workers	Inconsistent association ¹¹⁴⁻¹¹⁶
Vibrations	Engine drivers, diggers	Oligozoospermia, asthenozoospermia ¹¹⁷
<i>Chemical</i>		
Dibromochloropropane (pesticide)	Agricultural workers	Oligozoospermia and azoospermia, reversible in most cases, ¹¹⁸⁻¹²¹ reduced fertilisation rate ¹²²
Ethylene dibromide (pesticide)		Abnormal sperm parameters ¹⁰⁷
Carbaryl (pesticide)		No association ¹²³
Polychlorinated biphenyls	Agricultural workers	Abnormal sperm parameters ^{124,125}
Lead, cadmium, manganese	Metal workers, smelters, battery factory workers	Reduced fertility, mainly affecting female partners, ¹²⁶⁻¹³¹ no association ¹³²
Mercury	Dental amalgam	No association ¹³³
Acetone, carbon disulphide, glycol ethers (solvents)	Chemists, laboratory workers, painters	Abnormal sperm parameters, ^{135,136} reduced fecundability, ¹³⁷ oligospermia ¹³⁸
Toluene, styrene (solvents)	Plastic and printing industry	No association ^{139,140}
Anaesthetic gases	Dentists, anaesthetists	No association ^{141,142}

Stress: effetti inibitori sulla fertilità



Stress

Sessualità

Gametogenesi
e impianto

Patologie che
alterano
indirettamente
la fertilità

Stress e infertilità femminile

Implantation failure and miscarriage in the general population.

Lower pregnancy and live birth rates and higher spontaneous miscarriage rates in infertile women with higher workloads.

Stress and IVF outcome: higher stress levels and lower pregnancy and live birth rates.

Baseline levels of stress were also significantly inversely related to the number of oocytes retrieved and the fertilisation rate.

Anderson Aust N Z J Obstet Gynaecol. 2010

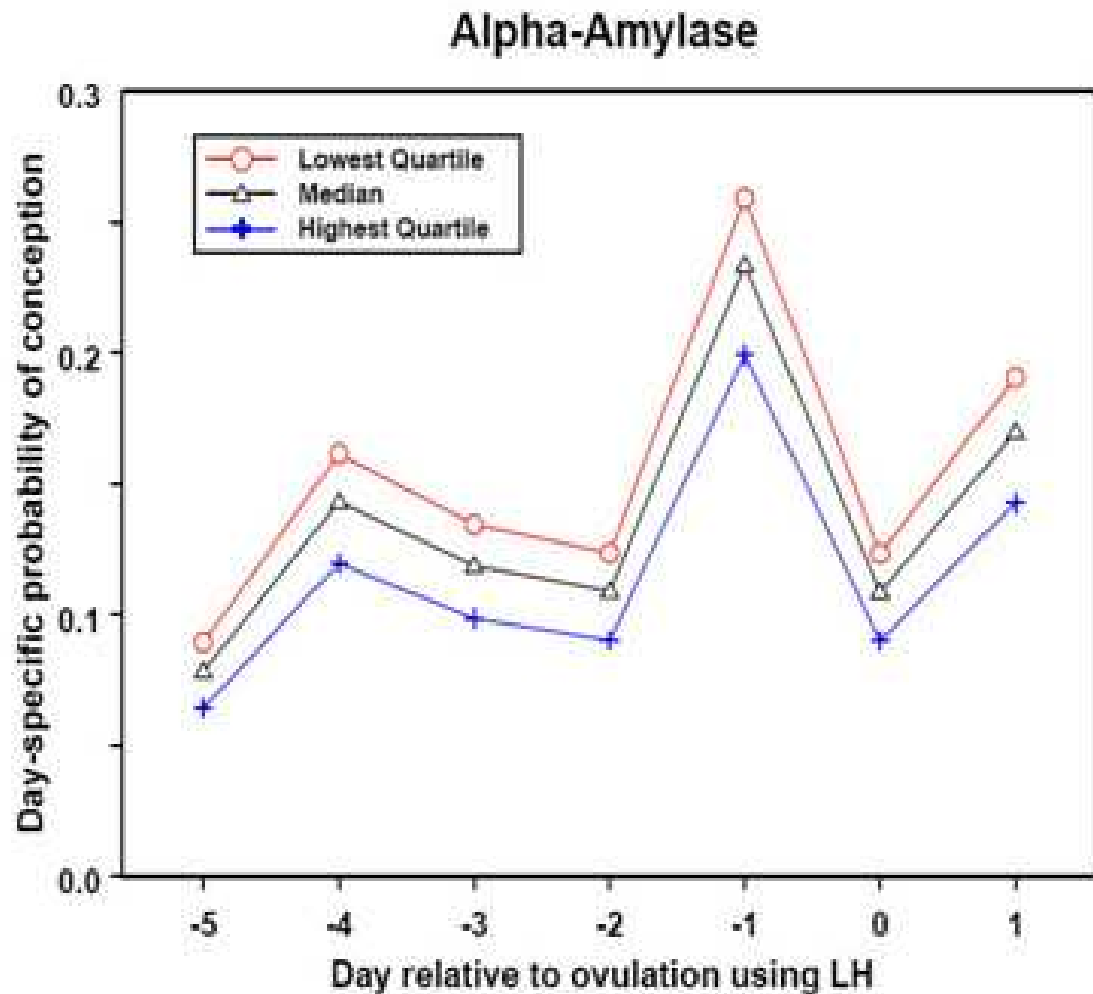
Stress e infertilità maschile

Severe depression is associated with reduced testosterone levels, impaired spermatogenesis and lower sperm concentration chronically depressed men.

Deterioration of the sperm parameters after significant acute stressor in those with high anxiety scores.

Psychological interventions reduce distress levels in infertile couples and may facilitate coping, improve quality of life and raise motivation for treatment and other lifestyle changes.

Amilasi = indicatore di stress e infertilità



- alpha-amylase is secreted into saliva digests starch and measures of the body's response to physical or psychological stress and catecholamines
- Highest quartile: **-15% fertility**

Guttmacher NIH News 2010

Stress reduces conception probabilities across the fertile window: **evidence in support of relaxation**

Alpha-amylase but not cortisol concentrations were negatively associated with fecundity in the first cycle (fecundity odds ratio = 0.85; 95% confidence interval 0.67, 1.09) after adjusting. Statistically significant reductions in the probability of conception across the fertile window during the first cycle attempting pregnancy were observed for women whose salivary concentrations of α -amylase were in the upper quartiles in comparison with women in the lower quartiles (highest posterior density: -0.284 ; 95% interval $-0.540, -0.029$).

Conclusion(s)

Stress significantly reduced the probability of conception each day during the fertile window, possibly exerting its effect through the sympathetic medullar pathway.

Lo stress ha effetti sulla PMA? Sembra di si

At least 24 studies have addressed the distress/IVF relationship. **Two thirds have found a significant relationship** on subsequent pregnancy rates: methodological flaws?

A prospective study in which 151 women were assessed prior to beginning an IVF or GIFT- **Stress was significantly related to number of retrieved and fertilized, pregnancy, live birth rate...** Further, the stress level on the day of the procedure was significantly related only to the number of retrieved and fertilized. At baseline, the frequency of no live birth was 93% lower in women with the least distress .

Patients should receive counseling, support, and education to decrease stress levels prior to treatment.

Domar, *Up ToDate* (2006) Wellesley, MA.
Klonoff-Cohen, *Fertil Steril* 2001 e 2004

Life events negativi= -11% PR nella PMA

RESULTS: Women who became pregnant reported fewer non-fertility-related negative life-events prior to IVF (Mean: 2.5; SD: 2.5) than women who did not obtain a pregnancy (Mean: 3.0; SD: 3.0) ($t(465.28) = 2.390, P = 0.017$). Logistic regression analyses revealed that the **number of negative life-events remained a significant predictor of pregnancy (OR: 0.889; P = 0.02)**, when controlling for age, total number of life-events, perceived stress within the previous month, depressive symptoms, and relevant medical factors related to the patient or treatment procedure, including duration of infertility, number of oocytes retrieved and infertility etiology. Mediation analyses indicated that the association between negative life events and IVF pregnancy was partly mediated by the number of oocytes harvested during oocyte retrieval.

CONCLUSION: A large number of life-events perceived as having a negative impact on quality of life may indicate chronic stress, and the results of our study indicate that stress may reduce the chances of a successful outcome following IVF, possibly through psychobiological mechanisms affecting medical end-points such as oocyte retrieval outcome.

Ebbesen Hum Reprod 2009

Lo stress di essere infertili peggiora i risultati della PMA

- **women who reported more marital distress required more treatment cycles to conceive (median 3) than women reporting less marital distress (median 2) (odds ratio [OR] = 1.20: Model $\chi^2(3) = 77.21, P < .001$).**
- **CONCLUSION(S): The findings provide evidence that infertility-related stress has direct and indirect effects on treatment outcome.**

Boivin Infertility-related stress in men and women predicts treatment outcome 1 year later Fertil Steril 2005

Allentare lo stress essendo messi nella lista d'attesa per PMA favorisce la fertilità

RESULT(S): Follow-up information was collected in 2005 and 2008. Of the 674 couples on the waiting list, 87% started IVF, and 13% dropped out before starting their first IVF cycle. Follow-up data were obtained for 85 of 86 patients (98.8%): 37% dropped out because of spontaneous pregnancy, 36% for personal reasons (passive censoring), and 27% for medical reasons (active censoring). Most of the pregnancies occurred within 3 months after the patient had been placed on the waiting list (30 of 32, 94%). Of the 54 censored couples, four became pregnant.

CONCLUSION(S): On a 6-month waiting list for IVF, 13% of the couples dropped out before starting treatment. **The single most important reason for dropout was (spontaneous) pregnancy. Most of these pregnancies occurred within 3 months, which suggests that psychological factors such as stress relief after being placed on the waiting list might be operative.**

Stress = principale causa di abbandono della PMA



The reason for discontinuation of IVF:

- **psychological burden in 26%**
- poor prognosis in 25%
- spontaneous pregnancy in 19%
- physical burden in 6%
- serious disease in 2%

Olivius Fertil Steril 2004

Drop out da lista PMA per stress: 22.3%

RESULTS: In our cohort 319 couples dropped out of fertility care, 76.8%, [95% confidence interval (CI): 72.2-81.4] on their own initiative and 23.2% (95% CI: 18.6-27.8) on doctor's advice. Percentage (95% CI) of couples discontinuing per stage were: Stage I 6.0% (3.4-8.6), Stage II 3.4% (1.5-5.5), Stage III 35.7% (30.5-41.0), Stage IV 23.5% (18.9-28.2), Stage V 17.9% (13.7-22.1) and Stage VI 13.5% (9.7-17.2).

Main reasons for dropout (% , 95% CI) were 'emotional distress' (22.3%, 17.7-26.8), 'poor prognosis' (18.8%, 14.5-23.1) and 'reject treatment' (17.2%, 13.1-21.4). The spontaneous ongoing pregnancy rate after discontinuation was 10% (6.7-13.3).

CONCLUSION: About half of the couples stopped before any fertility treatment was started and one-third stopped after at least one IVF cycle. The main reasons for withdrawal were emotional distress and poor prognosis. This insight may help to improve quality of patient care by making care more responsive to the needs and expectations of subfertile couples

Brandes Hum Reprod. 2009

Stress fa rinunciare PMA al 39% delle coppie negli USA

RESULT(S): Forty-seven subjects returned the questionnaire. **The most common reason for terminating treatment was stress (39%). Subjects reported that the two main causes of stress were the toll that infertility took on the couples' relationship and being too anxious or depressed to continue.** The top-rated suggestions for patient support were written information on how to deal with psychological stress and easy and immediate access to a psychologist or social worker.

CONCLUSION(S): Patients undergoing IVF in the United States report similar reasons for terminating treatment as patients in Europe and Australia. However, this is the first study to gather patient suggestions for treating the problem.

Stress: effetti negativi sulla sessualità

Stress e
disfunzioni
sessuali



Desiderio

Eccitazione

Orgasmo

Stress- eiaculazione precoce
– insoddisfazione relazionale
nelle coppie infertili – meno
rapporti- infertilità



Conclusions. PE is prevalent among infertile couples although the perceived incidence of the condition among men is higher than partner perceived incidence: 47% men; 25% women. Additionally, many men may overestimate the level of partner frustration related to PE.

PE is associated with lower relationship satisfaction in both men and women.

Shindel J Sex Med 2008

Infertilità come stressor di coppia



Unfulfilled self-expectations, social pressure, undergoing evaluation and treatment, disappointment with failures and the financial costs.

Infertile women have a significantly higher prevalence of **depressive symptoms and psychiatric disorders**

Infertile men appear to experience significant transient episodes of **impotence and sexual performance anxiety** which may contribute to difficulties in achieving natural pregnancy

Infertilità come stressor: bassa Quality of Life personale e sessuale

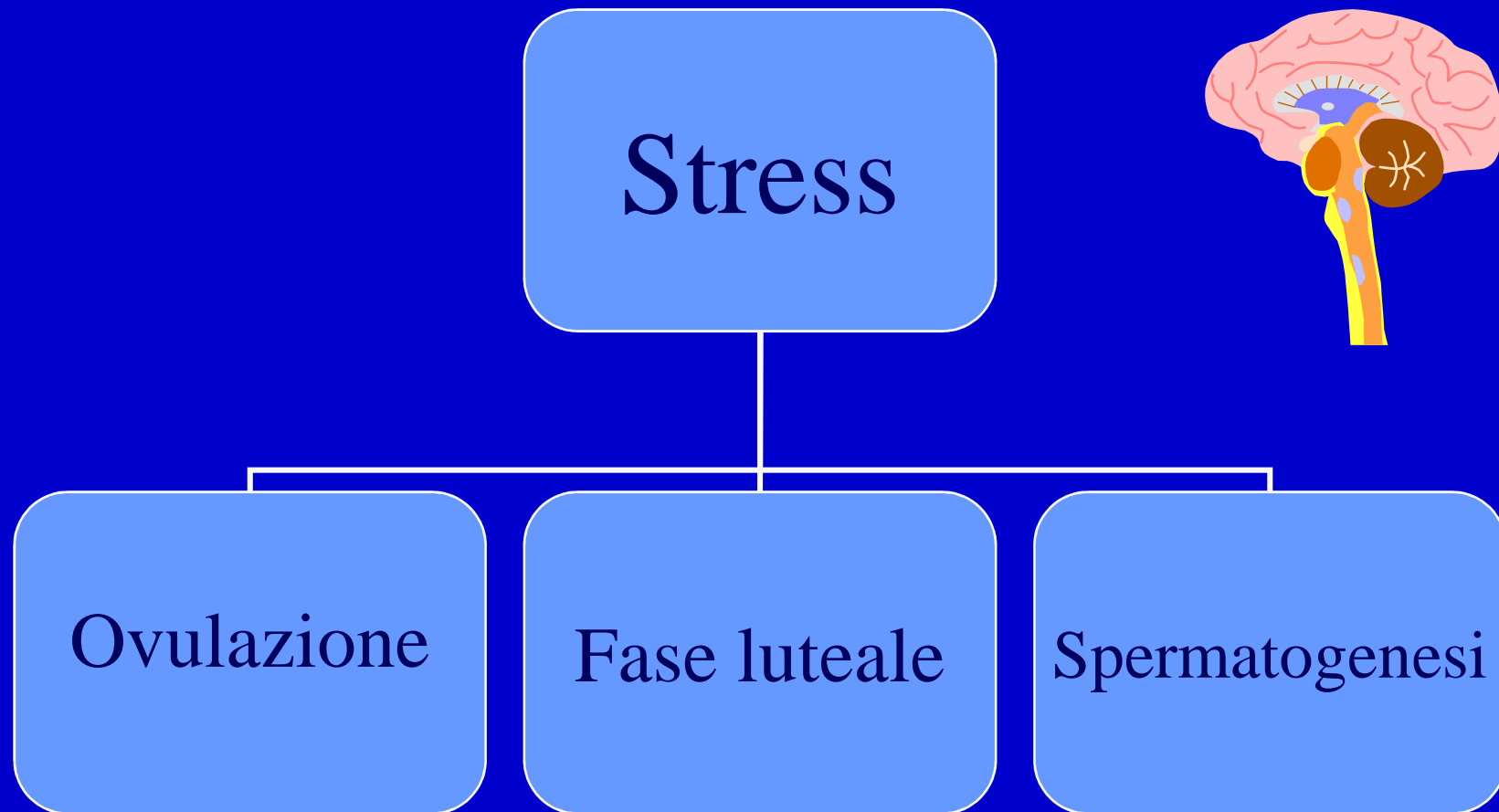


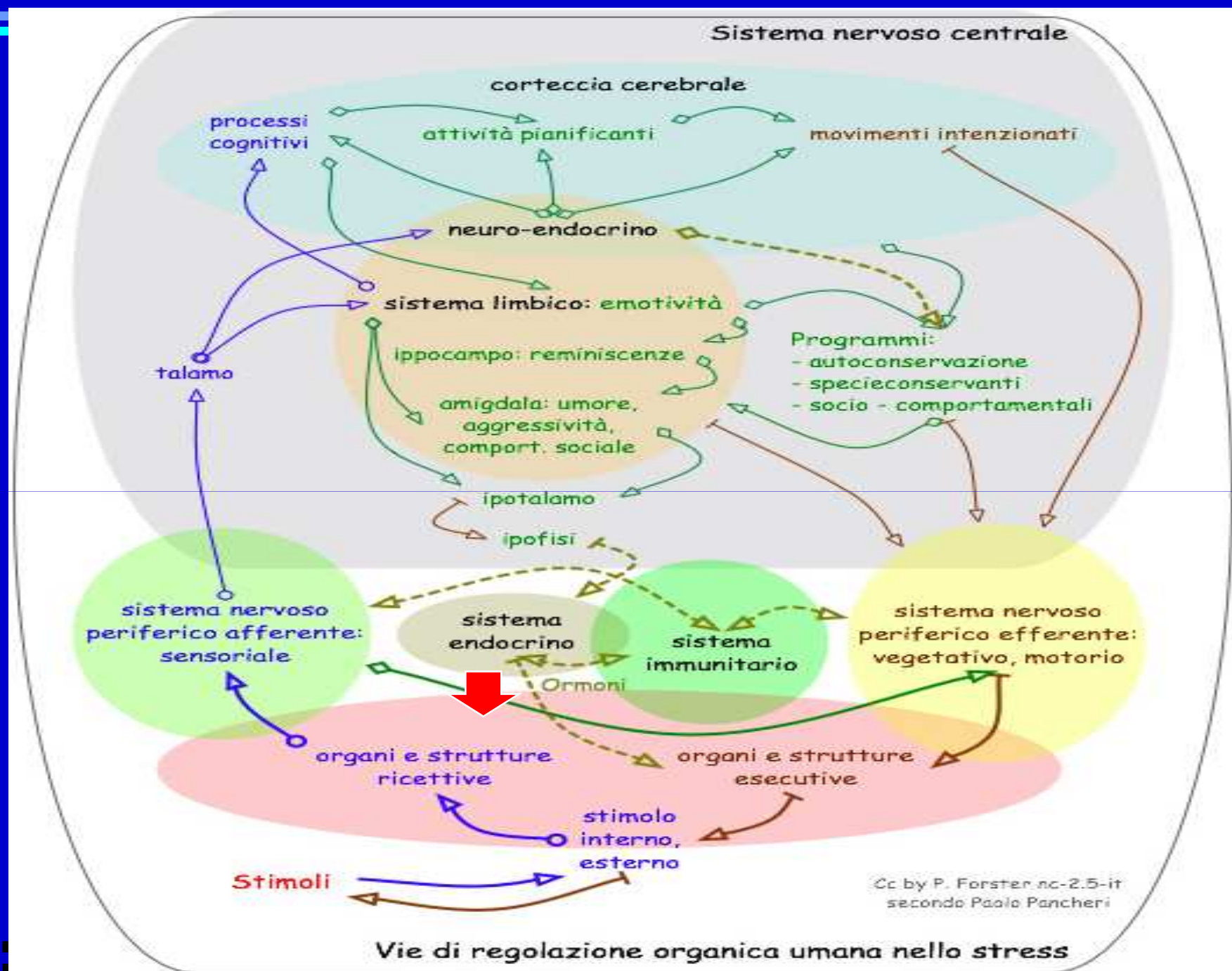
Male factor infertility was independently associated with worse Sexual (mean 39 vs. 30, standard deviation [SD] 2.7, $P = 0.004$) and Personal (mean 37 vs. 29, SD 3.8, $P = 0.04$) quality of life

Conclusions

Male partners in couples who perceive isolated male factor infertility have a lower sexual and personal quality of life compared with male partners of couples without perceived male factor infertility. Social strain is highest among couples without a clear etiology for infertility.

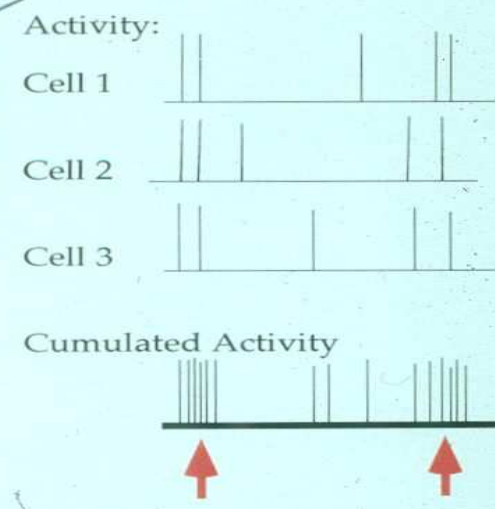
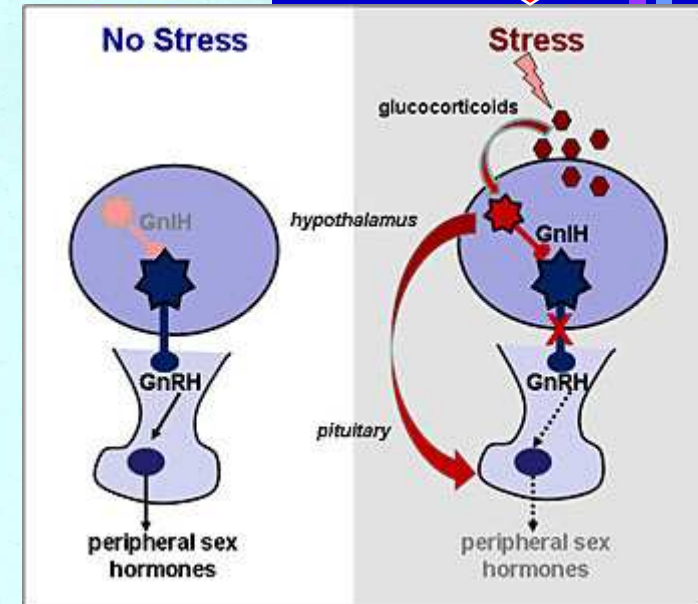
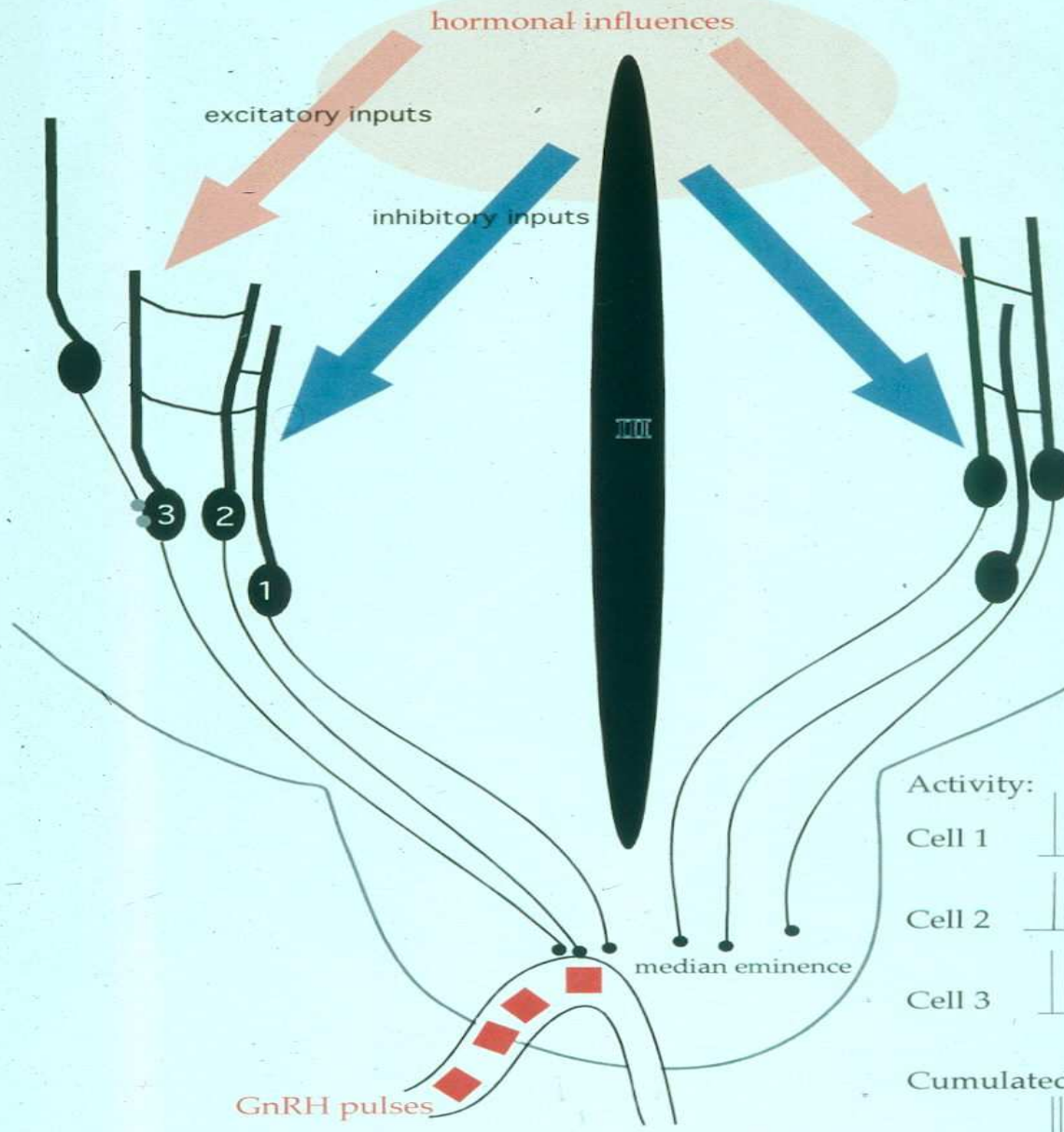
Stress: effetti su gametogenesi e impianto





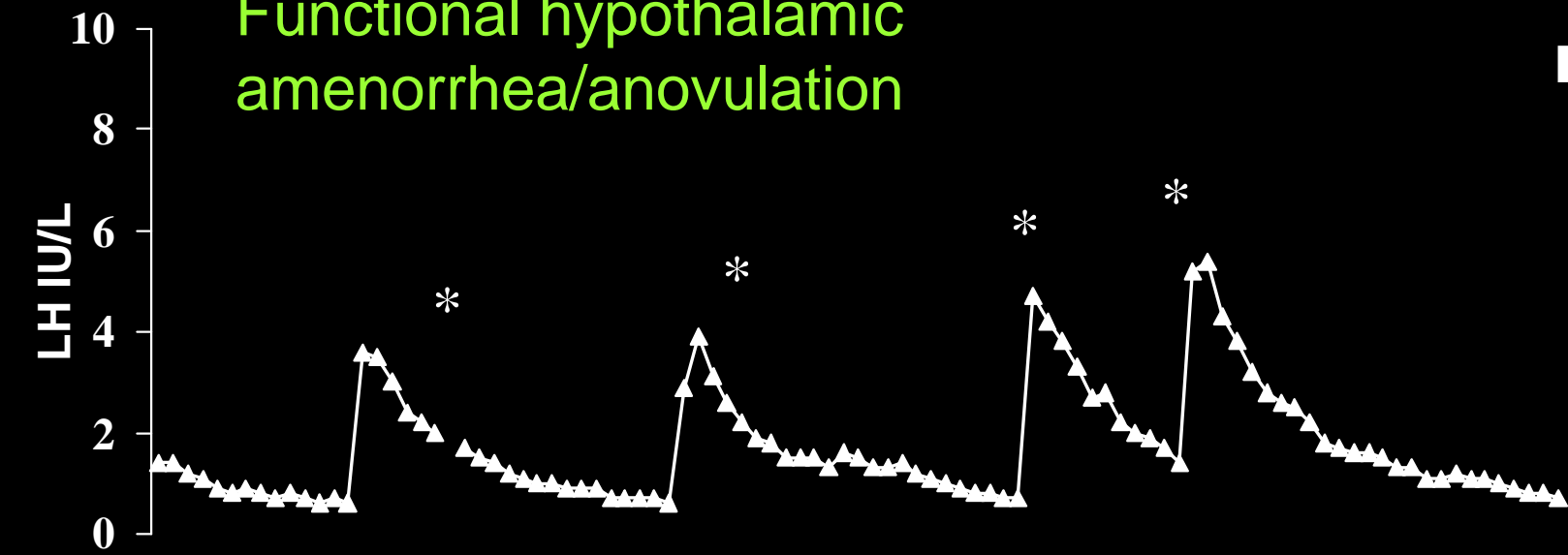
Cc by P. Forster, nc-2.5-it secondo Paolo Pancheri

GnRH Pulse Generator and Its Modulation



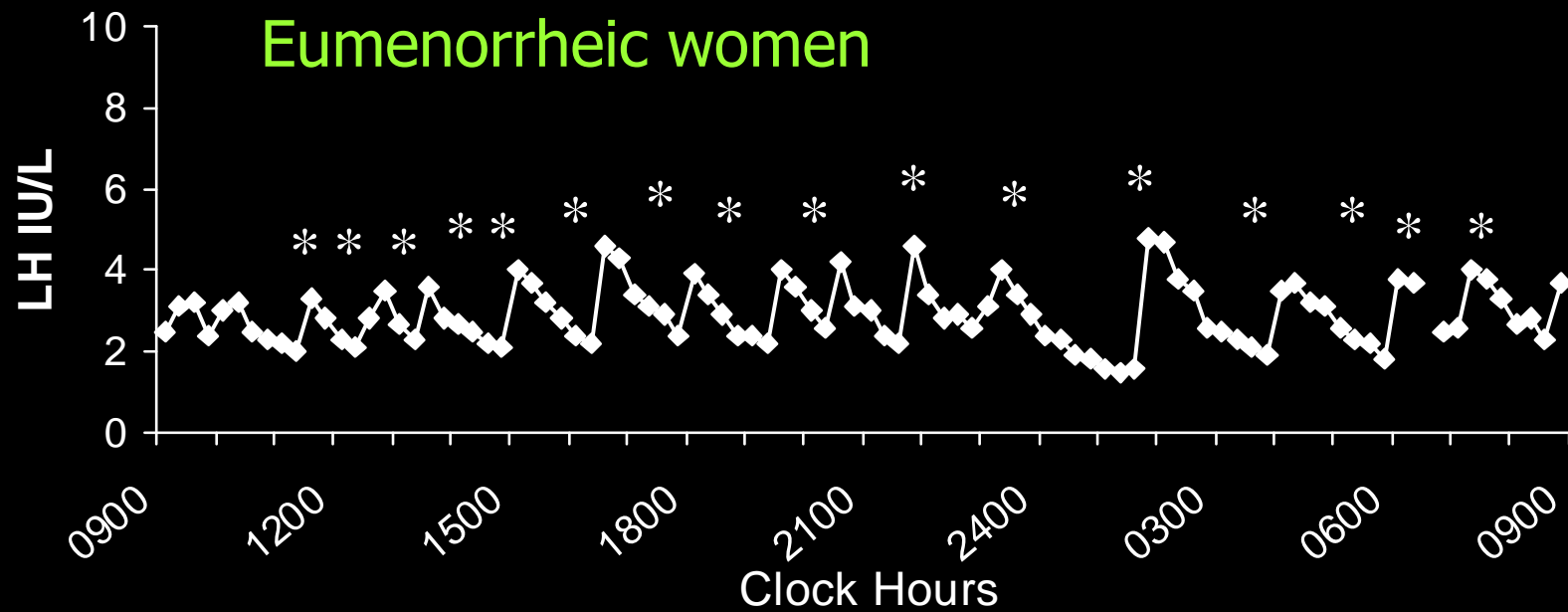
Functional hypothalamic amenorrhea/anovulation

FHA



Eumenorrheic women

EW



Stress acuto può indurre l'ovulazione

Results

Whereas the HPA axis exhibits positive responses in practically all phases of the ovarian cycle, acute-stress-induced release of LH is found under relatively high plasma levels of estradiol.

Acute stress may exert different effects on pituitary LH release and the steroid environment may modulate in a different way (inhibiting or stimulating) the pattern of response of the HPG axis elicited by acute stressors.

Conclusion

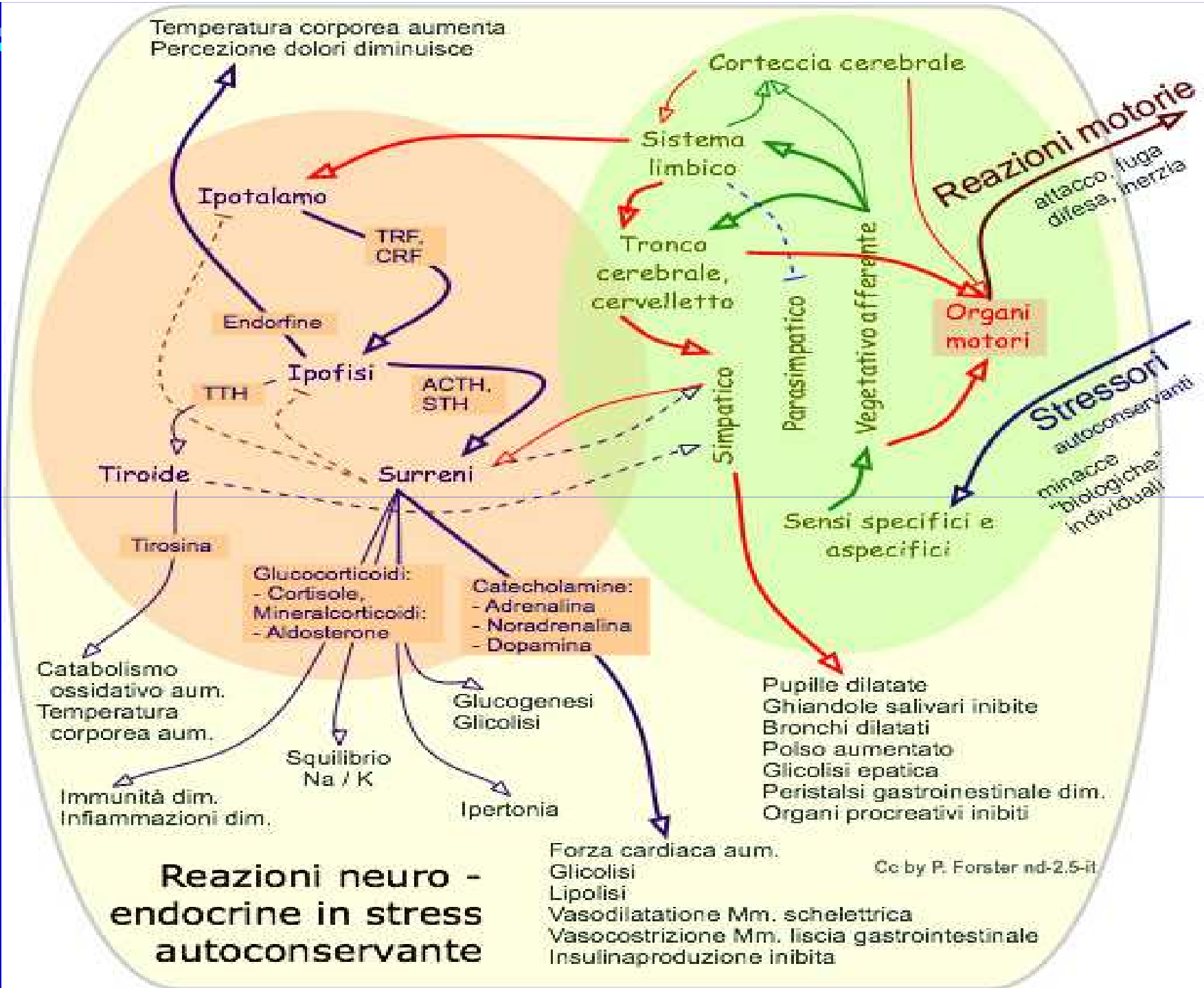
Women may be induced to ovulate at any point of the menstrual cycle or even during periods of amenorrhea associated with pregnancy and lactation if exposed to an appropriate acute stressor under a right estradiol environment.

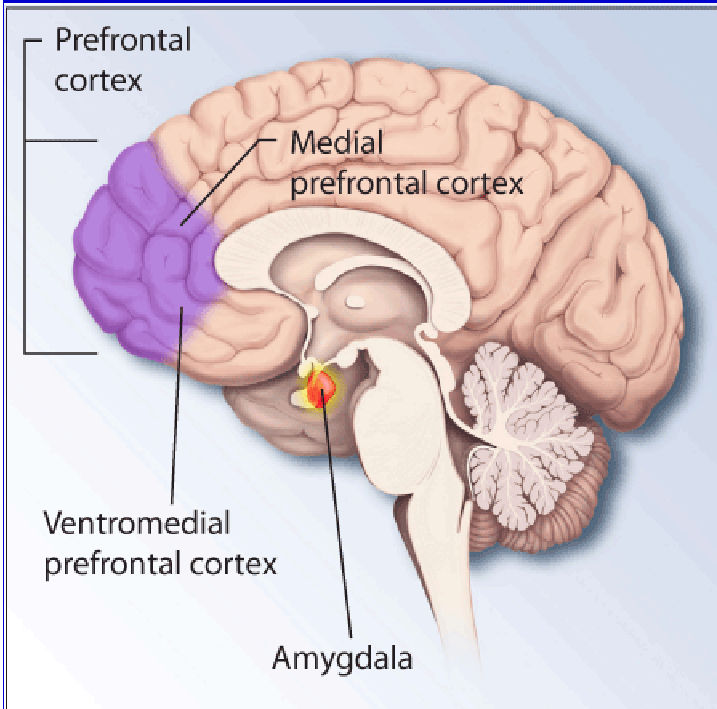
Attenzione alle gravidanze nei momenti poco opportuni di stress acuto!

Pregnancies resulting from single episodes of forced penile-vaginal intercourse (rape) is significantly higher (8.0% vs 3.1%)

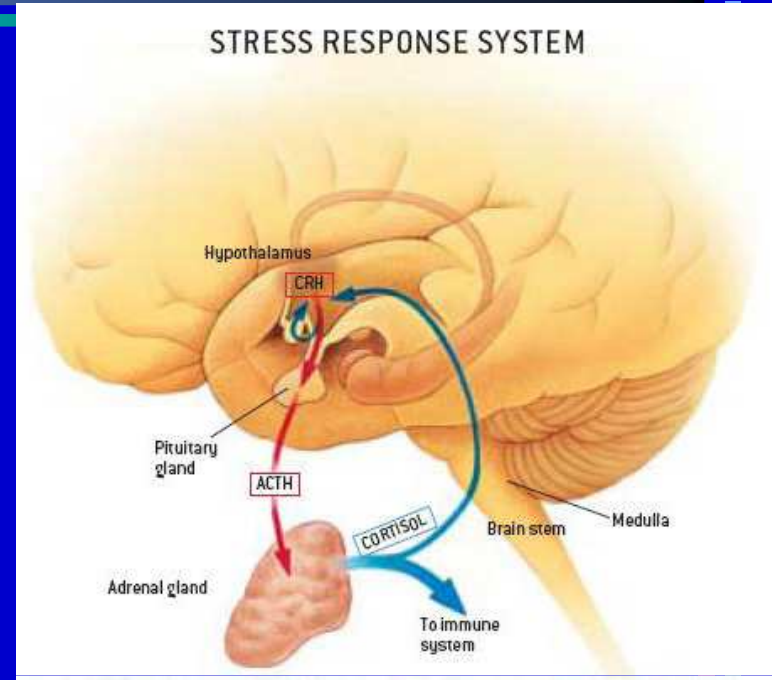
Species	Stressor	Phase of the cycle	LH release
Rhesus monkeys	30-min chair restraint	Mid-follicular and mid-luteal phases	Positive
	30-min intracerebroventricular administration of interleukin-1 α	Mid-follicular phase	Positive
Women		Early follicular phase	No release
	Bilateral ovariectomy plus total hysterectomy	Mid- to late-follicular phase	Positive
		Early- to mid-luteal phase	No release
	Cholecystectomy	Early- to mid-follicular	Positive
	Progressive submaximal treadmill exercise to exhaustion	Mid-follicular and mid-luteal phase	No release
	90-min submaximal bicycle exercise	Mid-follicular and mid-luteal phase	Decreased plasma levels of LH
	60-min progressive submaximal treadmill exercise	Mid-follicular phase	Positive
	Mid-follicular phase	Positive	
	Mid-luteal phase	No release	

Tarin Reprod Biol Endocrinol. 2010





Brain Structures Involved in Dealing with Fear and Stress



STRESS

↑CRH

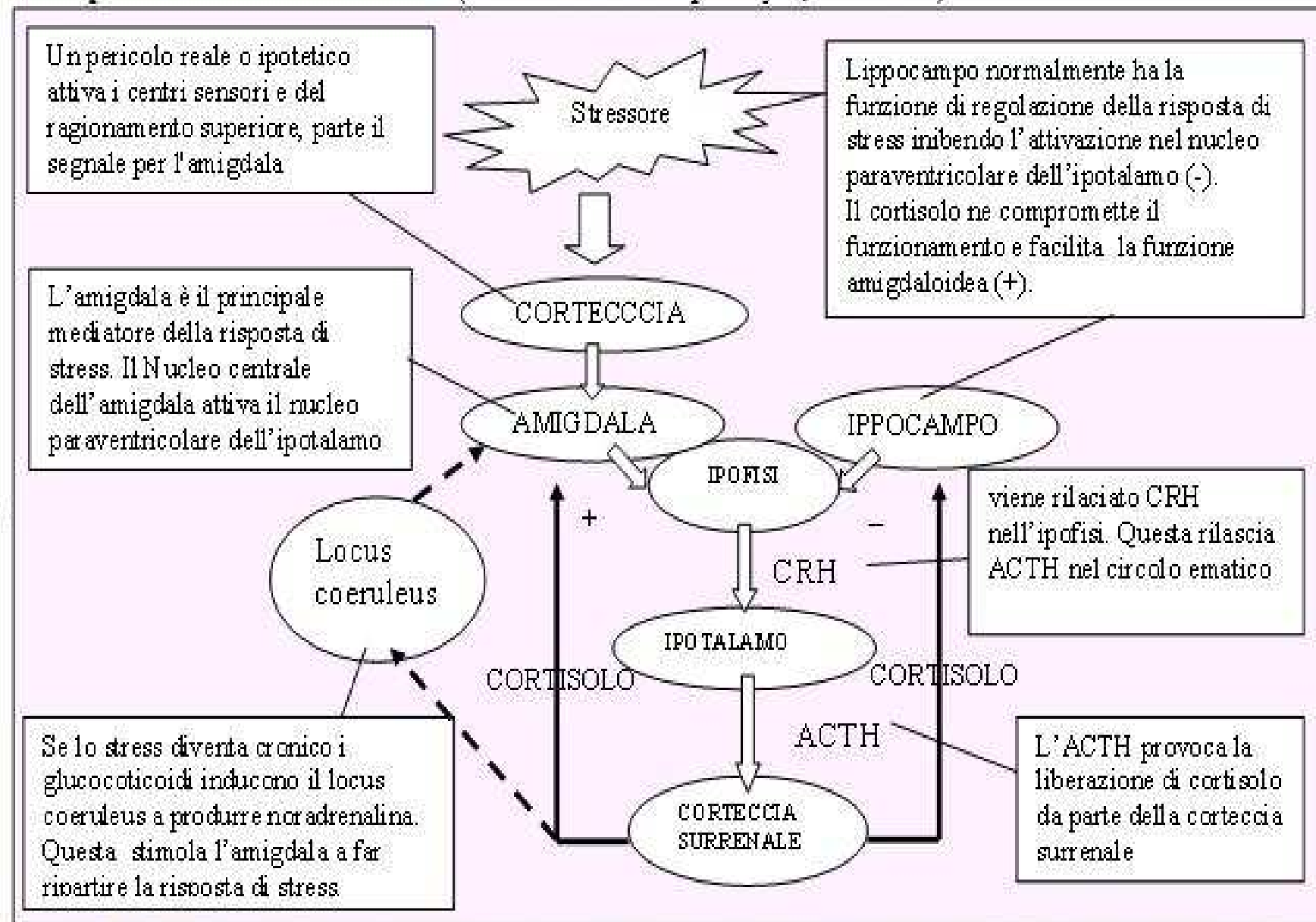
↑ACTH and β-endorphin

↑cortisol

↓T3, T4

↓GnRH

Esempio di circuito dello stress (Modificato da Sapolsky⁸, LeDoux⁹)



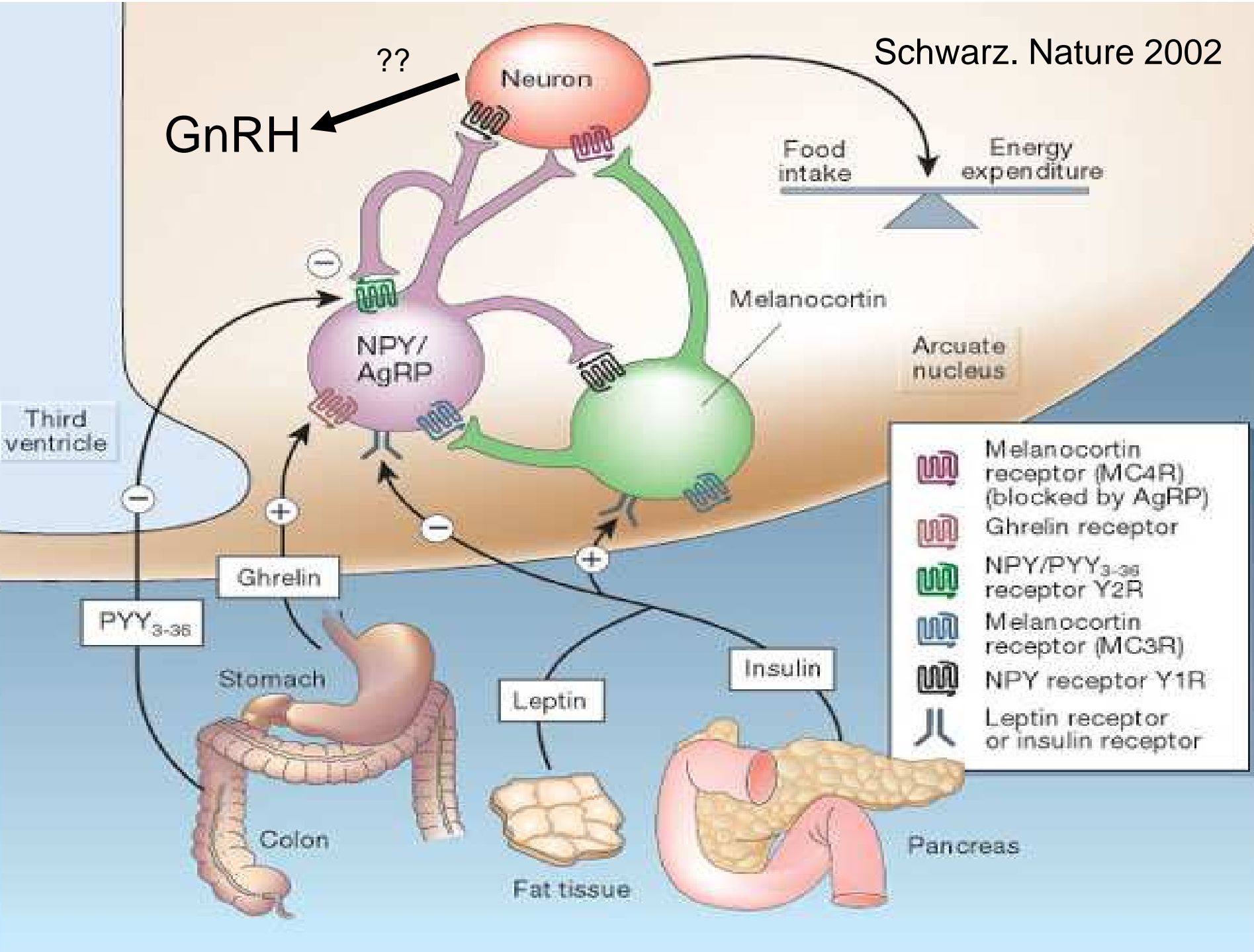
I circuiti dello stress sono diversi, ed essenzialmente agiscono in parallelo. Qui è evidenziata la produzione di cortisolo, il quale sembra avere un importante ruolo in diverse patologie come la depressione, associata ad atrofia dell'ipocampo.

La vulnerabilità ipotalamica: “hypothalamus fragilis”



- **Metabolic deficits**
 - Undernutrition relative to demand
 - Excess energy expenditure
- **Neurobiological factors**
 - Endocrine reactivity
 - Autonomic reactivity
- **Psychogenic variables**
 - Cognitive and personality style
 - Sensitization from psychological milieu, past and present

Schwarz. Nature 2002



Fabbisogno energetico del cervello

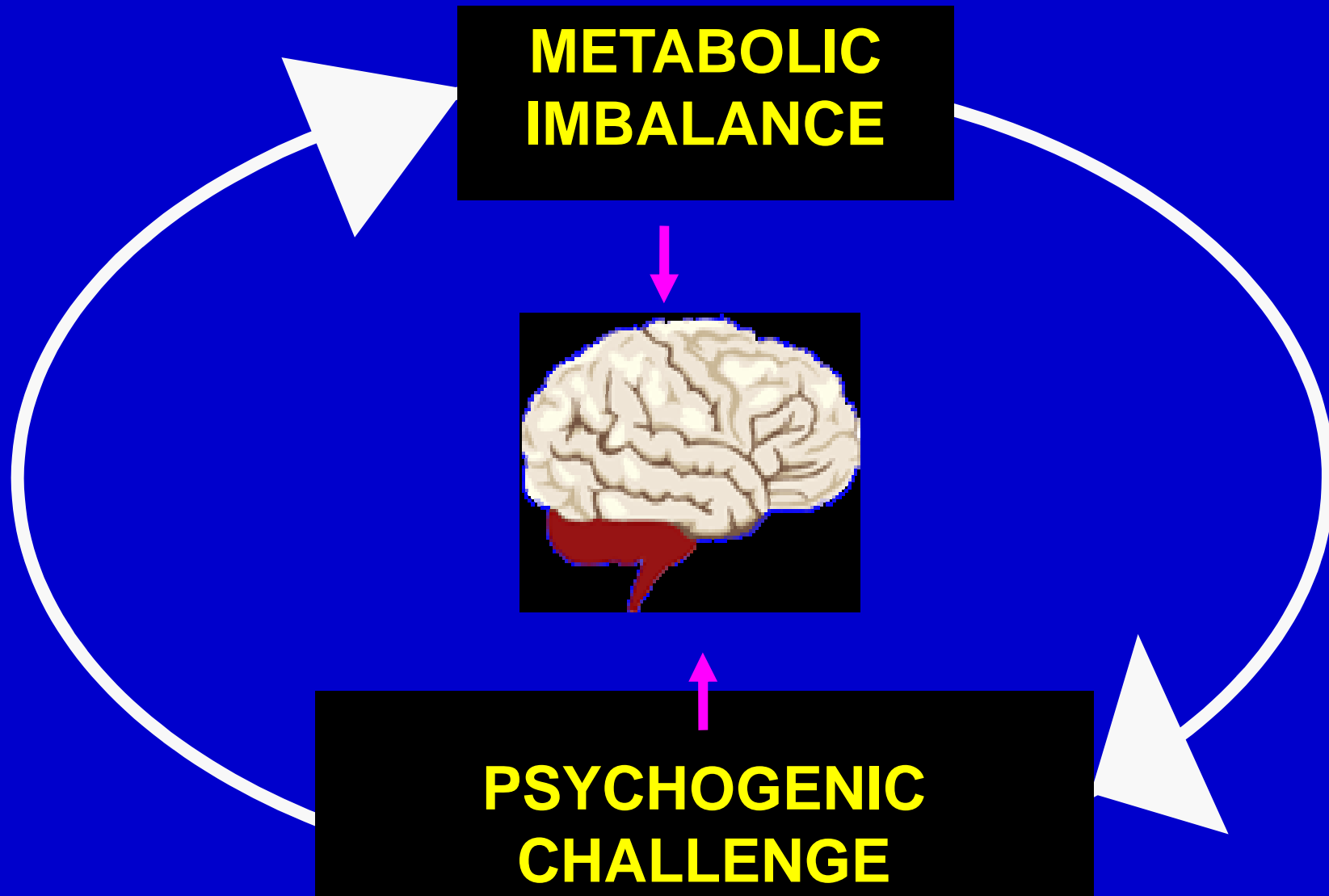
- Species difference in the energy demand of the brain
 - Rodents 3-5%
 - Monkeys 8-10%
 - Humans 20-25%
- Are humans uniquely sensitive to undernutrition?

Deficit energetico e pulsatilità dell'LH

↓ Energy	↓ LH pulse #	↓ Glucose	↑ Cortisol
40%	0	3%	10 nm/L
60%	16%	5%	20
80%	40%	15%	50

Loucks and Thurma JCEM 2003

Pathogenesis of functional hypothalamic anovulation

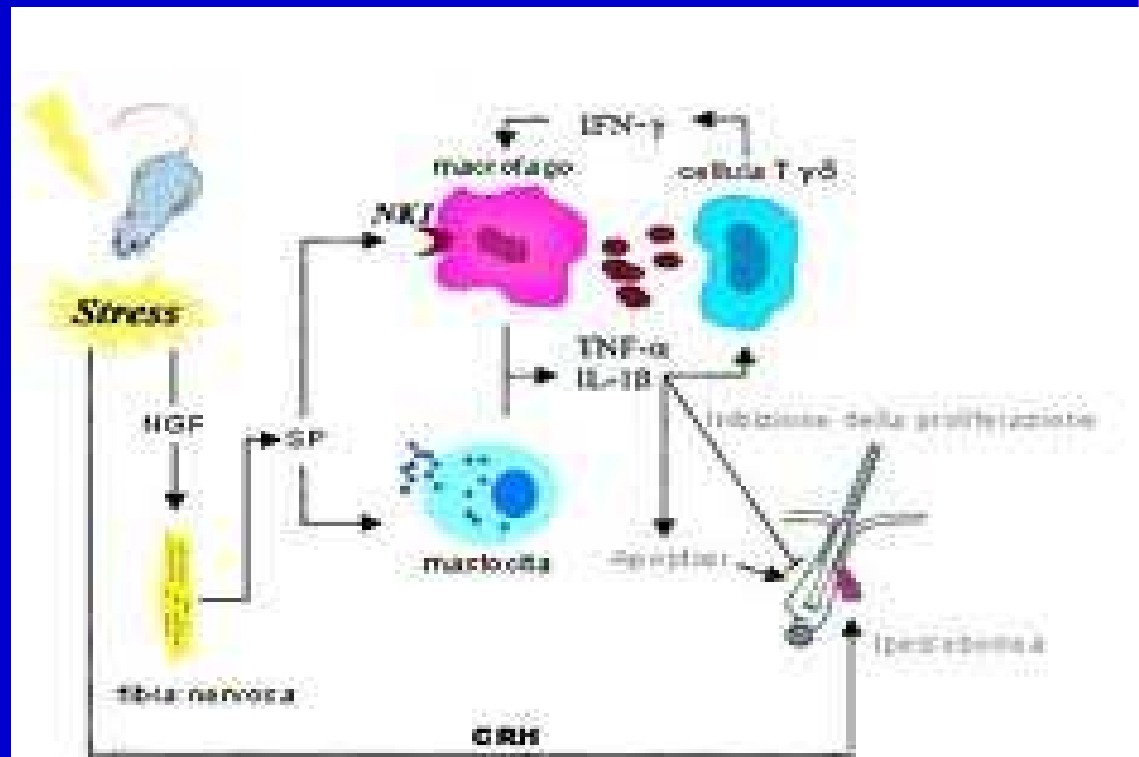




Stress NGF & SP inflammation

Neurotrophin nerve growth factor (NGF) and neuropeptide substance P (SP) are involved in stress responses: the 'cross-talk' between neuronal and immune cells, ultimately skewing the immune response towards inflammation. Lymphoid organs are highly innervated by noradrenergic nerve fibers

NGF & SP



Stress ed abortività?



‘pregnancy stress syndrome’ associated with over-activation of the hypothalamic–pituitary–adrenal (HPA) axis.

Localized inflammation in uterine tissue and depression of progesterone production.

Nakamura J Assist Reprod Genet 2008

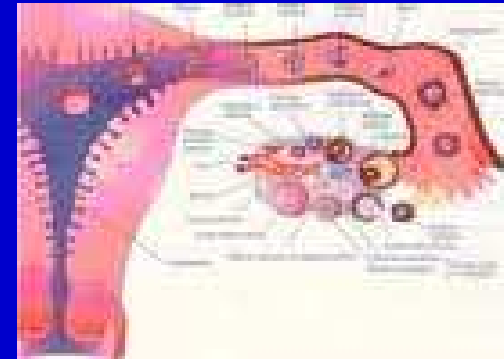
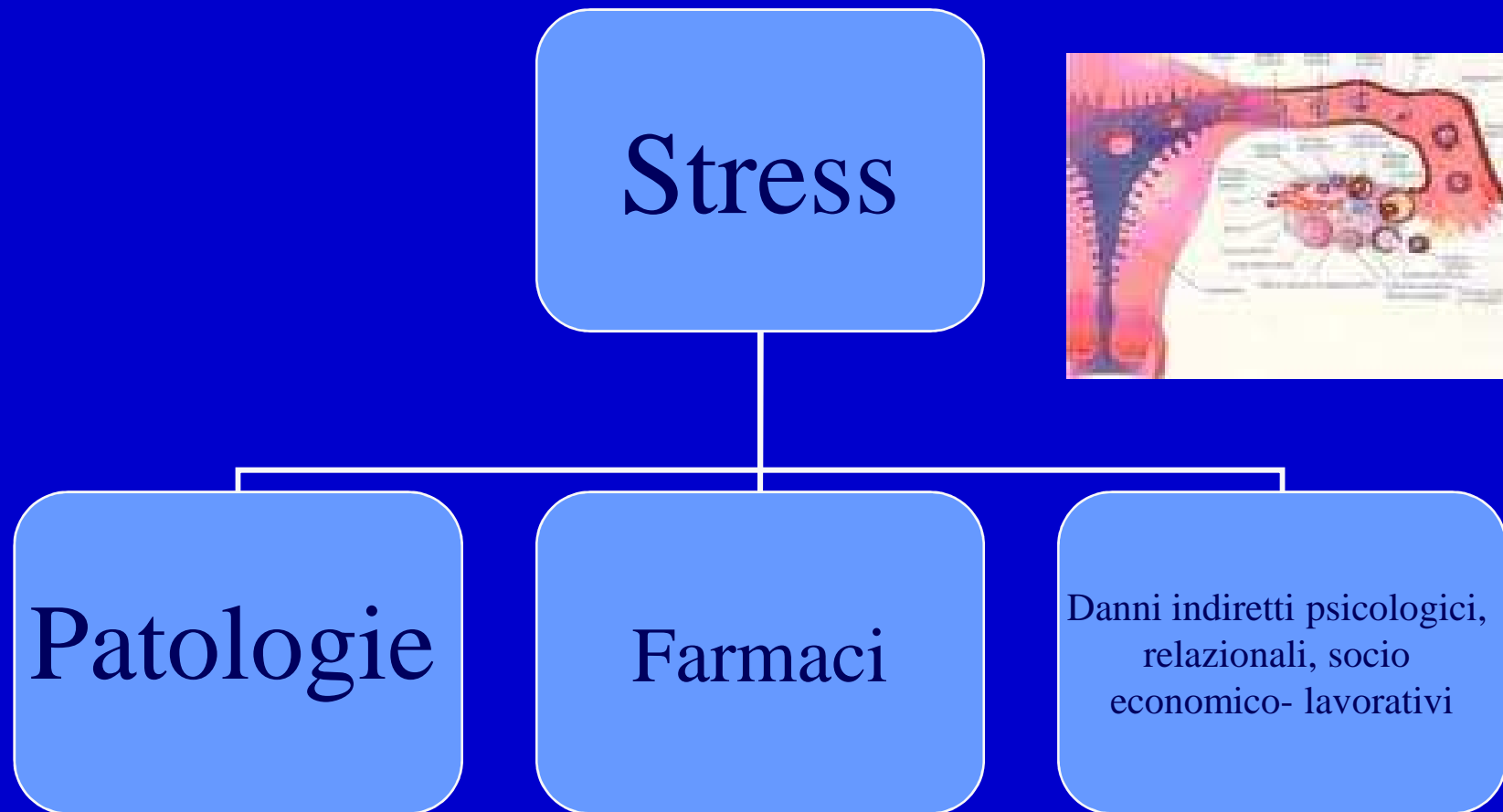
Stress altera i valori di LH nei poliziotti

Sources of psycho-social stressors for traffic police may be the relation with the public, exposure to episodes of criminality. The negative impact of stress in policemen appears with different kinds of troubles including mental health problems

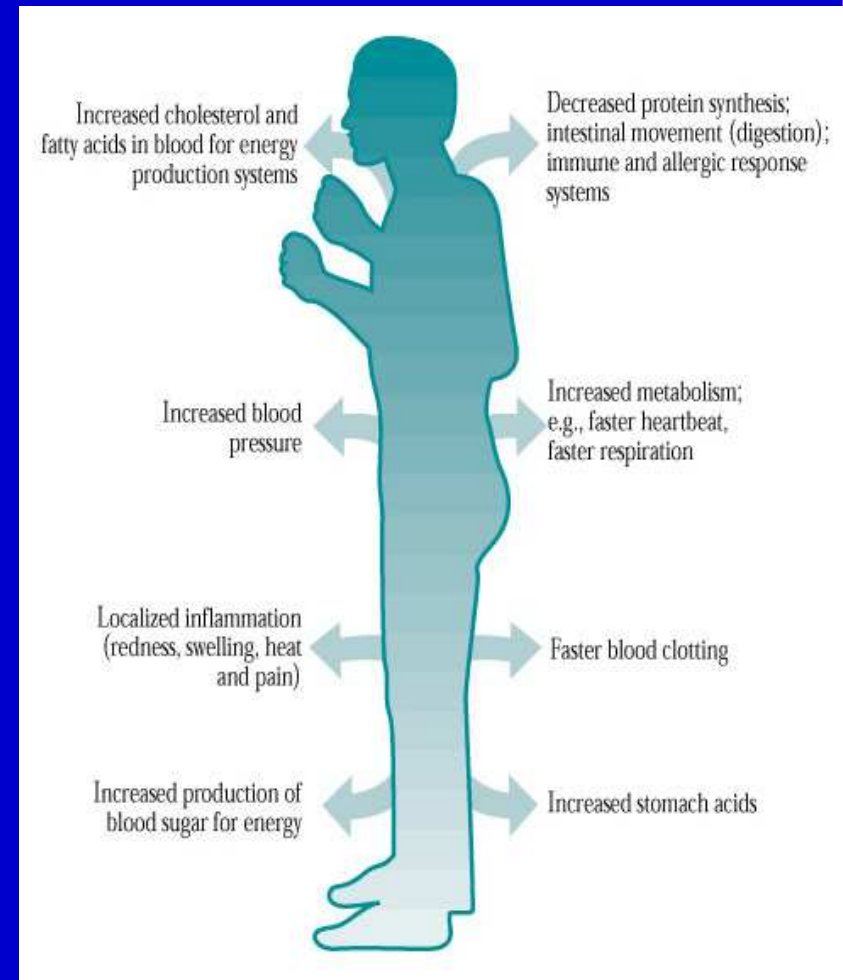
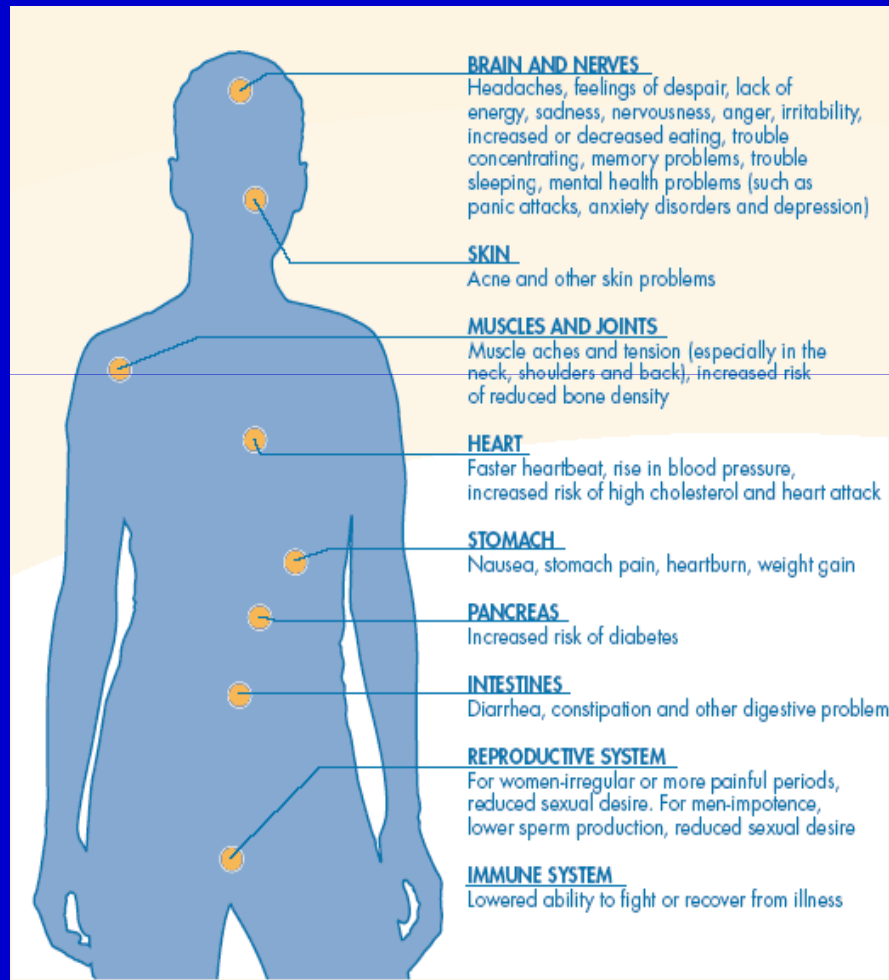
Mean age, mean working life, and mean LH plasma values in male traffic police and administrative staff.

	Traffic police (n. 166)	Administrative staff (n.166)	p
<i>Age (years)</i>			
Mean (SD)	43.8 (5.8)	44.2 (5.3)	n.s.
Min-max	31-59	31-59	
<i>Working life (years)</i>			
Mean (SD)	10.4 (7.5)	9.7 (5.5)	n.s.
Min-max	2-30	2-28	
<i>LH values (mUI/ml)</i>			
Mean (SD)	2.7 (1.1)	1.8 (0.7)	<0.001
Min-max	0.8-8	0.5-5	

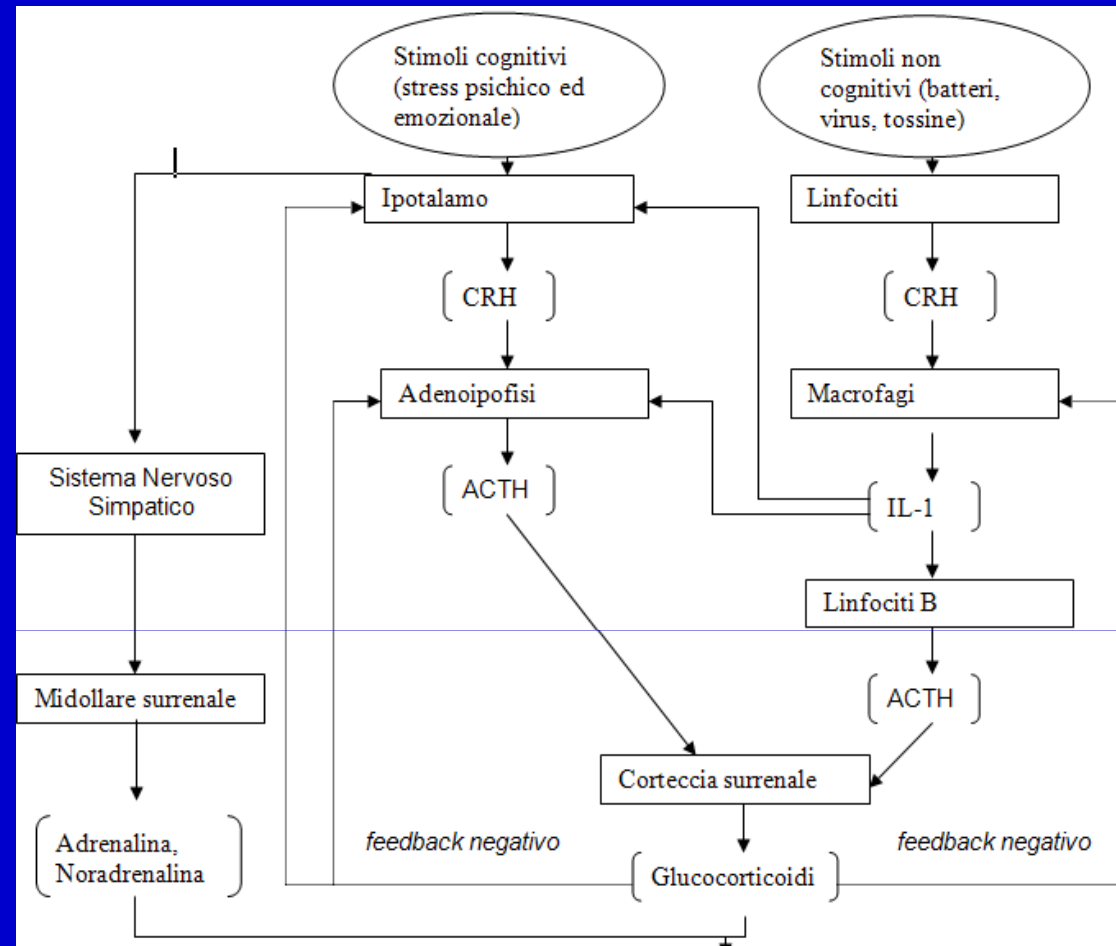
Stress: effetti indiretti sulla fertilità



Effetti indiretti multipli dello stress sulla fertilità: **patologie da stress**



Stress e immuno depressione



- Aumento del metabolismo (frequenza cardiaca, pressione arteriosa, sudorazione, respirazione)
- Aumento della concentrazione di zucchero e grassi nel sangue
- Contrazione dei muscoli scheletrici
- Confluenza del sangue dalle aree periferiche e dagli organi secondari verso cuore, polmoni, muscoli scheletrici
- Riduzione delle secrezioni e motilità gastroenteriche
- Innalzamento della soglia del dolore (betaendorfina)
- Diminuzione dell'attività del sistema immunitario

EBV e PCR = indicatori di stress cronico

- Epstein-Barr virus (EBV) antibody and
- Elevated CRP has also been associated with self-reported stress, fewer economic resources, chronic fear, and work demands. EBV infects 80-90% of adults remains in a latent state. Immunosuppression allows the EBV to reactivate. Increased levels of EBV IgG antibodies therefore provide an indirect measure of immune dysfunction by a wide range of chronic stressors
- C-reactive protein (CRP) are associated positively with chronic stress and inflammation that causes many stress related diseases.

Stress psicosociale autopercipito correla con gli indicatori di stress cronico

Epstein-Barr virus antibody levels stratified by psychosocial stressors

Variable	n	Mean Epstein-Barr Virus antibodies (enzyme-linked immunosorbent assay units)	P value
Perceived stressors index			.04
High	15	140.1 ± 72.5	
Low	166	101.4 ± 58.4	
Perceived discrimination			.03
Yes	36	160.6 ± 69.3	
No	147	131.0 ± 71.3	

C-reactive protein levels stratified by psychosocial stressors

Variable	n	C-reactive protein (mg/L)	P value
Buffers of stress index			.08
Low	15	2.9 (0.9–9.5)	
High	170	1.6 (0.6–5.0)	

Measures of self-reported psychosocial stress are associated with elevated levels EBV antibody in a low-income population of reproductive-age women.

Stress – abuso di Alcool - infertiltà

Heavy alcohol consumption causes: in men testicular atrophy, impotence, reduced libido and cause a deterioration in sperm and in women oestrogen and progesterone levels and it has been associated with anovulation, luteal phase dysfunction and impaired implantation and embryo development

What level of alcohol consumption has an effect? Heavy

European multicenter study 10 000 couples linked high (more than eight drinks a week) but not moderate alcohol consumption with decreased fecundity.

A positive dose–response association between even modest alcohol intake and infertility was shown

Pregnancy and alcohol: increased risks of spontaneous abortion, premature birth, low birth weight, foetal death and foetal alcohol spectrum disorder, including foetal alcohol syndrome.

Given the available data on alcohol, fertility and pregnancy, as well as the fact that the foetus is most vulnerable to the effects of alcohol exposure during the first weeks after conception, when a woman may not even be aware she is pregnant, the latest recommendation is that **people trying for conception avoid consuming alcohol altogether and that the woman continues to abstain from alcohol during pregnancy**

Anderson Aust N Z J Obstet Gynaecol. 2010

Stress – fumo - infertiltà

Smoking is a risk factor for infertility and that it also negatively affectsthe pregnancy outcome of ART

Meta-analysis:

OR for risk of infertility of 1.6 (95% CI = 1.34–1.91)

OR of pregnancy and live delivery per cycle 0.56 (95% CI = 0.43–0.73 and OR 0.54, 95% CI = 0.30–0.99 respectively)

OR of spontaneous miscarriage and ectopic pregnancy (OR 2.65, 95% CI = 1.33–5.30 and OR 15.69, 95% CI = 2.87–85.76 respectively)

OR for pregnancy per number of IVF cycles 0.66 (95% CI = 0.49–0.88)

Danni da fumo su fertilità e gravidanza

Active and passive smoking negatively affects fertility, the foetus and the outcome of ART cycles.

Oxidative damage to sperm DNA, lower sperm count and abnormal sperm fertilising capacity, motility and morphology.

Decrease significantly ICSI and IVF success rates.

Active and passive smoking on pregnancy: increase in the risk of spontaneous abortion, placenta praevia, ectopic pregnancy, foetal growth restriction, preterm birth and low birthweight.

Pregnancy rates were significantly decreased for smokers (19.4%) and passive smokers (20%) vs non-smokers (48.3%).

All people should be counselled to stop smoking prior to trying to conceive.

Stress – Marijuana - infertilità

Cannabinoid receptors are located in reproductive organs and can affect fertilisation, oviductal transport and foetal and placental development, predominantly by dysregulating signalling pathways involved in reproduction and by causing hormonal dysregulation.

Risk of primary infertility (RR 1.7, 95% CI = 1.0–3.0).

Cannabinoids negatively influence spermatogenesis by modulating the apoptosis of Sertoli cells by reducing testosterone production by Leydig cells and by inhibiting sperm motility, capacitation and acrosome reaction.

Intrauterine exposure to marijuana correlates with low birth weight, prematurity, congenital abnormalities and stillbirth and a slight impairment of higher cognitive function later on.

Stress – Cocaina/Oppiacei - infertilità

Cocaine has been shown to impair ovarian responsiveness to exogenous gonadotrophins and to adversely affect spermatogenesis in animals.

Abnormal sexual function is common in heroin-addicted men and persists after withdrawal.

Deterioration of all the sperm parameters, predominantly abnormal motility, has been demonstrated in the majority of heroin addicted males and to a lesser extent in methadone users.

Normal levels of serum gonadotrophins with a significant elevation in prolactin

and decrease in total and free testosterone levels were reported in opiate-addicted men.

The effects of cocaine and heroin use during pregnancy include placental abruption, preterm delivery, low birth weight, neonatal mortality, neonatal withdrawal syndrome and possible long-term neurobehavioral effects, some of which can be associated with poor prenatal care and other substance use.

Anderson Aust N Z J Obstet Gynaecol. 2010

Stress

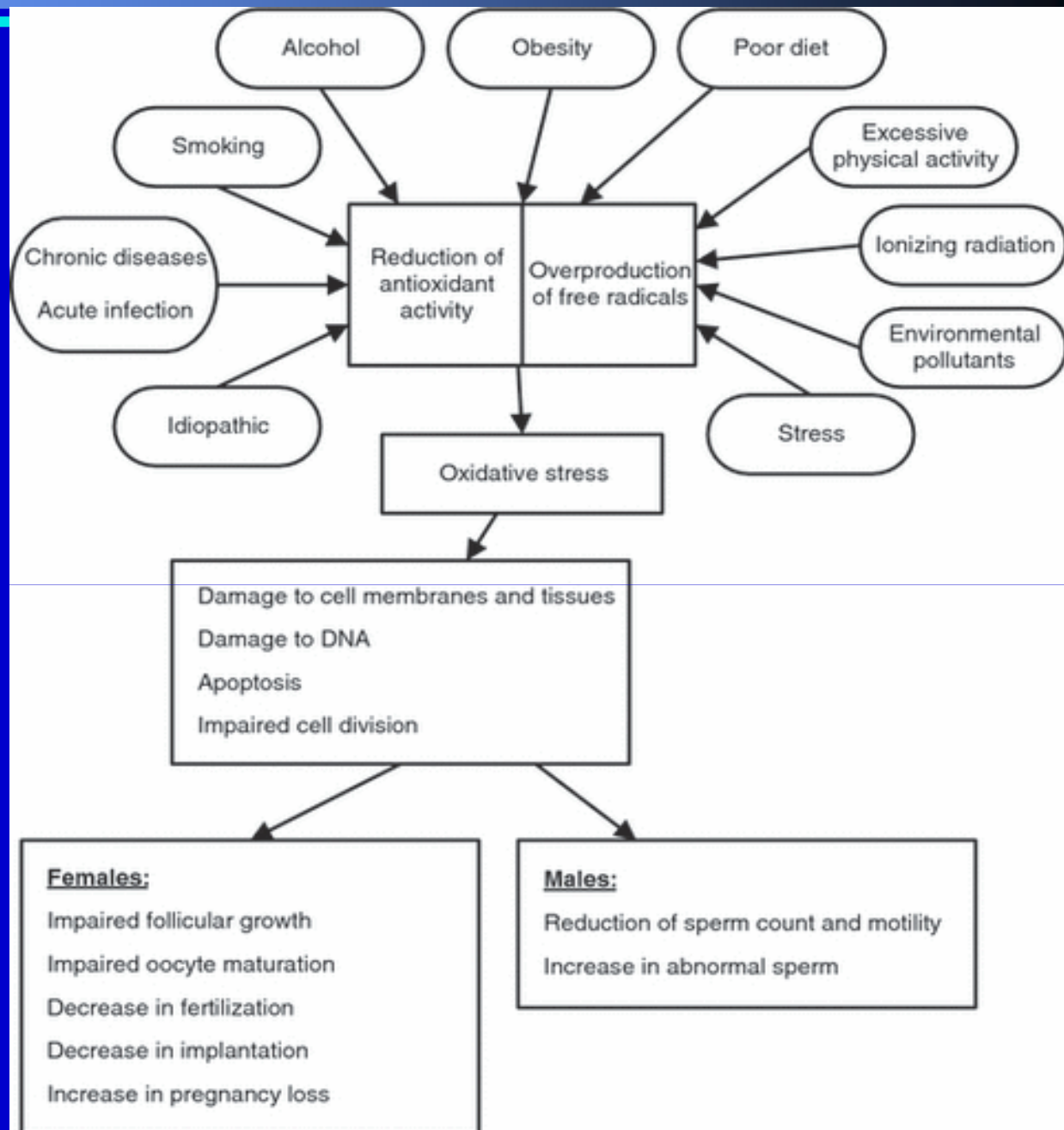
Malattia

Farmaci

Infertilità

Drugs	Effect on reproductive function
Antibiotics	
Penicillin G, ampicillin, cephalotin, spiramycin, gentamycin, neomycin, nitrofurantoin, cotrimoxazole	Reversible impairment of spermatogenesis
Dicloxacillin, tylosin, lincomycin, tetracycline, erythromycin, quinolones, neomycin, nitrofurantoin, cotrimoxazole	Reversible impairment of sperm motility
Antimalarials: quinine and its derivatives	Reversible impairment of sperm motility
Antischistosomal: niridazole	Reversible impairment of spermatogenesis and sperm motility
Antimetabolites/Antimitotics: colchicines, cyclophosphamide	Irreversible arrest of spermatogenesis and azoospermia
Non-steroidal anti-inflammatory drugs, Cox-2 inhibitors	Reversible impairment of follicle rupture and ovulation, impairment of tubal function
Anti-inflammatory 5-ASA and derivatives: mesalazine, sulfasalazine	Reversible impairment of spermatogenesis and sperm motility
Corticosteroids	Reversible impairment of sperm concentration and motility
Antiandrogens: cyproterone acetate, danazol, finasteride, ketoconazole, spironolactone	Reversible impairment of spermatogenesis and erectile dysfunction
Exogenous testosterone, GnRH analogues	Reversible impairment of spermatogenesis
Anabolic steroids	Reversible impairment of spermatogenesis (up to one year recovery), may induce hypogonadism by affecting pituitary-gonadal axis
Anti-oestrogens, eg clomiphene citrate	Reversible impairment of endometrial development
Anti-progestins, emergency contraceptive pills, progesterone-only pills	Impairment of implantation and tubal function
Local anaesthetics, halothane	Impair sperm motility
Antiepileptics: phenytoin	Reversible impairment of sperm motility
Antipsychotics	
Phenothiazine, antidepressants (particularly SSRIs), α blockers	Raise prolactin concentrations and lead to sexual dysfunction
Butyrophenones	Reversible impairment of spermatogenesis and sperm motility
Antihypertensives	
Calcium channel blockers (nifedipine)	Fertilisation failure
Beta blockers, α blockers (prazosin), α agonists (clonidine), thiazide diuretics, hydralazine, methyl dopa	Erectile dysfunction
H2 blockers: cimetidine, ranitidine	Raise prolactin concentrations and lead to impairment of luteal function, loss of libido and erectile dysfunction
Metoclopramide	Erectile dysfunction
Methadone	Depress spermatogenesis and sperm motility

Stress ossidativo e Infertilità



Stress: strategie per tentare di risolverlo



Stress



Stressor

Coping

Bilancio benefici/ costi
Revisione obiettivi

Strategie

Meno stressor



Migliore coping



Revisione strategie e obiettivi

VORREI UN UOMO VESTITO DI AZZURRO, COL CAVALLO ALATO.



VORREI UN UOMO APERTO DI MENTE E CHE MI CAPISCA.



VORREI UN UOMO "MASCIO" CON CUI STAR BENE.



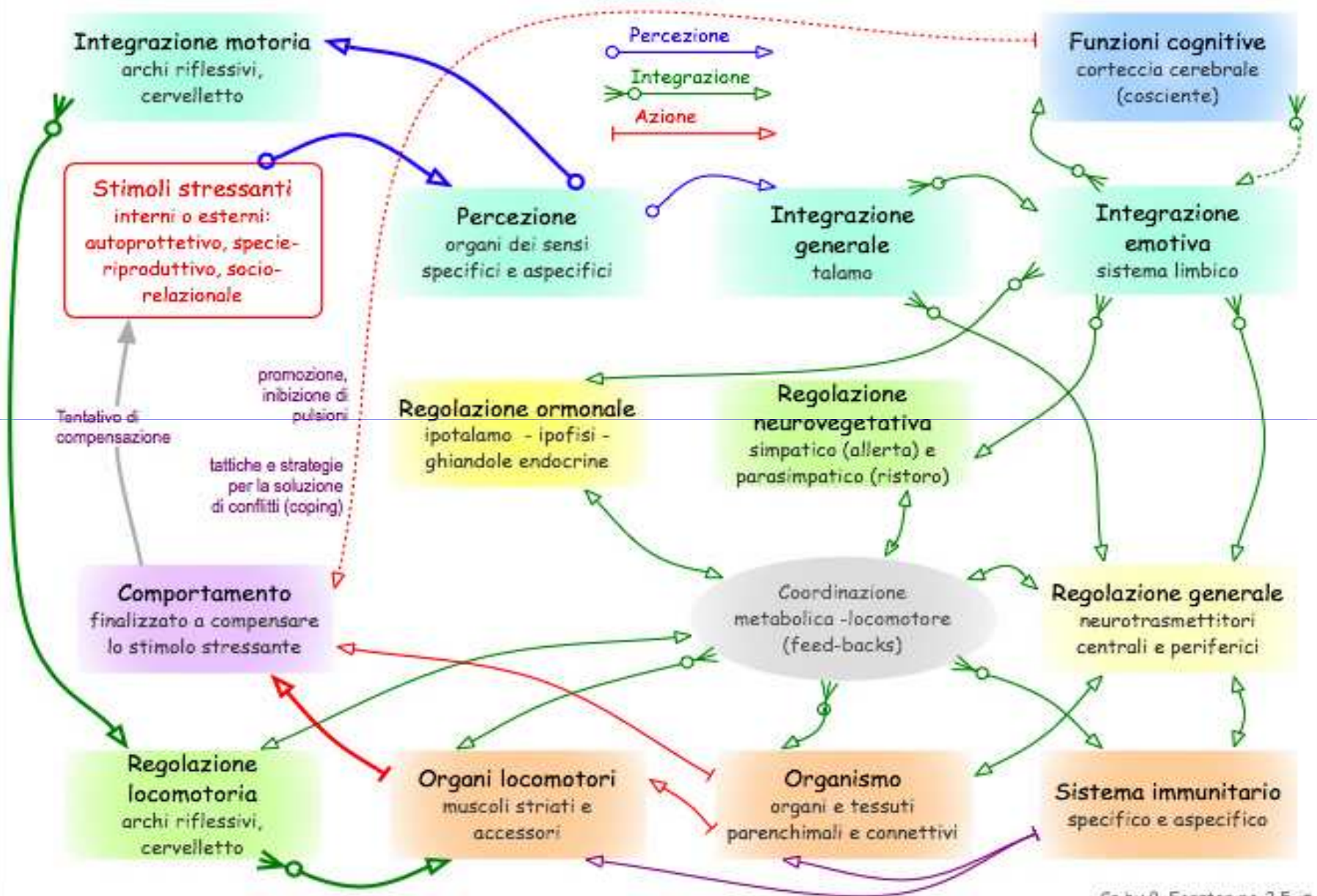
VORREI UN UOMO TRANQUILLO, BUONO E ...CHE NON MI MENEI.



VORREI UN UOMO MANGO A PAGARLO.



Reazione umana a stimoli stressanti



Efficacia della psicoterapia?

Forse, ma gli studi non sono di buona qualità

Review: “..we need high quality studies in order to address the effectiveness of psychosocial interventions unequivocally..”



Quadrato nero = efficace

Boivin Soc Sci Med. 2003

Intervention effects on pregnancy rates and effect sizes (*r*-statistic)

Studies	Pregnancy rate	Effect size (<i>r</i>)
<i>Counselling</i>		
Holzle et al. (2002)	Excluded	
Strauss et al. (2002) ^a	□	0.285
Emery et al. (2001) ^a	□	0.039
Christie & Morgan, 2000	Excluded	
McNaughton-Cassill et al. (2000)		
Wischmann et al. (2001a, b, 2002) ^a	□	0.016
Kemeter and Fiegl (1999)		
Pengelly et al. (1995)		
Connolly et al. (1993) ^a		
Liswood (1995) ^a		
Bents (1991)		
Brandt and Zech (1991)	Excluded	
Sarrel and deCherney (1985) ^a	■	0.506
Ellenberg and Koren (1982)	Excluded	
Bresnick and Taymor (1979); Bresnick (1981)		
<i>Focussed educational programmes</i>		
Tuschen-Caffier et al. (1999) ^a	■	0.928
McQueeney et al. (1997)	Excluded	
Stewart et al. (1992) ^a	□	0.177
Takefman et al. (1990) ^a	□	0.000
Wallace (1984, 1985)		
O'Moore et al. (1983)	Excluded	
<i>Comprehensive educational programmes</i>		
Domar et al. (2000a, b) ^a	■	0.258
Domar et al. (1990)		
Domar et al. (1992)		
Clark et al. (1995, 1998)	Excluded	

■ = positive intervention; □ no intervention effect. Exclu-

Intervention effects on negative affect

Studies	Depression			Anxiety		Psychiatric morbidity		
	BDI	HAD/HRSD	POMS	STAI	POMS	GHQ	BSI	MHI
<i>Counselling</i>								
Holzle et al. (2002)							□	
Strauss et al. (2002) ^a							□	
Emery et al. (2001) ^a	□			□				
Christie and Morgan (2000)								
McNaughton-Cassill et al. (2000)								
Wischmann et al. (2001a, b, 2002) ^a							□	
Kemeter and Fiegl (1999)								
Pengelly et al. (1995)								
Connolly et al. (1993) ^a			□	□	□	□		
Liswood (1995) ^a							□	
Bents (1991)								■
Brandt and Zech (1991)								
Sarrel and deCherney (1985) ^a								
Ellenberg and Koren (1982)								
Bresnick and Taymor (1979); Bresnick (1981)								
<i>Focussed educational programmes</i>								
Tuschen-Caffier et al. (1999) ^a								
McQueeney et al. (1997)	■							■
Stewart et al. (1992) ^a	■	■					■	
Takefman et al. (1990) ^a	□			□				
Wallace (1984, 1985) ^a			□	■	□			
O'Moore et al. (1983)				■				
<i>Comprehensive educational programmes</i>								
Domar et al. (2000a, b) ^a	□	□	□	■	■			
Domar et al. (1990)			■	■	■			
Domar et al. (1992)			□	■	■			
Clark et al. (1995, 1998)		■					■	

■ = positive intervention and □ = no intervention effect.

Note: BDI = Beck Depression Inventory; HAD = Hospital Anxiety and Depression Scale; HRSD = Hamilton Rating Scale for Depression; STAI = Spielberger State Anxiety Inventory; POMS = Profile of Mood Scale; GHQ = General Health Questionnaire; BSI = Brief Symptom Inventory or Symptom Checklist; MHI = Mental health Inventory.

Psico
terapia?
dipende
quale,
come è
condotta
...(e
anche
dalla
coppia)

Quadrato nero = efficace

Boivin Soc Sci Med. 2003

Intervention effects on non-affect measures

Studies	<i>Behavioural features</i>		<i>Infertility-specific measures</i>	
	Interpersonal functioning		Infertility distress	Target behaviour
	Marital	Social		
<i>Counselling</i>				
Holzle et al. (2002)	□			
Strauss et al. (2002) ^a	□		■	■
Emery et al. (2001) ^a				
Christie and Morgan (2000)				
McNaughton-Cassill et al. (2000)				■
Wischmann et al. (2001a, b, 2002) ^a	□		■	
Kemeter and Fiegl (1999)				
Pengelly et al. (1995)				■
Connolly et al. (1993) ^a	□	□		■
Liswood (1995) ^a	□	□		
Bents (1991)	■		■	
Brandt and Zech (1991)				
Sarrel and deCherney (1985) ^a				
Ellenberg and Koren (1982)				
Bresnick and Taymor (1979); Bresnick (1981)			■	
<i>Focussed educational programmes</i>				
Tuschen-Caffier et al. (1999) ^a	■			■
McQueeney et al. (1997)			■	■
Stewart et al. (1992) ^a				■
Takefman et al. (1990) ^a	□		■	
Wallace (1984, 1985)				■
O'Moore et al. (1983)				
<i>Comprehensive educational programmes</i>				
Domar et al. (2000a, b) ^a	■			■
Domar et al. (1990)				
Domar et al. (1992)				
Clark et al. (1995, 1998)				■

■ = positive intervention; □ no intervention effect.

Psico
terapia:
agisce su
infertility
distress,
ma
aumenta
la
pregnancy
rate? No
secondo
alcuni A

Quadrato nero = efficace

Boivin Soc Sci Med. 2003

Stress management & coping skills servono

Psychological interventions, especially those emphasizing stress management and coping-skills training, have been shown to have beneficial effects for infertility patients

Providing patients with information and instruction on self-care skills that address common problems (such as managing , resolving communication difficulties, and relieving anxiety) can mediate distress and facilitate cooperation with medical instructions. Patients who express symptoms of anxiety and/or depression should be assessed and referred for mental health counseling.

As first-line intervention, based on the evidence described above, we suggest relaxation techniques, stress management, coping-skills training, and group support.

In cases in which psychological treatment has not been effective for a patient, and the symptoms of anxiety and/or depression are significant, a referral for a psychopharmacological evaluation is warranted.

Cousineau Best Pract Res Clin Obstet Gynaecol 2007; 21: 293–308

Psicoterapia aumenta il benessere psichico e (forse) la pregnancy rate.

METHOD: Meta-analyses; efficacy of group and individual/couple therapies on negative emotional symptoms and promotion of pregnancy.

RESULTS: Group and individual/couple psychotherapy led to a decrease in feelings of anxiety. Upon termination of psychotherapy, a reduction of depressive symptoms in patients was greater after 6 months. Similar conception success rates.

Higher conception rate among patients following a psychotherapeutic intervention: 45% (18 studies) vs 14% (6 studies) in the control group.

CONCLUSION: Results are suggestive of positive effects of psychotherapy for infertile patients. However, these results must be viewed with caution due to methodological and informational bias within the studies analysed.

De Liz Hum Reprod 2005; 20: 1324–1332.

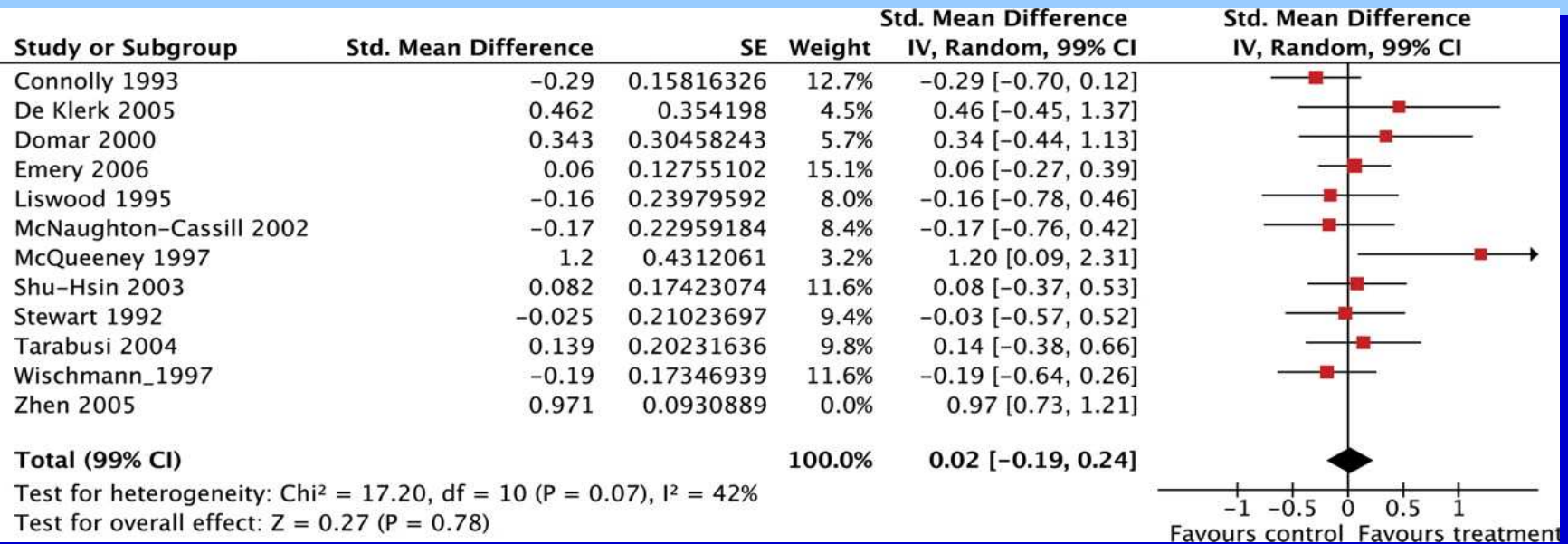
Psicoterapia aumenta la pregnancy rate: 1.42

Meta-analysis: controlled studies indicated no significant effect for psychological interventions regarding mental health (depression: ES 0.02, 99% CI: -0.19, 0.24; anxiety: ES 0.16, 99% CI: -0.10, 0.42; mental distress: ES 0.08, 99% CI: -0.10, 0.51). Nevertheless, there was evidence for the positive impact of psychological interventions on pregnancy rates (**RR 1.42, 99% CI: 1.02, 1.96**). Concerning pregnancy rates, significant effects for psychological interventions were only found for couples not receiving ART.

CONCLUSIONS Despite the absence of clinical effects on mental health measures, psychological interventions were found to improve some patients' chances of becoming pregnant.

Psicoterapia non migliora la depressione?

Effect of psychological interventions on depression (after excluding Zhen et al., 2005).



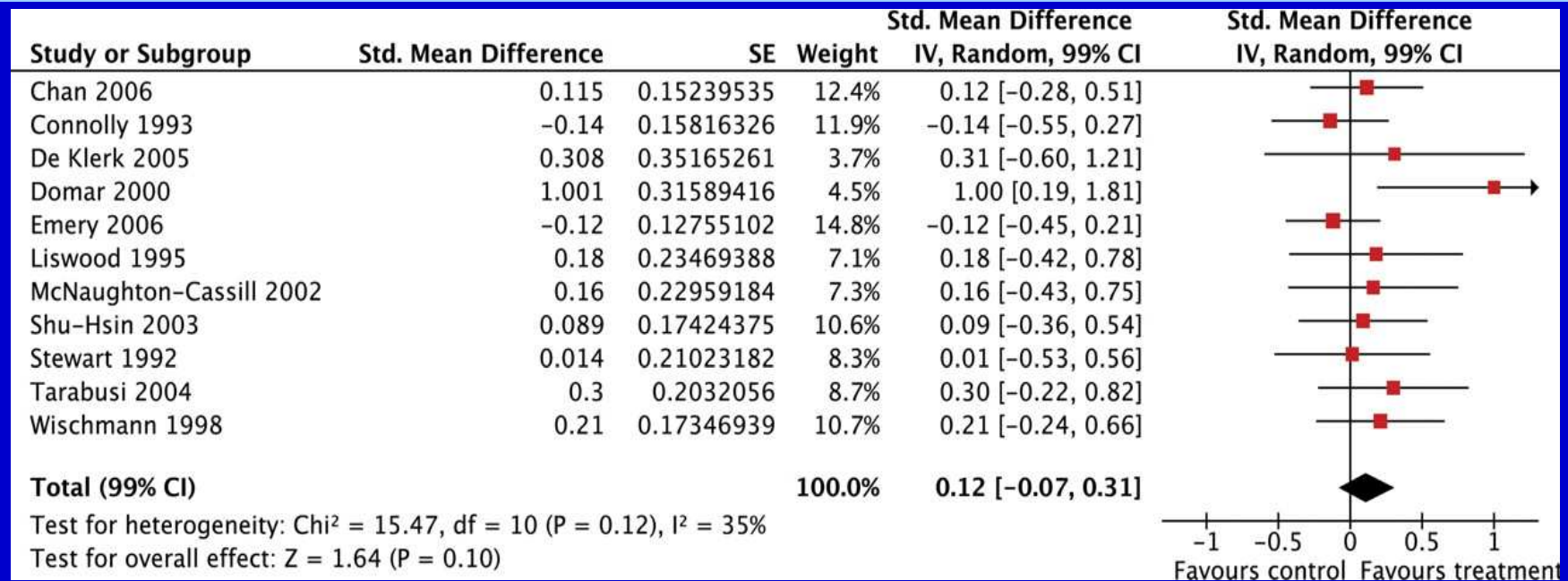
...”high levels of depressive symptoms, anxiety and distress among infertile patients are possibly only short-term reactions.

Psychological interventions which last longer may have a greater effect on infertile patients’ mental health and pregnancy rates”

Hämmerli K et al. Hum. Reprod. Update 2009;15:279-295

Psicoterapia migliora l'ansia

Effect of psychological interventions on state anxiety.



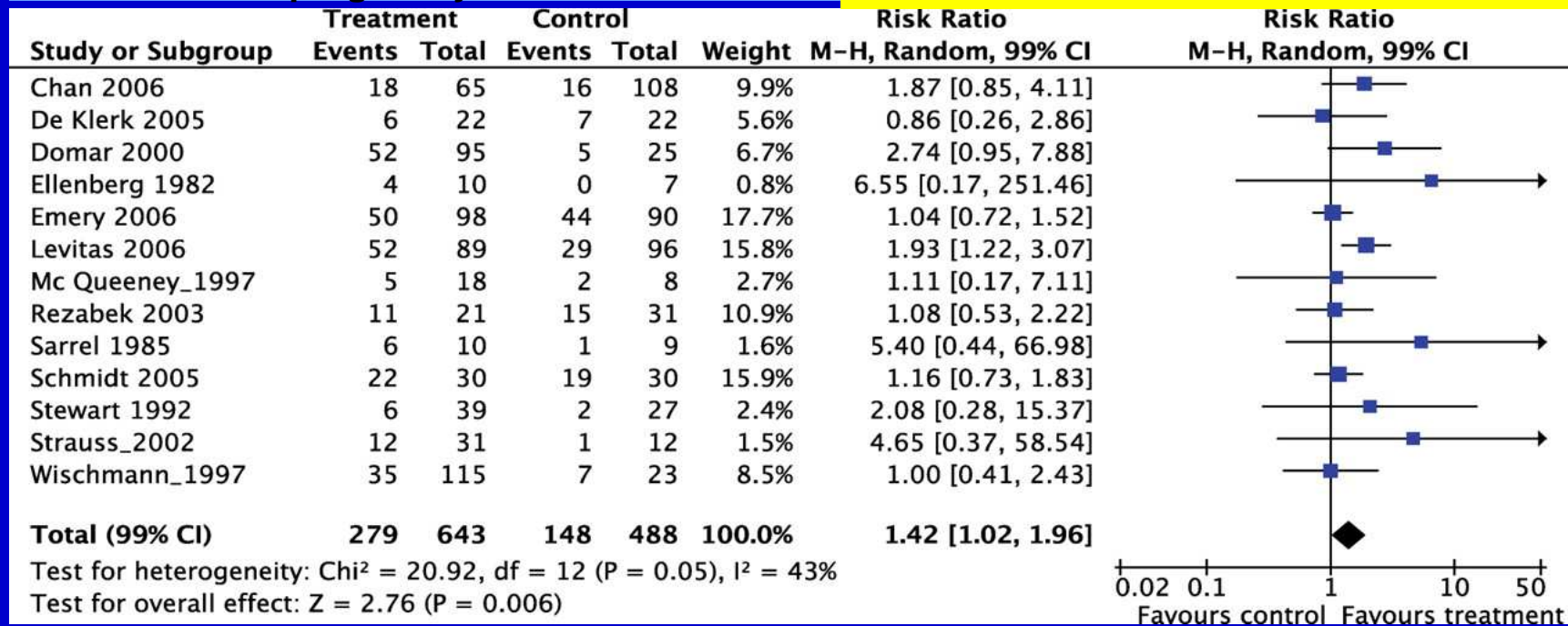
Psychological interventions might be more beneficial for women (trend) because: (i) women must bear the primary burden of medical treatment for infertility (ii) their wish for a child is more important to their life's plan (iii) in comparison with men, they have fewer available alternatives with which to stabilize their self-esteem

Hämmerli K et al. Hum. Reprod. Update 2009;15:279-295

Psicoterapia migliora la pregnancy rate!?

Effect of psychological interventions on pregnancy rate.

Number needed to treat of 5-7



Psychological interventions may positively impact sexual behaviour

Low levels of anxiety and depression are associated with lower dropout rate



Differenze di coping: maschio -femmina

- **RESULTS:** Women used proportionately greater amounts of confrontative coping, accepting responsibility, seeking social support and escape/avoidance when compared with men, whereas men used proportionately greater amounts of distancing, self-controlling and planful problem-solving. For men and women, infertility stress was positively related to escape/avoidance and accepting responsibility and negatively related to seeking social support, planful problem-solving and distancing.
- **CONCLUSIONS:** By analysing relative coping scores, this study identified key gender differences in how men and women cope with infertility. This was particularly true for men's coping processes that had previously remained hidden because of less frequent use of coping strategies when compared with women.

Peterson Gender differences in how men and women who are referred for IVF cope with infertility stress Hum Reprod 2006

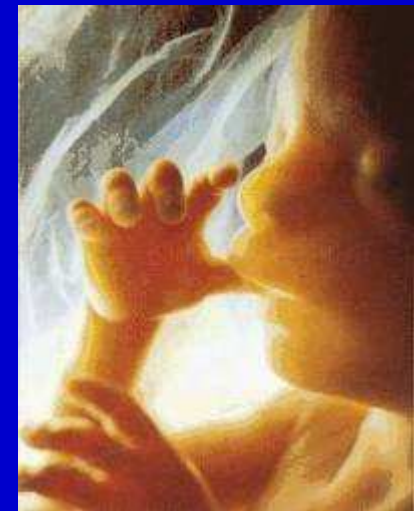
Stili di attaccamento e infertilità



- anxiety about themselves in relationships and blame themselves
- attachment anxiety, is related to negative appraisal and less adaptive ways of coping
- early intervention should be considered

Bayley T et al. Hum. Reprod. 2009;24:2827-2837

Cosa fare per capire ed aiutare le coppie infertili sotto stress?



Ascolto più Attivo: 4 orecchi

Linguaggio Verbale

- **Cosa dice?**

Comunicare
disponibilità
all'ascolto

Lasciar parlare

Limitare preconcetti,
"filtri cognitivi" e
cenni di assenso

25%



Non verbale

- **Cosa dice di se stessa?**

- **Come si relaziona?**

- **Cosa vuole veramente?**

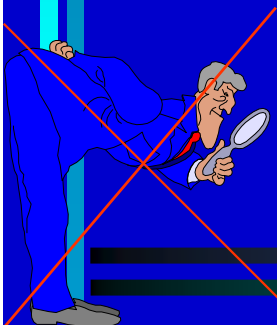
Ascoltare anche i silenzi

Somatizzare = non esprimere
direttamente a parole

75%



**Ascoltare il metamessaggio
ovvero cosa c'è dietro le parole**



Comunicazione più attenta

Linguaggio Verbale

Fare all'inizio domande aperte e poi sempre più specifiche

Chiarificare

Verbalizzare le emozioni

"quali sono le sue paure?"

Non Verbale

Guardare spesso negli occhi

Mimica consona alle emozioni

Postura che dimostra interesse

Distanza adeguata

Gestualità consapevole

Relazione consona



**Essere empatici, informare,
aiutare e rassicurare**