# Depressione Perinatale: Aspetti Neurobiologici e Farmacologici

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# Stress and Disease: Is Being Female a Predisposing Factor?

*J. Neurosc. Oct. 2007*

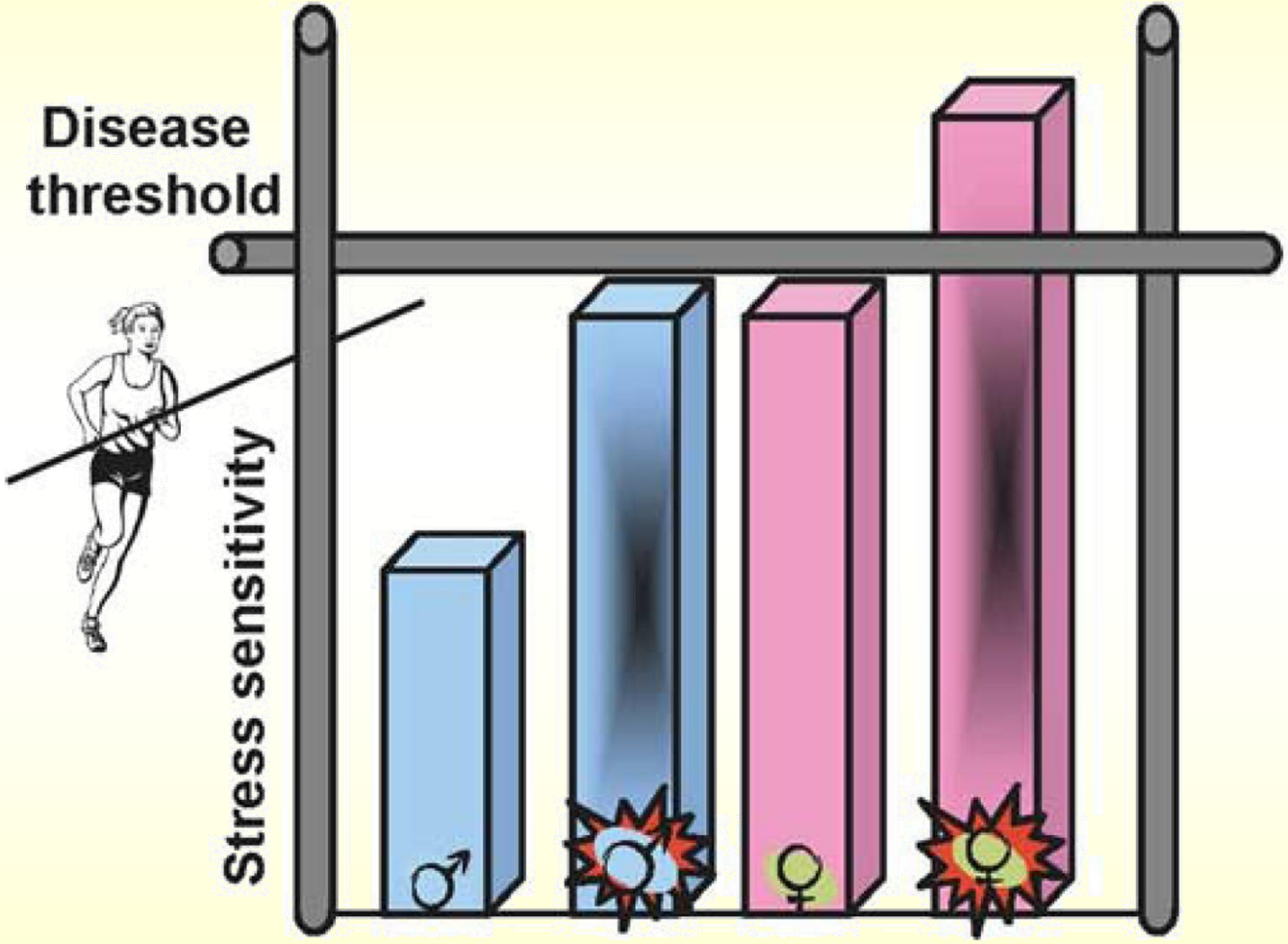
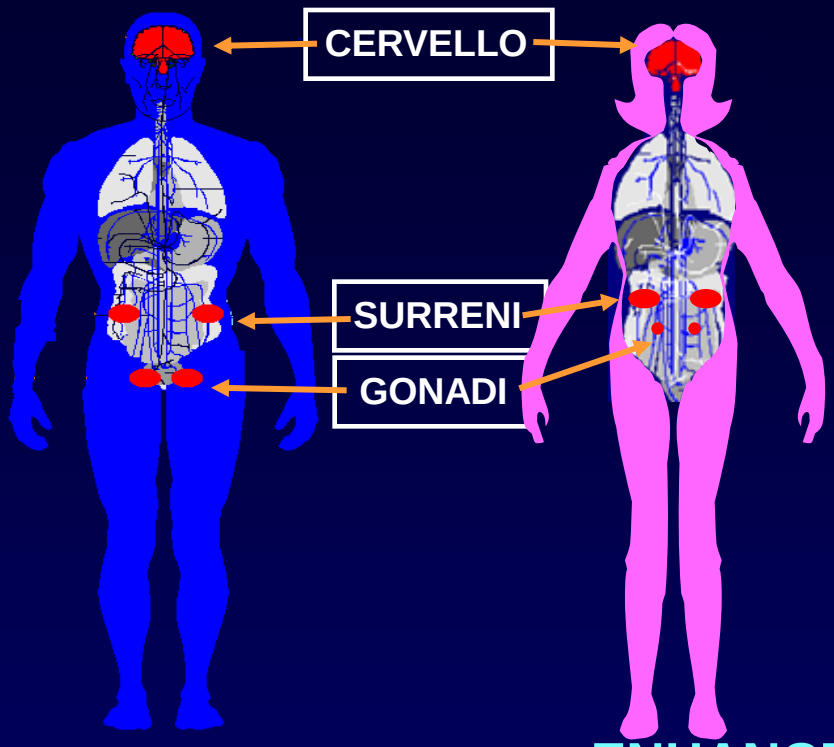



**Diagram depicting putative heightened female predisposition toward stressrelated disease.**

# Steroidi

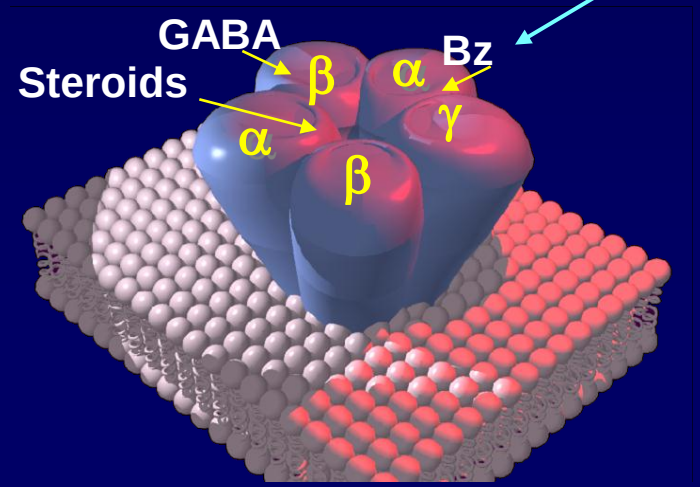



**Trofismo - Plasticità**

**BDNF - Neurogenesi**

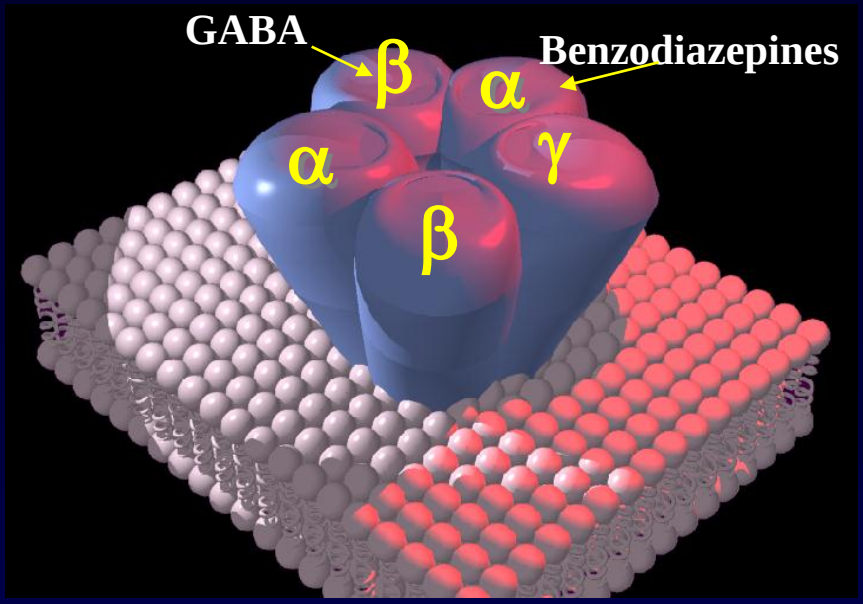
**Progesterone** **Estrogeni**

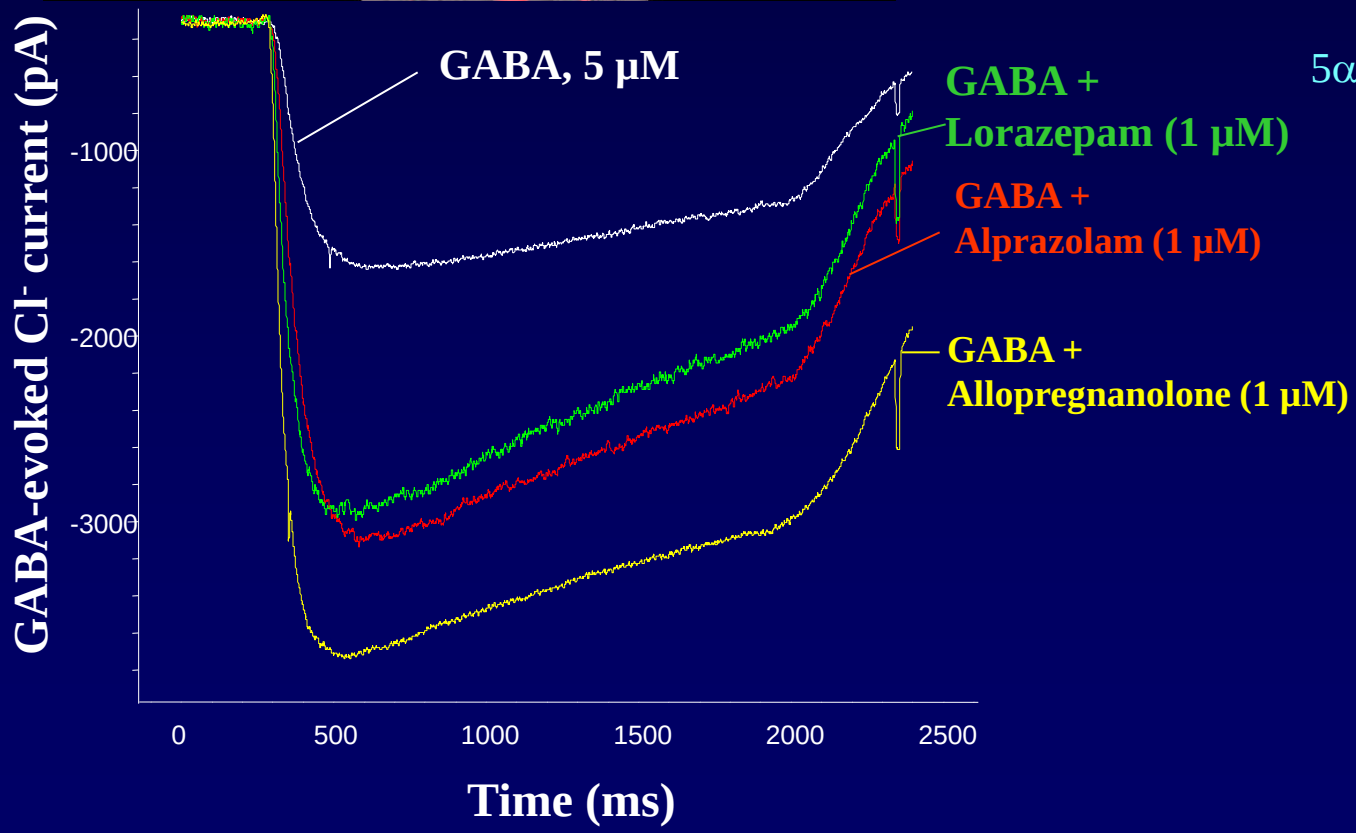
**ENHANCE THE GABAERGIC TRANSMISSION**




**PHARMACOLOGICAL EFFECTS**

**Anxiolytic**
**Anticonvulsant**
**Sedative-hypnotic**
**Anesthetic**




PROGESTERONE

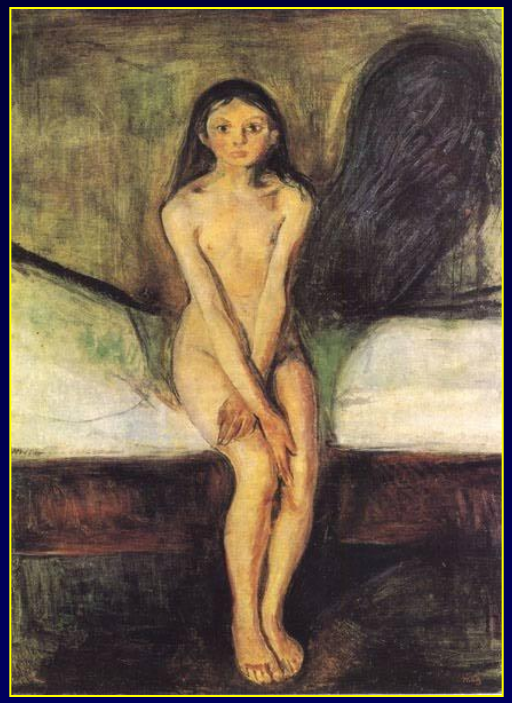
↓

5α-DIHYDROPROGESTERONE

↓

ALLOPREGNANOLONE

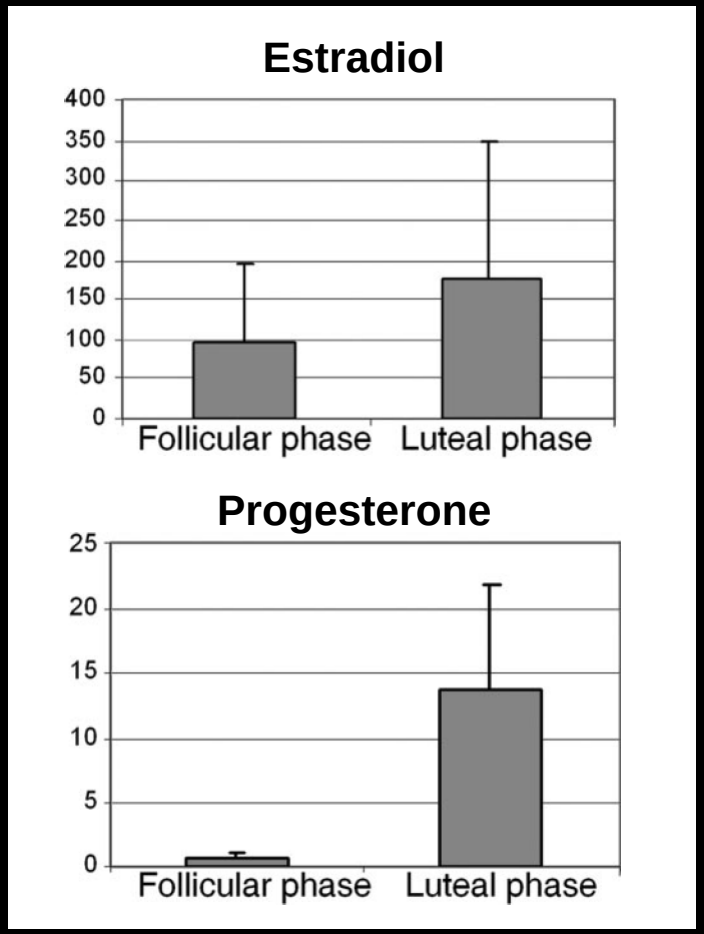
## *Pubertà - Ciclo mestruale – Gravidanza - Menopausa*

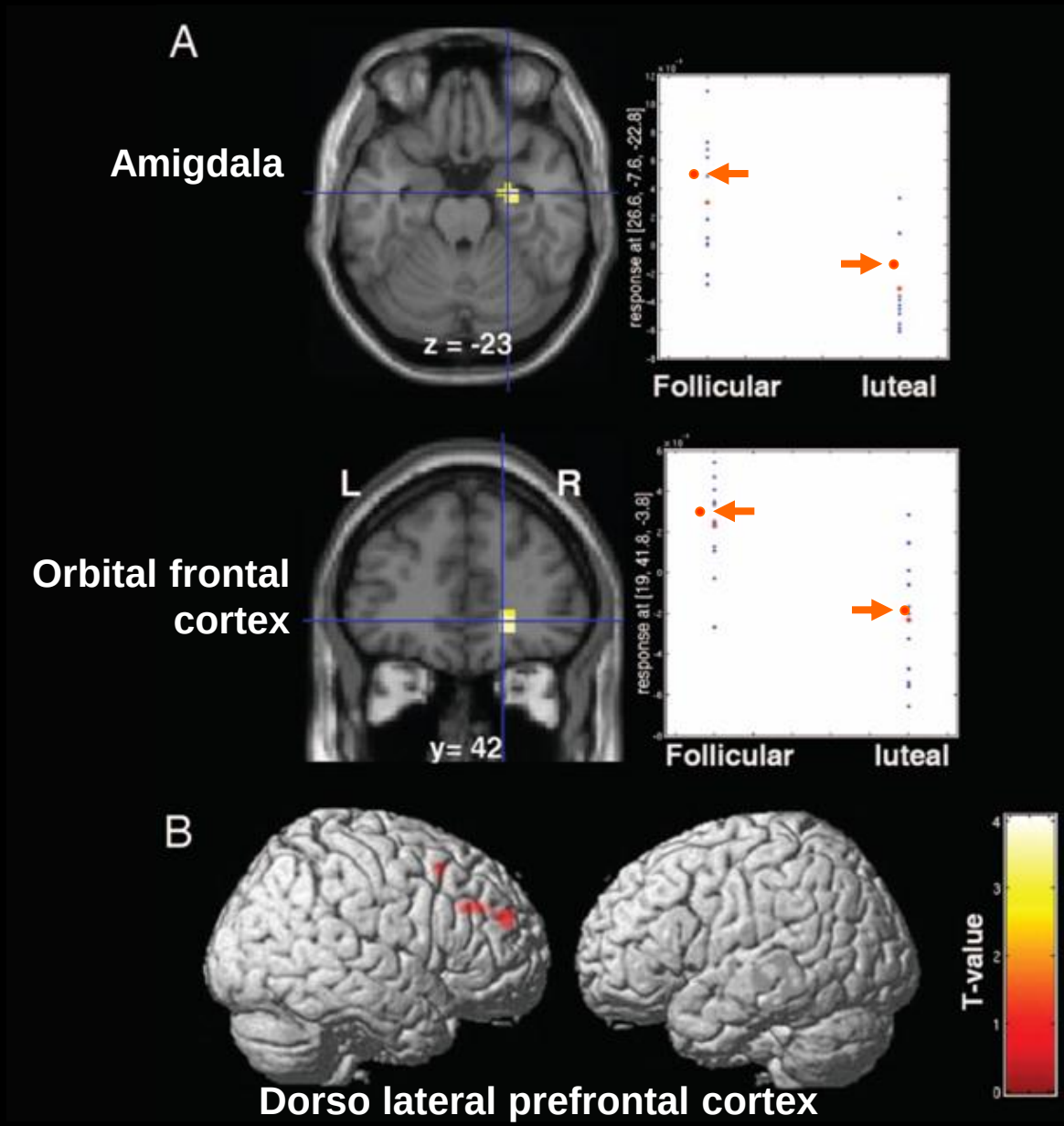


***In queste condizioni fisiologiche vi sono fluttuazioni degli ormoni e modificazioni del trofismo e eccitabilità neuronale***

# Menstrual cycle phase modulates reward-related neural function in women

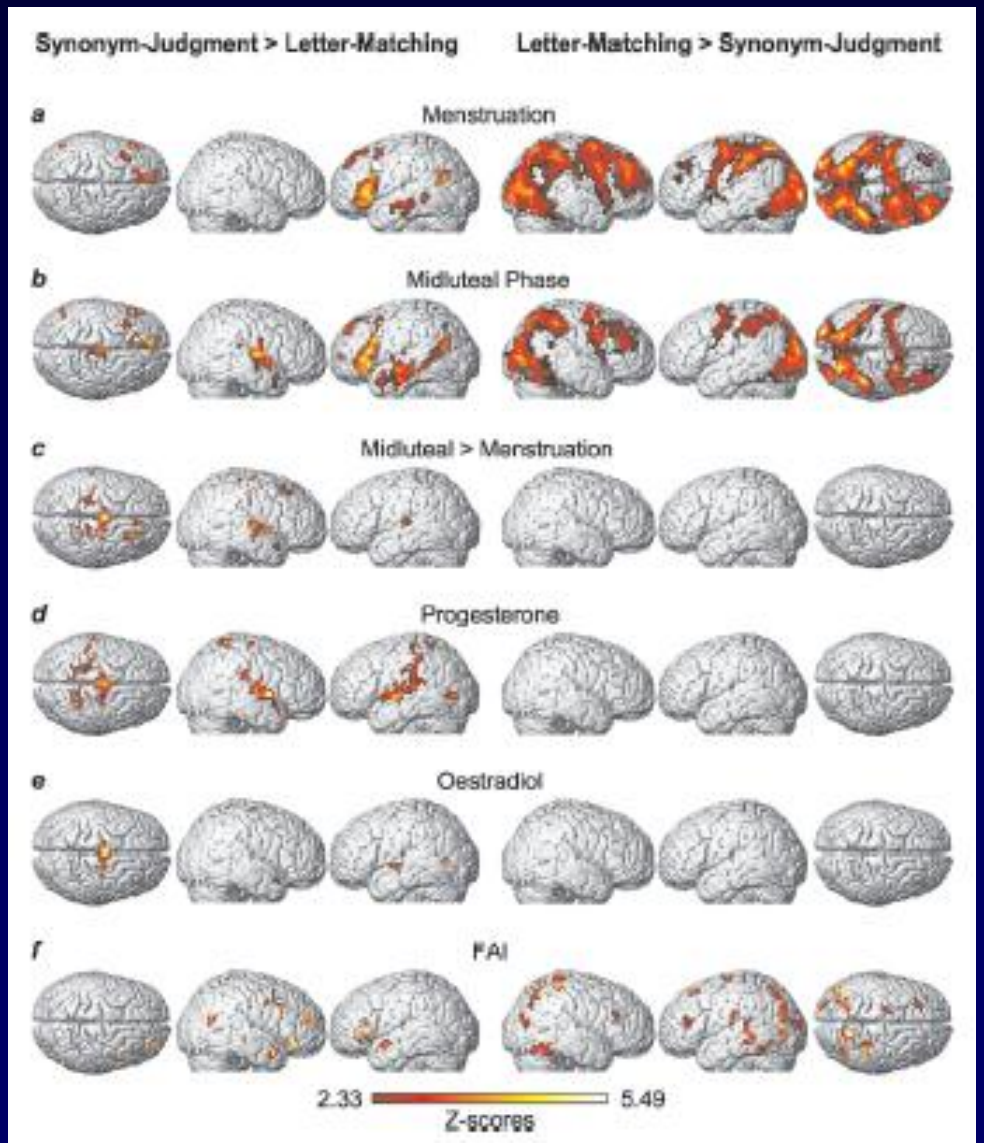
*J.C. Dreher, PNAS, 2007*

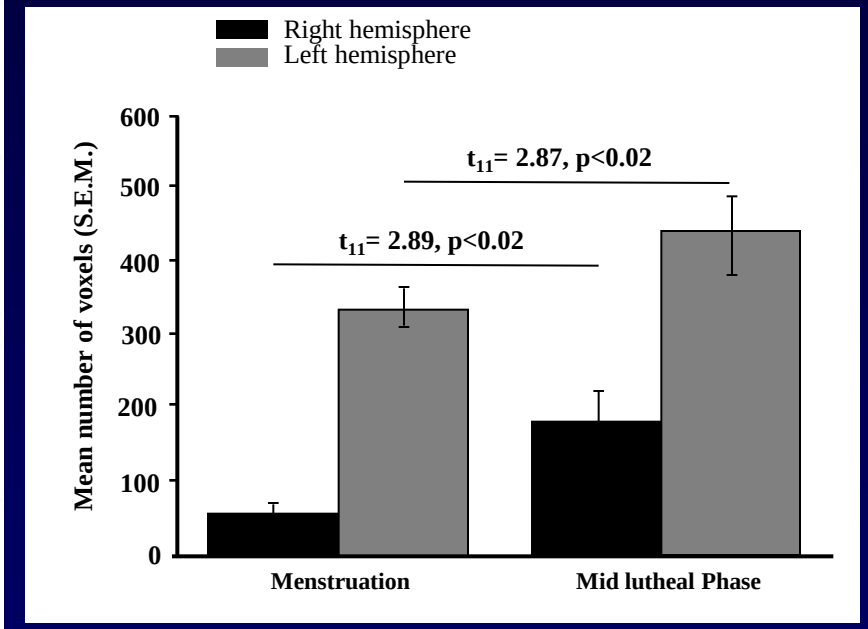


# “Menstrual cylcle-dependent neural plasticity in the adult human brain is hormone, task and region specific”

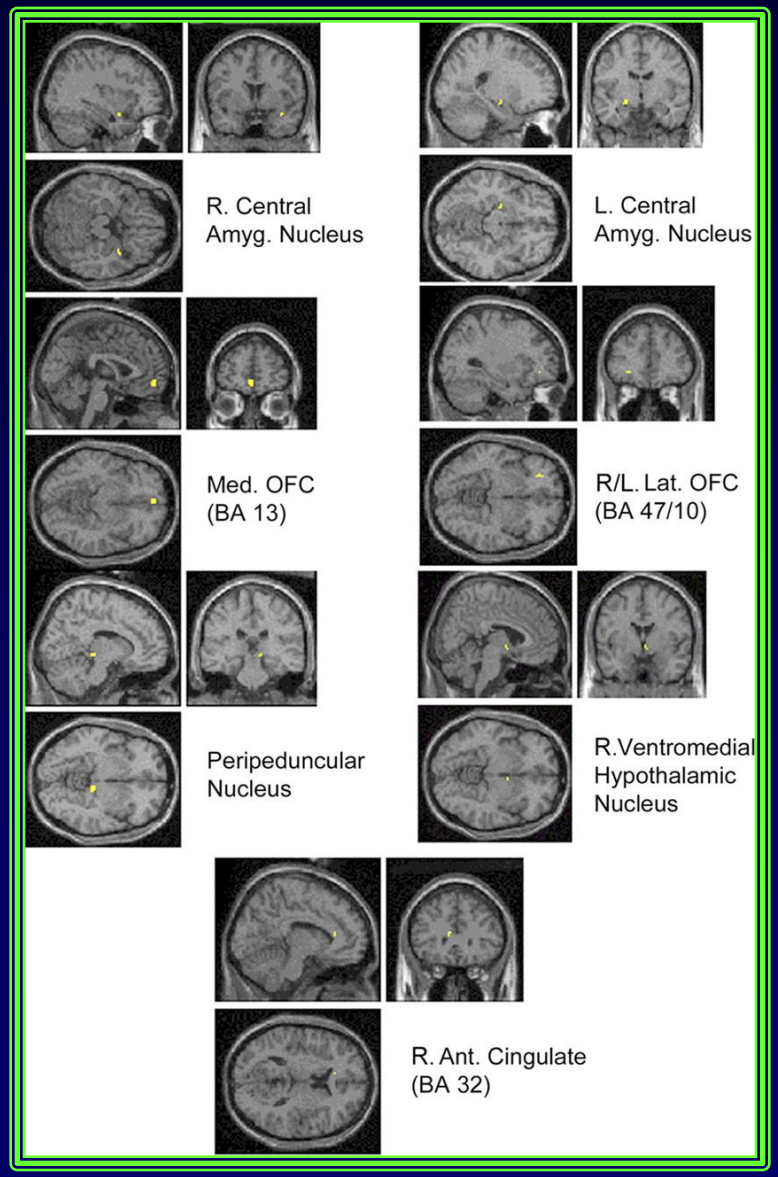
Fernandez G et al., *J Neurosci*, 23(9): 3790-3795 (2003)

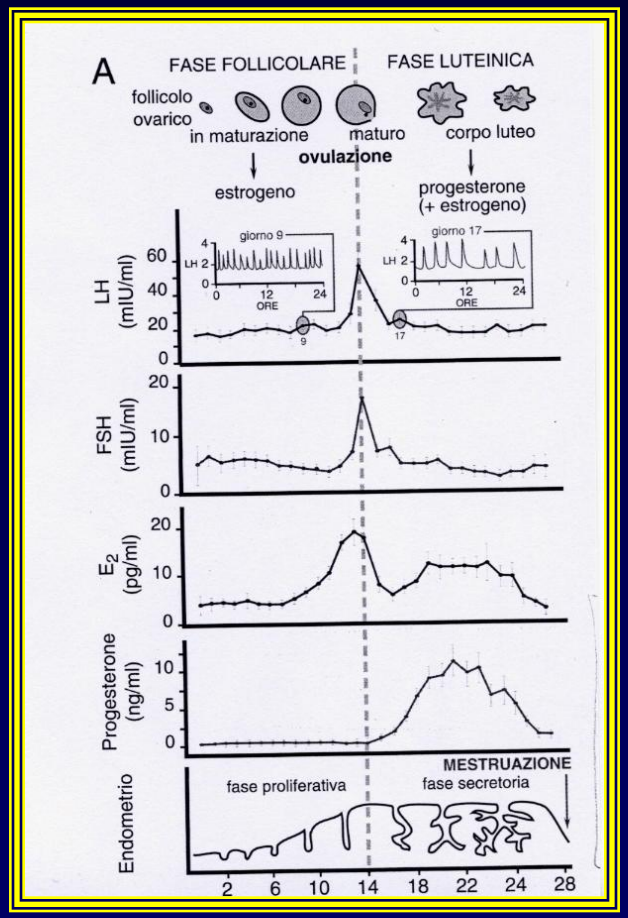


Goldstein J M et al. J. Neurosci. 2005

# Hormonal cycle modulates arousal circuitry in women using functional magnetic resonance imaging

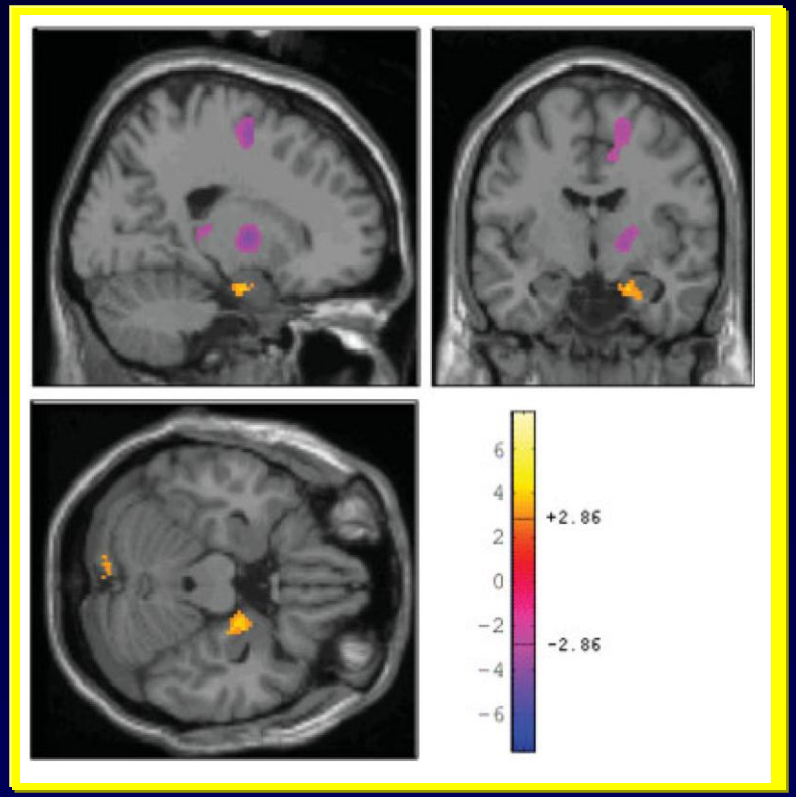


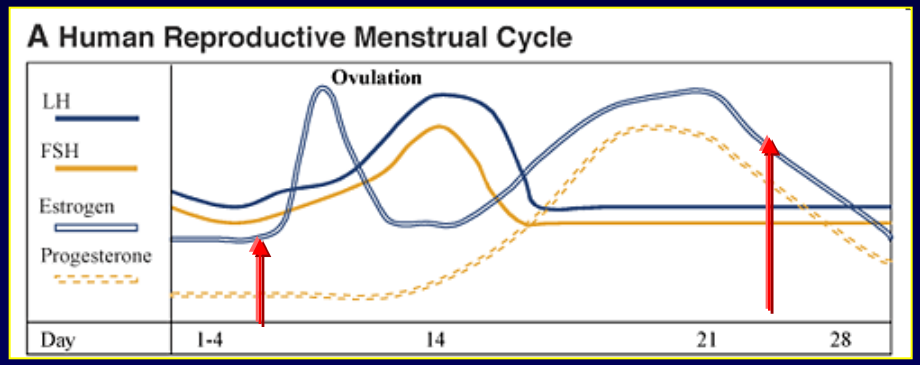




*Hippocampus, 2008*

# Hippocampal structural changes across mestrual cycle

Protopopescu et al.,



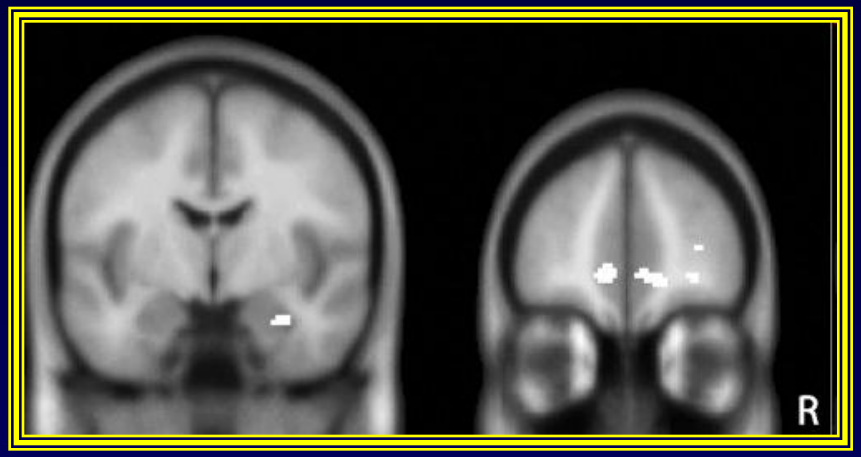

*Regions Showing Differential Gray Matter Volume by VBM in the Postmenstrual Versus Premenstrual Phases of the Cycle*

| | Volume (mm$^3$) | *x* | *y* | *z* | Z-score | *P* value |
|---|---|---|---|---|---|---|
| Postmenstrual > premenstrual | | | | | | |
| L occipital (lingual gyrus, BA18) | 1,464 | −6 | −80 | −16 | 3.62 | 0.0001 |
| R hippocampus/parahippocampus | 560 | 20 | −8 | −22 | 3.33 | 0.0004 |
| *L middle frontal gyrus* | *480* | *−42* | *16* | *44* | *3.42* | *0.0003* |
| Premenstrual > postmenstrual | | | | | | |
| L superior parietal lobule (BA7) | 1,016 | −22 | −54 | 66 | −3.88 | <0.0001 |
| R dorsal basal ganglia (globus pallidus/putamen) | 1,880 | 18 | −4 | 4 | −3.74 | <0.0001 |
| R medial frontal gyrus/anterior cingulate | 1,608 | 16 | −4 | 54 | −3.38 | 0.0004 |
| *R thalamus (pulvinar)* | *392* | *26* | *−30* | *8* | *−3.05* | *0.001* |

Voxel-wise *P*-value <0.005, cluster volume >0.5 cm$^3$; regions with spatial extents slightly below threshold are listed in italics.

Psychoneuroendocrinology, 2010

# Neural mechanisms underlying changes in stress-sensitivity across the menstrual cycle




Neutral

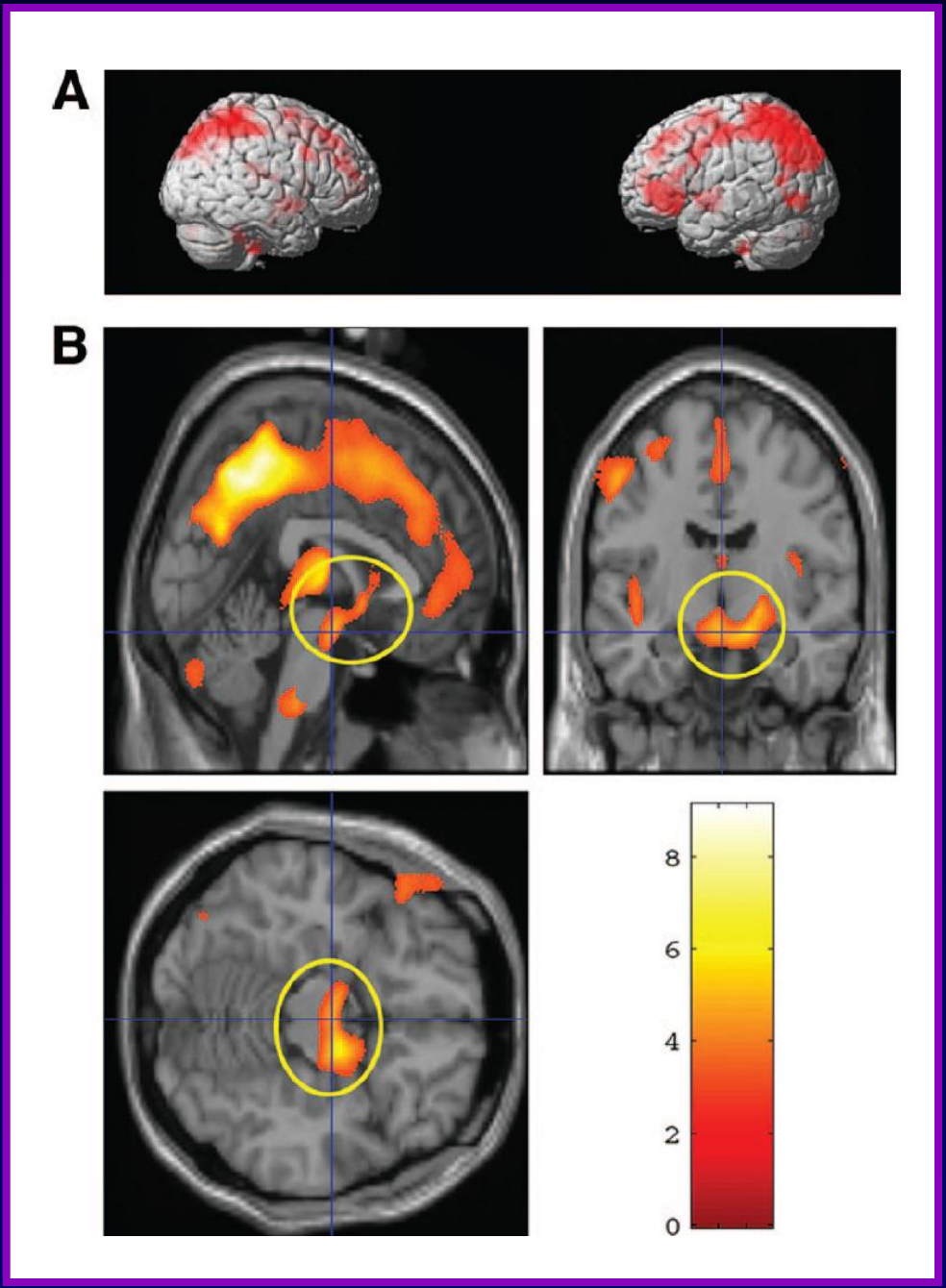
Fear

*The larger the increase in allopregnanolone concentration across the menstrual cycle was, the smaller the amygdala and medial prefrontal cortex responses were after stress induction in the late luteal phase*


OCTOBER 4, 2010
October 4, 2010
TIME
How the first nine months shape the rest of your life
The new science of fetal origins
BY ANNIE MURPHY PAUL
www.time.com

# The Plasticity of Human Maternal Brain: Longitudinal Changes in Brain Anatomy During the Early Postpartum Period

*Behavioral Neuroscience, 2010*



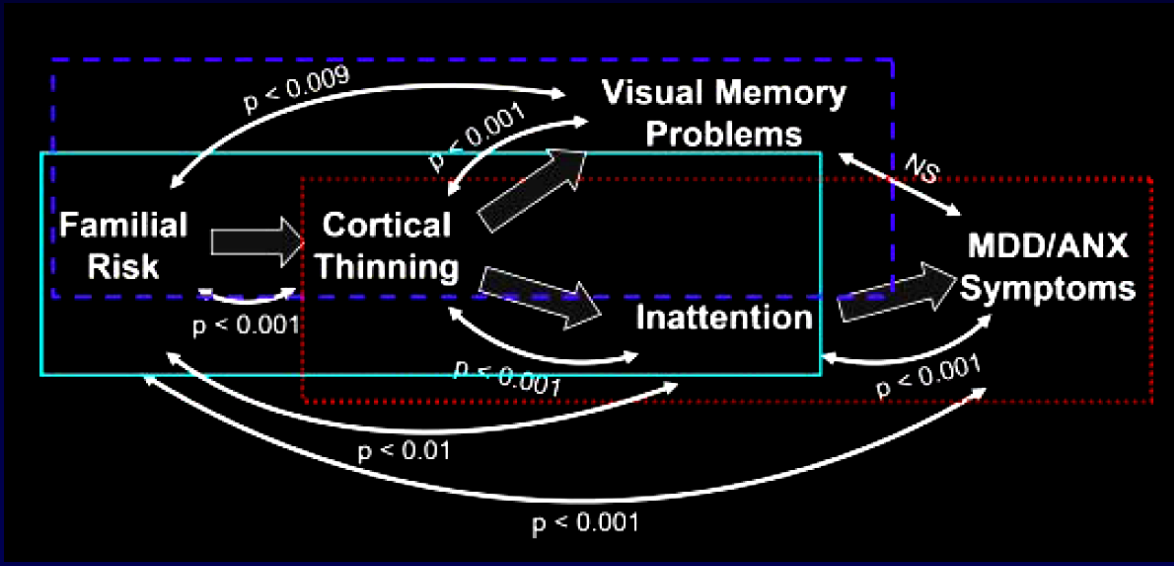
# The importance of childhood

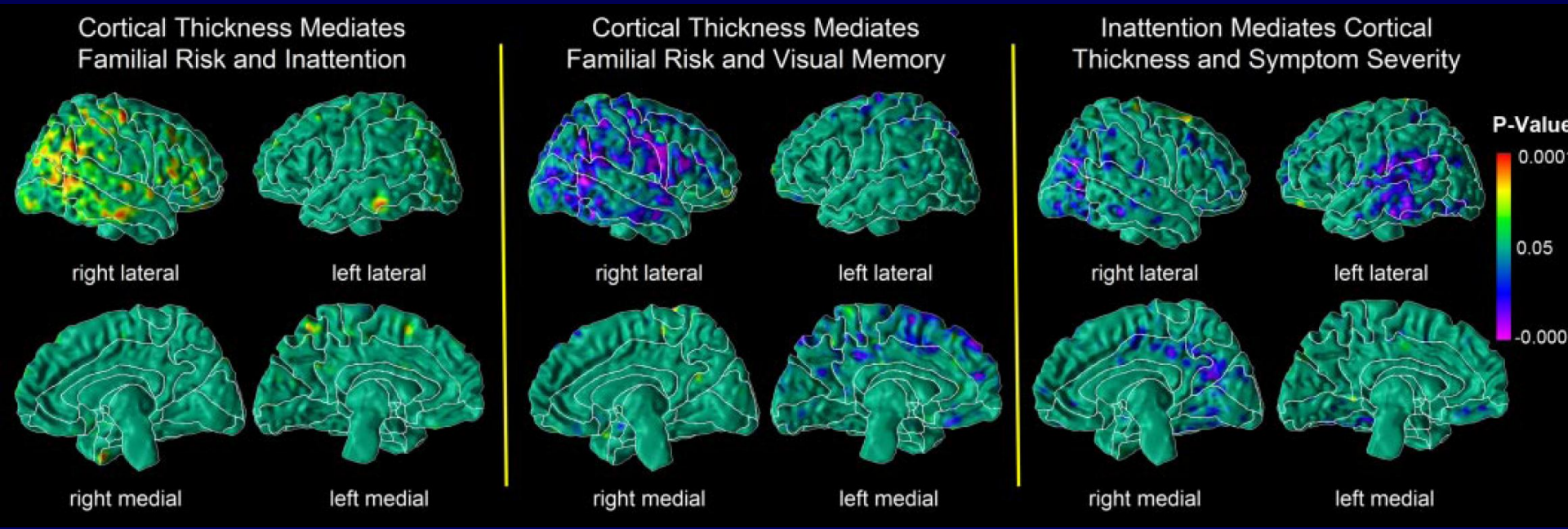
***Nature, October, 2010***

**The early relationship between parent and child is crucial to later development.**

# Cortical thinning in persons at increased familial risk for major depression

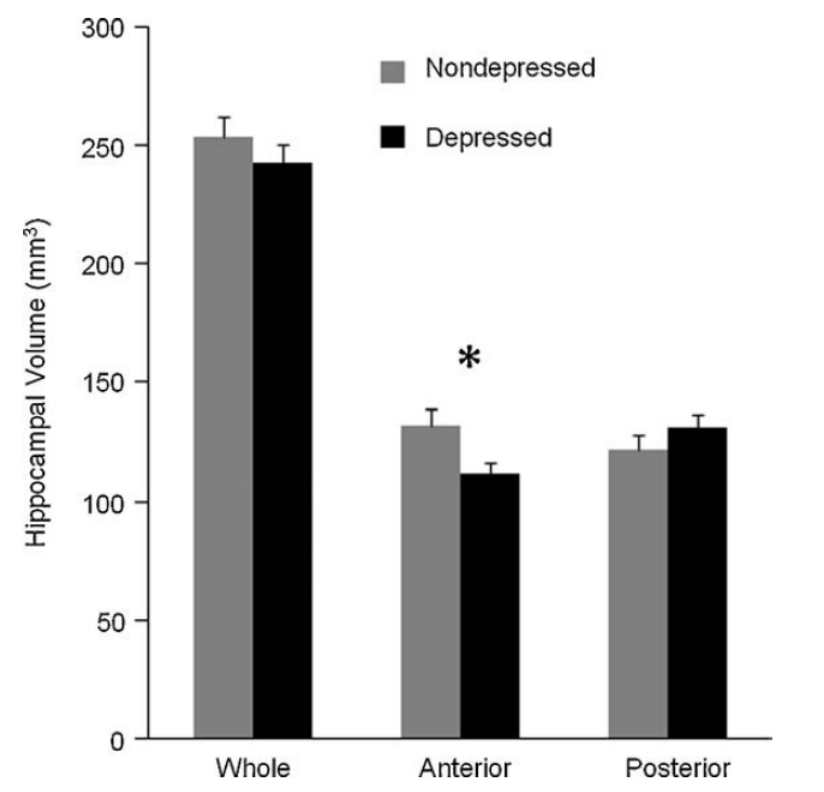
*PNAS, 2009*



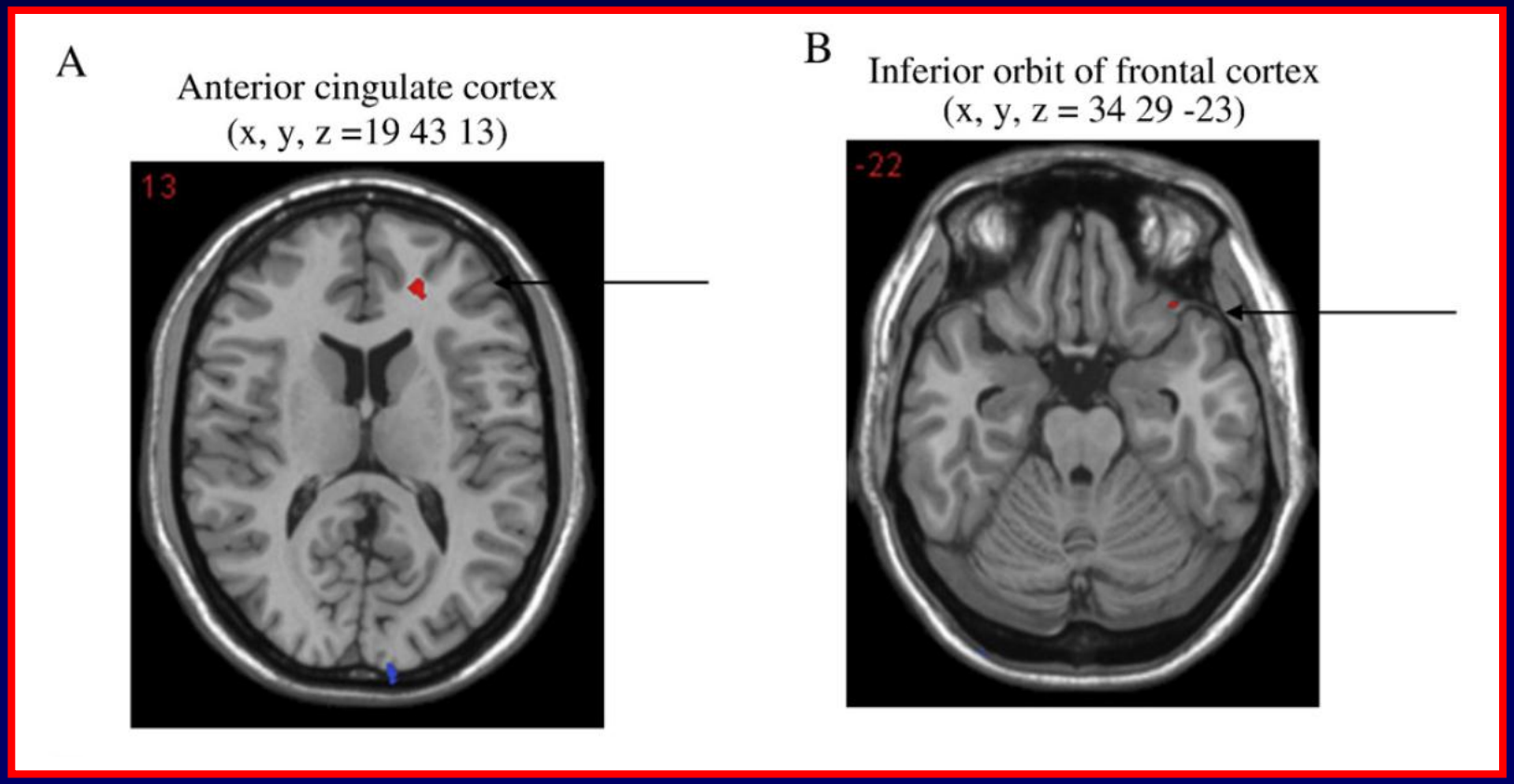
# Anterior hippocampal volume is reduced in behaviorally depressed female cynomolgus macaques

*Psychoneuroendocrinology, 2009*

# Gray matter reduction associated with emotion regulation in female outpatients with major depressive disorder: A voxel-based morphometry study

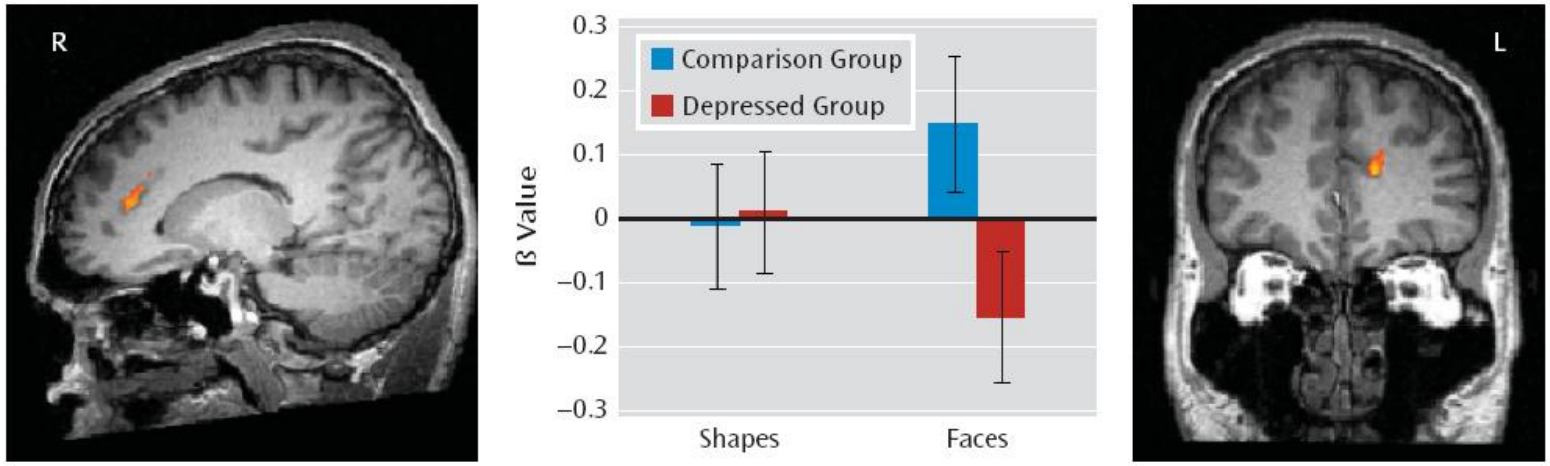
*Prog Neuropsychopharmacol Biol Psychiatry., 2009*



# Abnormally Reduced Dorsomedial Prefrontal Cortical Activity and Effective Connectivity With Amygdala in Response to Negative Emotional Faces in Postpartum Depression

*Am. J. Psychiatry, 2010*

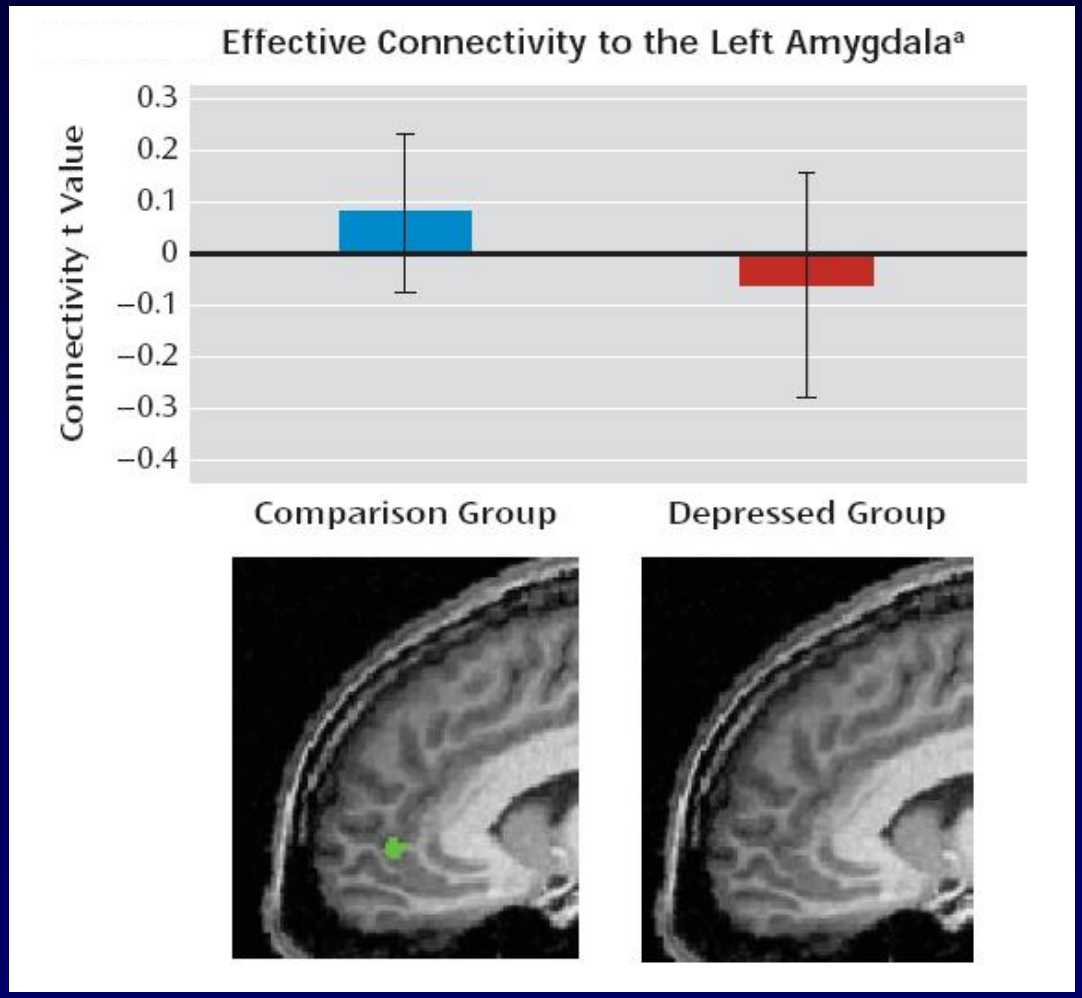
Group-by-Condition Interaction in the Dorsomedial Prefrontal Cortex Among Depressed and Healthy Mothers[a]




[a] Error bars represent the standard deviation of the mean ($F \geq 9.28$, $df = 1, 28$, $p < 0.05$).

# Abnormally Reduced Dorsomedial Prefrontal Cortical Activity and Effective Connectivity With Amygdala in Response to Negative Emotional Faces in Postpartum Depression

*Am. J. Psychiatry, 2010*



# Prenatal exposure to maternal depression, neonatal methylation of human glucocorticoid receptor gene (NR3C1) and infant cortisol stress responses

*Epigenetics, 2008*

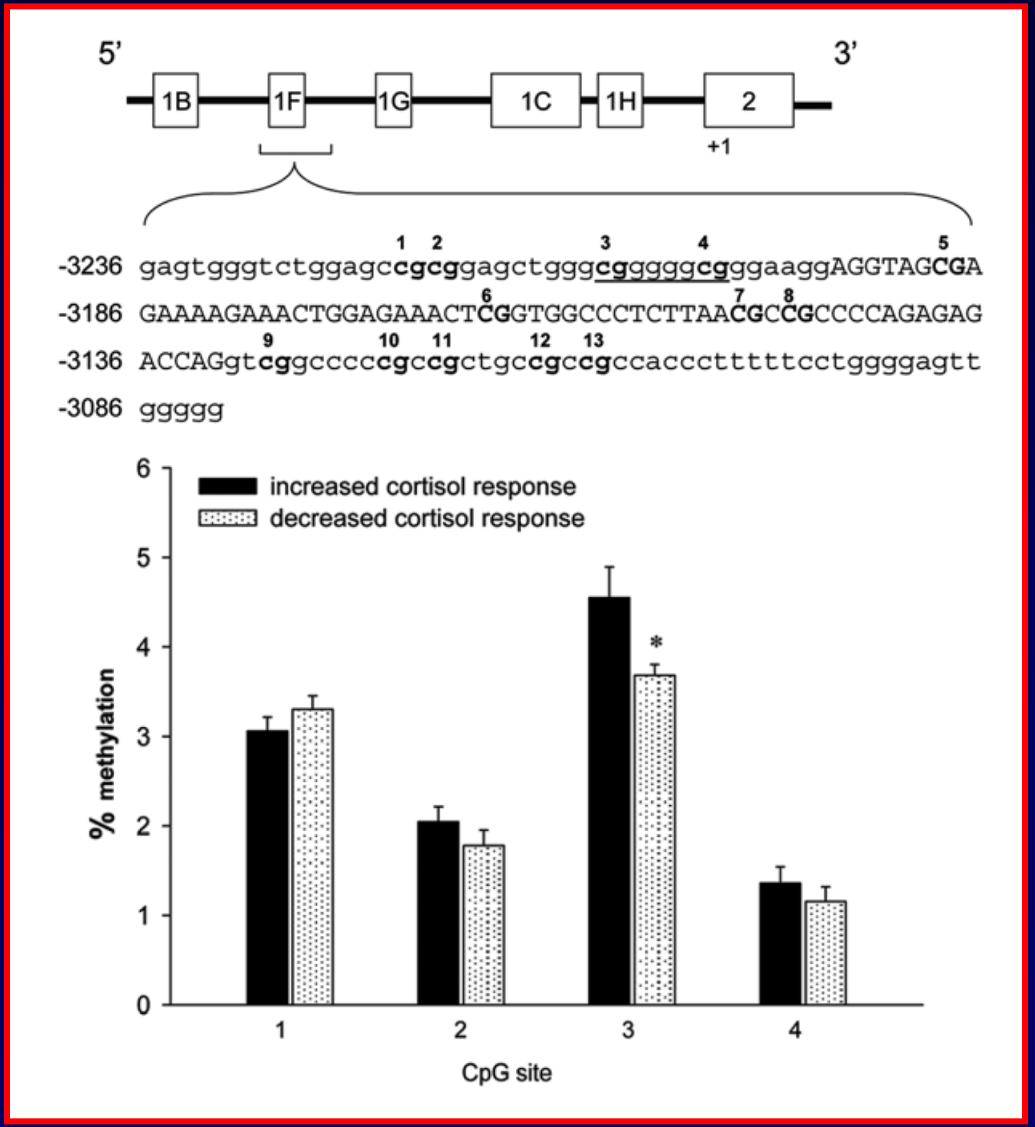


**Table 1.** Impact of Psychiatric Illness on Pregnancy Outcome

| Illness | Teratogenic Effects | Impact on Outcome: Obstetric | Impact on Outcome: Neonatal |
|---|---|---|---|
| Anxiety disorders | N/A | Increased incidence of forceps deliveries, prolonged labor, precipitate labor, fetal distress, preterm delivery, and spontaneous abortion | Decreased developmental scores and inadaptability; slowed mental development at 2 years of age |
| Major depression | N/A | Increased incidence of low birth weight, decreased fetal growth, and postnatal complications | Increased newborn cortisol and catecholamine levels, infant crying, rates of admission to neonatal intensive care units |
| Bipolar disorder | N/A | See major depression | See major depression |
| Schizophrenia | Congenital malformations, especially of cardiovascular system | Increased incidence of preterm delivery, low birth weight, small for gestational age, placental abnormalities, and antenatal hemorrhage | Increased rates of postnatal death |

***American College Obst. Gynecol., 2008***

# Clinical Considerations and Recommendations

- *What is the evidence regarding the safety and efficacy of treatment for depression during pregnancy?*

Most data related to antidepressants in pregnancy are derived from the use of selective serotonin reuptake inhibitors (SSRIs) (fluoxetine, sertraline, citalopram, and paroxetine). Overall, there is limited evidence of teratogenic effects from the use of antidepressants in pregnancy

***American College Obst. Gynecol., 2008***

Hindawi Publishing Corporation
Obstetrics and Gynecology International
Volume 2012, Article ID 698947, 12 pages

In summary, most studies on the use of SSRIs during pregnancy support that they are not major human teratogens. A small increased risk for cardiovascular anomalies, especially wit[illegible] There appears t[illegible] may be [illegible] na[illegible] ed [illegible] sient [illegible] for adverse long-t[illegible] of prenatal SSRI exposure. Discontinuation of treatment may pose risks, for example, higher frequency of relapse and increased risk of preterm delivery. Hence, the general benefit of treatment seems to outweigh the potential small risk of untoward effects on the embryo, fetus, or neonate.

"…SSRIs…are not major human teratogens. "

# Ippocampo
## CA3 e Giro Dentato

**Stress**

↑ Glucocorticoidi

↓ BDNF

**Diminuita neurogenesi**
**Atrofia/morte neuronale**

**Antidepressivi**

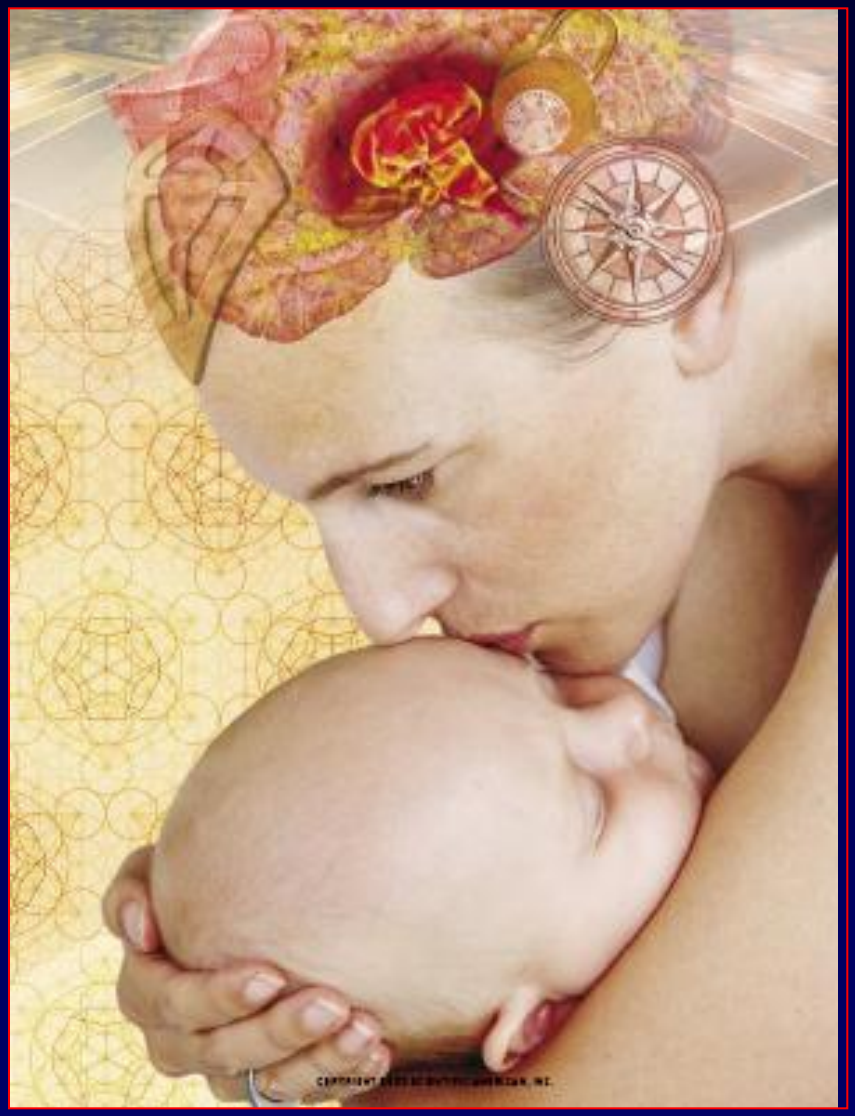
↑ NA/5HT

↑ BDNF

↓ Glucocorticoidi

**Aumentata neurogenesi**
**Aumentata sopravvivenza e crescita**

***Duman et al., 1999***



# The neuroplastic maternal brain

Kinsley , Hormones & Behavior 2008