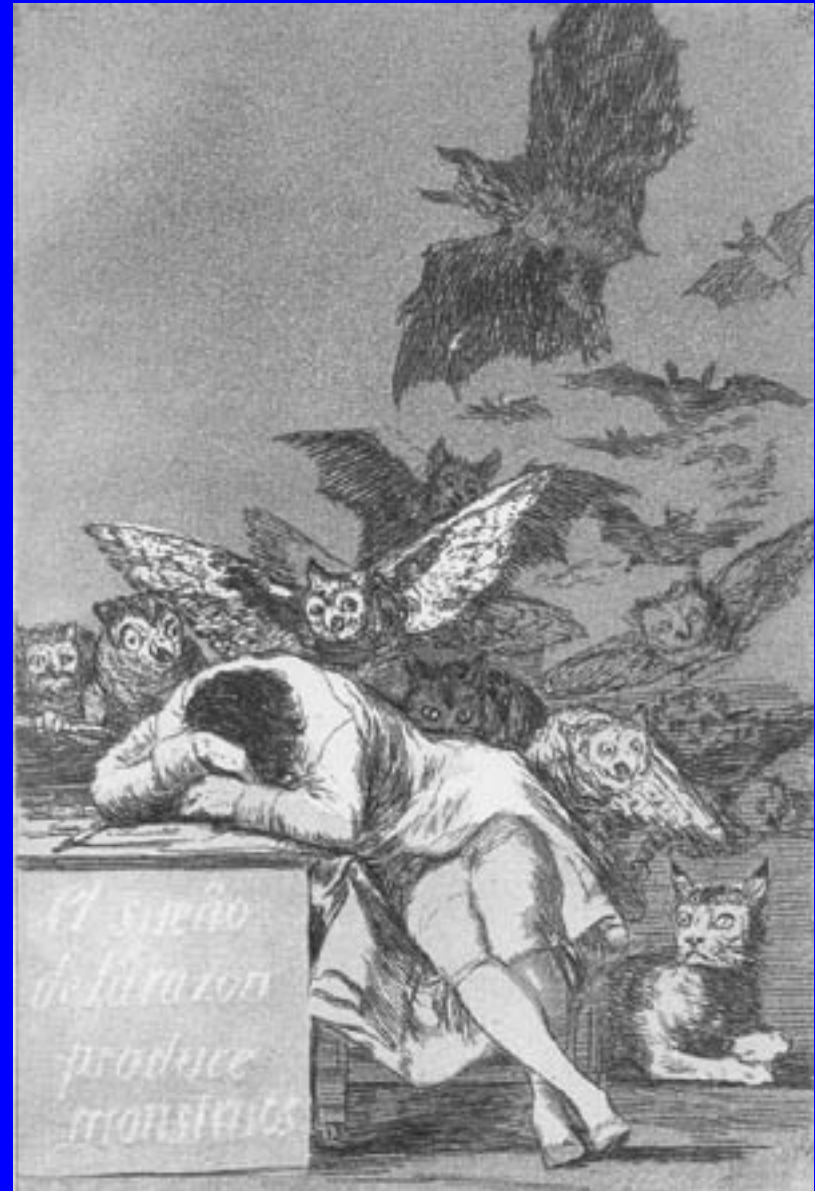


**Francisco de Goya**

***The Sleep of Reason  
Produces Monsters***

***El sueño de la  
razon produce  
monstruos, 1799***

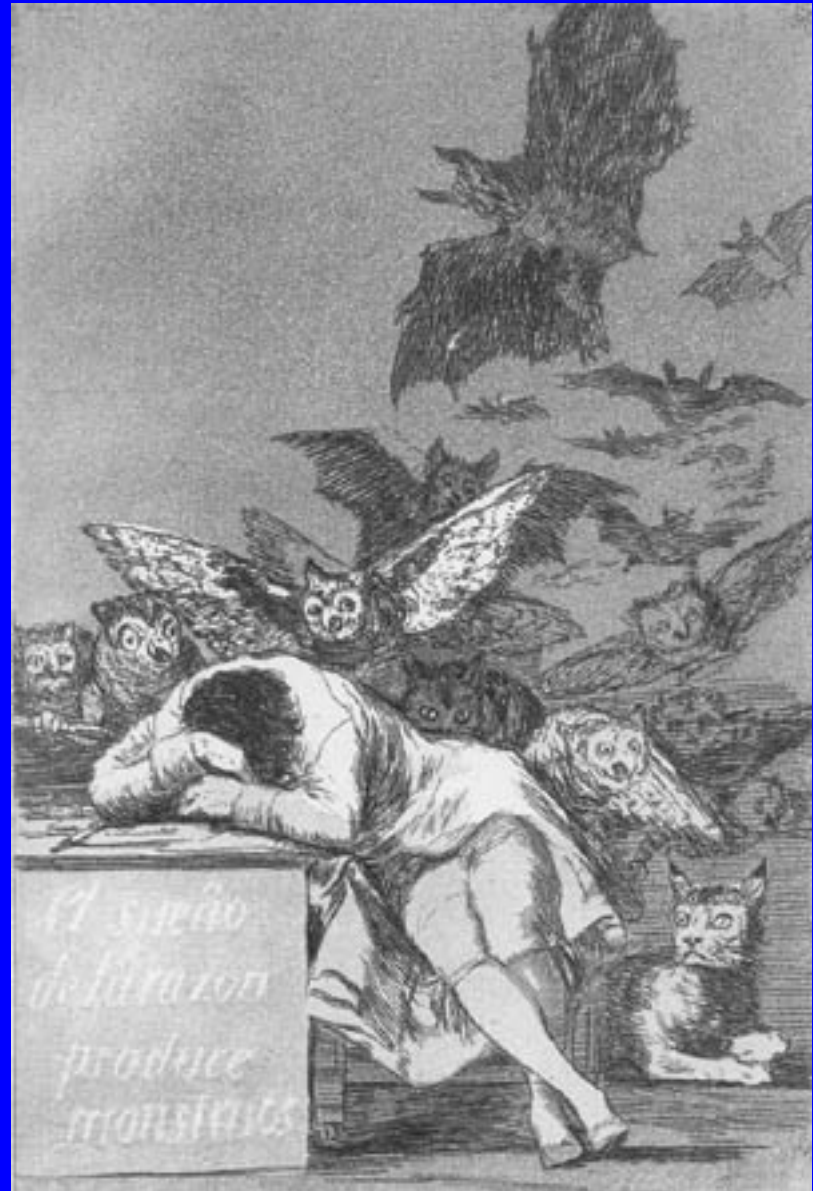


**Francisco de Goya**

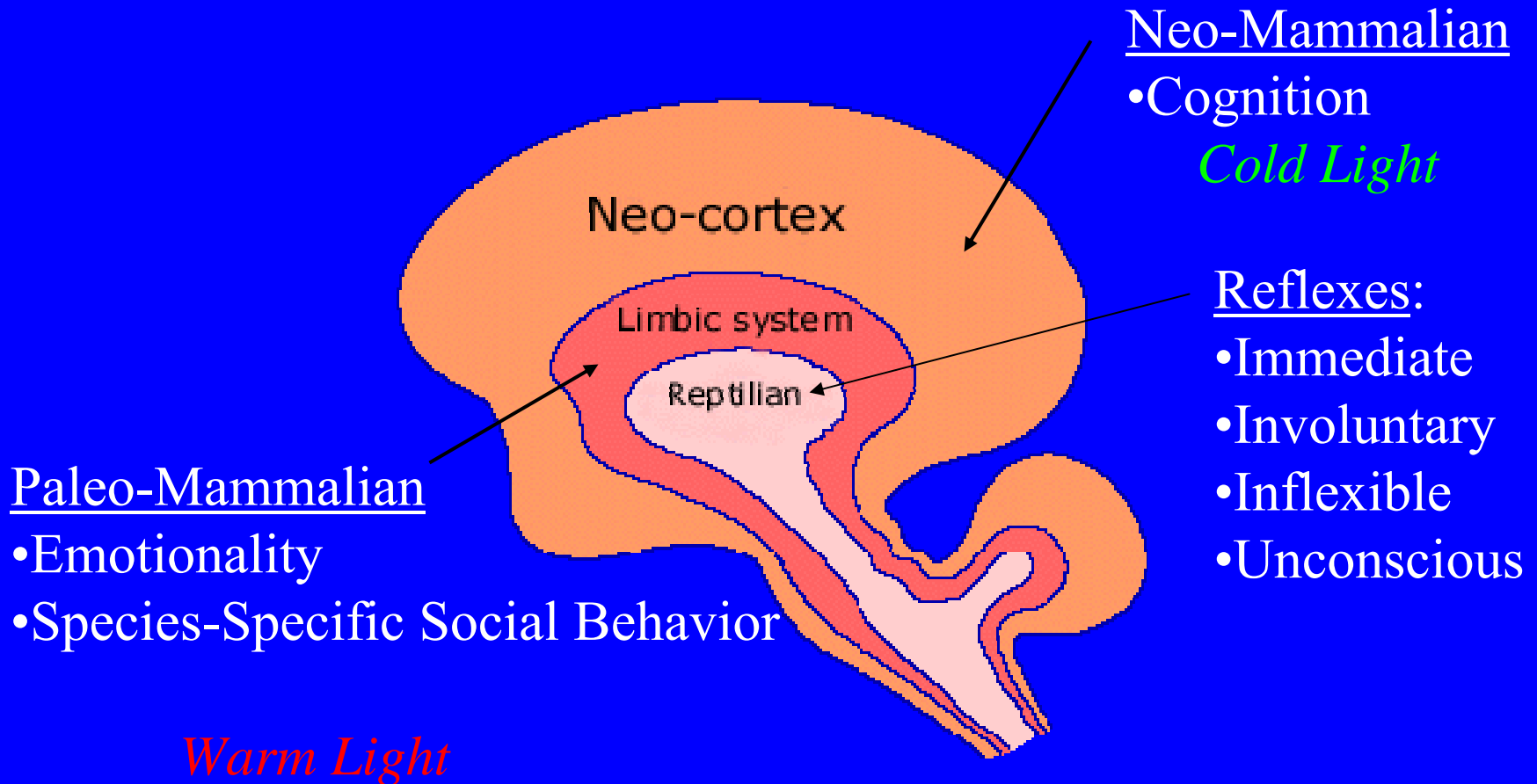
***The Sleep of Reason  
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monstruos, 1799***

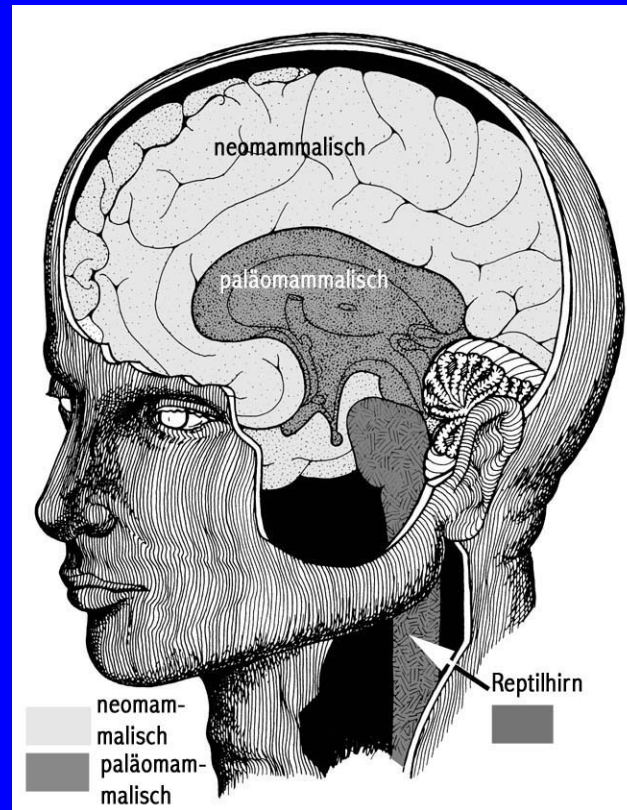
- Evolution & Organization of the Human Brain
- Biological underpinnings of PTSD (?)



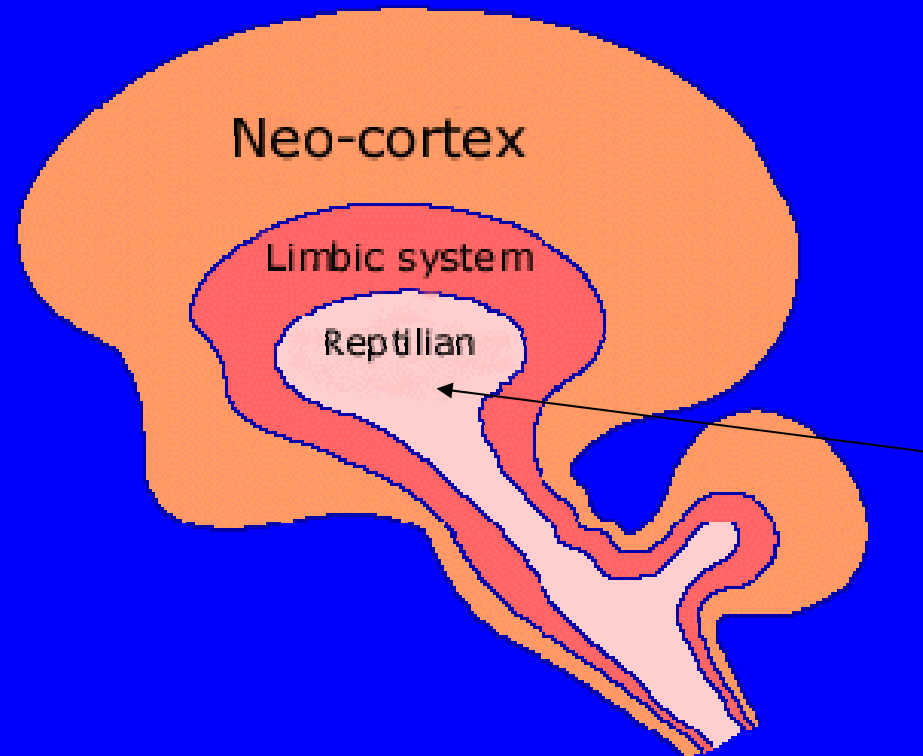
# Paul MacLean: The Triune Brain



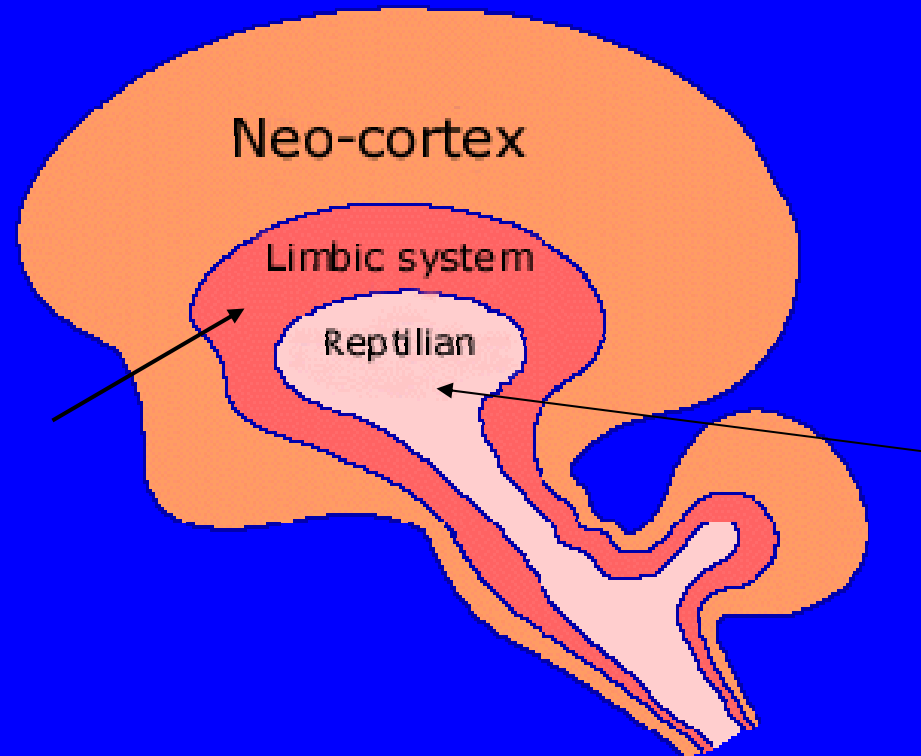
# Paul MacLean: The Triune Brain



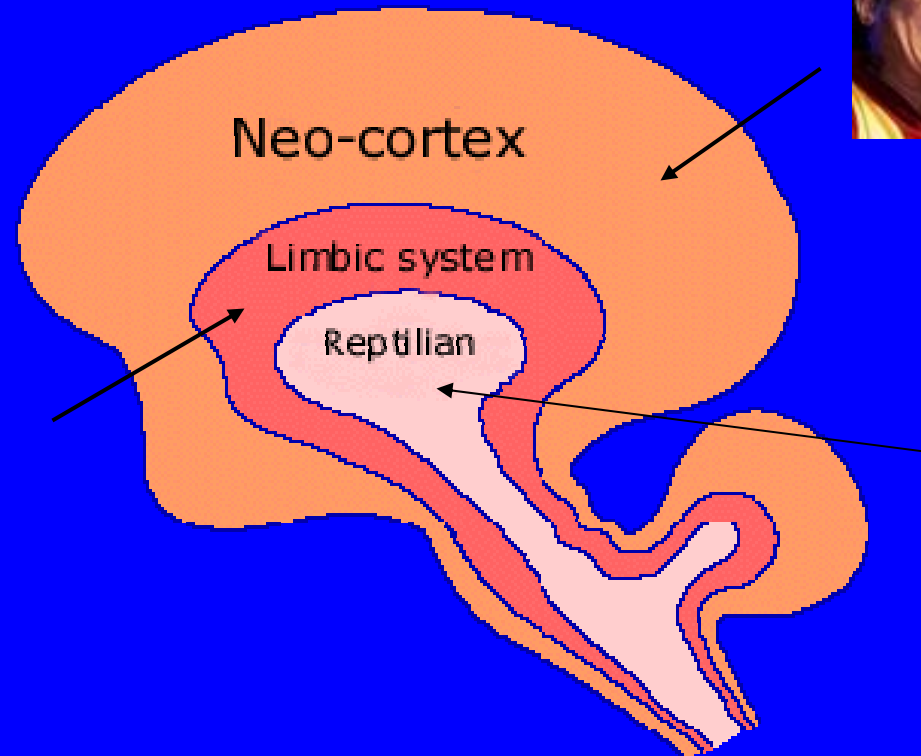
# Paul MacLean: The Triune Brain



# Paul MacLean: The Triune Brain

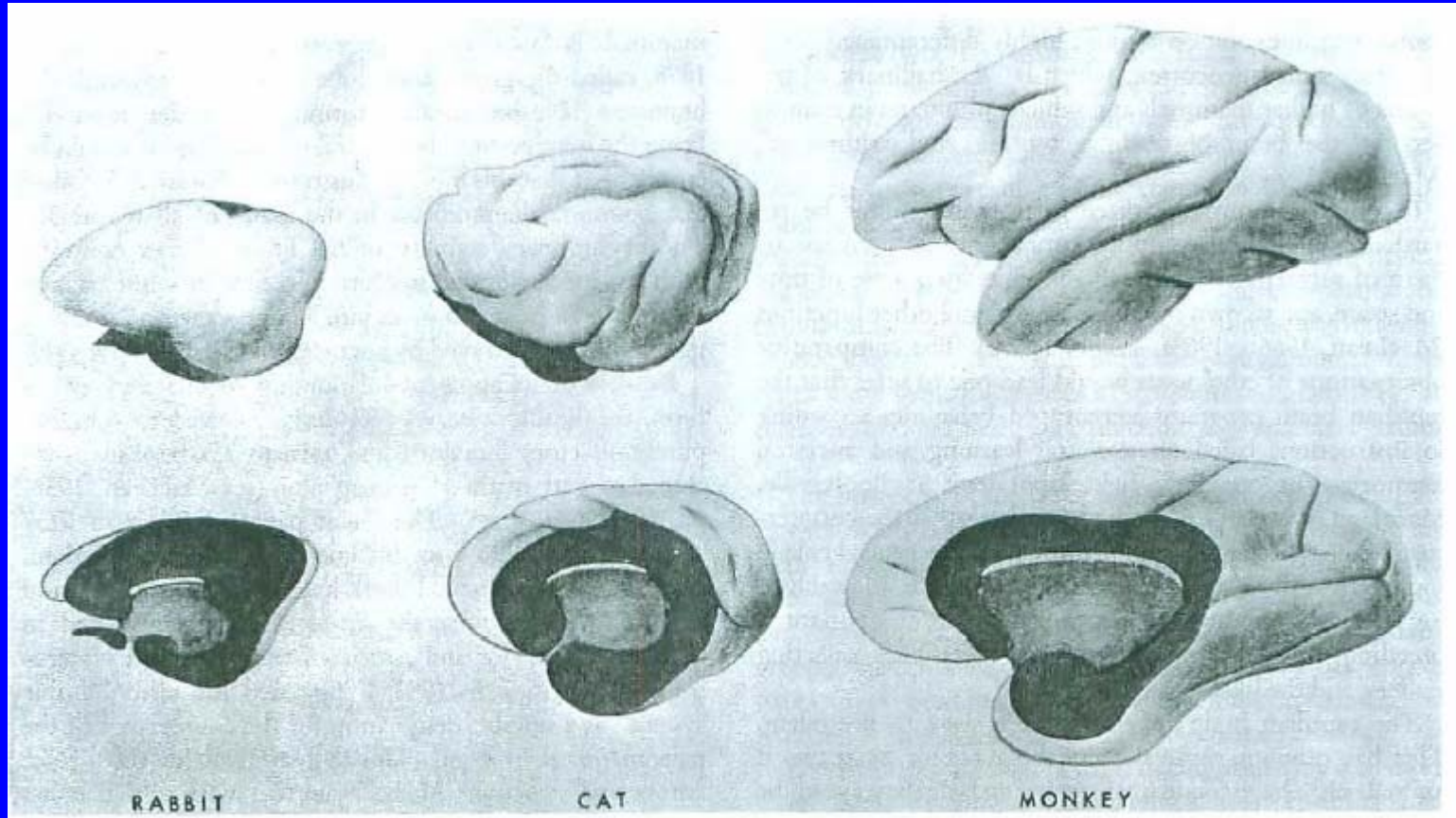


# Paul MacLean: The Triune Brain



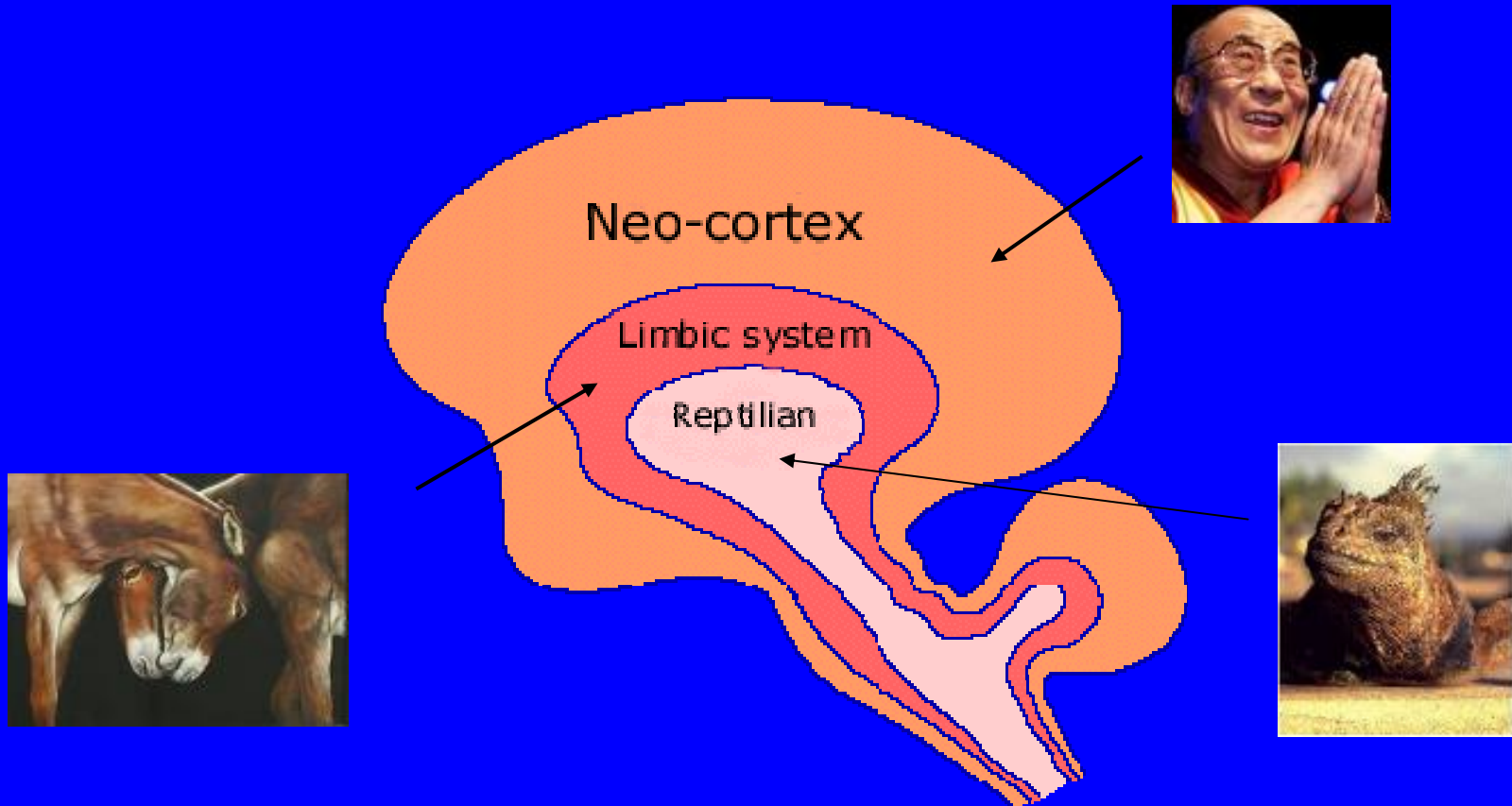


# Man: More Lama Less Mule

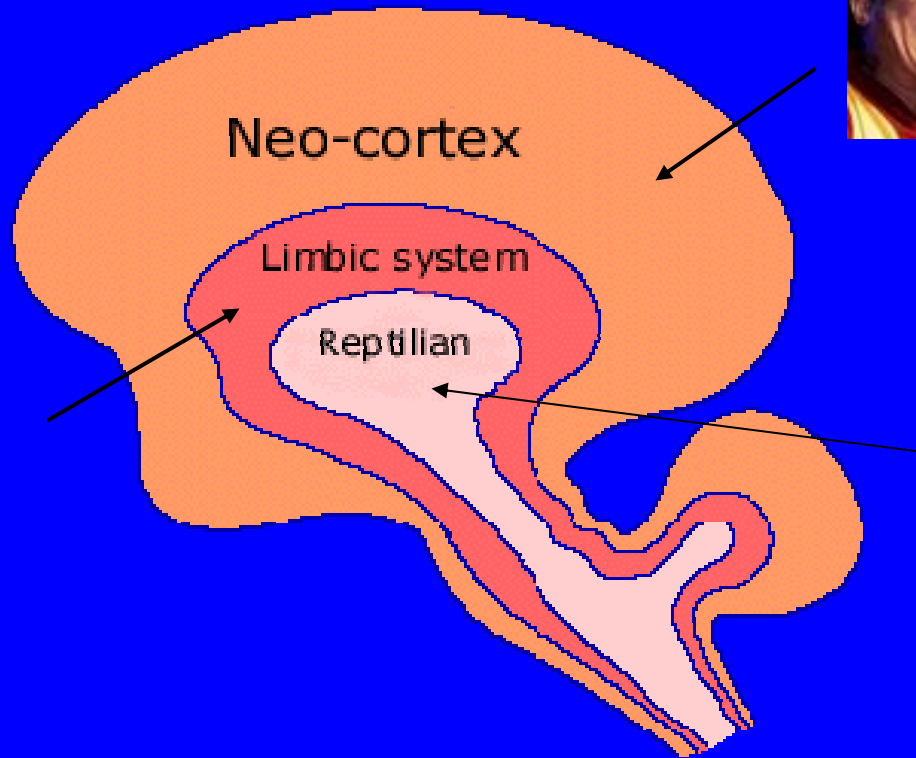




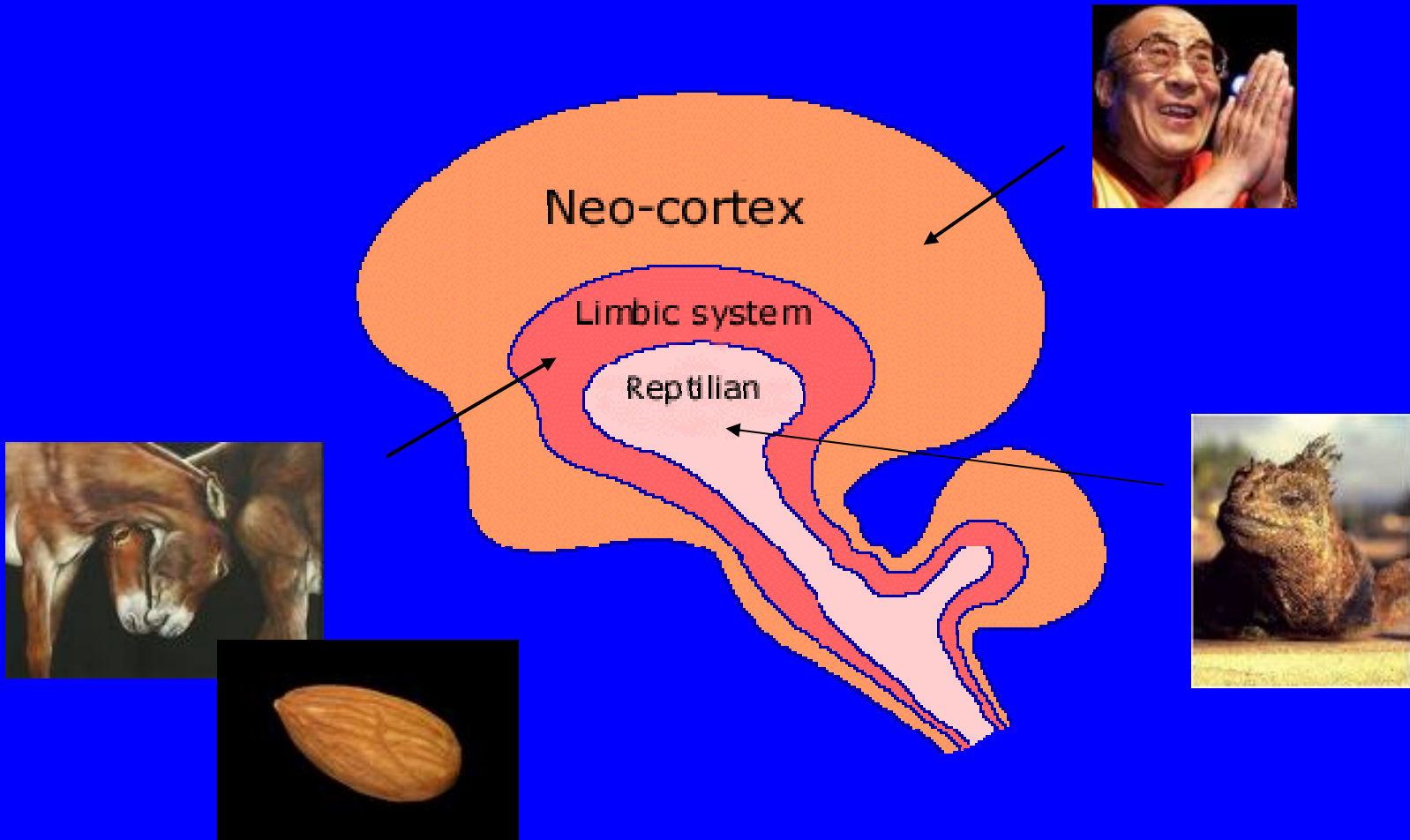
# Stimuli Entering the Brain: Evoke all 3 Response Propensities



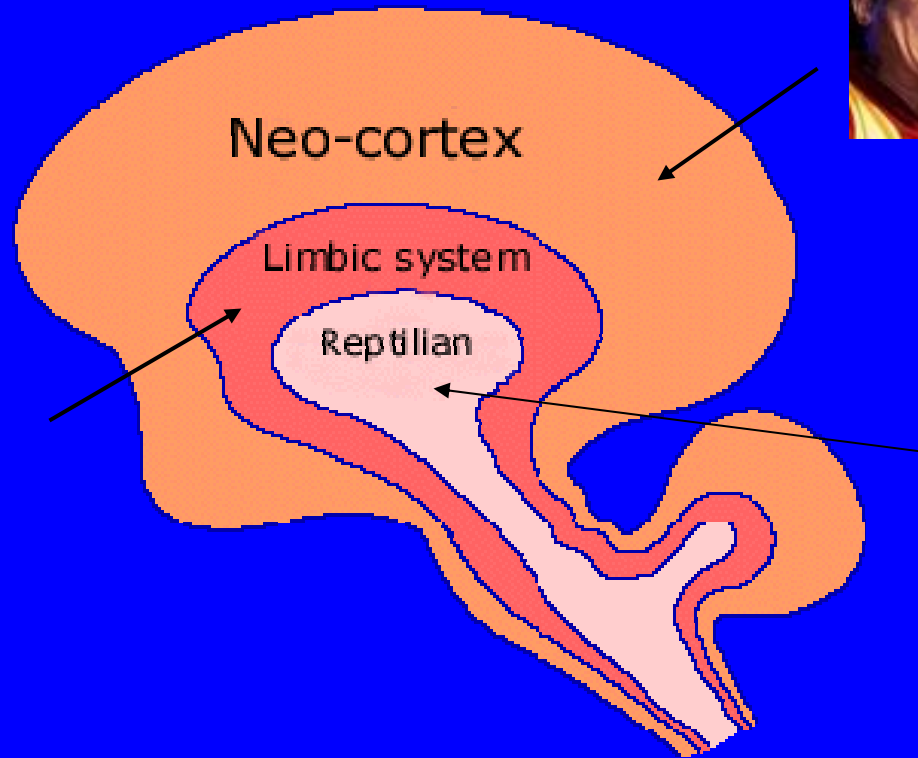
# The Well-Integrated Personality is a Well-Integrated Brain



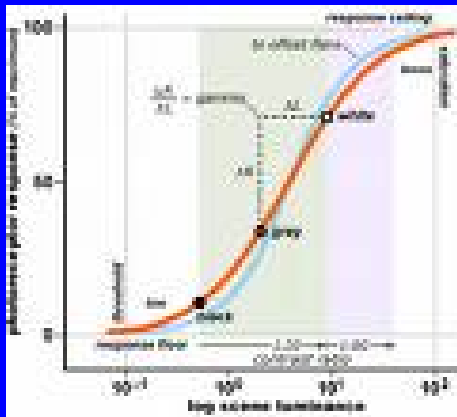
# The Amygdala is at the Apex of the Limbic System



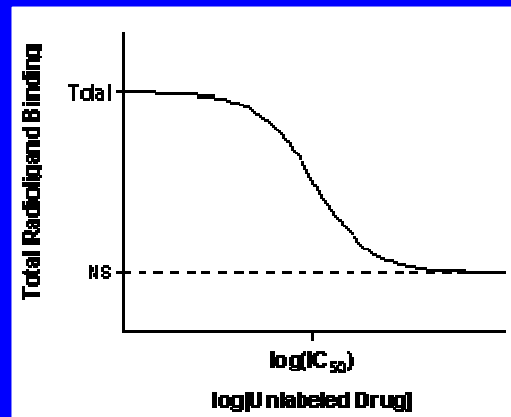
# All Three Brains can See “Blindsight”



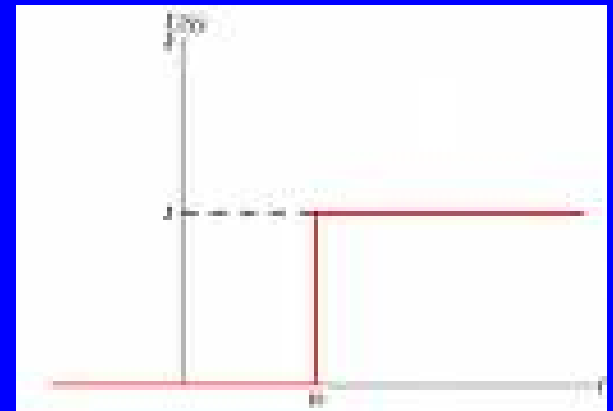
# Learning, Extinction, & Relearning



Acquisition  
Gradual

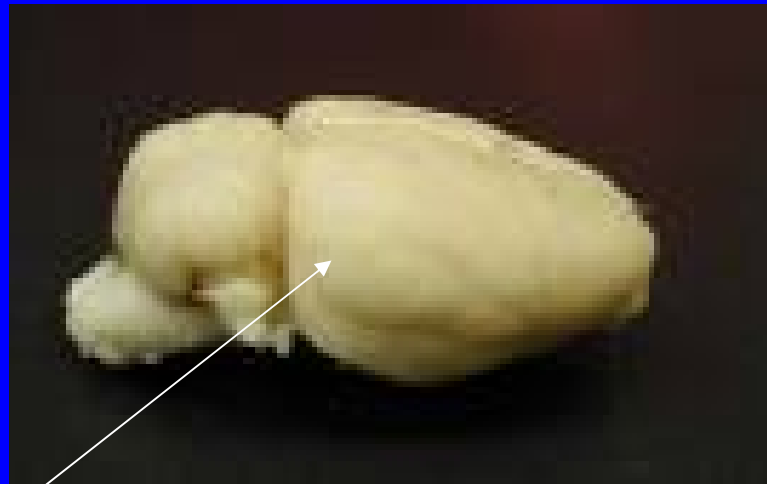


Extinction  
Gradual



Re-Acquisition  
Immediate

# Is Extinction “Unlearning”

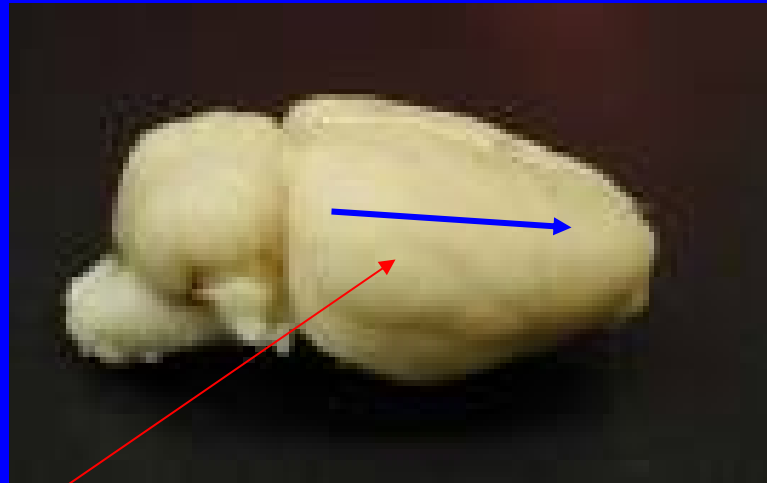


## Visual Cortical Lesions

- Can *Still* acquire a Conditioned Emotional Response (Fear)
- Cannot Extinguish !



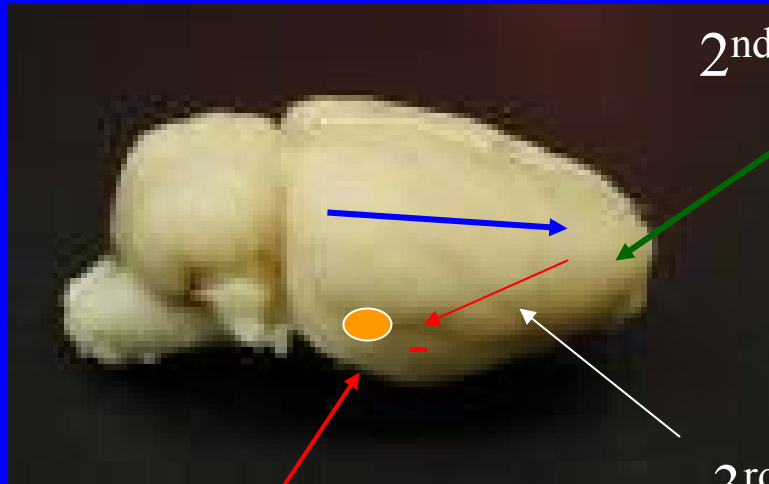
# Is Extinction “Unlearning”



Disruption of Visual Cortical Connections to Frontal Cortex

- Can *Still* acquire a Conditioned Emotional Response (Fear)
- Cannot Extinguish !

# Extinction is New Learning



2<sup>nd</sup>: The Frontal Cortex learns to Ignore the stimulus (for now)

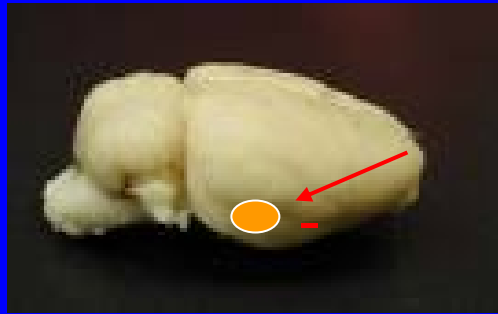


3<sup>rd</sup>: The Frontal Cortex Inhibits the Amygdala's Fear Response

1<sup>st</sup>: The Amygdala learns to fear a stimulus

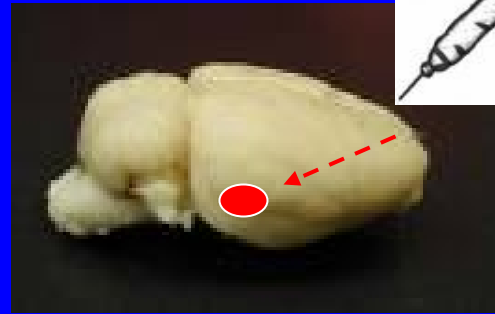


# Neomammalian Brain regulates Paleomammalian Brain



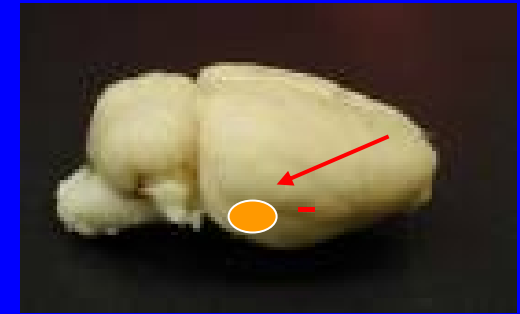
## Phase I:

- Extinction Acquired
- Ctx inhibits Amygdala
- No Fear Response



## Phase II:

- Cortex Anesthetized
- Inhibition Failure
- Fear Response Returns

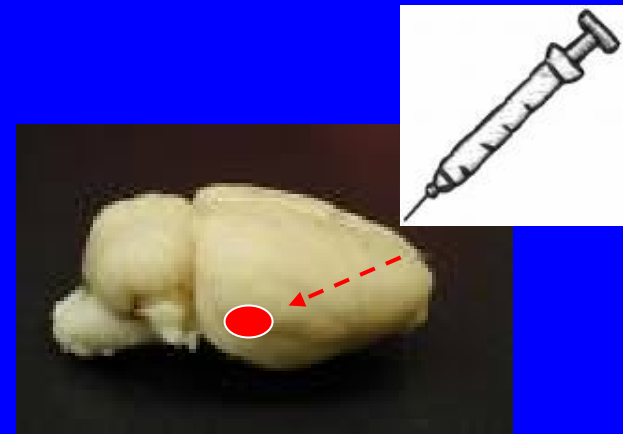
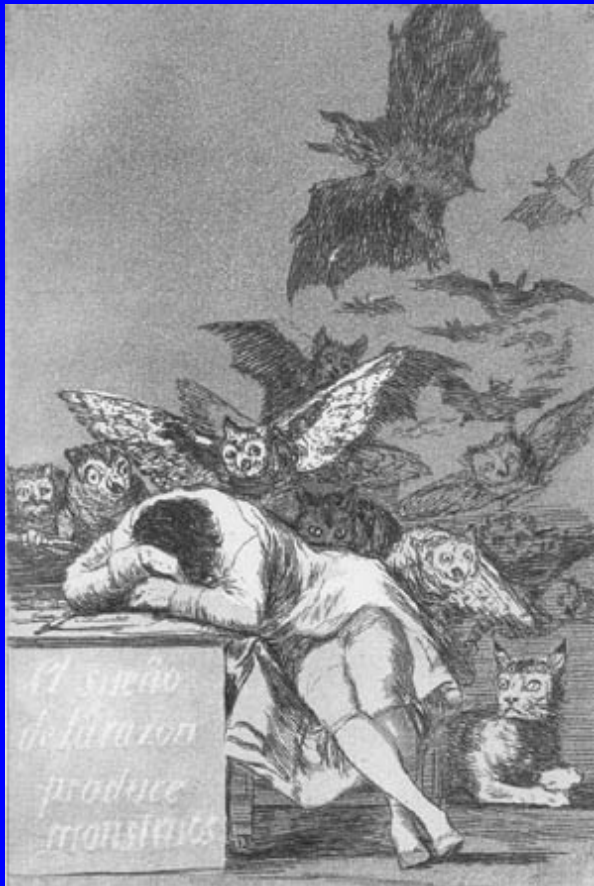


## Phase III:

- Cortex Wakes up
- Inhibition Returns
- Fear Response Subsides



# The Sleep of Reason Produces Monsters

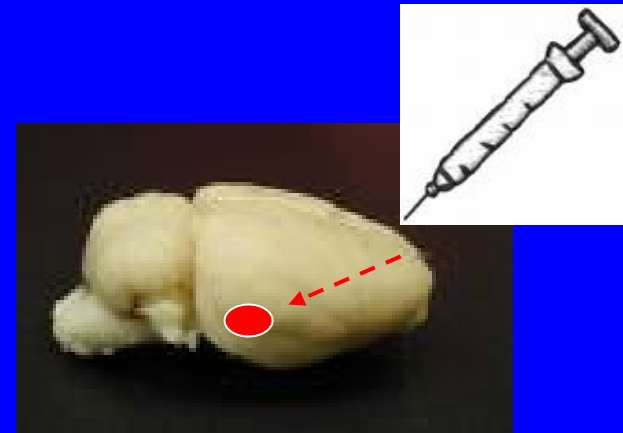
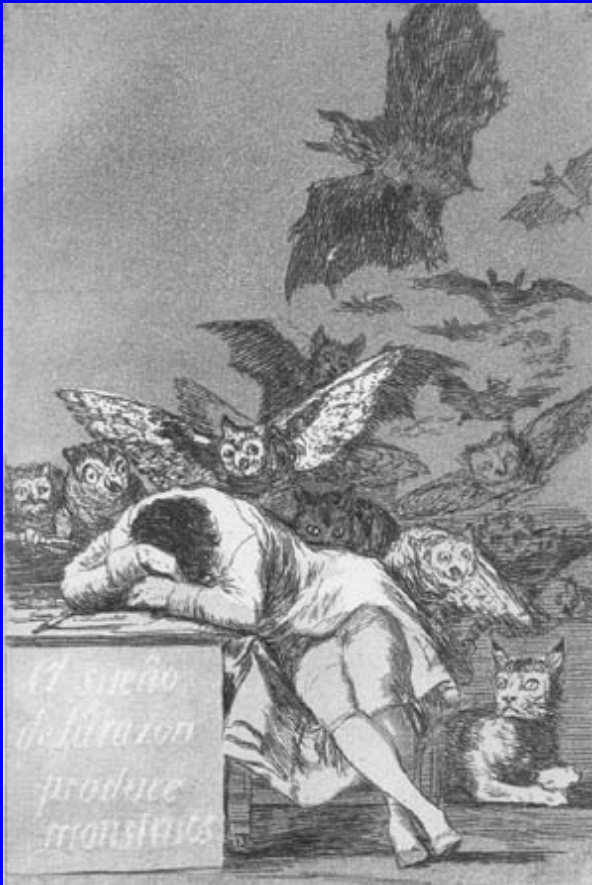


Phase II:

- Cortex Anesthetized
- Inhibition Failure
- Fear Response Returns



# PTSD: A Functional Disconnection Between Prefrontal Cortex & Amygdala?

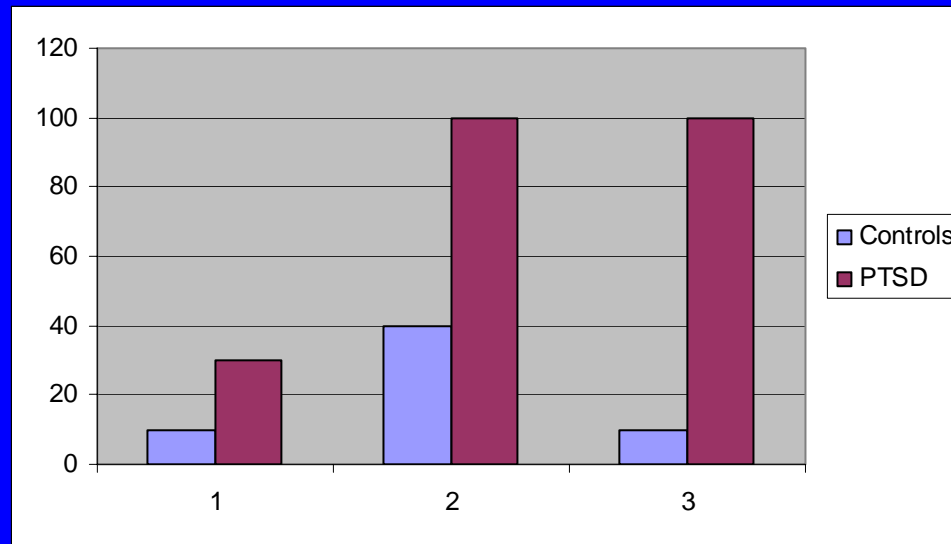


Phase II:

- Cortex Anesthetized
- Inhibition Failure
- Fear Response Returns



# Fear Potentiated Startle



1<sup>st</sup>



2<sup>nd</sup>

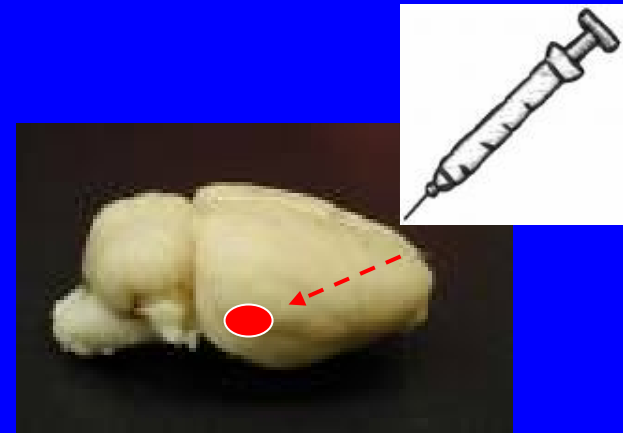
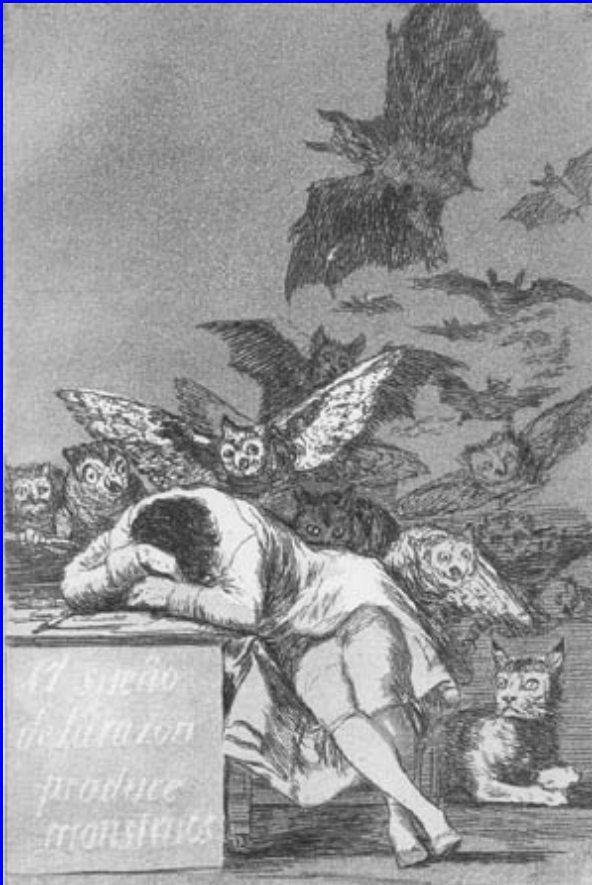
Phase 1: Elevated Startle to Unexpected White Noise

Phase 2: Fear of shock Potentiates Startle in all Subjects

Phase 3: PTSD Patients do not respond to Safety Cue



# PTSD: A Functional Disconnection Between Prefrontal Cortex & Amygdala?

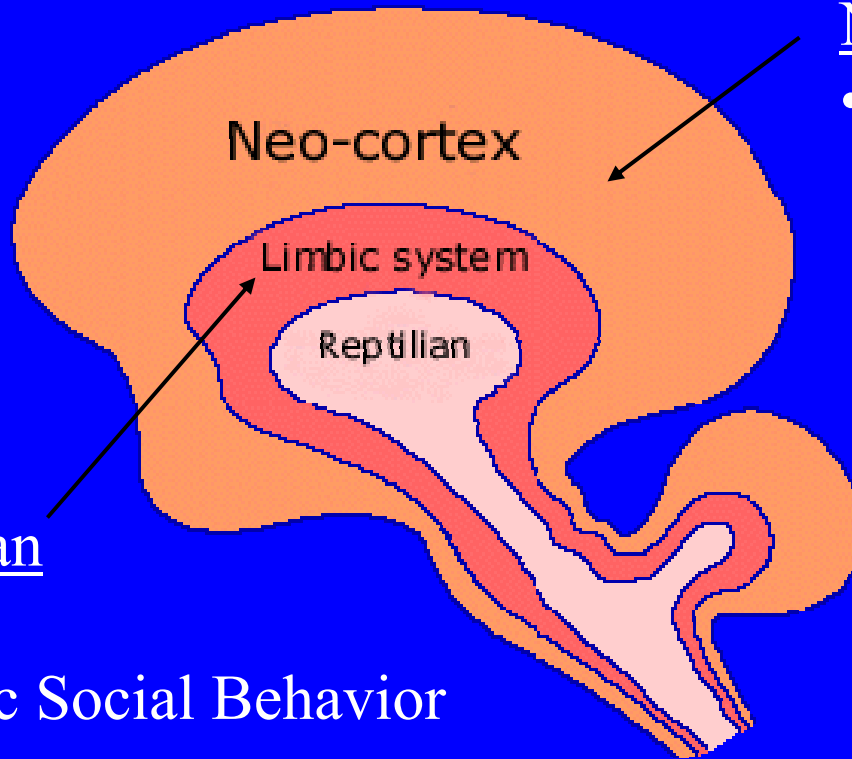


Phase II:

- Cortex Anesthetized
- Inhibition Failure
- Fear Response Returns



# Paul MacLean: The Triune Brain



Neo-Mammalian

- Cognition

*Cold Light*

Rene Descartes:

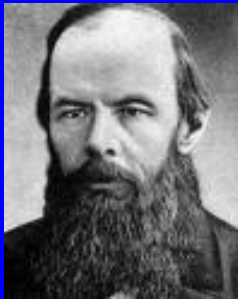
Cogito Ergo Sum

Paleo-Mammalian

- Emotionality
- Species-Specific Social Behavior

*Warm Light* Blaise Pascal: The Heart has it's Reasons  
of which Reason Knows Not

# The Heart has it's Reasons of which Reason Knows Not



Fyodor Dostoevsky: *The Idiot*

“A sensation of existence in the most intense degree”

Patient R.A.: “Each time this happens, thoughts occur very clear and bright to me...as if this is what the world is all about....[this is] the absolute truth.”

William James  
The Peripheral Theory of  
Emotionality  
Blasé Pascal & Solder's Heart



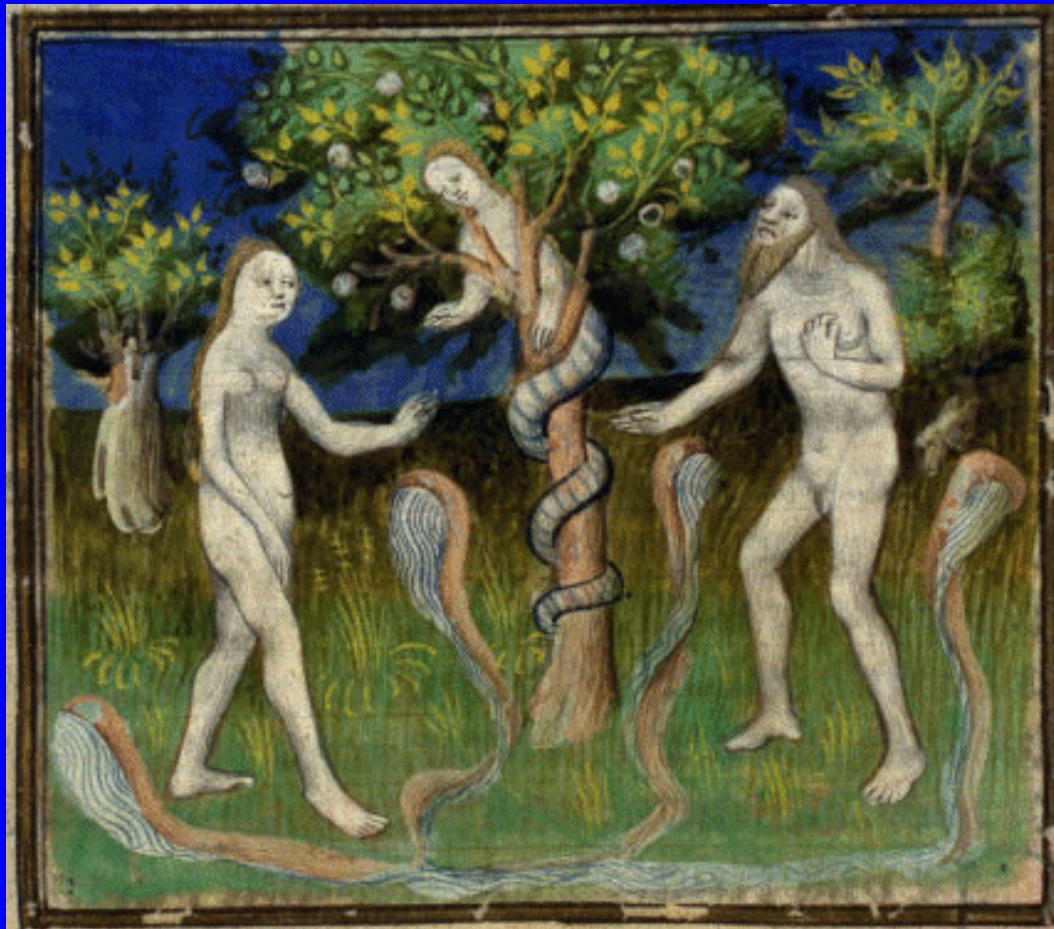
Vagal Nerve Stimulation  
For Intractable Depression

66-75% Ascending Sensory  
Fibers to the Amygdala

# What is the Appropriate Intervention?

- Insight Therapy?
- Cognitive Therapy?
- Exposure Therapy?

# Brain Stem Reflexes and the Knowledge of Good and Evil





# Brain Stem Reflexes and the Knowledge of Good and Evil



# Pre-Pulse Inhibition

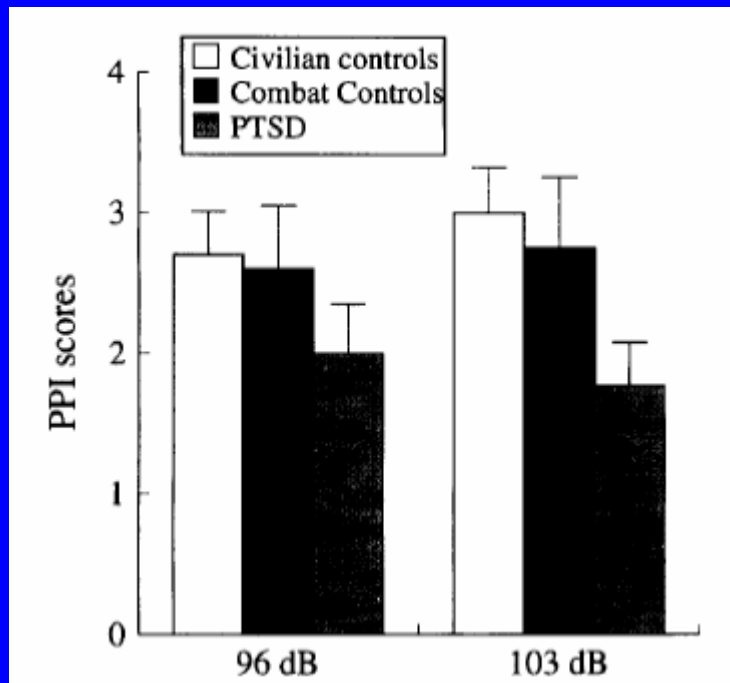
An initial benign stimulus:

Inhibits startle reflex to a subsequent strong stimulus

Not due to:

- Anticipation
- Warning
- Experience
- Learning

# PTSD: Hyper-Reactive to Benign Stimuli?



Grillon et al., 1996

# PTSD: Hyper-Reactive to Benign Stimuli?

Table 3. Mean (SE) Percent Prepulse Inhibition (PPI) in the Three Groups

	Session		Period		
	1	2			
	1	1	2	3S	3T
PTSD veterans <sup>a</sup>	64.6 (6.1)	71.1 (3.1)	61.8 (3.3)	76.7 (4.5)	82.7 (2.6)
Combat controls	81.2 (7.8)	79.3 (9.4)	57.6 (6.8)	78.2 (9.4)	88.4 (6.8)
Civilian controls	92.5 (3.7)	93.2 (1.9)	66.4 (6.8)	89.1 (3.4)	95.8 (7.3)

S, safe; T, threat.

<sup>a</sup> $p < .007$  compared to non-PTSD civilians.

Grillon et al., *Biological Psychiatry*, 1998

# Does PTSD Change Personality?

## or

# Is There a Vulnerable Personality?

Table 1  
Age and scores on the State-Trait Anxiety Inventory, the Mississippi Scale for Combat-Related Posttraumatic Stress Disorder (PTSD), and the Combat Exposure Scale (CES)

	Age		State anxiety		Trait anxiety		Mississippi		Scale CES	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
PTSD	41.8	1.7	55.7	12.3	62.4	8.1	127.7	20.6	28.7	7.7
Combat controls	43.2	6.4	32.2	8.0	35.8	12.2	70.7	11.6	20.6	11.6
Civilian controls	38.9	6.8	29.9	6.9	32.0	5.4				

Grillon et al.,  
1996

Table 1. Mean (SD) Age and Psychometric Scores

Group	Age (years)	Mississippi	CES <sup>a</sup>	Trait anxiety	State anxiety	
					Session 1	Session 2
PTSD veterans ( <i>n</i> = 34)	46.0 (3.4)	128.0 (20.3) <sup>b</sup>	27.5 (8.9) <sup>c</sup>	57.7 (10.4) <sup>d</sup>	50.8 (12.6) <sup>d</sup>	52.2 (11.7) <sup>d</sup>
Combat controls ( <i>n</i> = 17)	42.2 (4.8)	70.2 (17.0)	21.7 (9.3)	34.9 (10.8)	31.8 (8.2)	34.3 (6.4)
Civilian controls ( <i>n</i> = 14)	44.5 (3.9)	—	—	30.0 (5.2)	27.7 (5.4)	29.2 (2.6)

<sup>a</sup>Combat exposure scale.

<sup>b</sup>*p* < .0009 relative to combat controls.

<sup>c</sup>*p* < .03 relative to combat controls.

<sup>d</sup>*p* < .0009 relative to combat and civilian controls.

Grillon et al., 1998

# William James

## The Peripheral Theory of Emotionality



Vagal Nerve Stimulation  
For Intractable Depression

66-75% Ascending Sensory  
Fibers to the Amygdala

# PTSD and the Triune Brain

## The Paleo-Mammalian Brain:

- Too little inhibition from the Neo-Mammalian Brain (Limbic System)
- Too much excitation from the Reptilian Brain

# How's the Paleo-Mammalian Brain Doing?

The Paleo-Mammalian Brain regulates the release of stress hormones from the Adrenal Gland.

- Dopamine
- Nor-Adrenaline (Nor-Adrenalin)
- Adrenaline (Adrenalin)
- Cortisol – Increases expression of first three!!!!

Stress Hormones produce visceral arousal for Fight-or-Flight (Think William James Peripheral Theory of Emotion)



# How Does Cortisol Work?

Released by the adrenal gland in times of stress  
helps us deal with the stress (tiger)



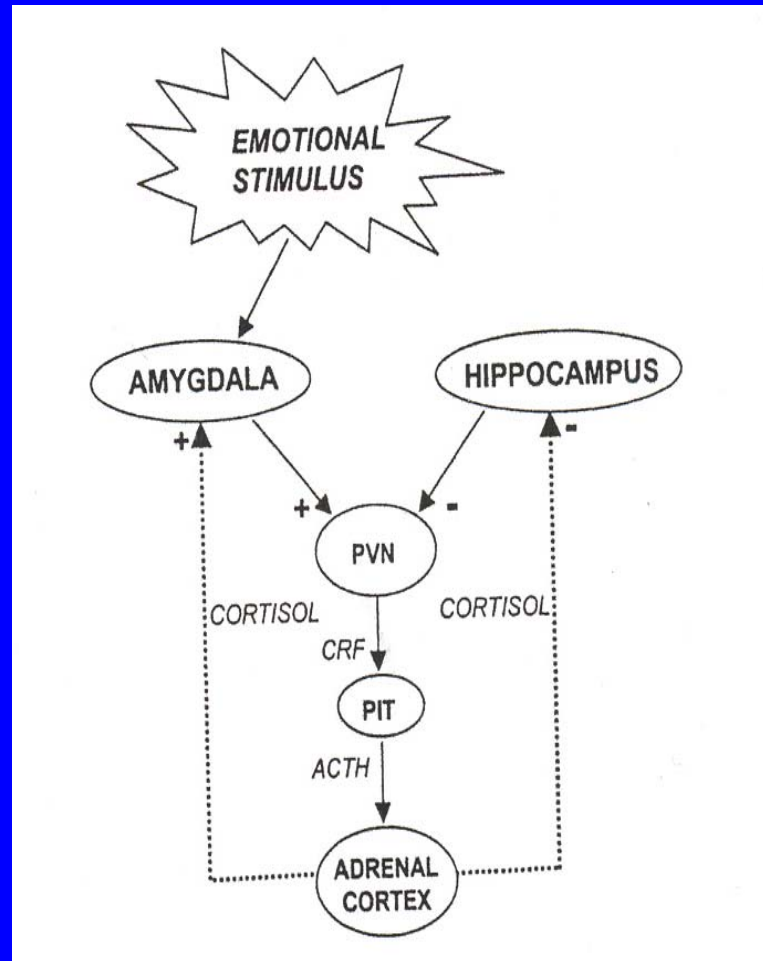
The **brain** tells the adrenal gland:  
when and how much cortisol to release

The **blood** takes some of this cortisol to the brain  
For a hormone to work it must have a **receptor**  
to bind with.

# Negative and Positive Feedback of Emotional Response

Positive Feedback Loop

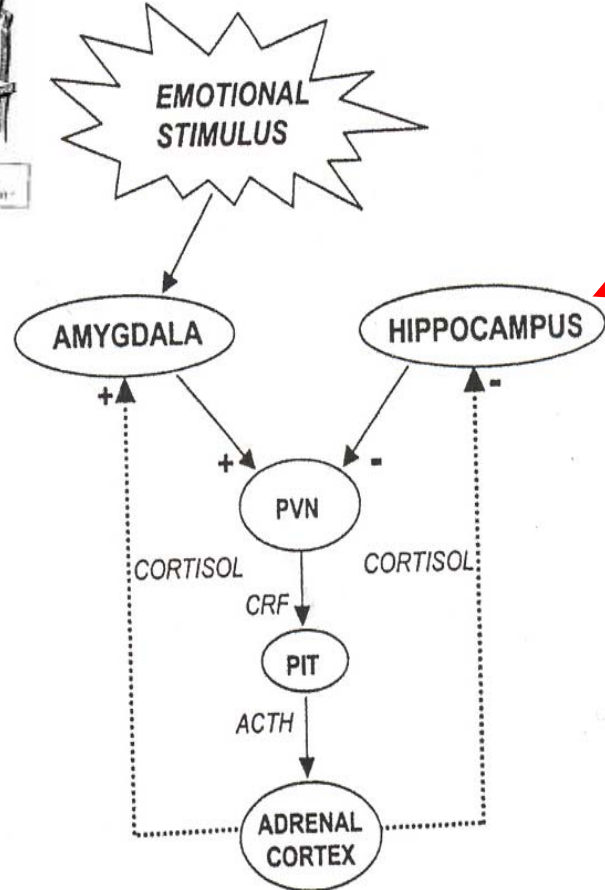
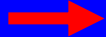
Does the *balance* Between these two Loops determine Personality?



Negative Feedback Loop

Cortisol is **Neurotoxic** To the Hippocampus

# Acute Tiger is Replaced by Chronic Boss



Negative Feedback Loop

Cortisol is **Neurotoxic** To the Hippocampus

*The Furnace Melts the Thermostat*

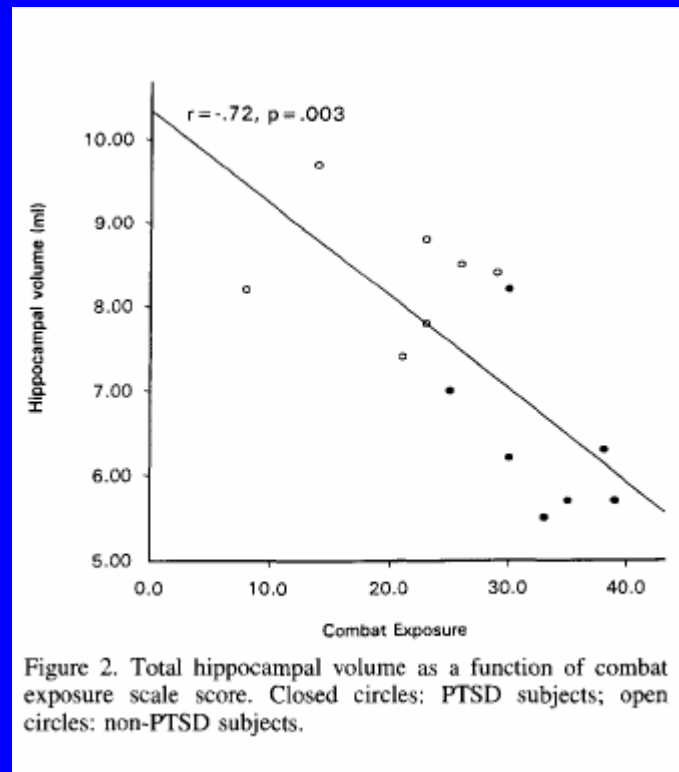


Positive Feedback Loop

Does the **balance** Between these two Loops determine Personality?

# The Melted Thermostat?

## Combat Exposure & Hippocampal Volume



Closed Circles:  
PTSD

Gervits et al., *Biological Psychiatry*, 1996

# The Melted Thermostat

## Exposure to Threats

Exposure to threats (script) in sexually abused women with PTSD:

- 122% higher cortisol at exposure vs. abused women w/o PTSD
  - Correlated with PTSD symptomology  $r=0.70$
- 69% higher cortisol during recovery
- 60% higher cortisol at anticipation
  
- Greater Increase in sympathetic arousal
  - Heart rate
  - Blood pressure (systole & diastole)
  - Skin Conductance
  - NOR-Epinephrine release

Elzinga, et. al.

# Elevated State Cortisol?

Adult sexual abuse is associated with elevated neuro-hormones  
In women with PTSD due to childhood sexual abuse  
Friedman et al., *Journal of Traumatic Stress*, 2007

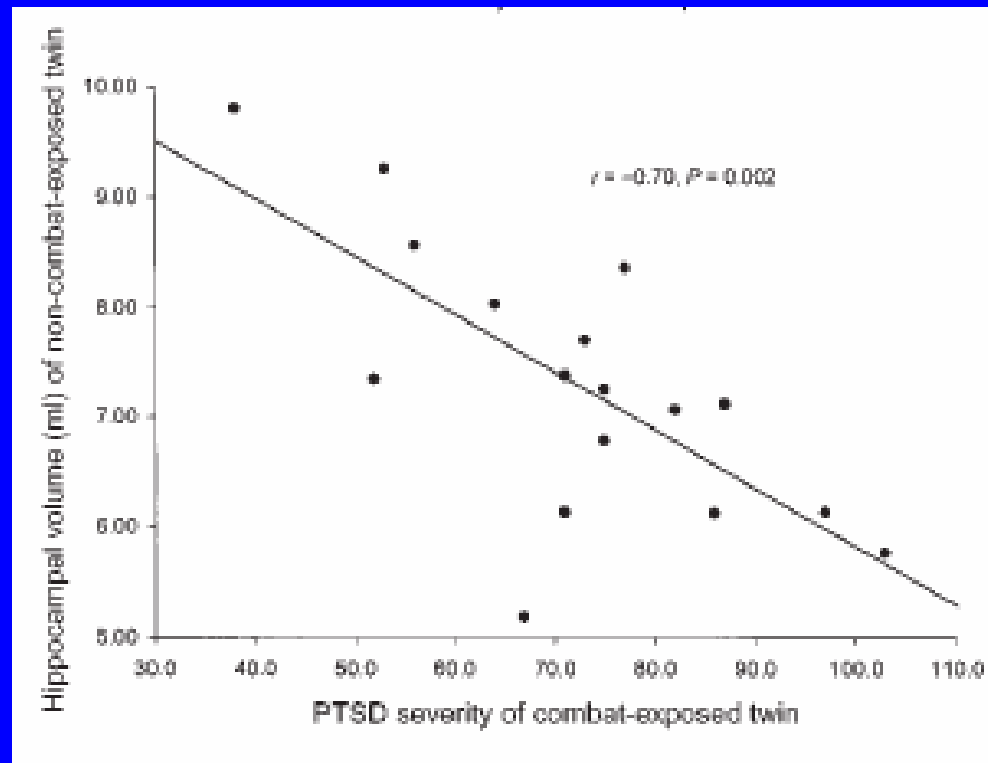
**Table 2.** Urine Variables for Women With PTSD Due to Child Sexual Abuse With ( $n = 35$ ) and Without ( $n = 34$ ) Adult Sexual Abuse

Urine variables	Group	<i>M</i>	<i>SD</i>	<i>t</i> (67)	Effect size ( <i>d</i> )
Cortisol ( $\mu\text{g}/\text{day}$ )	No ASA	36.2	9.9	4.34***	1.04
	ASA	52.0	18.8		
Norepinephrine ( $\mu\text{g}/\text{day}$ )	No ASA	31.1	9.7	3.14**	0.76
	ASA	40.9	15.5		
Epinephrine ( $\mu\text{g}/\text{day}$ )	No ASA	4.9	2.6	1.17	0.28
	ASA	5.6	2.8		
Dopamine ( $\mu\text{g}/\text{day}$ )	No ASA	194.6	49.0	4.28***	1.03
	ASA	249.3	56.8		

*Note.* PTSD = posttraumatic stress disorder; ASA = adult sexual abuse.

\*\*  $p < .01$ . \*\*\*  $p < .001$ .

# Cause or Effect?



Does a stressful personality  $\rightarrow$   $\downarrow$  Hippocampus  $\rightarrow$   $\uparrow$  Vulnerability to PTSD?

Gilbertson et al., *Nature Neuroscience*, 2002

# PTSD: High Co-Morbidity for Depression

## Major Depression:

- Elevated, unregulated cortisol levels
  - Dexamethasone Suppression Test
  - Metyrapone reverses Tx-resistant MD
- Atrophy of Hippocampus
- Deficits of Cognition & Long-Term Memory
- Anhedonia
  
- All AD Tx stimulate BDNF production in Hippocampus  
(Brain-Derived Neurotrophic Factor)
  - Serotonergics
  - NOR-Adrenergics
  - ECT (Most potent Tx & Inducer of BDNF)
  - Exercise
  - Estrogen & DHEA



# BDNF effects on Hippocampus

- ↑ Dendritic Arborization
- ↑ Synaptogenesis
- ↑ Neogenesis

## Currently Depressed patients:

- ↓ L & R Hippocampus vs. Remitted Patients
- Negative correlation between Hippocampal size & Duration of MD
- Negative correlation between Hippocampal size & # of Episodes

(Does smaller Hippocampus lead to more severe illness?)

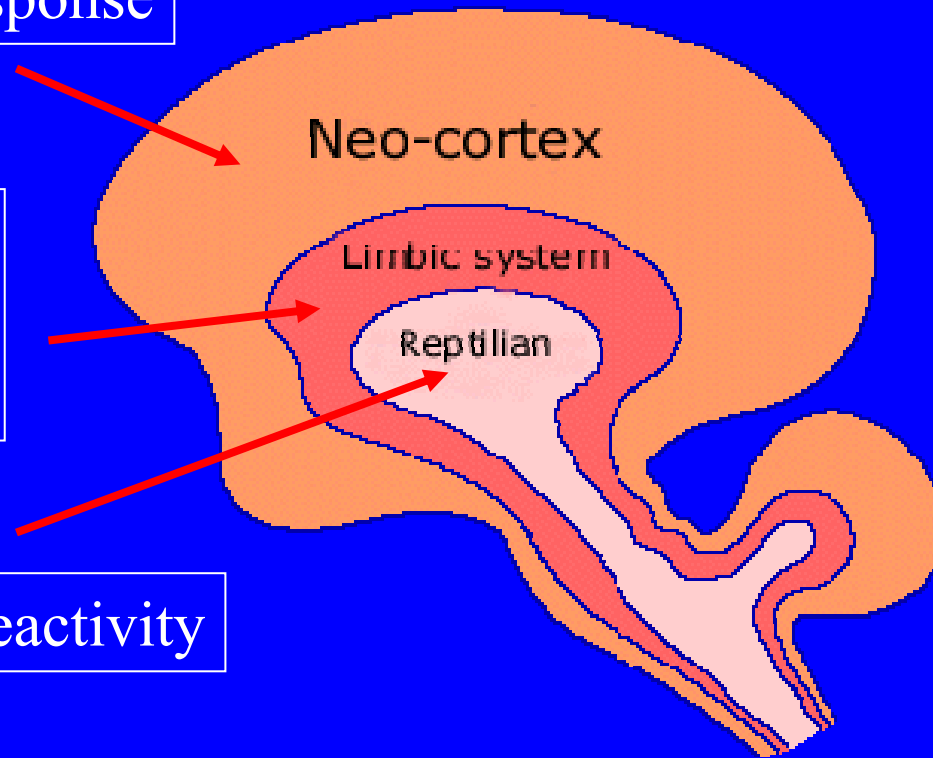
Caetano et al., *Psychiatric Research: Neuroimaging*, 2004

# A Model of PTSD

Lack of Inhibition  
of fear response

Atrophy  
&  
Depression

Hyper-Reactivity



# What about Impact of Families?



# Early Life Trauma

- Increased risk of PTSD in adulthood from other traumas  
Reduced capacity to cope with subsequent Stress?
- Increased risk of Alcoholism in adulthood from early traumas

# How does Nurturance lead to Permanent Changes in Adult Personality?

Licking & Grooming in infancy leads to a **Permanent Increase in:**

Cortisol receptors in the Hippocampus

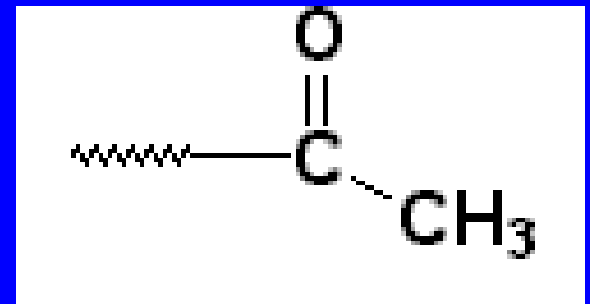
- The Negative Feedback Pathway
- Thus, tighter regulation of the stress response
  
- Even with cross-fostering
- Critical Period!

# How does Nurturance result in more Hippocampal Cortisol Receptors?

- Nurturance removes a Methyl Group ( $\text{CH}_3$ ) from the gene that codes for the Cortisol Receptor In Hippocampal neurons
- Methylation inhibits gene expression
- Demethylation promotes gene expression

# Nurturance does it Again!

- DNA is wrapped around a protein skeleton called **Histone**
- The tighter the wrap, the less gene expression
- Attaching an Acetyl group loosens the wrapping
  - Thus increasing gene expression
- Nurturance acetylates histones
  - Thus increasing gene expression



acetyl group

# Summing Up

## Mothering Style Permanently Alters:

- Genetic expression (De-Methylation, Acetylation)
- Brain biochemistry (Cortisol Receptors)
- Endocrine (hormone) physiology (cortisol expression)
- Personality & Behavior (Fear, Exploration, Stress Response)
- Loss of Memory & Cognition with Age
- Risk of Psychopathology (Learned Helplessness – Depression)?



# But Wait! – There's More!

High nurturance results in:

More benzodiazepine receptors in the Amygdala

- The emotion center of the brain
- Change is permanent
- What's a benzodiazepine?

Valium

There may be natural valium substances in the brain