Systems Biology and the Stress Response: From Pythagoras and the Epicurians to Modern Medicine

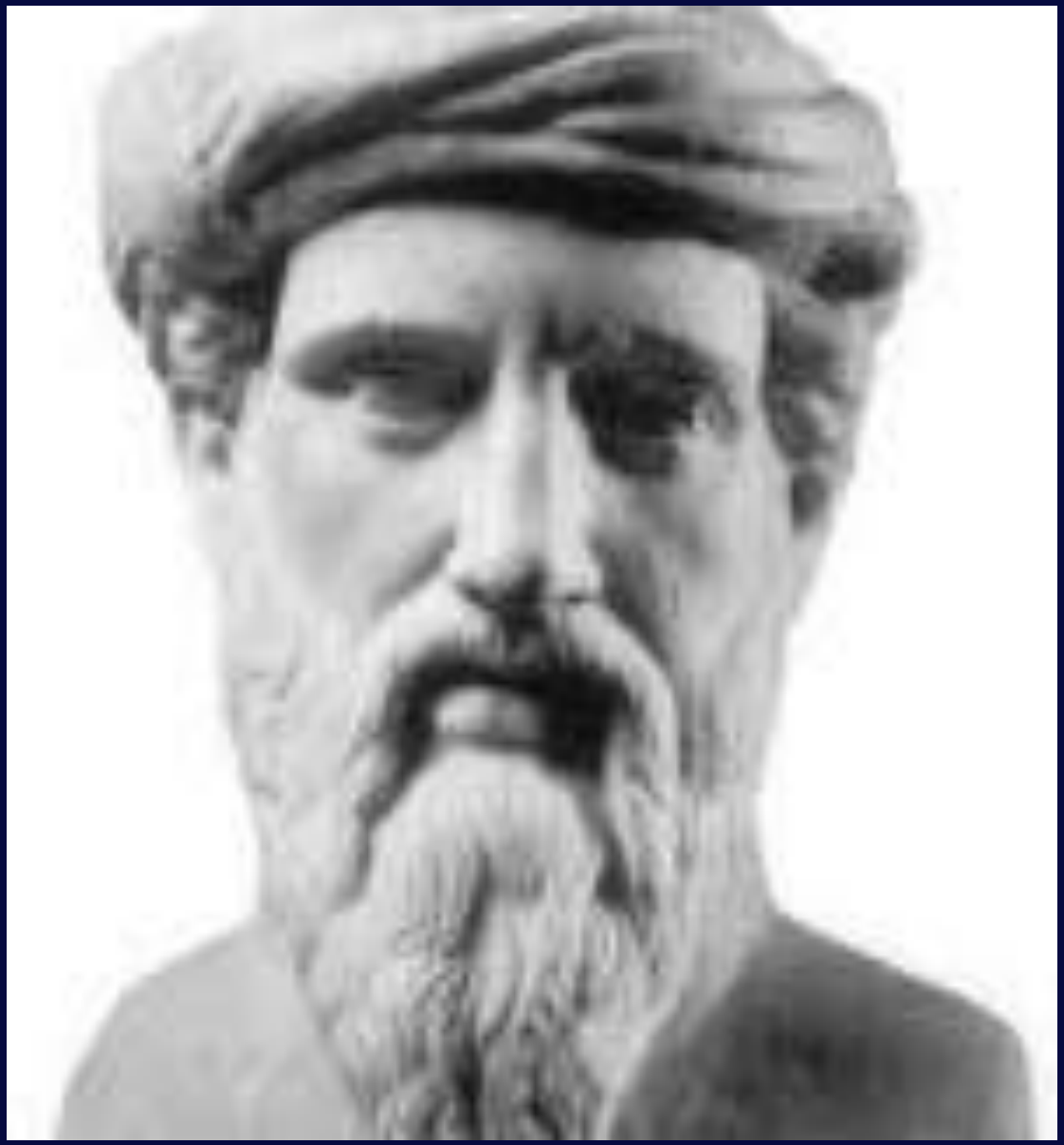
George P. Chrousos, MD,

Athens University, Athens, Greece

Physical and Emotional Stress

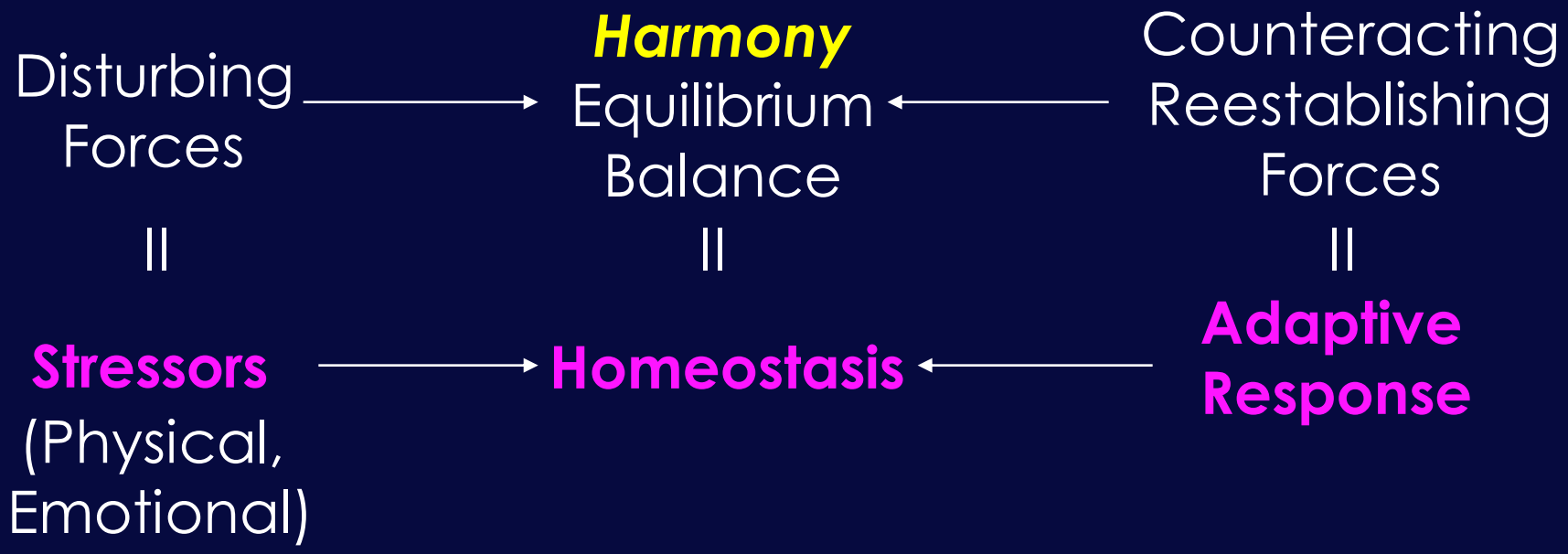
- Stress Concepts
- Stress Mechanisms
- Effects of Stress on the Organism
- Coping with Stress

G.P. Chrousos



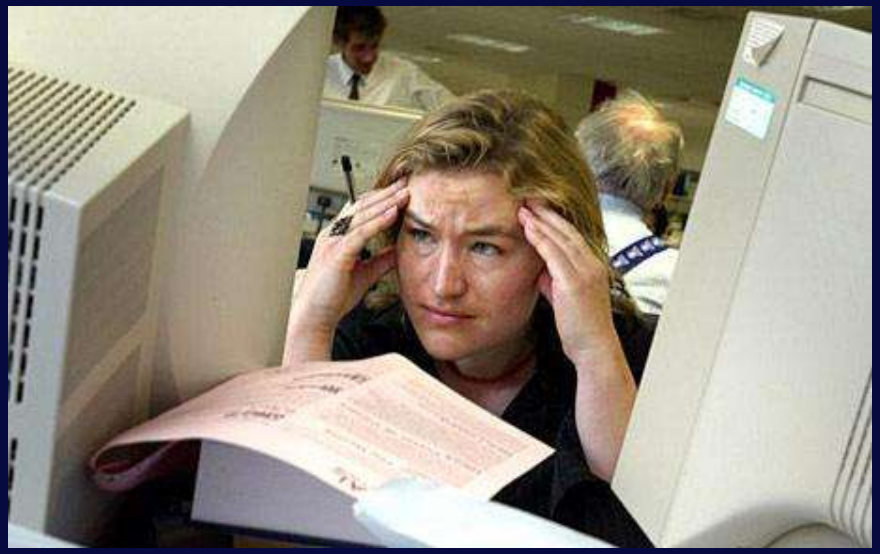
Pythagoras 6th century BCE

Complex Systems Theory



Pythagoras= *Harmony*
Alcmaeon=*Iso-nomia*
Walter Cannon= Homeostasis

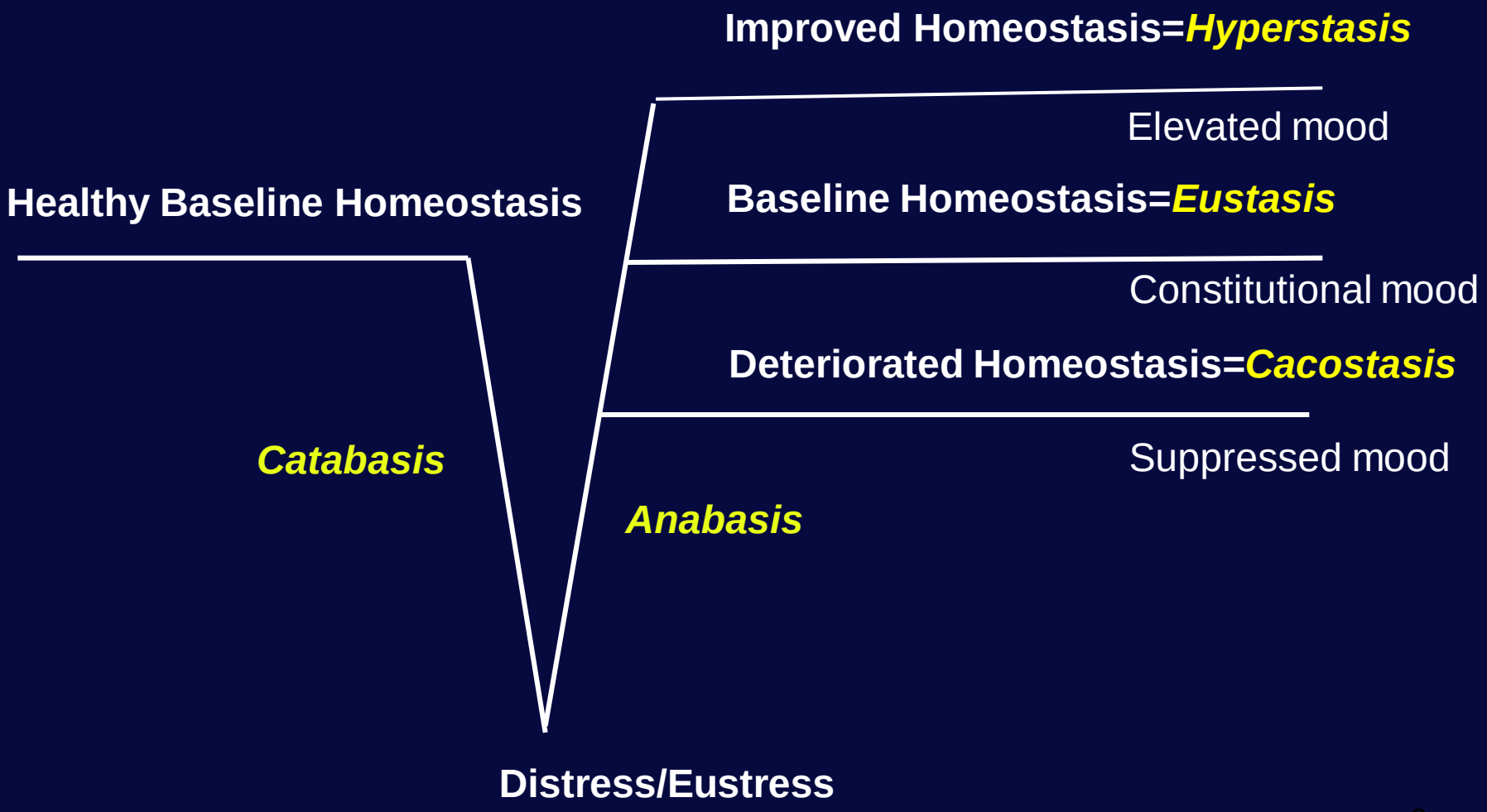
Stress is the State of Threatened (or Perceived as Threatened) Homeostasis



STRESS CONCEPTS

Pythagoras (580-489 BC)	**The *Harmony* of the *Cosmos***
Alkmaion (c. 500 BC)	**The intellect is based in the brain** **Health is the equipose of opposing forces: *«Isonomia»***
Empedocles (500-430 BC)	Matter consists of essential elements and qualities in opposition or alliance to one another
Hippocrates (460-375 BC)	A harmonious balance of the elements and qualities of life is health-Dysharmony is disease «***Nouson physeis iatroi =Vis medicatrix naturae»***
Aristotle	"***Eudaimonia"***
Stoics/Sceptics	***Ataraxia*** (imperturbability of mind, equanimity)
Epicurus (341-270 BC)	***Ataraxia*** (imperturbability of mind), ***Aponia*** (no pain) and "***Hedone***" (tranquil, non sensual pleasure) as desirable states «***Eustachius» = Good balance, Carpe diem= seize the day***
Thomas Sydenham (AD 1624-1689	Symptoms and signs of a disease arise also from the reaction of the patients system
Claude Bernard (1813-1878)	The "***milieu interieur***"
Walter Cannon (1871-1945)	***Homeostasis/Stress*** Bodily responses to emotions ***Fight or flight (and freeze) reaction***
Hans Selye (1907-1982)	The **general adaptation syndrome** (**the stress syndrome**) ***Diseases of adaptation***, ***Distress*** *vs*. ***Eustress***

Homeostasis over Time



G.P. Chrousos

Homeostasis over Time

Improved Homeostasis = *Hyperstasis*

Elevated mood

Healthy Baseline Homeostasis = *Eustasis*

Constitutional mood

Deteriorated Homeostasis = *Cacostasis*

Suppressed mood

Human Stressors

Daily hassles

Work stress (Effort Reward Imbalance,ERI)

Life transitions

Natural and unnatural catastrophies

Starvation, Excessive nutrition, Deficient exercise, Excessive exercise, Obesity

Socioeconomic status, Minority status (*Dignity*)

Job loss, Downsizing, Loss of control

Bereavement

Caretaking/ Pathologic empathy/*Unprincipled compassion*

Addictions/ Toxic substances

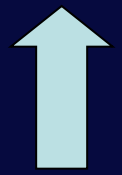
Inflammations (Traumatic, Infectious, Autoimmune, Allergic)

Anxiety, Depression, Personality disorder

Sleep deficiency

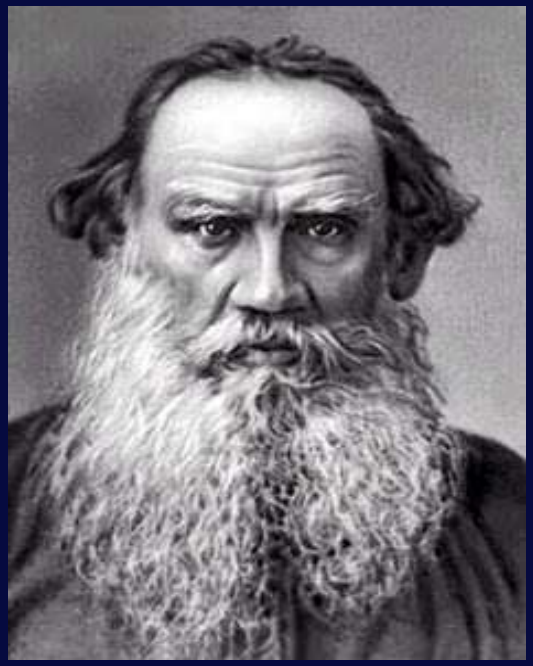
"CRITICAL" PERIODS OF LIFE

Prenatal, Early Childhood, Puberty
(Human brain ontogeny complete at 25-27 y)



Organizational Effects of Hormones

(CRH, glucocorticoids, sex steroids, cytokines)



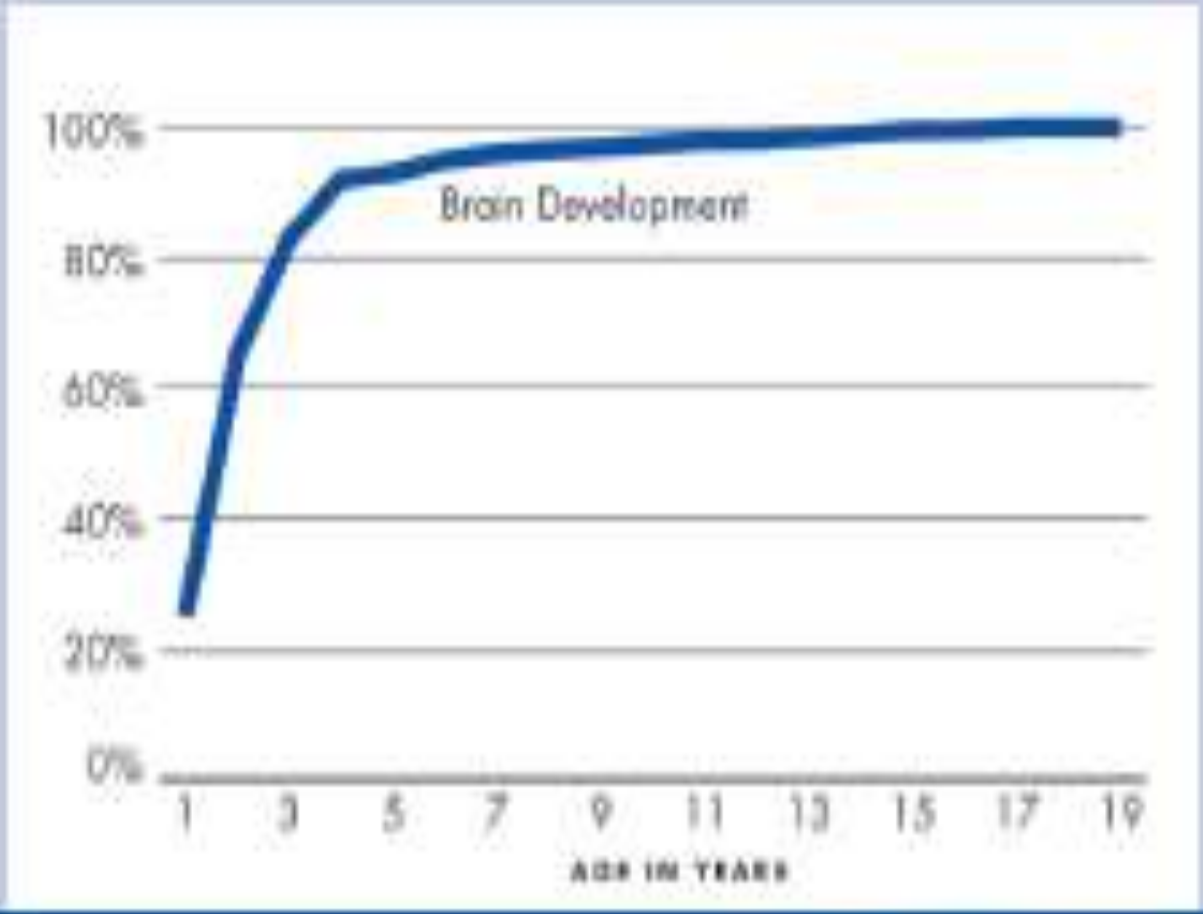
“From the child of five to myself is but a step. But from the newborn baby to the child of five is an appalling distance ”

Leon Tolstoy 19th century

"The past is never dead. It's not even past."

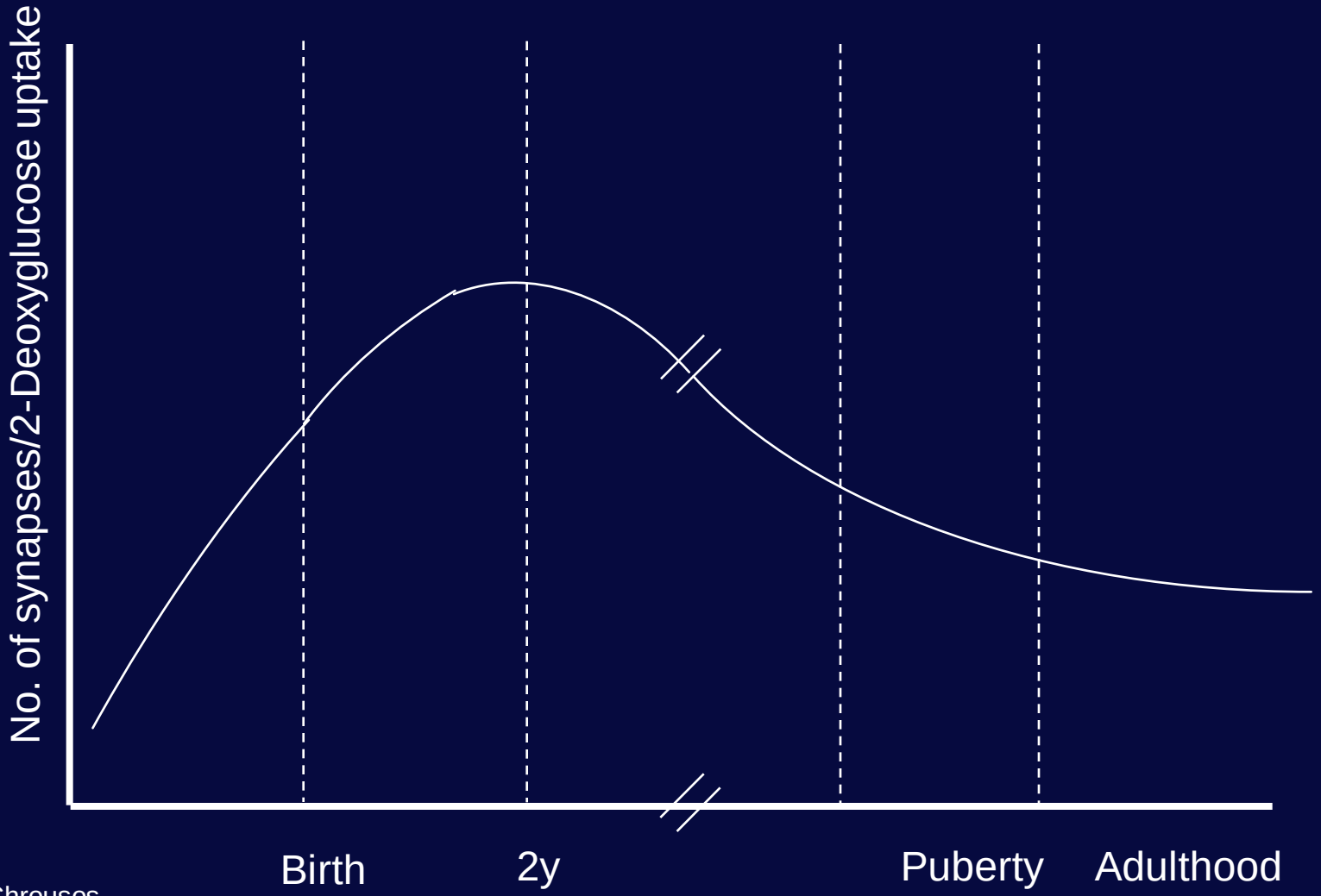
William Faulkner *20th century*

Brain Growth and Child Age



Source: RAND Corporation

THE DEVELOPING BRAIN

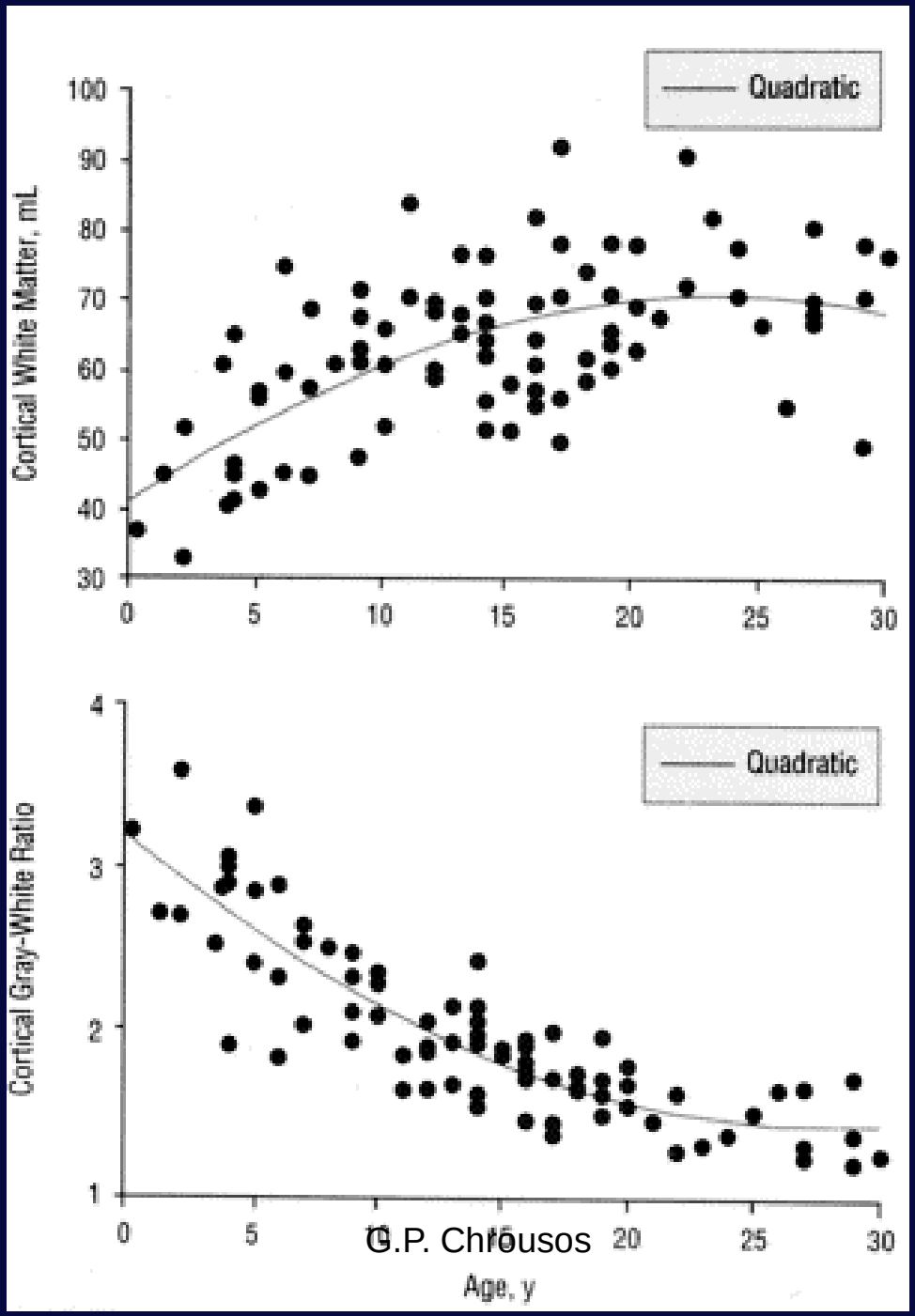


G.P. Chrousos

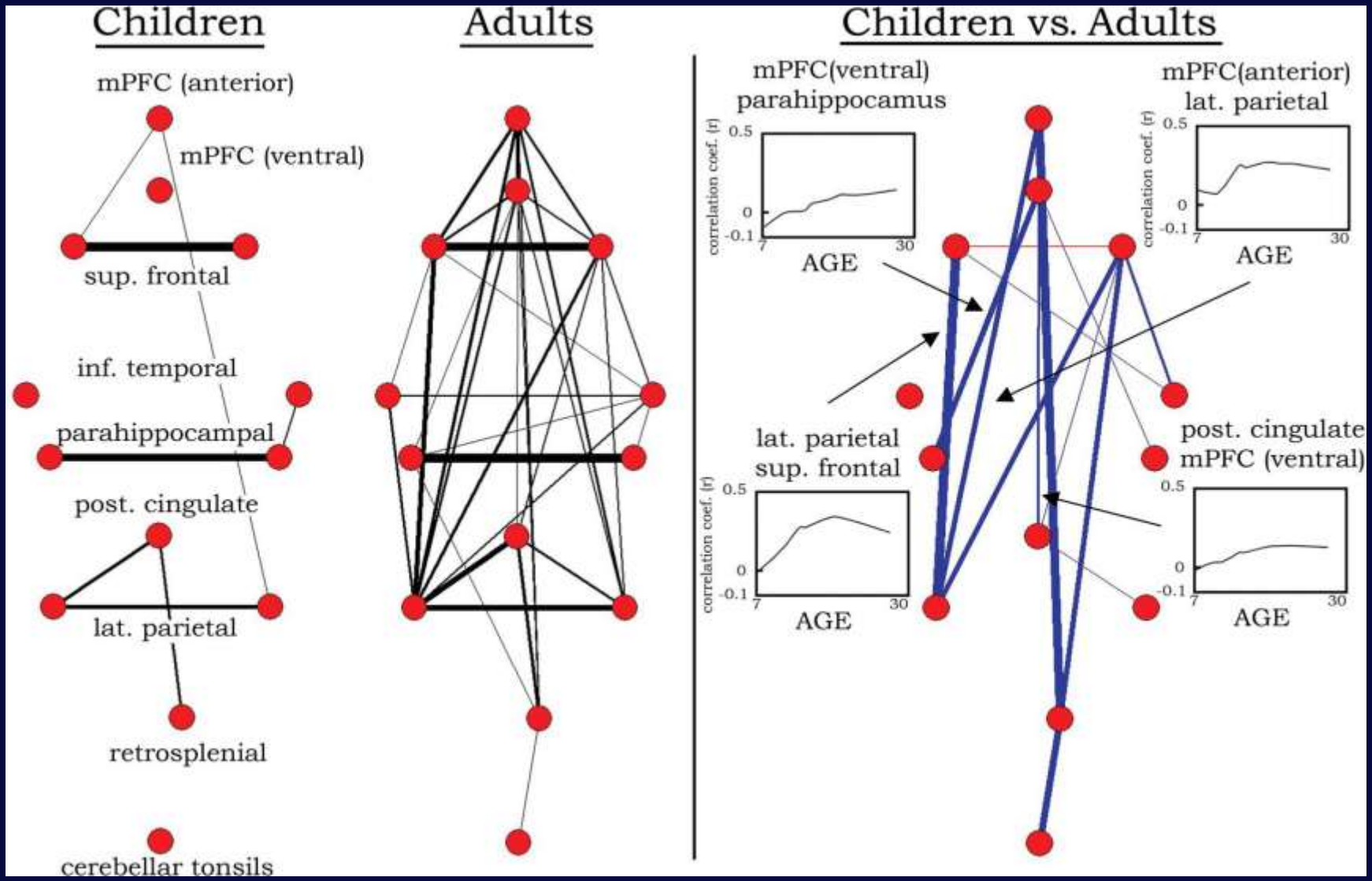
At Birth 6 Years Old 14 Years Old

SYNAPTIC DENSITY: Synapses are created with astonishing speed in the first three years of life. For the rest of the first decade, children's brains have twice as many synapses as adults' brains.

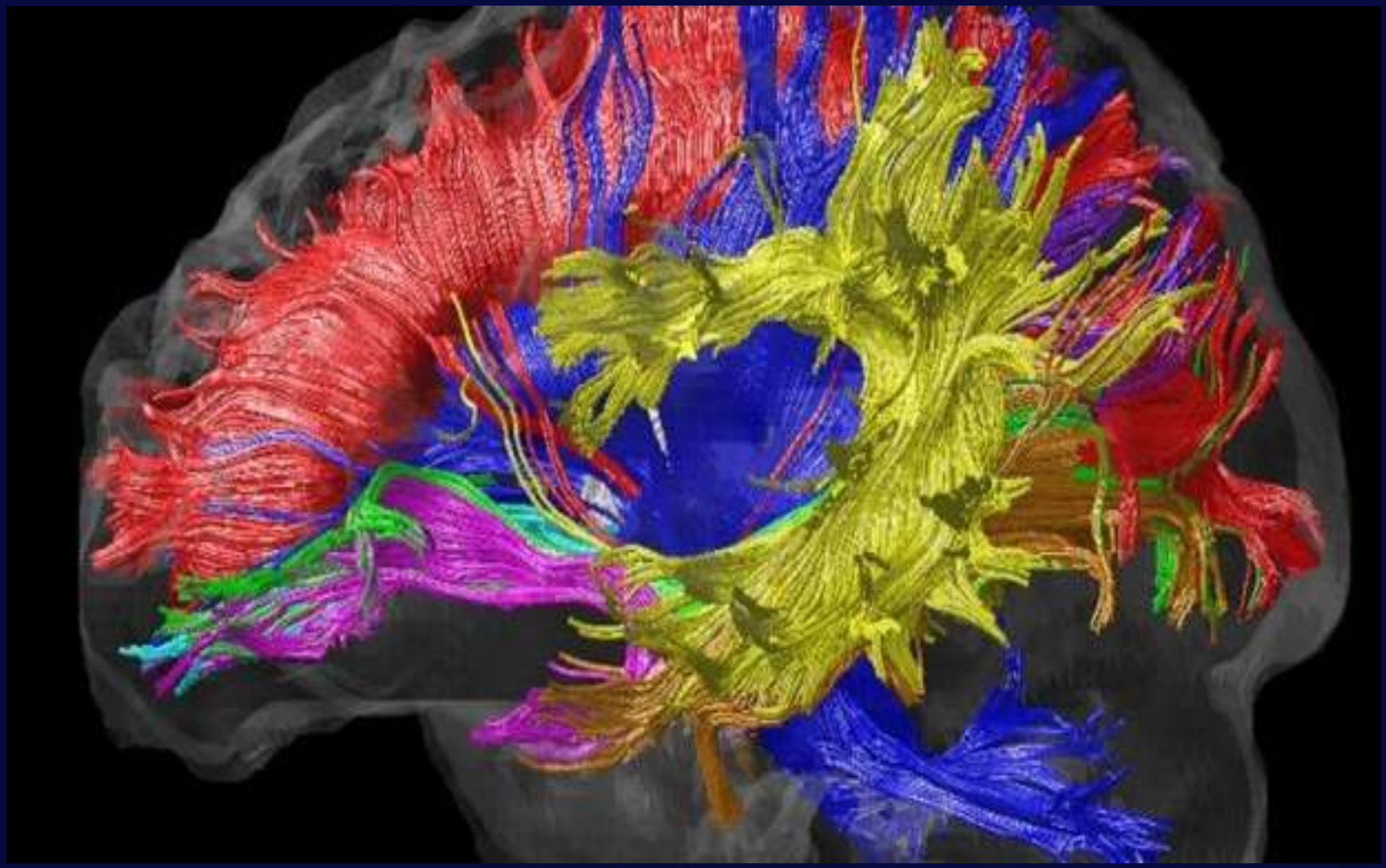
The brain loses the nervous circuits that are not used !


Quadratic
Cortical White Matter, mL
100
90
80
70
60
50
40
30
0
5
10
15
20
25
30
Quadratic
Cortical Gray-White Ratio
4
3
2
1
0
5
20
25
30
Age, y

Default Mode Network



Fair et al. PNAS 2008



Prefrontal/Frontal Lobe "Higher Functions"

- Interpretation of the environment, social cues
- Problem solving
- Planning
- Proper control of impulses

HOMEOSTATIC SYSTEMS

Pre-/Frontal Lobe/Logos

- Amygdala, fear/anger
- MCLS, reward/punishment
- Stress - CRH/LC-NE
- Cardiorespiratory
- Metabolic
- Immune/Inflammatory
- Fatigue - Pain
- Wakefulness/Sleep
- Clock

Physical and Emotional Stress

- Stress Concepts
- Stress Mechanisms
- Effects of Stress on the Organism
- Coping with Stress

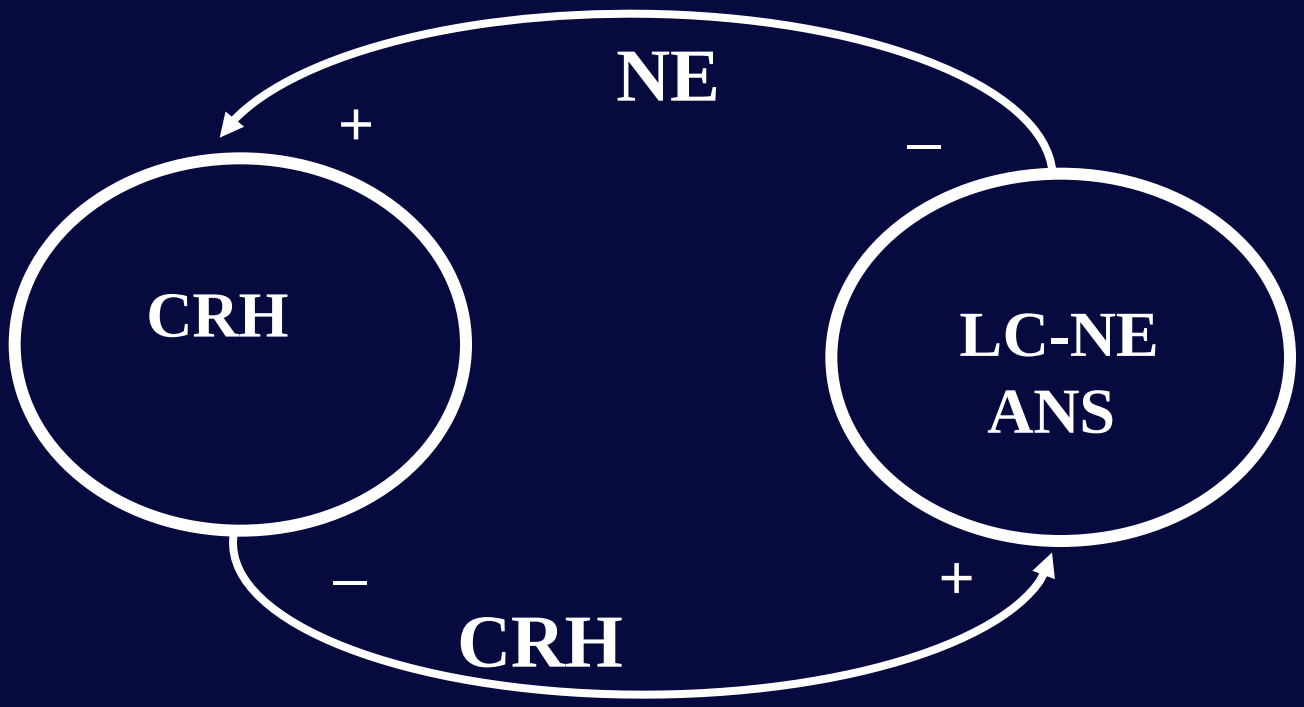
What Mediates the Adaptive Response?

The Stress System

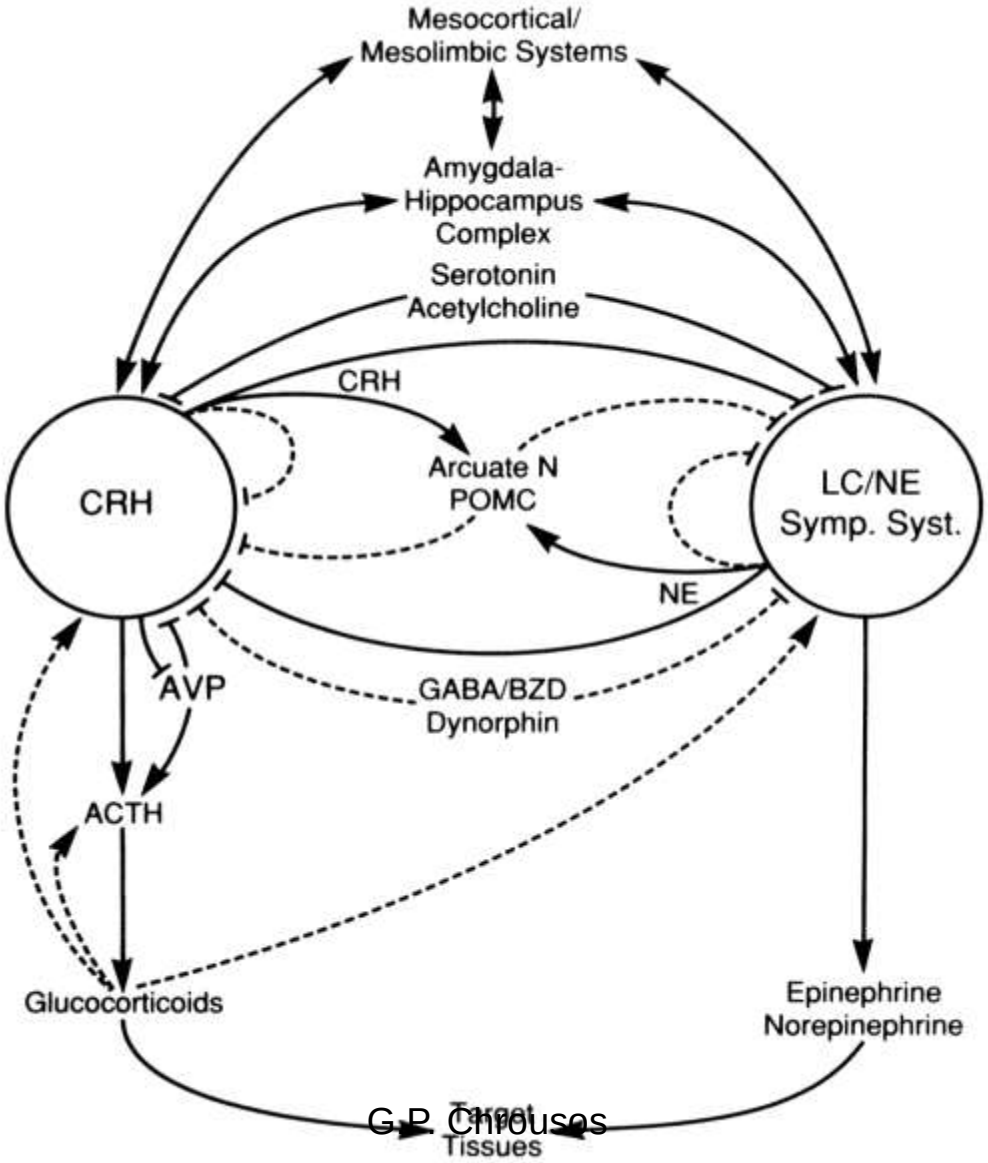
a. **CNS**
   1. CRH system
   2. *Locus caeruleus* (LC)-norepinephrine (NE)/autonomic (sympathetic) systems

b. **Periphery**
   1. HPA axis
   2. Autonomic (sympathetic) systems

Stress System

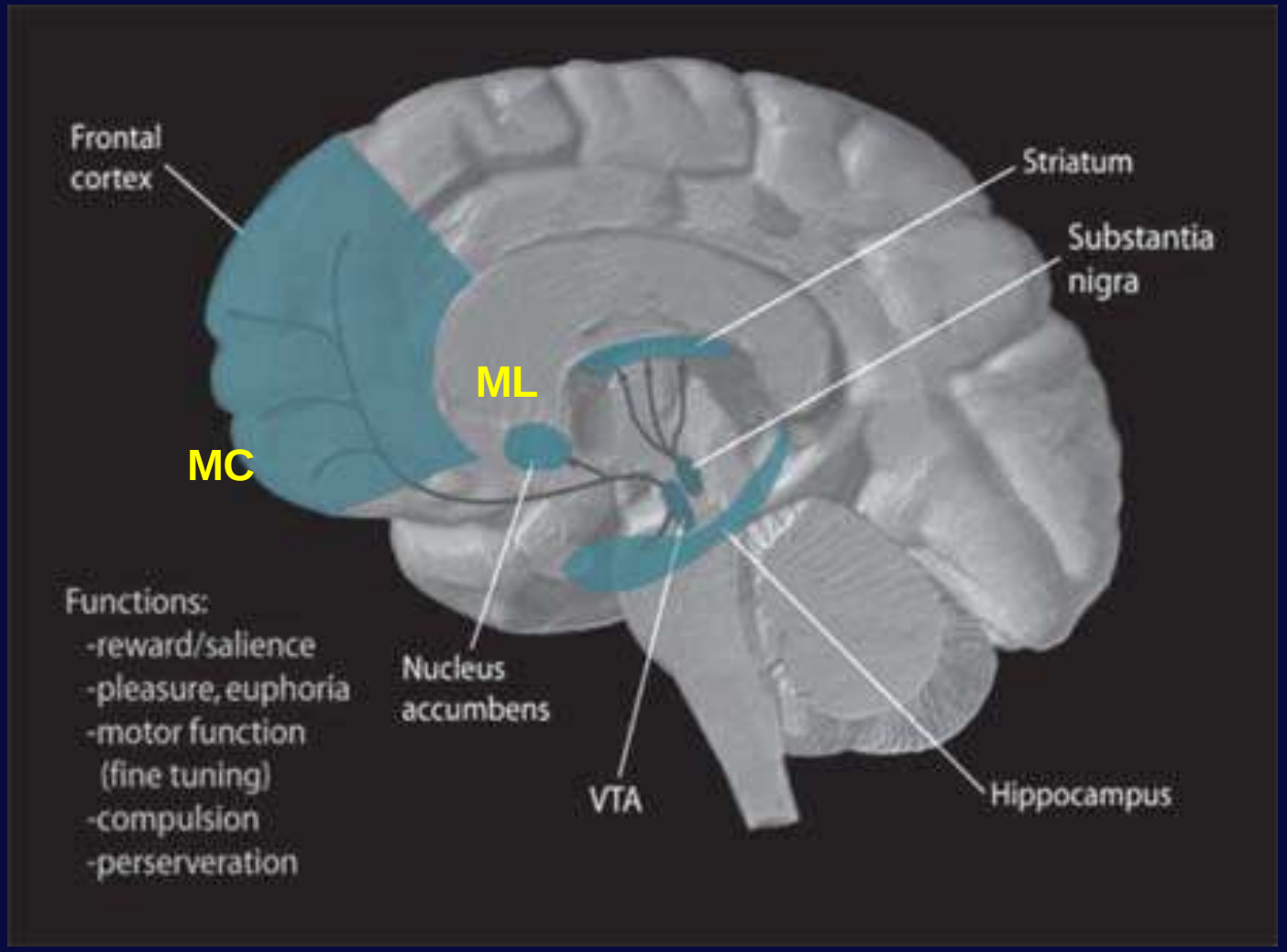


Stress System

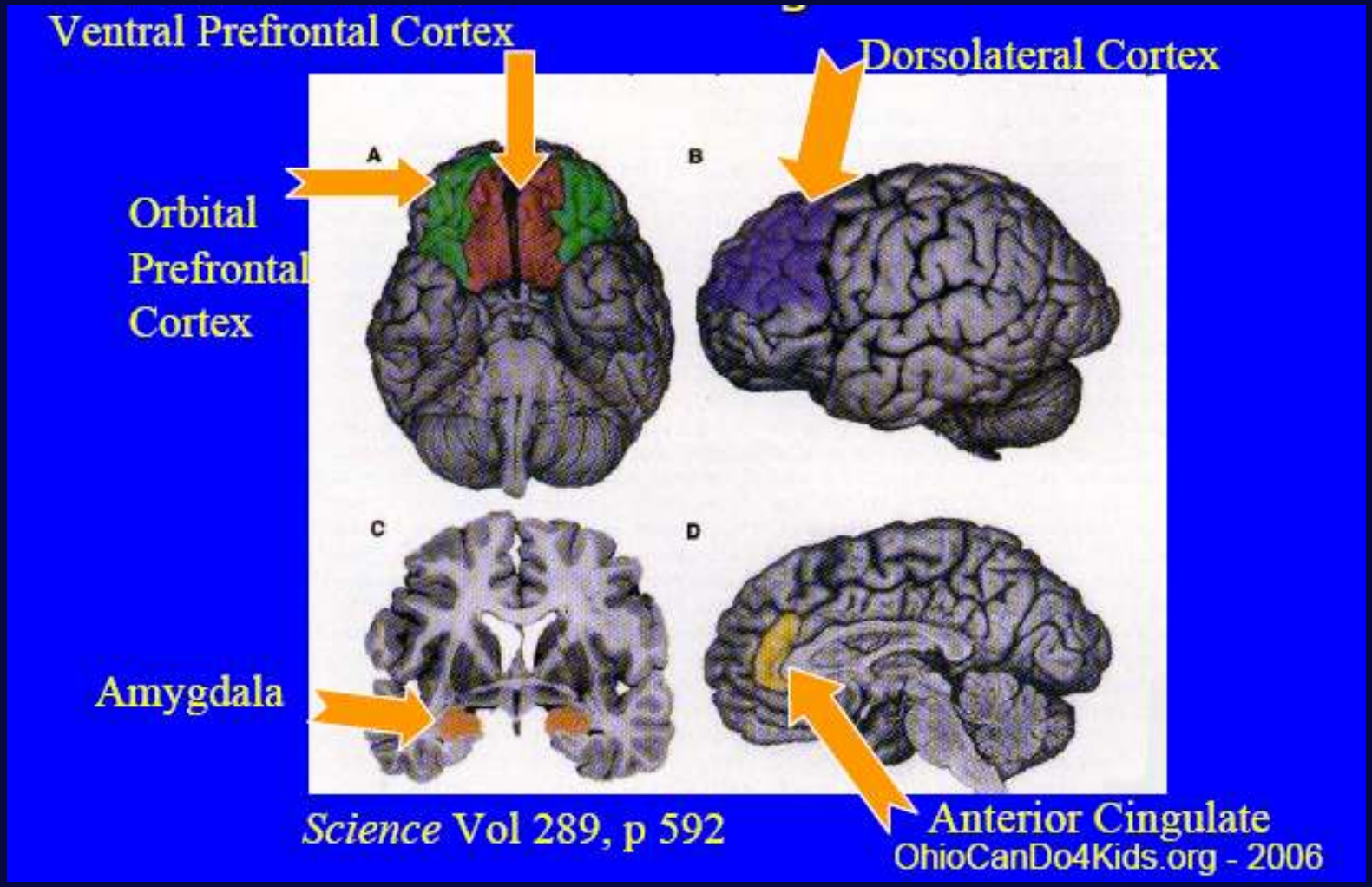


Chrousos
JAMA 1992

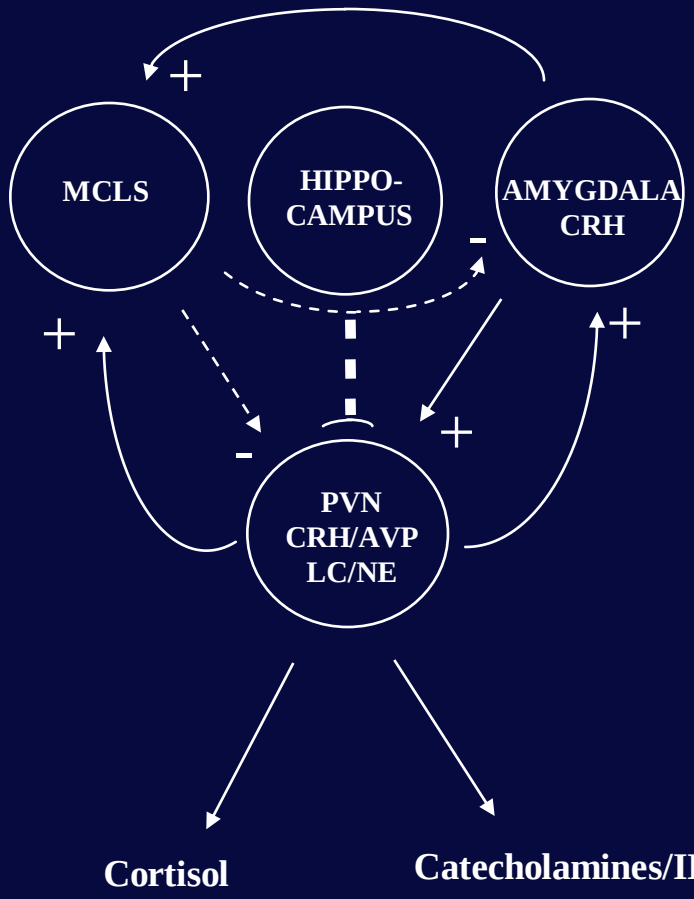
The Reward System



Structures related to emotional regulation



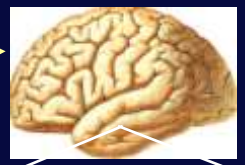
Acute Stress



Behavioral adaptation

Physical adaptation

G.P. Chrousos



STRESS SYSTEM
Amygdala CRH

HIPPOCAMPUS

CRH/AVP

LC/NE

ACTH

F

NE/E

iCRH

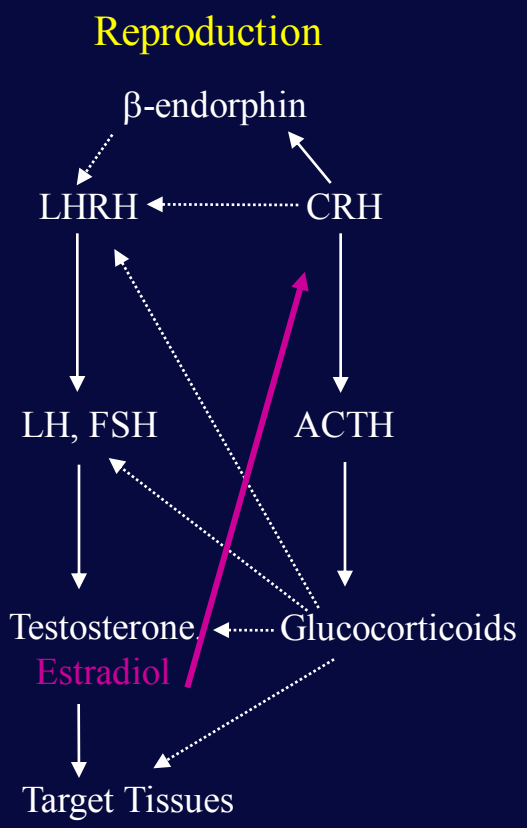
+

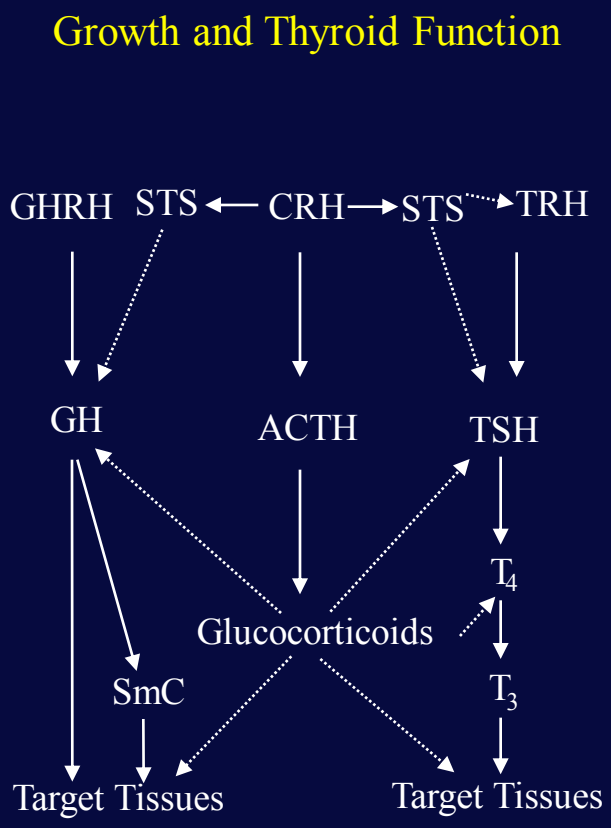
IL-6

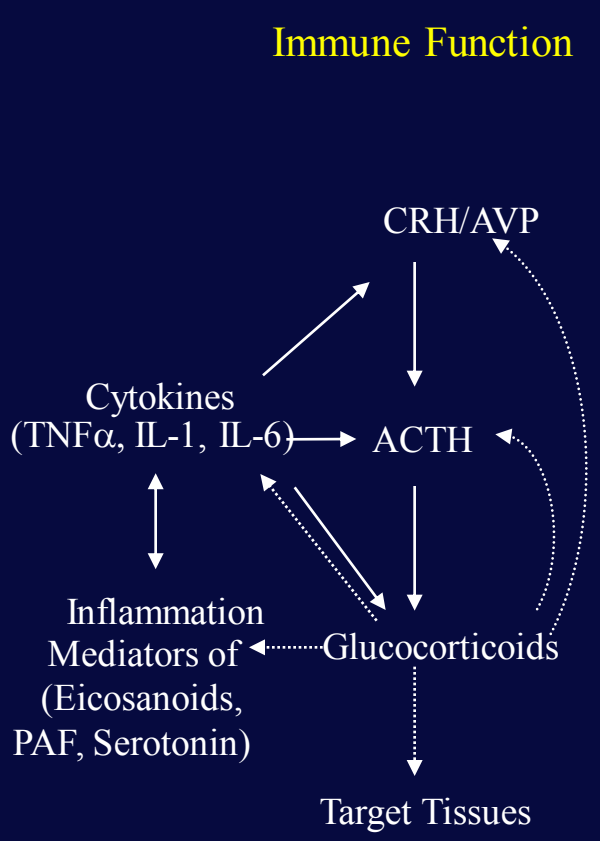
GH/IGF-1
LH/T
TSH/T_3

Inflammation

G.P. Chrousos







G.P. Chrousos JAMA 1992

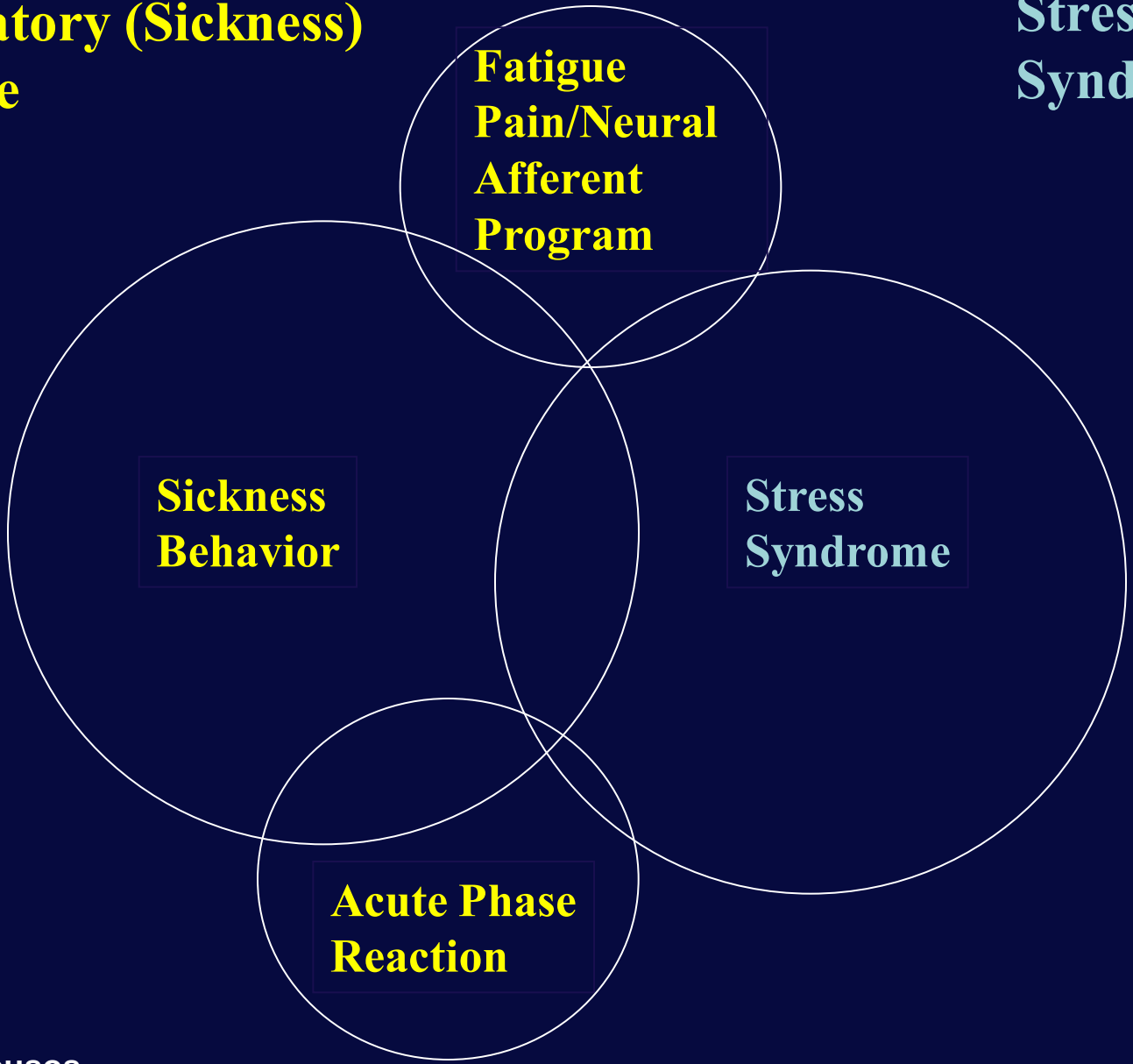
SICKNESS SYNDROME

ANOREXIA/NAUSEA
FATIGUE AND/OR DEPRESSED AFFECT
SOMNOLENCE
HYPERALGESIA ± HEADACHE
ELEVATED TEMPERATURE/ FEVER
INCREASED METABOLIC RATE

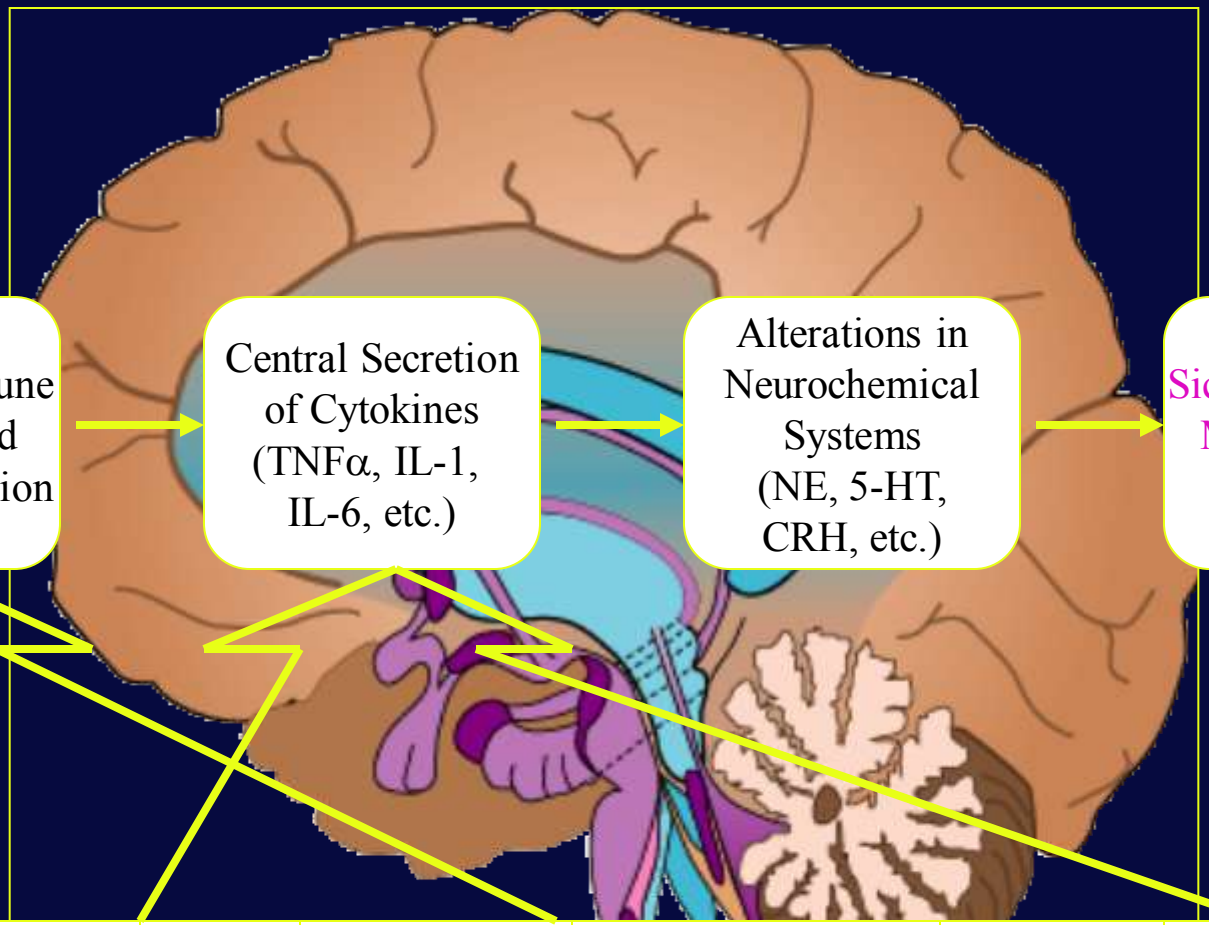
MOLECULAR EFFECTORS
INFLAMMATORY CYTOKINES/MEDIATORS

Inflammatory (Sickness) Syndrome

Stress Syndrome



G.P. Chrousos



Peripheral Immune Activation and Cytokine Secretion

Central Secretion of Cytokines (TNFα, IL-1, IL-6, etc.)

Alterations in Neurochemical Systems (NE, 5-HT, CRH, etc.)

Sickness Syndrome Manifestations

Peripheral Infections

Post Partum Period

Stress

Autoimmune Disease

Neurodegenerative Disease

Stroke, Trauma

Intracerebral Infections

G.P. Chrousos

Physical and Emotional Stress

- Stress Concepts
- Stress Mechanisms
- Effects Stress on the Organism
- Coping with Stress

Physical and Emotional Stress

- **Timing** (Critical periods=prenatal, first 5 y and adolescence)
- **Acuity**
- **Chronicity**

THE STRESS SYSTEM
Pathophysiology

Acuity *vs.* Chronicity
of Stress System Activation

THE STRESS SYSTEM
Pathophysiology

Acute effects of stress system activation

- Asthma, eczema, urticaria
- Migraine and tension headache
- Gastrointestinal pain
- Hypertensive episode, CVA, death (compromised host)
- Panic attack
- Cardiac ischemia, MI, Arrhythmia, death (compromised host)
- Psychotic episode

THE STRESS SYSTEM
Pathophysiology

Chronic effects of stress system malfunction

- Behavioral
  - *Logos & Self-regulation (early effects)*
  - Fear/Anger
  - Reward/Punishment
- Cardiovascular
- Metabolic
- Immune
- Pain and Fatigue
- Sleep

THE STRESS SYSTEM
Pathophysiology

Chronic effects of stress system activation:

- Anxiety, depression, addiction, anti-social behavior, psychosomatic disorders, fatigue, pain

- Loss of weight, poor growth, obesity, metabolic syndrome, smoldering inflammation, Immune dysfunction, atherosclerosis, CVD

- Osteoporosis

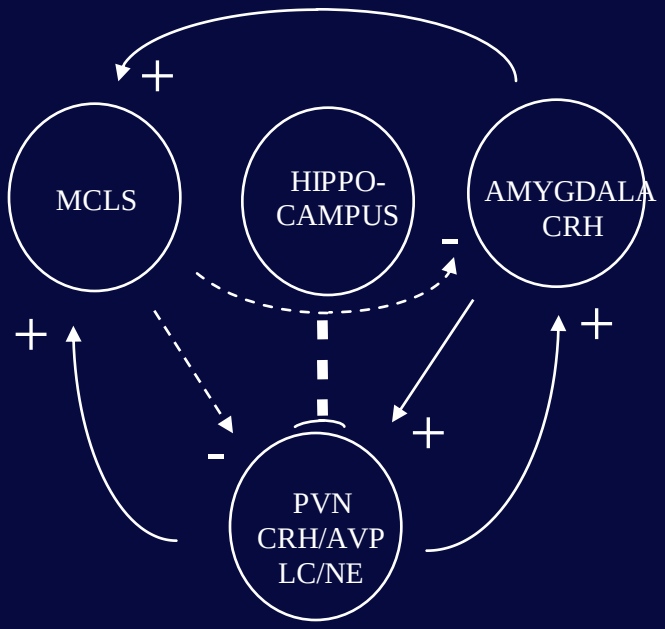
- Premature aging of all vulnerable organs, including the brain (neurodegeneration) and the skin

- Vulnerability to infections and cancer

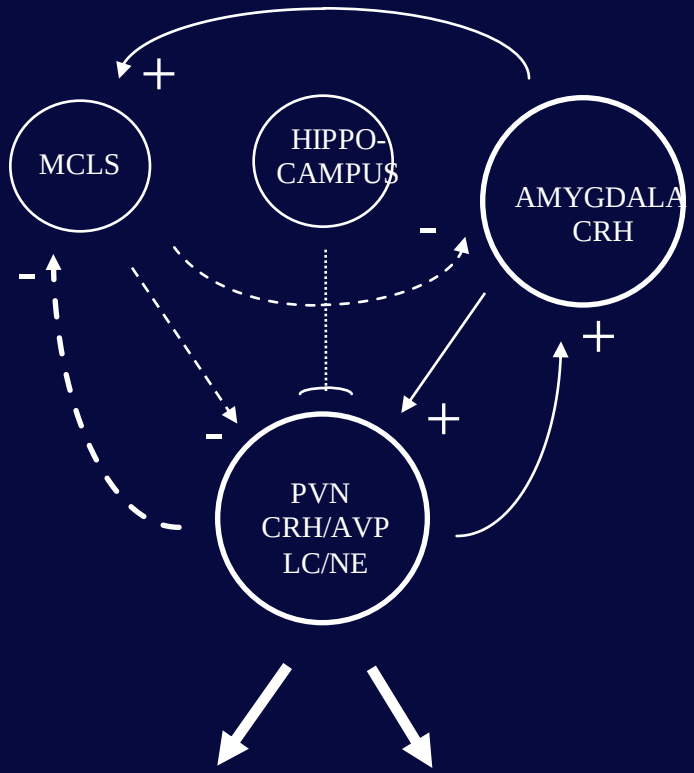
↑

CHRONIC NONCOMMUNICABLE DISEASES

Acute Stress



Stress Hyper-responsive Child/Adult



Cortisol + Catecholamines/IL-6

Behavioral consequences + **Somatic consequences**

Maladjustment disorders — Growth retardation
Anxiety, Depression — Metabolic syndrome X
Personality disorders — Cardiovascular disease
Addiction, Psychosomatics — Osteoporosis

Adjusment *vs.* Maladjustment

Sickness s.

G.P. Chrousos

HYPERCYTOKINEMIA

TRAUMA/ BURNS

INFECTIOUS ILLNESSES

AUTOIMMUNE INFLAMMATORY DISEASES

ALLERGIC INFLAMMATIONS

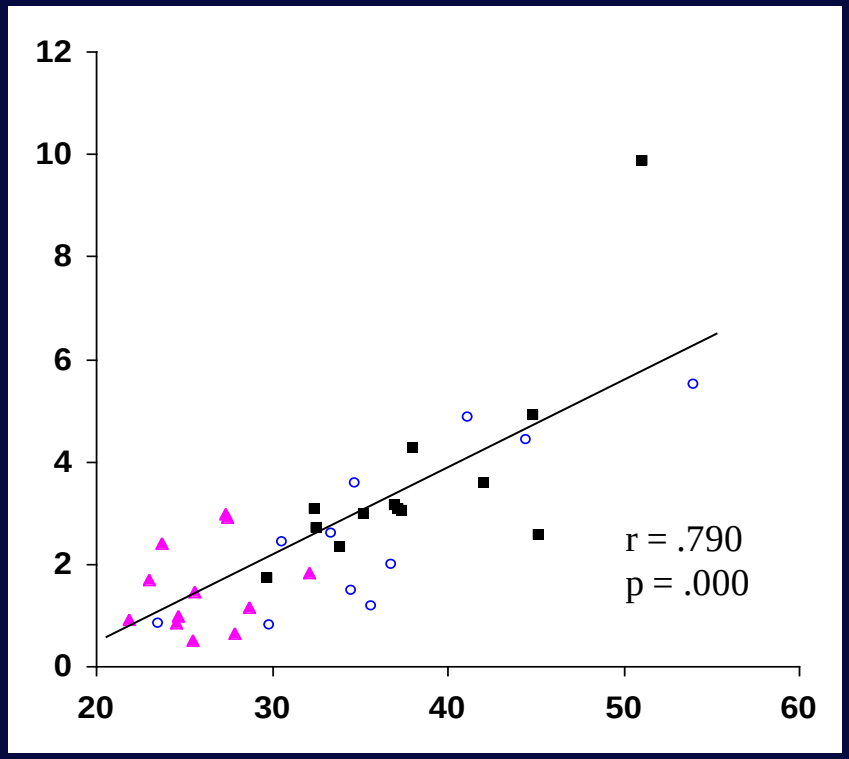
CNS INFLAMMATIONS

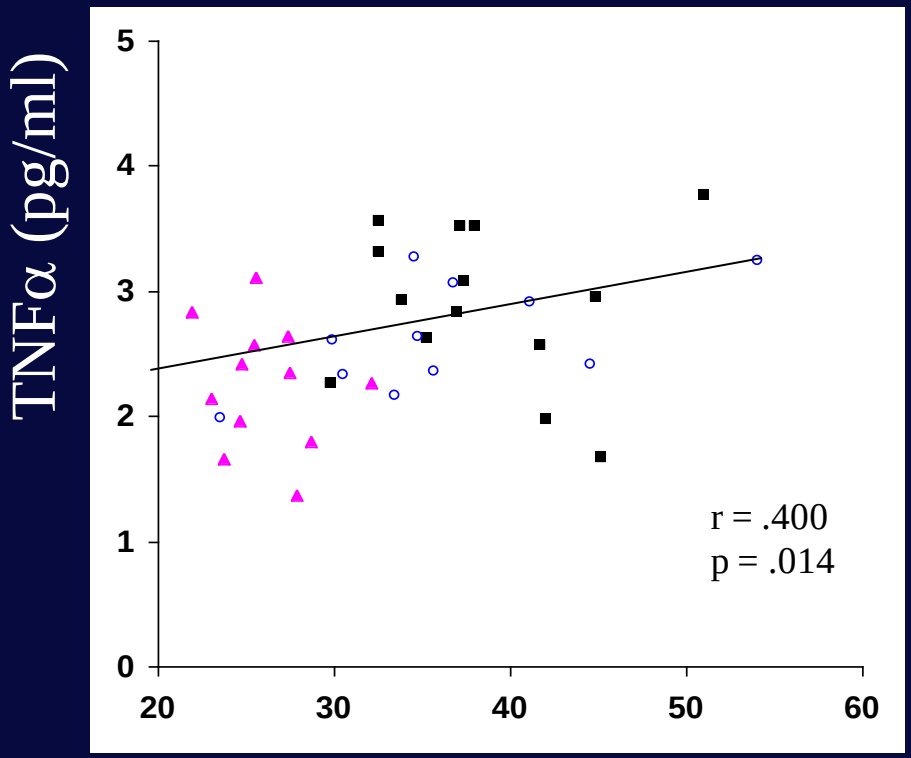
NONINFLAMMATORY STRESS

OBESITY/VISCERAL OBESITY

AGING

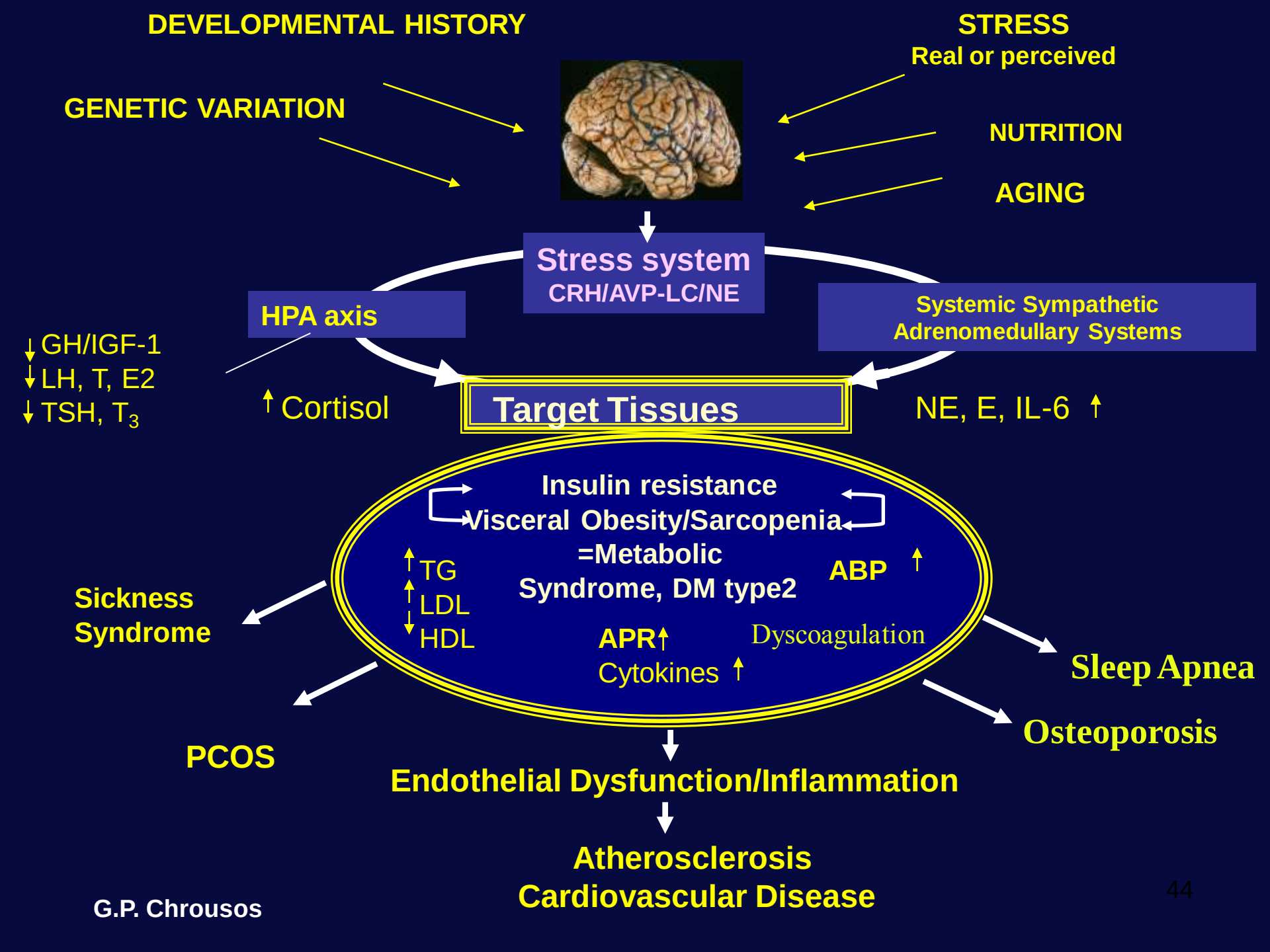
Both IL-6 and TNFα correlate with BMI



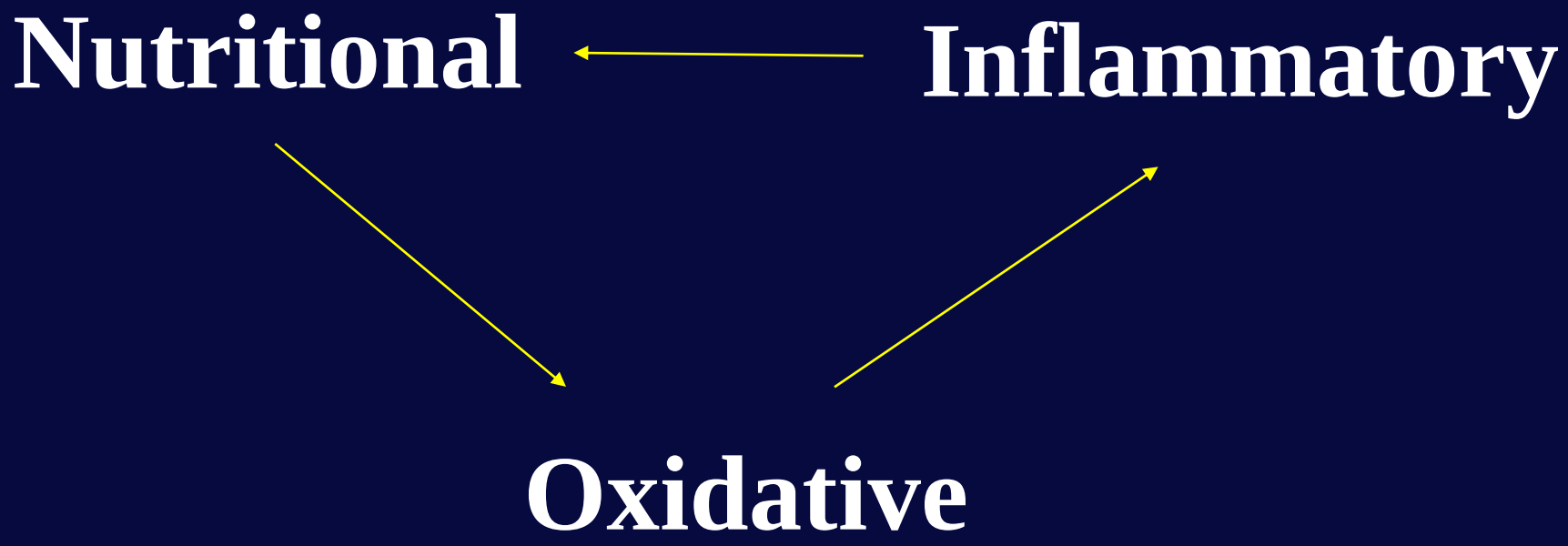


BMI

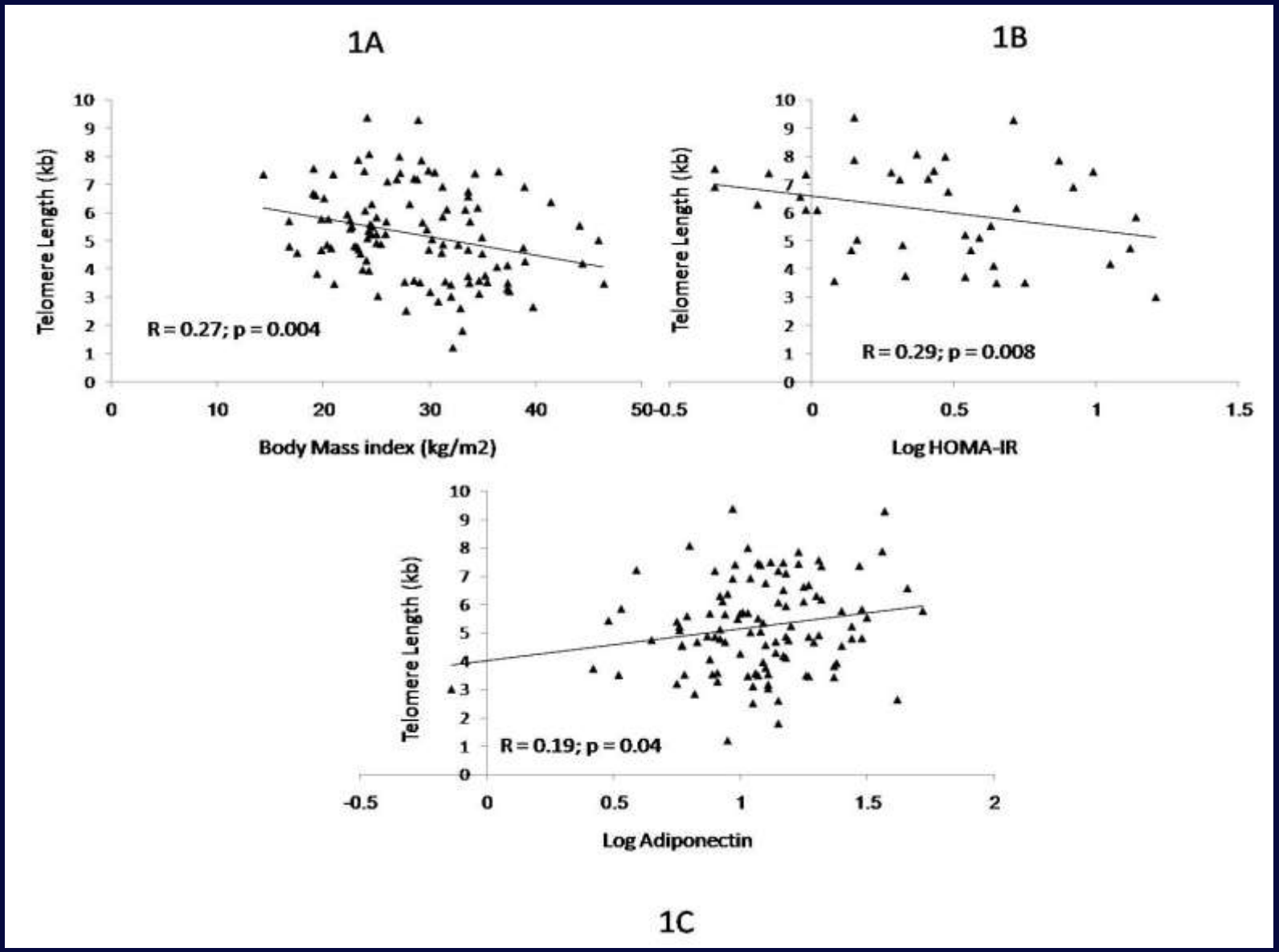
Vgontzas *et al.* JCEM 1997


DEVELOPMENTAL HISTORY
STRESS
Real or perceived
GENETIC VARIATION
NUTRITION
AGING
Stress system
CRH/AVP-LC/NE
HPA axis
Systemic Sympathetic
Adrenomedullary Systems
↓GH/IGF-1
↓LH, T, E2
↓TSH, T3
↑Cortisol
Target Tissues
NE, E, IL-6 ↑
Insulin resistance
Visceral Obesity/Sarcopenia
=Metabolic
Syndrome, DM type2
↑TG
↑LDL
↓HDL
ABP ↑
APR↑
Cytokines ↑
Dyscoagulation
Sickness
Syndrome
Sleep Apnea
PCOS
Osteoporosis
Endothelial Dysfunction/Inflammation
Atherosclerosis
Cardiovascular Disease
G.P. Chrousos

Cellular Stress



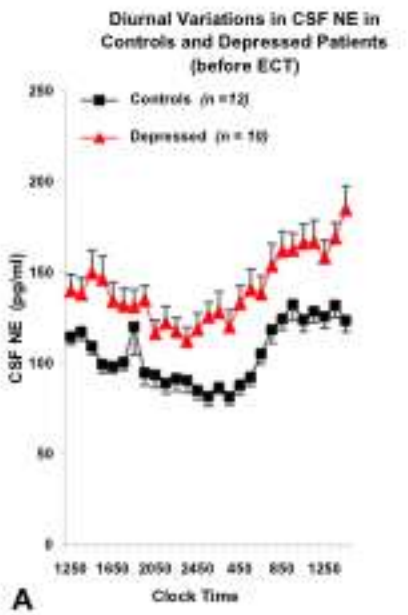
Cellular Stress

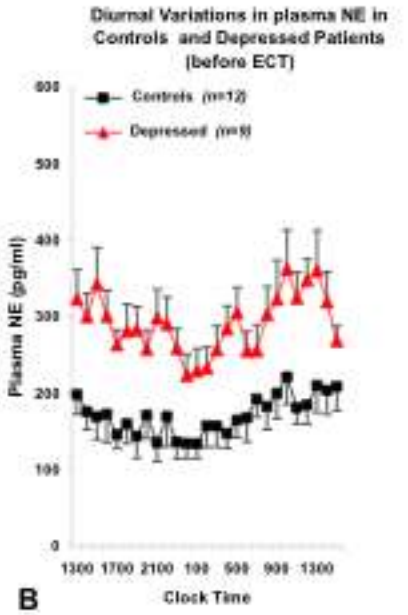

1A
Telomere Length (kb)
R = 0.27; p = 0.004
Body Mass index (kg/m2)
1B
Telomere Length (kb)
R = 0.29; p = 0.008
Log HOMA-IR
Telomere Length (kb)
R = 0.19; p = 0.04
Log Adiponectin
1C

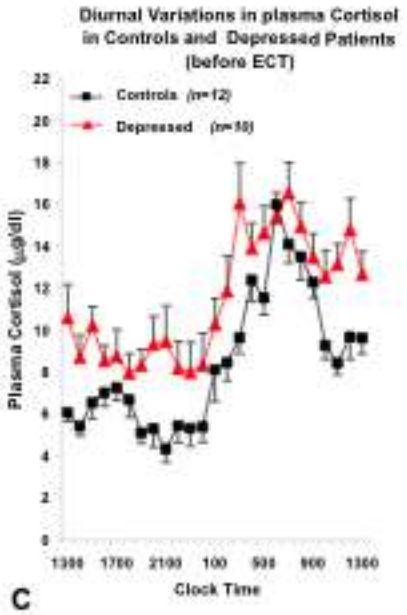
“Grief and fear when lingering provoke melancholia”

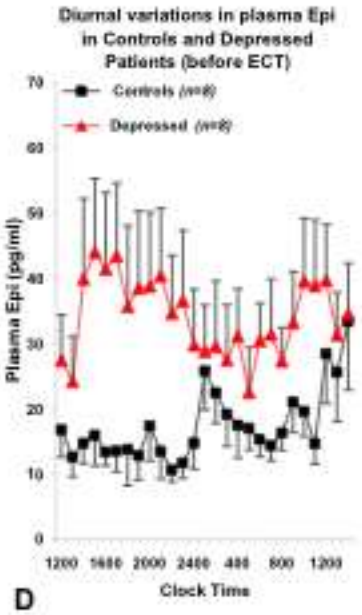
Hippocrates 460-479 BCE

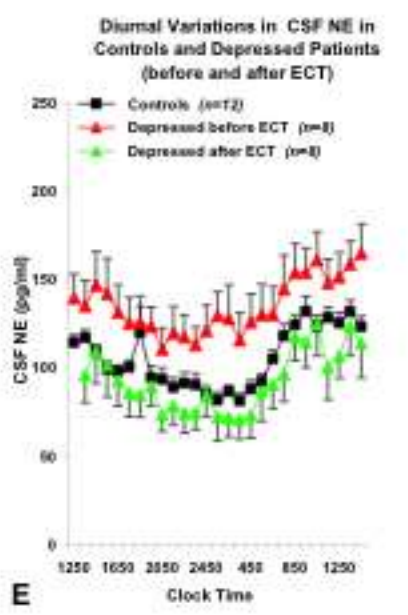
STRESS SYSTEM HYPERACTIVITY AND PARADOXIC OBESITY IN DEPRESSION

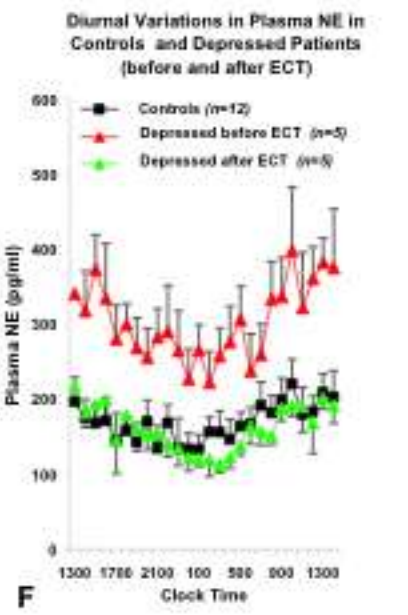

Diurnal Variations in CSF NE in Controls and Depressed Patients (before ECT)
Controls (n =12)
Depressed (n = 10)
CSF NE (pg/ml)
Clock Time
A

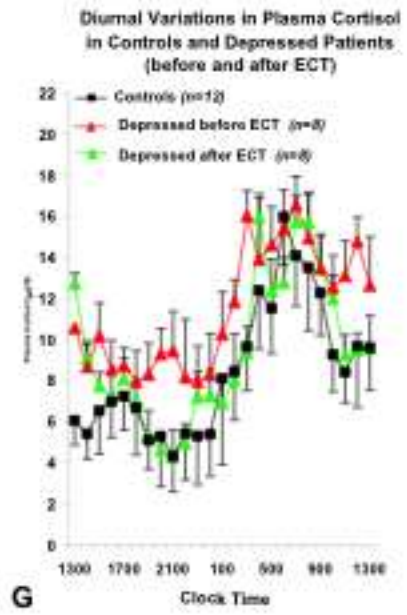

Diurnal Variations in plasma NE in Controls and Depressed Patients (before ECT)
Controls (n=12)
Depressed (n=9)
Plasma NE (pg/ml)
Clock Time
B

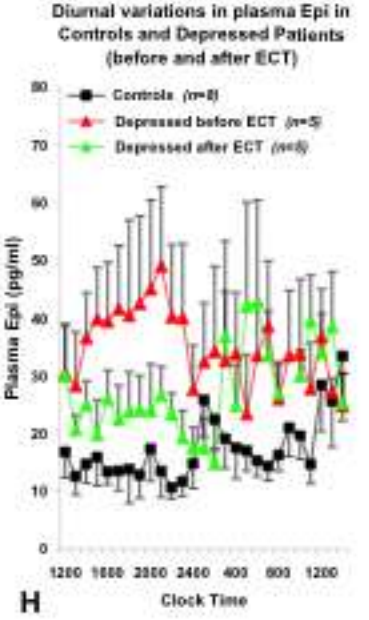

Diurnal Variations in plasma Cortisol in Controls and Depressed Patients (before ECT)
Controls (n=12)
Depressed (n=10)
Plasma Cortisol (µg/dl)
Clock Time
C


Diurnal variations in plasma Epi in Controls and Depressed Patients (before ECT)
Controls (n=8)
Depressed (n=8)
Plasma Epi (pg/ml)
Clock Time
D

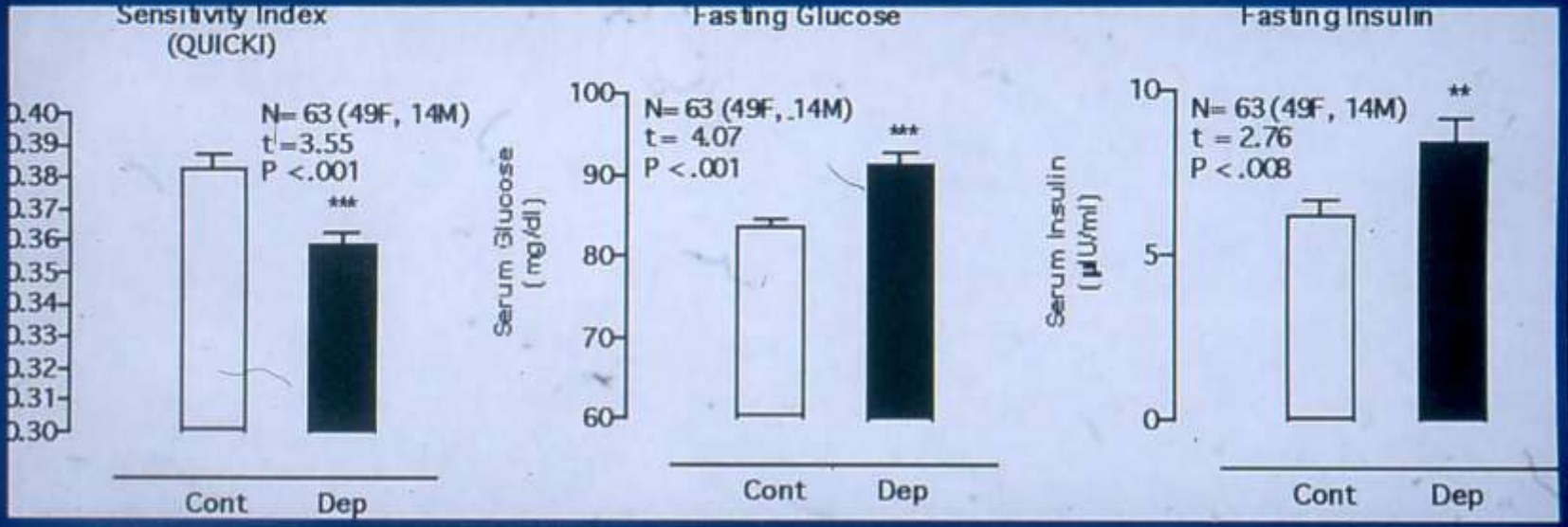

Diurnal Variations in CSF NE in Controls and Depressed Patients (before and after ECT)
Controls (n=12)
Depressed before ECT (n=8)
Depressed after ECT (n=8)
CSF NE (pg/ml)
Clock Time
E

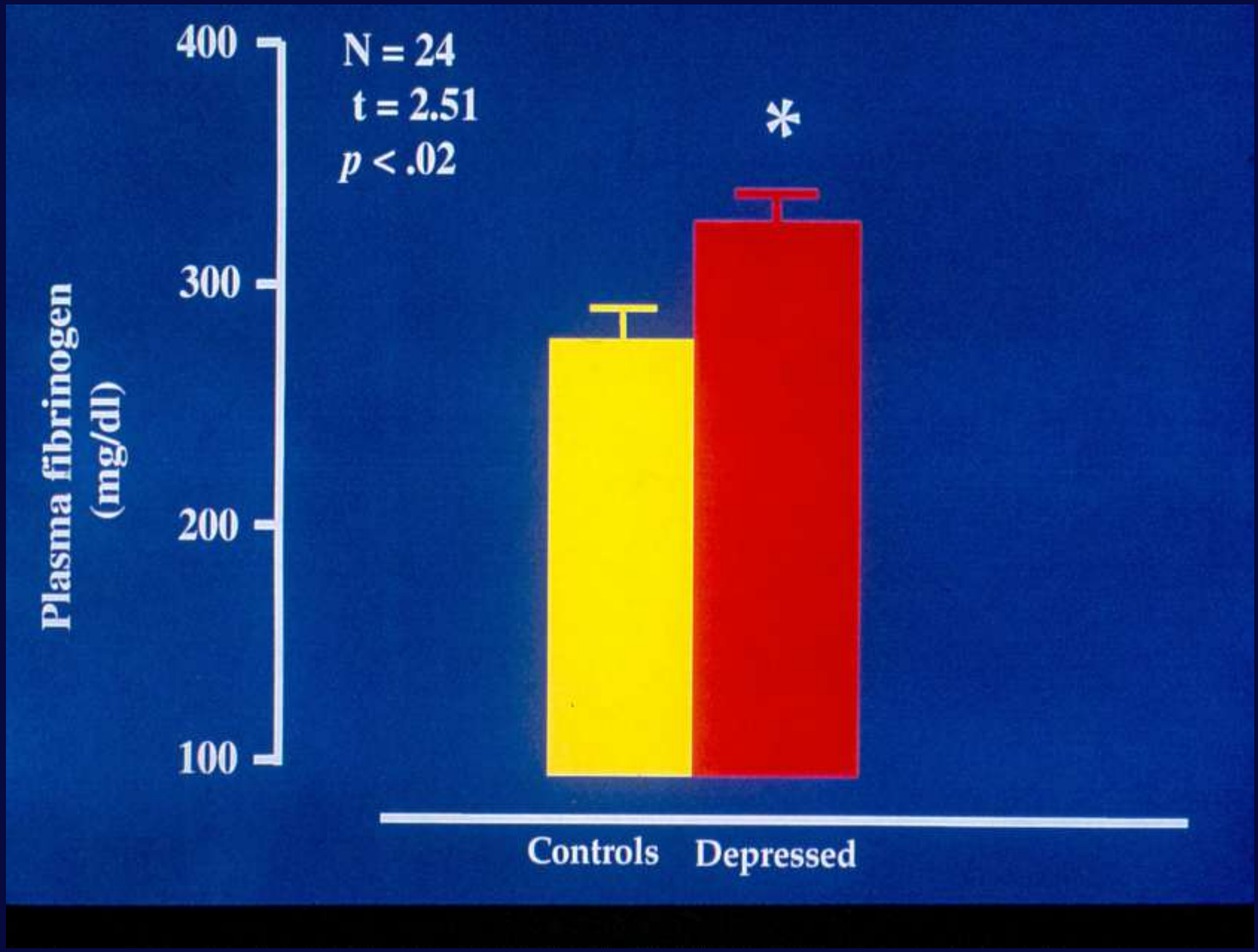

Diurnal Variations in Plasma NE in Controls and Depressed Patients (before and after ECT)
Controls (n=12)
Depressed before ECT (n=5)
Depressed after ECT (n=5)
Plasma NE (pg/ml)
Clock Time
F

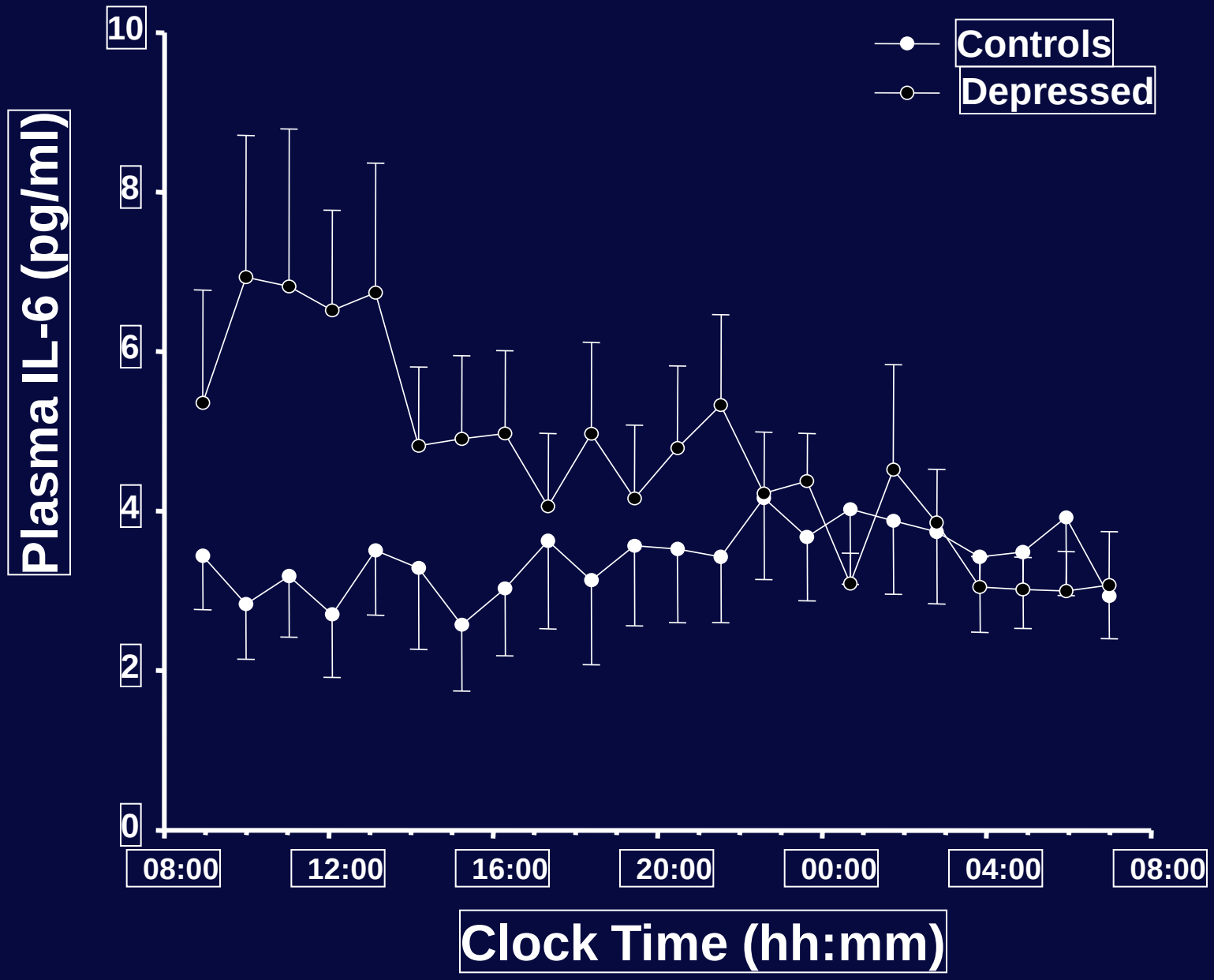

Diurnal Variations in Plasma Cortisol in Controls and Depressed Patients (before and after ECT)
Controls (n=12)
Depressed before ECT (n=8)
Depressed after ECT (n=8)
Clock Time
G


Diurnal variations in plasma Epi in Controls and Depressed Patients (before and after ECT)
Controls (n=8)
Depressed before ECT (n=5)
Depressed after ECT (n=5)
Plasma Epi (pg/ml)
Clock Time
H

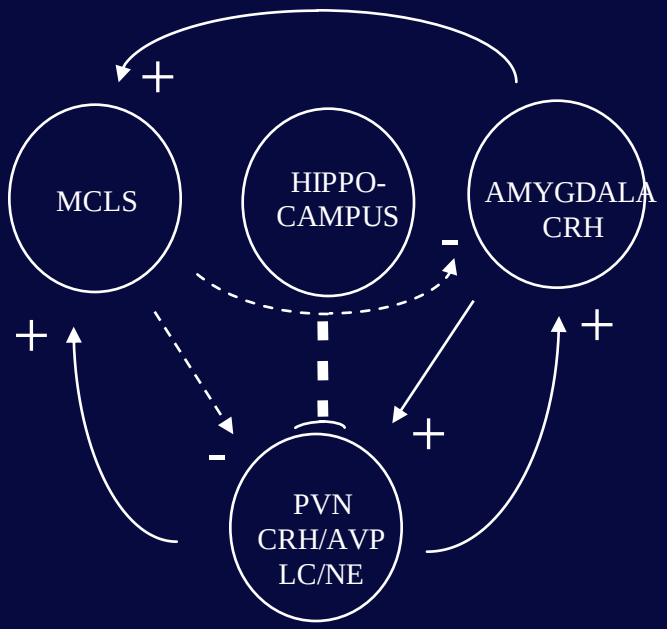
	Age	BMI	Fasting Serum Insulin	Fasting Serum Glucose	Insulin Sensitivity
Depressed	39.016 ± 1.218	24.6 ± 0.5	8.43 ± 0.71	91.16 ± 1.491	0.354 ± .004
Controls	38.079 ± 1.222	24.4 ± 0.4	6.21 ± .49	83.54 ± 1.1	0.381 ± .006
p value			*p*=.008	*p*=.0001	*p*<.0008



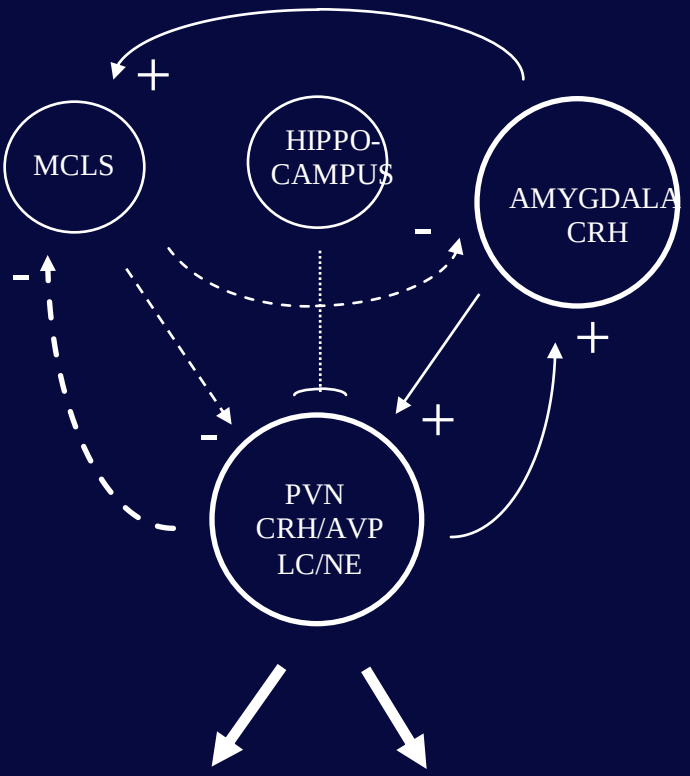

400
300
200
100
Plasma fibrinogen (mg/dl)
N = 24
t = 2.51
p < .02
*
Controls
Depressed


Controls
Depressed
Plasma IL-6 (pg/ml)
10
8
6
4
2
0
08:00
12:00
16:00
20:00
00:00
04:00
08:00
Clock Time (hh:mm)

Acute Stress



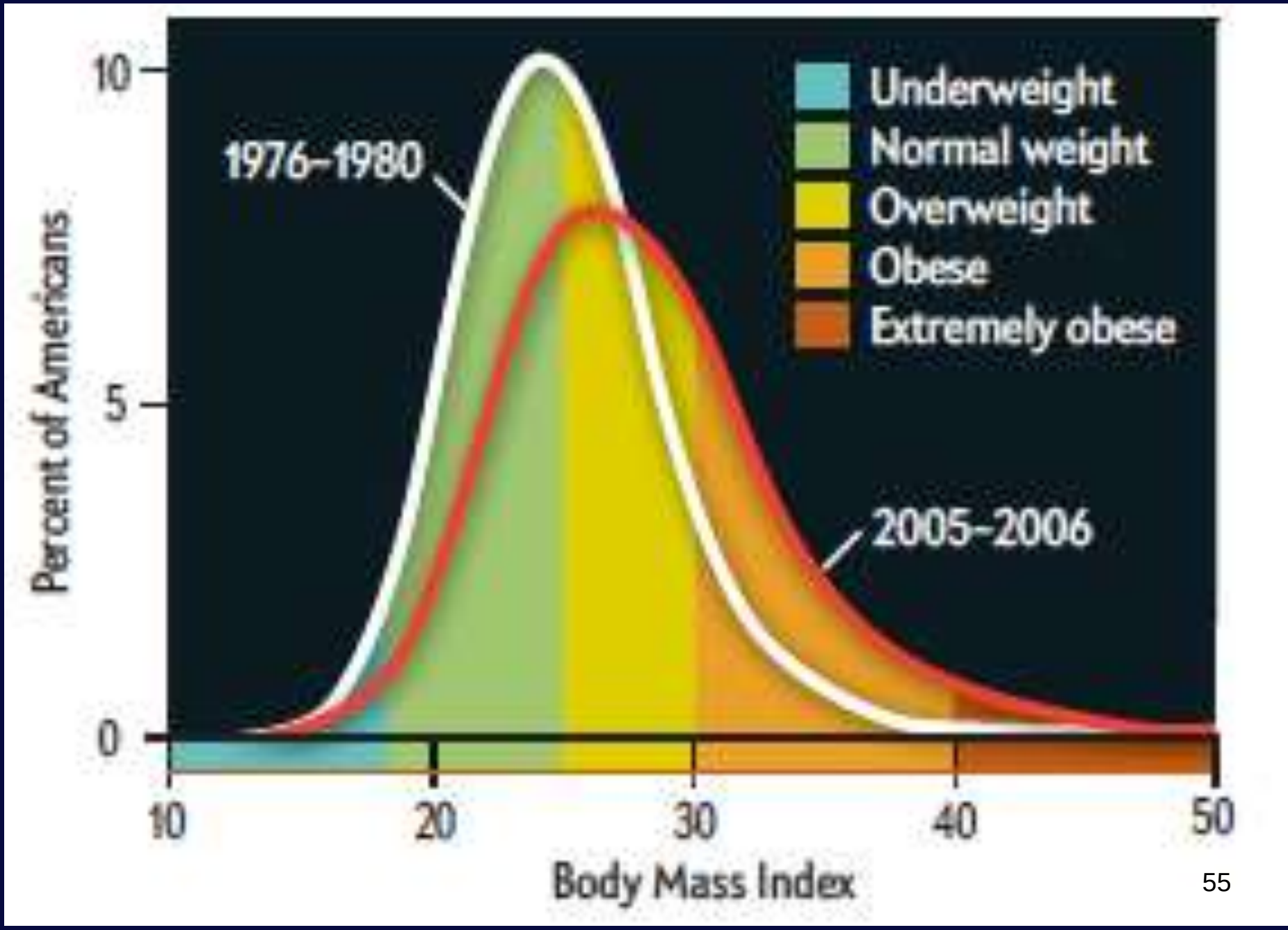
Melancholic Depression



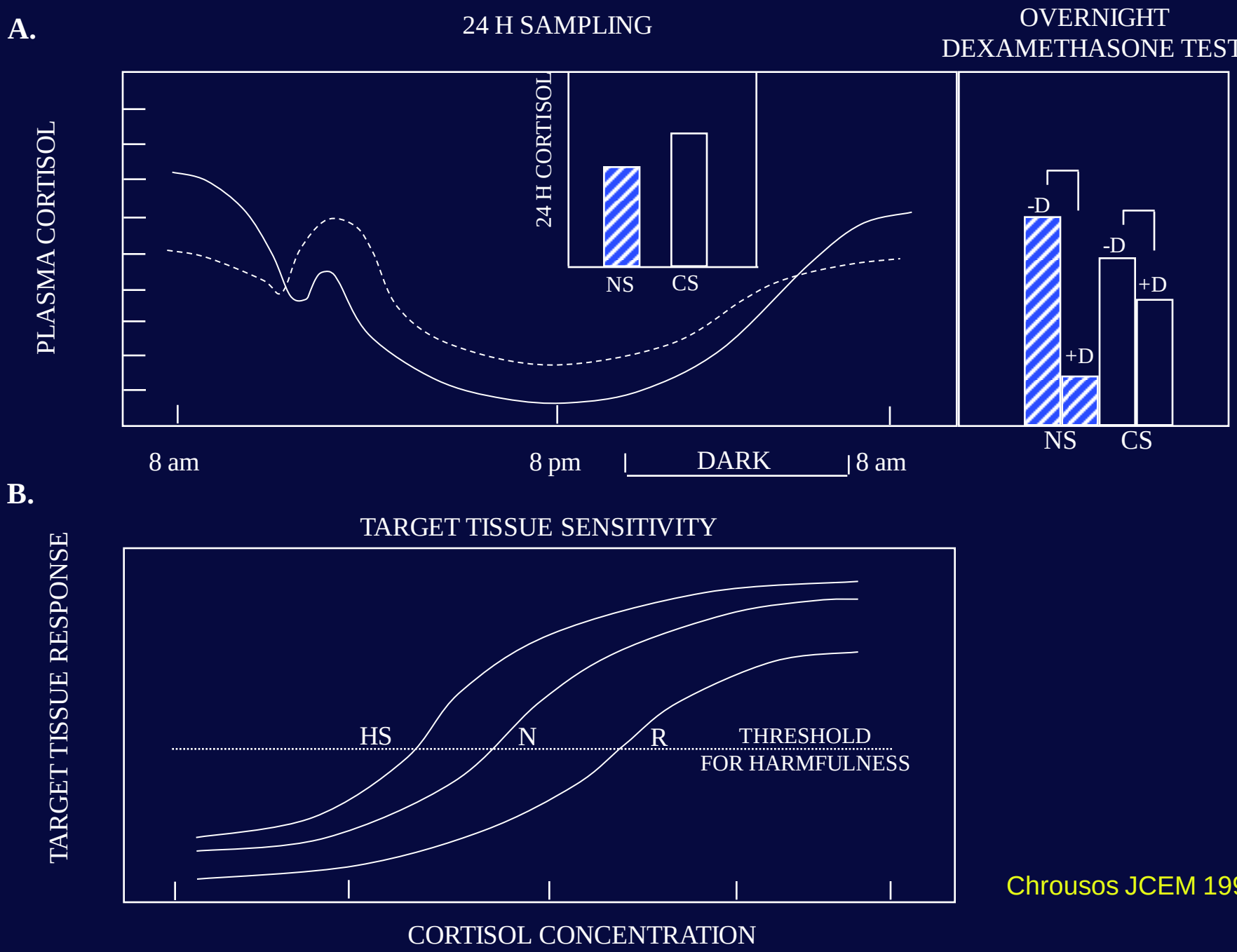
Cortisol + Catecholamines+IL-6

Behavioral consequences	+	Somatic consequences
Anhedonia,Fatigue,		**Metabolic syndrome X**
Insomnia, Anorexia.		Cardiovascular disease
Loss of libido		Osteoporosis

Sickness syndrome

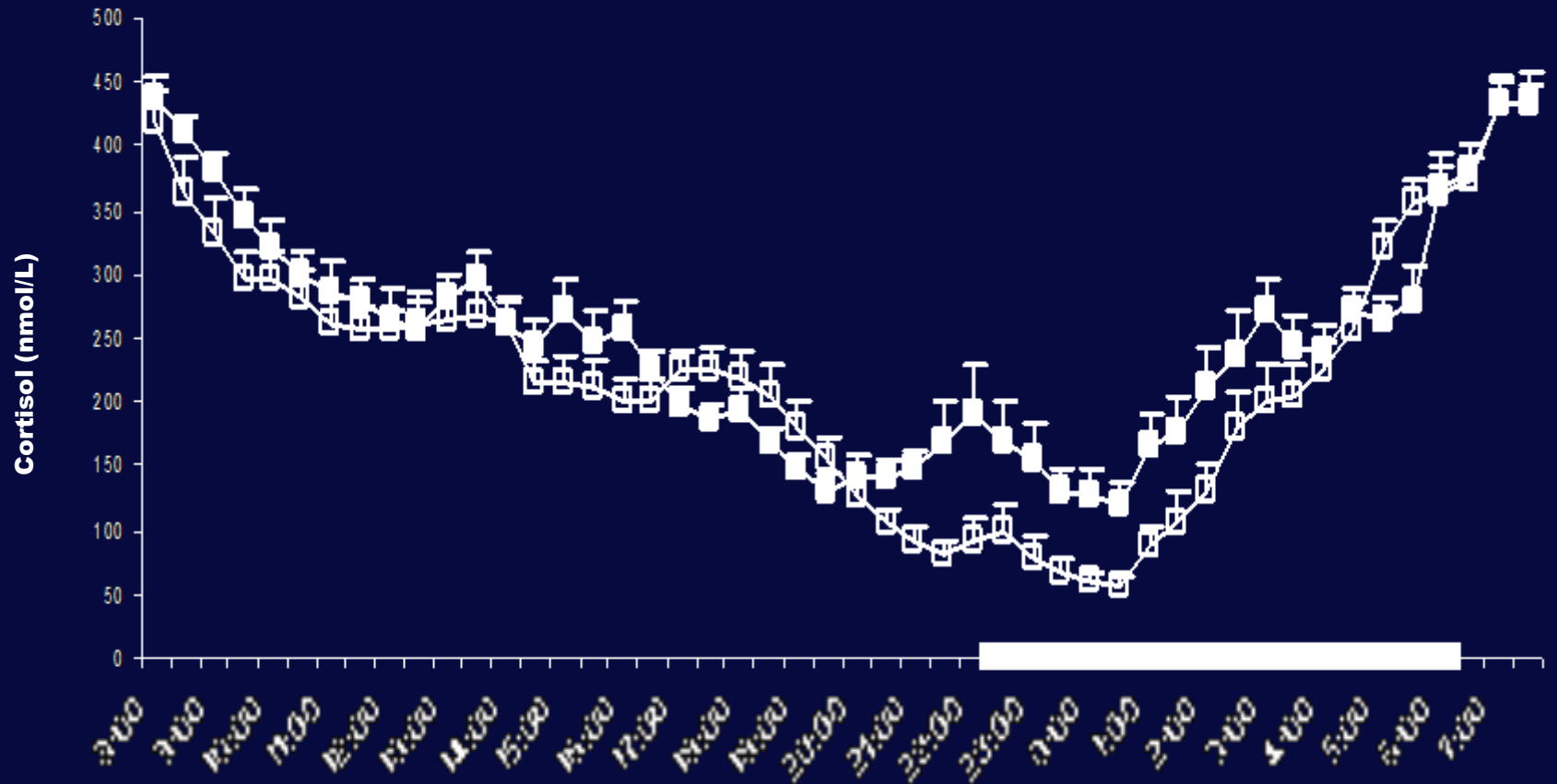

10
5
0
Percent of Americans
1976–1980
2005–2006
Underweight
Normal weight
Overweight
Obese
Extremely obese
10
20
30
40
50
Body Mass Index


Stress
Depression
Inflammation,
Sleep disturbances,
Fatigue
Metabolic Syndrome



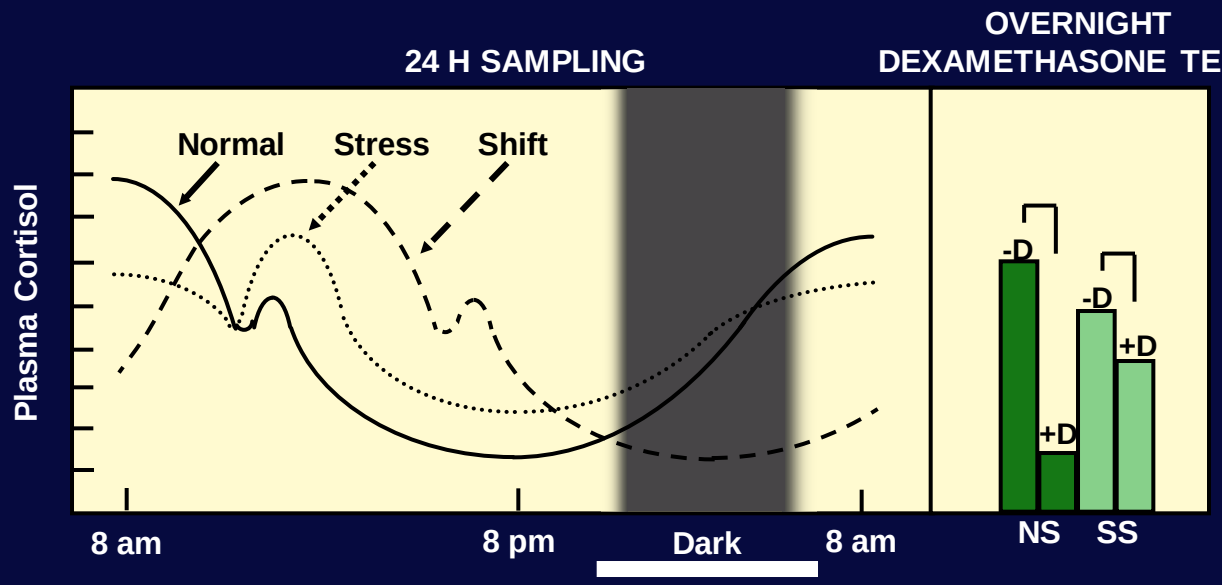
Chrousos JCEM 1998

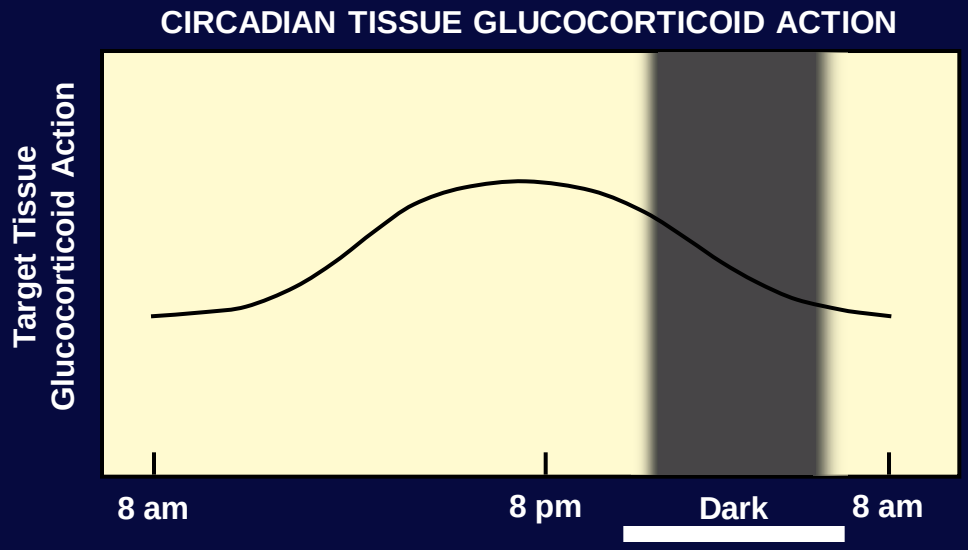
HPA axis and old age



Vgontzas *et al*. JCEM 2003

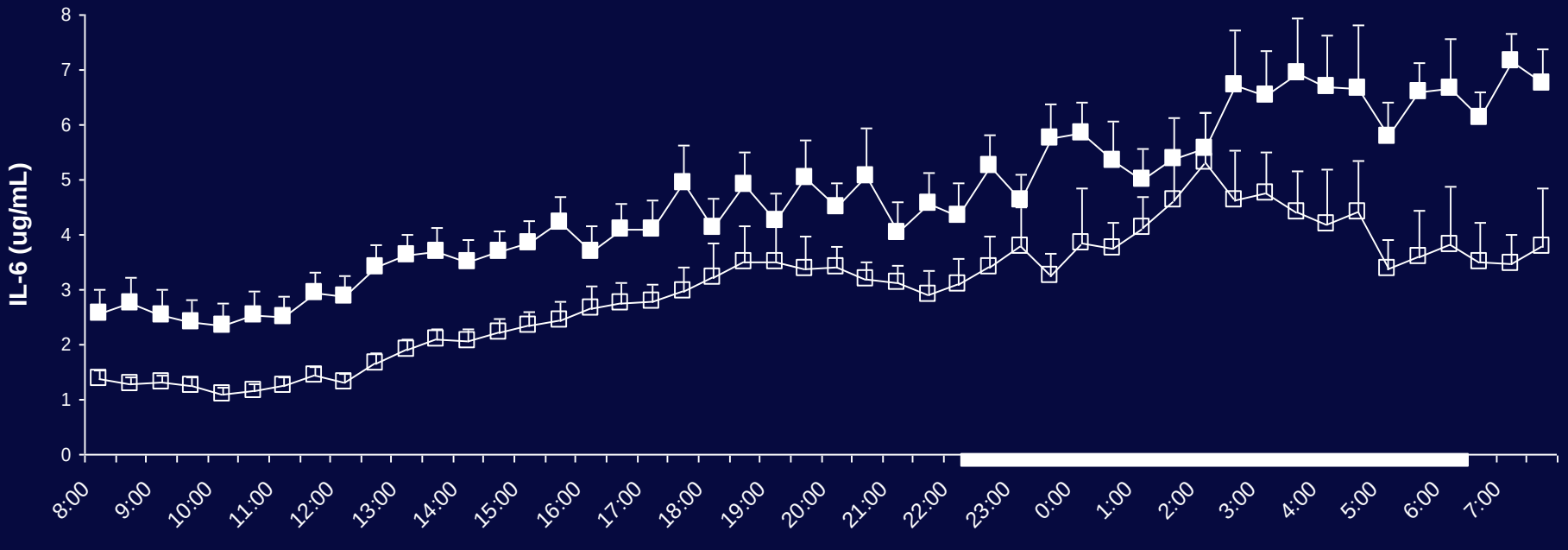
Uncoupling between Circadian Rhythm of Circulating Cortisol and Tissue Glucocorticoid Sensitivity





G.P. Chrousos

Cytokines and old age

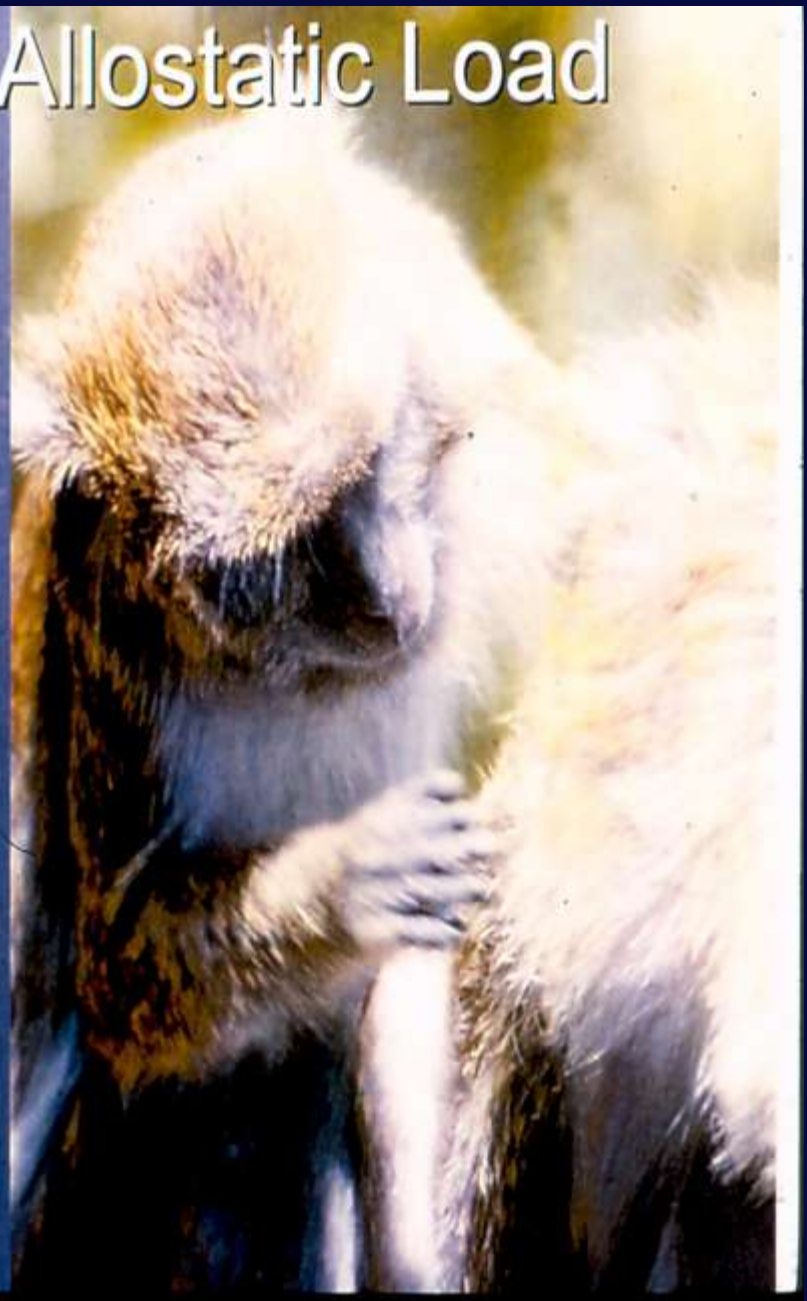


Time (Clock Hours)

Vgontzas *et al*. JCEM 2003

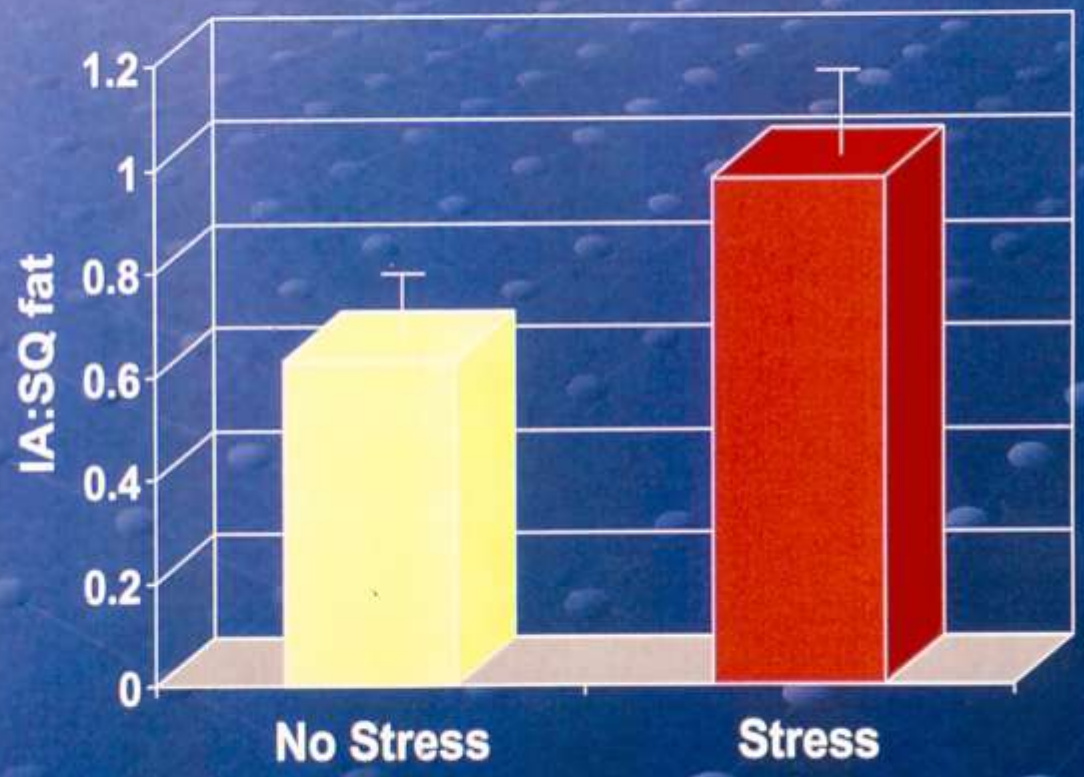
Animal Models of Allostatic Load

- Mild, Chronic (1000 days), Social Stress
- Atherogenic Diet
- Multiple System Measurements of Wear & Tear
- Morbidity/Mortality Endpoints



Social Stress Causes Visceral Fat Deposition

- Males
- Social reorg stress
- N=40



Jayo et al., 1993

THE STRESS SYSTEM AND THE METABOLIC SYNDROME

Cushing Syndrome

Pseudocushing Syndrome

Chronic Active Alcoholism

Melancholic Depression

Metabolic Syndrome

“Benign” Premature Adrenarche

Post Long Periods of Stress

Linkage Studies with GR

AIDS-related insulin resistance/lipodystrophy

Monkey Studies

Seasonal Depression

Atypical Depression

THE STRESS SYSTEM AND THE METABOLIC SYNDROME

Post Long Periods of Stress

Neoplasia Rx
Anorexia Nervosa
Malnutrition
Extreme Athleticism
Addictions

Disease and Disadvantage in the United States and in England

James Banks, PhD; Michael Marmot, MD; Zoe Oldfield, MSc; James P. Smith, PhD

***JAMA.* 2006;295:2037-2045.**

Context The United States spends considerably more money on health care than the United Kingdom, but whether that translates to better health outcomes is unknown.

Objective To assess the relative heath status of older individuals in England and the United States, especially how their health status varies by important indicators of socioeconomic position.

Disease and Disadvantage in the United States and in England

James Banks, PhD; Michael Marmot, MD; Zoe Oldfield, MSc; James P. Smith, PhD

***JAMA.* 2006;295:2037-2045.**

Americans:
CRP 20% higher
HDL 14 % lower

America's Sick Society

Paul Krugman

Editorial, Herald Tribune, 6 May 2006

—Being American seems to damage your health regardless of race and class.

—The richest third of Americans is in worse health than the poorest third of the English

—Bad habits do not explain the difference

Americans experience too much stress

Excess Deaths Associated with Underweight, Overweight, and Obesity

Flegal KM, Graubard BI, Williamson DF, Gail MH

JAMA. **2005;293:1861-1867.**

Risk of mortality is improving from NHANES I to NHANES II to NHANES III

Anti-stress and nutritional and other potential life extenders

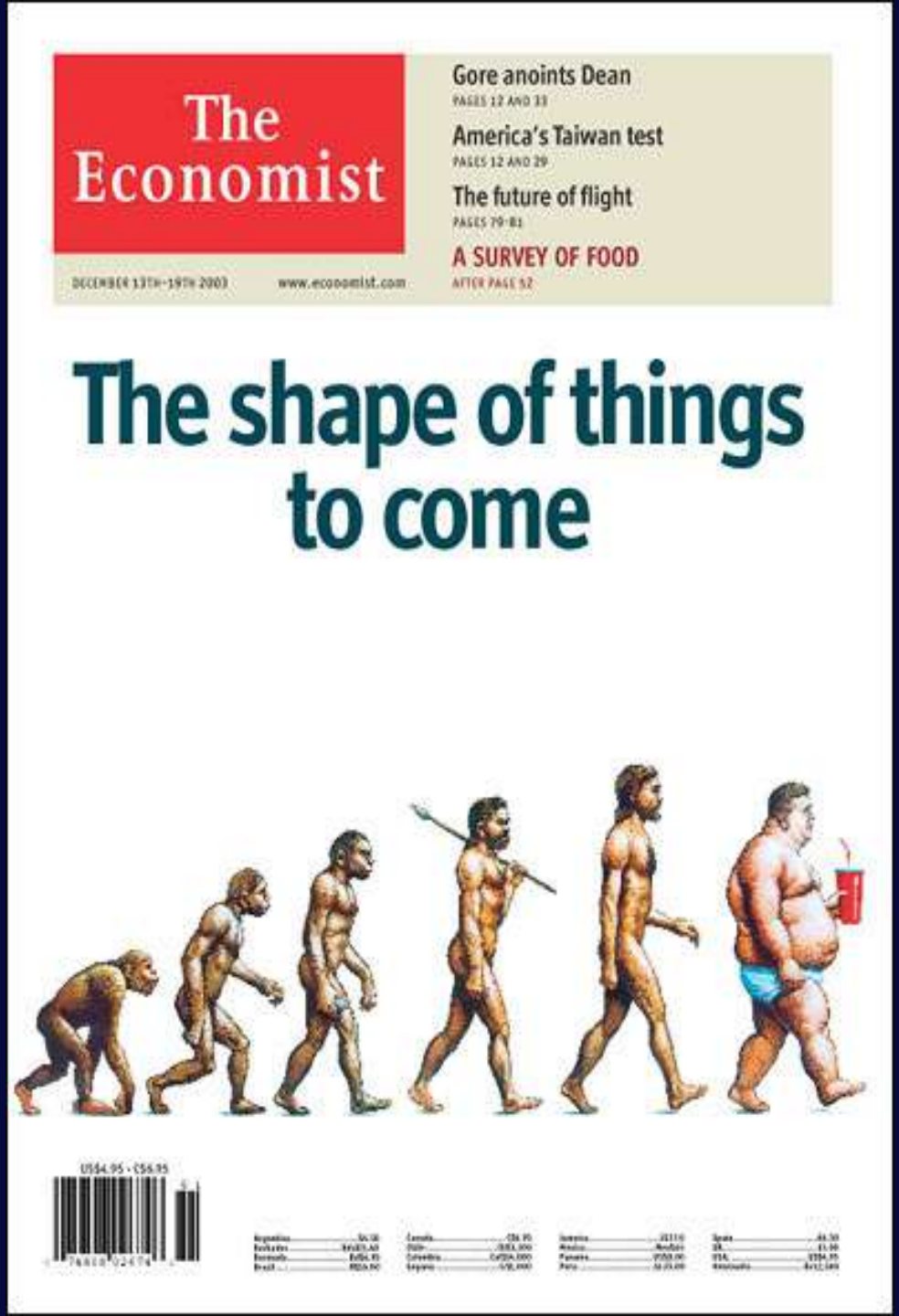
ANTI-STRESS- Beta-blockers, Anti-depressants, CEI, AT2-blockers

ANTI-INFLAMMATION- ω3 Fatty Acids, Unsaturated Fatty Acids, Statins, PPAR-γ agonists

ANTI-OXIDATION- Phytoestrogens, sulforafane

INSULIN SENSITIZATION- Diet, Exercise, Metformin, PPAR-γ agonists

ANTI-COAGULATION- Anti-platelet agents


The Economist
Gore anoints Dean
PAGES 12 AND 33
America's Taiwan test
PAGES 12 AND 29
The future of flight
PAGES 79-81
A SURVEY OF FOOD
AFTER PAGE 52
DECEMBER 13TH-19TH 2003
www.economist.com
The shape of things to come
US$4.95 · C$6.95

Selections of Genetic and Epigenetic Networks Participating in Functions Important for Human Survival and Species Preservation

RESPONSE TO SURVIVAL THREAT	SELECTIVE ADVANTAGE	CONTEMPORARY DISEASE
Combat starvation	Energy conservation	Obesity
Combat dehydration	Fluid and electrolyte conservation	Hypertension
Combat infectious diseases	Potent immune reaction	Autoimmunity/Allergy
Anticipate adversaries	Arousal/fear	Anxiety/insomnia
Minimize exposure to danger	Withdrawal	Depression
Prevent tissue strain/damage	Retain tissue integrity	Pain and fatigue syndromes

Chrousos, Amer J Med 2004

ENVIRONMENTAL STRESSORS

Starvation
Dehydration
Injurious agents-inflammations
Adversaries-anticipation
Adversaries-avoidance
Injury-minimization

Species *vs.* Individual

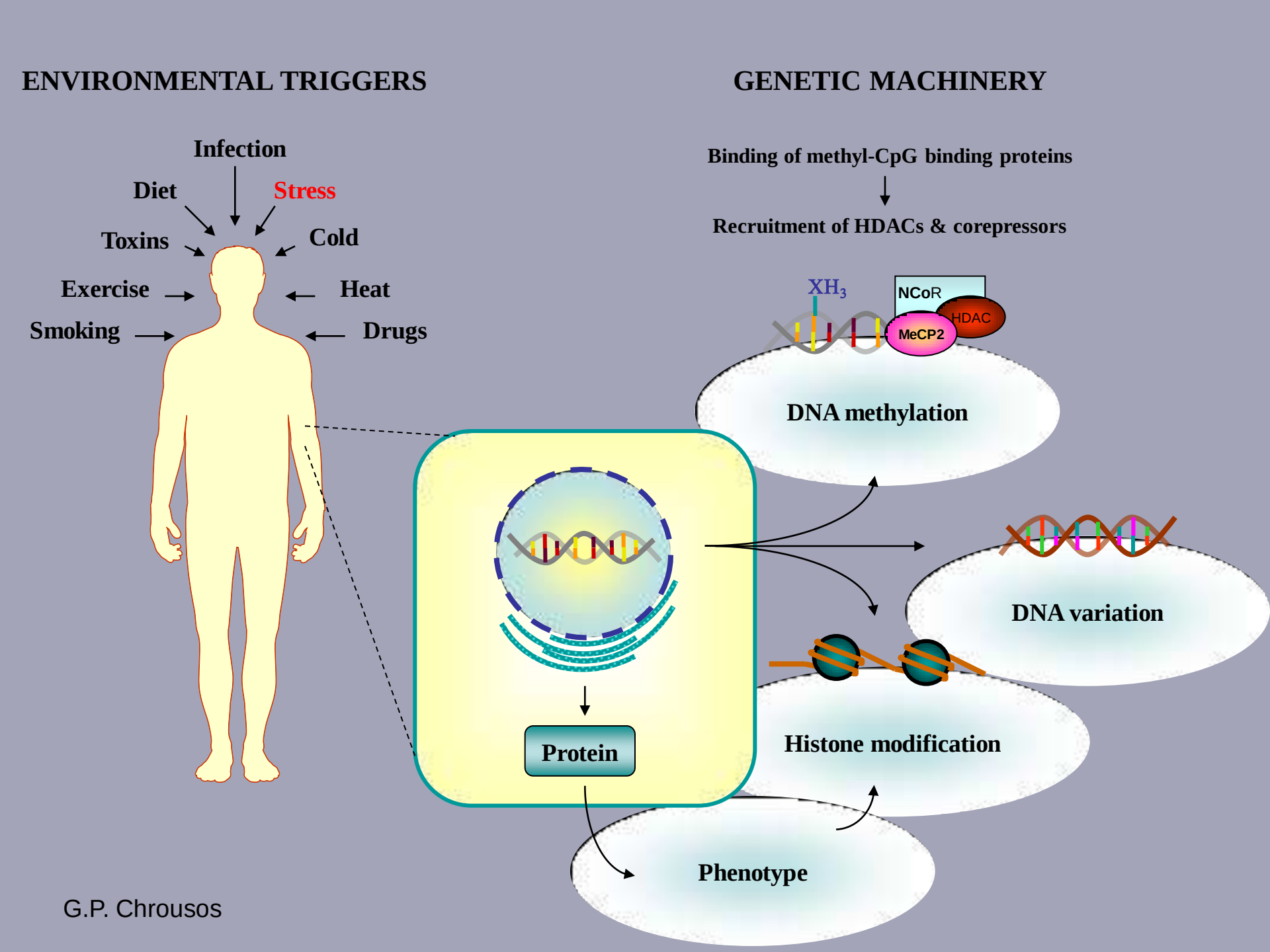
Evolution
Genetics
CNS complexity

Development
Epigenetics
CNS plasticity

Genotype

Epigenotype

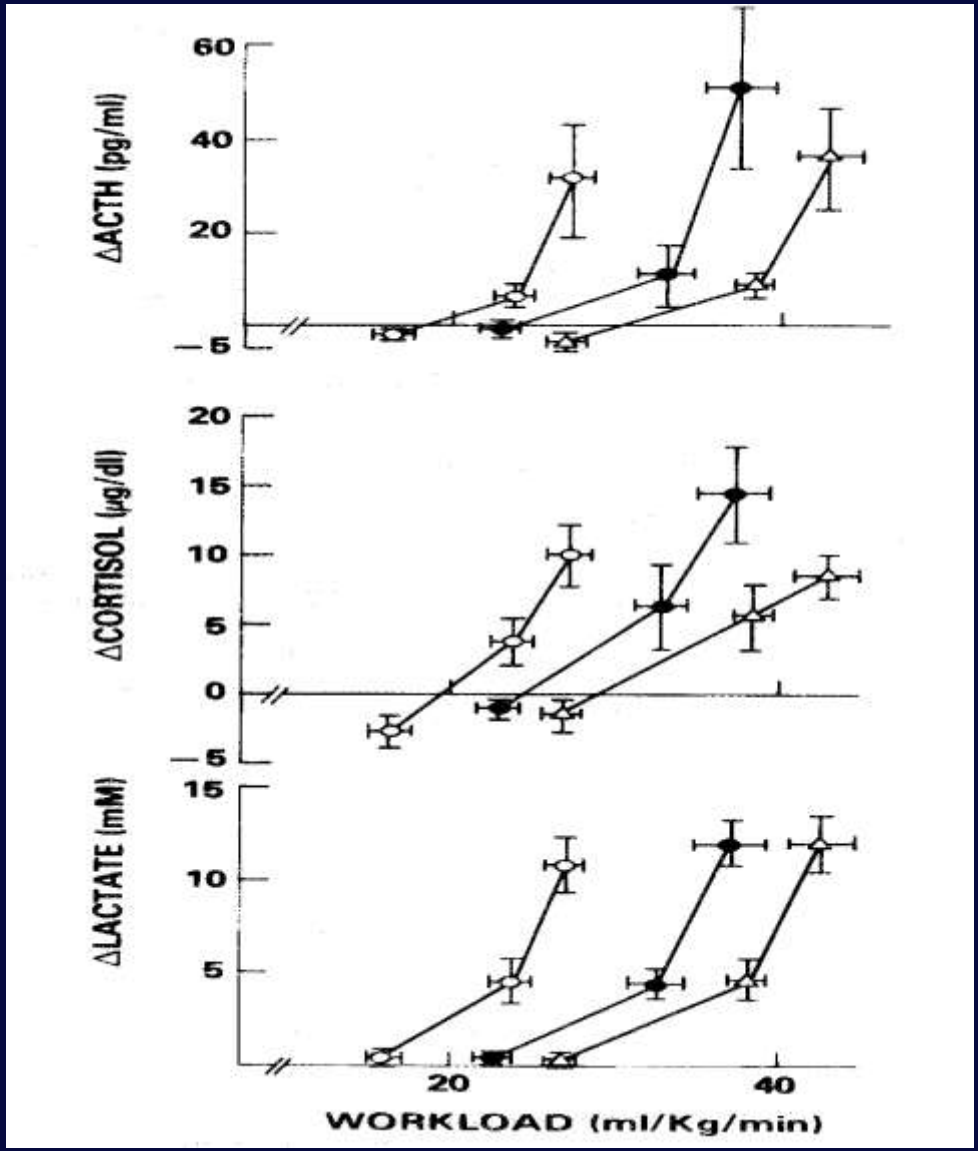
Phenotype


ENVIRONMENTAL TRIGGERS
GENETIC MACHINERY
Infection
Diet
Stress
Toxins
Cold
Exercise
Heat
Smoking
Drugs
Binding of methyl-CpG binding proteins
Recruitment of HDACs & corepressors
XH3
NCoR
HDAC
MeCP2
DNA methylation
DNA variation
Histone modification
Protein
Phenotype
G.P. Chrousos

THE STRESS SYSTEM
Chronic Pathophysiology

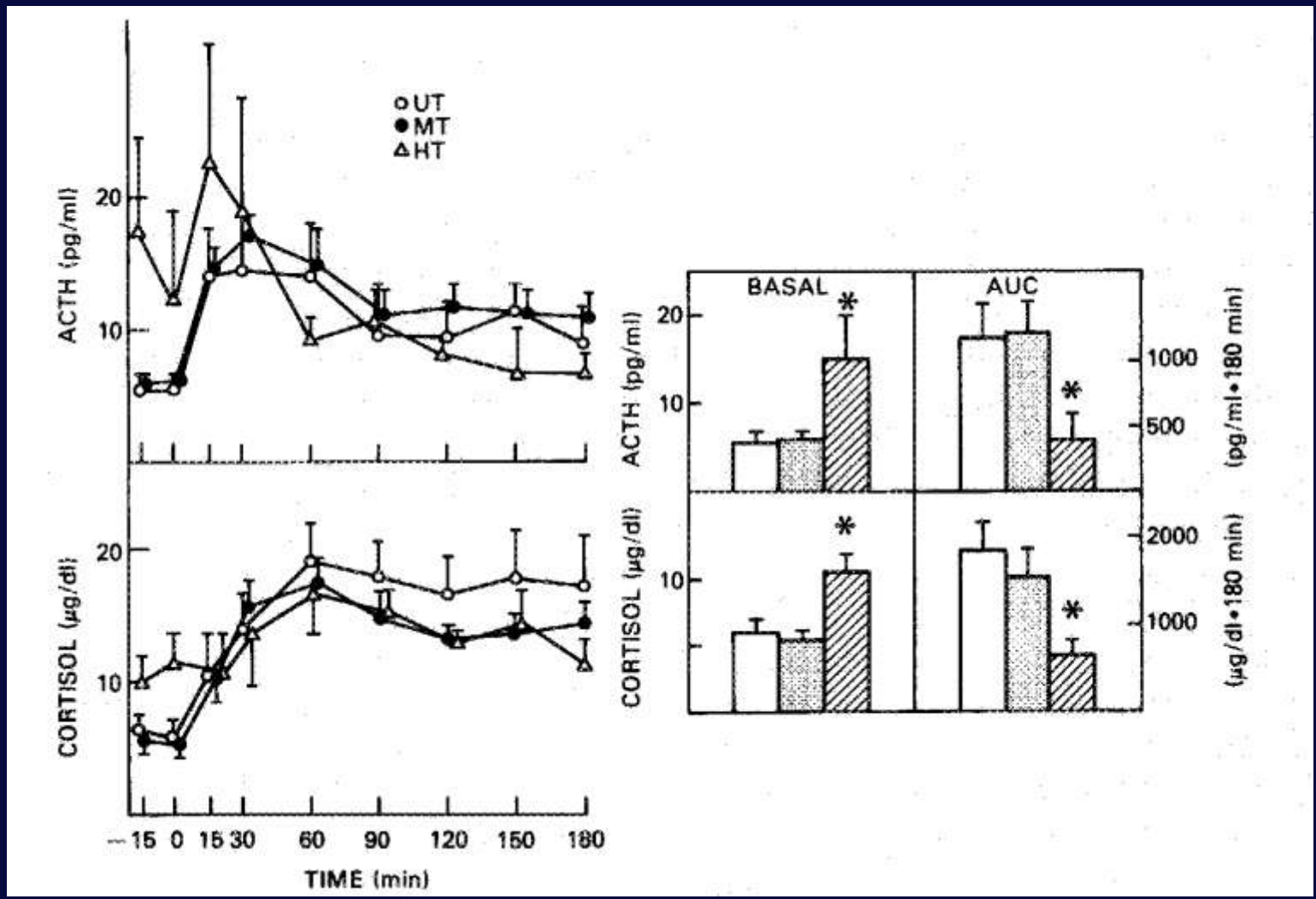
Chronic intermittent exercise bouts as a chronic stressor
Moderate *vs.* Excesssive

Exercise Stress: Three Fitness Groups
ACTH and Cortisol Responses

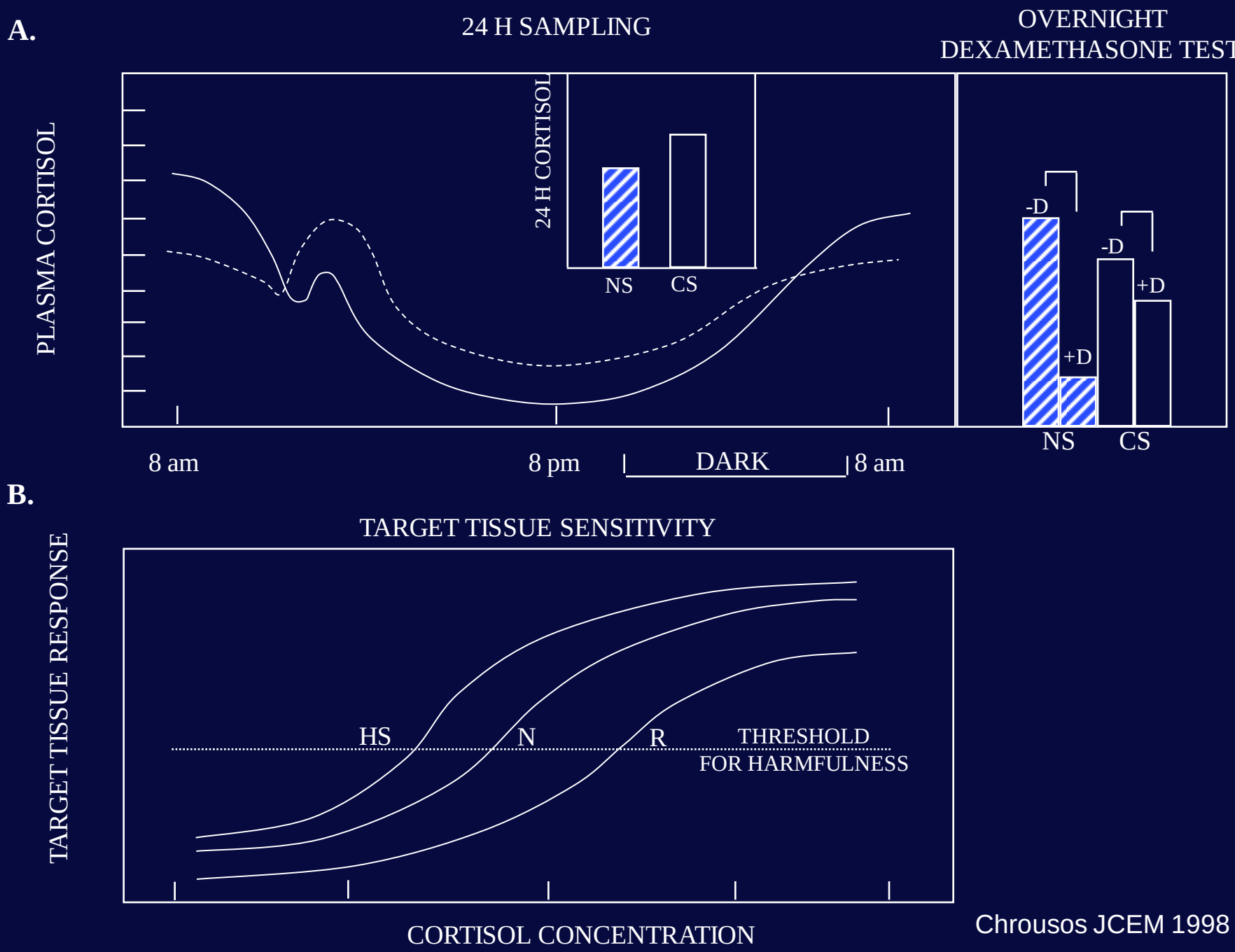


Luger *et al*. NEJM 1987

CRH Stimulation : Three Fitness Groups
ACTH and Cortisol Responses

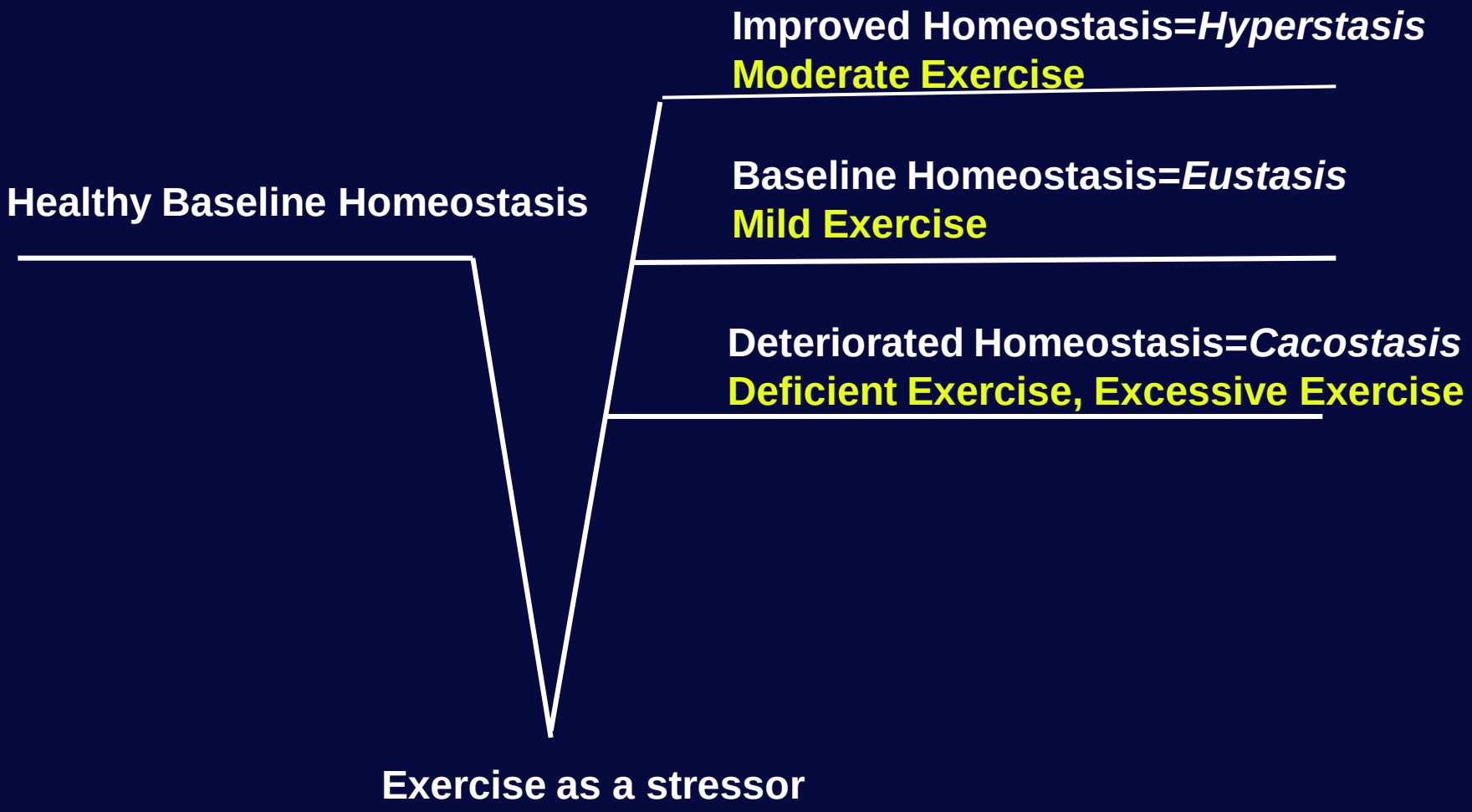


Luger *et al*. NEJM 1987



Chrousos JCEM 1998

Exercise over Time



G.P. Chrousos

Physical and Emotional Stress

- Stress Concepts
- Stress Mechanisms
- Effects of Stress on the Organism
- Coping with Stress

The constituents of Man:

“Φύσις, Εθος, Λόγος”

“Physis, Ethos, Logos ”

Aristotle

4th Century BCE

Dealing with Stress:

- **Alleviate/Eliminate Stressors**
- **Improve Coping**

Stress Coping-Management

What can we do about stress?

- **Social prerequisites**
- **Nutrition**
- **Exercise**
- **Sleep**
- **Timing regularity**
- **Experiencing “*Flow*”**

Basic Social Prerequisites

- Safety, Security
- Social Integration
- Competence
- Authenticity
- Autonomy

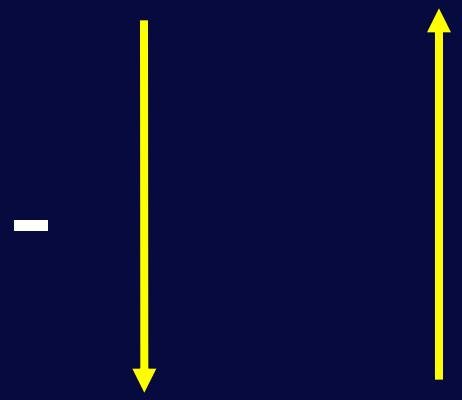
The Epicurian *Tetrapharmacon* Prescription

- ***We are not threatened by divine power***
- ***There is no life after death***
- ***It is easy to acquire what we need to be happy***
- ***It is easy to endure what makes us suffer***

Marcus Aurelius
(Meditations)
167 CE

"If you are distressed by anything external or internal, the pain is not due to the thing itself, but to your estimate of it; and this you have the power to revoke at any moment."

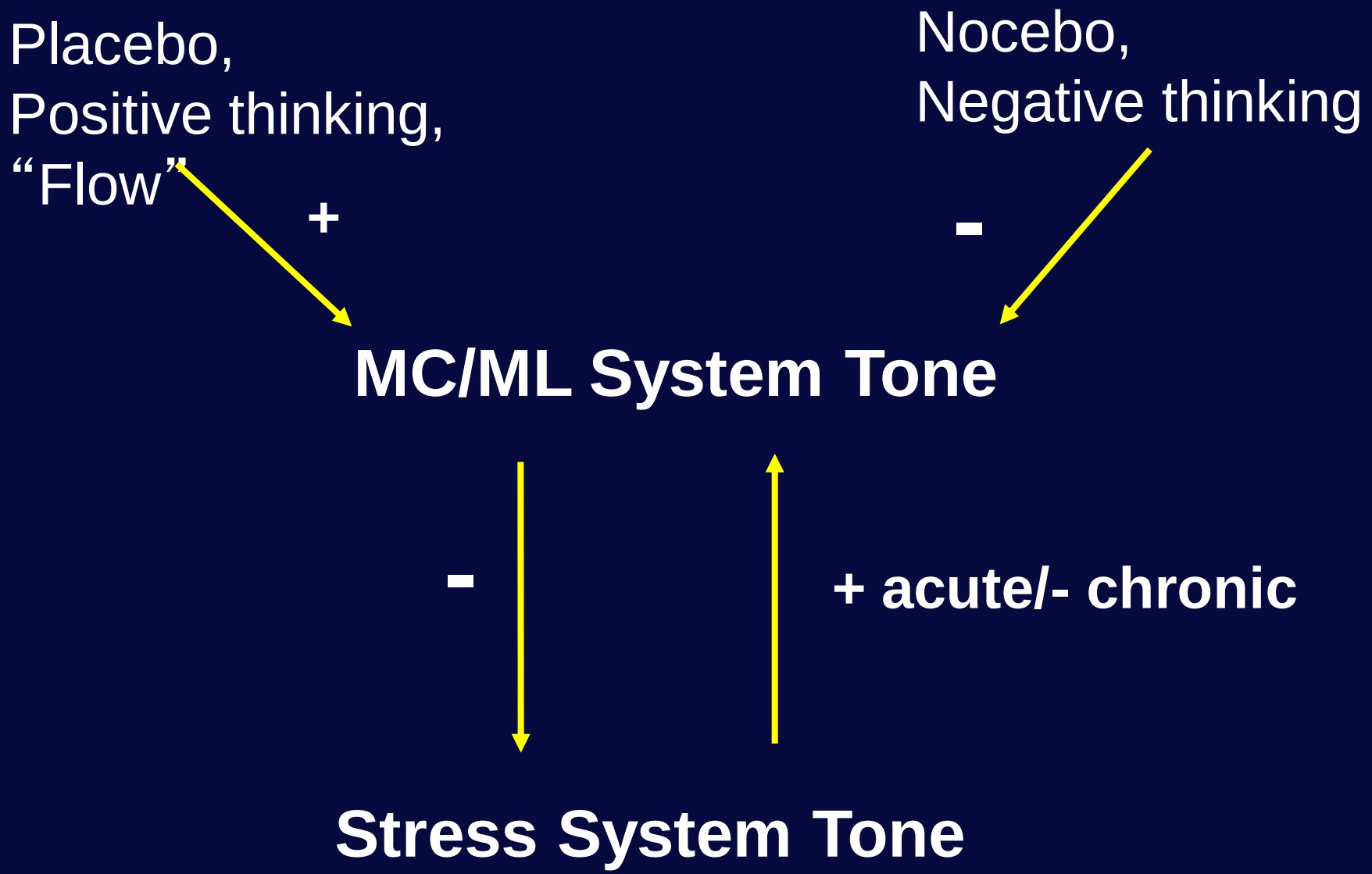
MC/ML System Tone

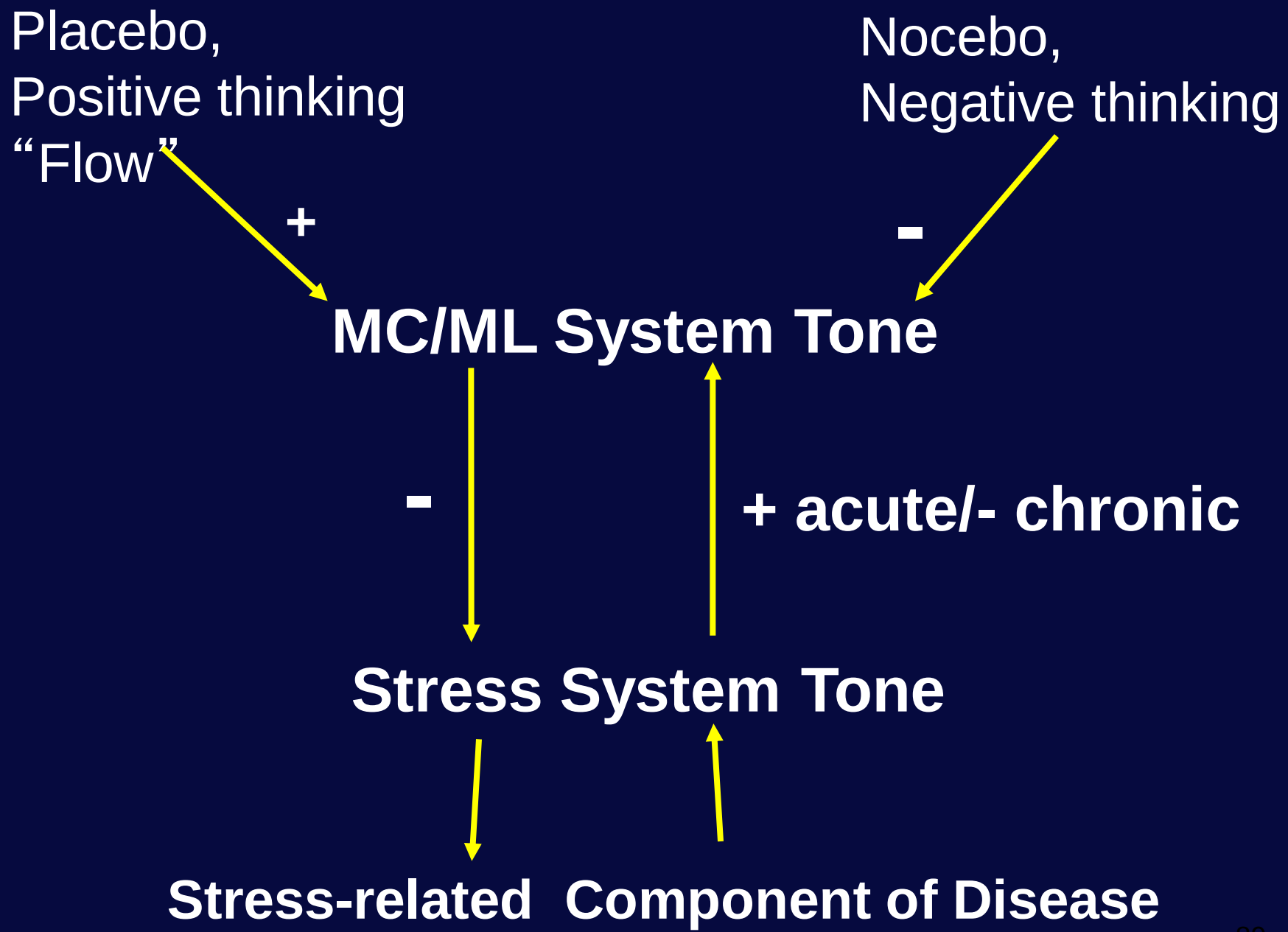


+ acute

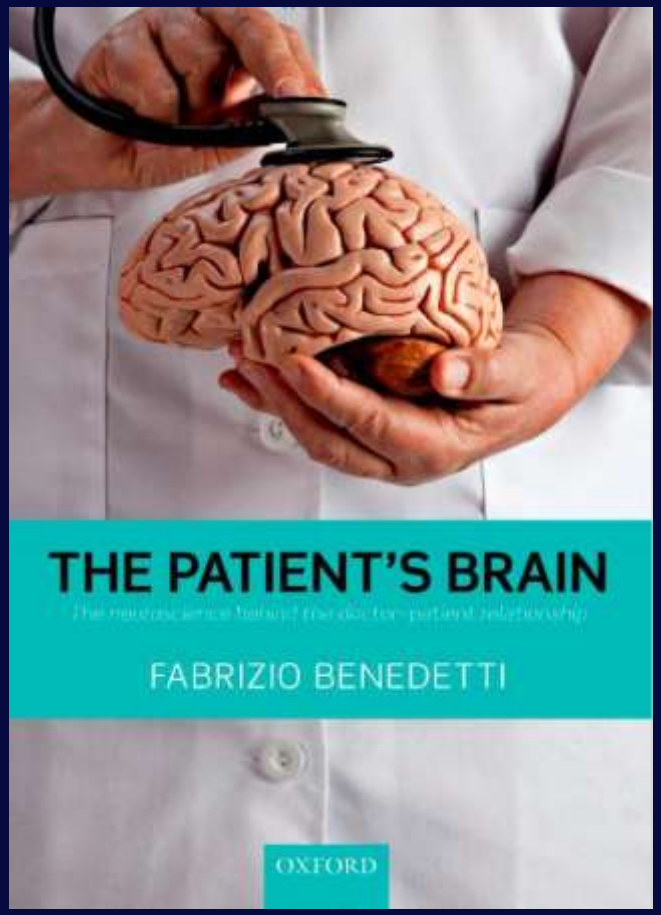
- chronic

Stress System Tone


Placebo,
Positive thinking,
“Flow”
+
Nocebo,
Negative thinking
-
MC/ML System Tone
-
+ acute/- chronic
Stress System Tone


Placebo,
Positive thinking
"Flow"
+
Nocebo,
Negative thinking
-
MC/ML System Tone
-
+ acute/- chronic
Stress System Tone
Stress-related
Component of Disease

Patient-doctor Relationship= A Strong Predictor of Response to any Therapy



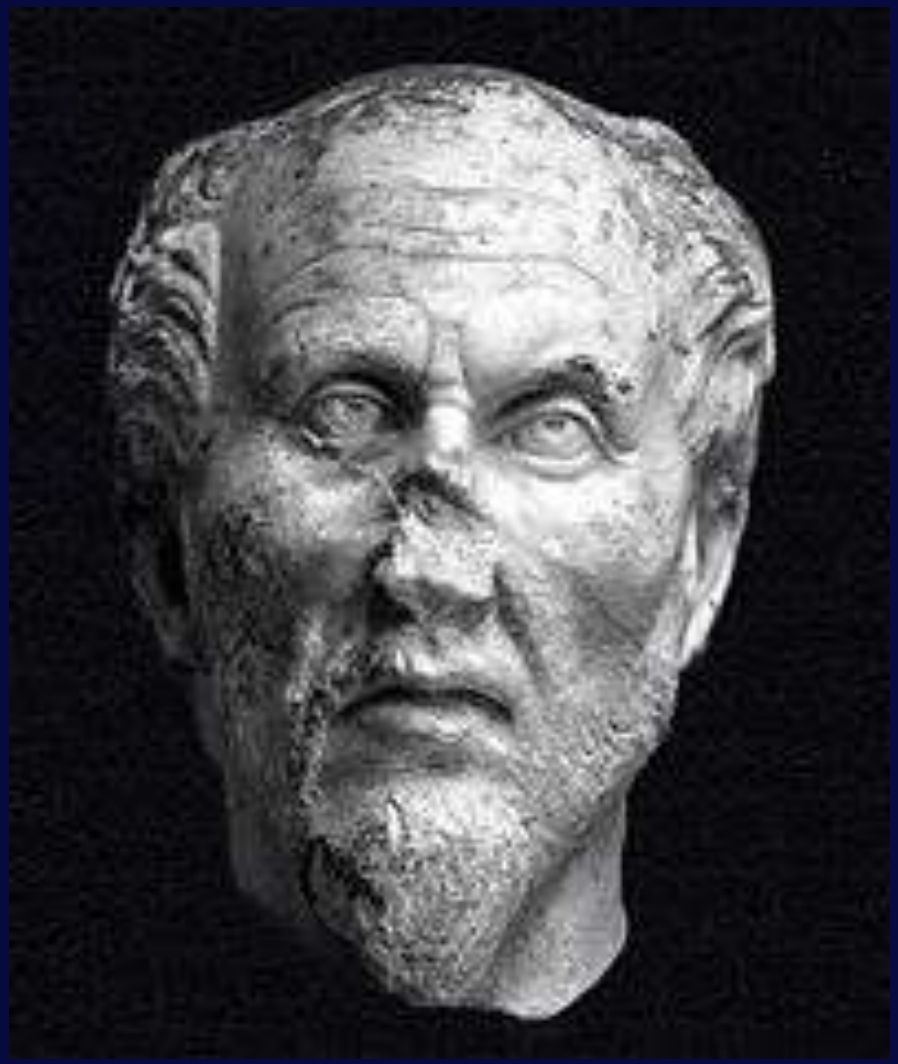
Maintaining a Young Mind: A Prerequisite for Eulongevity

Young Mind= Exploration ??

Eulongevity =Good and long living

Increasing level of happiness:
(+MC/ML System Tone)

- **Exploration**
- **“Flow”, Noopaedia**



Plotinos of Lycopolis, Egypt (ca. CE 204/5–270)

"You ask, how can we know the Infinite? I answer, not by reason. It is the office of reason to distinguish and define. The Infinite, therefore, cannot be ranked among its objects. You can only apprehend the Infinite by a faculty superior to reason, by entering into a state in which you are your finite self no longer—in which the divine essence is communicated to you. This is ecstasy. It is the liberation of your mind from its finite consciousness. Like only can apprehend like; when you thus cease to be finite, you become one with the Infinite. In the reduction of your soul to its simplest self, its divine essence, you realize this union—this identity".

Ancient Greek sage** Plotinos **(ca. CE 204/5–270) in a letter to Flaccus.

«....έδειξε με τις πράξεις του και την μέθοδο της λογικής του ότι για να είναι κάποιος ευτυχής πρέπει να είναι καλός.....»

"....he showed with his deeds and the method of his logic that for somebody to be happy one has to be good…"

Αριστοτέλης, Επικήδειος στον Πλάτωνα
Aristotle, Eulogy to Plato 4cent BCE

"Aristotelian Eudaimonia"

4 Qualities of Mind that Alleviate Suffering

- ***Metta = loving kindness***
- ***Karuna = compassion***
- ***Mudita = feeling the joy of others***
- ***Upekkha = ataraxia, equanimity***

Upekkha=Ataraxia

An equanimous mind holds all things in an ease-filled balance. From this place of equanimity, when we see people going about their everyday lives, friendliness (*metta*) is our natural response. When we see someone suffering, compassion (*karuna*) is our natural response. When we see someone who's happy, joy in their joy (*mudita*) is our natural response.

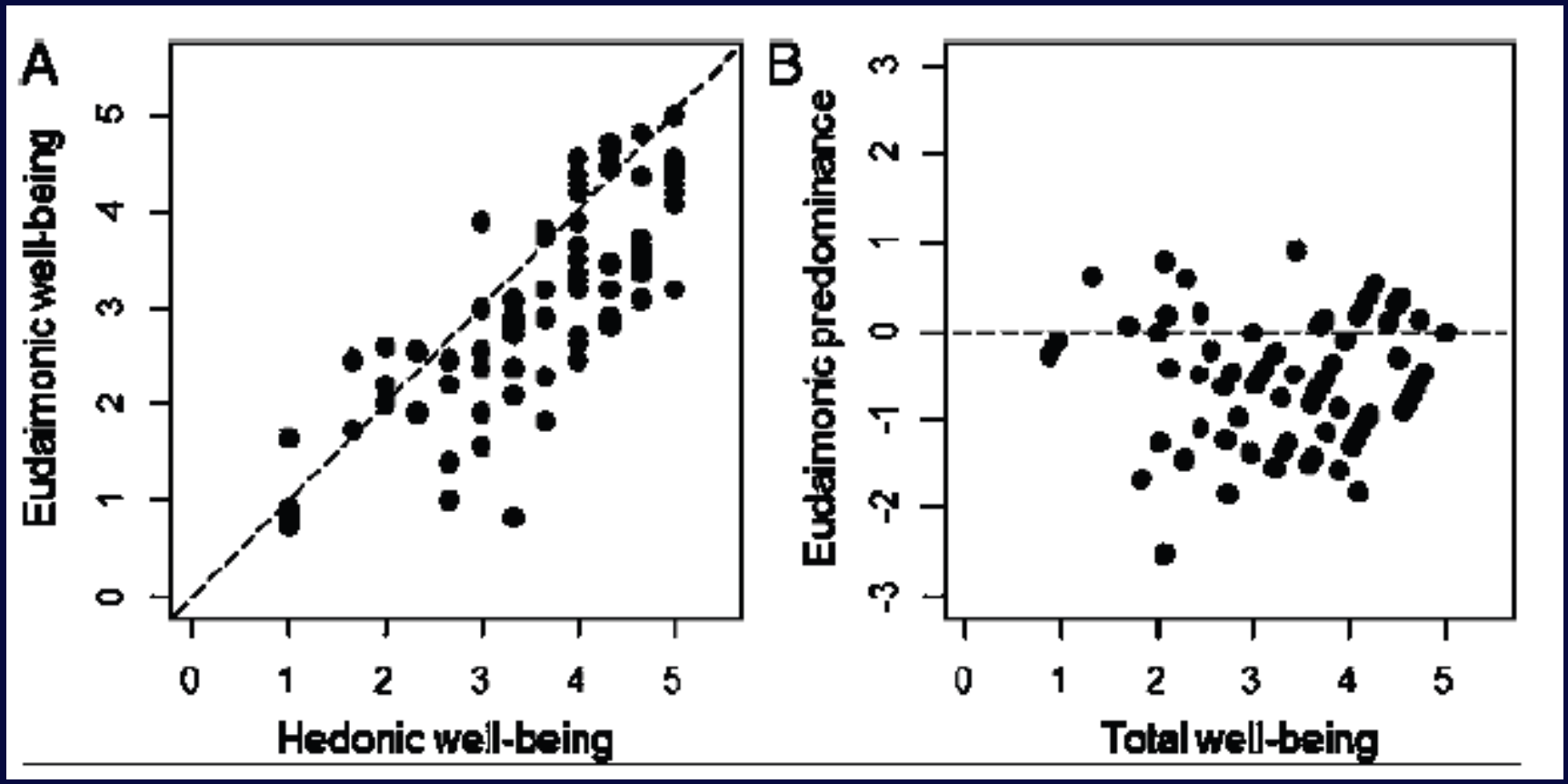
Sylvia Boorstein, *It is easier than you think, 1995*

ΑΤΥΧΟΥΝΤΙ ΣΥΝΑΧΘΟΝ

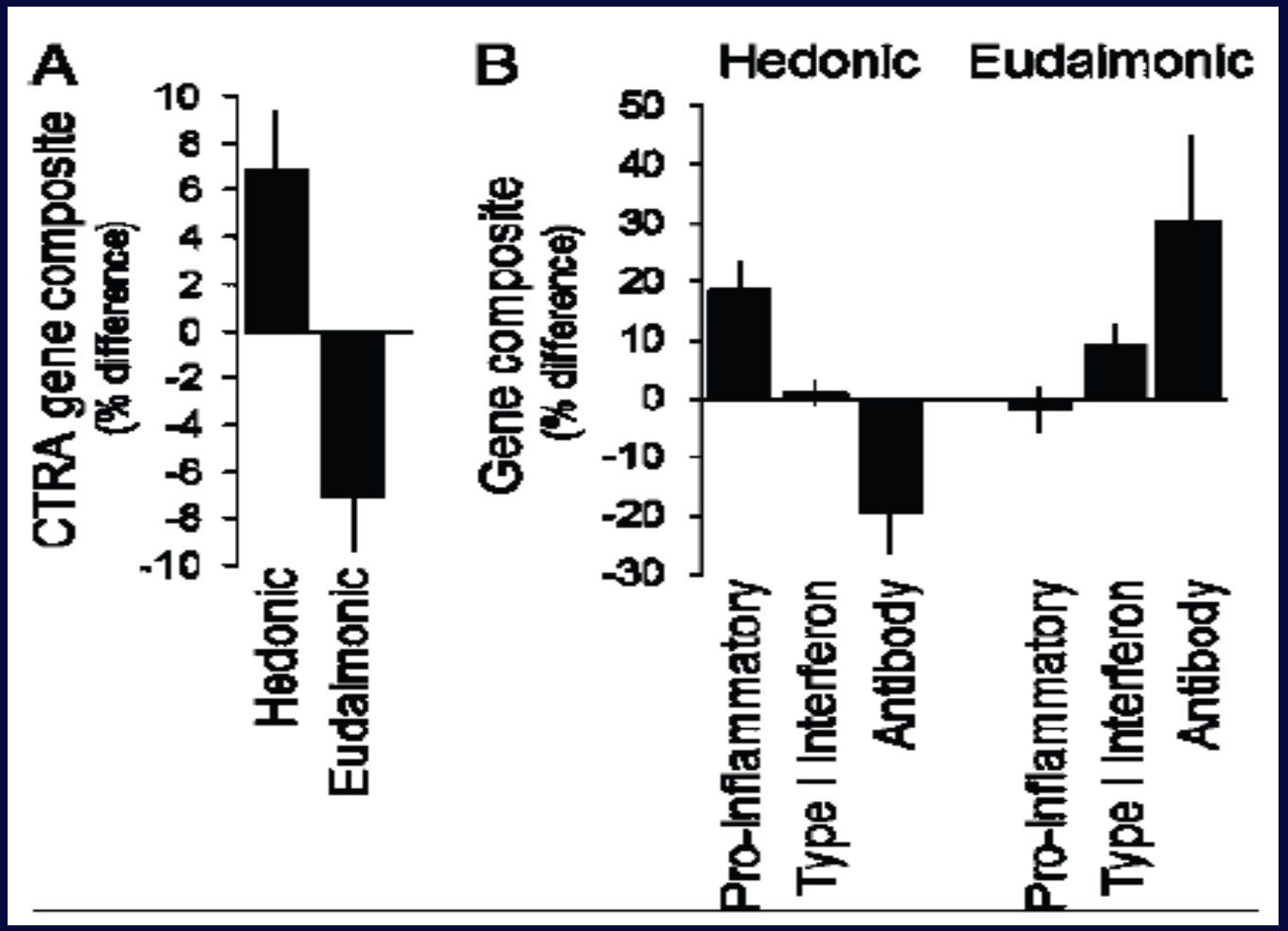
Show compassion to the unfortunate.

Those only are happy, who have their minds fixed on some object other than their own happiness; on the happiness of others, on the improvement of mankind, even on some art or pursuit, followed not as a means, but as itself an ideal end. Aiming thus at something else, they find happiness by the way..

J. Mill 19th C CE



Fredrickson BL *et al. PNAS* 2013; 110 (33): 13684-13689



Fredrickson BL *et al. PNAS* 2013; 110 (33): 13684-13689

What can we do about stress?

- **Social prerequisites**
- **Nutrition**
- **Exercise**
- **Sleep**
- **Timing regularity**
- **Experiencing “*Flow*”**
- **Be good-do good**
- **Have a sustained purpose beyond one’s self (*“transcedence”*)**

EYTYXIAN EYXON

Search for happiness

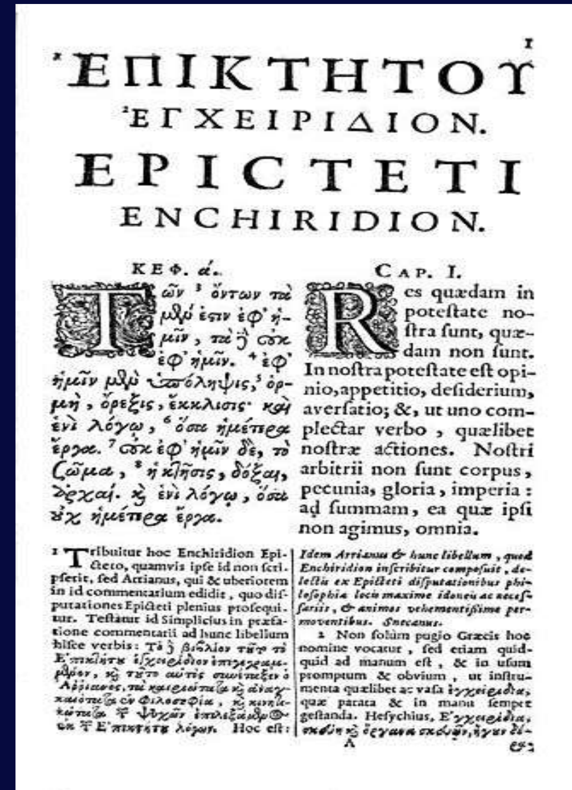
“I decided to be happy because this improves my health”

Voltaire 1694-1778

Συμπάσχει η ψυχή τω σώματι νοσούντι και τεμνομένω, το δε σώμα τη ψυχή

The soul suffers when the body is diseased or traumatized, while the body suffers when the soul is ailing

Aristotle



1

ἘΠΙΚΤΗΤΟΥ ἘΓΧΕΙΡΙΔΙΟΝ.

EPICTETI ENCHIRIDION.

ΚΕΦ. α.

Τῶν [3] ὄντων τὰ μέν ἐστιν ἐφ' ἡμῖν, τὰ δὲ οὐκ ἐφ' ἡμῖν. [4] ἐφ' ἡμῖν μὲν ὑπόληψις, [5] ὁρμή, ὄρεξις, ἔκκλισις· καὶ ἑνὶ λόγῳ, [6] ὅσα ἡμέτερα ἔργα. [7] οὐκ ἐφ' ἡμῖν δέ, τὸ σῶμα, [8] ἡ κτῆσις, δόξαι, ἀρχαί· καὶ ἑνὶ λόγῳ, ὅσα οὐχ ἡμέτερα ἔργα.

CAP. I.

Res quædam in potestate nostra sunt, quædam non sunt. In nostra potestate est opinio, appetitio, desiderium, aversatio; &, ut uno complectar verbo, quælibet nostræ actiones. Nostri arbitrii non sunt corpus, pecunia, gloria, imperia: ad summam, ea quæ ipsi non agimus, omnia.

1 Tribuitur hoc Enchiridion Epicteto, quamvis ipse id non scripserit, sed Arrianus, qui & uberiorem in id commentarium edidit, quo disputationes Epicteti plenius prosequitur. Testatur id Simplicius in præfatione commentarii ad hunc libellum hisce verbis: Τὸ δὲ βιβλίον τοῦτο τὸ Ἐπικτήτου ἐγχειρίδιον ἐπιγεγραμμένον, καὶ τοῦτο αὐτὸς συνέταξεν ὁ Ἀρριανός, [illegible] ἐν φιλοσοφίᾳ, καὶ [illegible] τῶν ψυχῶν [illegible] ἐκ τῶν Ἐπικτήτου λόγων. Hoc est: *Idem Arrianus & hunc libellum, quod Enchiridion inscribitur composuit, delectis ex Epicteti disputationibus philosophiæ locis maxime idoneis ac necessariis, & animos vehementissime permoventibus.* *Snecanus.*

2 Non solùm pugio Græcis hoc nomine vocatur, sed etiam quidquid ad manum est, & in usum promptum & obvium, ut instrumenta quælibet ac vasa ἐγχειρίδια, quæ parata & in manu semper gestanda. Hesychius, Ἐγχειρίδια, σκεύη καὶ ὄργανα σκευῶν, ἤγουν δί-

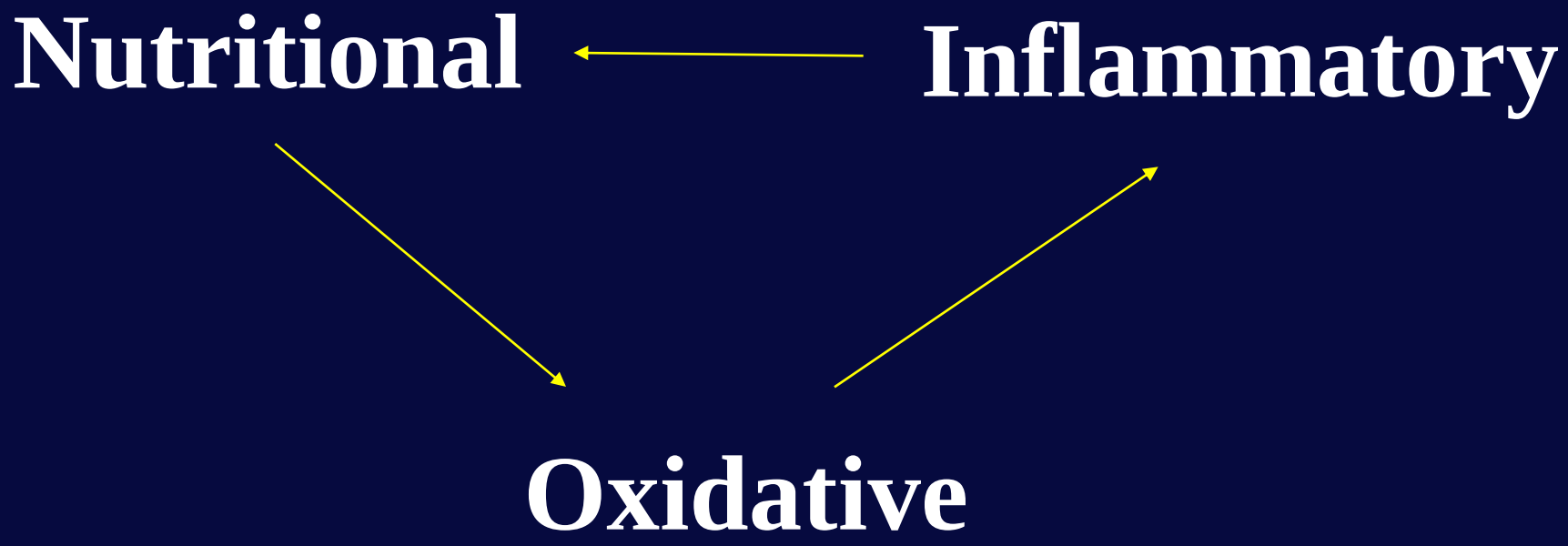
A

ἐγ-

'Be equanimous and remember not to believe easily'

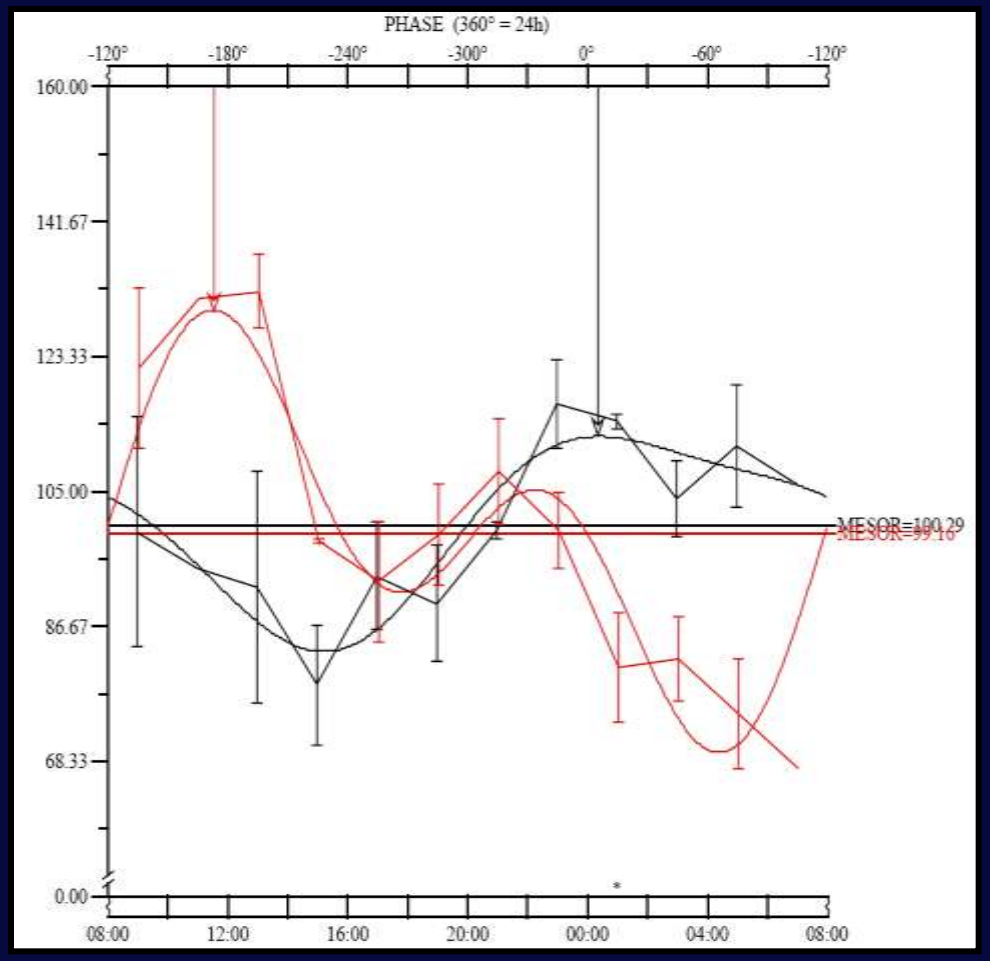
G.P. Chrousos

Cellular Stress



Cellular Stress

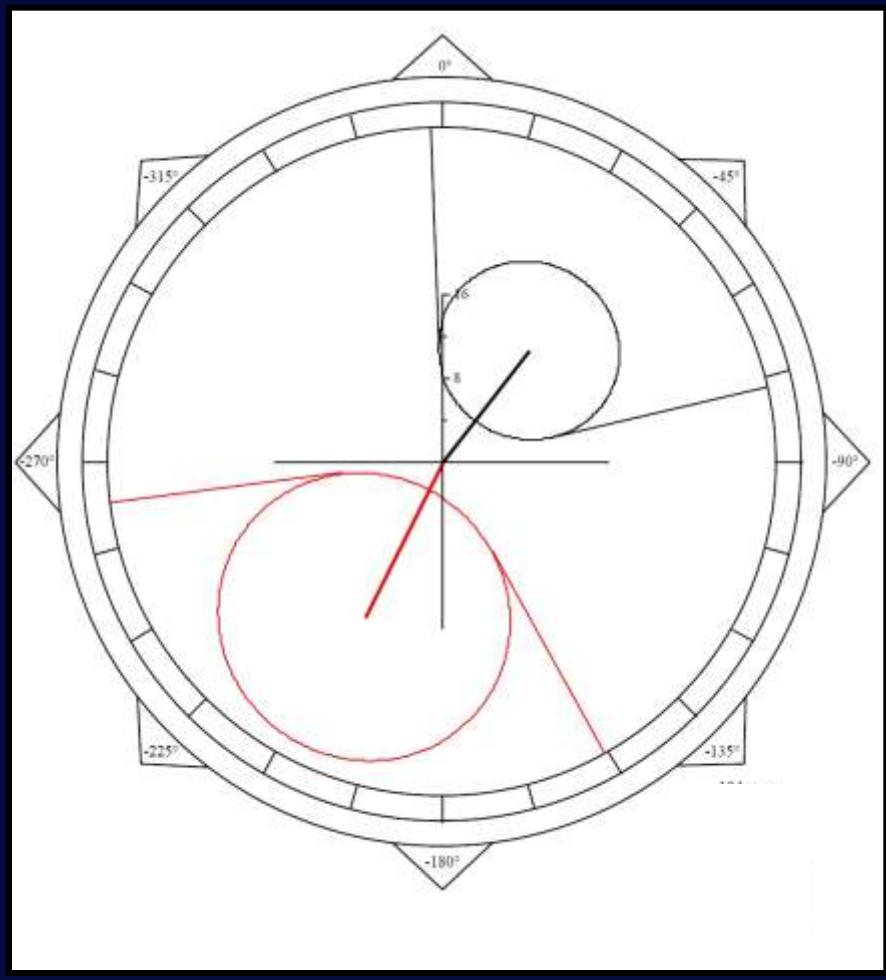

SPL



Clock time (hh:mm)

Controls

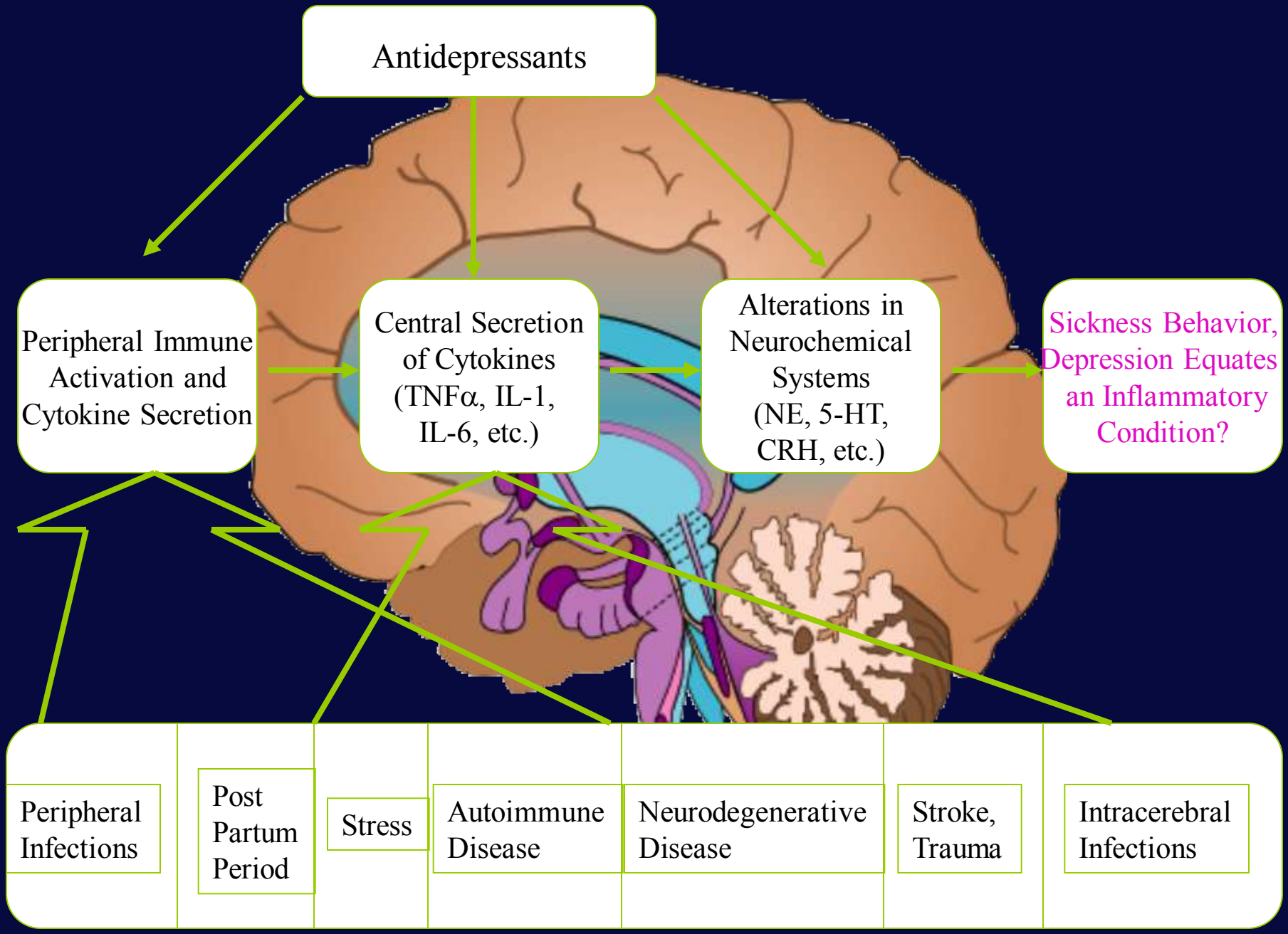
Depressed

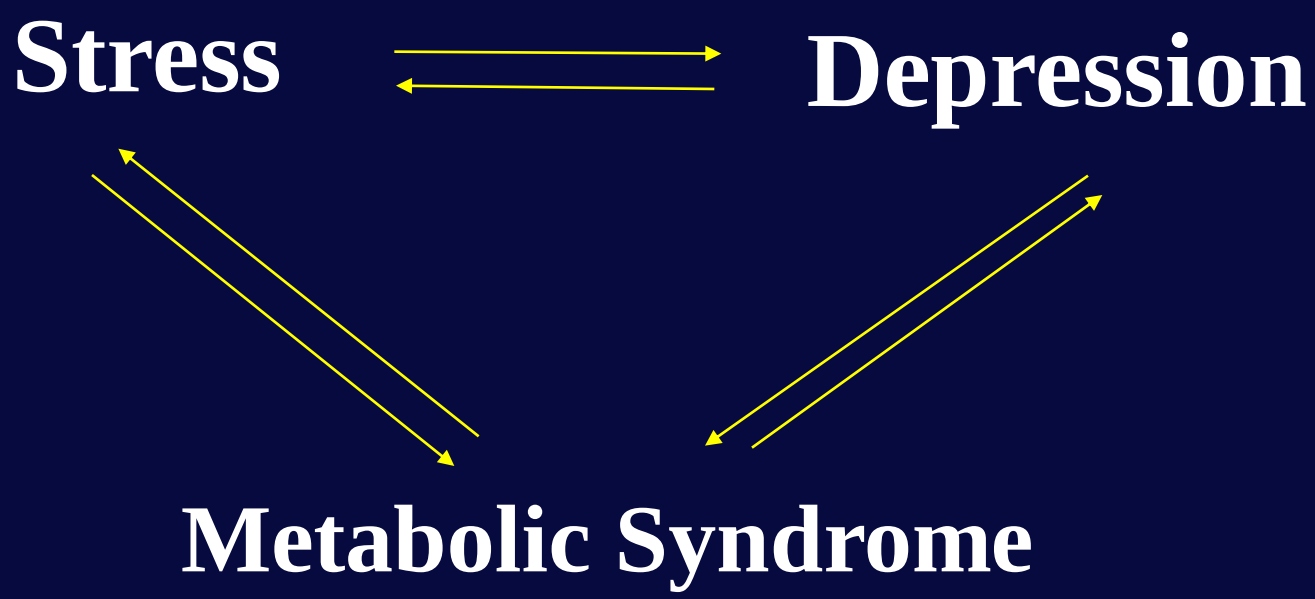


Pearson's correlations between mean 0800-2300 h plasma IL-6 levels and MVAS scores.

	Correlation coefficient	Probability value
Appetite	-0.61	0.07
Concentration	-0.64	0.05
Craving	-0.45	0.19
Guilt	-0.82	0.004*
Physical discomfort	-0.35	0.32
Sadness	-0.72	0.02
Self-esteem	-0.86	0.002*
Suicidal thoughts	-0.88	0.0007*
Tiredness	-0.75	0.02
Withdrawal	-0.21	0.56

Note: For each measure, a higher VAS score denoted better feelings.
*Correlations of IL-6 with guilt, self-esteem and suicidal thoughts remained significant after Bonferroni correction.


Antidepressants
Peripheral Immune Activation and Cytokine Secretion
Central Secretion of Cytokines (TNFα, IL-1, IL-6, etc.)
Alterations in Neurochemical Systems (NE, 5-HT, CRH, etc.)
Sickness Behavior, Depression Equates an Inflammatory Condition?
Peripheral Infections
Post Partum Period
Stress
Autoimmune Disease
Neurodegenerative Disease
Stroke, Trauma
Intracerebral Infections


Stress
Depression
Metabolic Syndrome

FAT MASS

VISCERAL FAT = ABDOMINAL ADIPOSE TISSUE

LEAN BODY MASS= SKELETAL MUSCLE MASS +BONE MASS

SYSTEMIC INFLAMMATION= EXTRACELLULAR WATER

BRAIN OEDEMA= EXTRACELLULAR WATER BRAIN

ENVIRONMENTAL STRESSORS

Phylogeny
Long-term

vs.

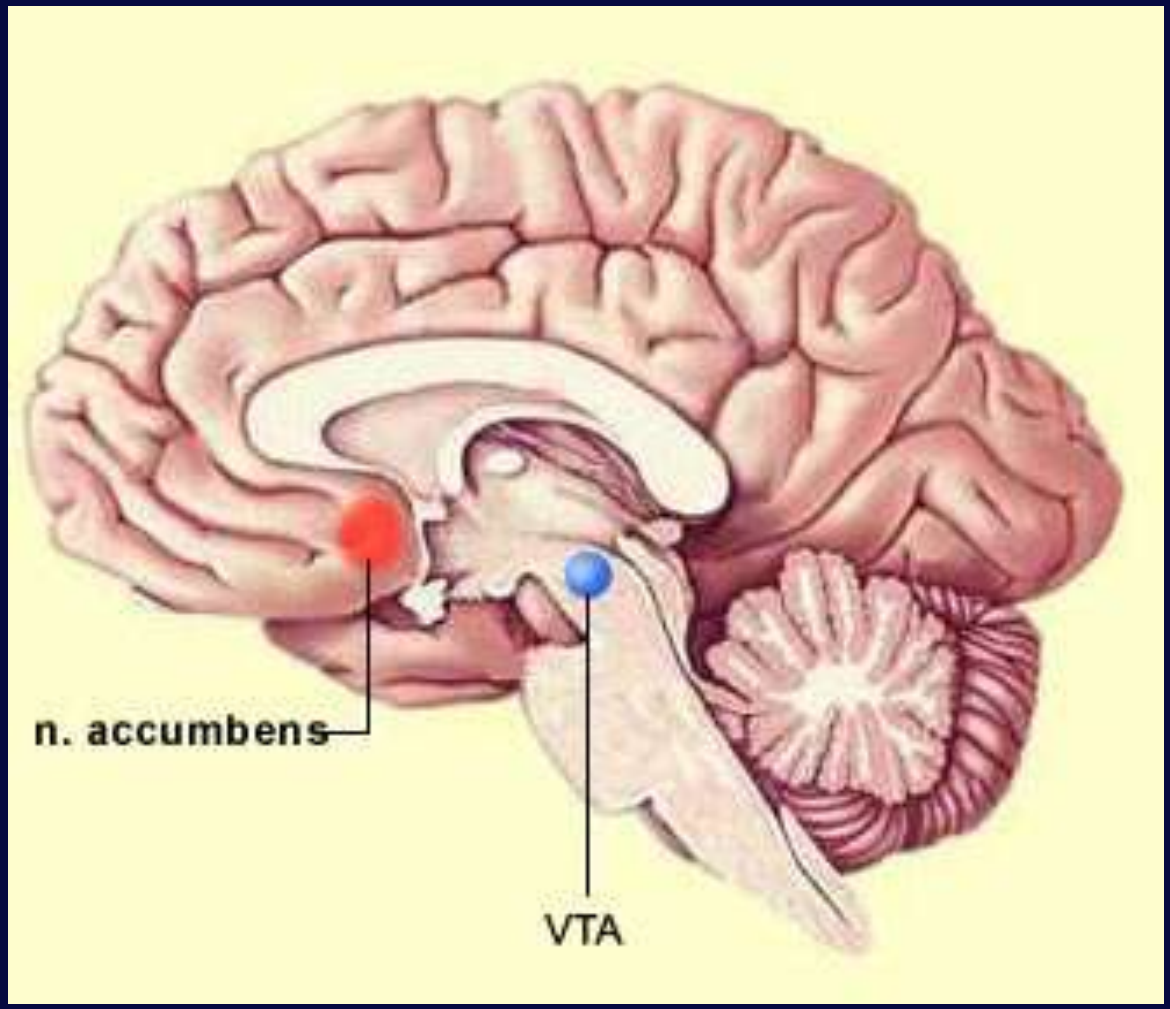
Ontogeny
Short-term

Evolution
Genetics
CNS complexity

Phenotype

Epigenetics
CNS plasticity

The Reward System



The Reward System