



ΕΛΛΗΝΙΚΟ ΙΝΣΤΙΤΟΥΤΟ ΠΑΣΤΕΡ
INSTITUT PASTEUR HELLENIQUE



United Nations
Educational, Scientific and
Cultural Organization



• UNESCO Chair on Adolescent Health Care
• National and Kapodistrian University of Athens
• Greece



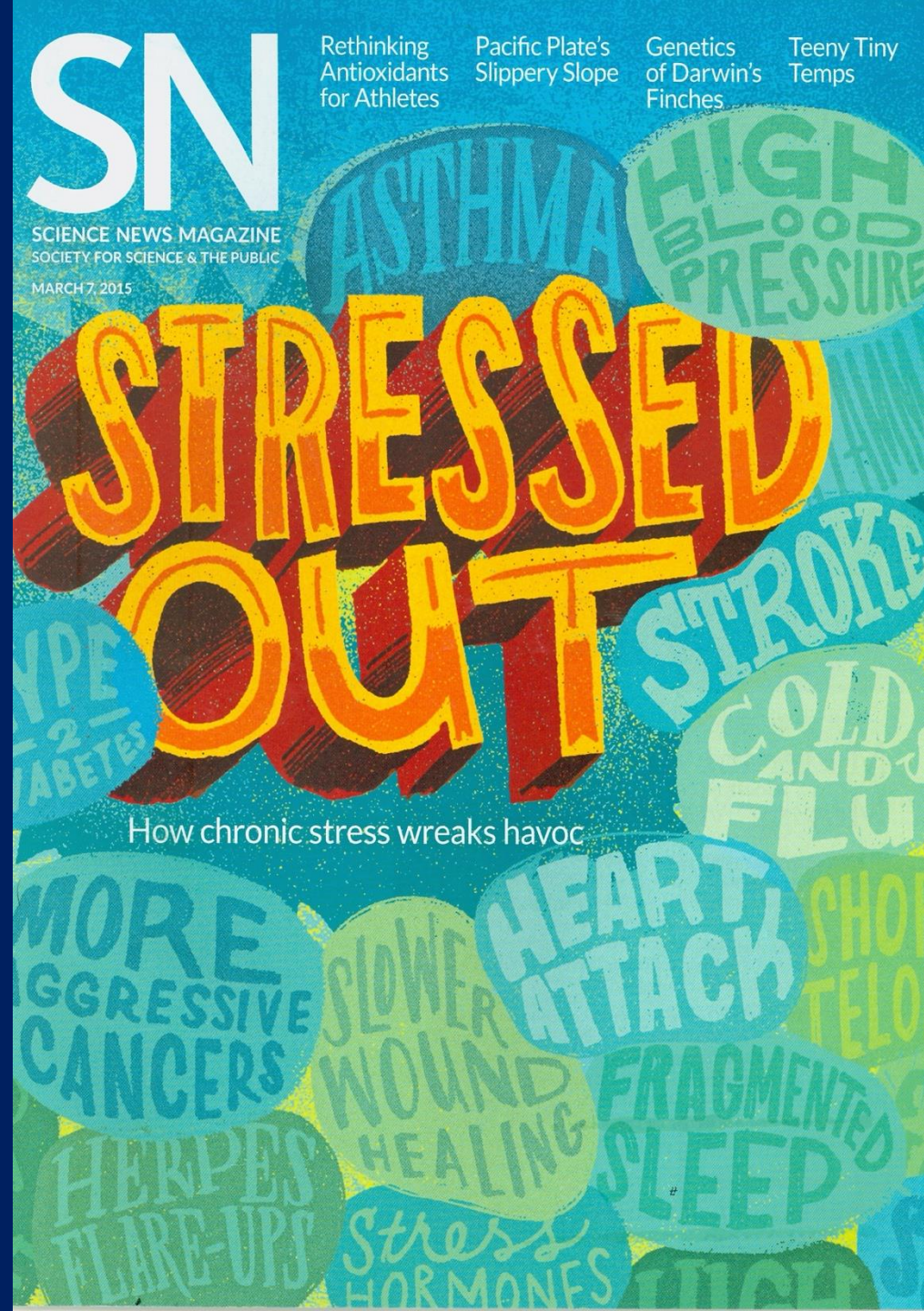
UNIVERSITY
RESEARCH INSTITUTE
**OF MATERNAL
AND CHILD HEALTH
& PRECISION MEDICINE**

Chronic Psycho-socio-economic, Techno-ecologic and Climatic Stress

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University Research Institute on Maternal and
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UNESCO Chair on Adolescent Health Care,
National and Kapodistrian University of Athens
Hellenic Pasteur Institute

“STRESSED”

“STRESSED OUT”

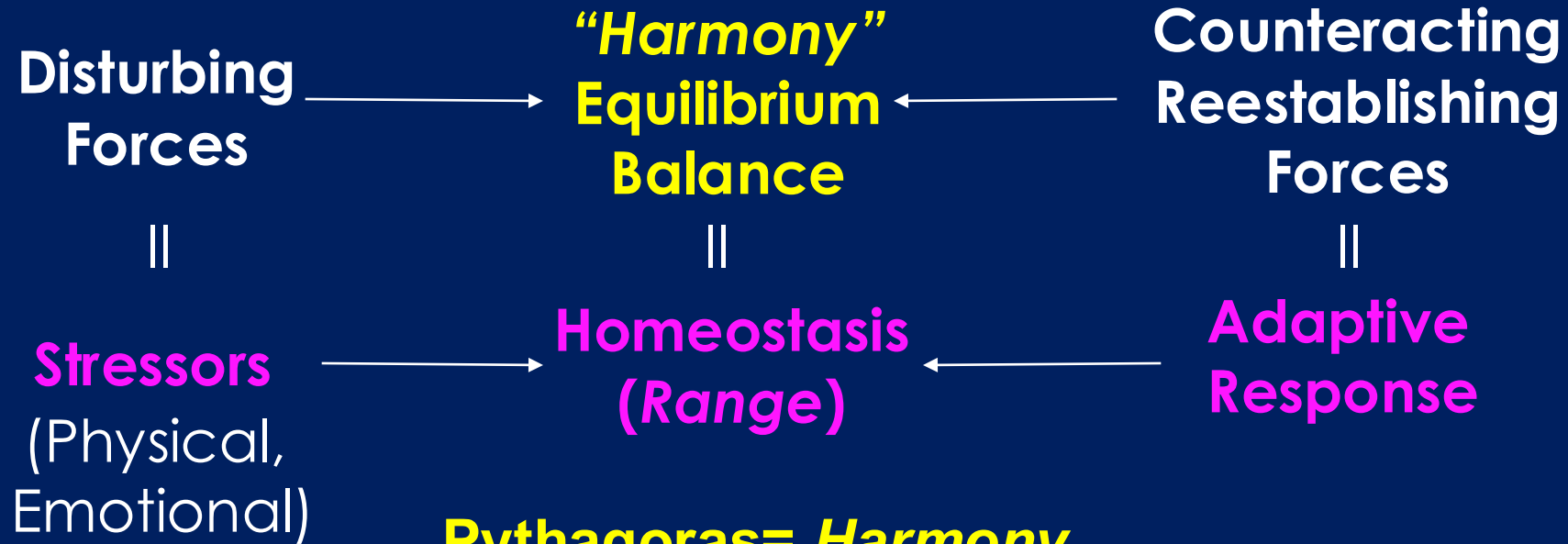


“ANXIOUS”

“BURNED OUT”

“DEPRESSED”

Complex Systems Theory



Pythagoras= *Harmony*

Alcmaeon= *Iso-nomia*

Hippocrates= *Eucrasia*

Epicurus= Eustatheia

Walter Cannon= Homeostasis

Επικούρεια Ευστάθεια *Epicurean “Eustatheia”*

**“ευστάθεια” : “σαρκός και ψυχής ευσταθές
κατάστημα”**

***eustatheia: “the balanced state of the flesh and
the soul”***

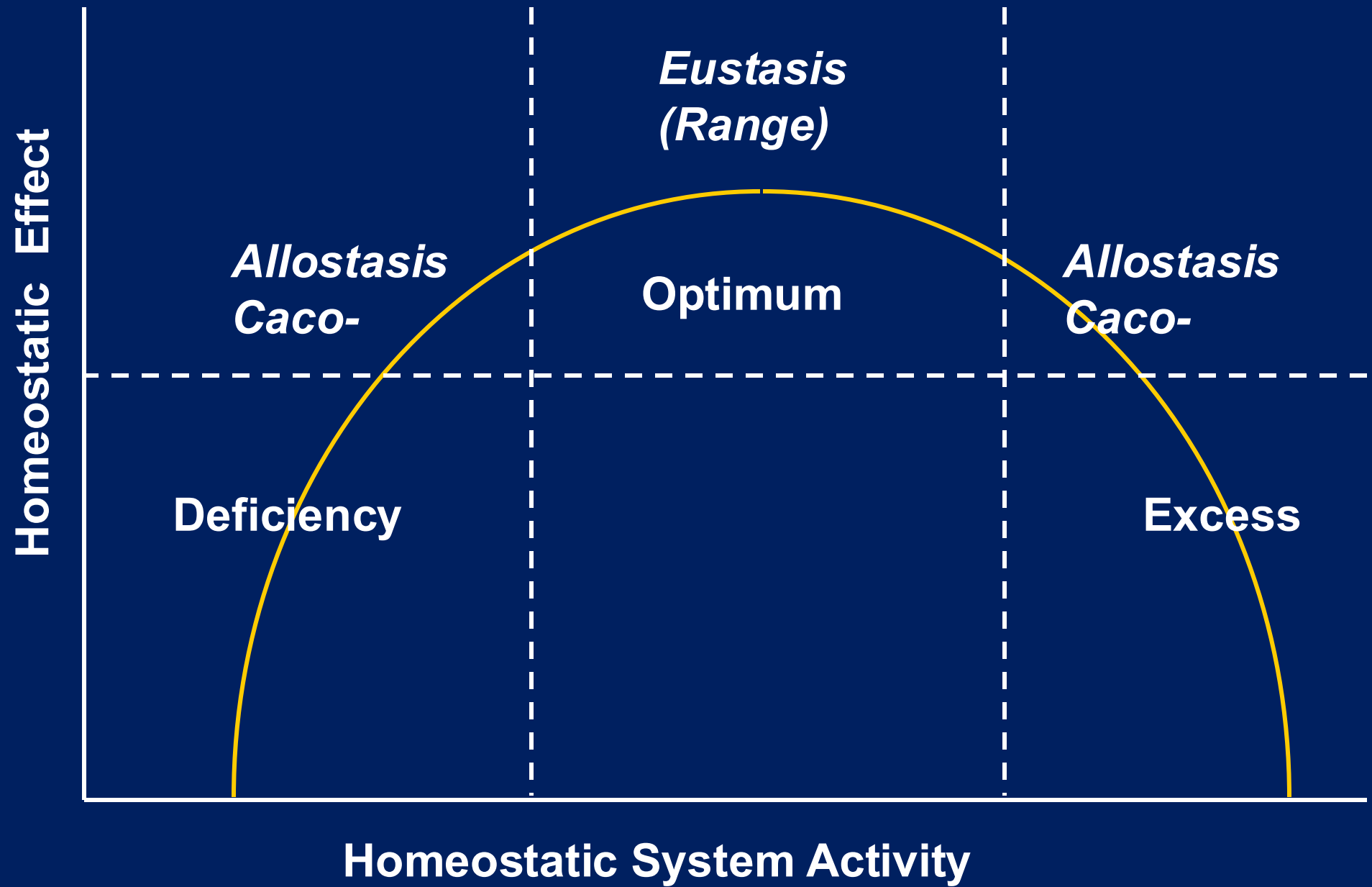
***Stress is the State of
Threatened (or Perceived as
Threatened) Homeostasis***

“*Mesotis*” in the inverse U Curve of Virtues

«Εστιν άρα η αρετή έξις προαιρετική, εν μεσότητι ούσα τη προς ημάς, ωρισμένη λόγω και ω αν φρόνιμος ορίσειεν. **Μεσότης δε δύο κακιών, της μεν καθ’ υπερβολήν της δε κατ’ έλλειψιν»**

*“Is thus virtue a voluntary habit, being in the middle from our point, defined by logic and practical wisdom. **The good is in the middle, between two evils, too much or too little”***

*Αριστοτέλης, Ηθικά Νικομάχεια
Aristotle, Nicomacheian Ethics*

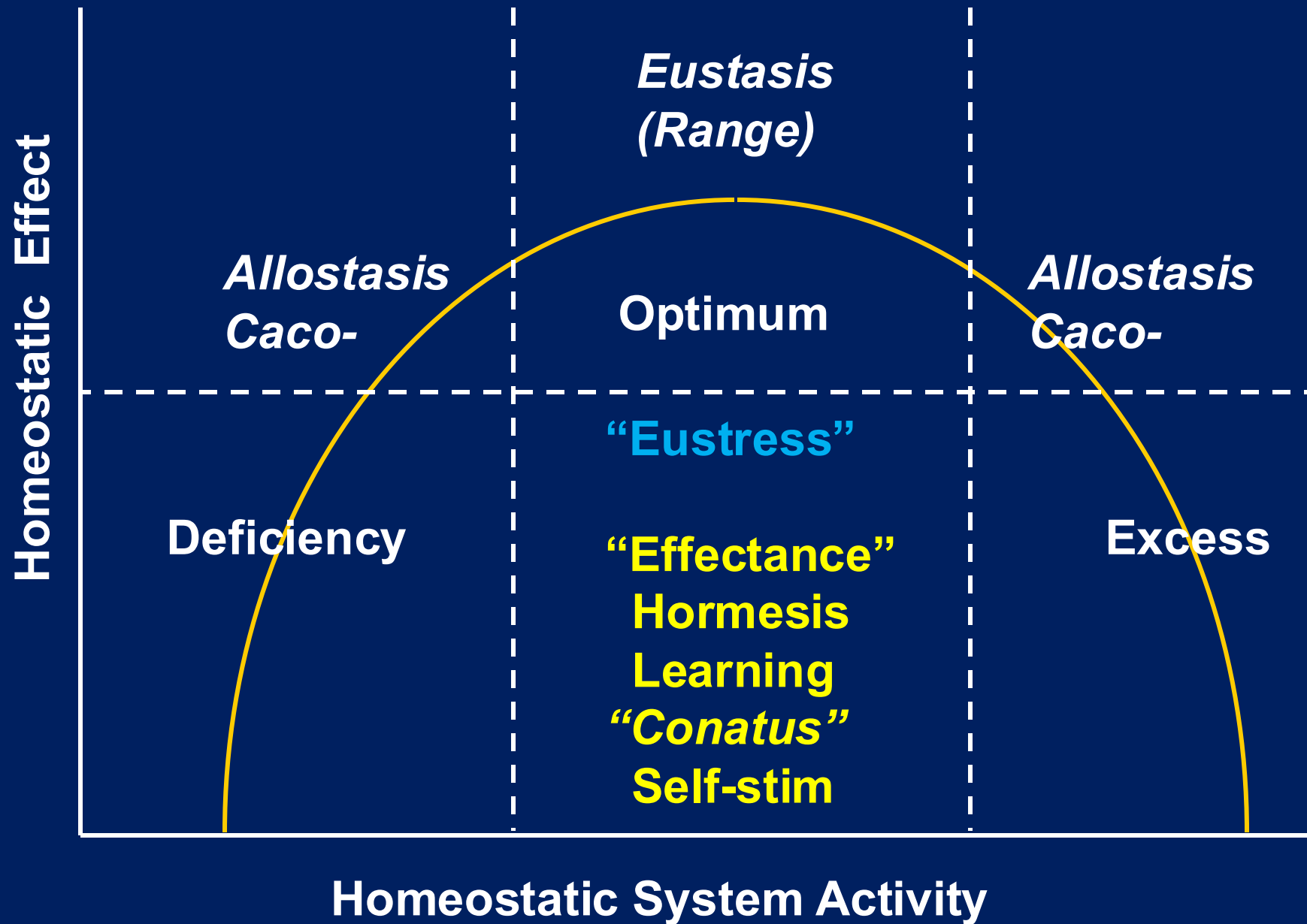


Eustress



Distress





4Fs

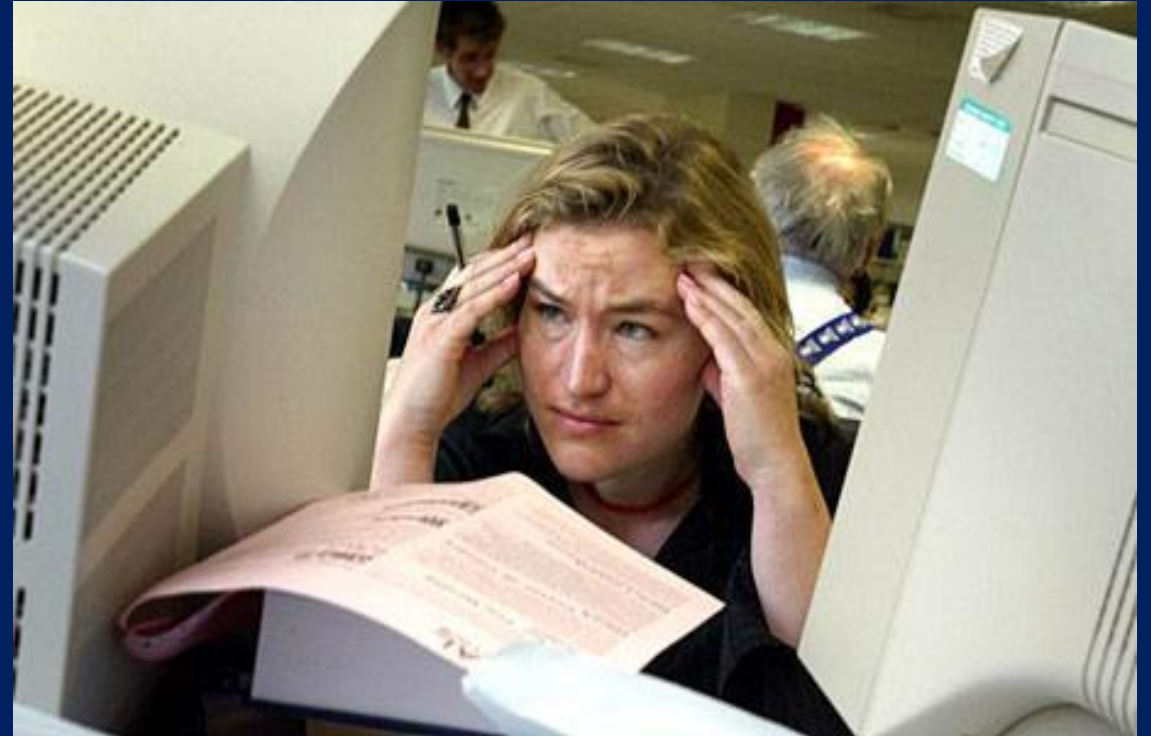
Acute vs. Chronic Stress



**Fight, Flight, Freeze, Fawn
Reaction (physiologic)**

G.P. Chrousos

4Fs



Chronic Psycho-socio-economic Stress (+Eco)
(Chronically activated Fight, Flight, Freeze, Fawn Reaction =
chronic, smoldering, waxing and waning of a Fear,
Anger, and "Paralysis", "Subservient" state) **(pathologic)**

Human Stressors

Daily hassles

Life transitions: Early life, puberty, adolescence, menopause, retirement

Natural and unnatural catastrophies, War, **Climate change**

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

Socioeconomic status, Minority status, Loneliness (Dignity)

Work stress (Effort Reward Imbalance, ERI), Unemployment (Dignity)

Job loss, Downsizing, Loss of control (Dignity)

Social Inequality (Dignity), Social Restriction (Dignity)

Bereavement

Caretaking/ Pathologic empathy *vs. principled compassion*

Addictions/ **Toxic substances, Environmental pollution (Techno-ecologic)**

Chronic diseases, Treatments

Inflammations (Traumatic, Infectious, Autoimmune, Allergic, **Para-inflammation**)

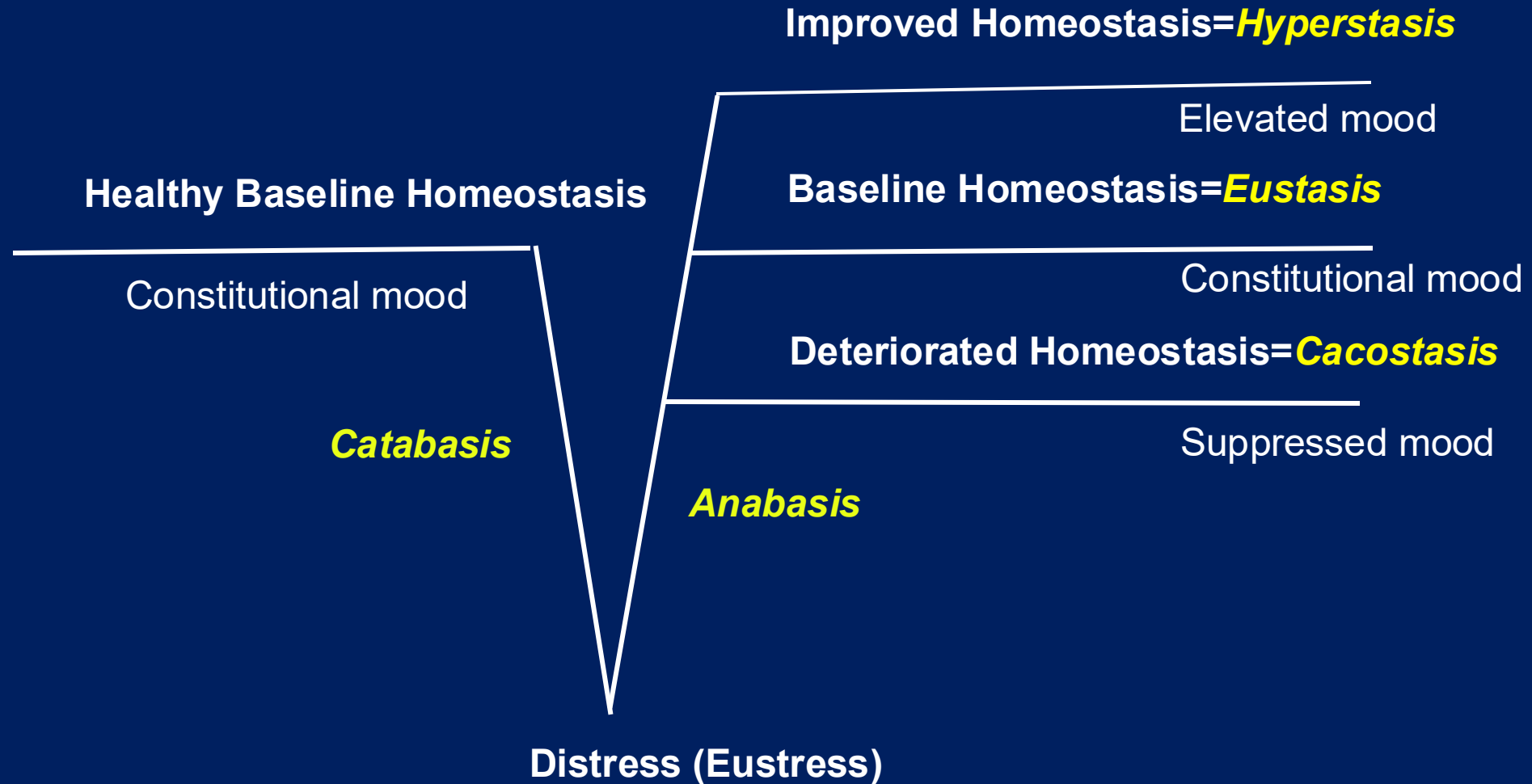
Anxiety, Depression, Personality disorders, Phobias

Sleep deficiency, Sleep excess

Uncoupling of the Clock: Jet-lag, “Social-jetlag”, Work-jetlag

Behavioral addictions: Digital technology-“Meta-modern stress”, “Cyborg stress”, Hikikomori s., NEET, Nomophobia (Nomo[bile]phobia)

Homeostasis over Time

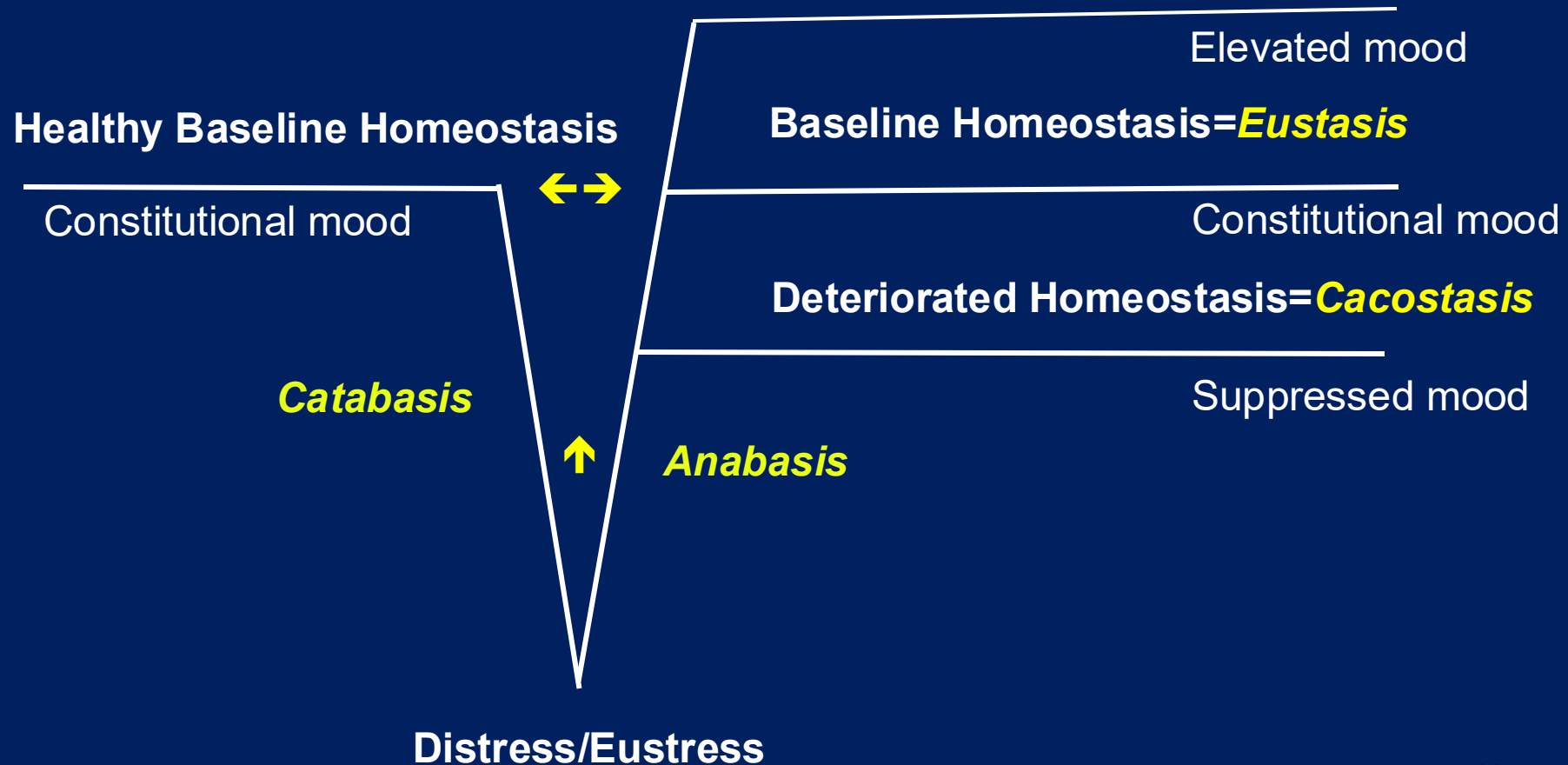


Homeostasis over Time

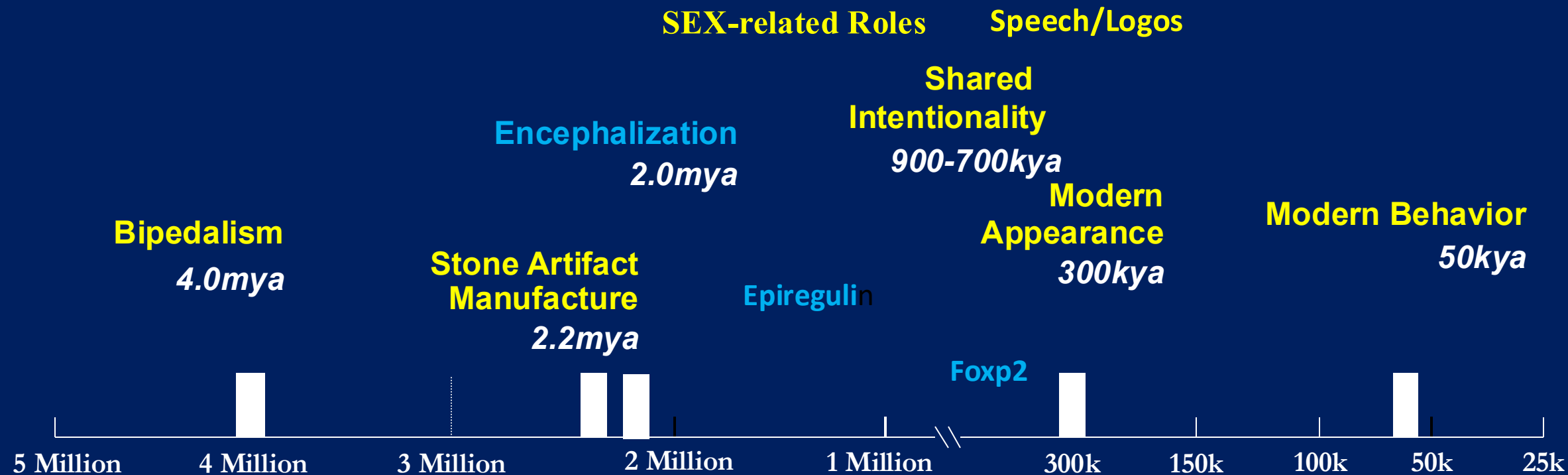
Psychosomatic Resilience = “*Ataraxia*”+ “*Aponia*”

- Small disturbance
- Quick recovery

Improved Homeostasis=*Hyperstasis*



***Resilience is the Ability of any
Organism to Resist to Stressors and
Return Rapidly to Homeostasis***



Years Ago

↑
ARHGAP11 Duplication
Brain ~380 g

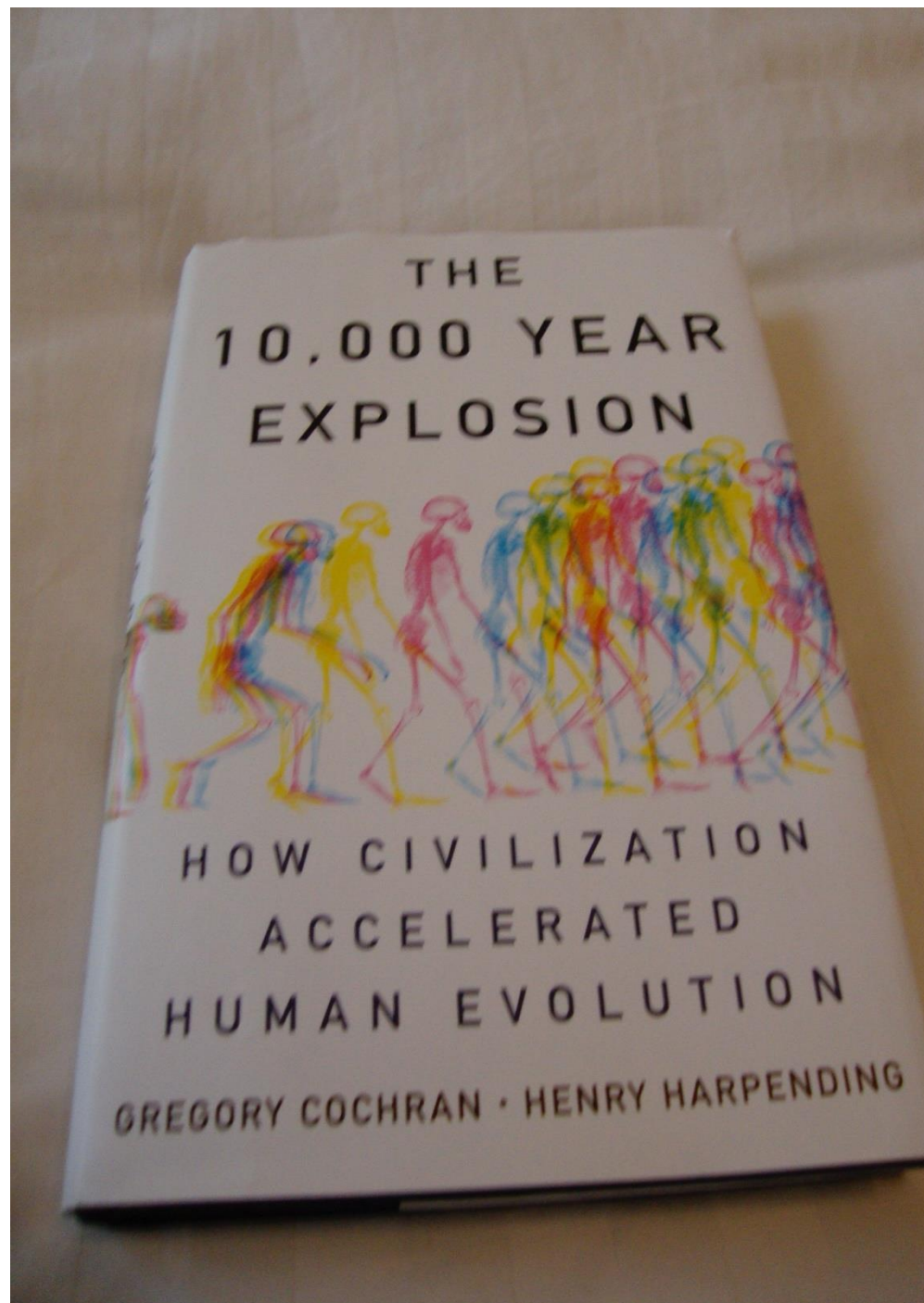
↑
ARHGAP11B Mutation
Brain from 380 to 1300- 1600g over 2 million years

↑
TKT L1 Frontal Mutation neocortex

↑
Near extinction "bottleneck" ~800 kya

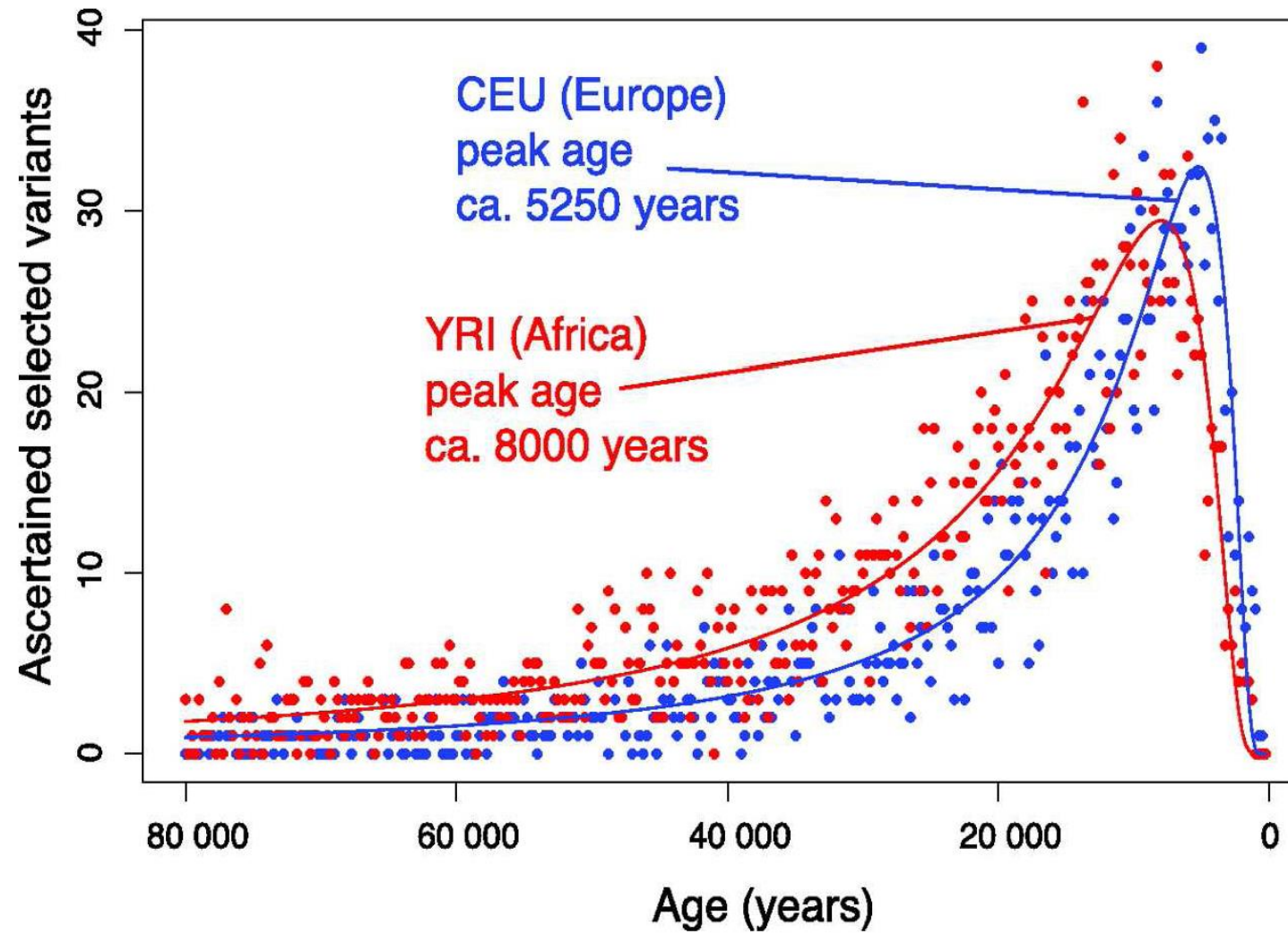
H. erectus= H heidelbergensis? Ancestor X

**Acceleration of Human
Genetic Evolution as a
function of Cultural
Evolution**



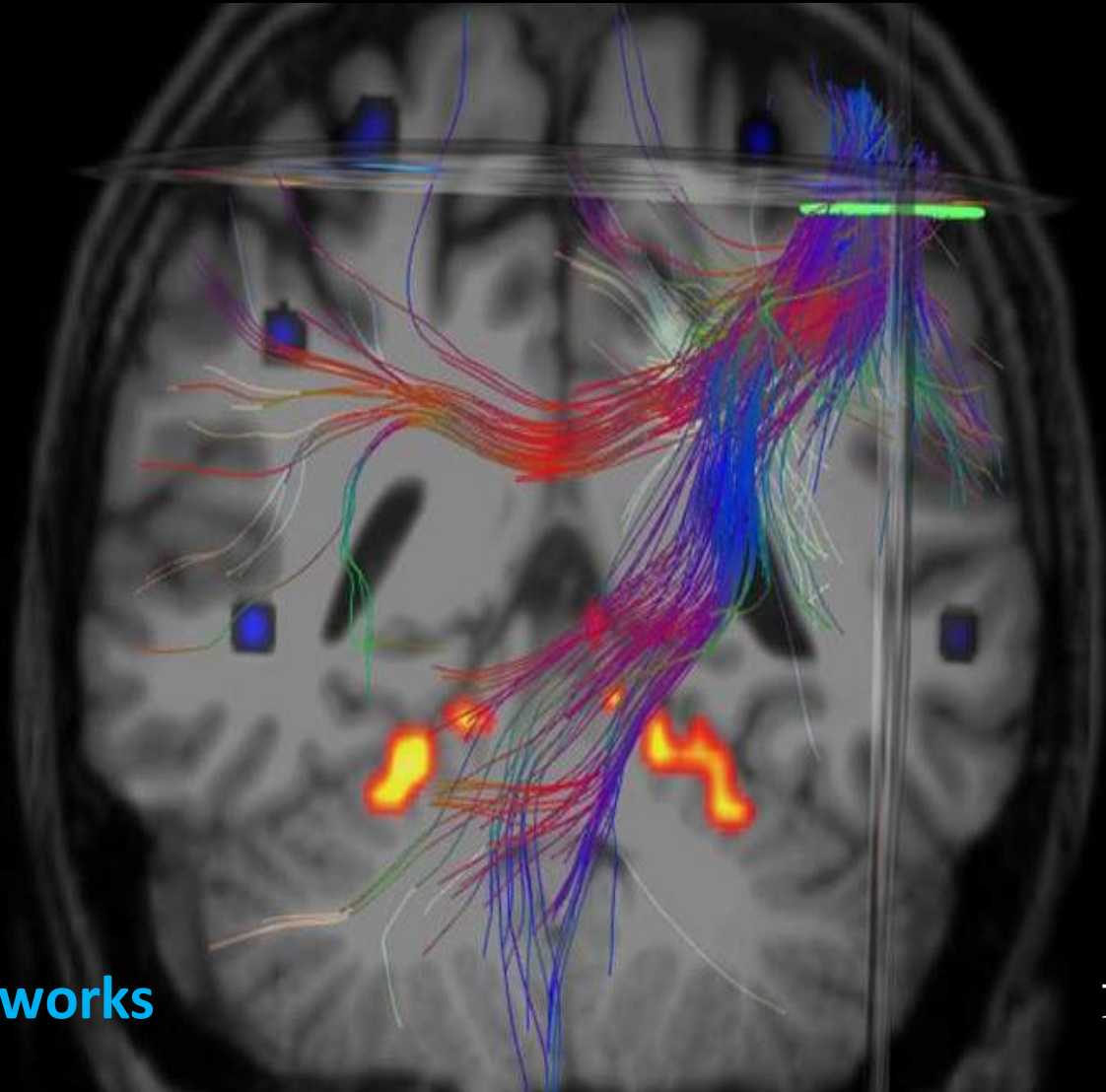
**A “Virtuous Cycle”
between Human
Genetic Evolution
and Culture**

Age distribution of ascertained selected alleles



Hawks et al. PNAS 2007

Intra vs. Inter- Network Connectivity



Many Neuronal Networks

fMRI, DTI, etc.

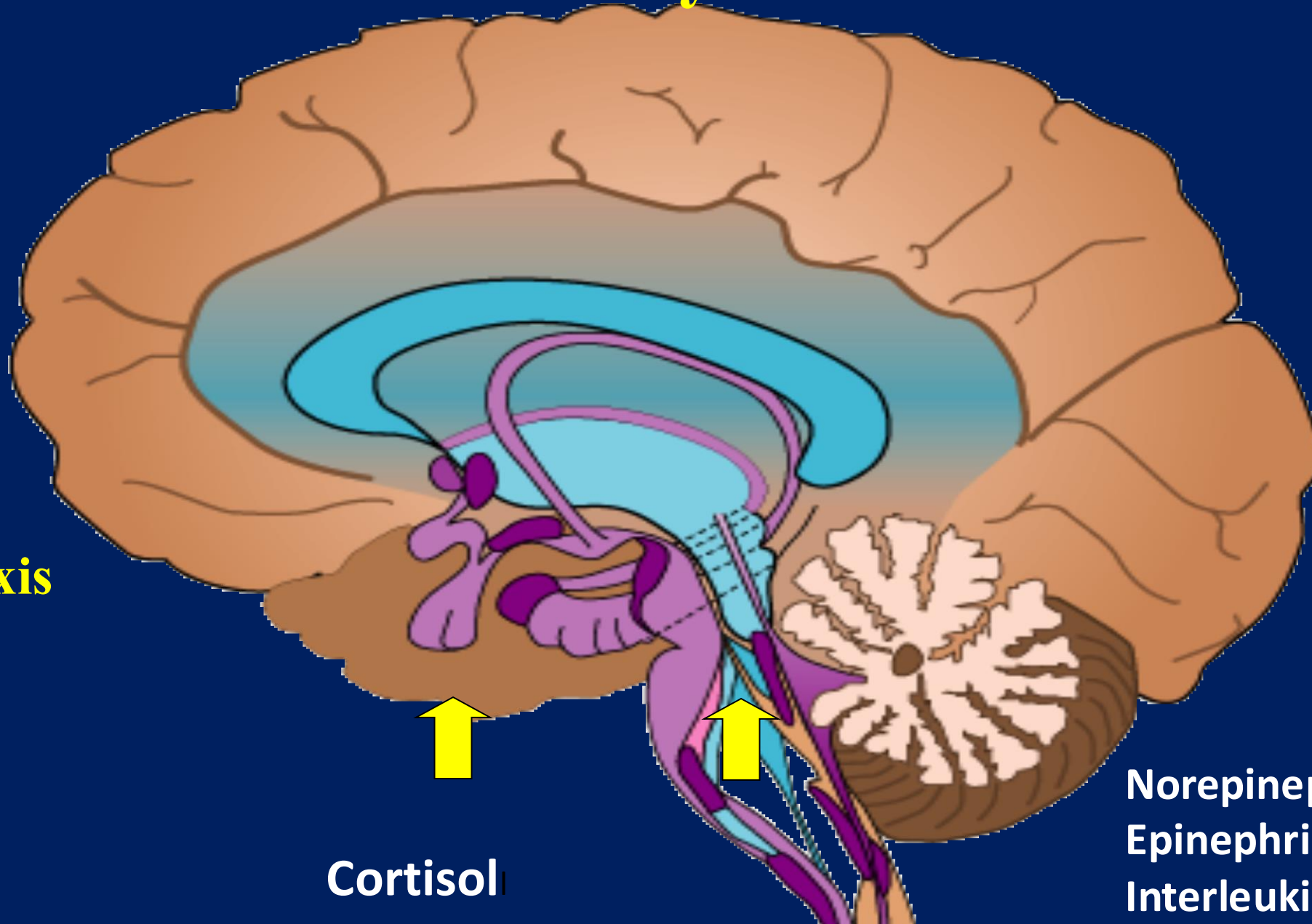
Stress System

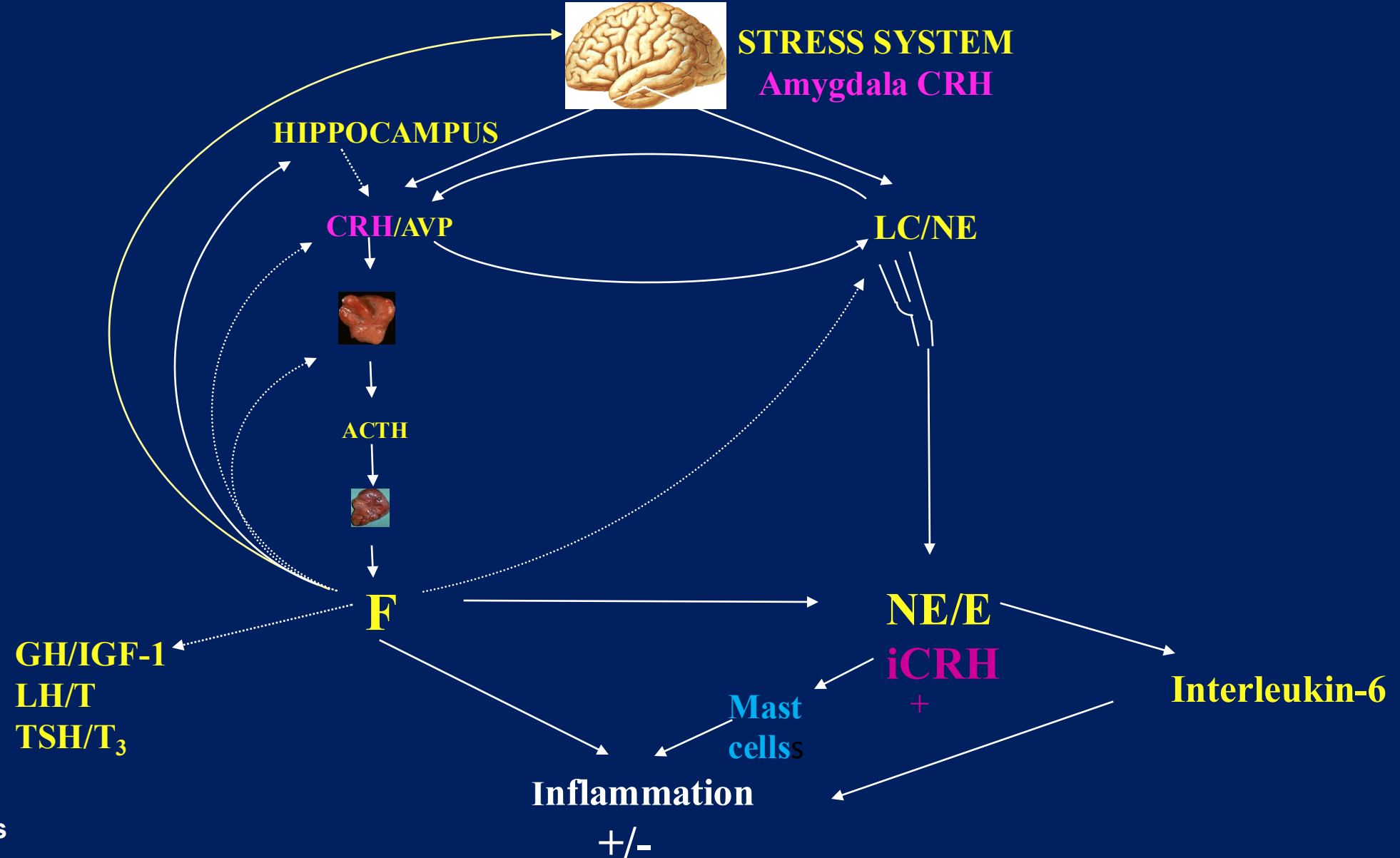
HPA Axis

LC-NE
System

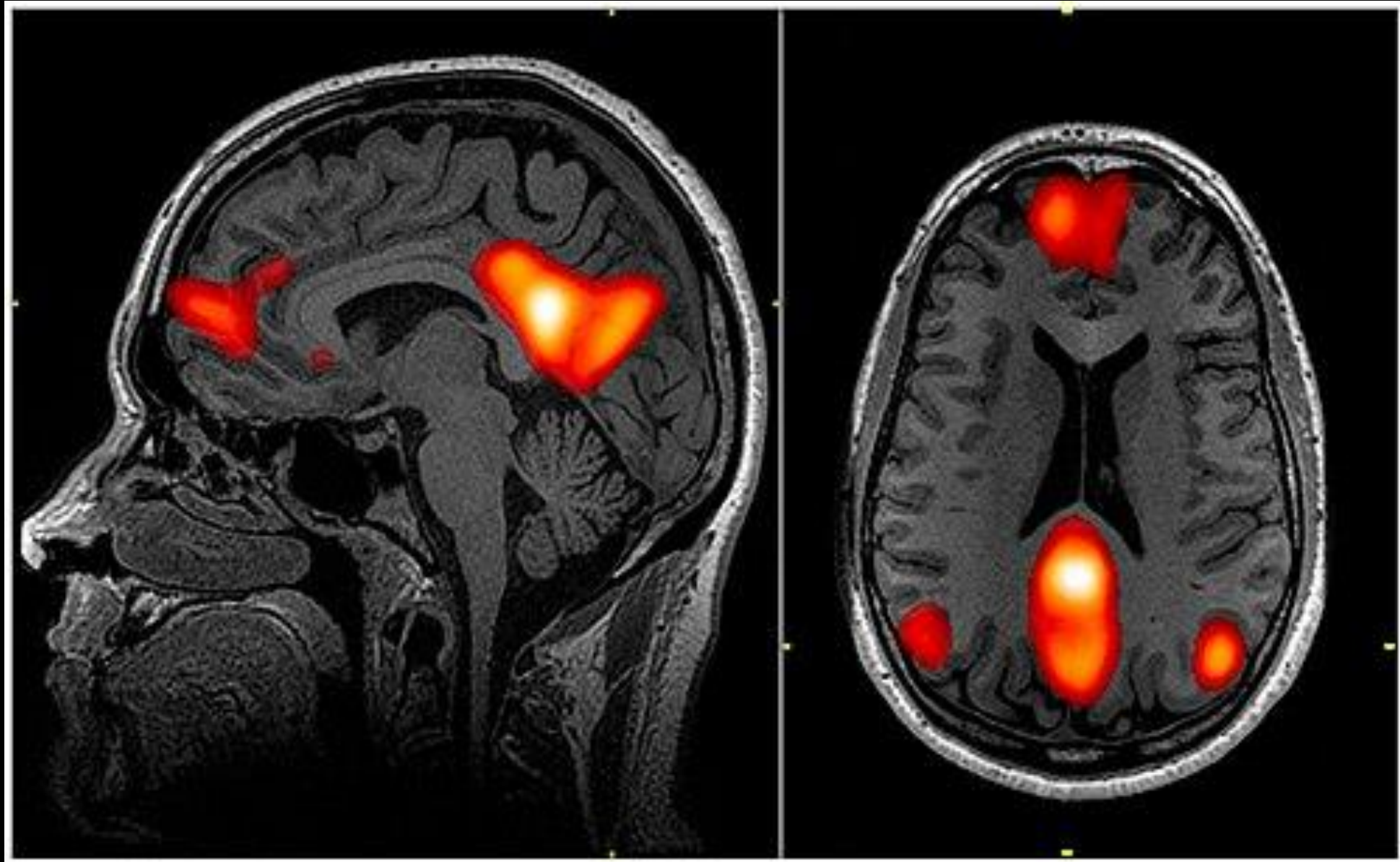
Cortisol

Norepinephrine
Epinephrine, iCRH,
Interleukin-6 (IL-6)

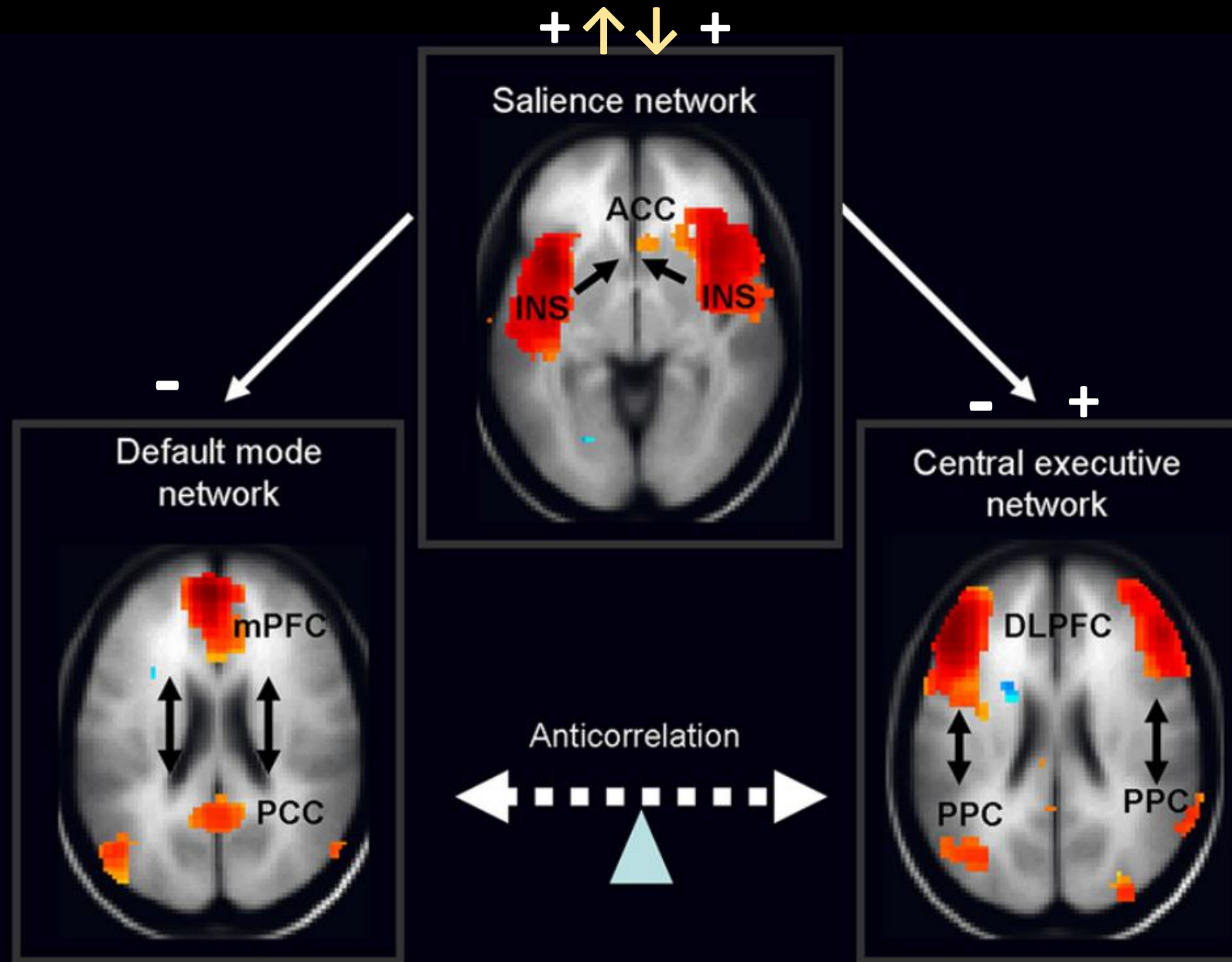


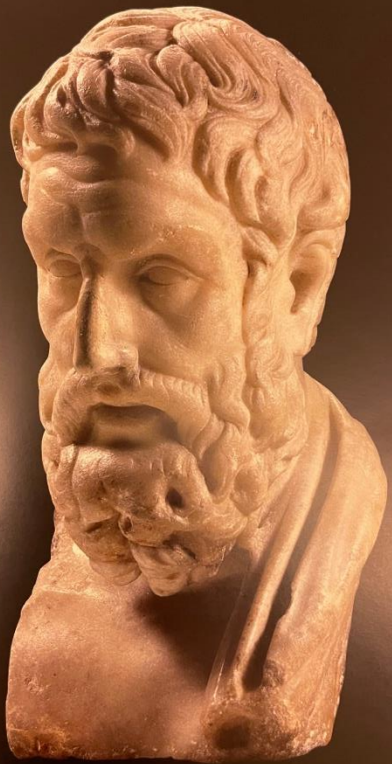


The Default Mode Neural Network (10% of the body energy), Self/Autobiography



Stress System



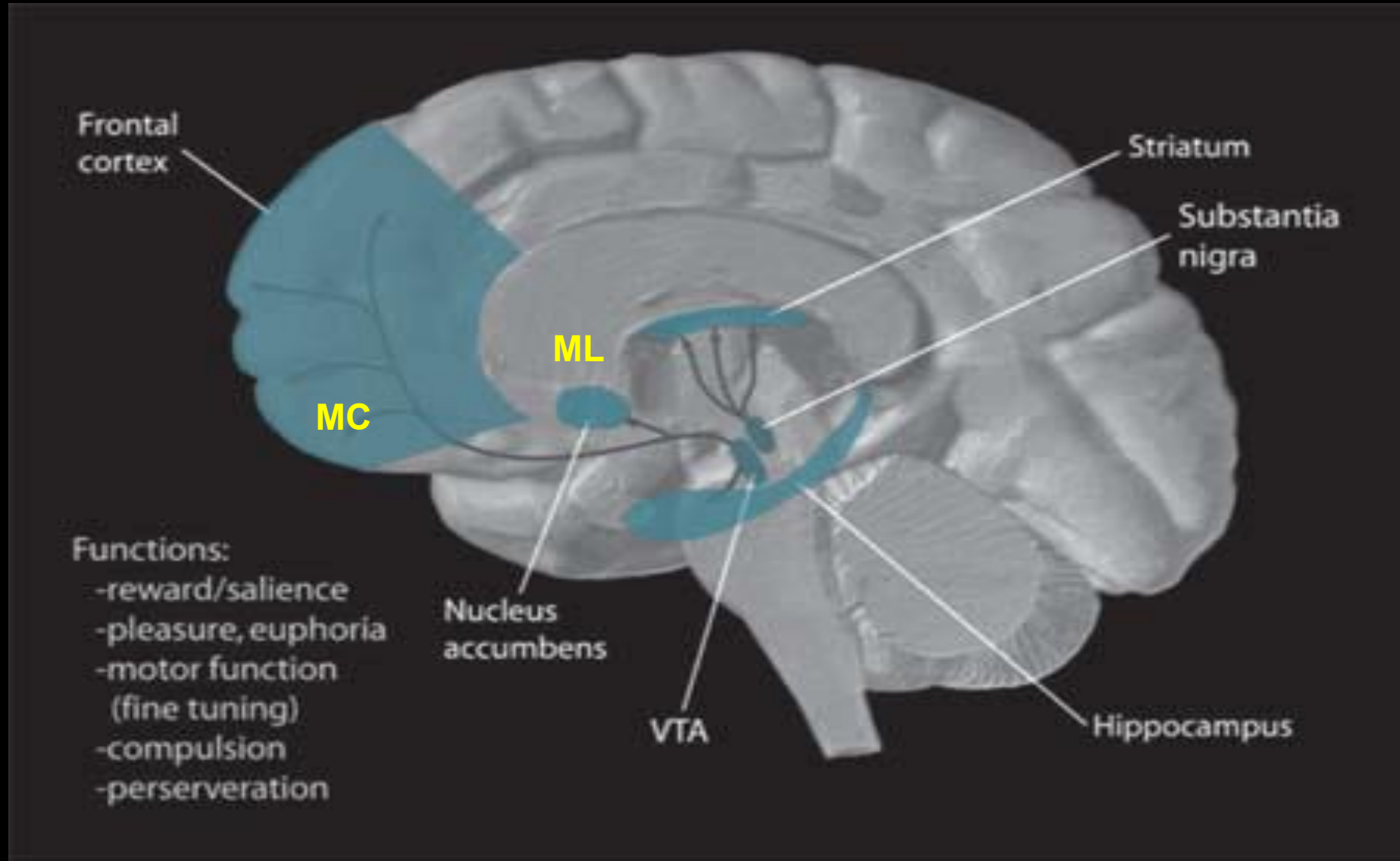


«ΤΗΝ ΗΔΟΝΗΝ ΑΡΧΗΝ ΚΑΙ ΤΕΛΟΣ ΛΕΓΟΜΕΝ ΕΙΝΑΙ ΤΟΥ
ΜΑΚΑΡΙΩΣ ΖΗΝ»

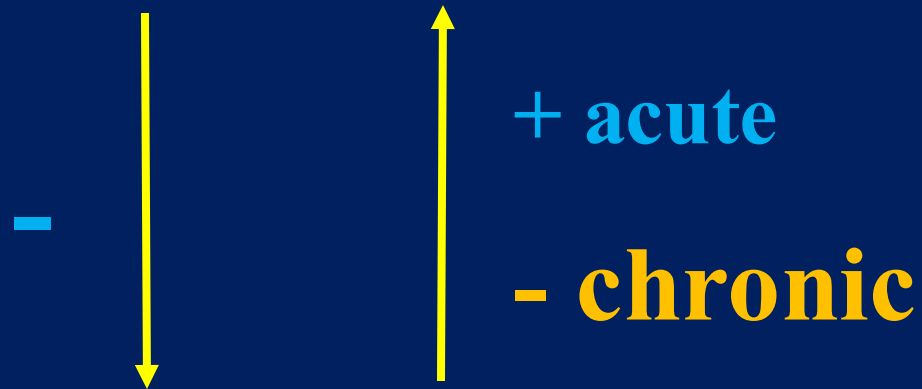
“WE CALL HEDONE THE BEGINNING AND THE END OF
LIVING EUDAIMONICALLY”

Επίκουρος
Epicurus

MC/ML “Reward” System

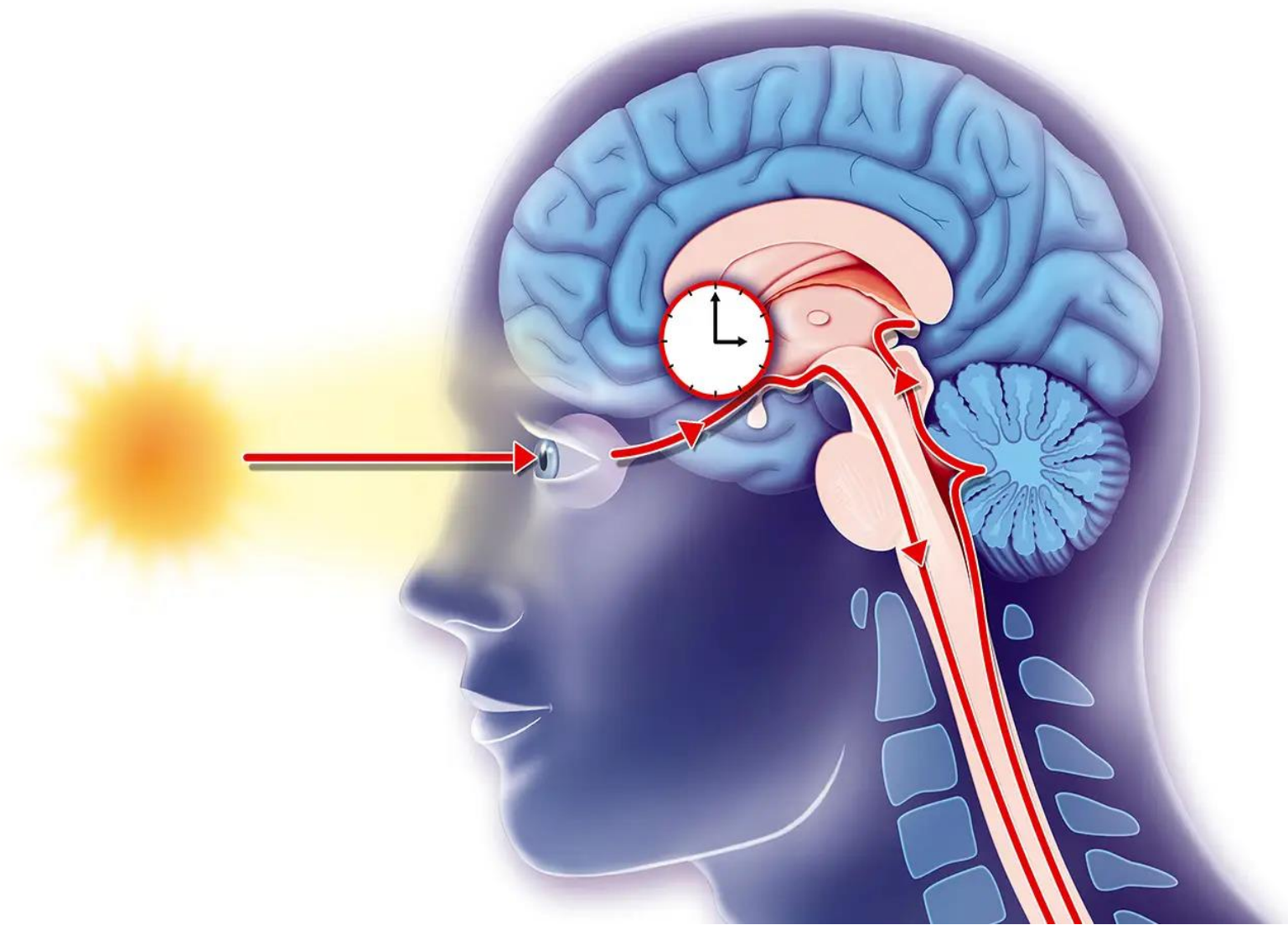


MC/ML “Reward” System Tone



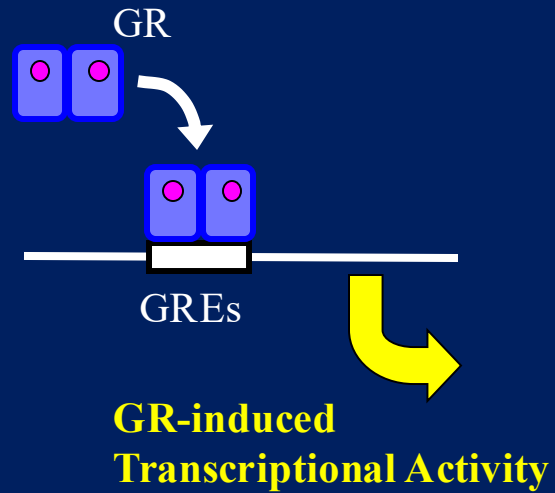
Stress System Tone

The Retino-hypothalamic Track

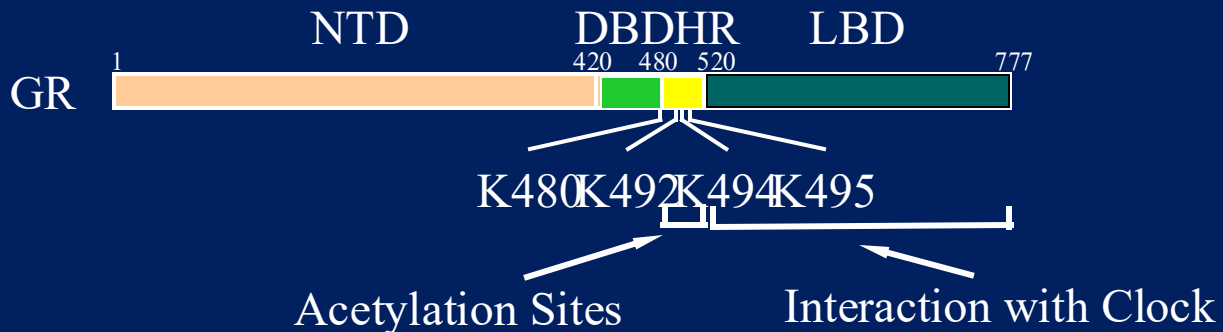
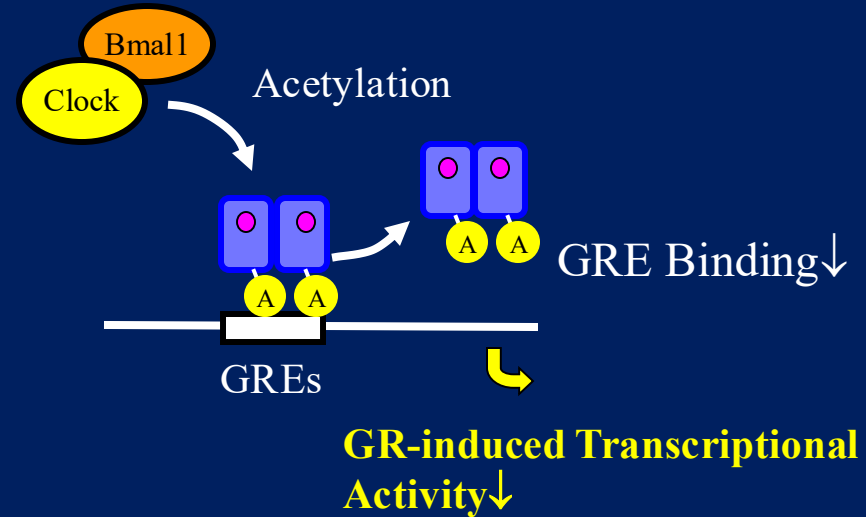


Clock/Bmal1 Represses GR Transcriptional Activity through Acetylation

In the Absence of Acetylation by CLOCK

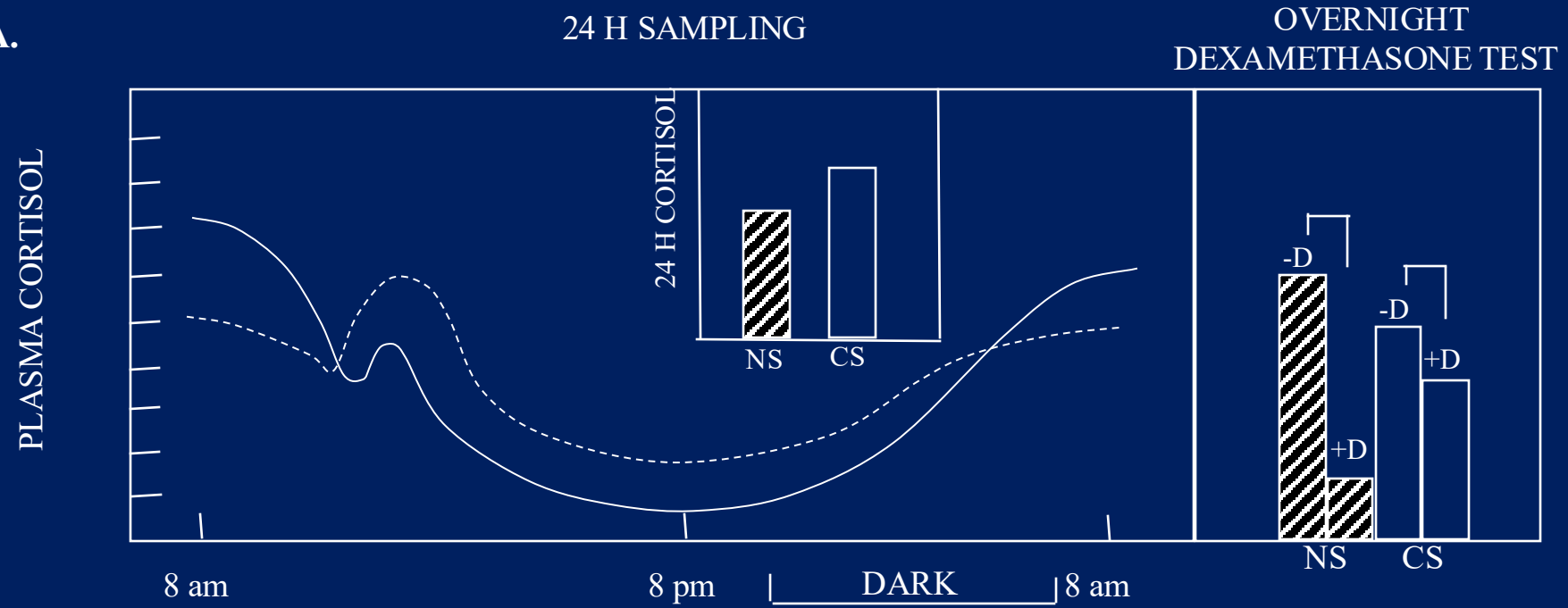


In the Presence of Acetylation by CLOCK

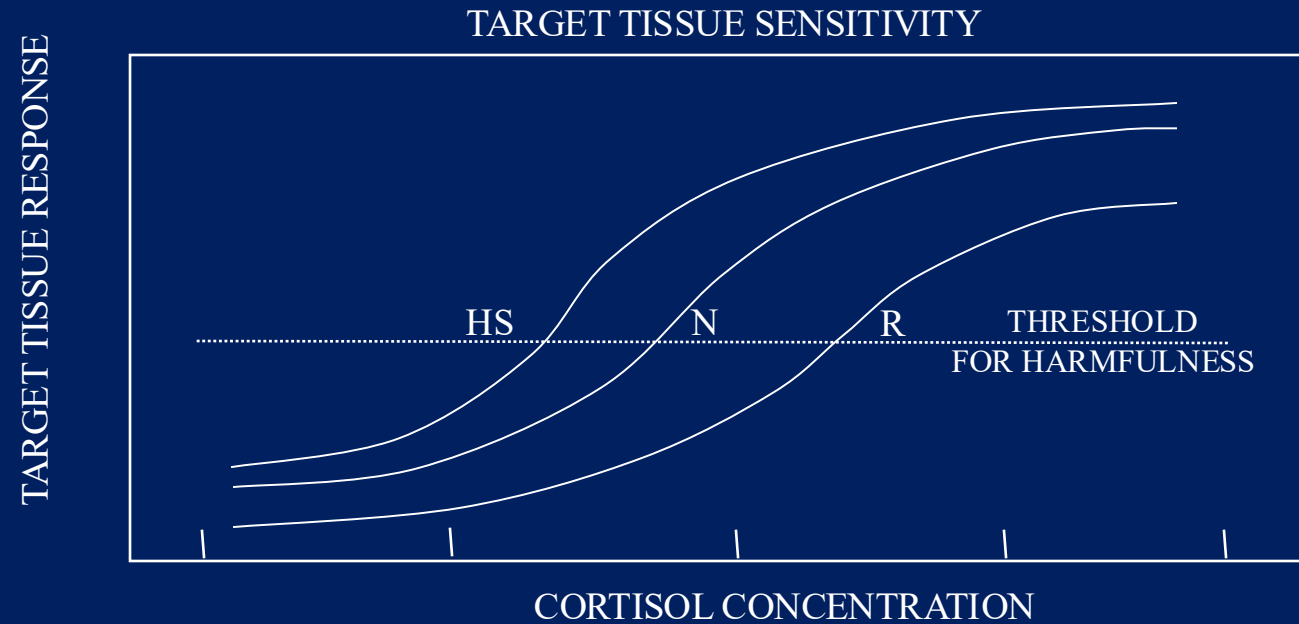


Nader et al. FASEB J. 2009
Charmandari et al. PLoS One. 2011

A.

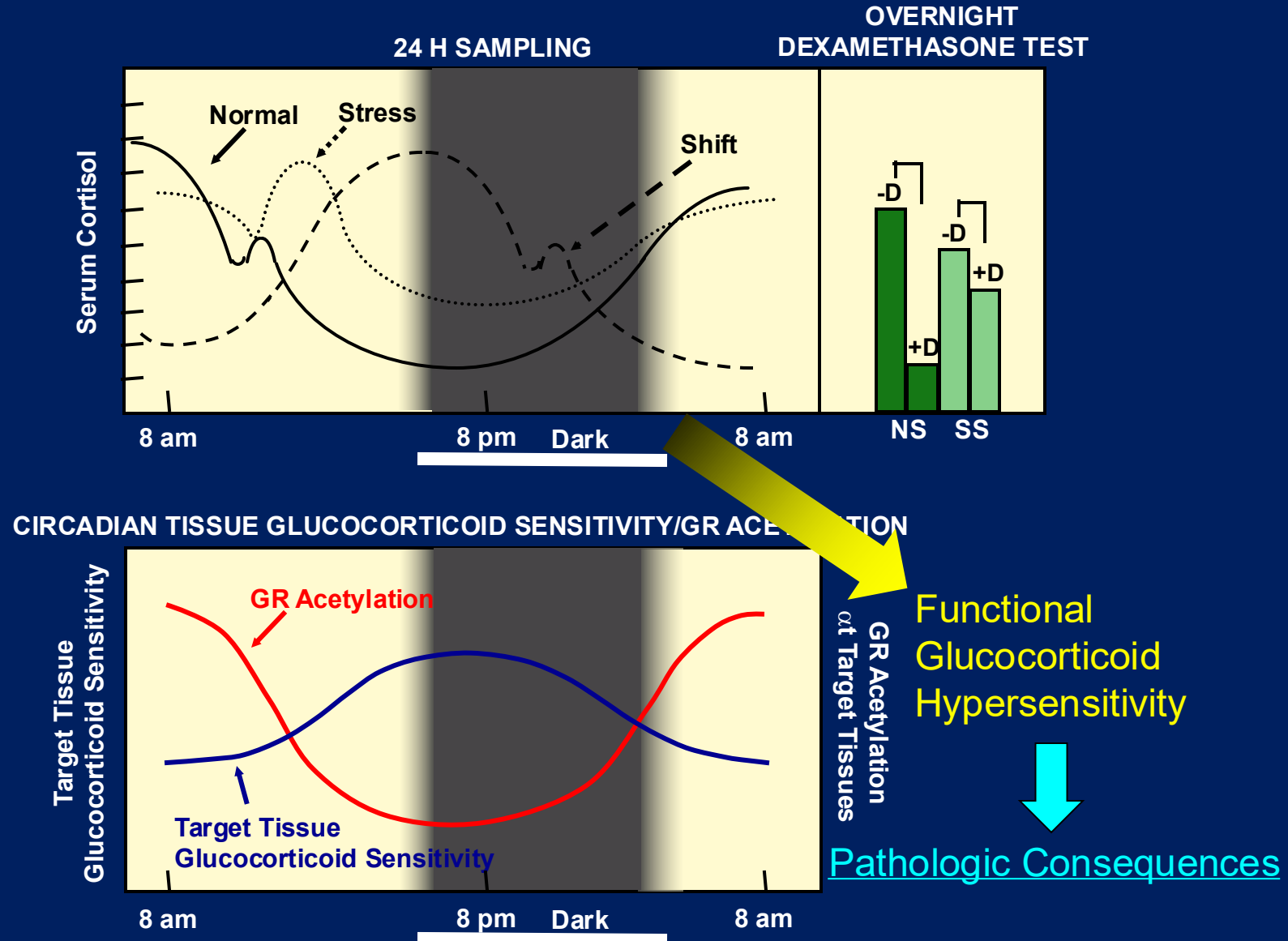


B.



Chrousos JCEM 1998

Uncoupling between Circadian Rhythm of SeCortisol and Tissue Glucocorticoid Sensitivity



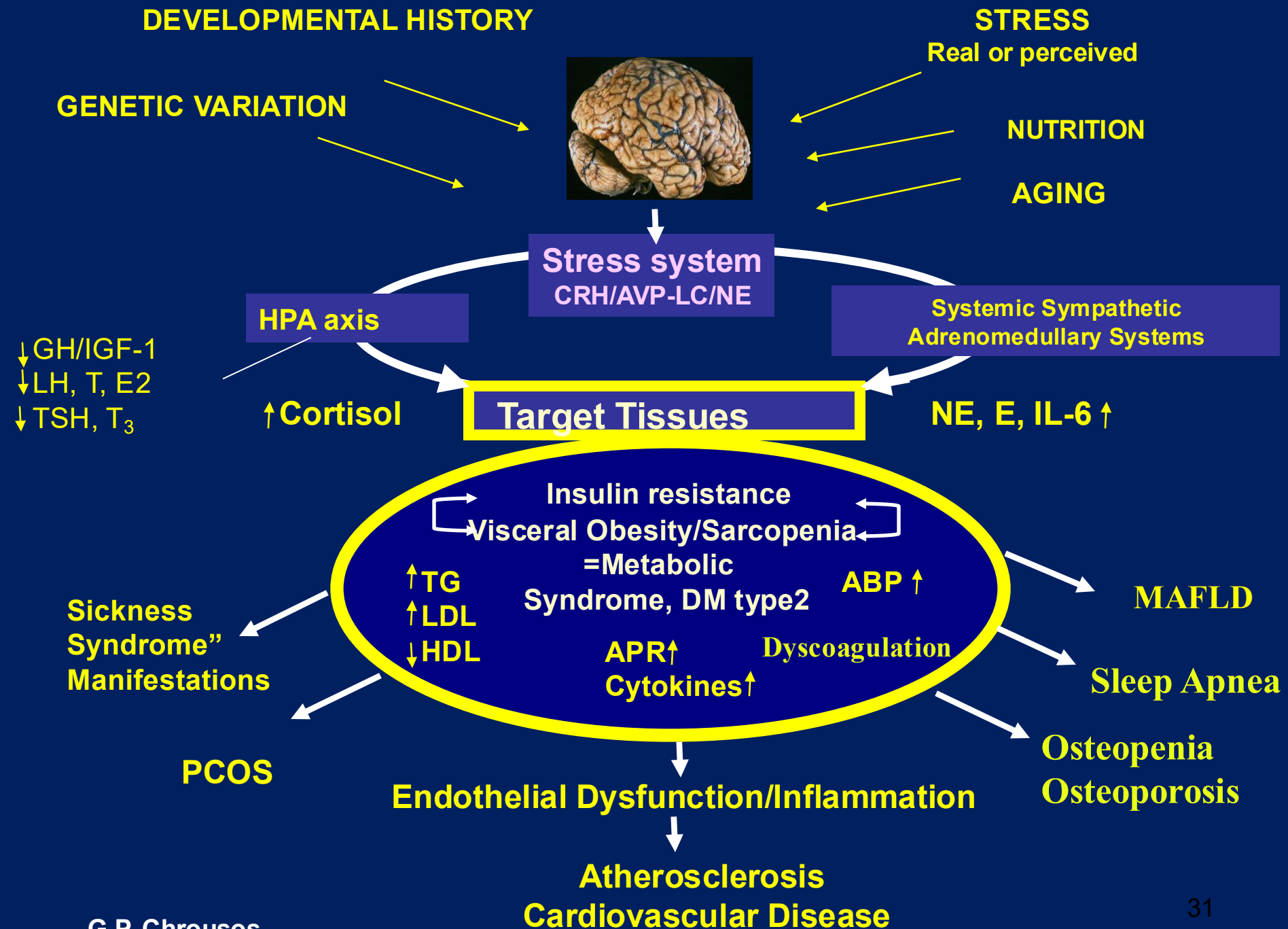
CHRONIC STRESS SYSTEM ACTIVATION

Pathophysiology

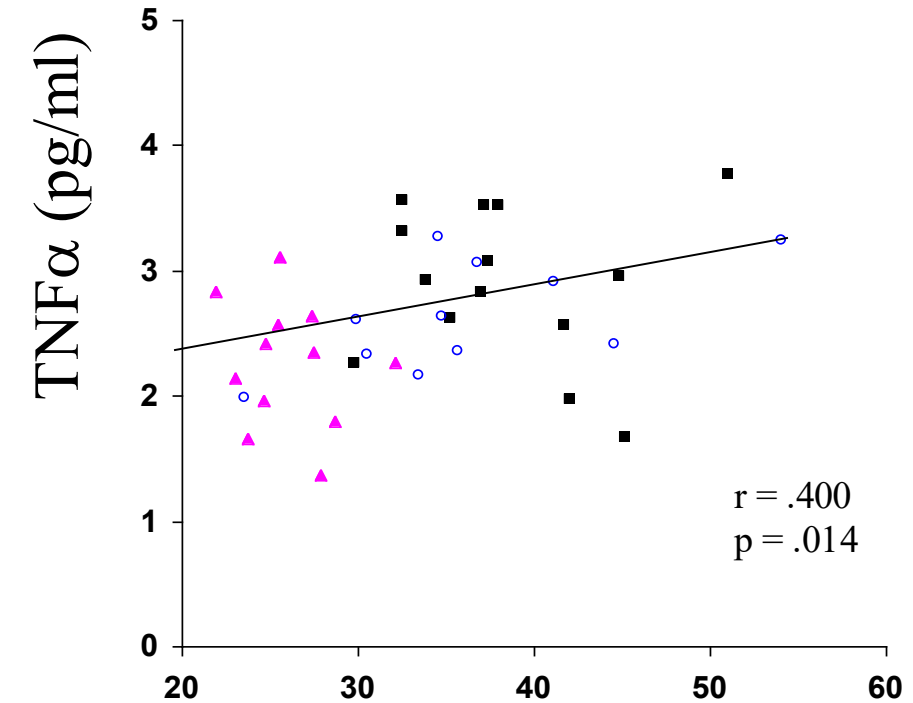
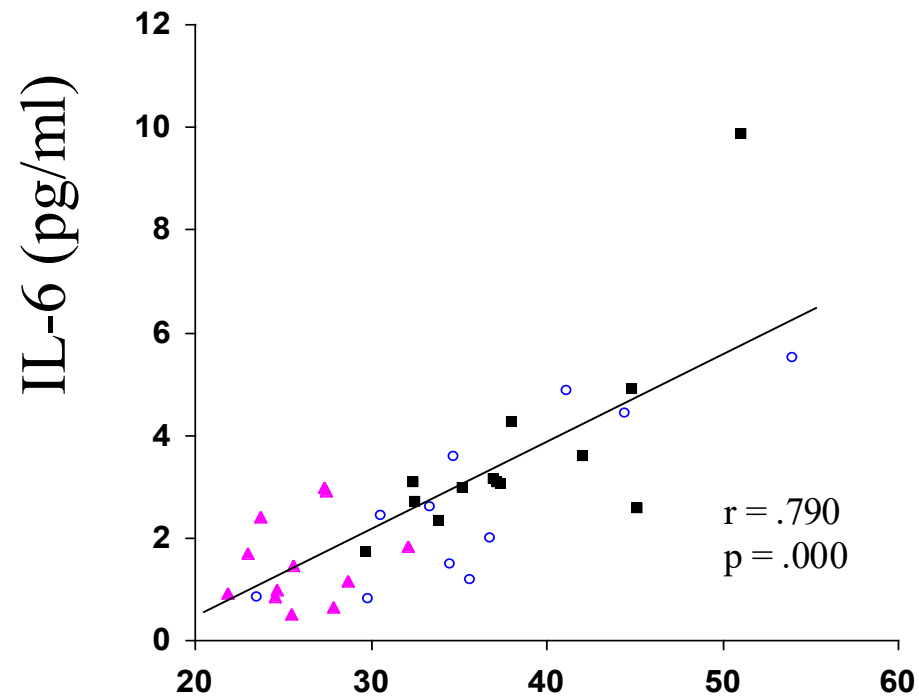
- Anxiety, depression, addiction, anti-social behavior, psychosomatic disorders, loss of libido, fatigue, pain
- Loss of weight, poor growth, obesity, metabolic syndrome, smoldering inflammation, immune dysfunction, autoimmunity/allergy, hypo-fertility, ED, atherosclerosis, CVD, dementia
- Osteopenia/Osteoporosis
- Premature aging of all vulnerable organs, including the brain (neurodegeneration) and the skin
- Vulnerability to certain cancers [+to certain infections]



CHRONIC NONCOMMUNICABLE DISEASES, + COMMUNICABLE



Both IL-6 and TNF α correlate with BMI



BMI

Vgontzas *et al.* JCEM 1997

**Chronic Psycho-
socio-economic Stress
Techno-ecologic,
Climatic**

**Stress System
/Inflammation Activation**

Sleep disorders,
Accelerated aging,
Increased cancer risk,
**Increased risk for
infections**

**Infections,
Environmental toxins**

“Chronic Stress and Inflammation Syndrome” (CSI Syndrome)

**Psychologic and Physical Manifestations, Overweight/obesity
Dysphoria, Medically Unexplained Symptoms (MUS),
Autoimmunity/Allergy, Hypochondriasis, Osteosarcopenia
= “Chronic Noncommunicable Diseases” +**

The
Economist

DECEMBER 13TH-19TH 2003

www.economist.com

Gore anoints Dean

PAGES 12 AND 33

America's Taiwan test

PAGES 12 AND 29

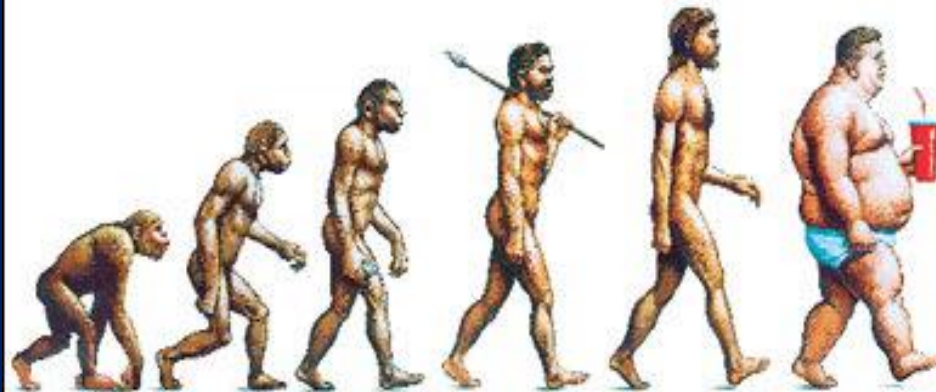
The future of flight

PAGES 79-81

A SURVEY OF FOOD

AFTER PAGE 52

The shape of things to come



Argentina	\$4.50	Canada	C\$6.95	Germany	€3.75	Spain	€4.50
Australia	A\$5.50	Chile	\$3.50	India	Rs 120	UK	£3.50
Benelux	€4.50	Colombia	\$3.50	Italy	€3.50	USA	\$4.95
France	€4.50	Costa Rica	₡10,000	Japan	¥1,000	South Africa	R12.50

Last 70 years

Epigenetic changes:

↑ Overweight/Obesity

↑ CSI Syndrome_s

ENVIRONMENTAL STRESSORS

- Starvation
- Dehydration
- Injurious agents-inflammations
- Adversaries-anticipation
-avoidance
- Injury-minimization
- Social bonding disruption
- Wrong decisions

Embryogenesis

- Maternal Stress
- Perinatal Stress

Species

vs.

Individual

Evolution

Genetics

CNS complexity

Development

Epigenetics

CNS plasticity

Genotype

Epigenotype

Phenotype

MUSCLE MASS

**Best predictor of morbidity
and life expectancy**

DEFINITIONS

- Osteosarcopenia vs. Overweight/Obesity vs. “Paradoxic”-(non)Obesity

Decreased bone mass:

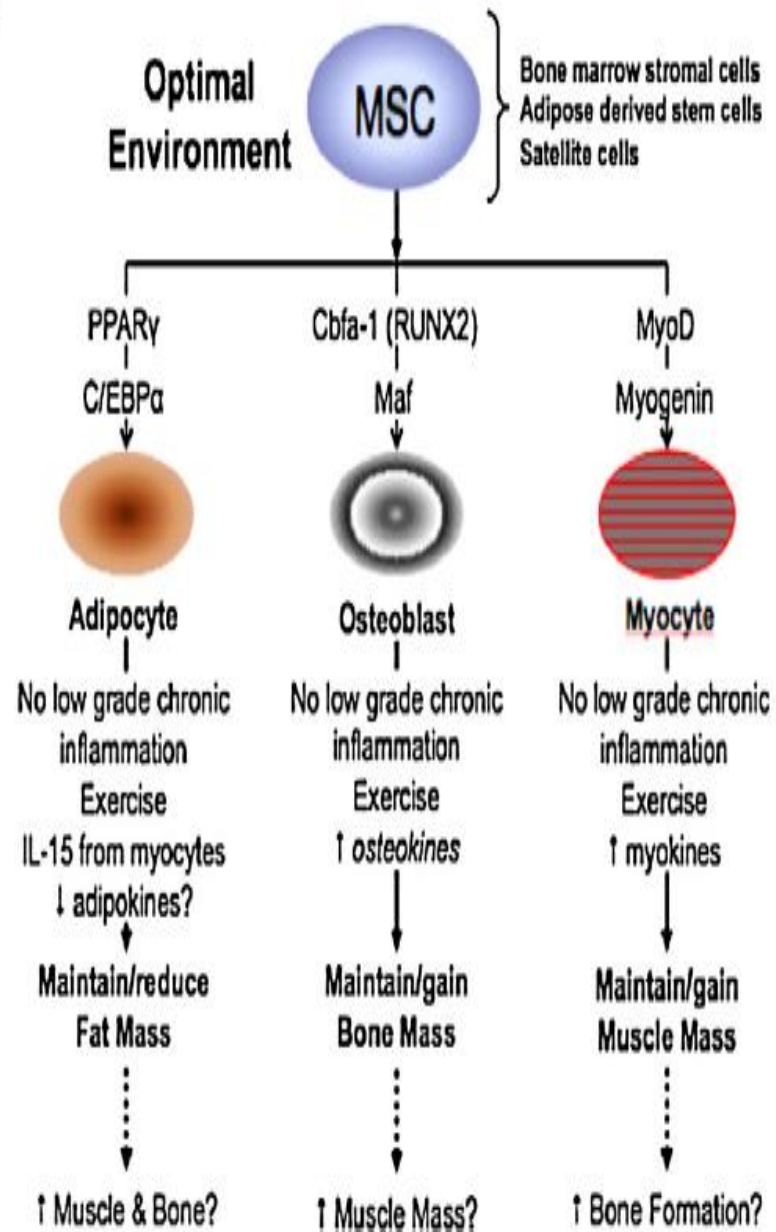
Osteopenia vs. Osteoporosis

T-scores from -1 to -2.5 vs. <-2.5

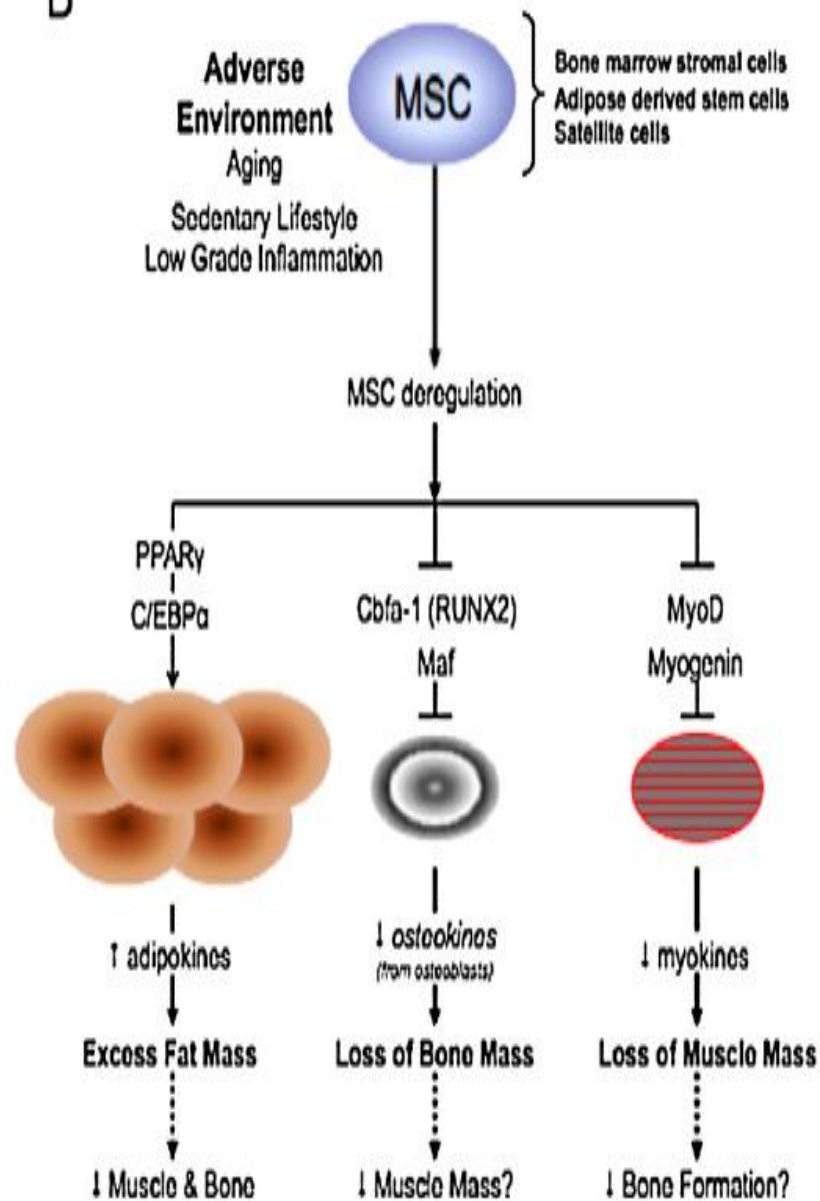
Decreased muscle mass:

Sarcopenia vs. Sarcasthenia +/- lipoatrophy
(cachexia, frailty)

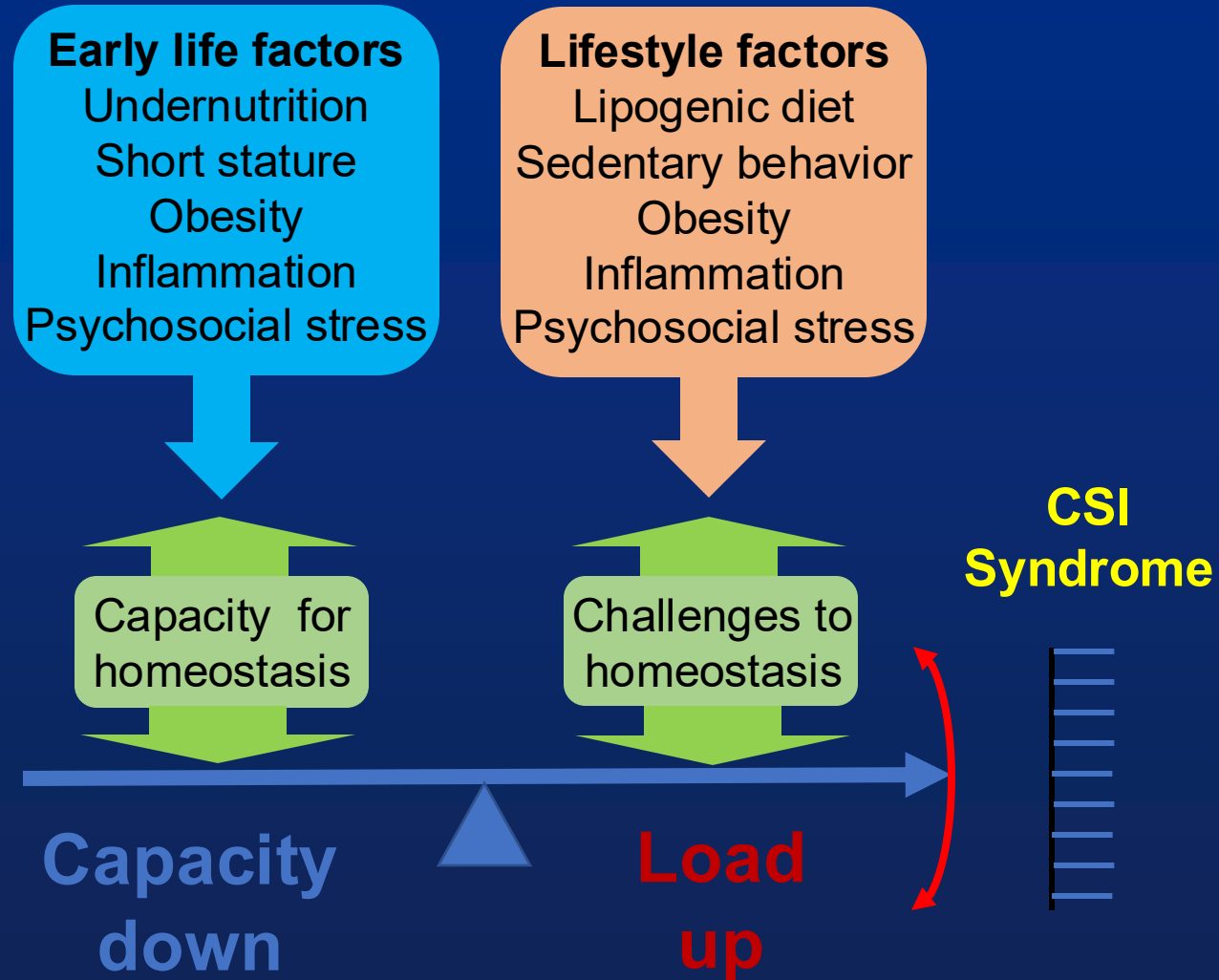
A

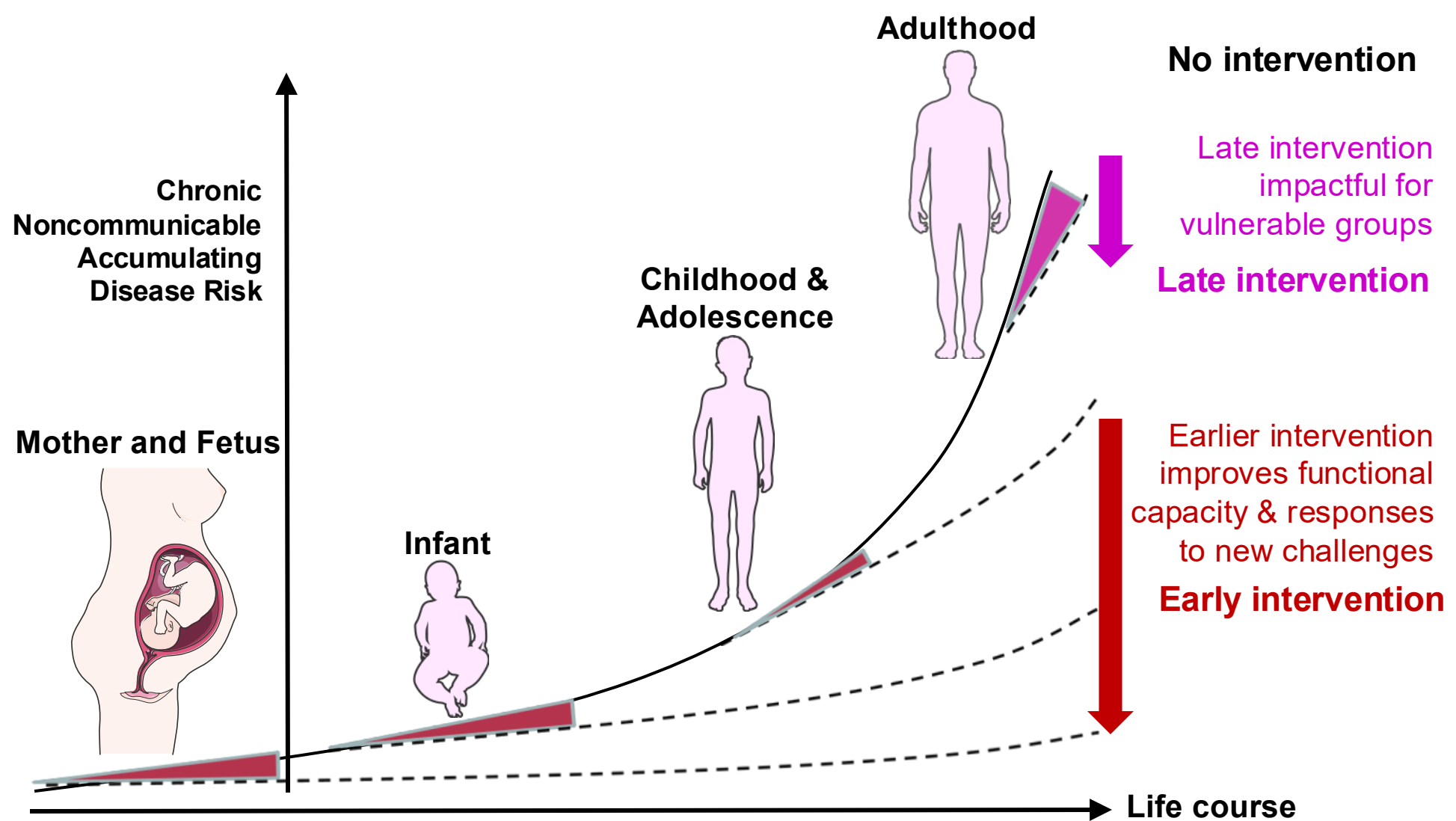


B



The capacity-load conceptual model





Developmental epigenetic plasticity

Inadequate response to stressors

Evaluation/Monitoring of a Stressed Subject

- History, MUS, Physical examination
 - Appropriate questionnaires (PST, Anxiety, Depression, QOL, etc.)
 - Heart Rate Variability measures (Autonomic nervous system)
 - Body Composition (Sarcopenia, Visceral fat, IMAT, Bone density)
 - Biochemical tests (Stress, Inflammation, Metabolic and Aging Markers)
 - Sleep study
 - Research tools (EEG, Loreta EEG, HEG (NIRS), Functional Imaging, etc.)
-

The constituents of Man:

“Φύσις, Εθος, Λόγος”

“Physis, Ethos, Logos”

*Genetics, Epigenetics, Reason
(Environment)*

Aristotle

4th Century BCE

***“Κράτιστον δη προς αλυπίαν φάρμακον ο λόγος
και η δια τούτου παρασκευή προς πάσας του βίου
μεταβολάς”.***

***“The best medicine to attain consolation is
Logos, and through it the preparation for all the
vicissitudes of life”.***

Πλούταρχος Plutarch

The 5 Classic Lifestyle “Musts” for Hyperstatic Resilience

- **Healthy Nutrition**
 - **Moderate Exercise**
 - **Proper Sleep**
 - **Circadian Regularity**
 - **Stress Management**
-

What can we do about stress?

- **Social prerequisites**
 - Nutrition
 - Exercise
 - Sleep
 - Circadian regularity
 - Stress Management
 - Eustress-Effectance-Hormesis-Learning
 - Experiencing “*Flow*”
 - “Noopedia” methods
 - “Meaning- in-life”
-

Basic Social Prerequisites

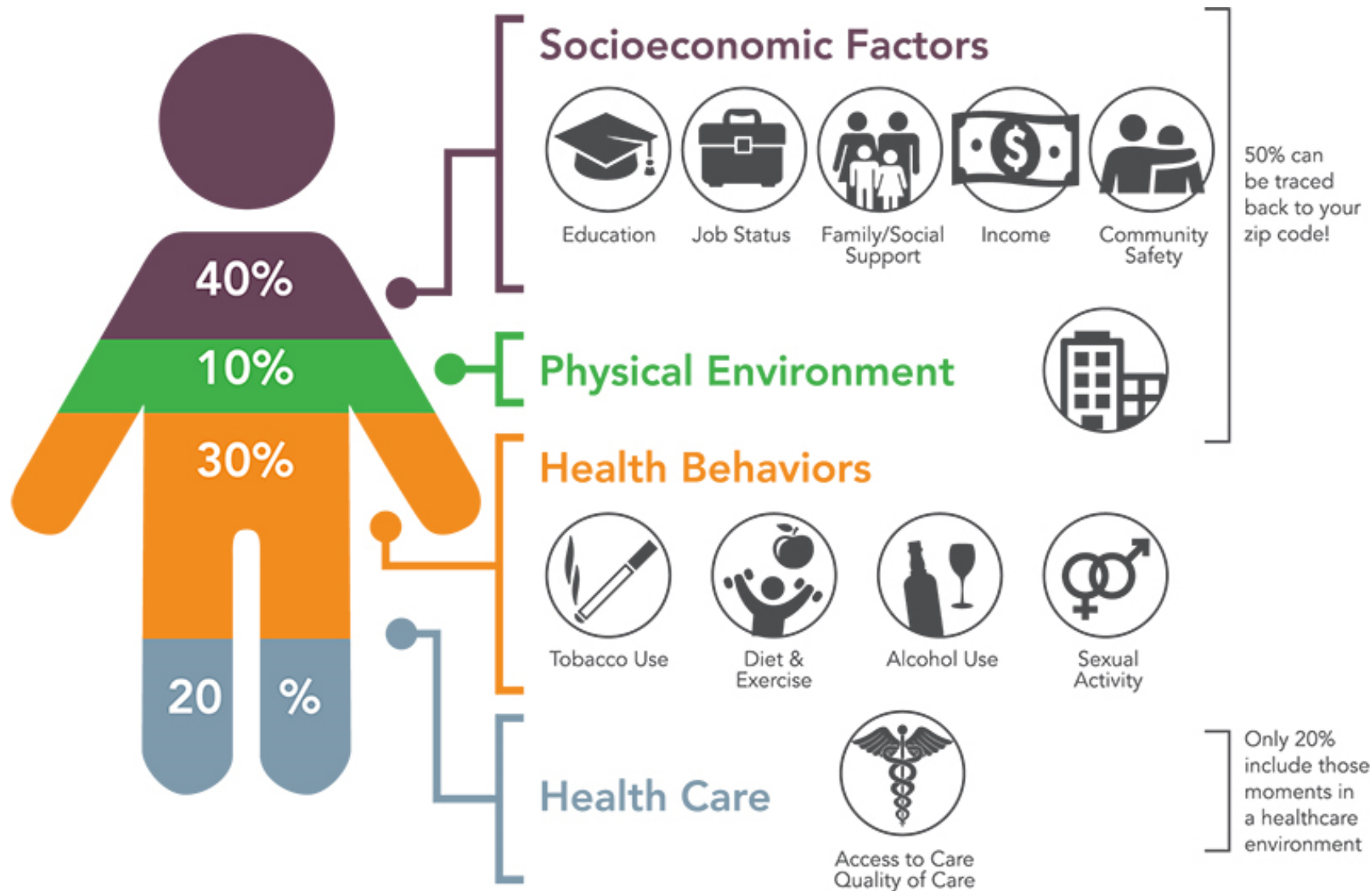
- **Safety, Security**
- **Social Integration**
- **Competence**
- **Authenticity**
- **Autonomy**
- **Environment**

Lifestyle Factors

Chronic Stress
Chronic Disease

The diagram illustrates the relationship between visible and hidden factors in health. An iceberg is shown with a small portion above the water line and a much larger portion submerged. The visible part is labeled 'Lifestyle Factors' and includes 'Chronic Stress' and 'Chronic Disease'. The submerged part is labeled with four categories: 'Daily Living Conditions', 'Family Structure', 'Economic Structure', and 'Social Structure'. The water line is marked by a dashed white line. The submerged part is divided into four colored sections: green, grey, blue, and orange, each representing one of the four categories. The background is a solid light blue.

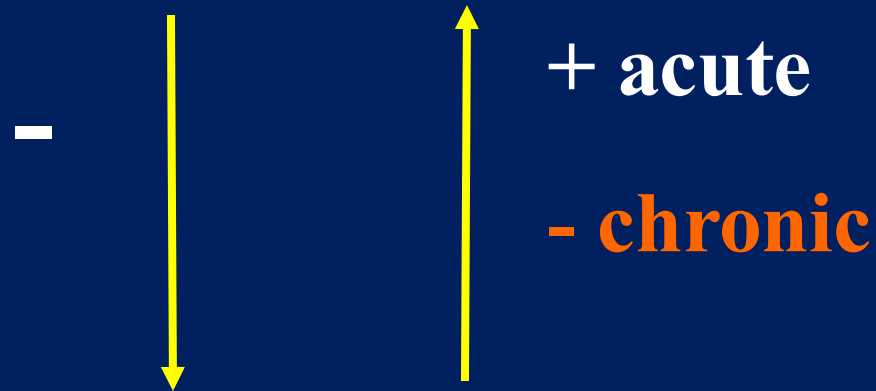
Daily Living Conditions
Family Structure
Economic Structure
Social Structure



Source: Institute for Clinical Systems Improvement, Going Beyond Clinical Walls: Solving Complex Problems (October 2014)

POSITIVE PSYCHOLOGY

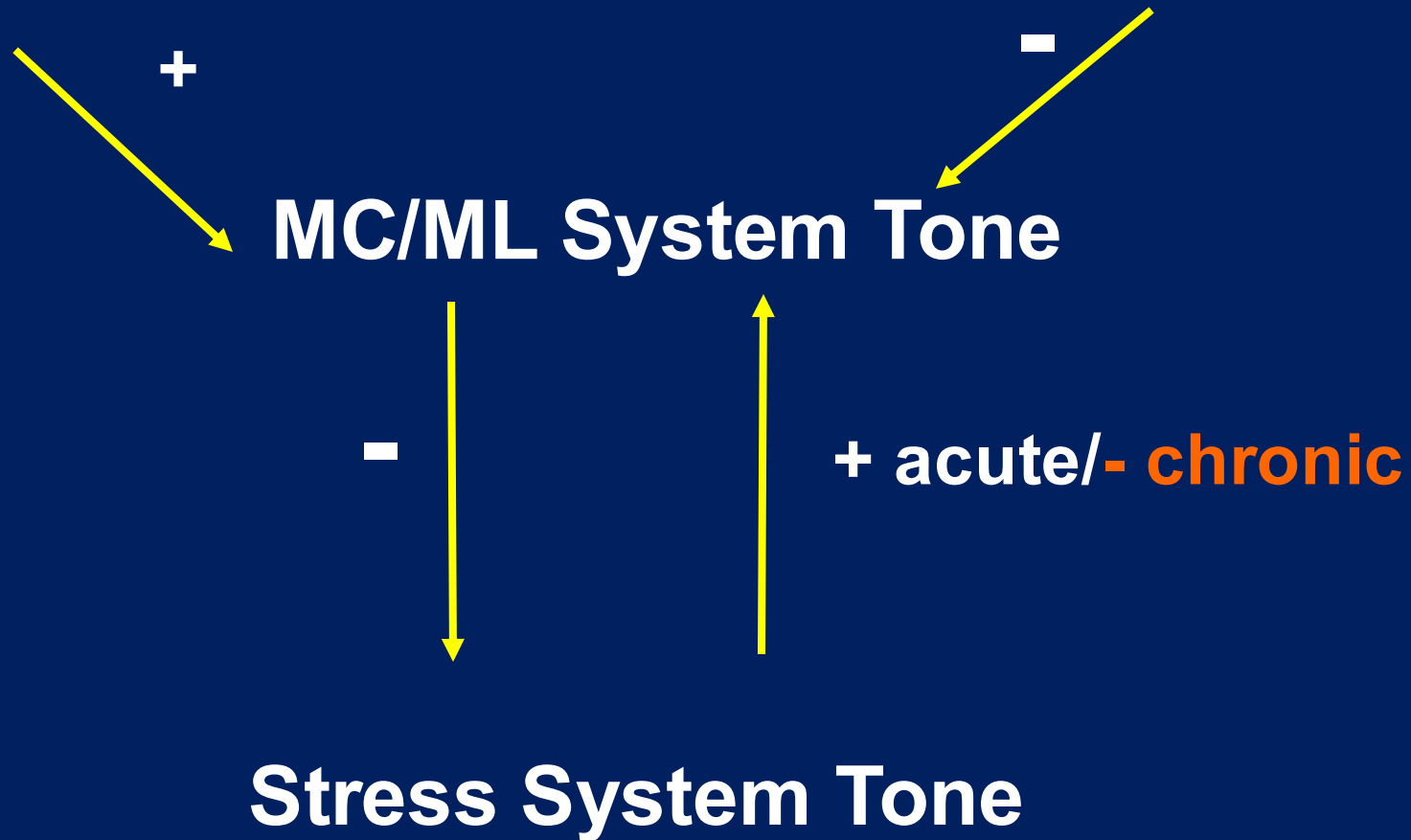
MC/ML (Reward) System Tone



Stress System Tone

Placebo,
Positive thinking/words/actions,
Compassion, Learning,
“Flow”, “Noopedia” methods
“Meaning-in-life”

Nocebo,
Negative/thinking/words/actions,
Stressful empathy, Stultification
No “pathos”
No “meaning-in-life”



Holistic Approach to Stress Management

- **Lifestyle changes** (Daily routine, nutrition, exercise, sleep, social support)
- **Life skills training/SEL** (Problem solving, emotion management, resilience, coping with change, communication skills, etc.)
- **Relaxation techniques training** (Breathing, PMR, TM, Mindfulness, EFT, etc.)
- **Professional support*** (Counselling, PSM, CBT, DBT, ACT, EMDR, etc.)

*Psychology, Psychiatry