

# **Computer Models of Stress, Allostasis, and Acute and Chronic Disorders**

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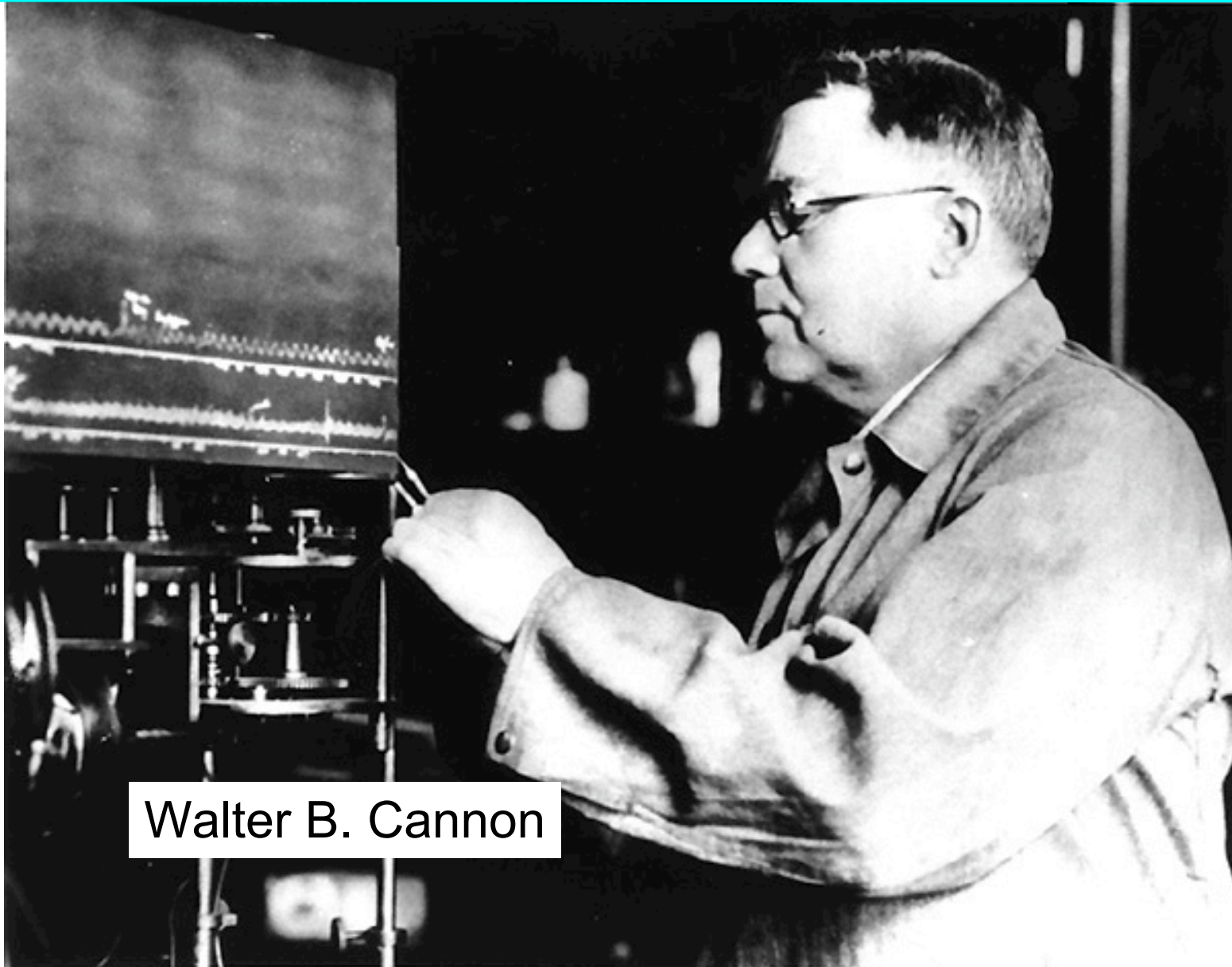


## Topics of this Lecture

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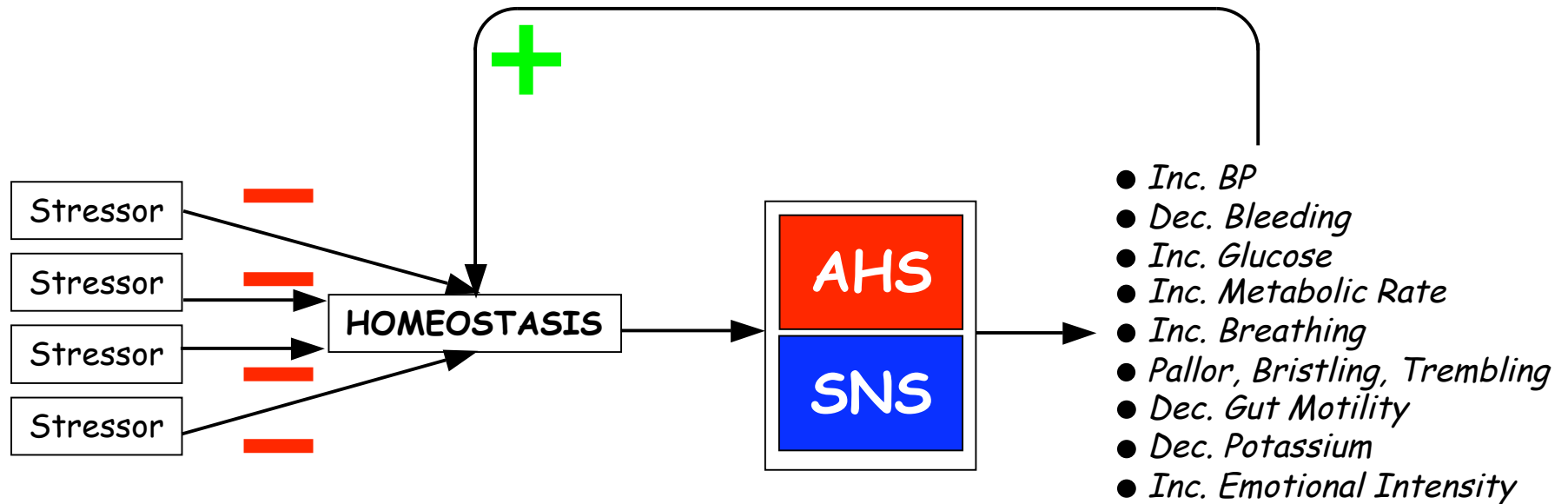
- Evolution of concepts of stress and distress
- Is there a unitary sympathoadrenal “fight-or-flight” system?
- Is stress the non-specific response of the body to any demand?
- What is Scientific Integrative Medicine?
- A homeostatic definition of stress
- Can one define distress in a manner that does not assume pathology?
- Examples of applications of Scientific Integrative Medicine to mind-body disorders

## Cannon: Father of Homeostasis



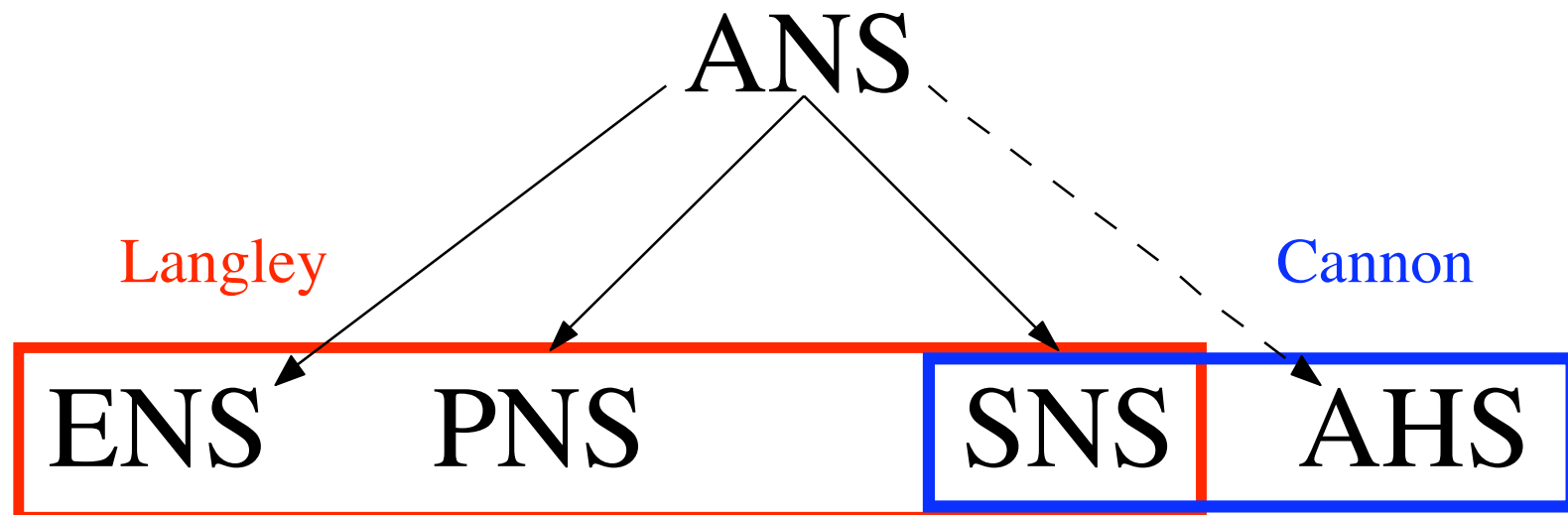
Walter B. Cannon

# Cannon's Views on Stress and Homeostasis



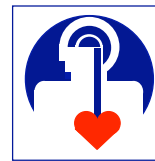


# Cannon's "Sympathoadrenal" System

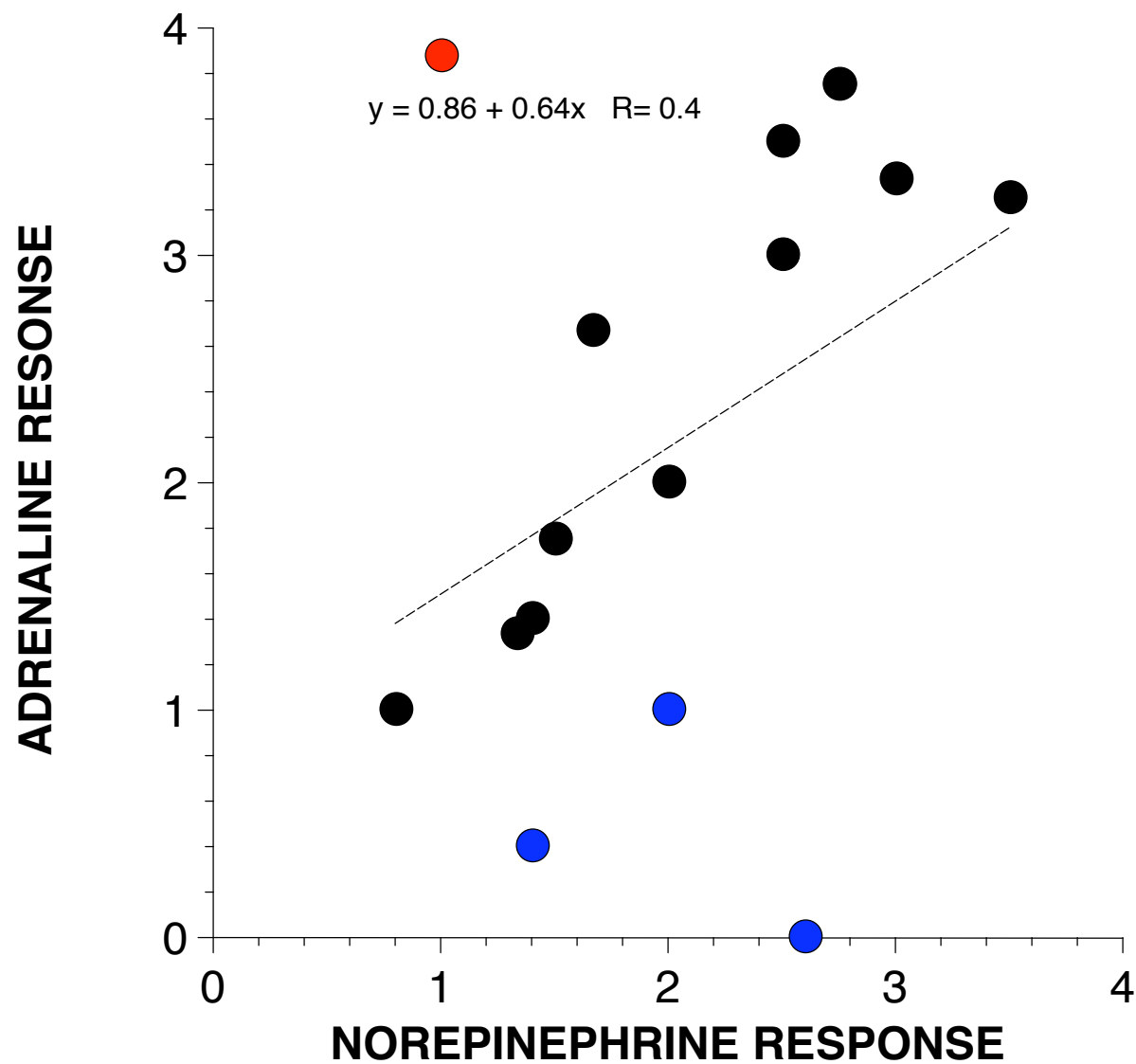


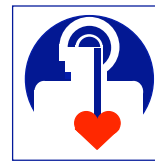
# SNS-AHS Functions in Emergencies



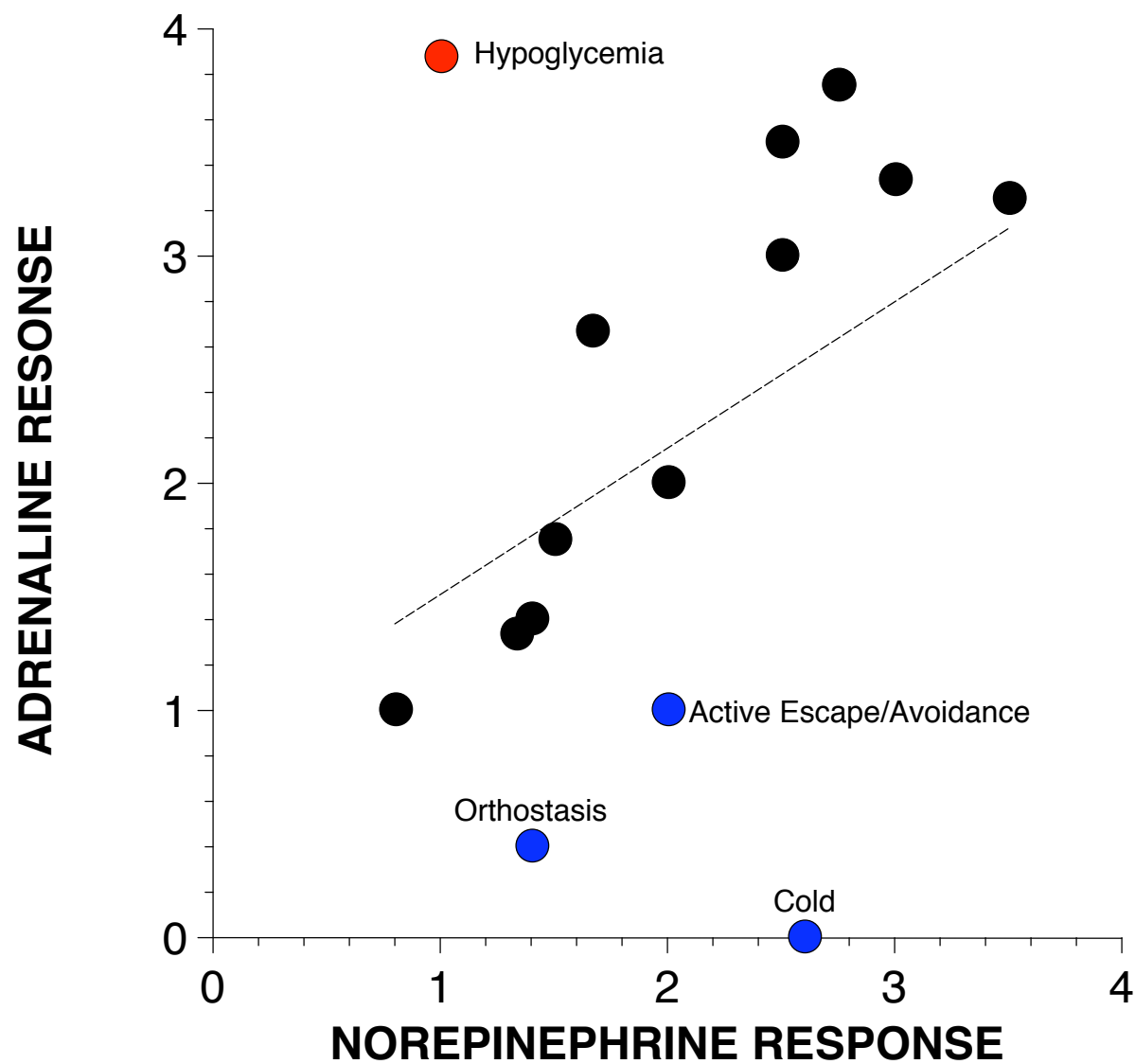


## AHS-SNS Relationship Across Stressors





## AHS-SNS Relationship Across Stressors



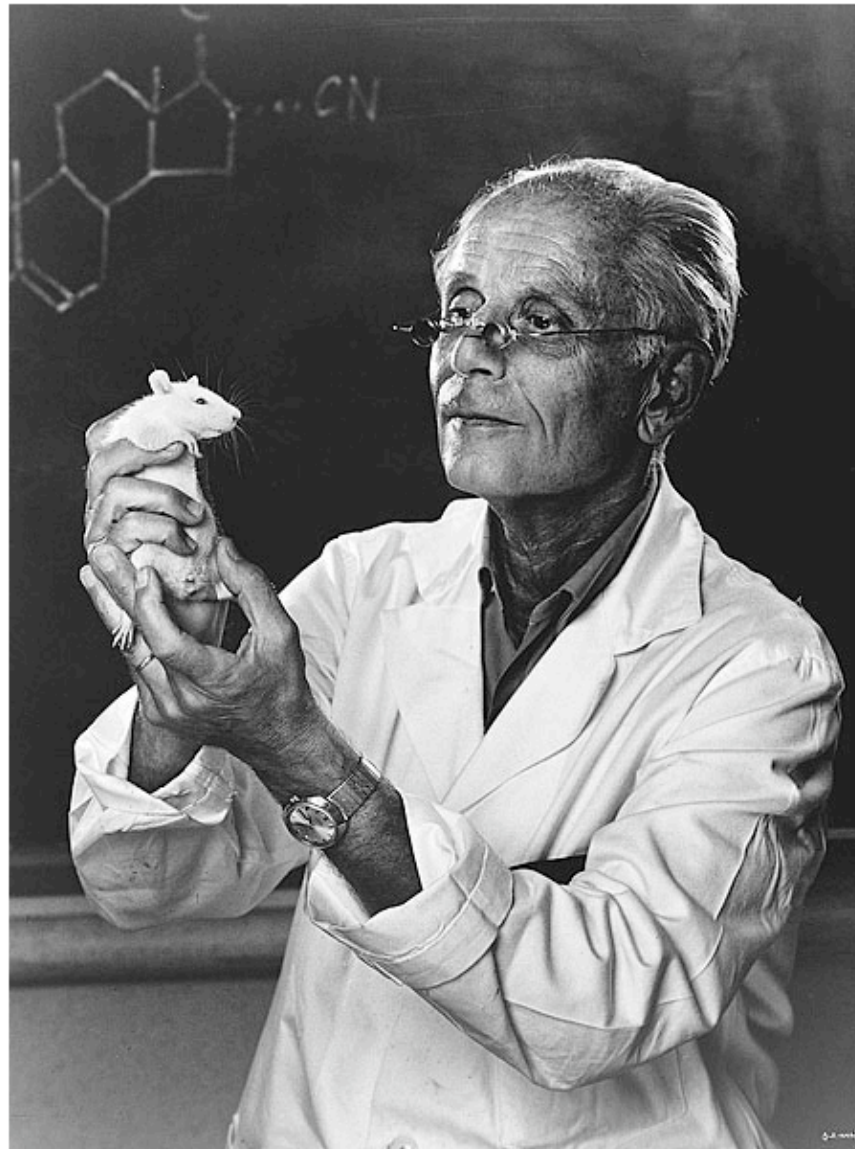


## Differential SNS vs. AHS Activation

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	SNS	AHS
2-DG	+	++++
Distress	+	+++
Neurocardiogenic syncope	+	++++
Orthostasis	++	+
Mild exercise	++	+
Cool temperature at skin of back	+++	0
Mild core hypothermia	+++	+

# Hans Selye





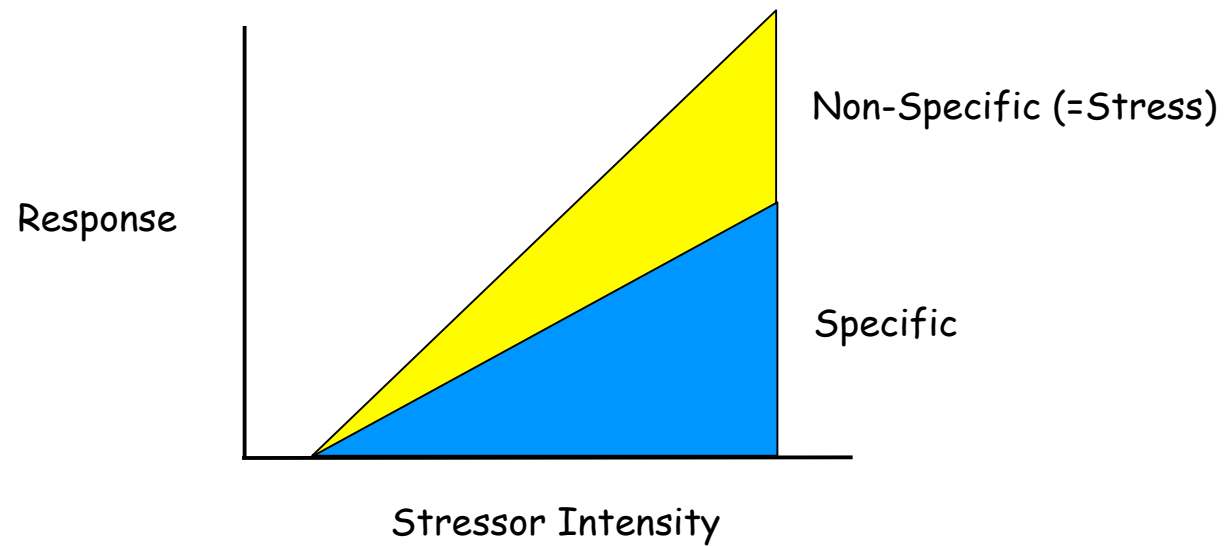
## Selye's Concept of Stress

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“...the **nonspecific** response of the body to any demand made upon it.”

*The doctrine of non-specificity*

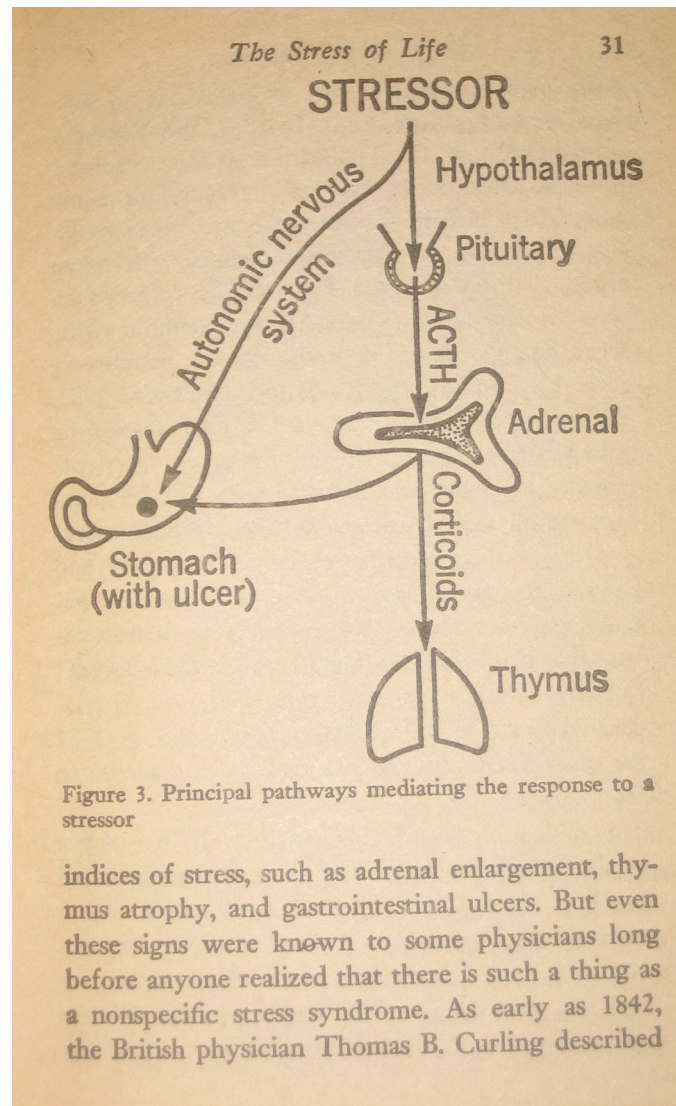
# Selye's Concept of Stress



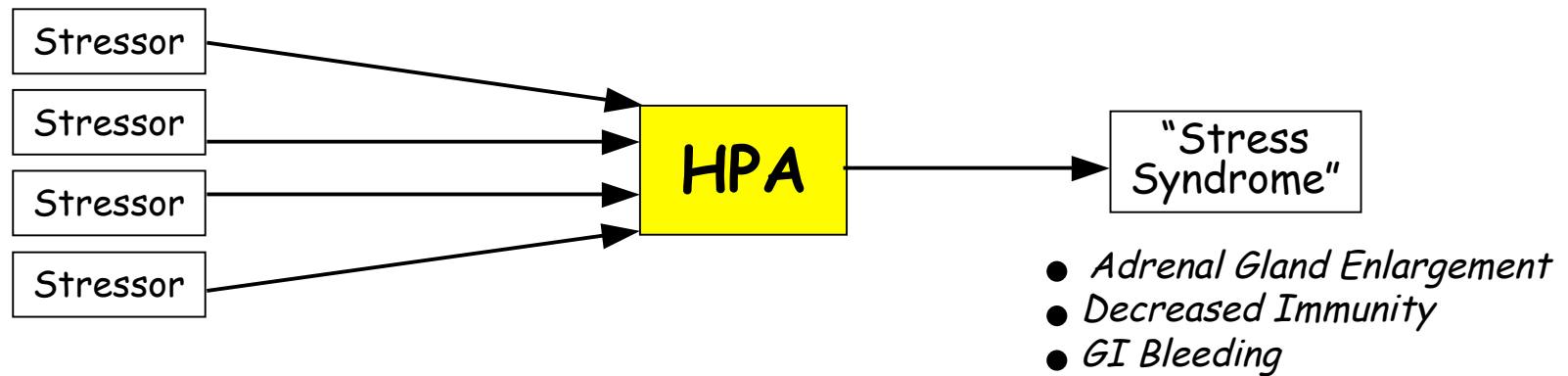




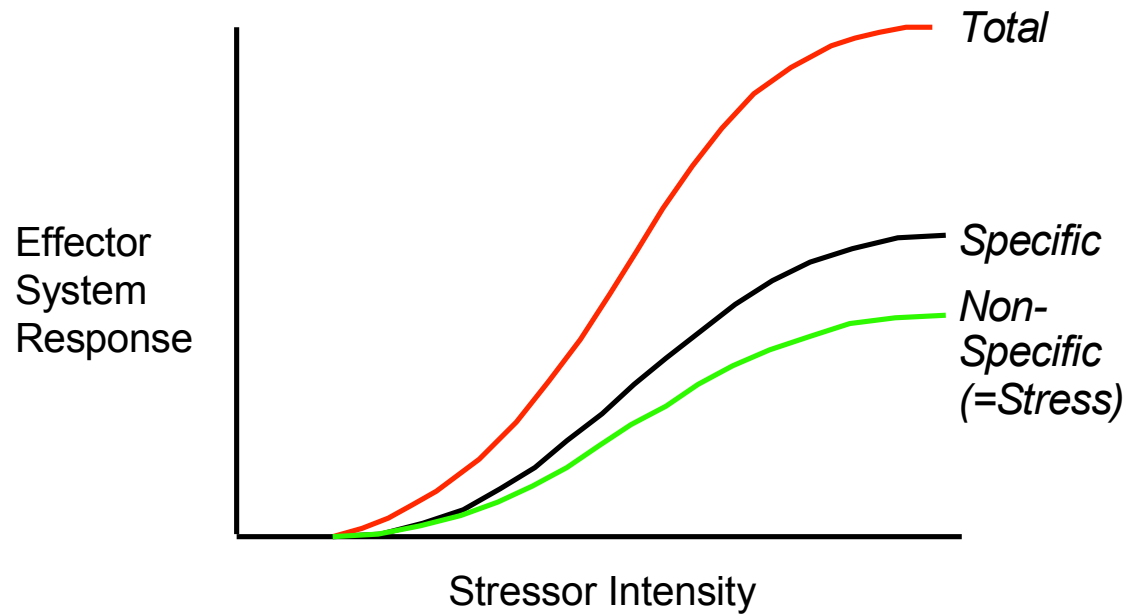
## Emphasis on the Adrenal Cortex



# Selye's Concept of Stress

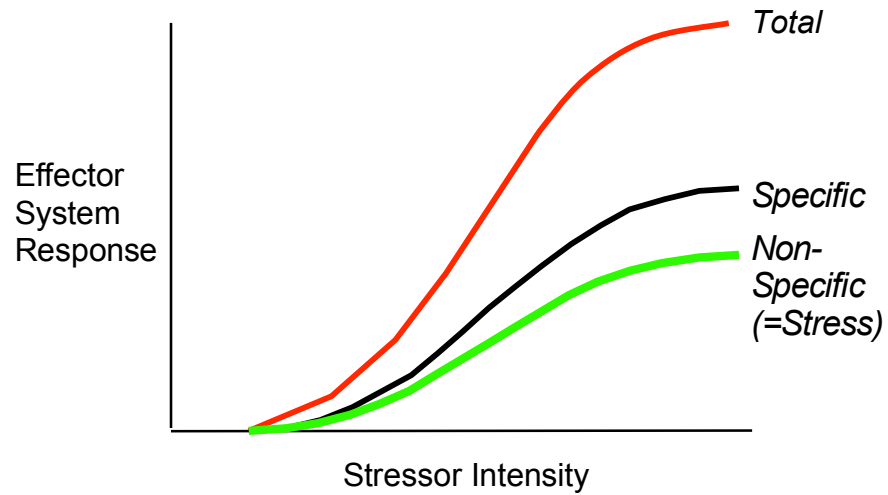


# Selye's Doctrine of Non-Specificity

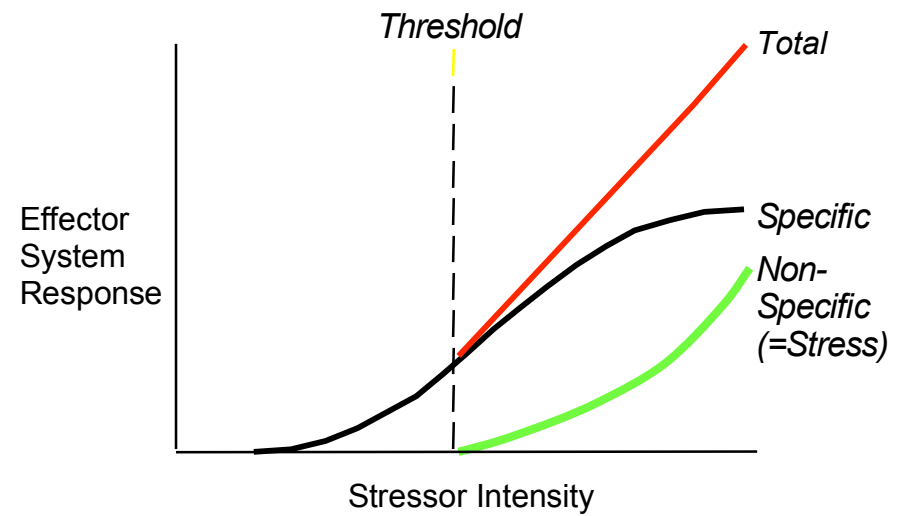




# The Threshold Concept



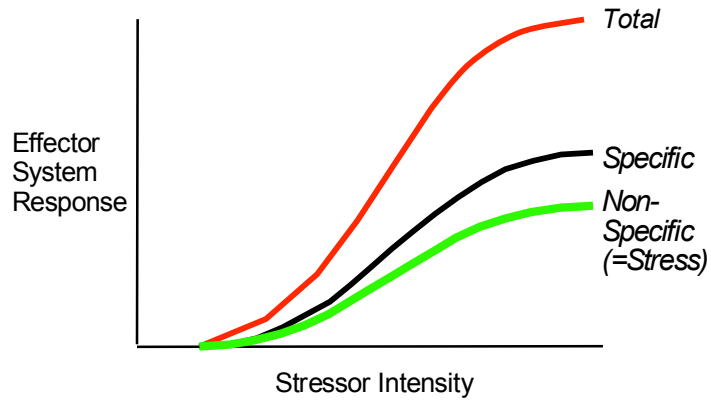
Selye



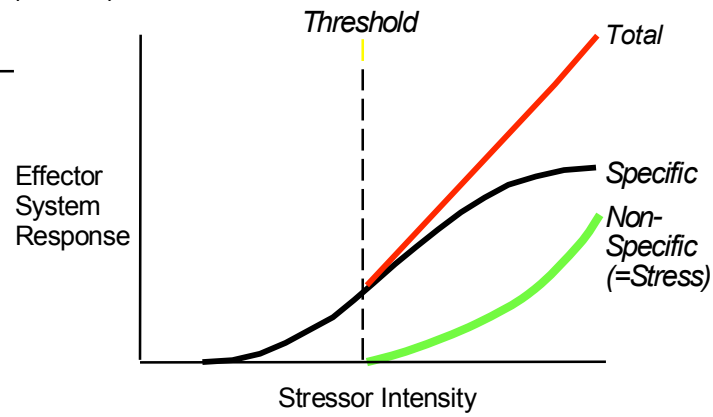
Chrousos/Gold



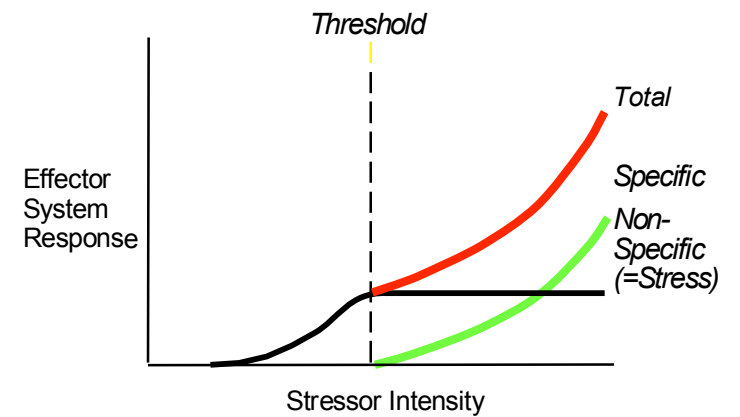
# Testability



Testable



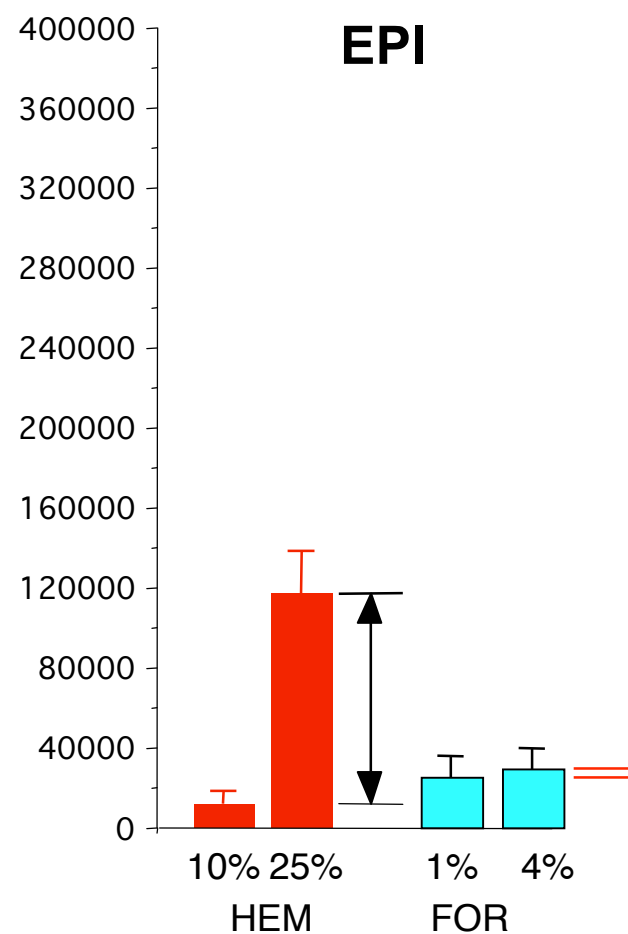
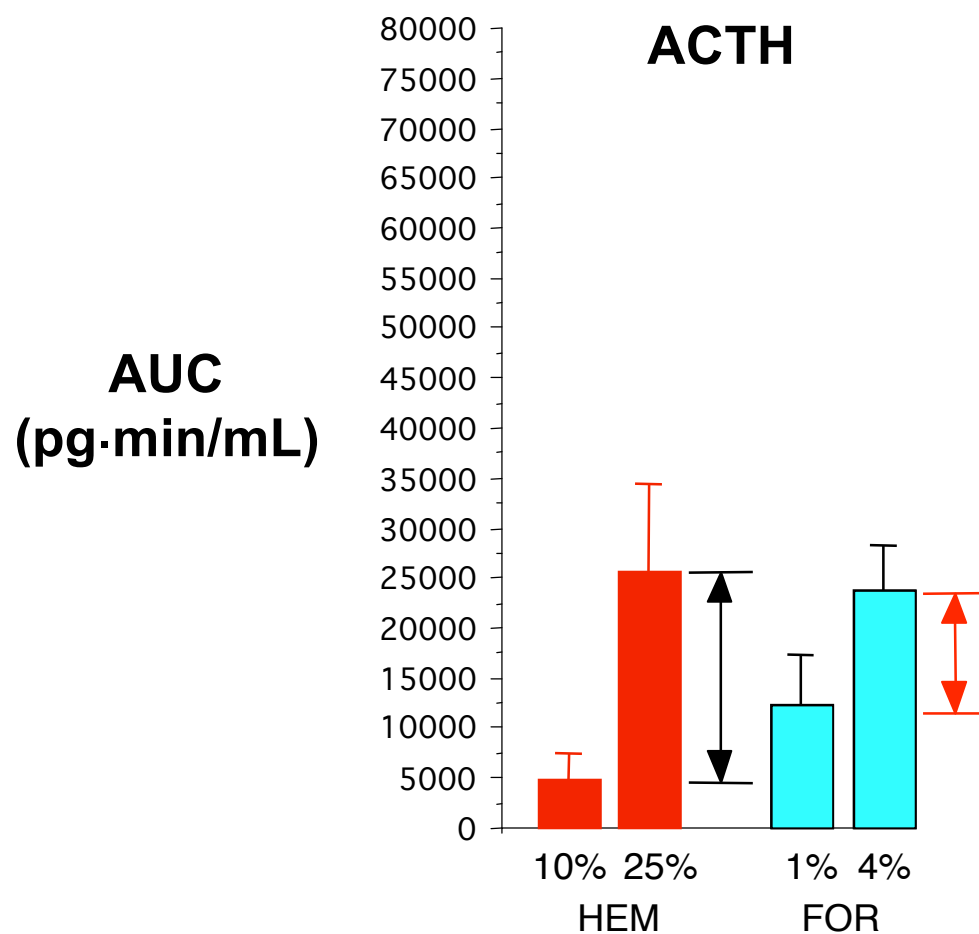
Untestable

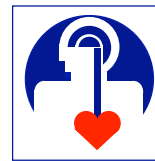


Testable

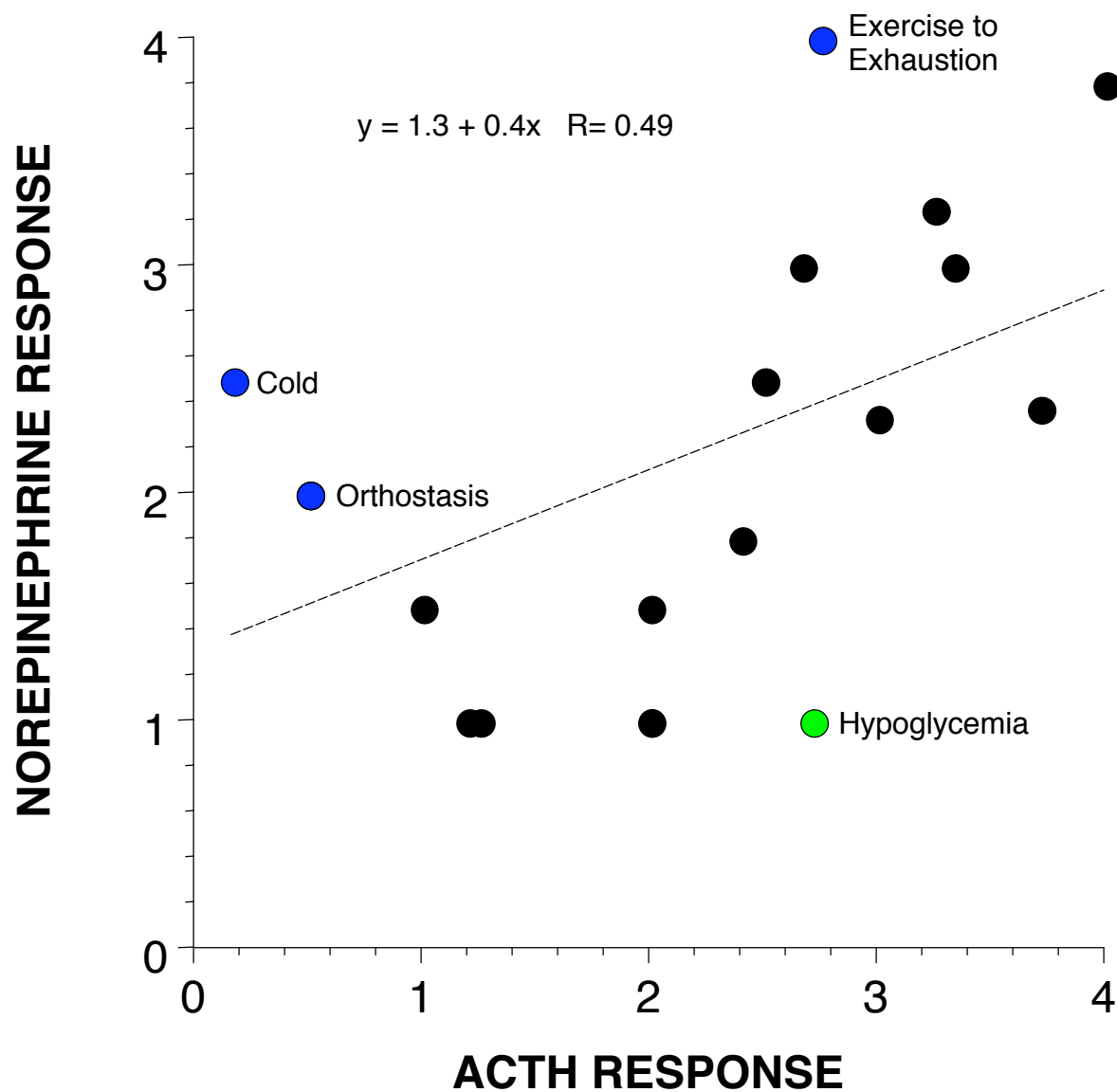


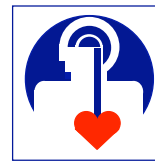
## Test of Non-Specificity



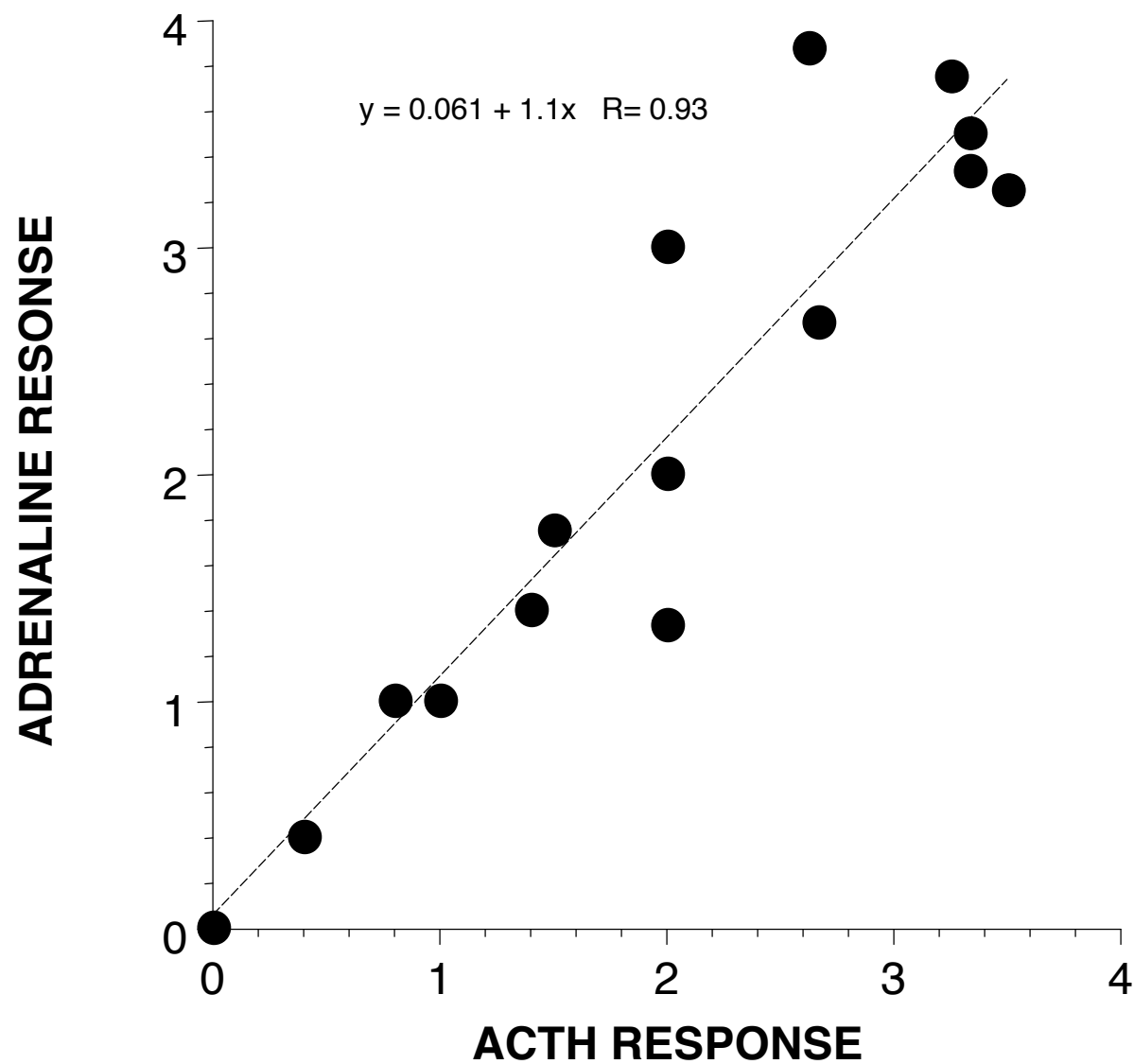


## SNS-HPA Relationship Across Stressors





## AHS-HPA Relationship Across Stressors







## Primitive Specificity

Stressor	Autonomic	Somatic
Hemorrhage	$\boxed{\text{AHS} = \text{HPA}} > \text{SNS}$	Pica
Hypoglycemia	$\boxed{\text{AHS} = \text{HPA}} > \text{SNS}$	Hunger
Water depriv.	$\text{AVP} > \text{SNS}$	Water seeking
Cold	$\text{SNS} > \boxed{\text{AHS} = \text{HPA}}$	Hand rubbing
Salt depriv.	$\text{RAS} > \text{DA} > \text{SNS}$	Salt hunger
Fight	$\text{SNS} > \boxed{\text{AHS} = \text{HPA}}$	Clench, grimace
Flight	$\text{SNS} = \boxed{\text{AHS} = \text{HPA}}$	Escape
Fright	$\boxed{\text{AHS} = \text{HPA}} = \text{SNS}$	Trembling, Fawning
Faint	$\text{AHS} = \text{PNS} = \text{AVP}$	Swooning, Hyperventilation



## Selye's Concept of Distress

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“**Damaging** or unpleasant stress is distress.”

“...**harmful**, unpleasant stress.”

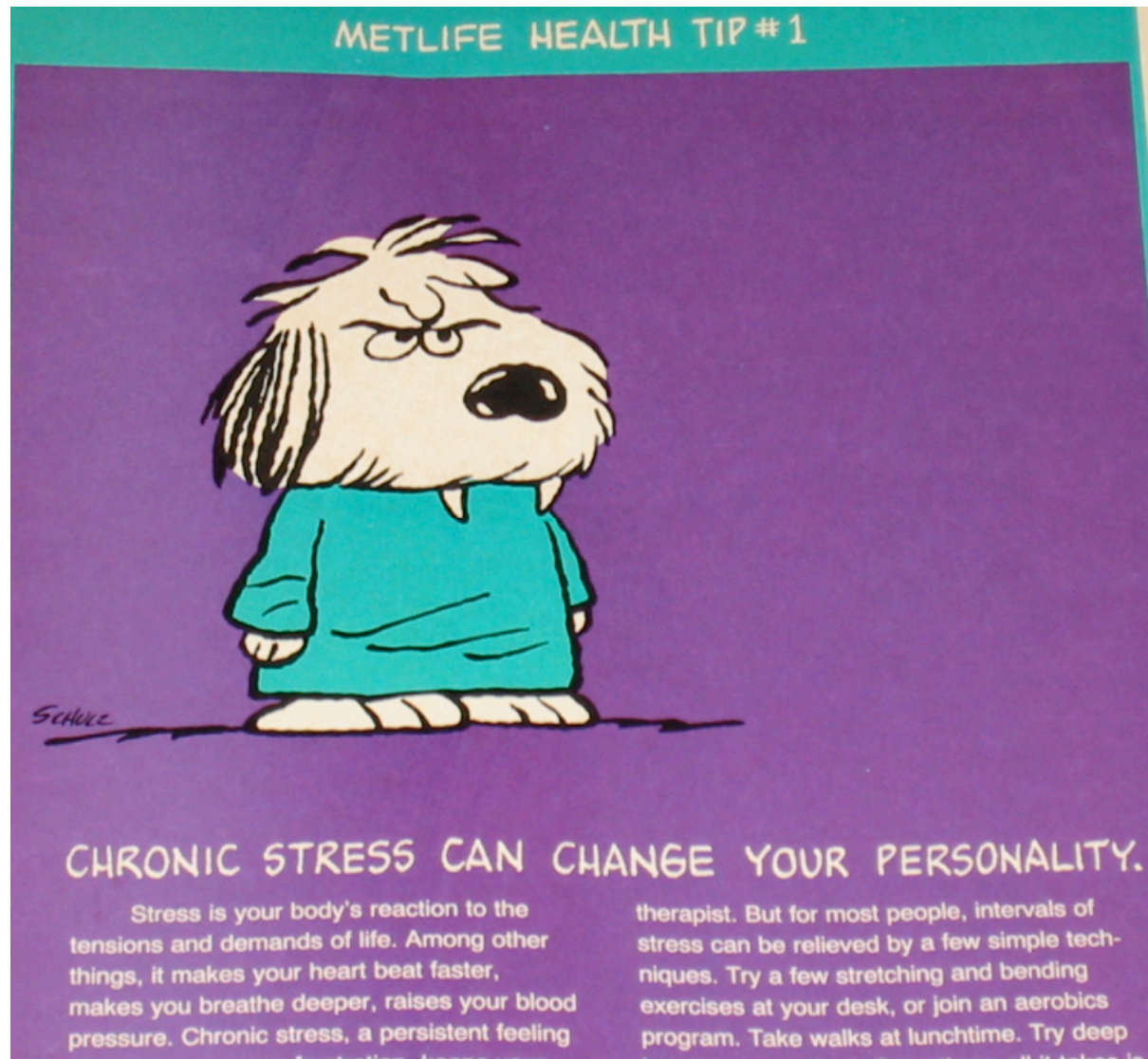
*Duality of assumed pathology and aversiveness*

## Assumption of Pathology (Physical)





## Assumption of Pathology (Psychological)





## Characteristics of Distress

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Distress is a form of stress that is characterized by:

- Consciousness (sensed failure to cope)
- Aversiveness
- Instinctively communicated signs
- Adrenal gland activation

*Note: No assumption of pathology.*





## Definitions of Stress and Distress

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Stress is a **condition** where expectations, whether genetically programmed, established by prior learning, or deduced from circumstances, do not match the current or anticipated perceptions of the internal or external environment, and the **sensed discrepancy** elicits primitively specific compensatory responses.

Distress is a form of stress that is characterized by consciousness, aversiveness, instinctively communicated signs, and **adrenomedullary and adrenocortical activation**. There is no assumption of pathology.

# Scientific Integrative Medicine

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Scientific integrative medicine applies systems thinking to understand clinical disorders of homeostasis.

*Goldstein DS. In Battle C O (Ed) Essentials of Public Health Biology:  
A Companion Guide for the Study of Pathophysiology.  
Sudbury, MA: Jones and Bartlett Publishers, 2009, pp. 251-262*

# Scientific Integrative Medicine

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- Not a discipline, single disorder, or group of disorders
- An approach, or **a way of thinking**
- Emphasis on **feedback-regulated systems**
  - Complexity
  - Adaptive changes
  - Mind-body syndromes & chronic degenerative diseases
- Emphasis on **wellness & prevention**



# Concepts of Scientific Integrative Medicine

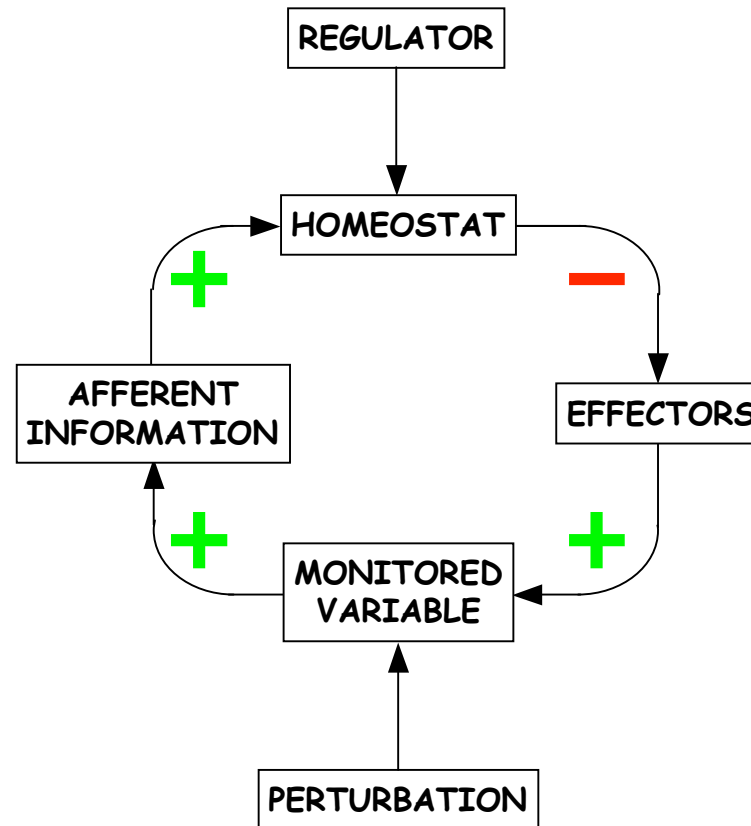
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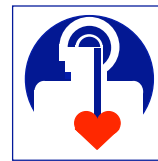
- Negative feedback regulation
- Multiple effectors
- Shared effectors
- Positive feedback
- Homeostatic definitions of stress & allostatic load
- Compensatory activation and effective treatment



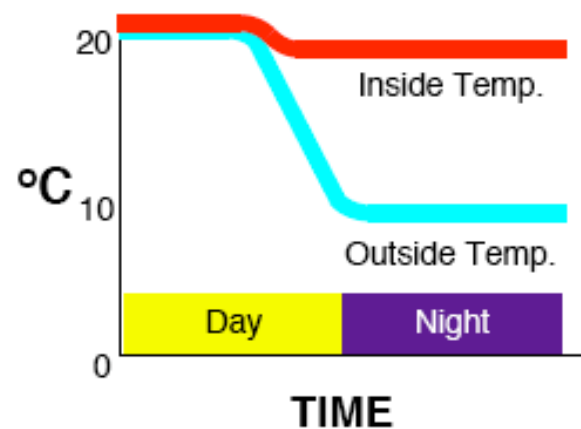
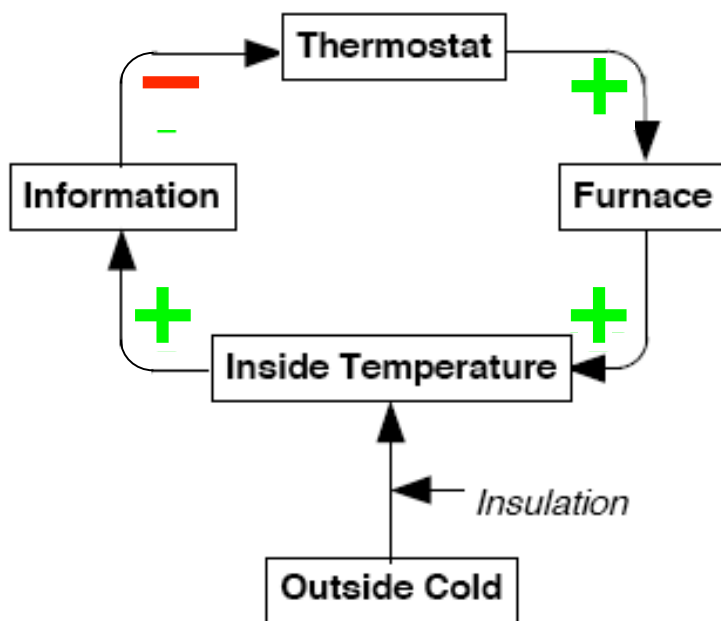
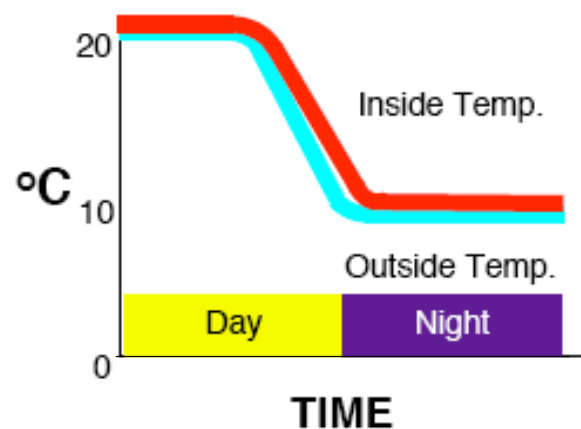
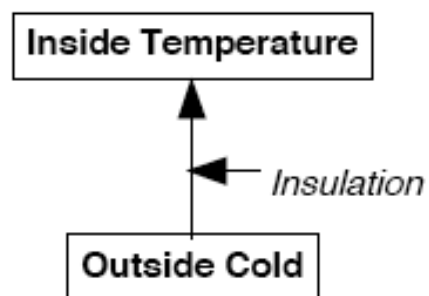
# A Homeostatic System

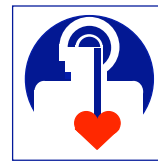


*Goldstein DS. Adrenaline and the Inner World:  
An Introduction to Scientific Integrative Medicine.  
Baltimore, MD: The Johns Hopkins University Press, 2006*

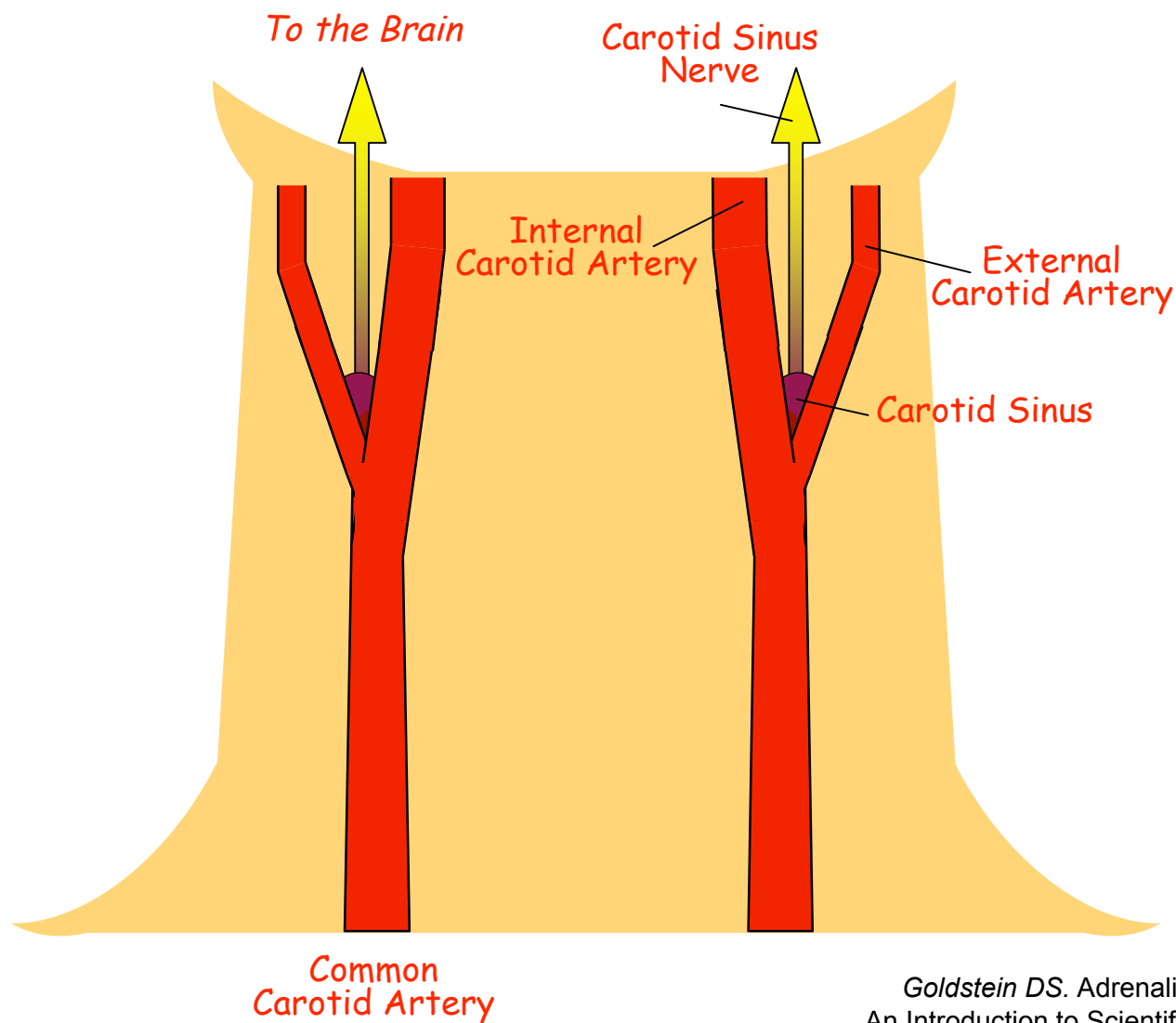


# Negative Feedback Regulation

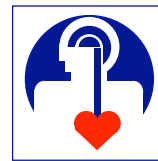




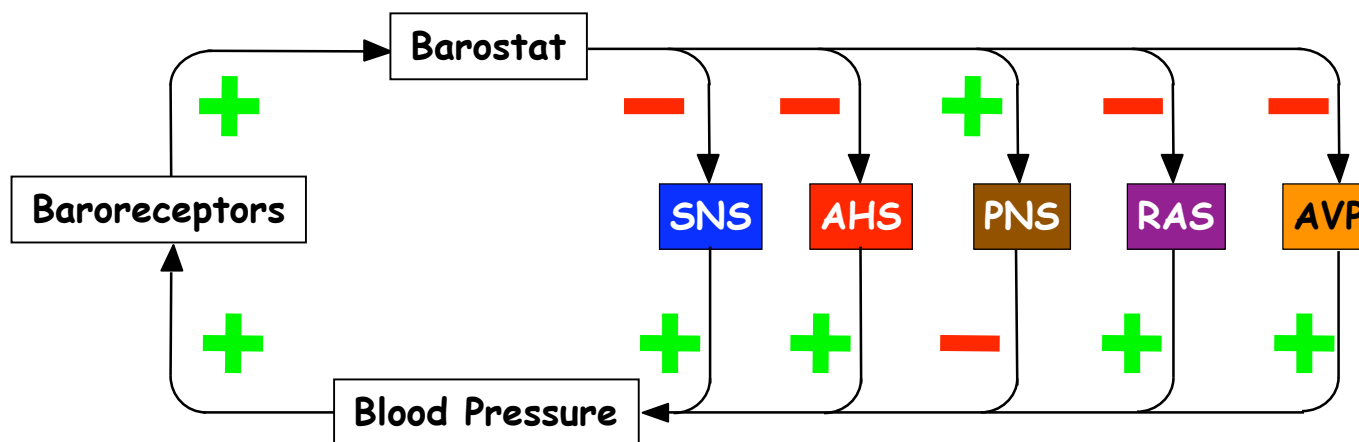
# The Sleeper Hold



Goldstein DS. Adrenaline and the Inner World:  
An Introduction to Scientific Integrative Medicine.  
Baltimore, MD: The Johns Hopkins University Press, 2006



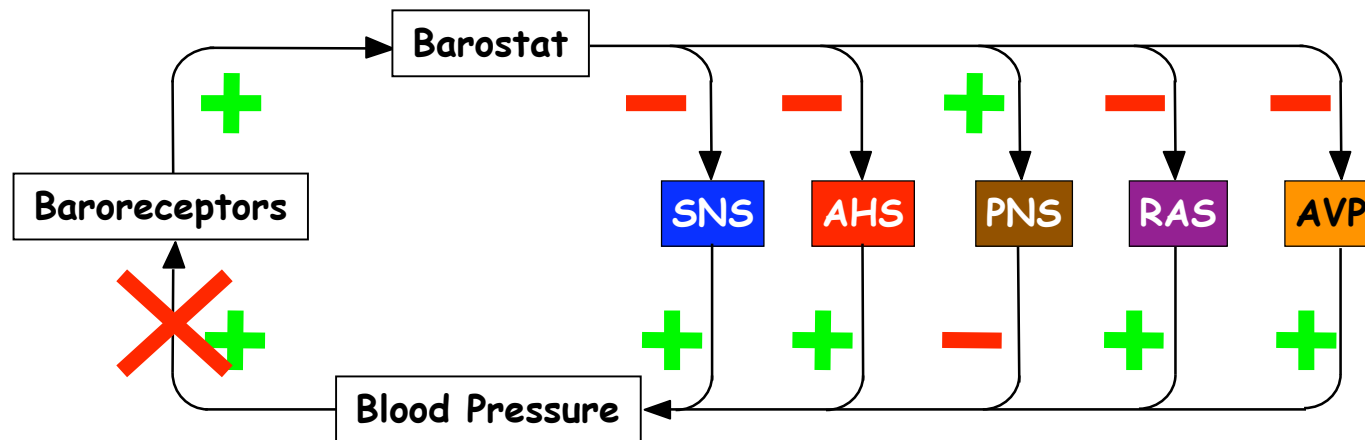
# The Arterial Baroreflex



*Goldstein DS. Adrenaline and the Inner World:  
An Introduction to Scientific Integrative Medicine.  
Baltimore, MD: The Johns Hopkins University Press, 2006*

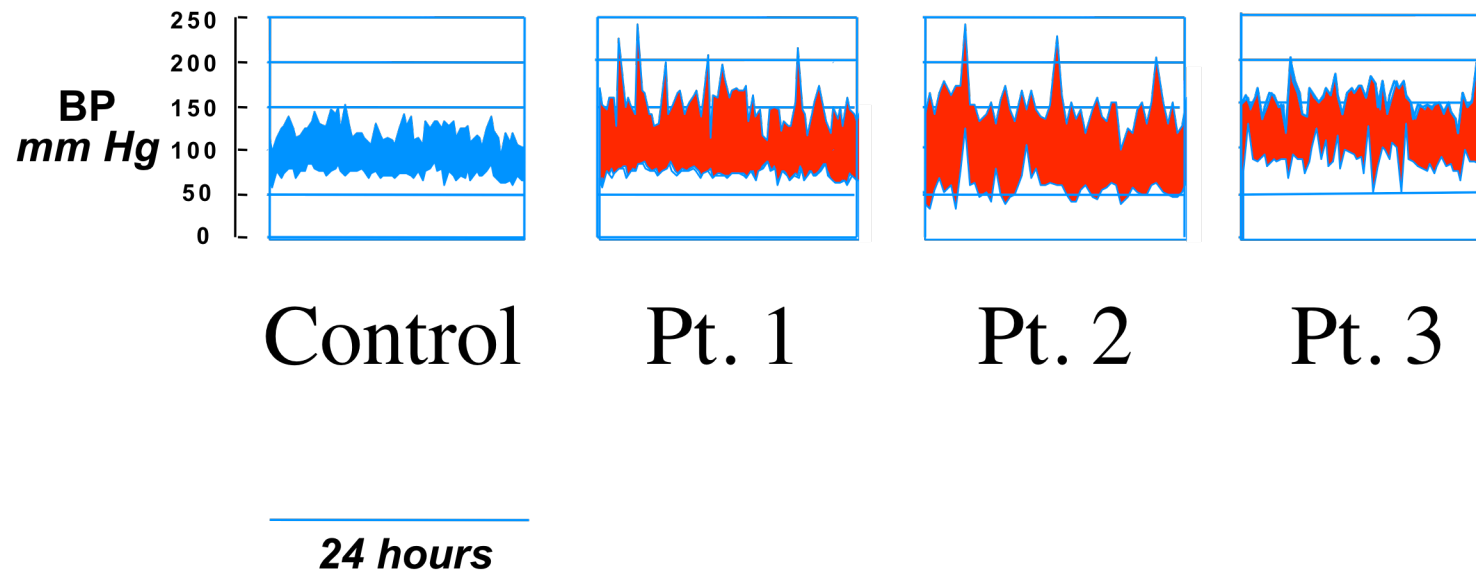


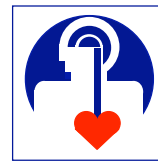
# Baroreflex Failure



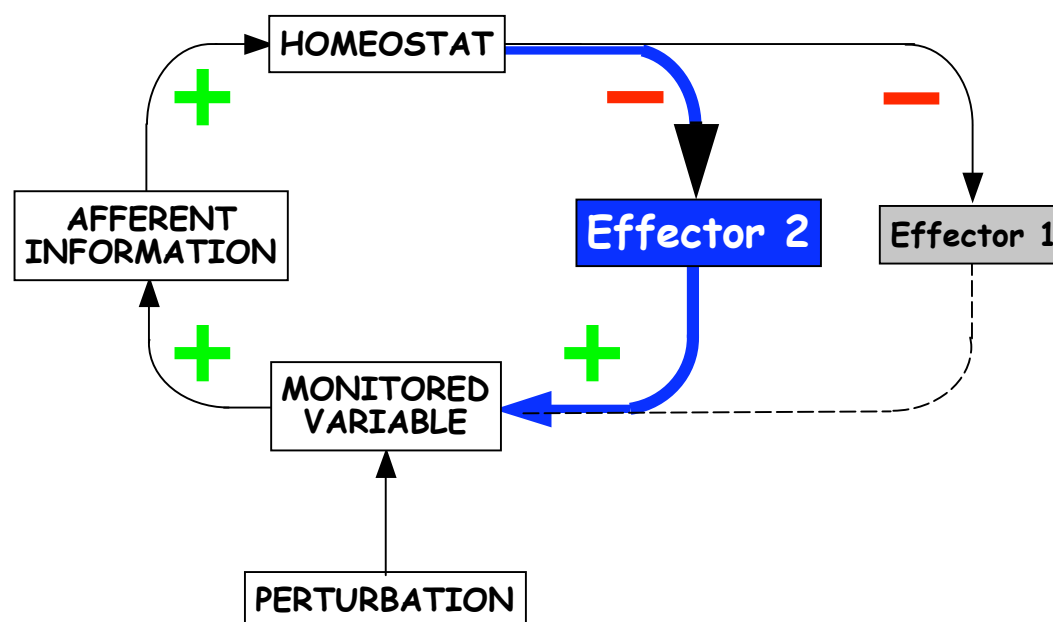
Goldstein DS. Adrenaline and the Inner World:  
An Introduction to Scientific Integrative Medicine.  
Baltimore, MD: The Johns Hopkins University Press, 2006

# BP Variability from Barostat Disruption

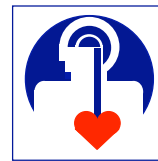




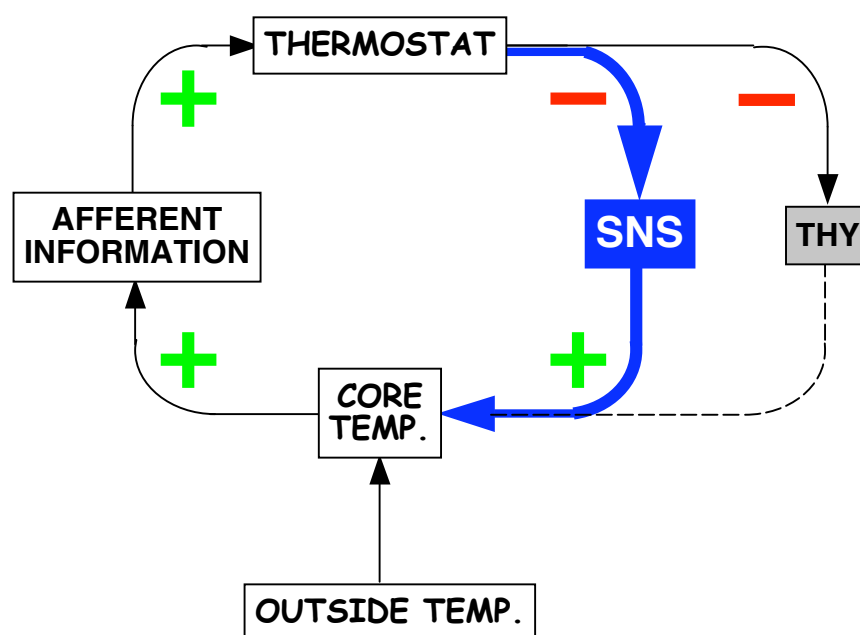
# Compensatory Activation

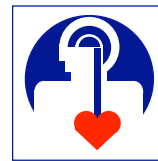




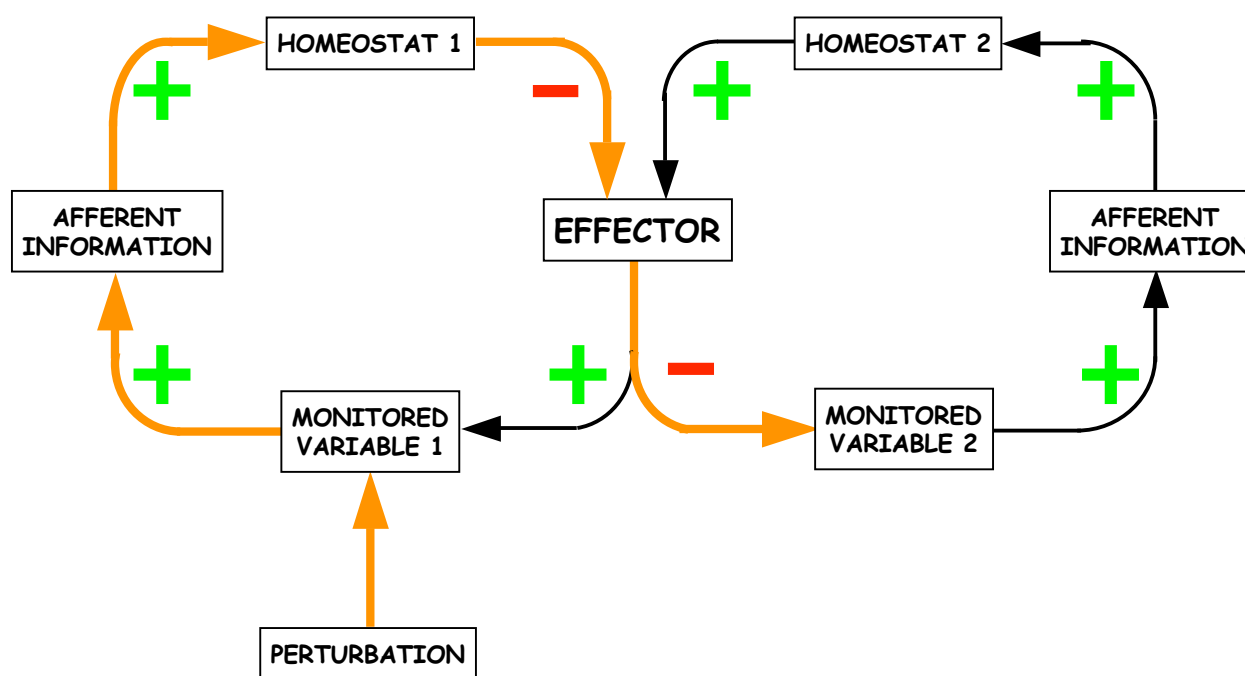


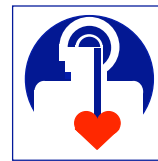
# Compensatory Activation



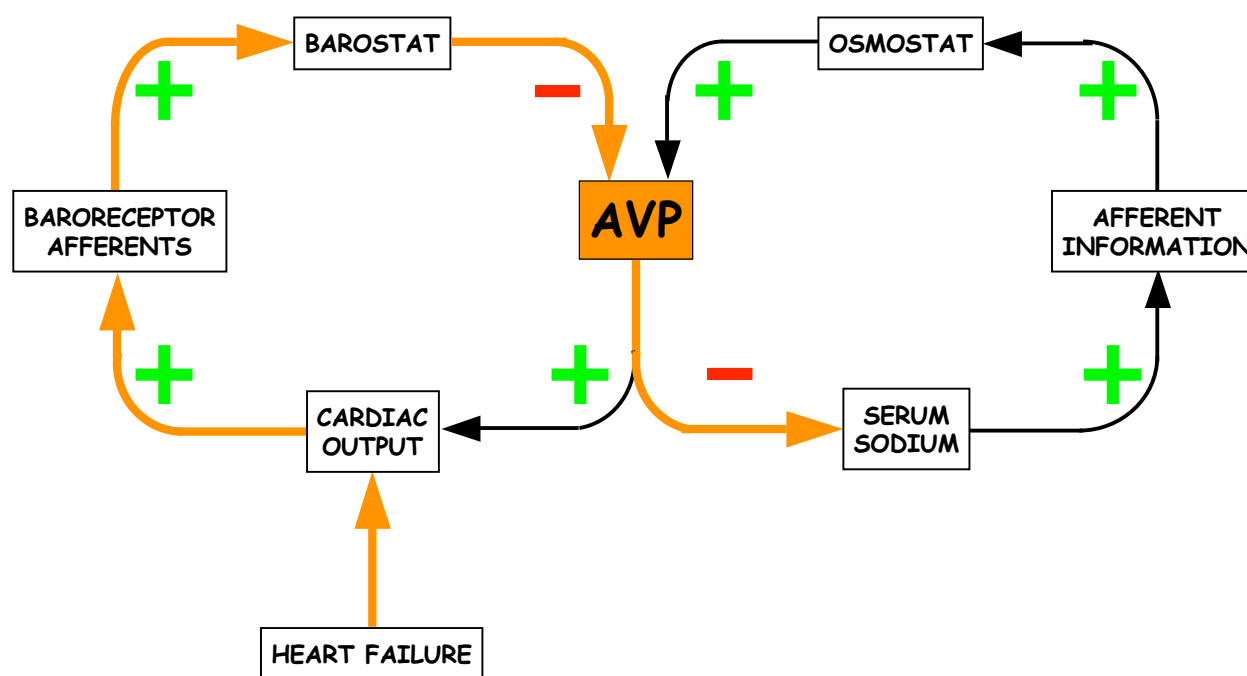


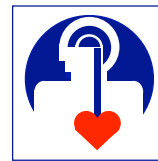
# Effector Sharing



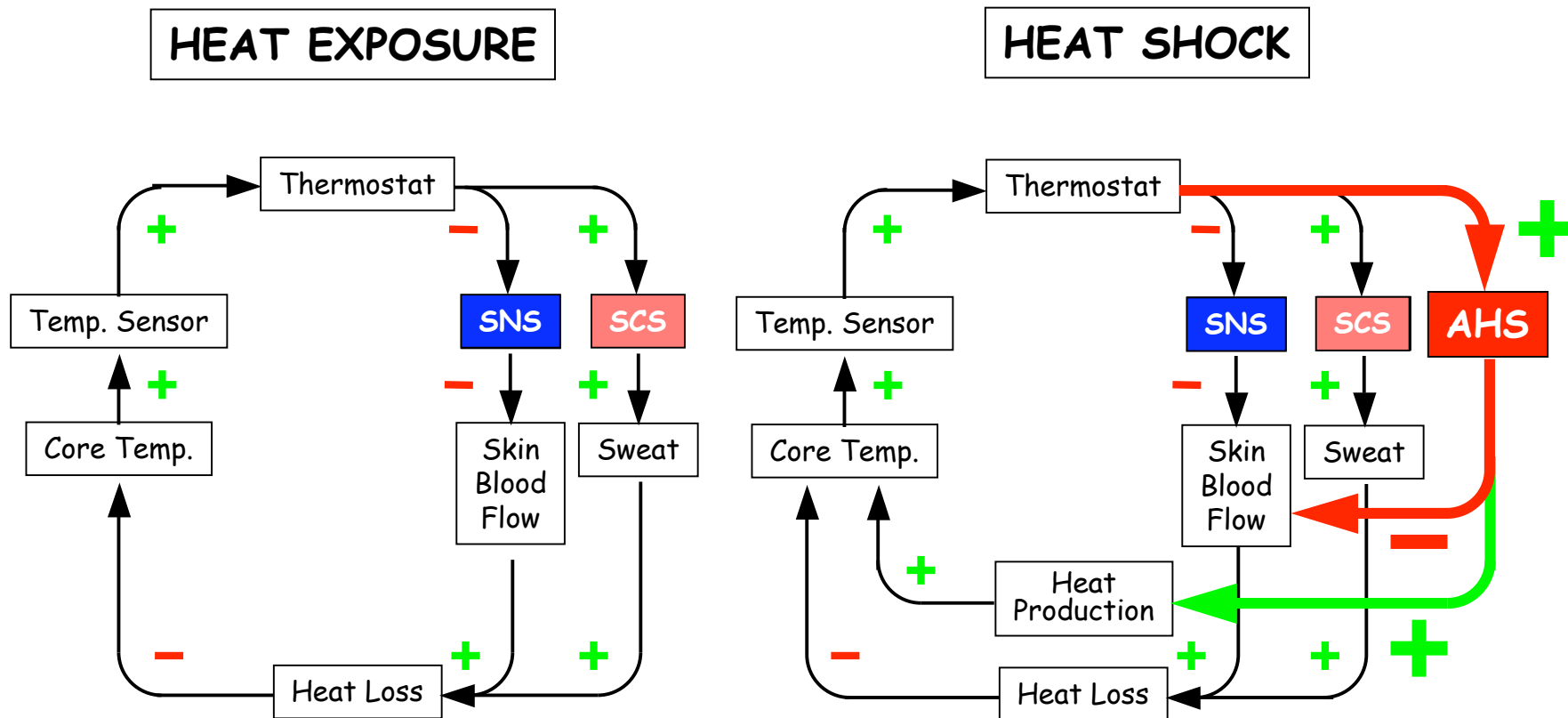


# Effector Sharing



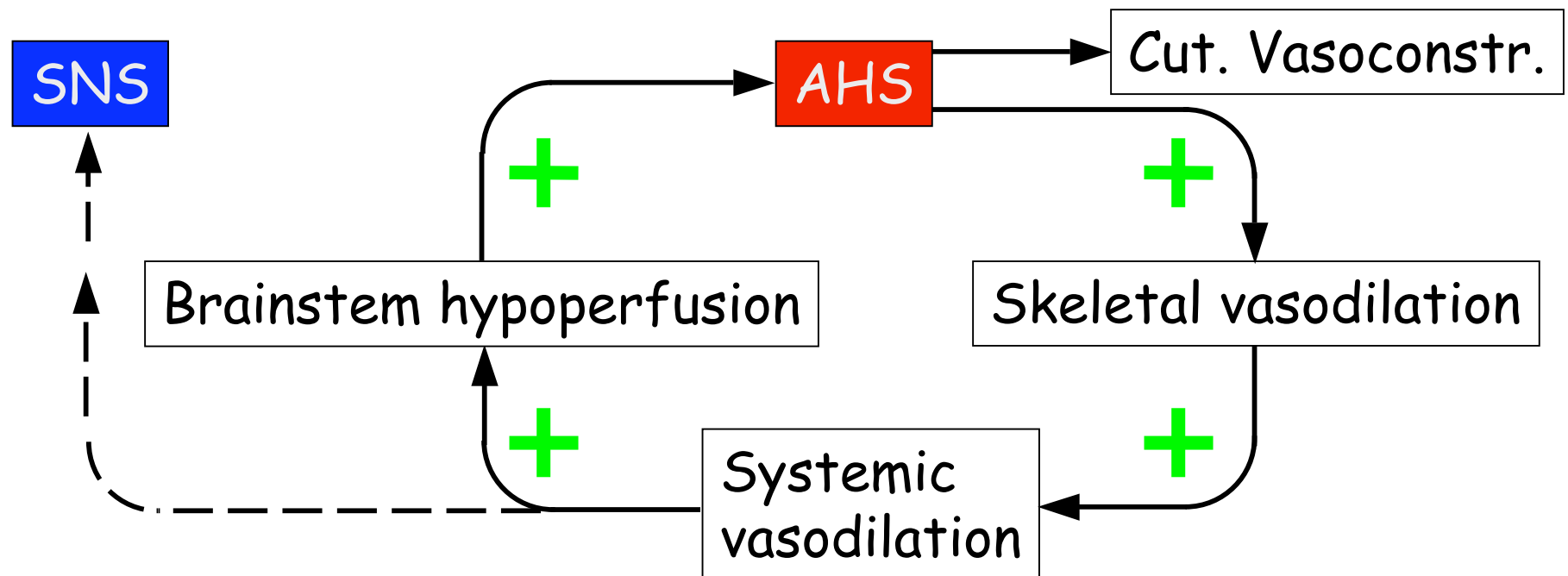


## Positive Feedback: Heat Shock



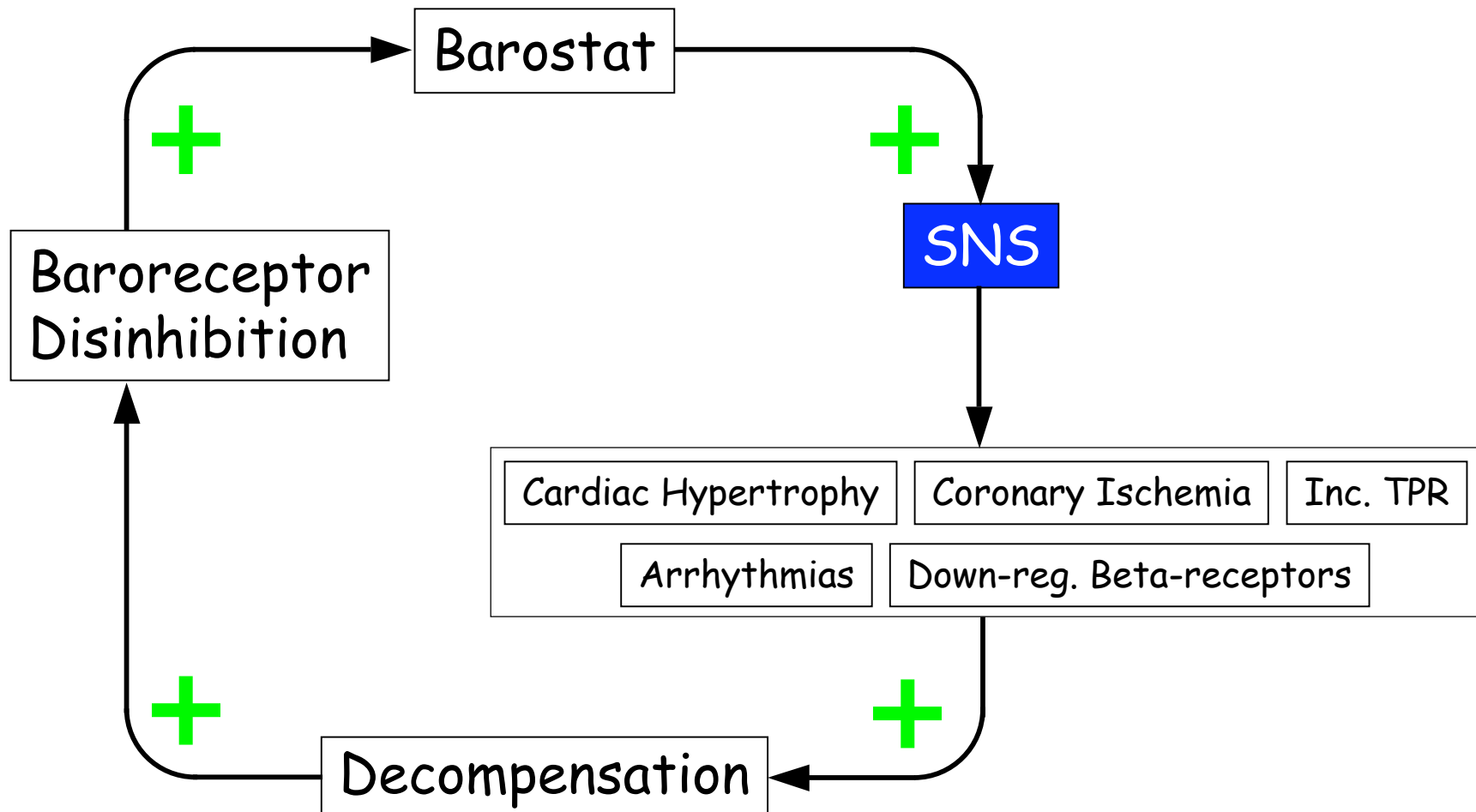
Goldstein DS. Adrenaline and the Inner World:  
An Introduction to Scientific Integrative Medicine.  
Baltimore, MD: The Johns Hopkins University Press, 2006

# Syncope from Positive Feedback





## Positive Feedback Loops in Heart Failure





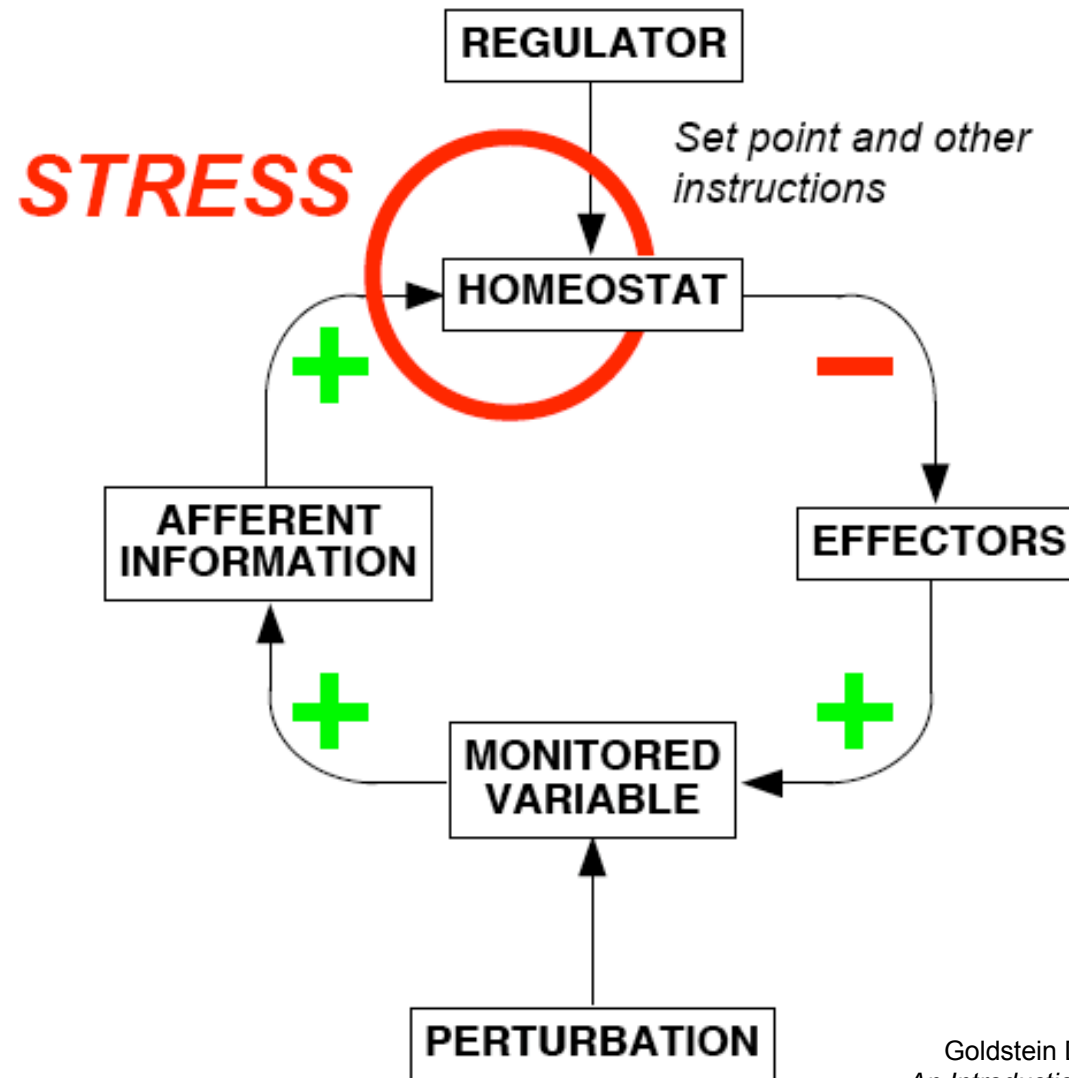
## Definition of Stress

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Stress is a **condition** where expectations, whether genetically programmed, established by prior learning, or deduced from circumstances, do not match the current or anticipated perceptions of the internal or external environment, and the **sensed discrepancy** elicits primitively specific compensatory responses.



# Homeostatic Definition of Stress

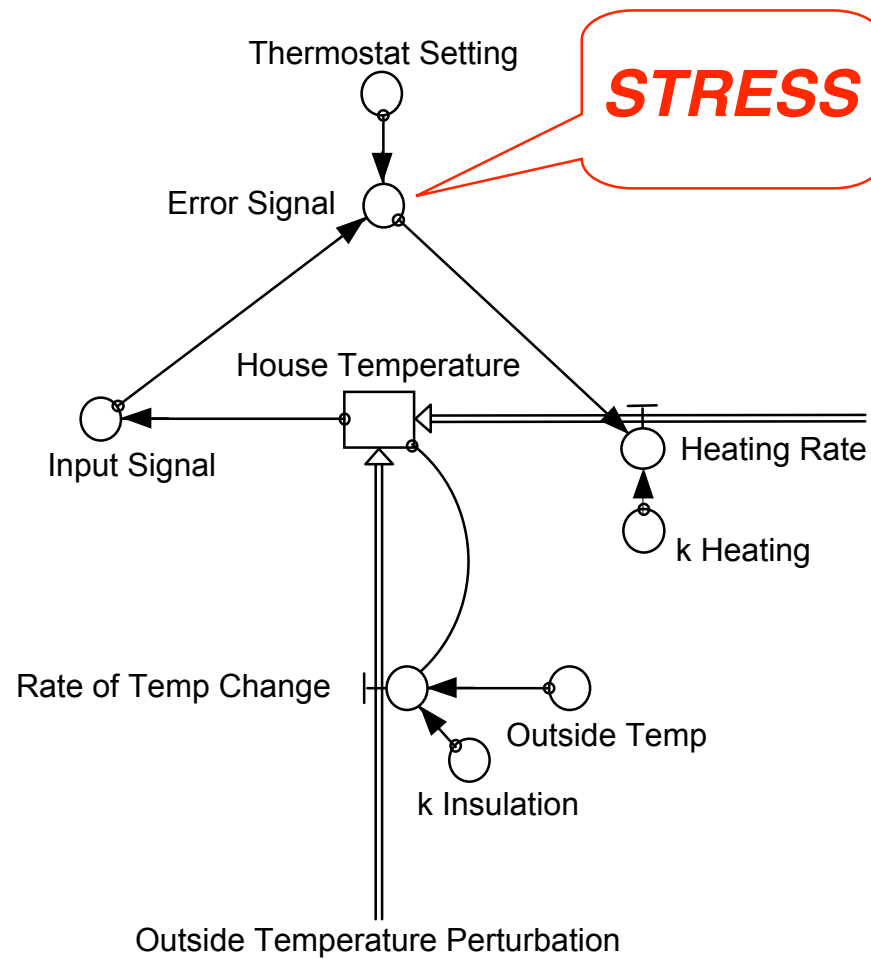


Goldstein DS. *Adrenaline and the Inner World: An Introduction to Scientific Integrative Medicine*. Baltimore, MD: The Johns Hopkins University Press, 2006



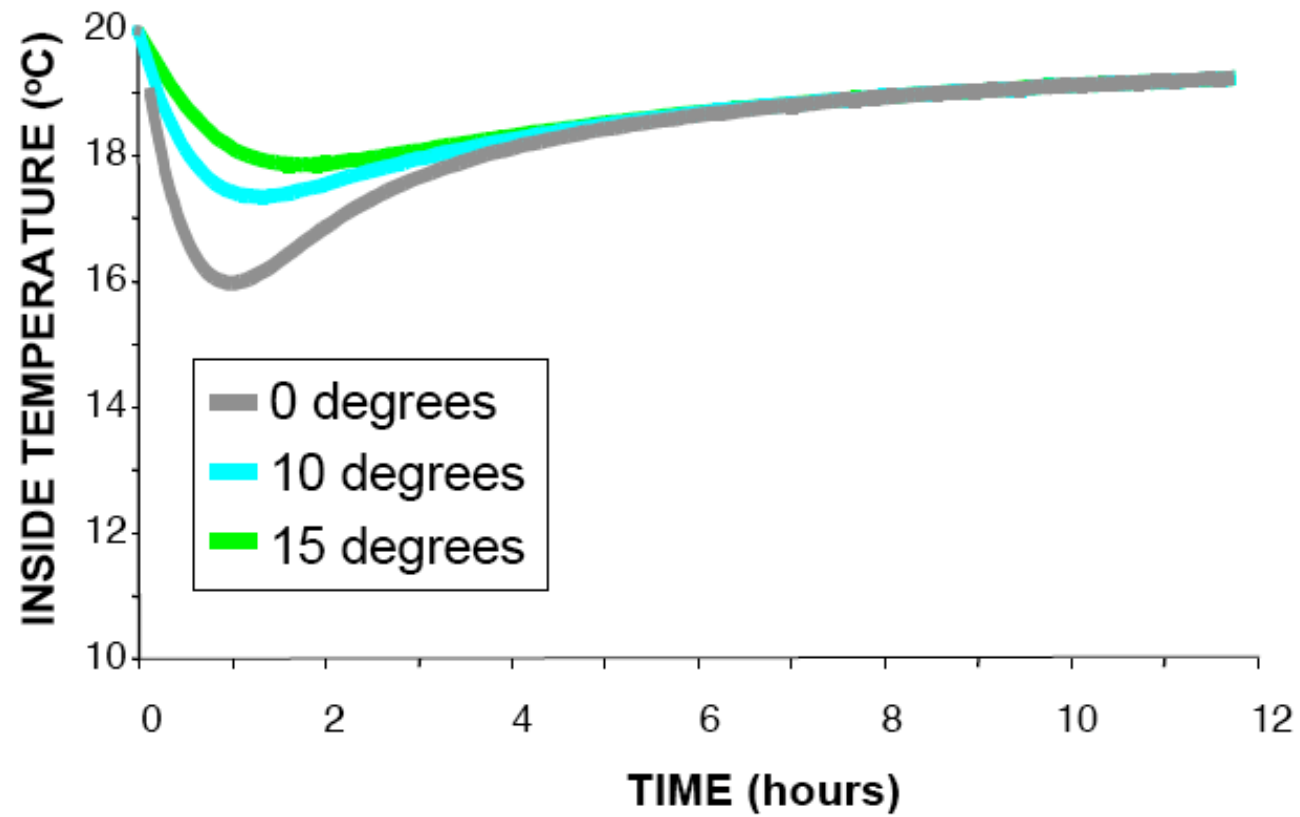


# Computer Model of Stress



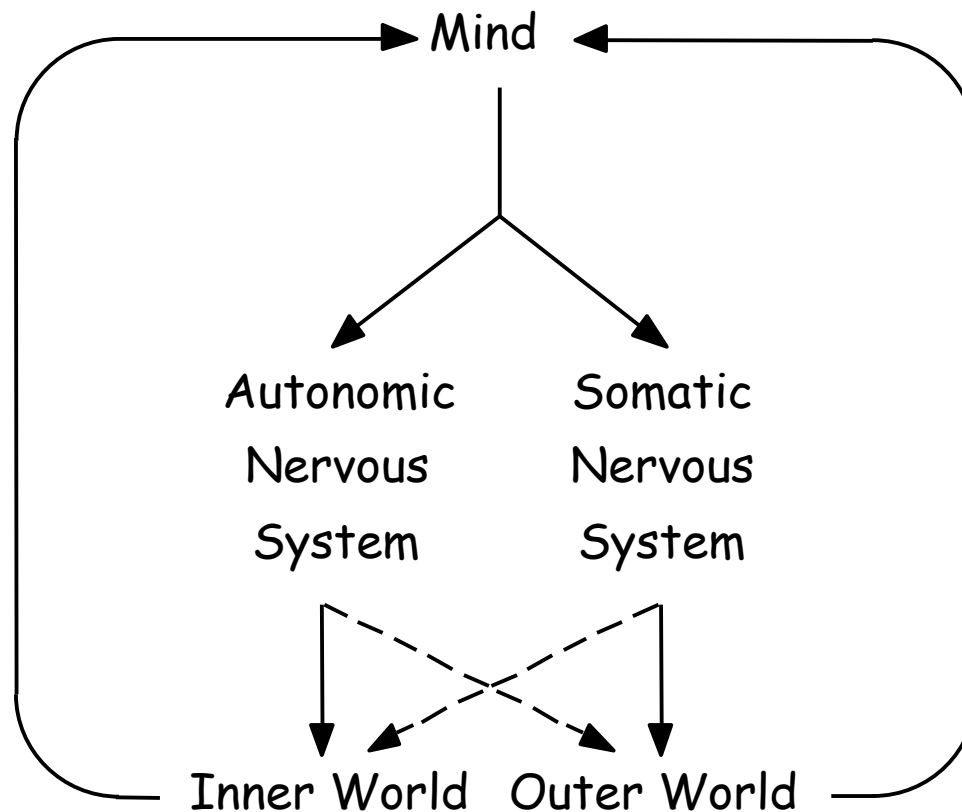


# Regulation of Temperature





# The Mind-Body “Problem”



# Functional Catecholamine System Disorders

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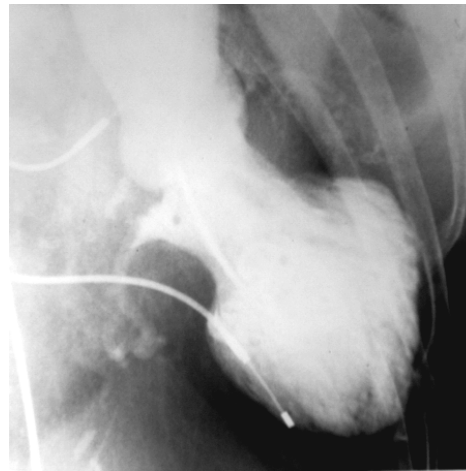


- *Takotsubo* cardiopathy
- Neurocardiogenic syncope
- Postural tachycardia syndrome

# *Takotsubo* Cardiopathy



a



b



c



# Stress Cardiomyopathy

**Table 2.** Plasma Catecholamine and Neuropeptide Levels.\*

Variable	Patients with Stress Cardiomyopathy (N= 13)			Patients with Killip Class III Myocardial Infarction (N=7)			Normal Value
	Day 1 or 2	Day 3, 4, or 5	Day 7, 8, or 9	Day 1 or 2	Day 3, 4, or 5	Day 7, 8, or 9	
	median (interquartile range)						
Catecholamine precursor (pg/ml)							
Dihydroxyphenylalanine	2859 (2721–2997)†	2495 (2386–2761)†	1656 (1065–2011)	1282 (1124–1656)	1203 (1193–1873)	907 (749–937)	1755‡
Catecholamines (pg/ml)							
Epinephrine	1264 (916–1374)†	1044 (733–1118)†	348 (180–550)	376 (275–476)	330 (220–385)	275 (220–311)	37‡
Norepinephrine	2284 (1709–2910)†	1573 (1235–2589)†	1142 (525–1252)	1100 (914–1320)	829 (727–914)	541 (516–660)	169‡
Dopamine	111 (106–146)†	77 (63–110)	56 (47–77)	61 (46–77)	61 (61–77)	38 (30–61)	15‡
Neuronal metabolites (pg/ml)							
Dihydroxyphenylglycol	2706 (2382–3131)†	2689 (2246–2842)†	2161 (2093–2416)§	1625 (1412–1702)	1583 (1497–1668)	1259 (1191–1446)	800‡
Dihydroxyphenylacetic acid	2758 (2573–3077)	2598 (2354–2892)†	1345 (1194–1682)	1513 (1211–1648)	1228 (1026–1362)	1009 (908–1059)	1497‡
Extraneuronal metabolites (pg/ml)							
Metanephrine	178 (140–187)	509 (385–789)	659 (590–738)§	106 (89–124)	203 (177–213)	205 (189–243)	59‡
Normetanephrine	216 (130–319)	456 (229–569)	661 (551–696)§	160 (145–170)	196 (181–209)	271 (225–288)	55‡
Peptides (pg/ml)							
Neuropeptide Y	186 (162–236)§	185 (158–214)†	136 (90–182)§	77 (60–90)	69 (61–71)	60 (40–65)	51¶
Brain natriuretic peptide	1033 (805–1783)§	450 (205–684)	142 (72–236)	264 (192–483)	268 (249–574)	297 (142–419)	10–93
Serotonin and metabolite (pg/ml)							
5-Hydroxytryptamine	2585 (2165–2816)†	2379 (2290–2900)†	1602 (864–1989)	1308 (1074–1721)	1214 (1114–1643)	1065 (1003–1251)	1004**
5-Hydroxyindoleacetic acid	5596 (4531–7380)	7839 (5698–9644)	6471 (3308–7074)	3977 (3604–6074)	4607 (4128–6003)	4282 (3887–4416)	6730**

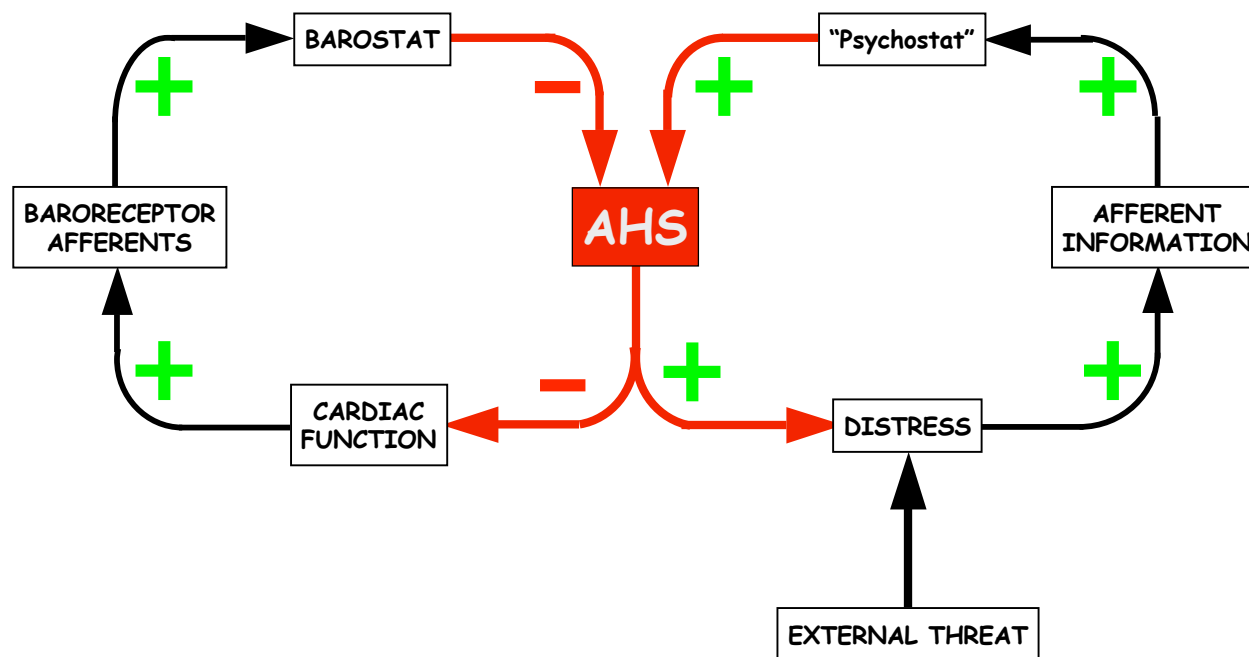
\* All P values are for comparison of levels in patients with Killip class III myocardial infarction measured at similar times.

† P<0.005.

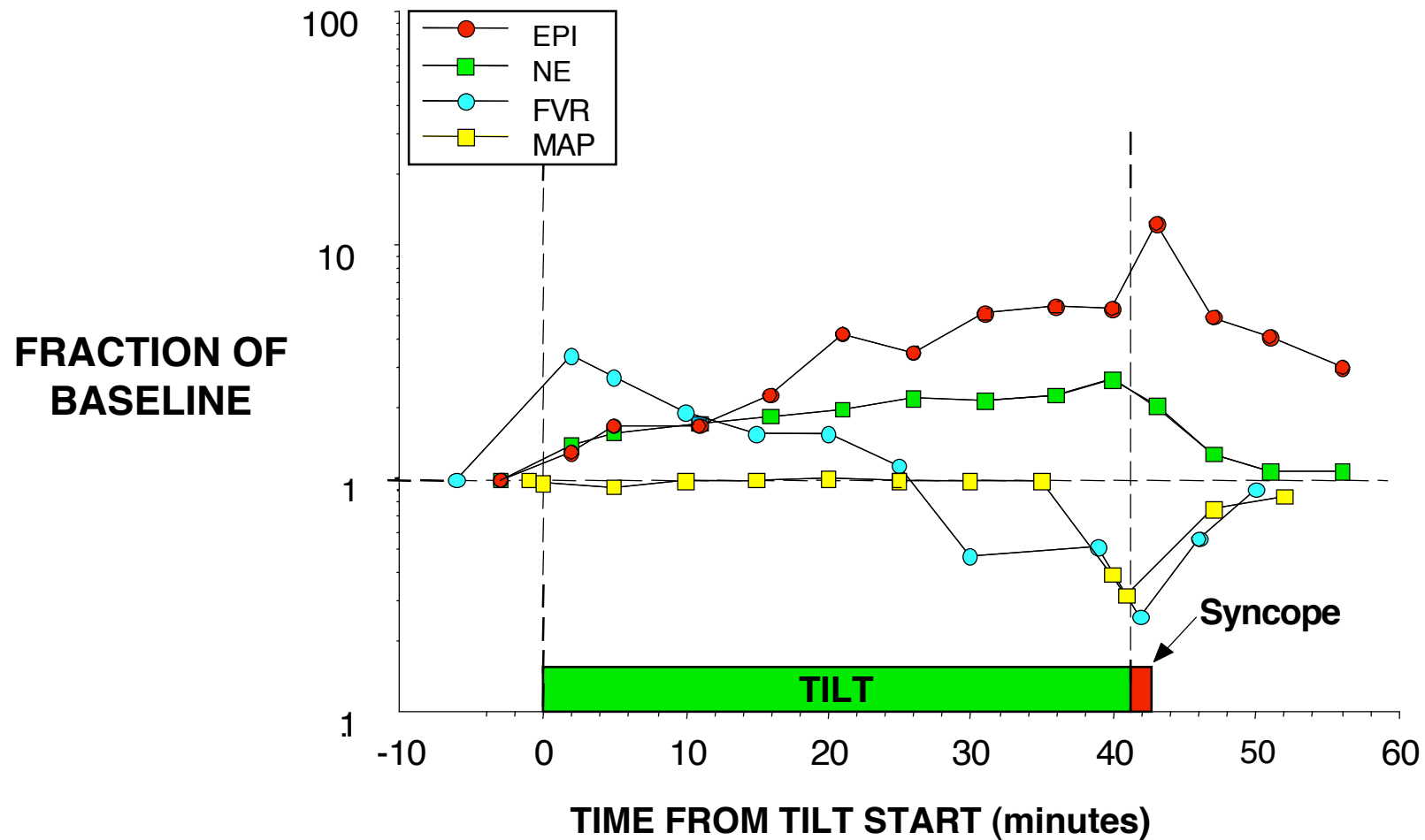
‡ Data are from Goldstein et al.<sup>11</sup>

§ P<0.01

# Positive Feedback: *Takotsubo* Cardiopathy

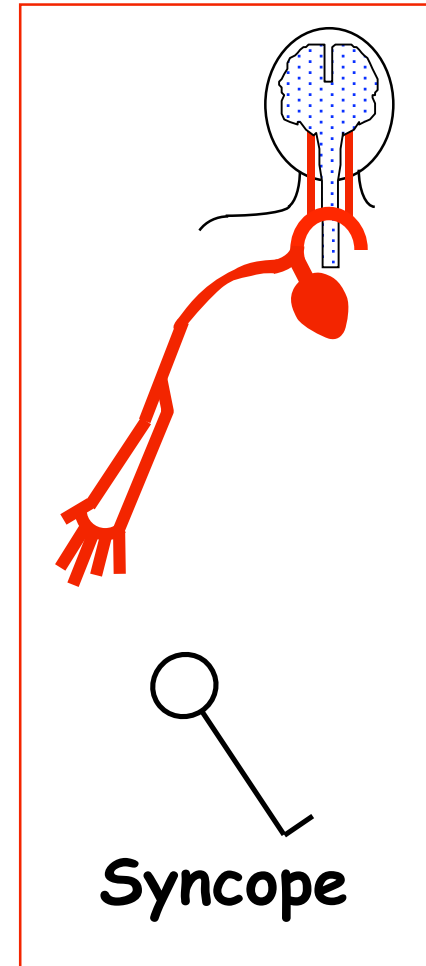
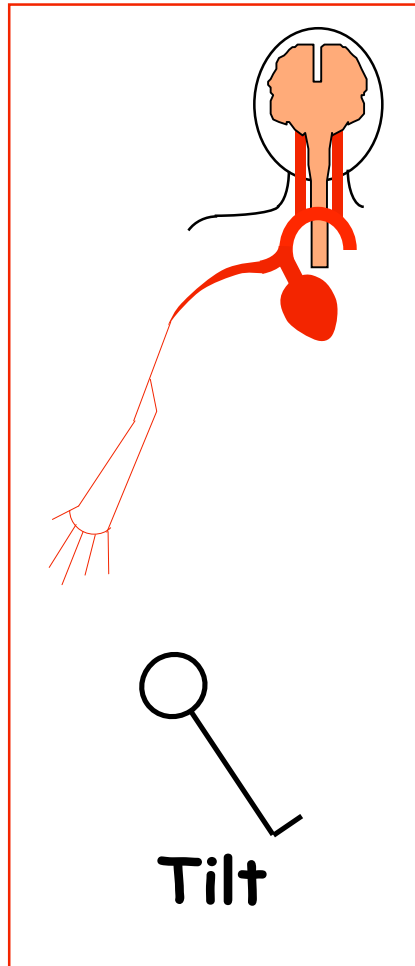
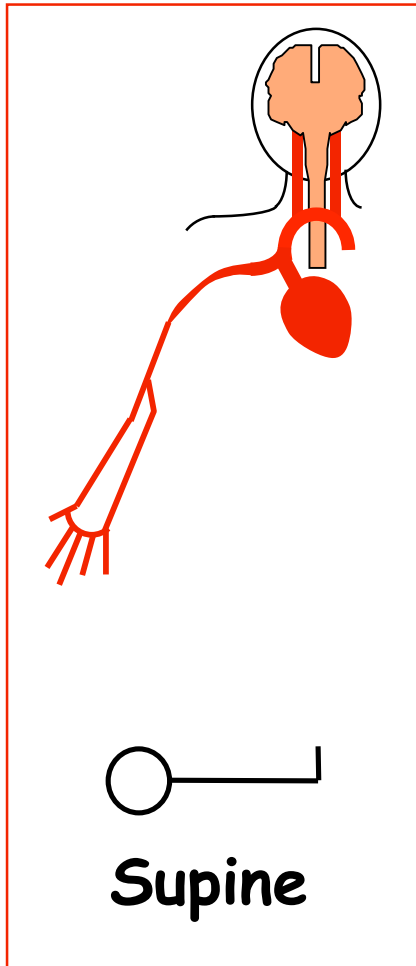


# “Sympathoadrenal Imbalance” before Fainting





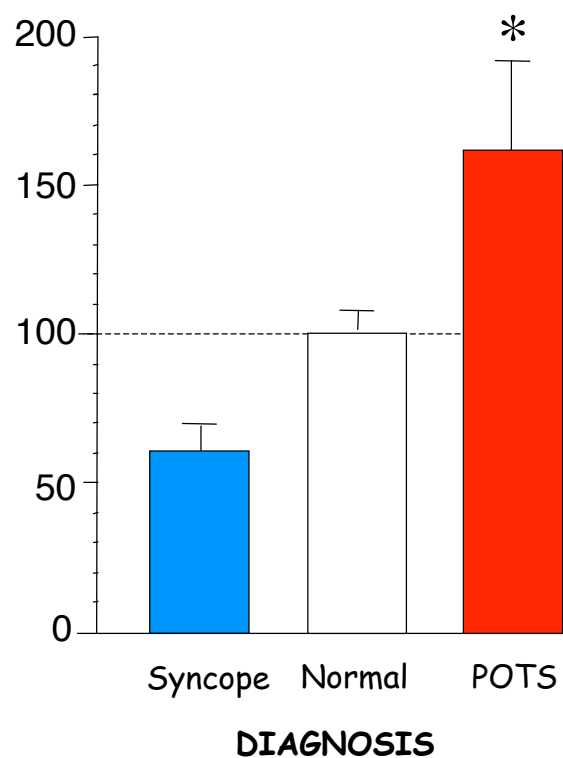
# Hemodynamics of Tilt-Induced Fainting



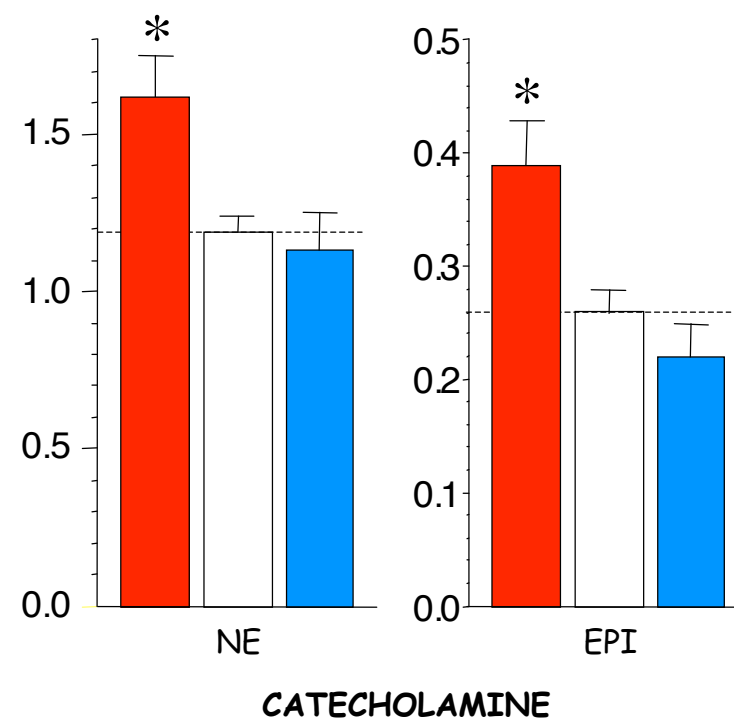
# SNS & AHS Activation While Supine in POTS

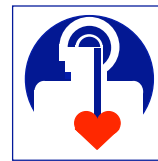


CARDIAC NE SPILLOVER (pmol/min)

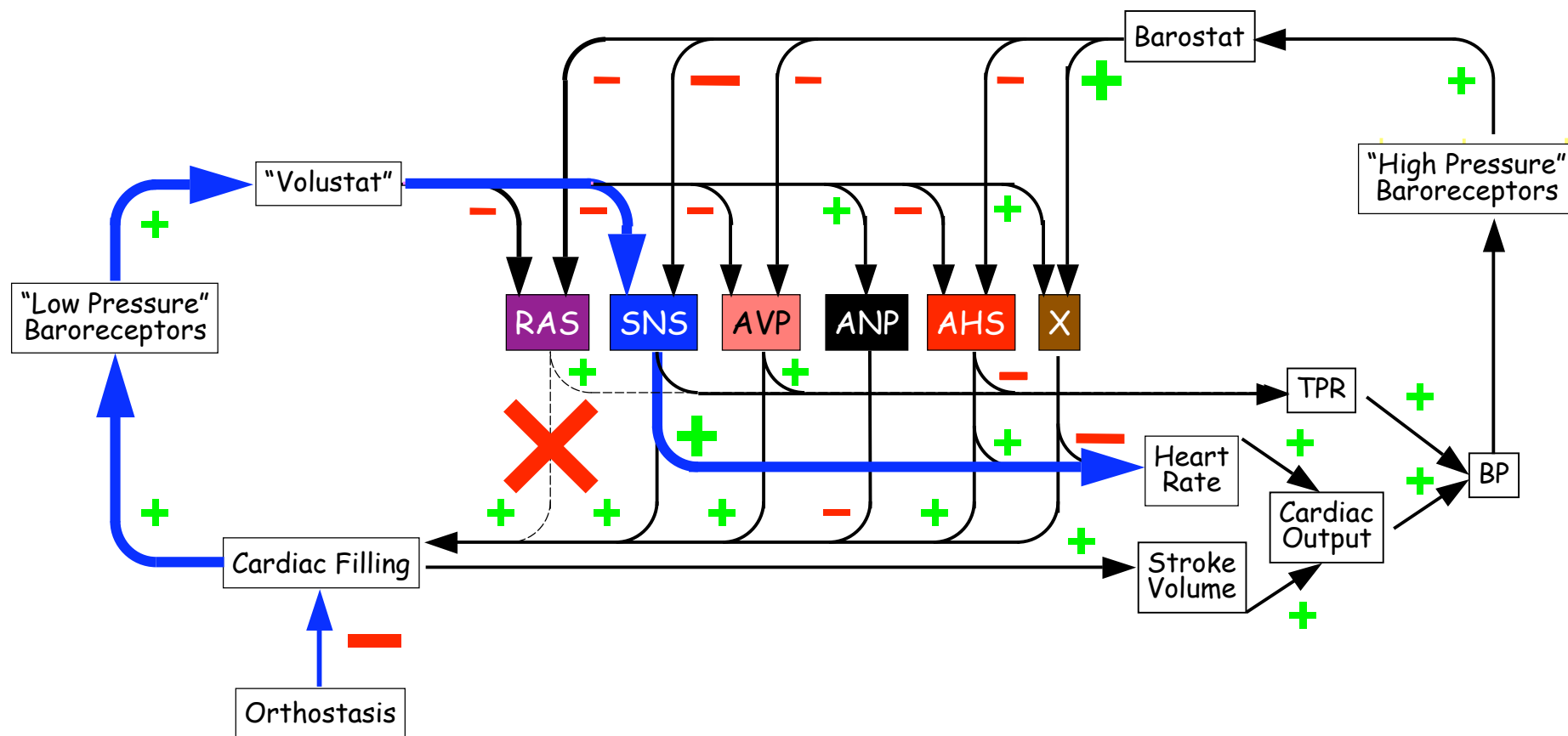


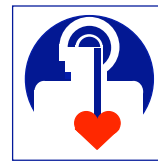
ARTERIAL PLASMA CONCENTRATION (nmol/L)



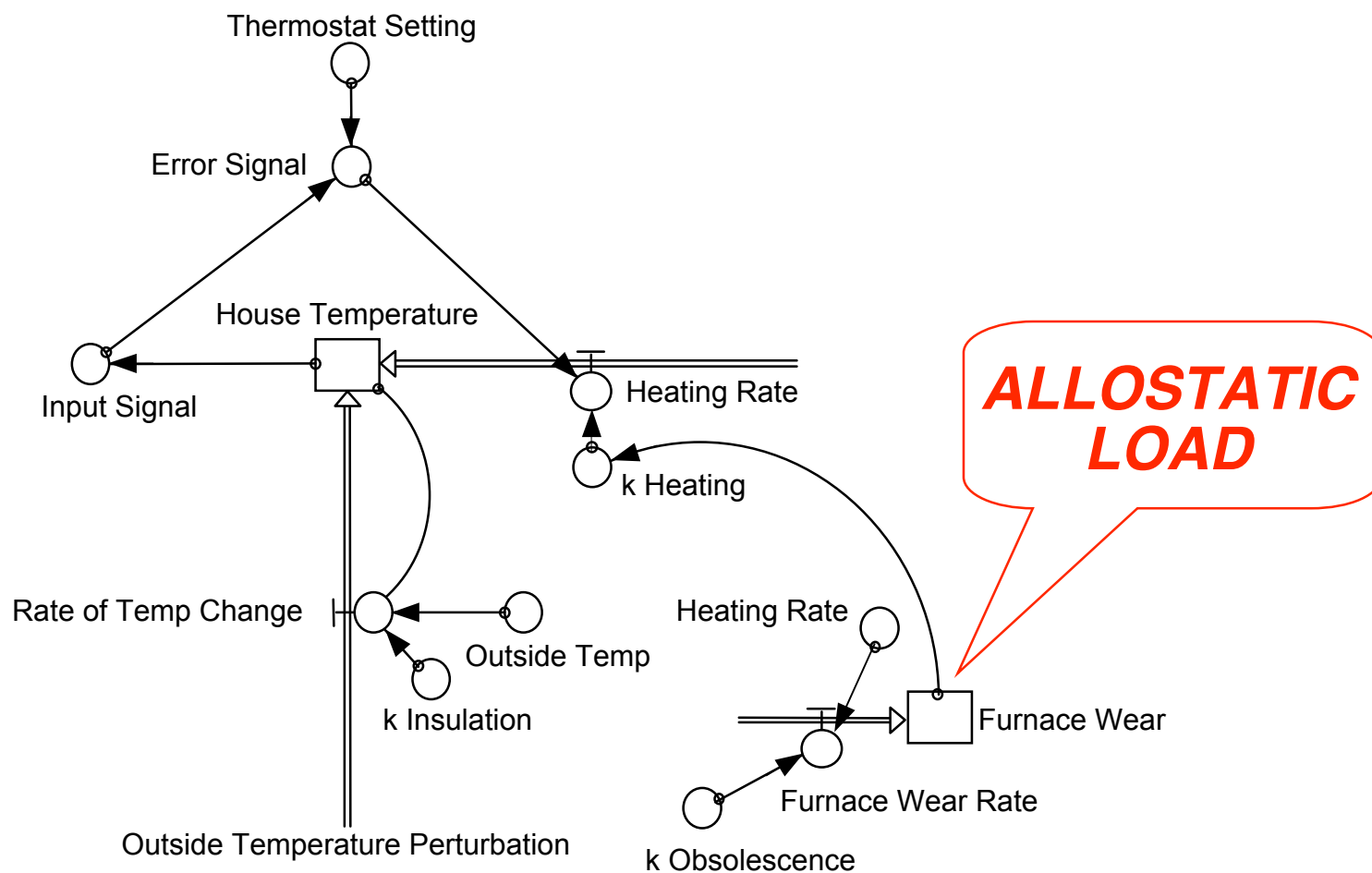


# Model of Orthostatic Tachycardia in POTS

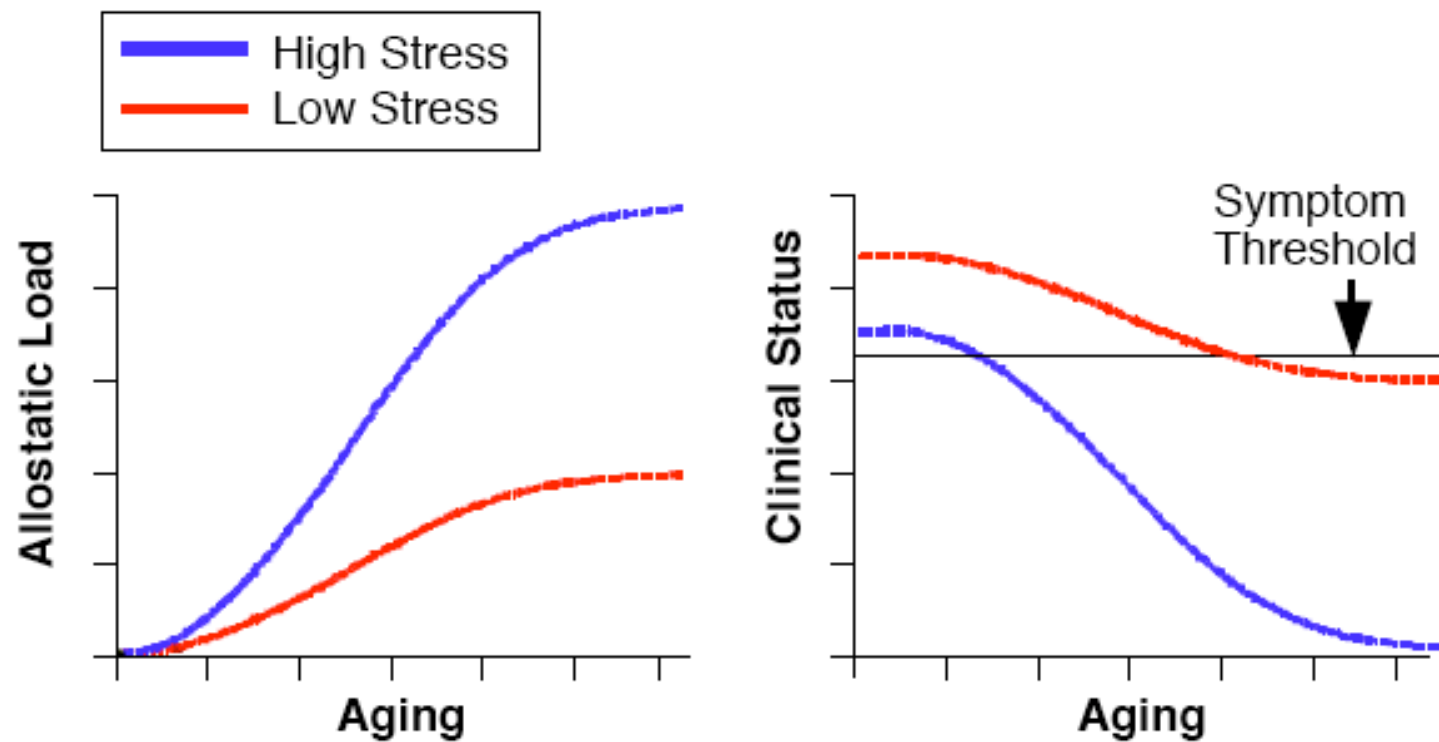




# Computer Model of Allostatic Load



# Predictions of Stress and Allostatic Load on Clinical Status





## Conclusions

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- Across stressors there is closer agreement of adrenomedullary with HPA activation than with sympathoneural activation.
- Stress responses have a degree of primitive specificity.
- Scientific Integrative Medicine provides a framework for teaching, research, and practices that maximize wellness and decrease personal and societal burdens of disease.
- A homeostatic definition of stress allows for modeling and hypothesis testing, and a definition of distress is proposed that does not assume pathology.
- Mind-body disorders are multi-disciplinary, crossing traditional boundaries of cardiology, neurology, endocrinology, and psychiatry.
- Computer models can predict effects of stress, aging, and allostatic load and aging on clinical status.



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