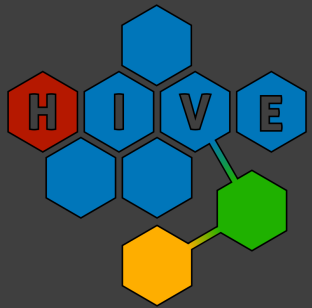


# NeuroBehavioural Medicine: Stress and Disease



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Hybrid Interactive  
Virtual Environments

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# Learning Outcomes

- Describe different theoretical stress models
- Explain physiological and psychological responses to stress
- Evaluate the complex pathways linking psychological stress to disease
- Critically appraise the associations between stress and disease



# What is stress?



- 
- Stress is defined as the body's nonspecific **response or reaction** to **demands** made on it, or to **disturbing events** in the environment (Rosenham & Seligman, 1989; Selye, 1974)
  - Stress arises when individuals **perceive** that they cannot adequately **cope** with the demands being made on them or with demands being made on them, or with threats to their well-being (Lazarus, 1966)
  - Personal and environmental events that cause stress are referred to as **stressors** (Lazarus, 1990)

# Theories of Stress

- Fight-or-flight theory (Cannon, 1932)
- General Adaptation Syndrome (Selye, 1956)
- Cognitive Appraisal Theory (Lazarus & Folkman, 1984)
- Generalised Unsafety Theory of Stress (Brosschot et al., 2018)



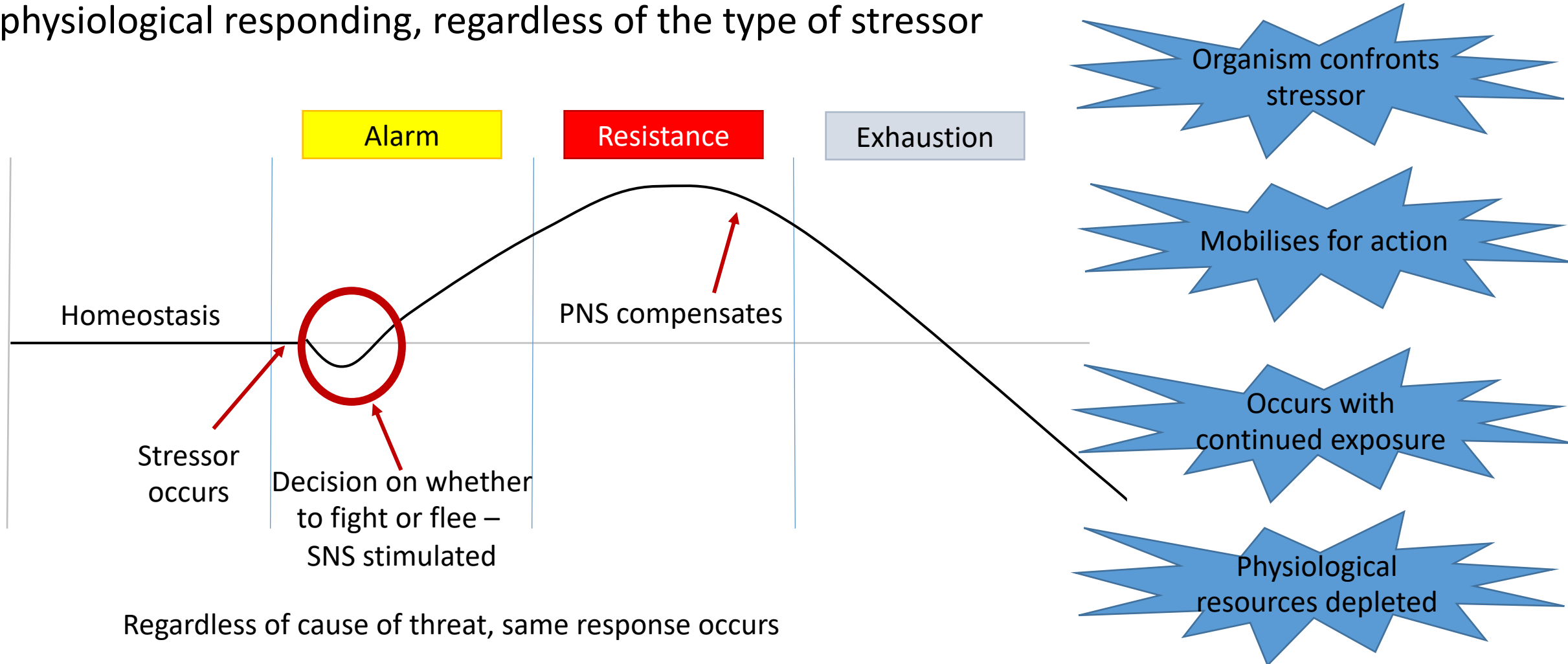
# Cannon: Fight or Flight Response

- When an organism perceives threat, body is rapidly motivated and aroused via
  - Sympathetic nervous system
  - Endocrine system
- Physiological response mobilizes organism to attack threat (aggressive, active response) or flee (withdrawal)
- **Adaptive** role, as allow for rapid response to threat (i.e., SAM and acute stress), but **can also be harmful** (i.e., chronic activation of HPA axis where dysregulation can cause both physical and psychological harm)



# Selye: General Adaptation Syndrome

- Non-specific response: the body responds to stress with the same pattern of physiological responding, regardless of the type of stressor



# Criticisms of model

- Limited role given to psychological factors
  - Cognitive appraisal is important
  - Responses influenced by perceptions, individual differences, pre-existing physical and mental health
- Not all stressors produce same physiological response
- Damage may result from continued activation ('resistance') as opposed to depletion of physiological resources
- Stress is assessed as an outcome
- Debilitating effects of anticipation of stress (e.g., worrying about exams)



# Lazarus & Folkman Cognitive Appraisal Theory

- Stress results from imbalance between demands & resources
- Psychological stress occurs when an individual perceives environmental demands as exceeding her/his adaptive capacity
- The interpretation of the stressful event is more important than the event itself
- Takes anticipatory anxiety into account



# Lazarus & Folkman: Cognitive Appraisal Theory

- Appraisal involves a two-step process:
  - Primary appraisal process – assessment of situation
    - Is the event positive, neutral or negative?
    - Has harm been done?
    - Is there a threat of future/further damage?
    - How challenging is the event?
  - Secondary appraisal process – assessment of coping abilities & resources
    - Are coping abilities & resources sufficient to overcome harm, threat, and/or challenge posed by the event?



# Importance of appraisal in the experience of stress

- Interpretation of a stimulus, presented in a given situation, results in production of stress response IF the stimulus is considered to be a threat (brain regions and neurocircuitry involved, e.g., CSTC, amygdala)
- Study by Speisman, Lazarus, Mordkoff, & Davidson (1964)
  - Undergrad students & airline execs viewed a gruesome film depicting tribal initiation rites (penile subincision)
  - Four experimental conditions included whereby participants in each group were exposed to 1 of 4 soundtracks:
    - Trauma
    - Denial & reaction formation
    - Intellectualization
    - No soundtrack (silent)

# Important of appraisal in the experience of stress

Stress responses significantly greater during the trauma track

Non-threatening commentary reduced stress produced by the same event

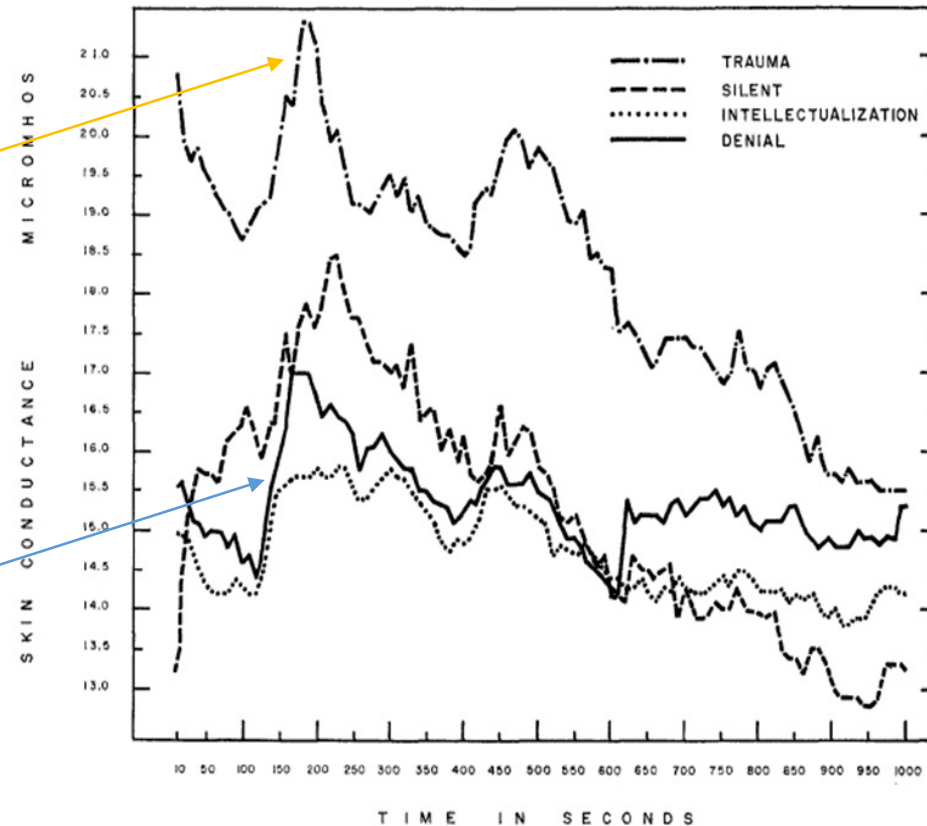


Fig. 2. Skin-conductance patterns during the subincision film as determined by the various sound-track conditions.

# Generalised Unsafety Theory of Stress

- Proposed by Brosschot et al. (2018), emphasising importance of perceived safety as opposed to perceived danger
- Stress response is always active, or on standby, perception of safety in environment regulates and inhibits response
- PFC (important in decision-making and mediating behaviour) crucial in keeping the 'brakes' on the amygdala, inhibiting sympathetic arousal

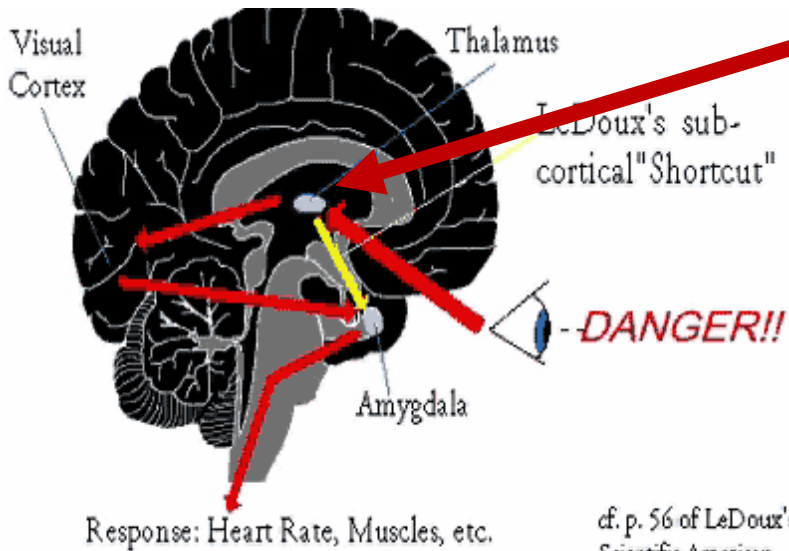
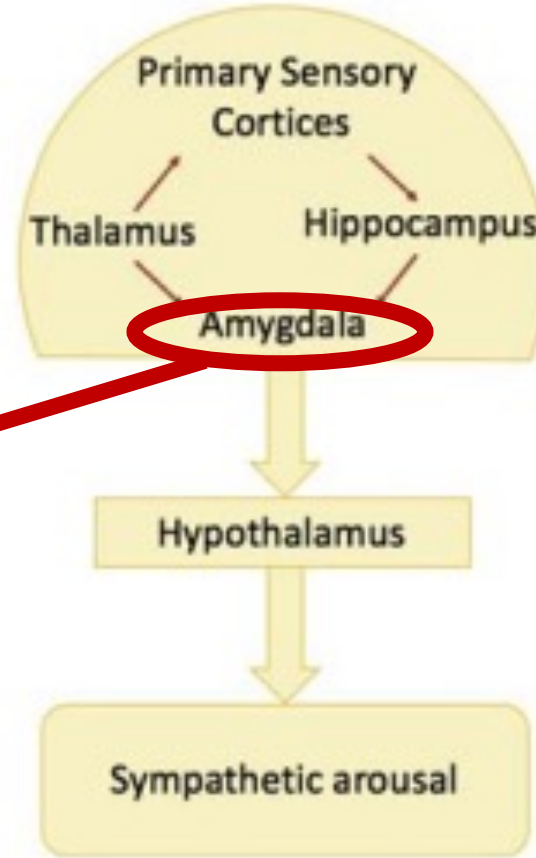
# What makes potential stressors more likely to be appraised as stressful?

- Negative events produce more stress than positive events. Exception being among people who hold negative self-views (low self-esteem), positive life events can lead to increase in illness
- Events that are seen as uncontrollable or unpredictable are more stressful than those viewed as controllable and predictable (i.e., learned helplessness)
- People who are overloaded tend to be more stressed than those with fewer tasks
- Ambiguous events more stressful than clear-cut events
- People are more vulnerable to stress in central life domains than in peripheral ones

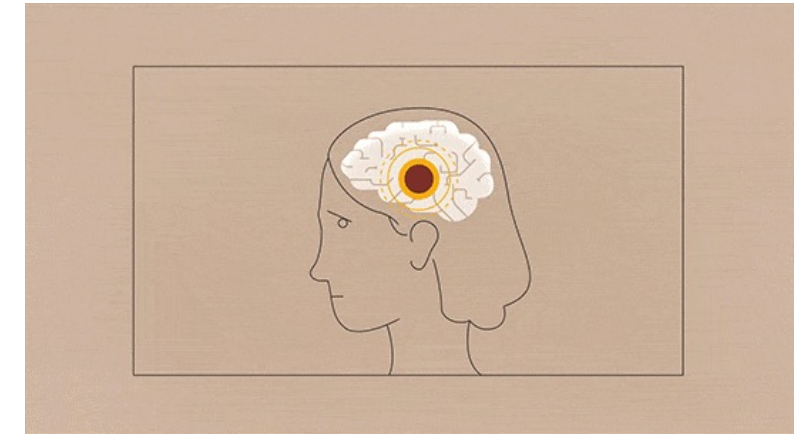
# Physiology of stress

- To understand the stress response, we must possess a fundamental knowledge not only of psychology but of physiology as well – George Everly
- Stress response is mediated by the stress system, partly located in CNS and partly in periphery
- When events are encountered that are perceived as stressful, a cascade of changes in the CNS, cardiovascular, endocrine and immune systems is triggered
- Introduction of a stressor activates the autonomic nervous system (ANS), which consists of two branches:
  - Sympathetic nervous system
  - Parasympethic nervous system

# How the brain reacts to a stressor



cf. p. 56 of LeDoux's  
Scientific American  
article, June, 1994.

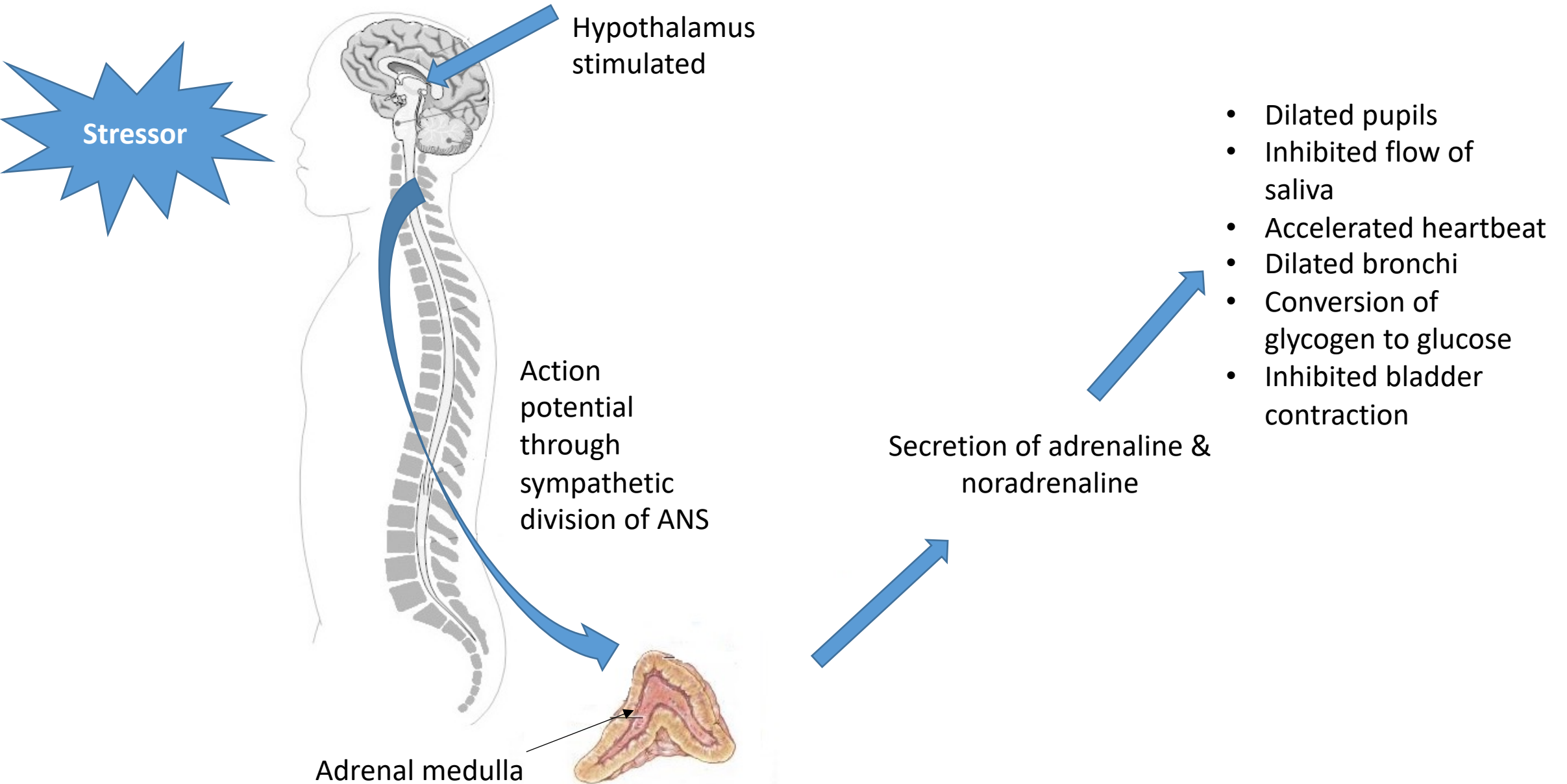




# Physiology of stress - SAM

- Stress response involves two inter-related systems:
  - Sympathetic-adrenal-medullary system (SAM)
  - Hypothalamic-pituitary-adrenal axis (HPA)
- SAM – Cannon's fight or flight response (GAS – Alarm stage)
- Perception of threat (via amygdala) leads to hypothalamus activating sympathetic nervous system. Sympathetic arousal (via autonomic nerves) stimulates medulla of adrenal glands
- Leads to secretion of catecholamines: Adrenaline & noradrenaline
- Induces physiological changes that include increase in heart rate and blood pressure, constriction of peripheral blood vessels, increased sweating

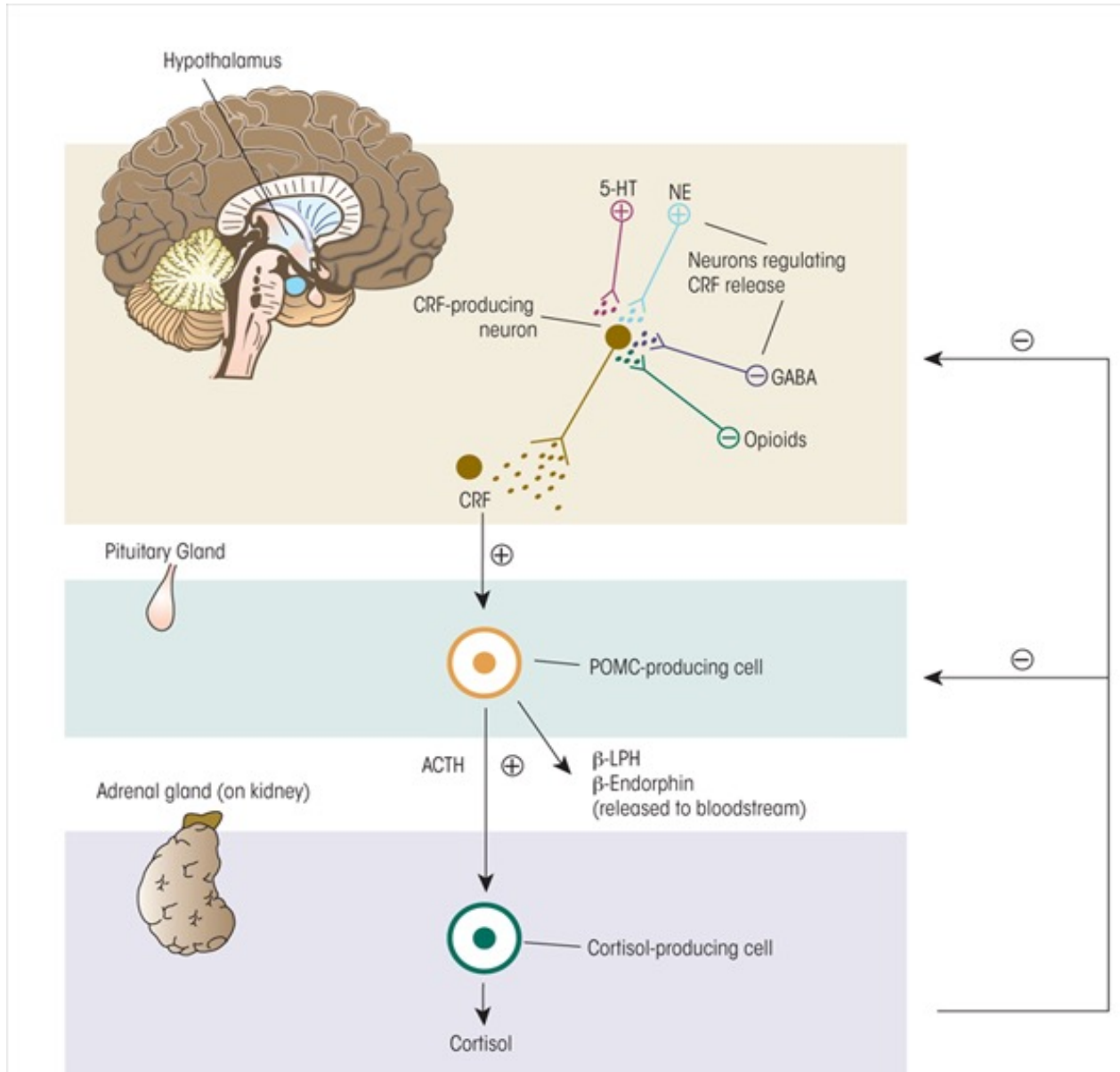
# Physiology of stress - SAM



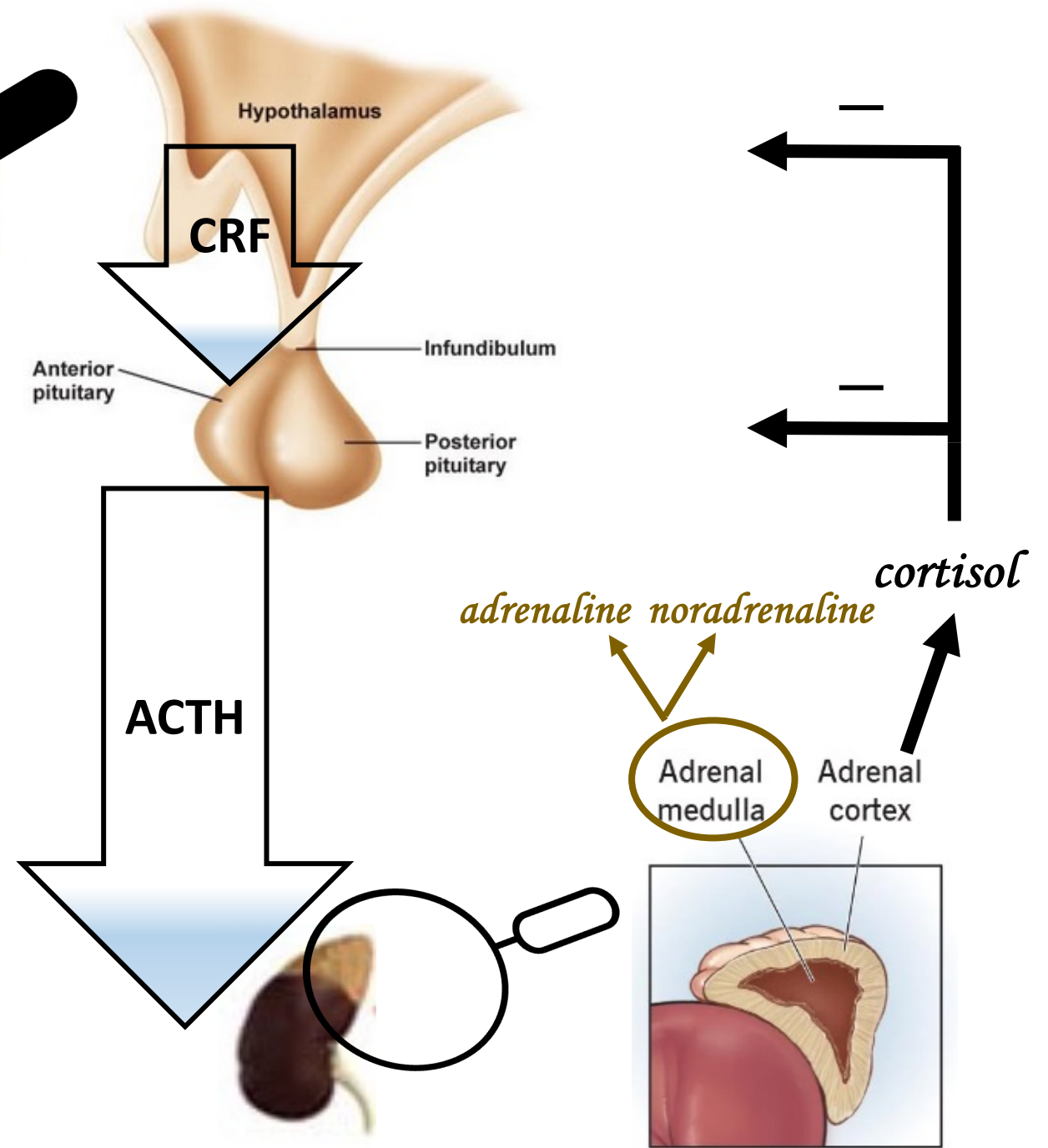
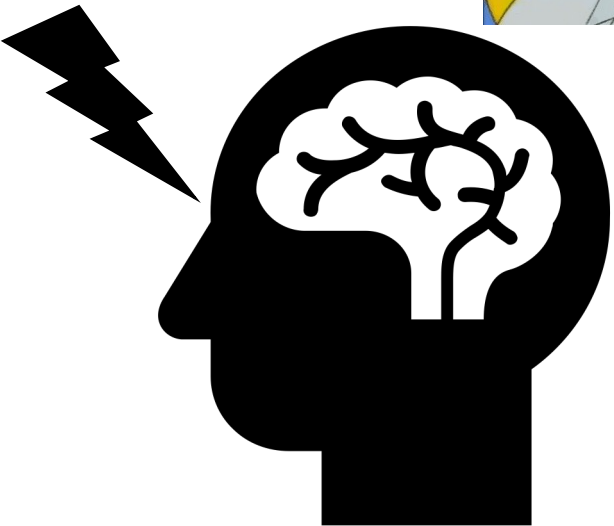
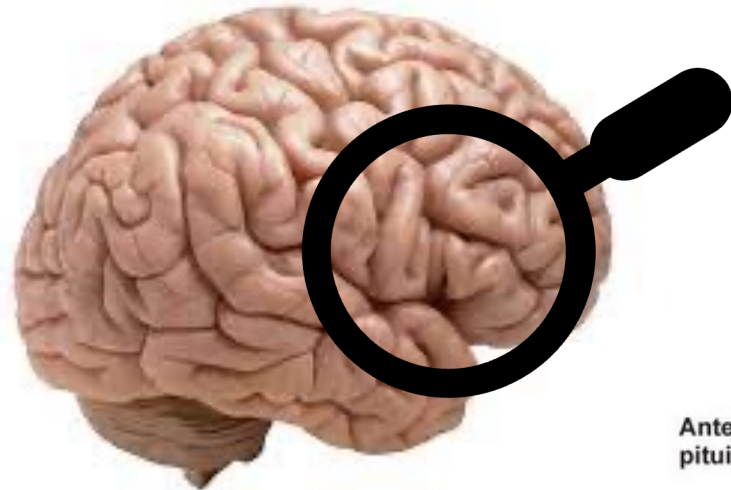
# Physiology of stress - HPA

- HPA axis – Selye's General Adaptation Syndrome (resistance)
- Resistance leads to hypothalamus secreting corticotropin-releasing factor hormone (CRH/CRF) and arginine vasopressin (AVP)
- This elicits production of adrenocorticotropin hormone (ACTH) via binding of CRF to CRF receptors on the anterior pituitary gland
- ACTH binds to receptors on adrenal cortex, stimulates release of cortisol
- Cortisol regulates:
  - Anti-inflammatory responses
  - Metabolism of carbohydrates
  - Gluconeogenesis

# Physiology of stress - HPA



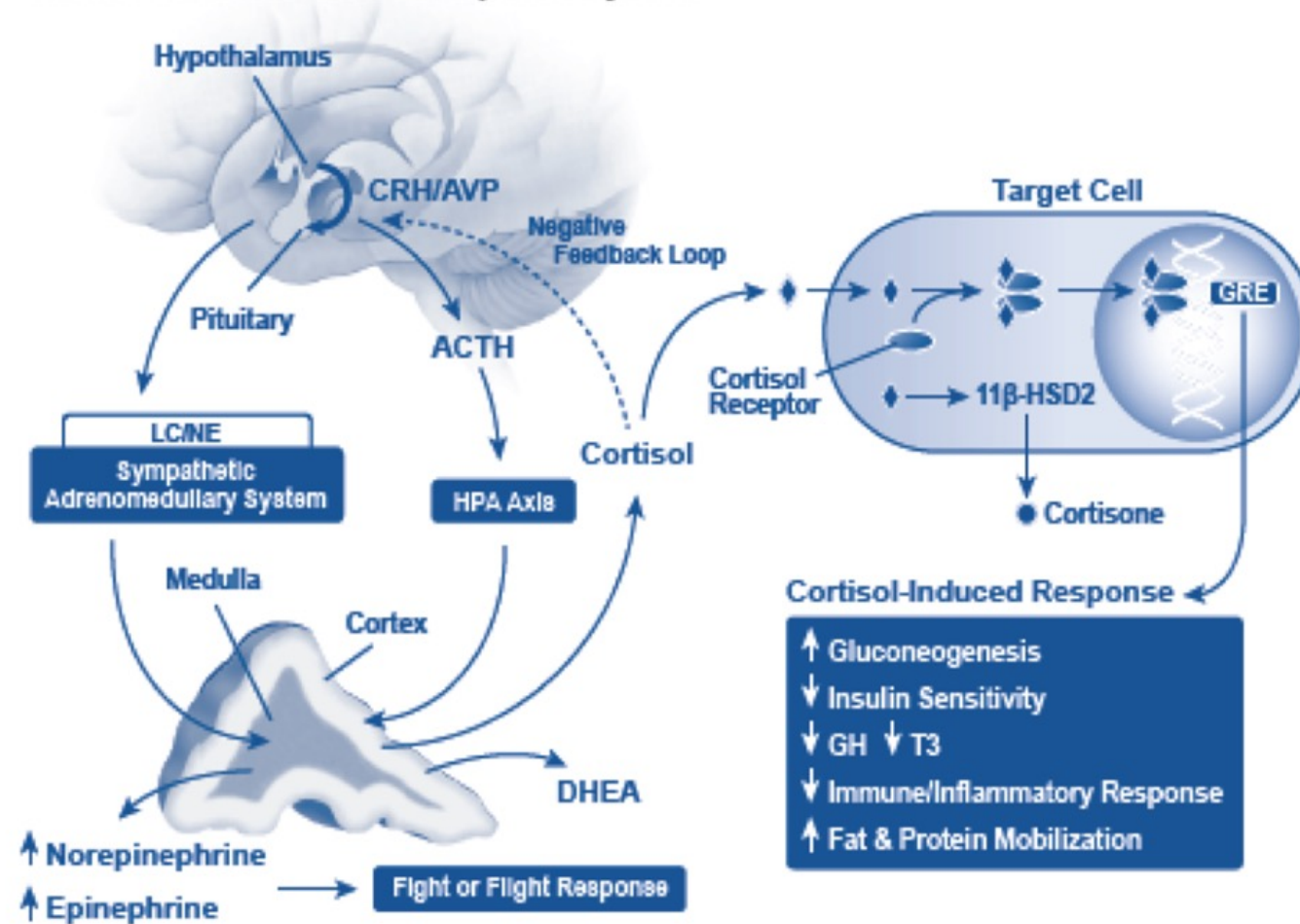
- Presence of **stressor** leads to release of **cortisol** for several hours following initial exposure
- Once **stressor is removed** and cortisol concentration reached, **negative feedback** to **hypothalamic** release of **CRF**, & pituitary release of **ACTH**, occurs. **Homeostasis returns**
- **Continued** and/or repeated **exposure** to stressor leads to **chronic activation** of HPA axis. **Impairs negative feedback** of cortisol
- Chronic activation leads to **long-term stress**, **physical** and **mental** health concerns





# Physiology of stress: stress response summary

Figure 1  
The HPA Axis and Stress Response System



# Chronic stress response

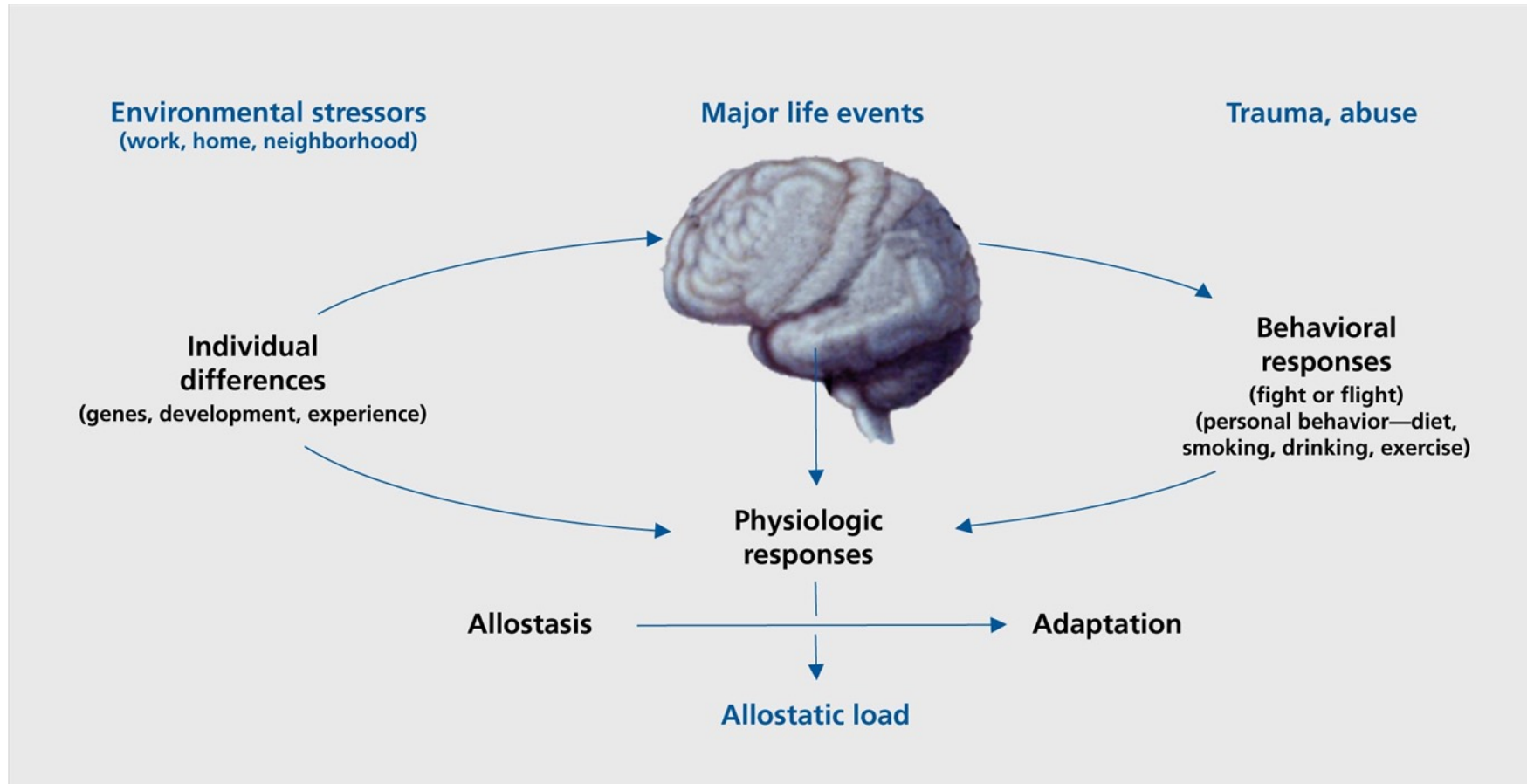
- Physiological changes take place in response to stress, purpose short-term mobilization of organism
- Stress response is **maladaptive** if the system is **chronically activated** or **fails to terminate** when the **threat is no longer present**
- Chronic activation linked to health problems:
  - Elevated blood pressure
  - Corticosteroids have immunosuppressive effects
  - Prolonged cortisol secretion has been associated with destruction of neurons in the hippocampus
- Long-term stress linked to **chronic HPA axis activation**



# Chronic stress response

- Cumulative biological toll of chronic over-stimulation of stress system (i.e., exhaustion) is referred to as **allostatic load** (McEwen)
- **Allostasis** refers to **fluctuations** in the body's physiological systems to **meet stressful demands**
- Over long intervals, release of primary hormonal mediators (glucocorticoids & catecholamines) can have damaging effects, leading to **wear and tear (allostatic load)**, and illness
- Accelerated disease process made worse if **avoidance behaviours** are used to cope with stress (e.g., poor diet, smoking, drinking, etc.)

# Chronic stress response: Allostatic load



Source: McEwen, *JAMA*, 1993, **153(18)**: 2093-2101.

# Assessing & measuring stress

- Stress can be measured both subjectively & objectively
- Methods of measuring stress include:
  - Self-reports of perceived stress, stressful life events, emotional distress
  - Behavioural measures such as task performance under stress
  - Physiological measures such as skin conductivity, heart rate, blood pressure
  - Biochemical markers such as elevated catecholamine & cortisol levels (cortisol-to-DHEA ratio)
  - Brain activity (e.g. the hypothalamus)
- Each have strengths & weaknesses (e.g. self-report biases; non-specificity of biological markers)

# Measuring perceived stress (Cohen, 1983)

Instructions: The questions in this scale ask you about your feelings and thoughts during the last month. In each case, please indicate with a check how often you felt or thought a certain way.

1. In the last month, how often have you felt that you were unable to control the important things in your life?

\_\_\_0=never \_\_\_1=almost never \_\_\_2=sometimes \_\_\_3=fairly often \_\_\_4=very often

2. In the last month, how often have you felt confident about your ability to handle your personal problems?

\_\_\_0=never \_\_\_1=almost never \_\_\_2=sometimes \_\_\_3=fairly often \_\_\_4=very often

3. In the last month, how often have you felt that things were going your way?

\_\_\_0=never \_\_\_1=almost never \_\_\_2=sometimes \_\_\_3=fairly often \_\_\_4=very often

4. In the last month, how often have you felt difficulties were piling up so high that you could not overcome them?

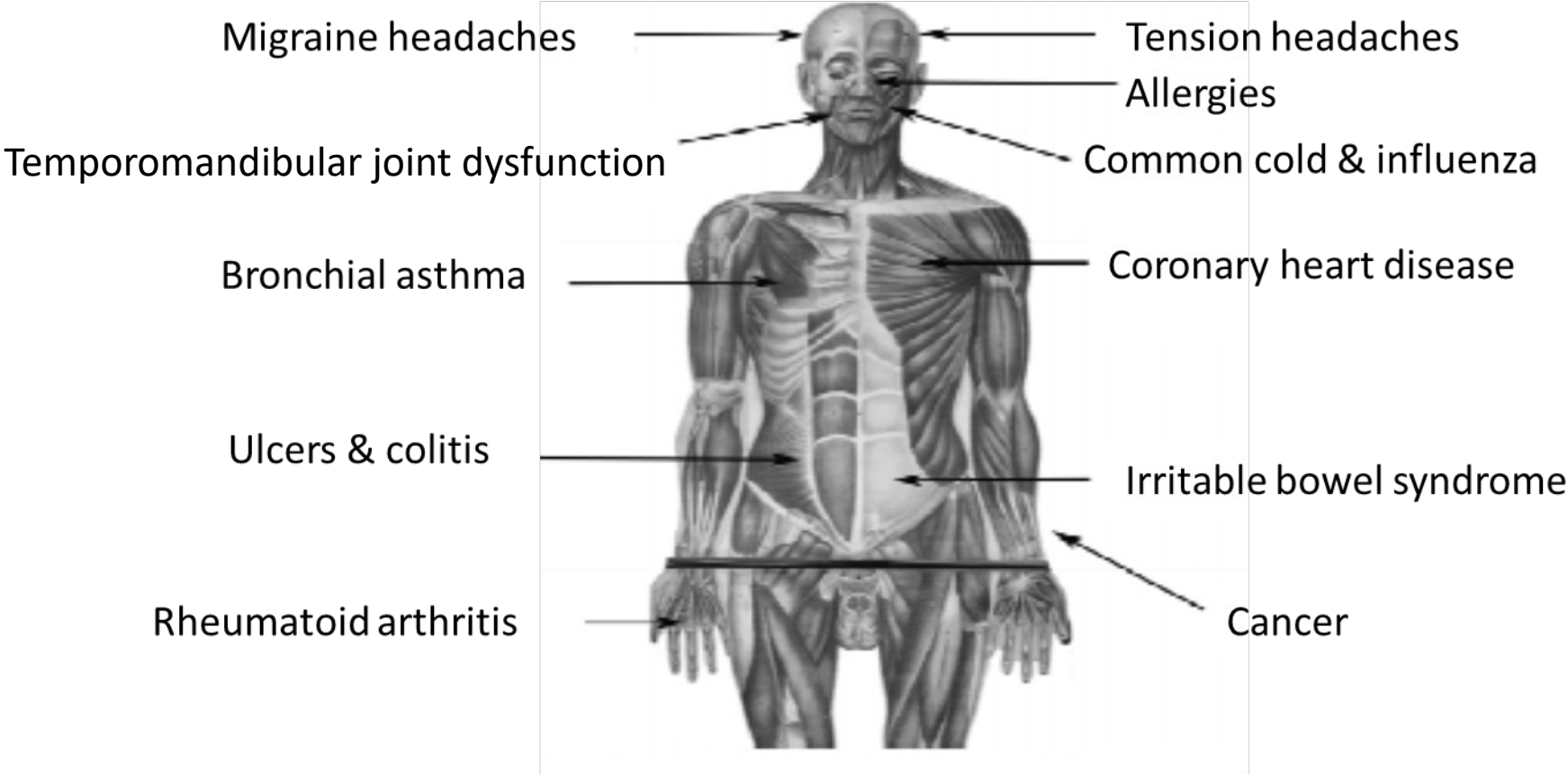
\_\_\_0=never \_\_\_1=almost never \_\_\_2=sometimes \_\_\_3=fairly often \_\_\_4=very often

# Pathways linking chronic psychological stress to disease



Source: Taylor, Health Psychology

# Physical effects of chronic stress

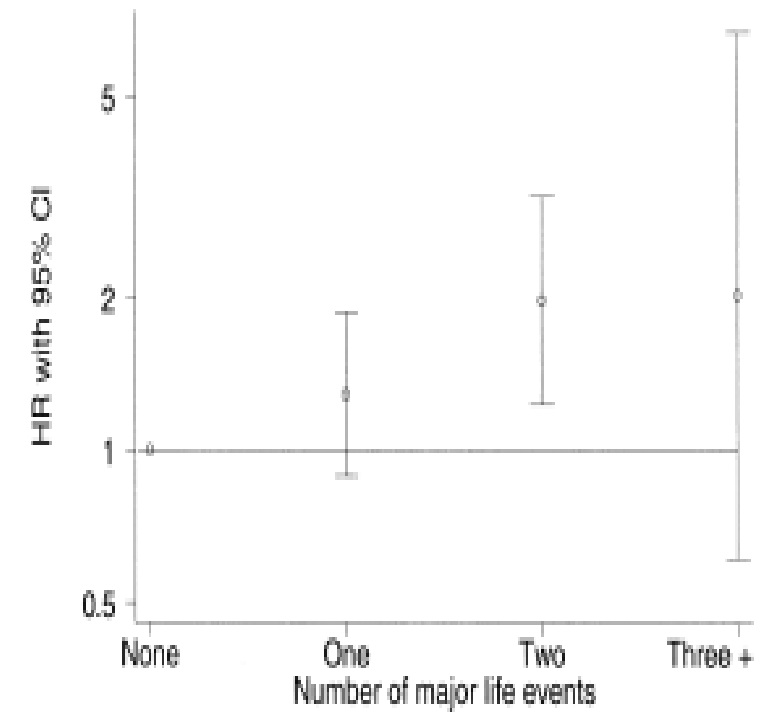


Source: Seaward, 1999.



# Stressful life events and risk of breast cancer in 10,808 women: A cohort study

- Finish Twin Cohort established to investigate **genetic**, **environmental**, and **psychosocial** determinants of chronic disease
- Hazard ratios for breast cancer observed for stressful life events (3 highest included **divorce/separation**; **death of spouse**; **death of close relative/friend**)
- Study revealed a **connection** between accumulation of **life events** during **5 years prior** to baseline assessment and **increased risk of breast cancer** during **15 years of follow-up**
- Direct link between physiological changes associated with life events & breast carcinogenesis?



**FIGURE 1.** Adjusted hazard ratio (HR) for breast cancer according to the number of five major life events, Finnish Twin Cohort Study, 1982–1996. Bars, 95% confidence interval (CI). The five major life events included the death of a husband, divorce/separation, personal illness or injury, the death of a close relative or friend, and loss of a job. Hazard ratios were adjusted for age, zygosity, marital status, social class, number of children, use of oral contraceptives, body mass index, alcohol use, smoking, physical activity, stress of daily activities, life satisfaction, and neuroticism.



# Stress and upper respiratory disease

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Investigated association between **psychological stress** & susceptibility to **common cold**

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Participants assessed for **degree of stress** on 3 measures, experimentally exposed to **1 of 5 cold viruses** or **placebo**

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Psychological stress associated with **increased risk of acute infectious respiratory** illness.

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Effect of stress on cold **independent** of transmission (i.e. **host resistance** as opposed to differential exposure)

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Findings suggest that stress is associated with **suppression** of different **immune processes**. Larger samples required, more controlled studies (stress & infectious agent)

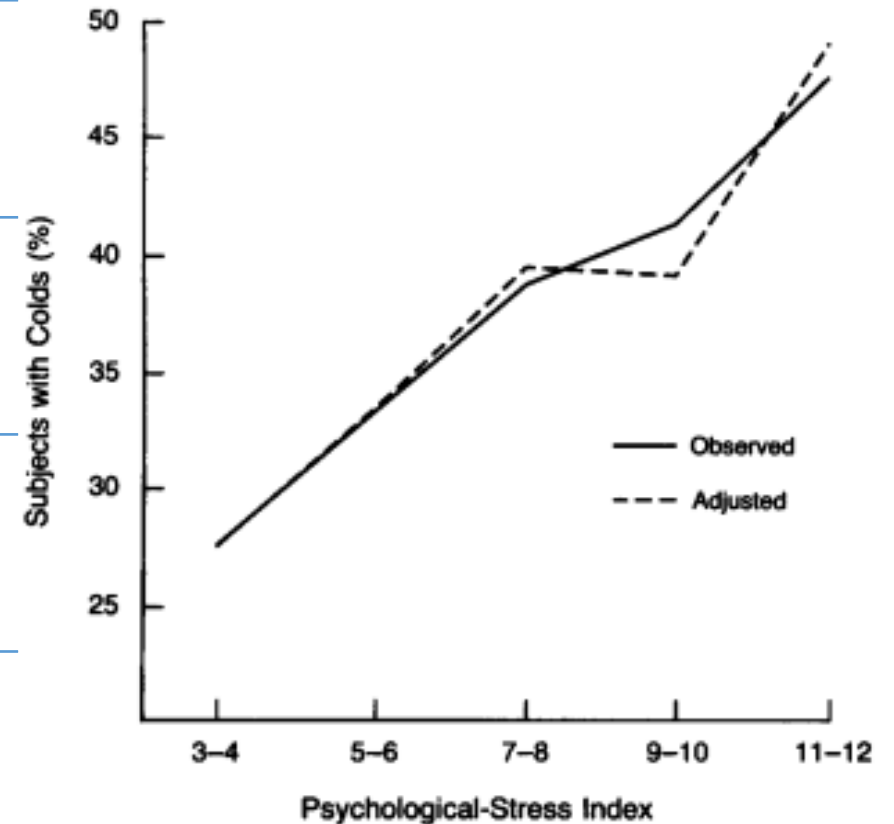


Figure 1. Observed association between the Psychological Stress Index and the Rate of Clinical Colds and the association adjusted for standard control variables

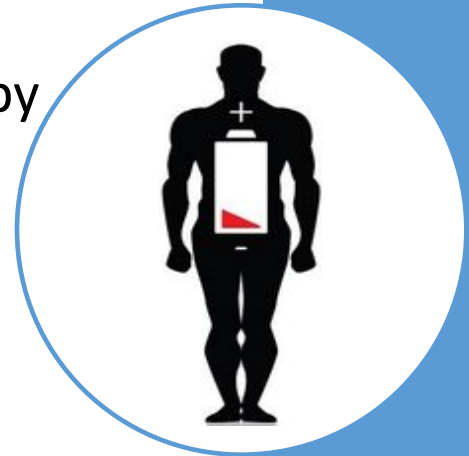
# Negative health behaviours and stress

**Unstandardized Parameter Estimates and Hazard Ratios (HRs) From Gompertz Hazard Models of the Risk of Death Among US Adults: 1990–1997**

	Model 1		Model 2	
	b (SE)	HR	b (SE)	HR
<b>Stress and health behaviors</b>				
Perceived stress	0.047** (0.018)	1.05	-0.060 (0.148)	0.94
Smoking				
Packs smoked per day among current smokers	0.438** (0.042)	1.55	0.377** (0.083)	1.46
Packs smoked per day among former smokers	0.128** (0.038)	1.14	0.081 (0.049)	1.09
No history of smoking	Reference		Reference	
Stress by packs smoked per day among current smokers			0.036 (0.032)	1.04
Stress by packs smoked per day among former smokers			0.033* (0.016)	1.03
Alcohol consumption <sup>a</sup>				
(No. of drinks) <sup>0.5</sup>	-0.703** (0.165)	0.50	-0.446* (0.180)	0.64
(No. of drinks) <sup>1.0</sup>	0.180** (0.038)	1.20	0.115** (0.032)	1.12
Stress by (No. of drinks) <sup>0.5</sup>			-0.162 (0.150)	0.85
Stress by (No. of drinks) <sup>1.0</sup>			0.042 (0.038)	1.04
Physical inactivity				
Physical inactivity index	0.266** (0.029)	1.31	0.182** (0.048)	1.20

# Can we adapt to stress?

- Most individuals adapt well to moderate or predictable stressors (e.g., noise, crowding)
- Vulnerable individuals (children, elderly, the poor) adversely affected by stress (little control over environment, limited resources)
- Behavioural effects of adaptation to stress include helplessness, poor concentration/memory
- Physiological effects include habituation (decreased responsiveness to stimulus following repeated exposure), increased allostatic load & chronic strain, compromised immune system
- Large individual difference that are influenced by environmental & genetic factors



# Climate anxiety

Hickman, C. *et al.* 2021. Preprint at <http://dx.doi.org/10.2139/ssrn.3918955>

## Young people's climate anxiety revealed in landmark survey

Children worldwide worry about the future and feel let down by governments, a huge study on attitudes towards climate change has found.

Tosin Thompson

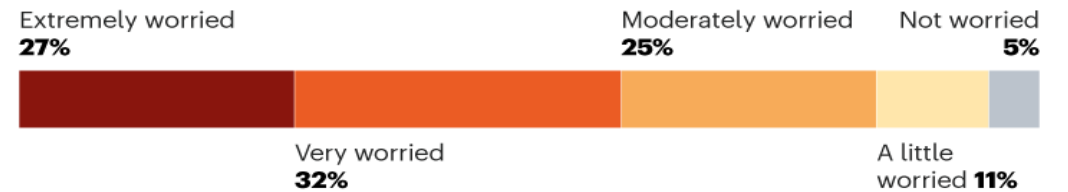


Children at a School Strike for Climate protest in Sydney, Australia. Credit: Richard Milnes/Shutterstock

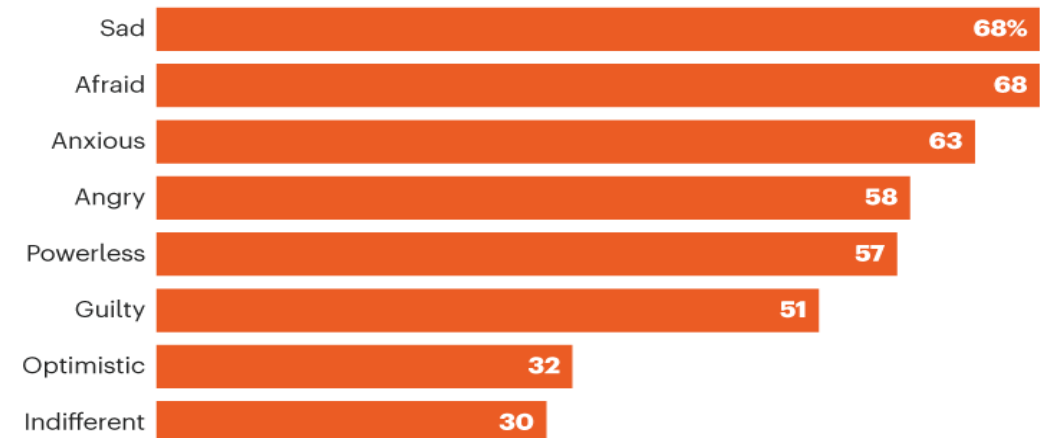
## CLIMATE ANXIETY

A survey of 10,000 young people shows that negative feelings about climate change can cause psychological distress.

### How worried are you about climate change?



### Climate change makes me feel...



# Mental health & chronic stress

- Persistent sensitization of CNS & long-term activation of stress response in early life increases susceptibility to affective disorders (e.g., depression, bipolar) & anxiety disorders (e.g., phobias, panic, GAD, OCD, PTSD)
- Anxiety is considered abnormal if distress:
  - Is out of proportion to stressful event or,
  - Occurs in the absence of direct physical threat or,
  - Continues after stressor has been removed or,
  - Leads to excessive worry & becomes worse with time
- Effects of chronic stress highlight the inextricable link between physical & mental health (e.g., depression as a risk factor for medical morbidity & mortality in coronary heart disease)



# Post-traumatic stress disorder (PTSD)

- May develop following exposure to extreme stressor (e.g., war, natural disasters, sexual assault, physical abuse, crime)
- Symptoms include reliving aspects of trauma (flashbacks), excessive vigilance, guilt, detachment (psychic numbing), poor sleep, impaired memory, exaggerated startle response, persisting > 1 month
- Associated with chronic changes to HPA & SAM system, may produce chronic mental & physical health effects
- Predicts poor physical health & poor health habits (e.g., drinking)
- The more trauma a person is exposed to, the greater the risk of PTSD

# Summary

- Psychological stress occurs when an individual perceives environmental demands as exceeding adaptive capacity
- The stress response is mediated by the stress system, which is located in both CNS and peripheral organs, and includes:
  - Sympathetic-adrenal-medullary (SAM) system
  - Hypothalamic-pituitary-adrenal axis (HPA)
- Chronic stress is a major contributor to psychosocial & physical pathological conditions
- Exposure to extreme stressors can result in PTSD
- Pathways between stress & disease are complex
  - Direct physiological effects & behavioural changes
  - Possibility of reporting bias, reverse causation, & shared underlying causes



# Recommended reading



## Core reading

- Hassoulas A. 2021. Chapter 6 *'The role of stress in health and disease'* in *A Prescription for Healthy Living*

## Recommended supplementary

- Godoy, L.D. et al. 2018. A comprehensive overview on stress neurobiology: basic concepts and clinical implications. *Front Hum Neurosci*, 12:127. Doi: 10.3389/fnbeh.2018.00127