HARVARD MEDICAL SCHOOL

Harvard Program in Refugee Trauma

Neuroscience of Stress and Resiliency

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Disclosures

I have the following relevant financial relationship with a commercial interest to disclose:

- Lecture HONORARIA AND TRAVEL
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- Johns Hopkins University Press; Belvoir Press; University of Chicago/Ivy Press----ROYALTIES

Stress

- **Stress:** what the brain does to itself and the rest of the body when faced with a **separation threat** or challenge endangering one's attachments. (Linking stress physiology with attachment theory)
- **Normal, Tolerable** and **Toxic Threat Stress---Yerkes Dodson Law**
- **Allostasis (stability in the face of change)** and **Allostatic Loading**
- **Hormesis:** A form of **Stress Resilience**. A biphasic effect of tolerable intermittent stress that can lead to stress inoculation and even post-traumatic growth, but if overwhelming or persistent to illness.

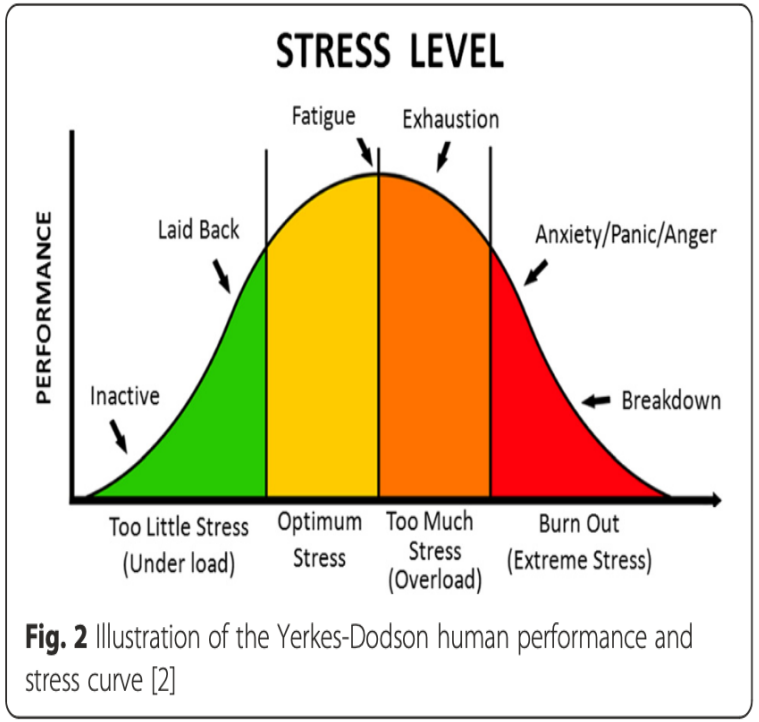


Fig. 2 Illustration of the Yerkes-Dodson human performance and stress curve [2]

COMBAT AND OPERATIONAL STRESS CONTROL

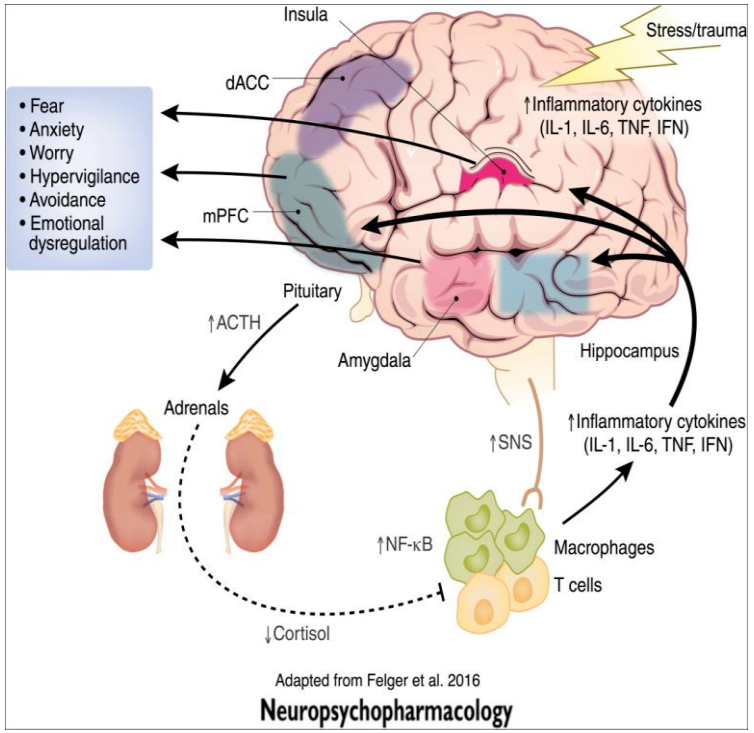
JAMES C. WEST, MD, CHRISTOPHER H. WARNER, MD Chapter 37 in Fundamentals of Military Medicine, 2019

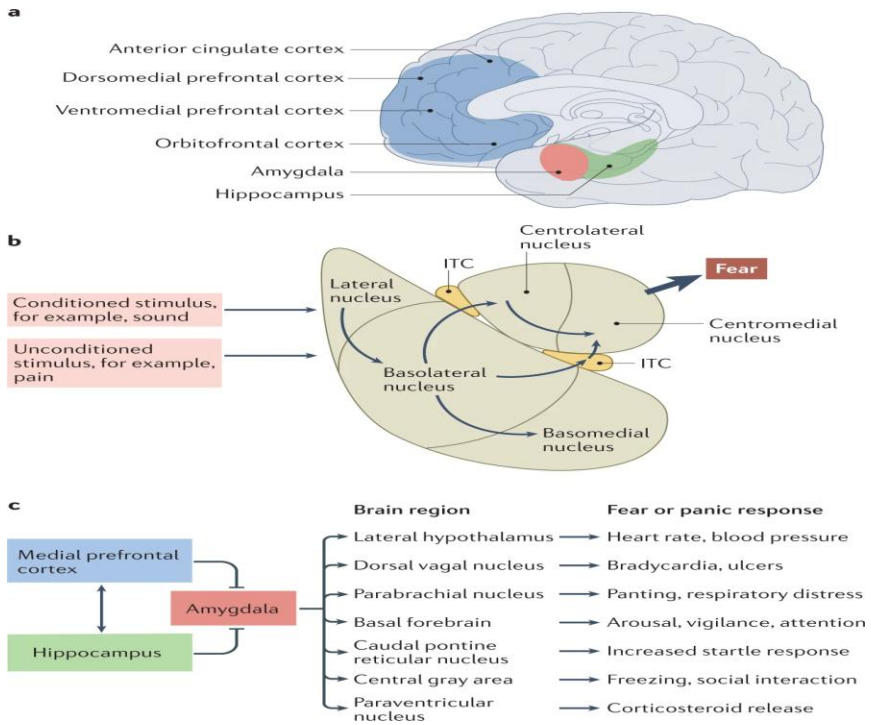
READY	REACTING	INJURED	ILL
DEFINITION • Adaptive coping • Effective functioning • Well-being FEATURES • In control • Calm and steady • Getting the job done • Playing • Sense of humor • Sleeping enough • Ethical and moral behavior	DEFINITION • Mild and transient distress or loss of function FEATURES • Anxious • Irritable, angry • Worrying • Cutting corners • Poor sleep • Poor mental focus • Social isolation • Too loud and hyperactive	DEFINITION • More severe and persistent distress or loss of function TYPES • Trauma • Fatigue • Grief • Moral injury FEATURES • Loss of control • Can't sleep • Panic or rage • Apathy • Shame or guilt	DEFINITION • Clinical mental disorders • Unhealed stress injuries TYPES • PTSD • Depression • Anxiety • Substance abuse FEATURES • Symptoms persist > 60 days after return from deployment

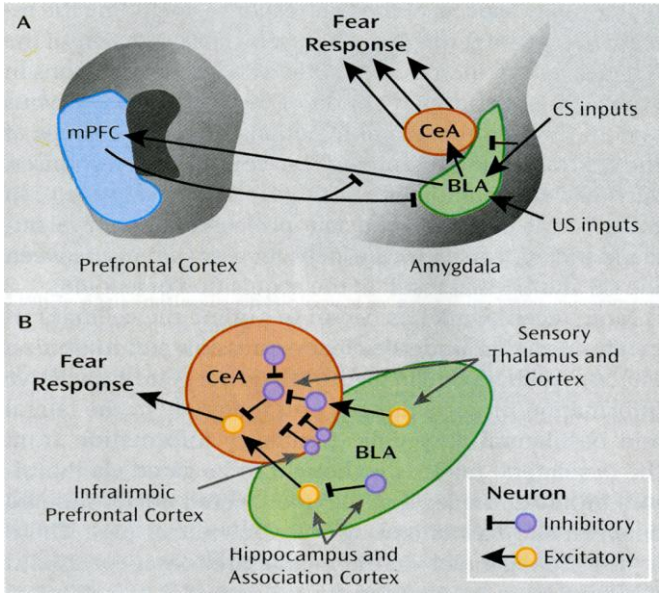
- The combat and operational stress continuum model with its four color-coded stress zones.
- Reproduced from: Nash WP. US Marine Corps and Navy combat and operational stress continuum model: a tool for leaders. In: Ritchie EC, ed. Fort Detrick, MD: Borden Institute; 2011: Figure 7-1.

Stress Response Systems/ Emotion Regulation and Entropy

*Neuropsychopharmacology Reviews,*2016; Ressler et al, 2022; Jovanovic and Ressler, 2010;







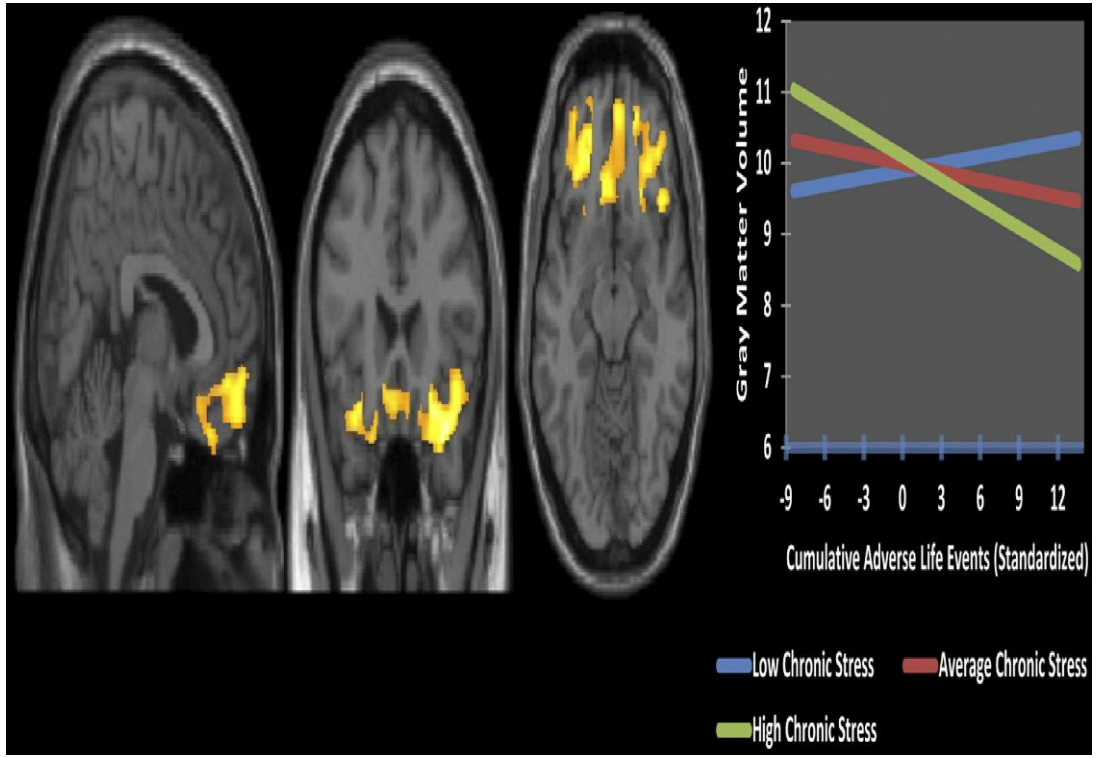
PFC VOLUME CHANGES WITH STRESS

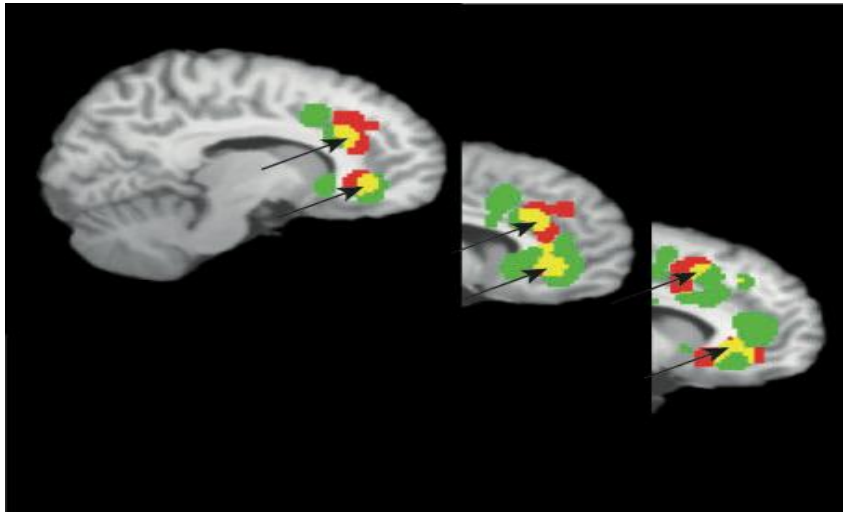
Ansell et al, 2012 *Biol Psychiatry*

A META-ANALYSIS OF THE ANTERIOR CINGULATE CONTRIBUTION TO SOCIAL PAIN

ROTGE ET AL, 2015

- Interaction of **greater subjective chronic stress** and **greater cumulative life events** a/w **smaller volume** in the mPFC, IC and ACC regions.
- **These areas are central to emotion regulation but also to attachment solution decision-making.**
- **They also mediate social pain.**

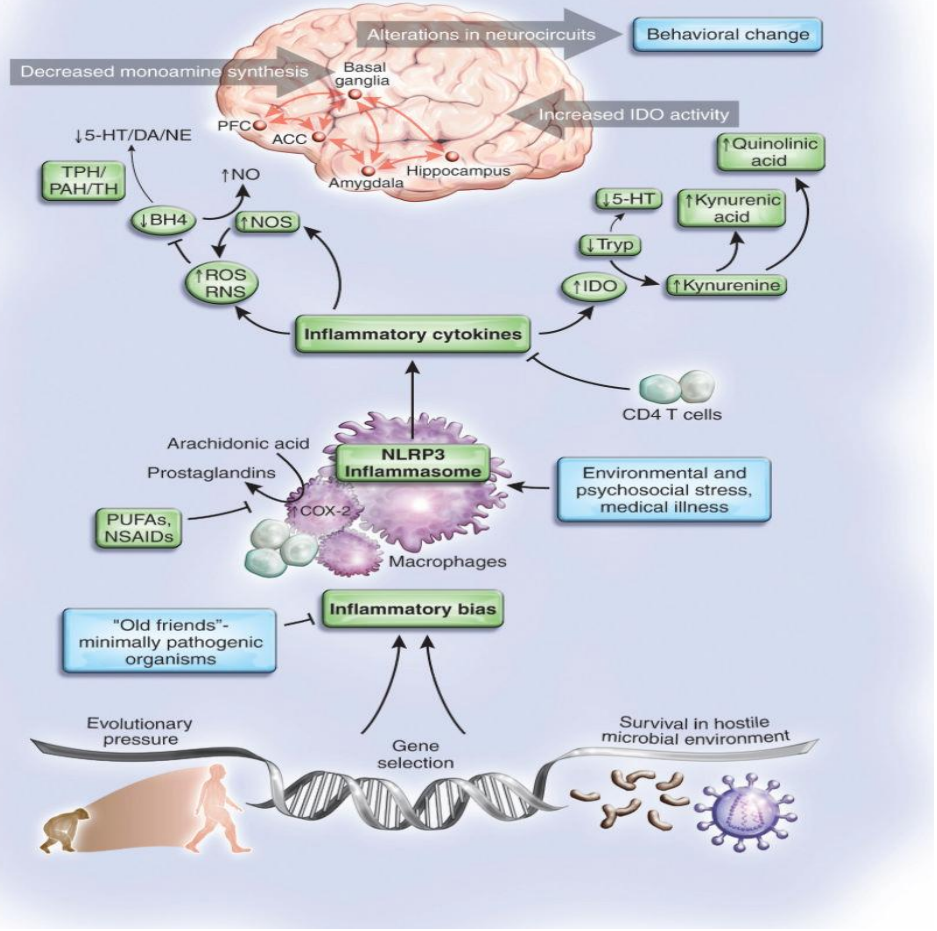




The Evolutionary Legacy of an Inflammatory Bias and a Social Attachment Bias

Raison and Miller
Brain Behav Immun. 2013

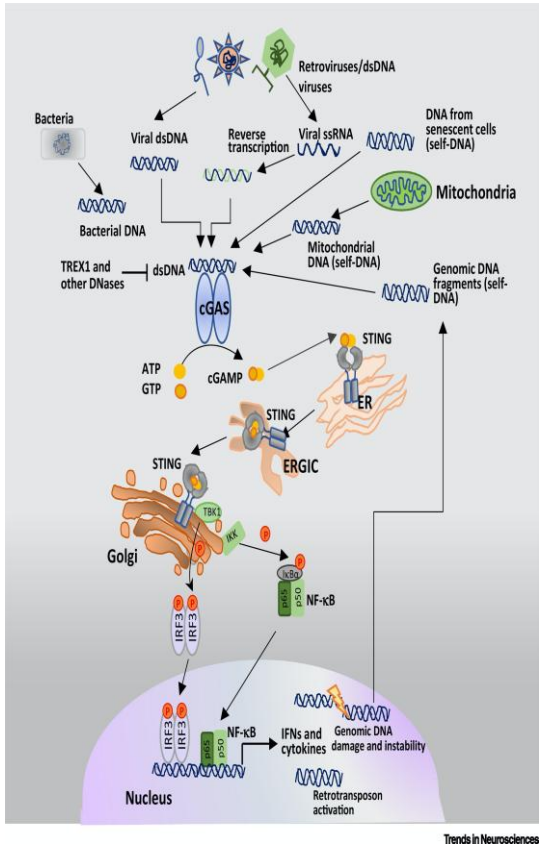
- **Hostile microbial environment** → genetically-based **inflammatory bias.**
- **Nucleotide-binding oligomerization domain-like receptor proteins (NLRPs)** help regulate immune response to invasion by microorganisms **and** to stress by forming an **inflammasome.**
- **Social-environmental signals** of **surprise** are "listened for" reflecting the risk of wound/injury related microbial assault can →innate IRS. (Slavitch and Cole, 2013)
- Such **uncertainty-based separation challenge signals for the mammal** may include: 1) **social conflict**; 2) **evaluation**; 3) **rejection**; 4) **isolation**; 5) **exclusion**
- **Inflammatory bias** (CDs) and **Social Attachment bias** (NCDs) become enmeshed and may conflict as in a viral pandemic.

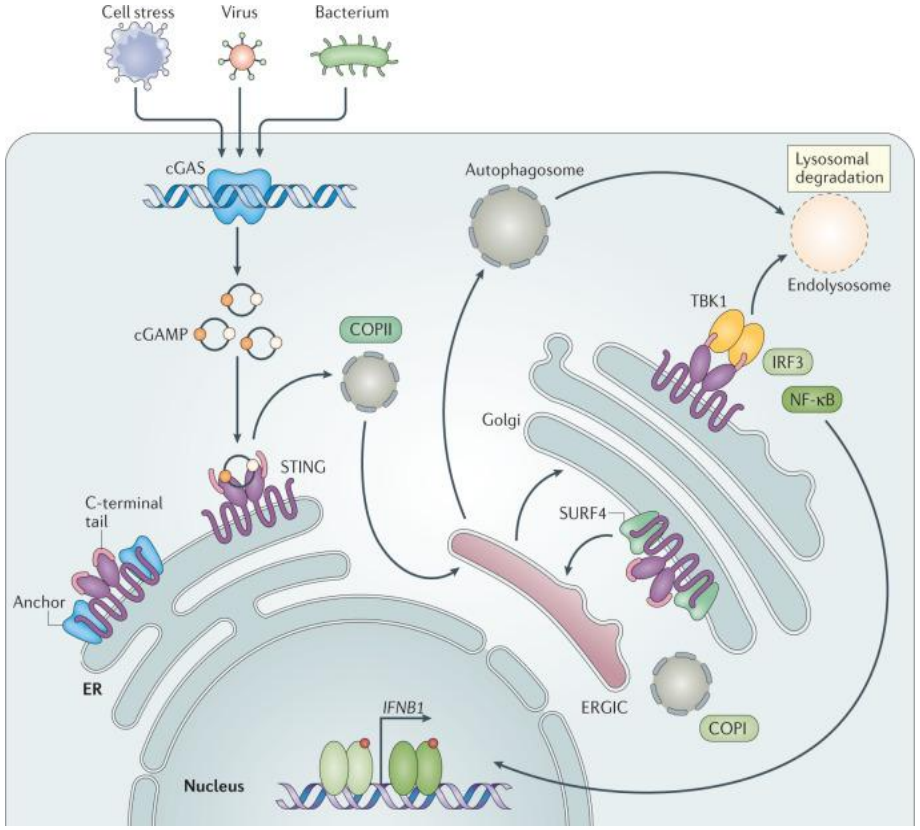


Signaling by cGAS–STING in Neurodegeneration, Neuroinflammation, and Aging

Decout et al. The cGAS-STING pathway as a therapeutic target in inflammatory diseases. *Nat Rev Immunol*. 2021;21(9):548-569.

- The **cyclic GMP–AMP synthase (cGAS)–stimulator of IFN genes (STING)** pathway, a component of the innate immune system, senses cytosolic DNA, which triggers an IFN-mediated response.
- Not only to microbial DNA, but also to self-DNA, both mitochondrial and genomic, which enters the cytosol from senescent or dying cells.
- In the brain, activation is elicited predominantly by microglia.
- Excessive engagement of cGAS–STING in the brain → neuroinflammation and neurodegeneration.
- Targeting of the cGAS–STING pathway may afford therapeutic benefits in aging and age-related neurodegenerative disorders.
- E.G.: ALS: TAR DNA binding protein of 43kDA (TDP-43)→ mtDNA spillage→ cGAS-STING→ upregulated innate immune response--> neuroinflammation; miR-218 activity in neurons may be impaired in ALS





Holmes Rahe Life Stress Unit Scale

RANK	LIFE EVENT	STRESS VALUE
1.	**Death of a spouse/life partners**	100
2.	**Divorce**	73
3.	**Marital Separation**	65
4.	**Detention in jail**	63
5.	**Death of a close relative**	63
6.	**Major personal illness or injury**	53
7.	Marriage	50
8.	**Getting fired**	47
9.	Marital Reconciliation	45
10.	**Retirement**	45
11.	**Change in family member's health**	44

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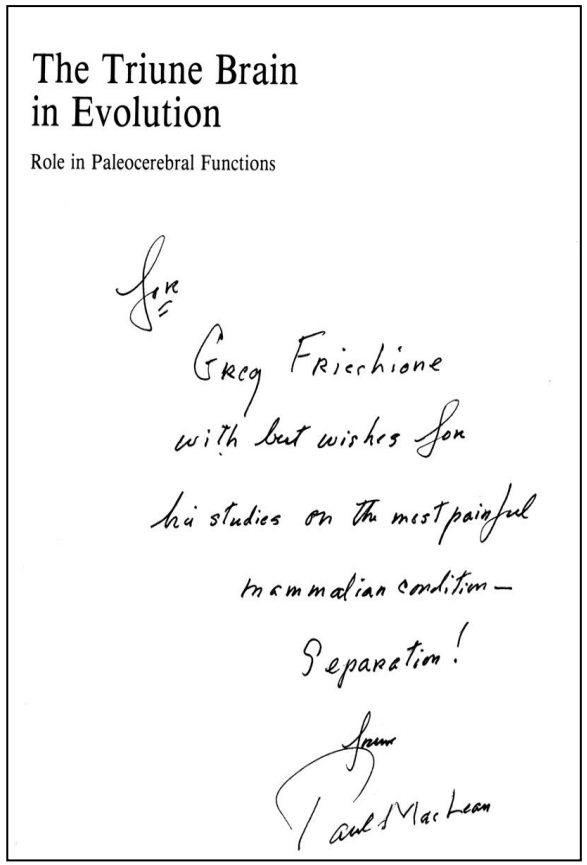
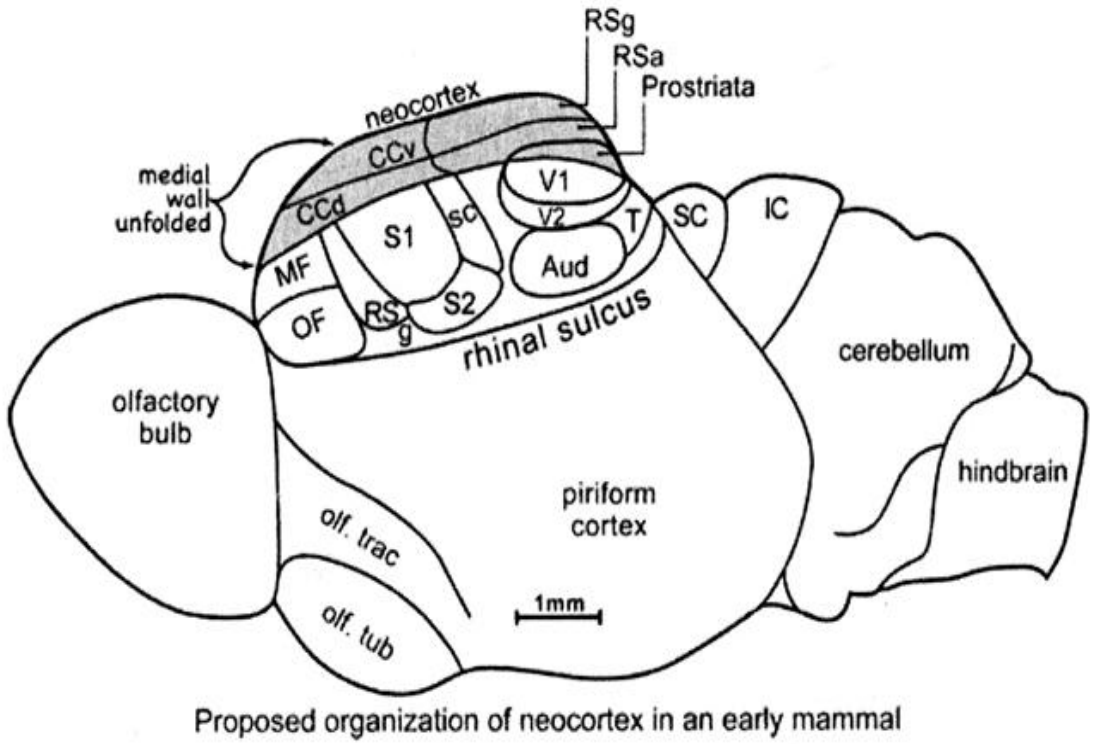


Our patients cannot escape their evolutionary heritage, which was best described by the great English psychiatrist **John Bowlby** who gave us modern attachment theory:

”Man's environment of evolutionary adaptiveness is always one of secure base attachment

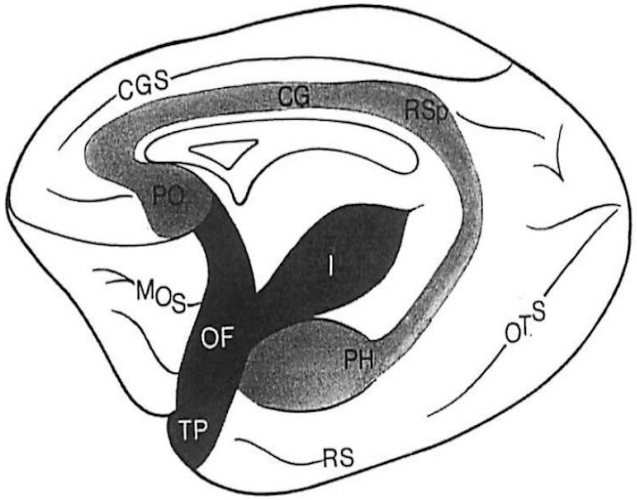
Early Mammal Brain---
Kass, 2014



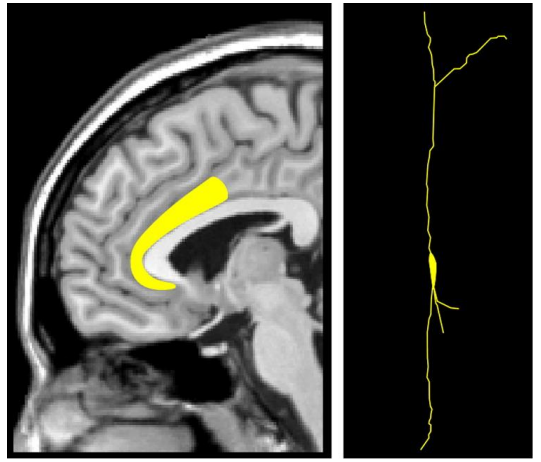
Proposed organization of neocortex in an early mammal

Figure 1. The proposed organization of the neocortex of an early mammal based on a cladistic analysis of the cortex of extant mammals and proportions of neocortex reflected in the endocasts of the skulls of early mammals. Neocortex was small relative to olfactory (piriform) cortex together with the olfactory bulb. Areas of neocortex included primary somatosensory area S1 flanked by rostral (RS) and caudal (CS) somatosensory fields and a second somatosensory area, S2. A taste or gustatory area (g) may have been present. Auditory cortex (Aud) included one (A1) or two primary areas and possibly secondary areas. Visual cortex included a primary area (V1), a secondary area (V2), a temporal visual field (T), and prostriata. Frontal cortex included orbital frontal (OF) and medial frontal (MF) areas but no motor cortex. Cortex of the medial wall of the cerebral hemisphere included granular (RSg)

The ACC and the Attachment Solution



- The Confluence of the 2 ancient brain moieties (Mesulam, 2000)—The "where" (hippocampocentric) and the "what" (olfactocentric) required to make response selections (ACC) to avoid or approach, separate or attach.
- The **Mammalian Behavioral Triad** (McLean): maternal nurturance, separation cry, and play (ACC)
- **Four attachments**: 1) Metabolic energy source- food, water, money (vertebrates) 2) Sexual Objects (vertebrates) 3) Parental and Social Objects (mammals and birds) 4) Future Objects (primates and cetaceans and elephants?)
- Kluver Bucy Syndrome
- Evolutionary stress and developmental stress both involve **separation challenges to these 4 attachments**;
- Emergent probability that natural selection rewards individuals and groups who have a variation that promotes an **attachment solution**.



The Neural Regulation of Pain

Eisenberger NI, Lieberman MD. **Why rejection hurts: a common neural alarm system for physical and social pain.**
Trends Cogn Sci. 2004 Jul;8(7):294-300

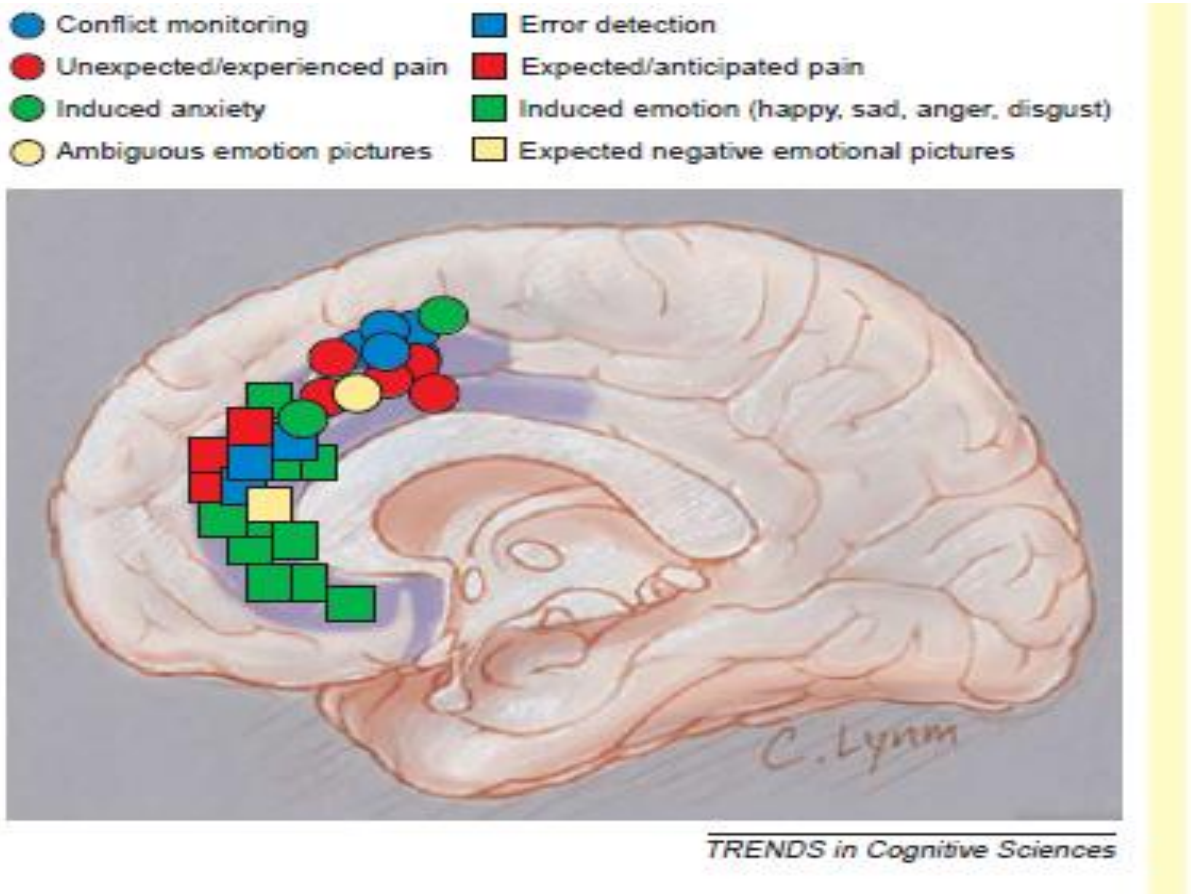
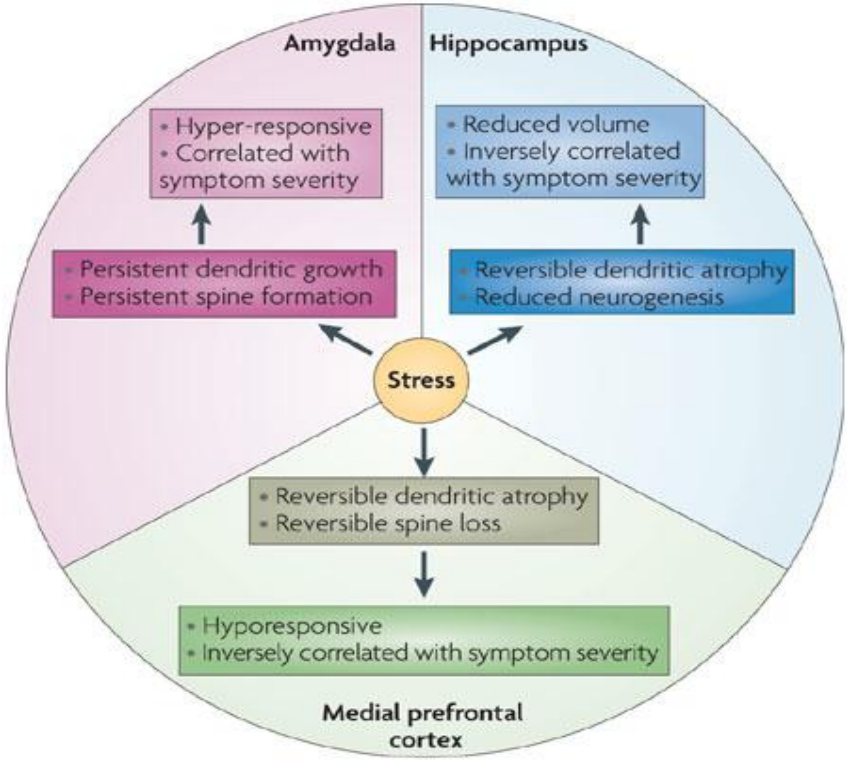


Figure I. A subsample of studies that activated rostral ACC (rACC) vs. dorsal ACC (dACC). Tasks involving conflict that contained a symbolic representation of conflict (denoted by squares) activated rostral-ventral ACC, whereas tasks involving conflict that did not contain a symbolic representation of conflict (circles) activated dACC.

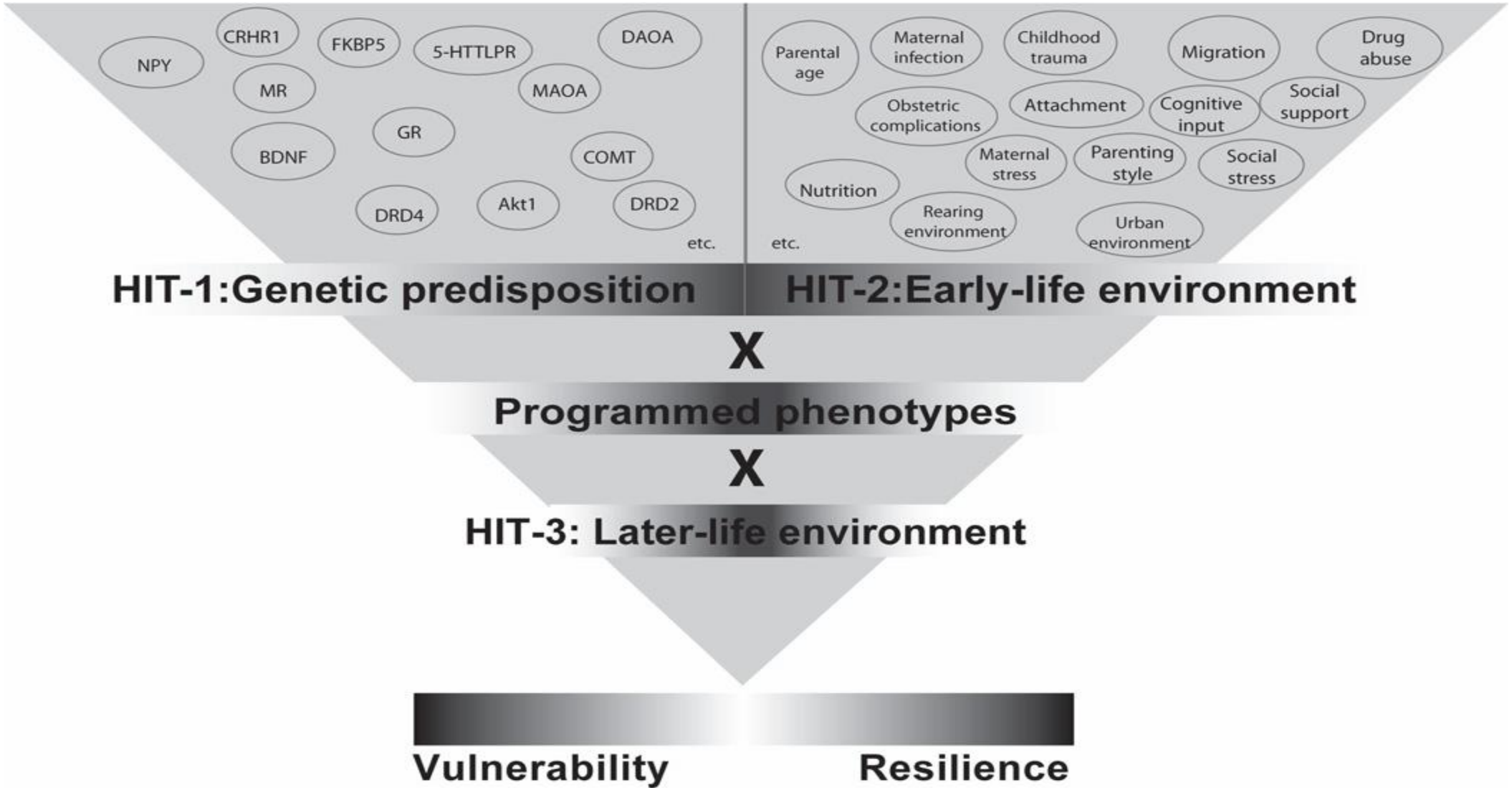
PTSD and The Brain

- **PTSD:** anxiety disorder after trauma. May relate to **increased amygdala attention to threat** cues. (El Khoury-Malhame, 2011)
- Extinction of fear **responses to threat cues is impaired in PTSD;** dysfunctional activation of fear extinction brain regions, i.e., **BLA, hippocampus, vmPFC, and dACC**. (Milad, 2009)
- **PTSD**: **structural and functional compromise of the ACC**, a/w impairment of ability to regulate the **amygdala**.
- **ACC** volume is smaller a/w combat-related **PTSD**, broadly consistent with ACC hypofunctionality. (Woodward 2006)
- Val158Met genotype moderates the effect of **PTSD**-related processes on right ACC volume. (Schulz-Heik, 2011)
- **PTSD** is associated with decreased activity in the **DLPFC**. (Reichert, 2006) (Cohen, 2004)
- **DLPFC** in post-mortem PTSD brains: 119 dysregulated genes, **highest C/W mitochondrial dysfunction;** oxidative phosphorylation and cell-survival/apoptosis and neurological diseases. (Su, 2008)
- **Roozendaal, McEwen & Chattarji.**
  ***Nature Reviews Neuroscience* 10, 423-433 (June 2009)**



The three-hit concept of vulnerability and resilience: towards understanding adaptation to early-life adversity outcome.

Daskalakis NP, Bagot RC, Parker KJ, Vinkers CH, de Kloet ER, *Psychoneuroendocrinology*. 2013;38(9):1858-1873.



Adverse Childhood Events and Toxic Stress

64% of 17,000 adults surveyed reported at least one ACE. 13% had 4 or more ACEs. (Felitti et al, 1998)
59% of 26,229 adults. 15% had 4 or more ACEs (CDC, 2010)
65-83% of 42,272 children in the Balkan Epidemiology Study of Child Abuse and Neglect had at least 1 ACE.

ACEs lead to:

1) Health Risk Behaviors;
2) CVD and CVA, Ca, Liver Disease, COPD, autoimmune diseases and metabolic syndrome;
3) Mental health problems including 4.5 x risk of MDD and 12.2-15.3 x risk of suicide;
4) Reduced well being, work problems, early death by 20 years, high health care utilization.

- **TABLE 1 Summary of CDC-Kaiser ACE Study Findings (Larkin, Sheilds and Anda, 2012)**

Outcomes associated with the ACE Score

Prevalent diseases: Ischemic heart disease, cancer, chronic lung disease, skeletal fractures, sexually transmitted diseases, liver disease

Risk factors for common diseases/poor health: Smoking, alcohol abuse, promiscuity, obesity, illicit drug use, injection drug use, multiple somatic symptoms, poor self-rated health, high perceived risk of AIDS

Mental health: Depressive disorders, anxiety, hallucinations, panic reactions, sleep disturbances, memory disturbances, poor anger control

Sexual and reproductive health: Early age at first intercourse, sexual dissatisfaction, teen pregnancy, unintended pregnancy, teen paternity, fetal death

General health and social problems: High perceived stress, headaches, impaired job performance, relationship problems, marriage to an alcoholic, risk of perpetrating or being a victim of domestic violence, premature mortality in family members

Problems from the longitudinal follow-up of the study cohort

Prescribed medications: Total prescriptions, prescribed multiple classes of drugs, psychotropics, bronchodilators

Diseases: Chronic obstructive pulmonary, autoimmune, lung cancer

Mortality: Premature mortality, lung cancer

- Note. A complete bibliography of ACE Study publications listed by topic area is available at http://www.cdc.gov/ace/.

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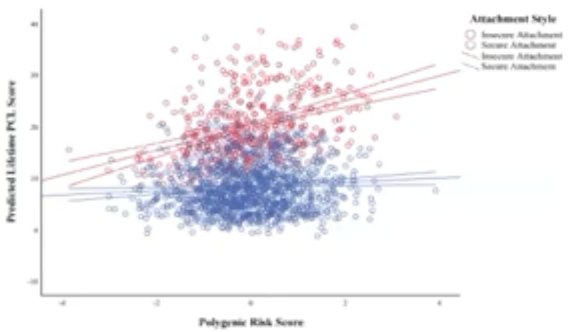
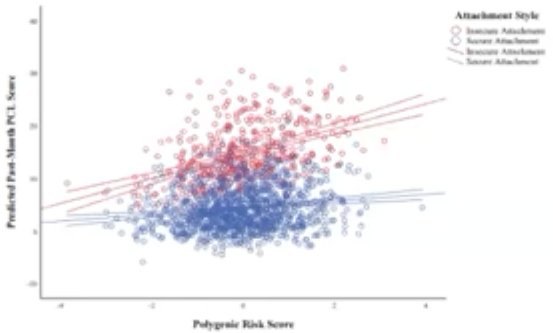
Attachment style moderates polygenic risk for PTSD in US military veterans

Lifetime PTSD



Current PTSD



Linear regression analysis of Re-experiencing PRS, Attachment style, and PTSD symptom Clusters

	Re-experiencing			Avoidance			Emotional Numbing			Hyperarousal		
	β	*t*	*p* Value	β	*t*	*p* Value	β	*t*	*p* Value	β	*t*	*p* Value
Lifetime												
PRS	.15	3.68	$2.45 \times 10^{-4*}$	.04	0.91	.36	.13	3.35	$8.23 \times 10^{-4*}$	.14	3.43	$6.22 \times 10^{-4*}$
Attachment style	−.21	9.23	$9.06 \times 10^{-20*}$	−.23	9.51	$6.79 \times 10^{-21*}$	−.34	15.26	$4.61 \times 10^{-49*}$	−.26	11.58	$8.37 \times 10^{-30*}$
PRS-by-attachment style	−.16	3.90	$9.90 \times 10^{-5*}$	−.02	0.38	.71	−.10	2.55	.01*	−.10	2.53	.01*
Past Month												
PRS	.06	1.28	.20	.12	1.91	.06	.15	2.33	.02*	.05	0.83	.41
Attachment style	−.20	6.17	$1.03 \times 10^{-9*}$	−.15	4.62	$4 \times 10^{-6*}$	−.27	8.39	$1.86 \times 10^{-16*}$	−.25	7.63	$3.95 \times 10^{-14*}$
PRS-by-attachment style	−.13	2.12	.03*	−.16	2.54	.01*	−.13	2.11	.03*	−.05	0.74	.46

β values represent standardized beta coefficients, with insecure attachment as the reference group.
PRS, polygenic risk score; PTSD, posttraumatic stress disorder.
*Significant after false discovery rate correction for multiple tests.

Mendelian Randomization analysis of the genetic mediation between attachment style and PTSD

Exposure	Outcome	GWS *p* Value Threshold Applied	IVW Estimate	Lower 95% CL	Upper 95% CL	Cochran's Q
PTSD Diagnosis	Attachment style	30	0.13	0.12	0.13	.05
		08	0.14	0.13	0.15	.83
		1×10^{-5}	0.20	−0.01	0.41	.47
		1×10^{-8}	0.54	−0.04	1.12	.58
PTSD Symptoms (PCL)	Attachment style	30	0.04	0.04	0.04	.03
		05	0.13	0.12	0.13	1
		1×10^{-5}	0.17	0.11	0.24	1
		1×10^{-8}	0.17	−0.02	0.35	1
Attachment Style	PTSD diagnosis	30	0.33	0.31	0.34	1
		05	0.34	0.31	0.37	1
		1×10^{-5}	0.60	0.20	1.01	.54
		1×10^{-8}	–	–	–	–
Attachment Style	PTSD symptoms (PCL)	30	0.27	0.27	0.28	1
		05	0.29	0.27	0.31	1
		1×10^{-5}	0.32	−0.17	0.81	.21
		1×10^{-8}	–	–	–	–

Although one-sample Mendelian randomization was performed using National Health and Resilience in Veterans Study data, genetic instruments were selected based on their association with large-scale genetic studies of re-experiencing (proxy for PTSD/PCL) and "been in a confiding adult relationship as an adult" (UK Biobank Field ID 20522, proxy for attachment styles).
CL, confidence limit; GWS, genome-wide significance; IVW, inverse-variance weighted; PCL, PTSD Checklist; PTSD, posttraumatic stress disorder.

- Attachment style moderated polygenic risk for PTSD.
- Higher re-experiencing PRS was associated with greater severity of PTSD symptoms. This was observed only in veterans with an insecure attachment style
- PRS-by-attachment style interaction was associated with greater severity of re-experiencing, numbing, hyperarousal, and avoidance PTSD symptoms.
- Bidirectional effects were observed between attachment style and diagnosis and severity of PTSD.

Tamman et al., *Biological Psychiatry*, 2021

Risk following Disasters and Traumas

- **Severity of Exposure**

The amount of exposure to the disaster c/w risk of future mental problems.

Both individual and community exposure play a role.

Those that directly experience the disaster, followed by those in close contact with victims, will experience more lasting impact than those who only had indirect experiences, such as news of the enormity of the devastation.

The current literature shows that injury and life threat are most predictive of likelihood of psychological impairment.

- **Gender and Family Variables**

Almost always, women or girls were affected more adversely than were men or boys.

The presence of children in the home increases the stressfulness of disaster recovery.

Marital stress has been found to increase after disasters.

- **Children**

Research on the reactions of children to natural disasters is limited, yet children generally exhibit more severe distress after disasters than do adults.

- **Individual Risk Factors**

Pre-disaster functioning, secondary stressors and psychological resources are important in determining resilience.

Factors such as bereavement, injury to self or another family member, life threat, panic or similar emotions during the disaster, horror, separation from family (especially among youth), extensive loss of property, and displacement have been found to predict adverse outcomes.

Risk following Disasters and Traumas

- **Higher Risk for Developing Countries**

Disasters occurring in developing countries cause more numerous and severe mental health consequences than do disasters in developed countries.

On average, natural disasters in developing countries had more severe effects than did incidents of mass violence in developed countries; usually human-caused disasters are more serious.

- **Reduced or Negative Social Support**

Social support both a risk and resilience factor.

Social support can **deteriorate** following disasters due to toxic stress and the need of individuals to get on with their own lives.

Negative social support (e.g., minimizing problems or needs, unrealistic expectations regarding recovery, playing down a person's pain) c/w long-term post-trauma distress.

Following mass trauma, previous **in group-out group divisions** (i.e., racial, religious, ethnic, social, and tribal), even those that may have been socially resolved, may again become apparent, as people try to gain access to much needed resources.

In families, conflicts may arise because differing exposure levels among family members sets up different courses of recovery that often are not well understood among family members, or family members may serve as distressing reminders to each other of the circumstances surrounding the disaster.

Neuropsychiatric Evaluation

- The Neurology of Trauma
- The Psychiatry of Trauma
- The Frontal Network Syndromes of Trauma:

  ---the irritable, disinhibited, poor emotion regulation version (TBI)

  ---the apathetic abulic akinetic version (TBI)

  --- the PTSD version

Complex Partial Seizures

Substance Use Disorder

Post-Acute Phase

- **4 to 8 weeks (between 1 and 2 months)** after the trauma or disaster.
- Patients have usually achieved basic security and physical and emotional safety and support
- Those with symptoms-anxiety, insomnia, nightmares and flashbacks, numbing and detachment, avoidance→ should have screening for PTSD

Post-Acute Phase

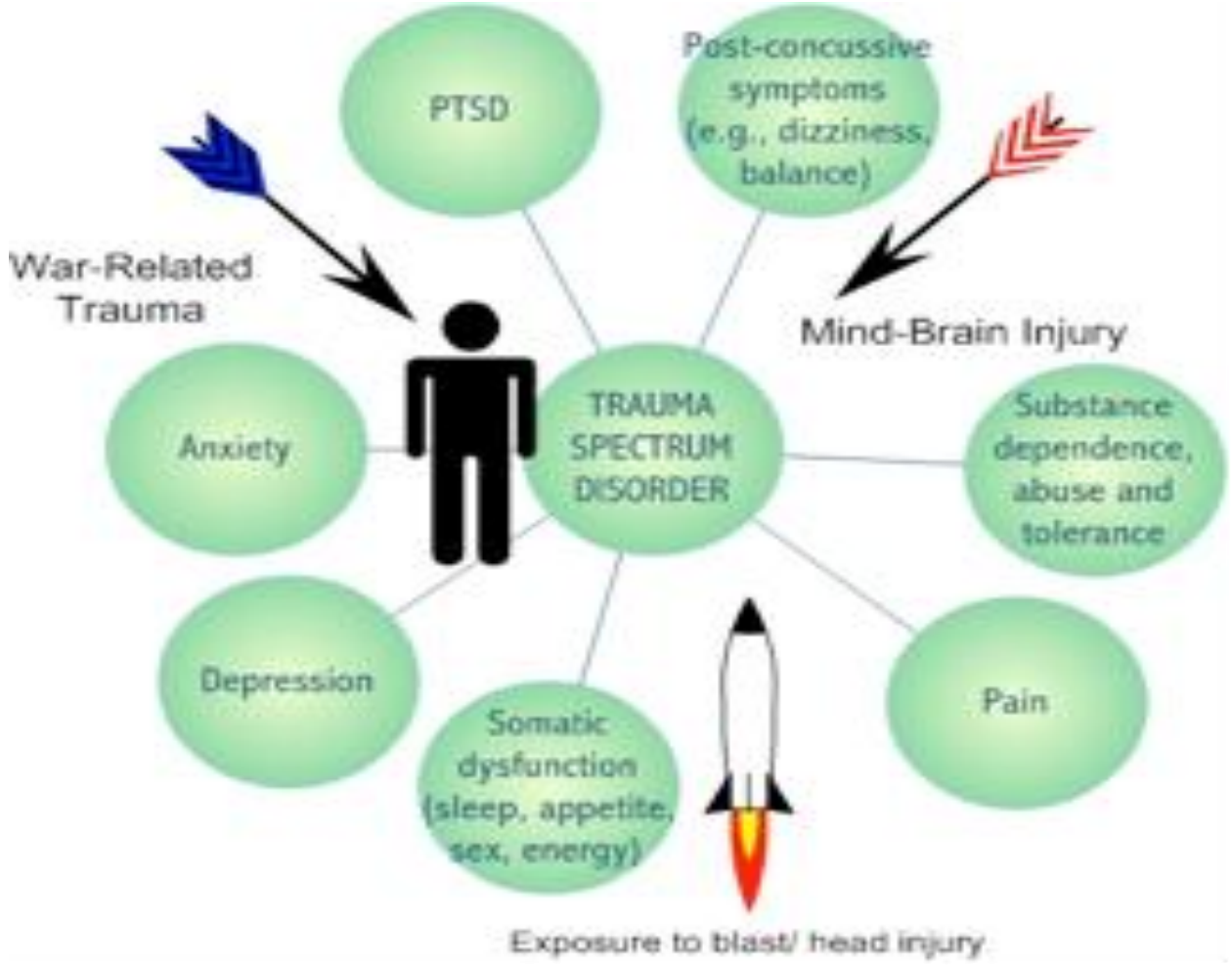
- R/O PTSD, depression, GAD, PD, substance abuse etc.
- Substance Abuse Relapse: trauma increases vulnerability.
- Detoxification availability
- Psychiatry evaluation
- Social Services
- 12 step programs
- Intensive outpatient management
- Importance of cueing
- **Consider medications:** SSRIs, anxiolytics, anti-hypertensives (prazosin, clonidine, guanfacine), AEDs
- Arrange and ensure f/u with psychiatry since patients will often have tendency to miss appointments and you won't hear about compliance or side effects of antidepressant trials

Post-Acute Phase

- Severe Mental Illnesses: those with schizophrenia and severe BPI are among the most vulnerable in the setting of disaster.
- Disconnection from treatment supports and risk of loss of med management; lose meds, forget to refill, stop meds to be more alert.
- Schizophrenia: increase in paranoia and disorganization and agitation and aggressiveness.
- BPAD: irritability, elation, hyper-activation, sleeplessness, agitation, pressured speech, poor judgment, grandiosity.
- Geriatric: need to sensitize relief and health workers about older people's health needs post disaster; development of relevant clinical guidelines for chronic disease management post-disaster in developing countries and the advocacy of building in geriatric related components in disaster medical relief programs. **Chan 2009: Am J Disaster Med**

The Trauma Spectrum

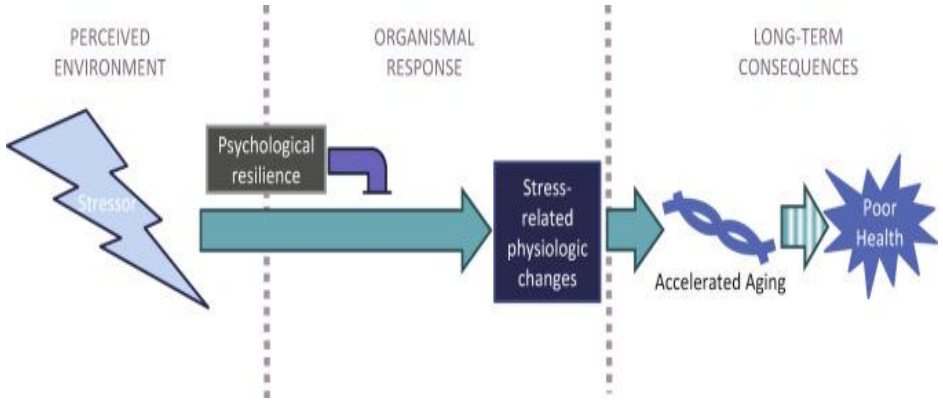
BHI/Samueli Institute Project



Psychological and biological resilience modulates the effects of stress on epigenetic aging

Harvanek et al, 2021

- Hypothesis: stress a/w accelerated biological aging, measured via GrimAge Acceleration (GAA); relationship mediated by stress-related physiologic changes such as insulin resistance and HPA signaling and that strong psychological resilience factors are protective against the negative consequences of stress on aging.
- Relationships predictive, not causal, as study was cross-sectional and thus directionality of relationships cannot be conclusively examined.
- Assessed impact of cumulative stress (CAI), stress physiology, and resilience (Difficulties with Emotion Regulation Scale (DERS) and Self-Control Survey-Brief (SCS-B) on accelerated aging in a community sample (*N* = 444).
- Cumulative stress was associated with accelerated GrimAge (*P* = 0.0388) and stress-related physiologic measures of adrenal sensitivity (Cortisol/ACTH ratio) and insulin resistance (HOMA).
- After controlling for demographic and behavioral factors, HOMA correlated with accelerated GrimAge (*P* = 0.0186). Remarkably, psychological resilience factors of emotion regulation and self-control moderated these relationships.



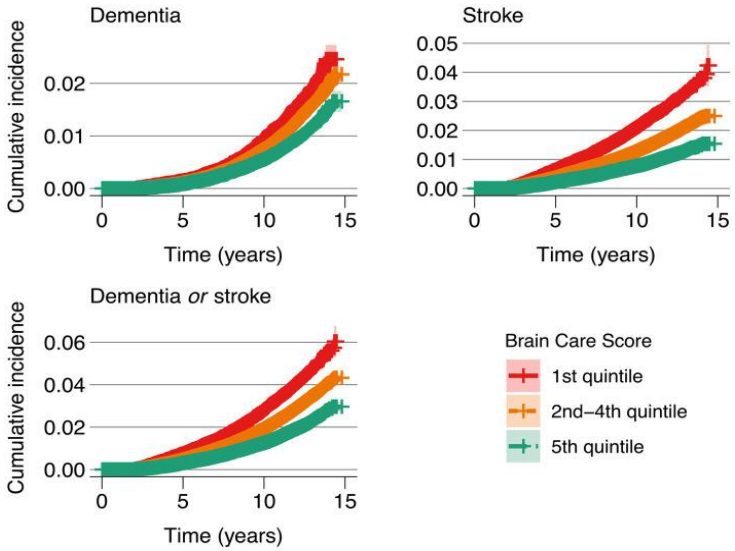
Stress and the Metabolic Syndrome- Precursor to NCDs

(McGill A-T. Arch Public Health. 2014)

- **Chronic stress, early trauma, hypercortisolemia and immune dysfunction** contribute to the development of **metabolic syndrome** disorders
- **Impaired glucose and lipid metabolism, oxidative stress**, disrupted neurohormonal regulation and compromised intracellular Ca++ handling are pathogenic factors
- **Inefficient oxidation of energy forces central and non-adipose cells to store excess toxic lipid leading to obesity and metabolic syndrome.**
- **Oxidative stress** and **metabolic inflammation**, or **immunoactivation** **(Margolies, 2015)**, allow susceptibility to infectious, degenerative atherosclerotic cardiovascular, autoimmune, neurodegenerative and dysplastic diseases.

The Predictive Validity of a Brain Care Score for Dementia and Stroke: Data from the UK Biobank Cohort (Singh et al, 2023)

- The BCS (median: 12) was derived for 398,990 UKB participants (mean age: 57; females: 54%). There were 5,354 incident cases of dementia and 7,259 incident cases of stroke recorded during a median follow-up of 12.5 years. A five-point higher BCS at baseline was associated with a **59%** (95%CI: 40-72%) lower risk of dementia among participants aged **<50.** Among those aged **50–59,** the figure was **32%** (95%CI: 20-42%) and **8%** (95%CI: 2-14%) for those aged **>59 years**. A five-point higher BCS was associated with a **48%** (95%CI: 39-56%) lower risk of stroke among participants aged **<50, 52%** (95%CI, 47-56%) among those aged **50–59,** and **33%** (95%CI, 29-37%) among those aged **>59.**
- Cumulative incidence of dementia, stroke, and dementia *or* stroke at baseline, stratified by Brain Care Score quintile group Legend. The red line corresponds to the cumulative incidence of the low-scoring BCS group (1st quintile: total BCS scores from 1 to 9), the orange line corresponds to the middle three BCS quintiles (total BCS scores from 10 to 13), and the green line corresponds to the high-scoring BCS group (5th quantile, total BCS scores from 14 to 19).



McCANCE Brain Care Score™

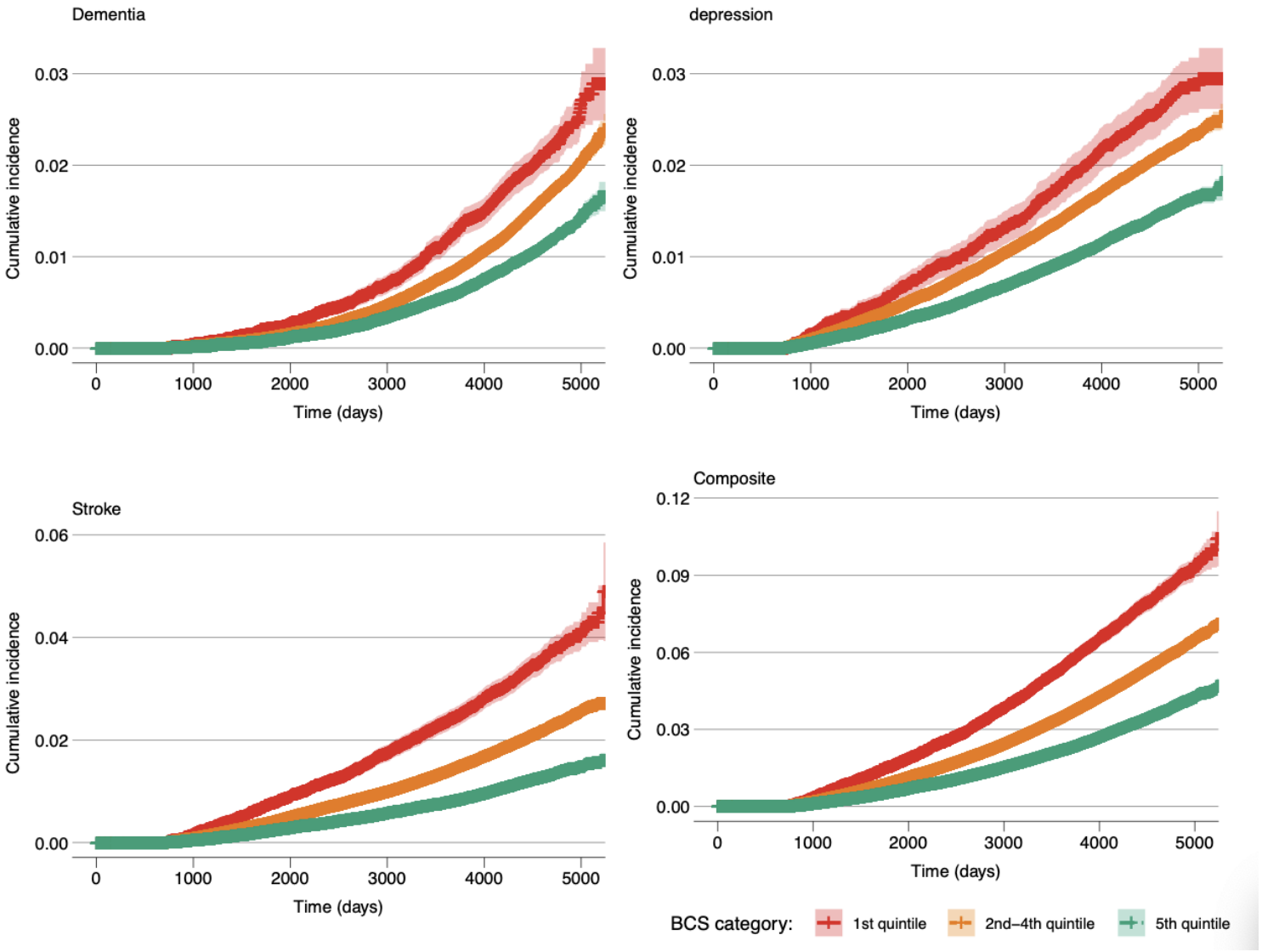
MASSACHUSETTS GENERAL HOSPITAL
McCANCE CENTER FOR BRAIN HEALTH

Category		Criteria / Description	Rank	Score
Physical	Blood Pressure	Resting blood pressure greater than 140/90, with or without treatment	0	
		Resting blood pressure 120-139/80-89, with or without treatment	2	
		Resting blood pressure less than 120/80	3	
	Blood Sugar	Hemoglobin A1c greater than 6.4	0	
		Hemoglobin A1c between 5.7 and 6.4	1	
		Hemoglobin A1c less than 5.7	2	
	Cholesterol	190 or higher	0	
		No treatment required or less than 190 mg/dL	1	
		If cardiovascular disease is present, LDL is in accordance to the latest CDC recommendations	1	
	BMI	Lower than 18.5 kg/m²	1	
		18.5-25 kg/m²	2	
		25-29.9 kg/m²	1	
		Greater than 30 kg/m²	0	
Lifestyle	Nutrition	**Dietary habits:** • 4.5 servings of fruit and vegetables per day; • 2 servings of lean protein per day • 3 or more servings of whole grains per day • Less than 1,500 mg of sodium per day • Less than 36 oz of sugar sweet beverages (soda, juice, etc.) per week		
		Typical weekly diet does not include at least 2 of the recommendations above	0	
		Typical weekly diet includes 2 or more of the recommendations above	1	
		Typical weekly diet includes 3 or more of the recommendations above	2	
	Alcohol	4 or more alcoholic drinks per week	0	
		2-3 alcoholic drinks per week	1	
		0-1 alcoholic drink per week	2	
	Smoking	Current smoker	0	
		Never smoked or quit more than a year ago	3	
	Aerobic Activities	Less than 150 minutes of moderate or 75 minutes of high intensity physical activity per week	0	
		At least 150 minutes of moderate physical activity (ex. walking) or 75 minutes of high intensity physical activity per week	1	
	Sleep	Untreated sleep disorder and/or sleeps <7hrs per night	0	
		Treated sleep disturbances and 7-8 hours of routine sleep per night	1	
Social Emotional	Stress	High level of stress that often makes it difficult to function	0	
		Moderate level of stress that occasionally makes it difficult to function	1	
		Manageable level of stress that rarely makes it difficult to function	2	
	Social Relationships	I have few or no close connections other than my spouse or children	0	
		I have at least two people, other than my spouse or children, that I feel close with and could talk about private matters or call upon for help	1	
	Meaning in Life	I often struggle to find value or purpose in my life	0	
		I generally feel that my life has meaning and/or purpose	1	

The components above reflect the latest, scientific based key contributors to brain health. It is important to discuss your score with a healthcare professional.

Total Brain Care Score (0-21)

McCance Brain Care Score™ 2020. © The General Hospital Corporation. All rights reserved.



UKB Studies:

Higher BCS and lower risk of Dementia, Stroke and Late-Life Depression (Singh, Rosand et al)

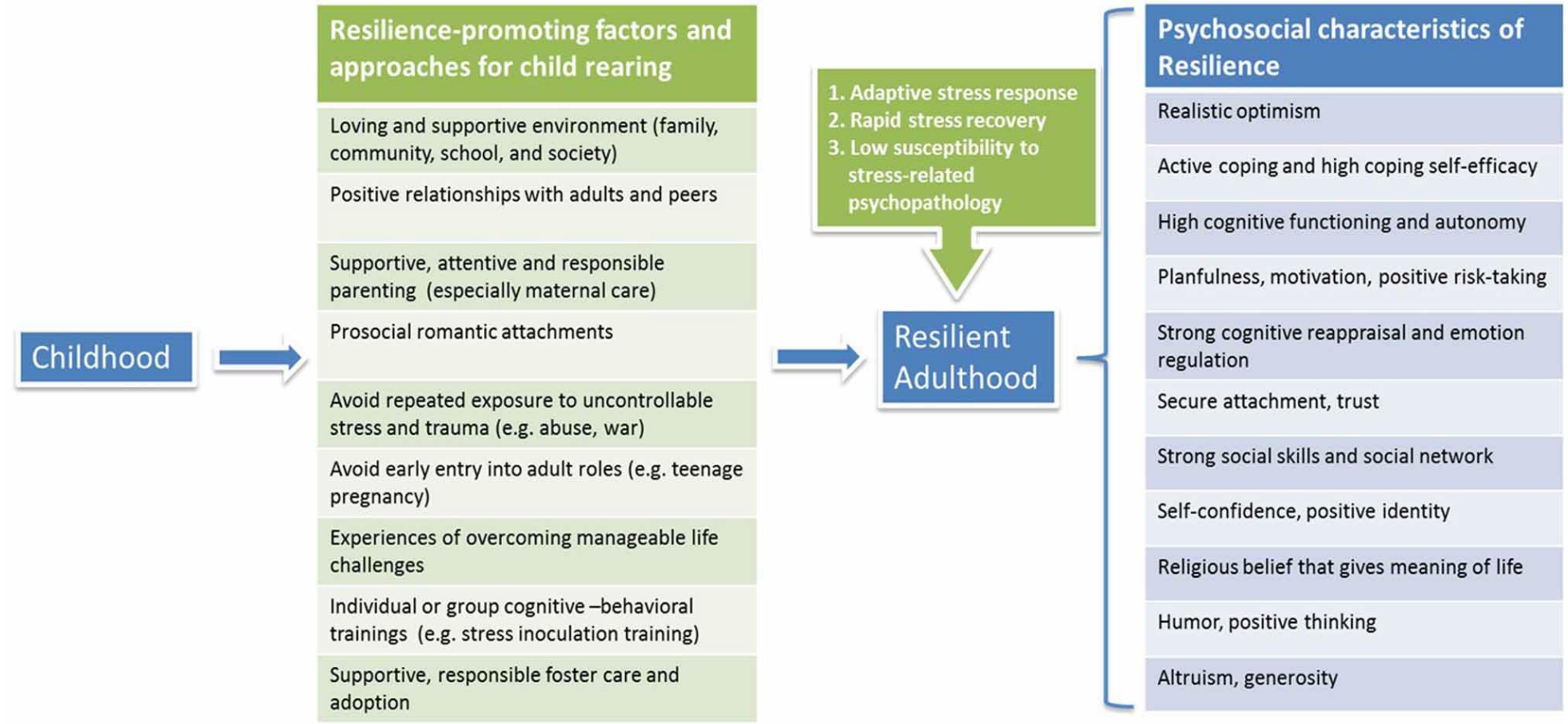
- **What Can Be Done?**

The Relation to Resilience

Understanding Resilience

(Southwick/Charney)

(Wu et al, Frontiers in Behavioral Neuroscience, 2011; 7:1-15)
(Wu et al, 2013)



Human Resilience

Mind Body Medicine Equation

Stress (separation threats) X ACEs

---------- = Allostatic =

Resiliency (attachment solutions)

- experiencing/ mastering hormetic stress
- relaxation response
- mindfulness
- social support/pro-sociality
- cognitive skills
- positive psychology
- spiritual connectedness
- exercise/mindful exercise
- nutrition/low glycemic diet
- sleep hygiene
- healthy habits

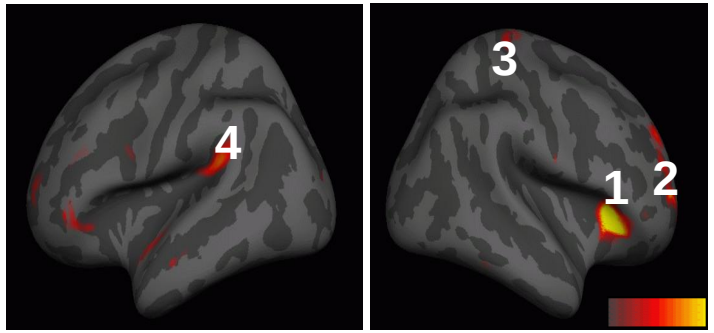
Load

Vulnerability to Illness

Relaxation Response

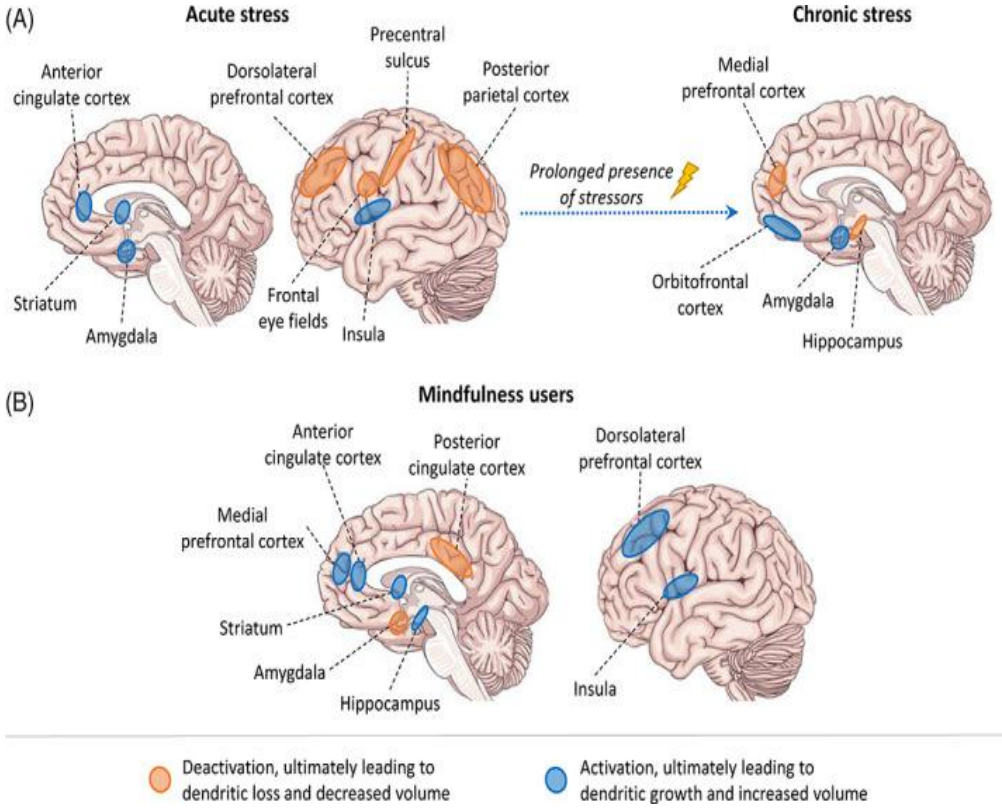
(Benson, 1975)

- Self induced stimulus
- **Break train of everyday thought**
- Integrated physiological mechanisms are entrained when a subject engages in a **repetitive mental or physical activity** and passively ignores distracting thoughts.
- Vehicles: meditation including MBSR, prayer, yoga, Tai Chi/Qigong, autogenic training
- Physiological changes: ↓O2 consumption, ↓HR, ↓arterial BP, ↓Resp rate c/w
- ↓metabolic demands. ↑HRV and parasympathetic tone.
- Reduces cellular stress by increasing mitochondrial oxidative phosphorylation pathway gene activation and by reducing **NF-kB pathway gene activation**
- Cortical regions thicker in meditators than in controls: (1) insula, (2) Brodmann area 9/10, (3) somatosensory cortex, (4) auditory cortex. Lazar S et al. *Neuroreport*. 2005;16:1893.



Mindfulness

- Non-judgmental attention to experiences in the present moment to achieve self-awareness and transcendence in everyday life (Kabat-Zinn, 1994) (Vago and Silbersweig, 2012)
- Start with **Focused Attention** (empty mind of everyday thinking to decrease mental proliferation and focus on a single point, e.g, breath, word, phrase, prayer) to elicit **relaxation response**.
- Move to **Insight/Open Monitoring** (no object of focus but receptive in nonjudgmental way to all physical and mental phenomena that arise).
- Can then add **ethical value qualities** (loving-kindness, compassion, self-compassion, forgiveness) OR can do **visual imagery** and add hypnotic suggestion for analgesia for example.
- Mindfulness practices (MBSR, MBCT, MBRP, ACT, DBT) are thought to enhance attention and emotion regulation; stress, burnout, chronic pain, SUDS, anxiety, depression, personality d/o (Guendelman et al, 2017)
- van der Heide A, Meinders MJ, Speckens AEM, Peerbolte TF, Bloem BR, Helmich RC. Stress and Mindfulness in Parkinson's Disease: Clinical Effects and Potential Underlying Mechanisms. *Mov Disord*. 2021;36(1):64-70



Meditation and Attachment

- Meditation and realization of impermanence of all “thing-like” objects including self; a “release from mental fixations,” or non-attachment (*Sanskrit: virāga*) (Sahdra et al., 2010**)**
- **But meditation creates a state of relaxation commensurate with somatic markers reminiscent of the physiological profile that signifies secure attachment.** (Fricchione, 2011) Relaxed meditative state→ feeling of connection in the present reminiscent of mother-child attunement. [Psilocybin studies pending]
- PNS predominance: lower HR and BP, decreased GSR, increased belly respiratory amplitude, decreased chest respiratory rate and increased high-frequency HRV and RSA. (Tang et al, 2009) (Craigmyle, 2013)
- Increasing shifts in respiratory modulation of heart rate or RSA, reflect higher levels of experience. (Peressutti et al, 2010)
- Children with a history of neglect and those with disordered, insecure attachment showed greater sympathetic reactivity and less vagal regulation as reflected in RSA decreases on separation and increases on reattachment than did children with ordered, secure attachment. (Oosterman et al, 2010)
- In the **attunement-misattunement-reattunement** process, mothers show significant vagal withdrawal during the separation challenge in the Strange Situation test while the infants, particularly those with insecure attachment styles also showed vagal withdrawal.
- Mothers and infants, especially those with insecure attachment, showed elevated salivary alpha-amylase suggesting increased allostatic loading during the separations. (Hill-Soderlund et al, 2008)

Compassion Training and Health Care and Wartime Trauma

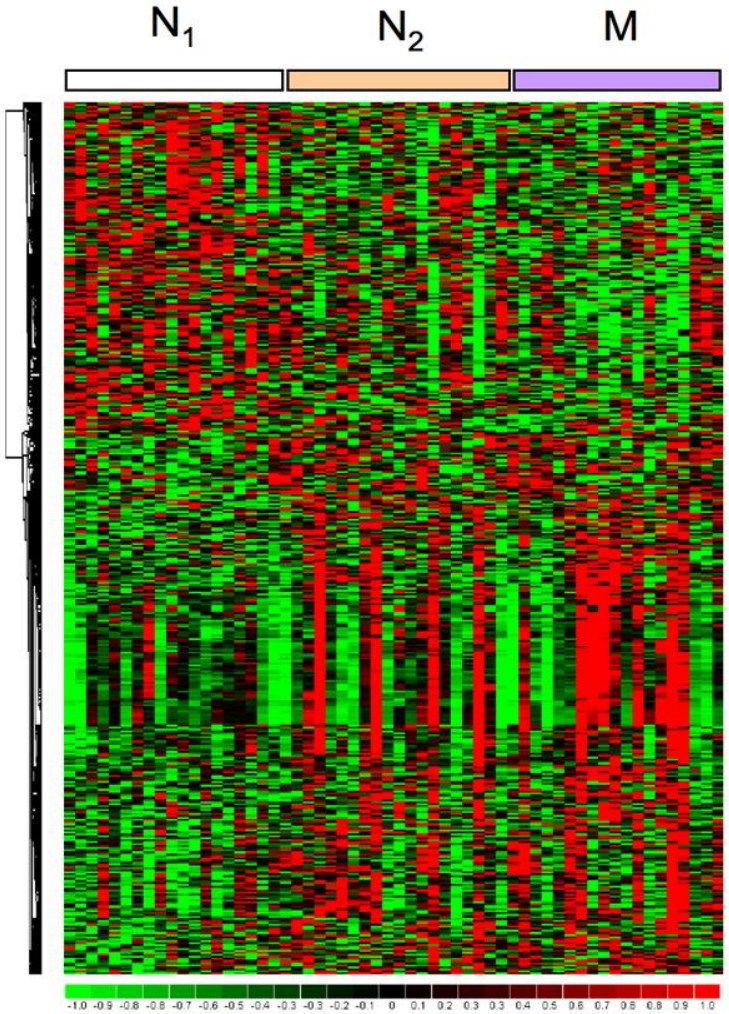
Weng HY, Lapate RC, Stodola DE, Rogers GM, Davidson RJ. Visual Attention to Suffering After Compassion Training Is Associated With Decreased Amygdala Responses. *Frontiers in Psychology*. 2018;9:771

- Meditation may improve affective responding through **reduced amygdala reactivity**; heightened amygdala-vmPFC connectivity during affective stimuli may reflect a potential mindfulness effect on emotion regulation ability. (Kral et al, *Neuroimage*, 2018)
- Preliminary findings (small sample size): engaging in **compassion as an emotion regulation strategy towards suffering** resulted in increases in visual attention to images depicting suffering compared to non-suffering.
- **Compassion may be useful in pro-social situations where attention needs to turn toward suffering, such as when a doctor aids a patient.**
- fMRI study of physician diagnostic salience suggests that R frontoparietal attention network is engaged as neural substrate for awareness of self-generated diagnostic responses. Perhaps meditation in general and compassion meditation in particular affects the functional status of the physician brain and its behavioral outputs. (Melo et al, *Scientific Reports*, 2018)

Benson-Henry Institute
Stress Management And Resilience Training

- **Session 1: The SMART Program**
  Session 2: The RR-
  Relaxation Response
  Session 3: Mindful Awareness & Acceptance-
  Mindfulness
  Session 4: Components of Stress and Resilience-
  Separation Stress; Social Connection and Pro-social Behavior
  Session 5: Automatic Thoughts-
  Cognitive Skills
  Session 6: Building a Positive Perspective-
  Positive Psychology and Acceptance
  Session 7: Healing States of Mind-
  Belief and Conscious Positive Expectation-Spiritual Connection
  Session 8: Staying Resilient:-
  Exercise and Nutrition and Sleep Hygiene and Humor

Mind-Body Practice Regulates How Key Genes Are Turned On and Off



- In PBMCs:
- Enhanced expression of genes associated with
  - energy metabolism and mitochondrial function
  - insulin secretion
  - telomere maintenance
- Reduced expression of genes linked to the ***Conserved Transcriptional Response to Adversity:*** ***increase NF-kB/decrease Type I IFN***
  - innate inflammatory response: decrease in NF-kB pathway
  - stress-related pathways
- Potential mechanisms for positive health effects

Bhasin MK et al. 2013. PLoS ONE 8:e62817

Refugee Resilience

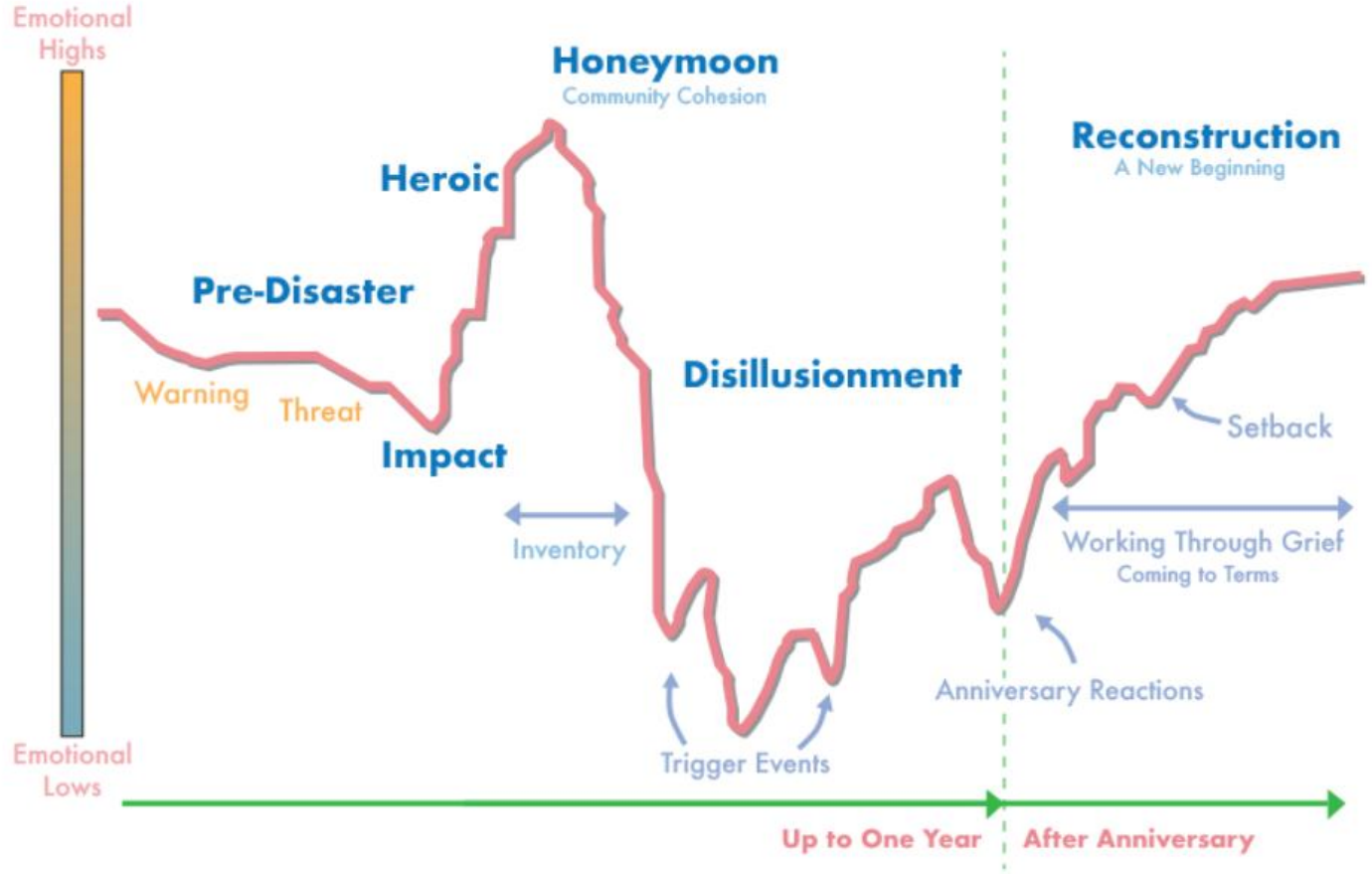
Definition of a Refugee

(Stoddard, Ursano and Cozza, 2018)

- *One who owing to well founded fear of being persecuted for reasons of race, religion, nationality, membership in a particular social group or political opinion, is outside the country of his nationality, and is unable or, owing to such fear, is unwilling to avail himself of the protection of that country*…. UNHCR
- Scale of trauma to displaced persons and refugees from natural and manmade disasters and war is frequently overwhelming and hard to understand.
- In the coming years with the pandemic, climate change related disasters and the fracturing of global cooperation leading to conflicts, there will likely be more refugees with traumatic stress complicated by nationalistic hostility on the part of destination countries.

Phases of Emotional Response to Disasters

(Myers and Zunin, 2000)



Using Information About Biology and Trauma

Educate your patients:

- Frame reexperiencing the event(s), hyperarousal, sleep disturbances, and other physical **symptoms as physiological reactions to extreme stress.**
- Communicate that **treatment and other wellness activities can improve both psychological and physiological symptoms** (e.g., therapy, meditation, exercise, yoga). You may need to refer certain clients to a psychiatrist who can evaluate them and, if warranted, prescribe psycho-tropic medication to address severe symptoms.
- Discuss traumatic stress symptoms and their physiological components.
- Explain links between traumatic stress symptoms and substance use disorders, if appropriate.
- **Normalize trauma symptoms.** For example, explain to clients that their symptoms are not a sign of weakness, a character flaw, being damaged, or going crazy.
- Support your patients/clients by helping them frame their ***TRAUMA STORY*** and provide a message of hope—that they are not alone, they are not at fault, they have come through heroically and recovery is possible and anticipated.

Susceptibility and Resilience

- The susceptibility and resilience of populations to trauma and stress is quite variable.
- **Major determinants: preparedness, SES, h/o previous trauma.**
- Proximity to another recent disaster or trauma.
- **At risk populations: children, women, disadvantaged, minorities, SMI**
- Children affected greatly by media representations
- **Majority will show normal responses following disaster**: varying responses to loss, distress, ASR, acute grief, resilient and altruistic behavior and post traumatic growth…
- Psychopathology after disasters: ASD, Panic, Depressive reaction, substance abuse, suicidality, relapse of prior SMI and exacerbation of personality disorders.
- Post-acute disorders and syndromes: depression, PTSD, persistent complex bereavement, panic disorder, SUD, pain and suffering
- **Resilience** and **Post traumatic growth** with new skills and competencies and wisdom.

Resilience Factors

- **Human resilience:** a large number naturally recover from disasters over time and move on, without experiencing debilitating mental health issues.
- **Resilience Factors** following disasters.

1. Social Support: key ingredient to post-disaster recovery.

-Facilitates well-being and limits psychological distress following mass trauma.

-Social connectedness increases knowledge essential to disaster recovery

-Provides opportunities for social support activities, including practical problem-solving, emotional understanding and acceptance, sharing of traumatic experiences, normalization of reactions and experiences, and mutual instruction about coping.

2. Coping Self-Efficacy

-Predictive of psychological outcomes.

-When individuals feel optimistic, they tend to do better following a disaster. It is not so much general self-efficacy, but the specific sense that one can cope with trauma-related events that has been found to be beneficial to recovery from disasters.

3. Hope

Favorable outcomes more likely after experiencing disasters or mass trauma in those who maintain one or more of the following characteristics:

- Optimism (because they can retain hope for their future)
- Positive expectancy
- A feeling of confidence that life and self are predictable
- Belief that there is a high probability that things will work out as well as can reasonably be expected
- Belief that outside sources act benevolently on one's behalf (i.e., responsive government)
- Belief in God
- Positive superstitious belief (e.g., "I'm always lucky, things usually work out for me")
- Practical provisions, including housing, employment, financial resources

Field Approaches

(Galea, 2003)

- Survivors' reactions should not necessarily be regarded as pathological or even as precursors of subsequent disorder.
- Many transient stress reactions in the aftermath of mass violence, and such reactions may occur, occasionally, even years later.
- Rather than traditional diagnosis and treatment, most survivors are likely to need support and resources to ease the transition to normalcy.
- Some have great distress and require screening and, at times, clinical intervention.
- Programs should not focus narrowly on any one aspect of behavioral health. Interventions should seek to address multitude of effects of disasters, foster protective mediating factors, and reduce vulnerability factors. (**The Stress/ Resilience Mind Body Medicine Equation**).
- ***Norris, Friedman, and Watson (2002)*** recommend:
- **Integrate primary and psychiatric care.**
- **Support natural groups and maintenance of routine social activities.**
- **Give indigenous networks resources to foster helping each other.**

Social Separation Challenges and Attachment Solutions

- **Social Support for:** Isolation, marital and family discord, social conflict, job strain, unemployment, physical morbidity, retirement, social inequalities, including race and pathological bias.
- Trauma Story (Mollica) and the hero
- Trauma-informed care (SAMHSA):
- **Trauma-informed approach** reflects adherence to **six key principles:**

--Safety

--Trustworthiness and Transparency

--Peer support

--Collaboration and mutuality

--Empowerment, voice and choice

--Cultural, Historical, and Gender Issues

Trauma Informed Care

Trauma-specific intervention programs generally recognize the following:

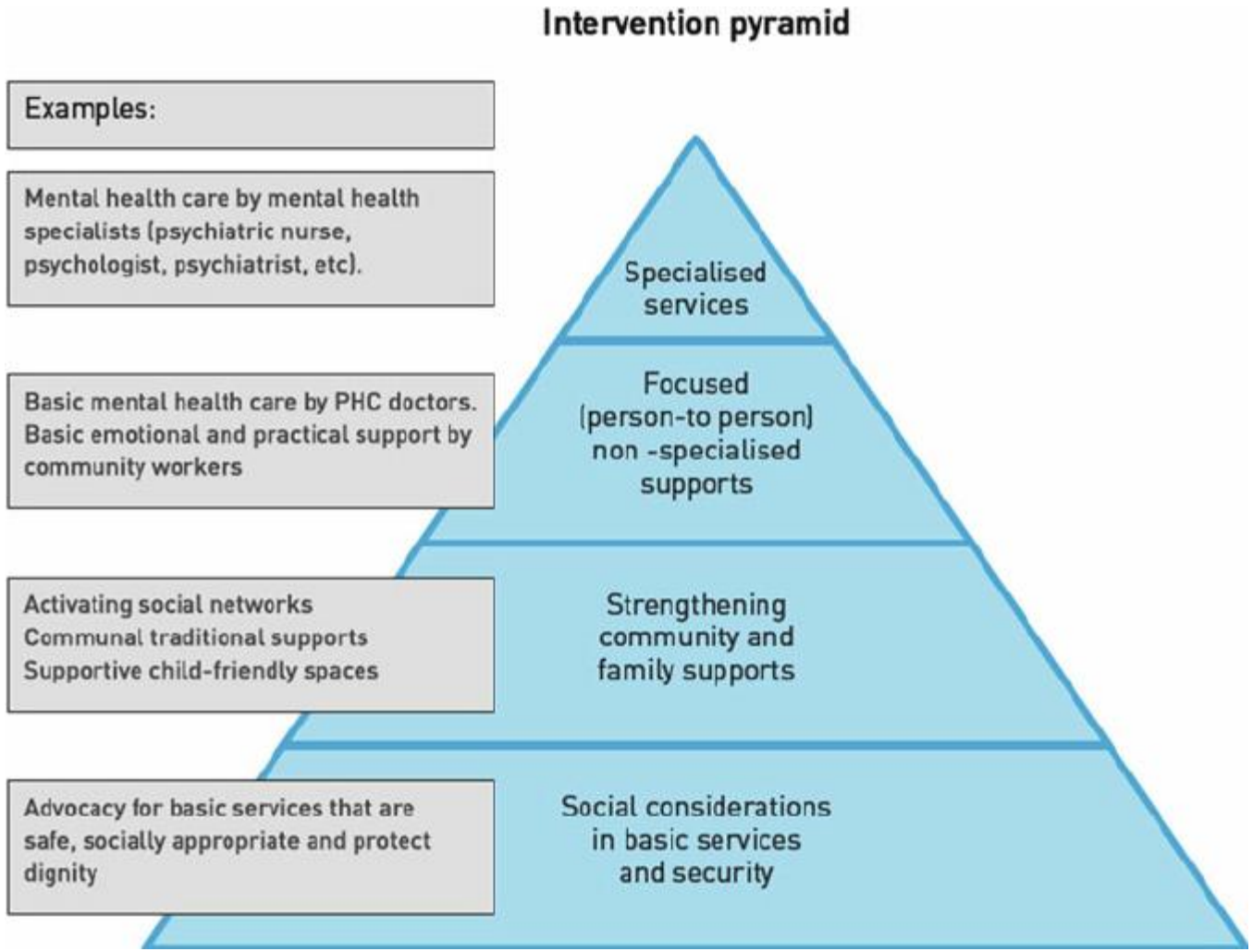
- Survivor's need to be respected, informed, connected, and hopeful regarding their own recovery
- Interrelation between trauma and symptoms of trauma such as substance abuse, eating disorders, depression, and anxiety
- Need to work in a collaboration with survivors, family and friends of the survivor, and other human services agencies in a manner that will empower survivors and consumers

Examples:

- **Risking Connection®** emphasizes concepts of empowerment, connection, and collaboration. The model addresses issues like understanding how trauma hurts, using the relationship and connection as a treatment tool, keeping a trauma framework when responding to crises such as self-injury and suicidal depression, working with dissociation and self-awareness, and transforming vicarious traumatization.
- **Seeking Safety** is designed to be a therapy for trauma, post-traumatic stress disorder (PTSD), and substance abuse. Key principles are safety as the overarching goal, integrated treatment, a focus on ideals to counteract the loss of ideals in both PTSD and substance abuse, knowledge of four content areas (cognitive, behavioral, interpersonal, and case management), and attention to clinical processes.

Intervention Pyramid for Mental Health and Psychosocial Support in Humanitarian Emergencies

(IASC Reference Group, 2016)



HPRT Approach: The H5 Model of Refugee Trauma and Recovery

(Mollica)

Figure 1: The Five Overlapping Dimensions and Core Elements of the H[5] Model

Harvard Program in Refugee Trauma 12-Point Toolkit for Self-Care and the Healing Process

Harvard Program in Refugee Trauma

Cambridge, MA

affiliations:

Harvard Medical School

Massachusetts General Hospital

© 2003 Harvard Program in Refugee Trauma

What You Can Do

1. Take care of your family, friends, and loved ones first
2. Know your personal and organizational mission statement
3. Achieve clinical and cultural excellence
4. Engage in peer supervision and consultation
5. Monitor and Regulate empathy
6. Practice reflection: Spiritual and artistic
7. Utilize deep breathing, mindfulness, and meditation
8. Conduct daily, personal self-care activities; taking care of body and mind
9. Create beautiful, natural healing environments
10. Evaluate self-care goals
11. Transform the institutional “apparatus” to a caring one
12. Restore human dignity

© 2003 Harvard Program in Refugee Trauma

Summary

Resilient Responses to Trauma (Attachment Solutions)

Many people find healthy ways to cope with, respond to, and heal from trauma. Often, people automatically reevaluate their values and redefine what is important after a trauma. Such resilient responses include:

- **Increased bonding with family and community and pets—social support.**
- **Redefined or increased sense of purpose and meaning.**
- **Increased commitment to one's values and a personal mission.**
- **Revised priorities.**
- **Increased pro-social charitable giving and volunteerism.**
- **Integrate stress management and resilience training including DBT if necessary.**

Evolutionary Resilience

Resilience/Attachment Solutions

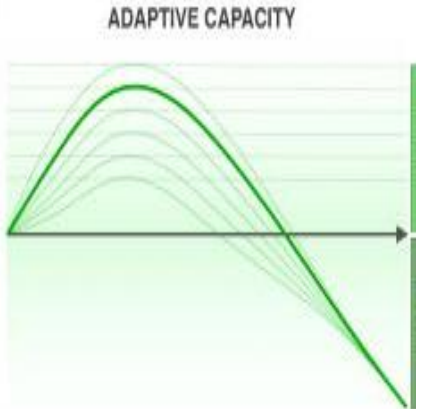
---------- = Propensity to Health

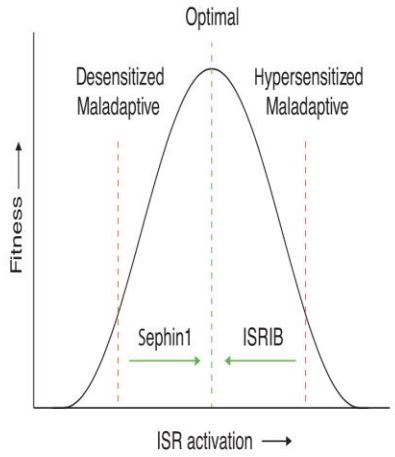
Stress/Separation Threats

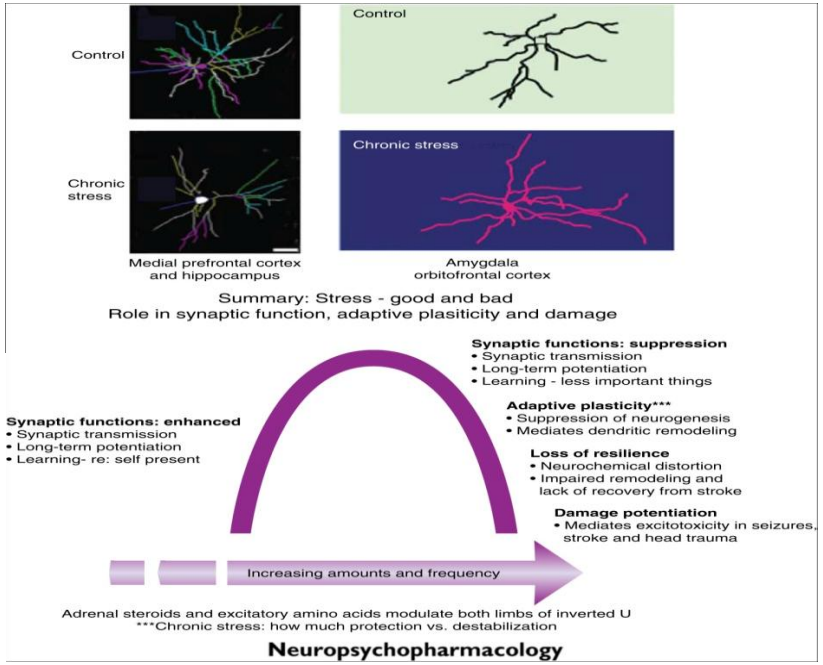
The Mammalian Behavioral Triad: separation cry, maternal nurturance and play. (MacLean, 1990)

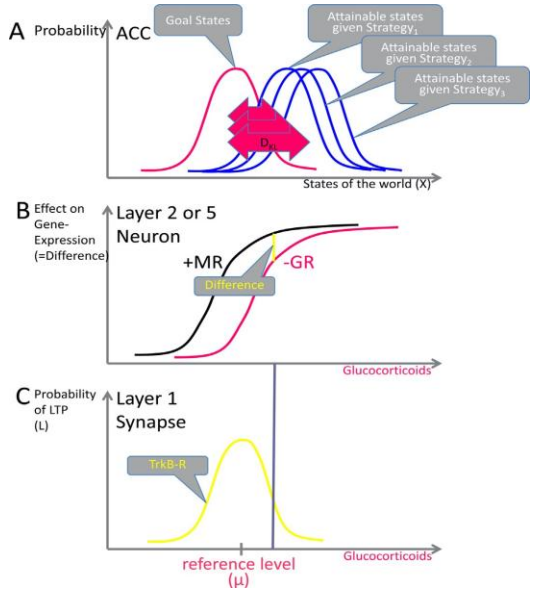
The Bell Shaped Curve and Hormesis: Any process within

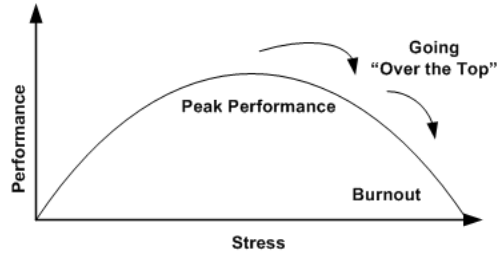
a Markov Blanket (*entities with a permeable interface between inside and outside, enabling a two-way exchange and conditional independencies*)that exhibits a bi-phasic response reflected in a Bell Shaped Curve in response to exposure to increasing amounts of a substance or condition such as stress.





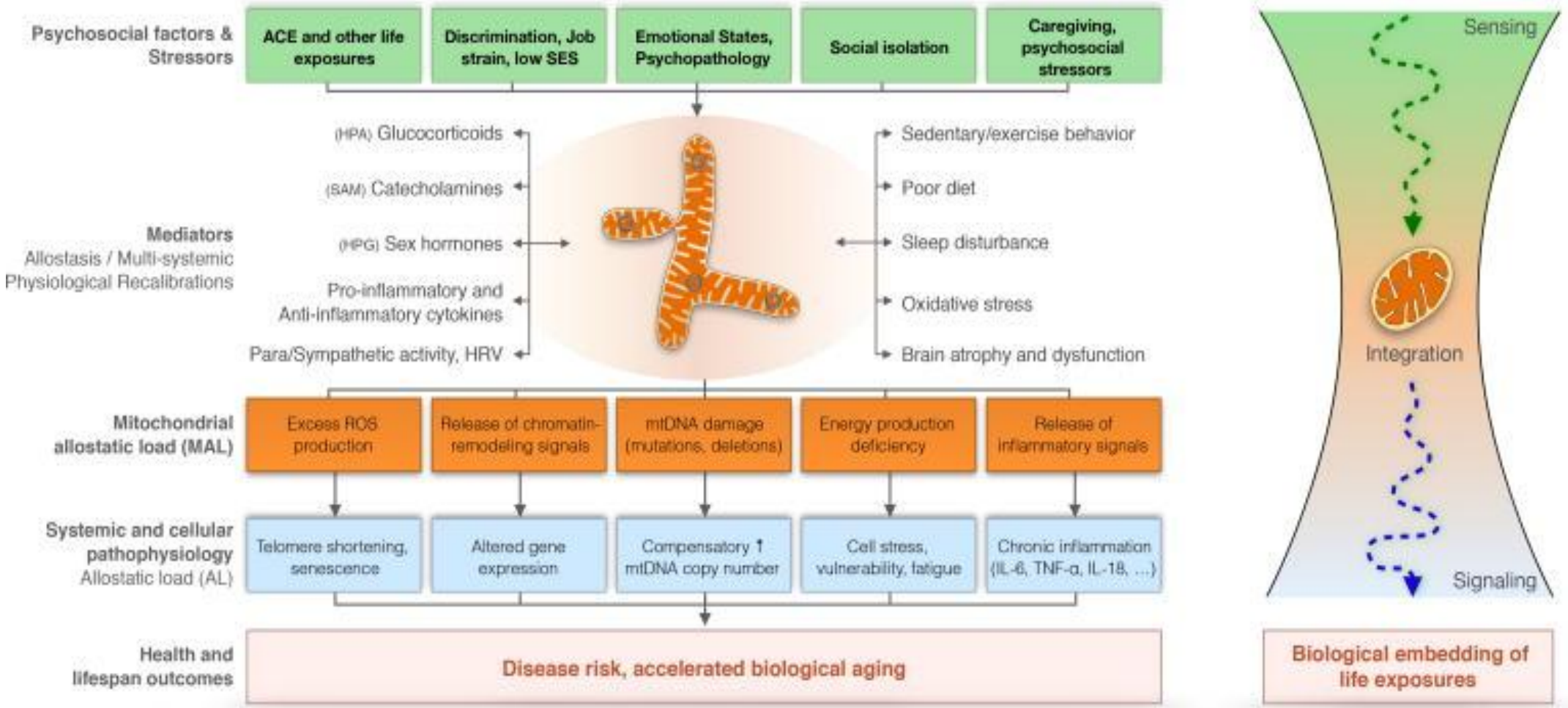






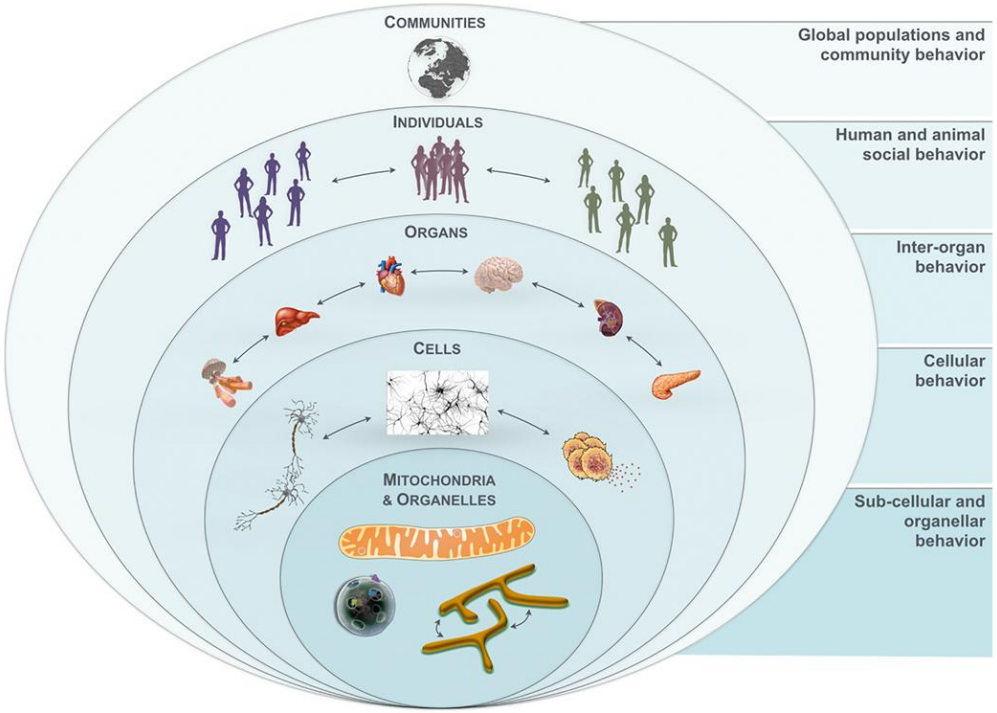
The Mitochondrial Stress Perspective

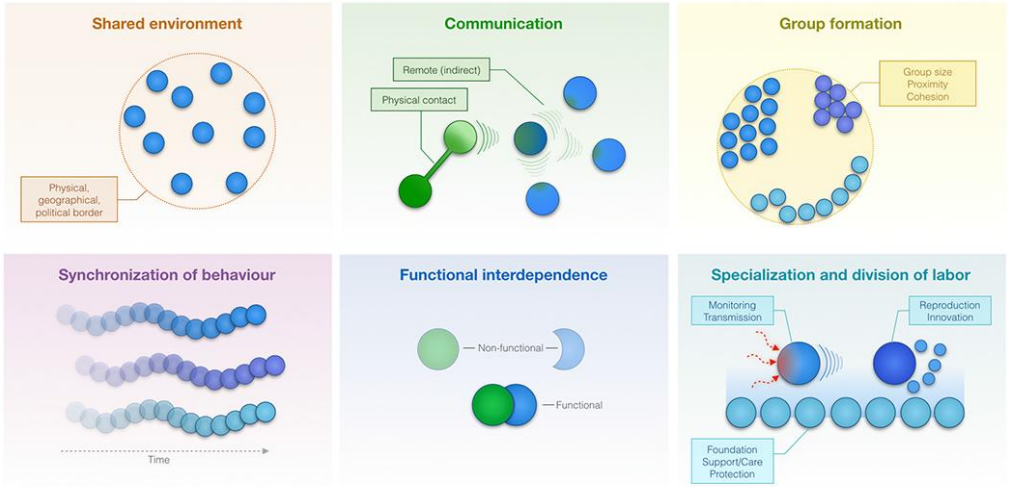
Picard and McEwen, 2018



The social nature of mitochondria: Conserved principles of social behavior across levels of complexity.

Picard and Sandi, 2020

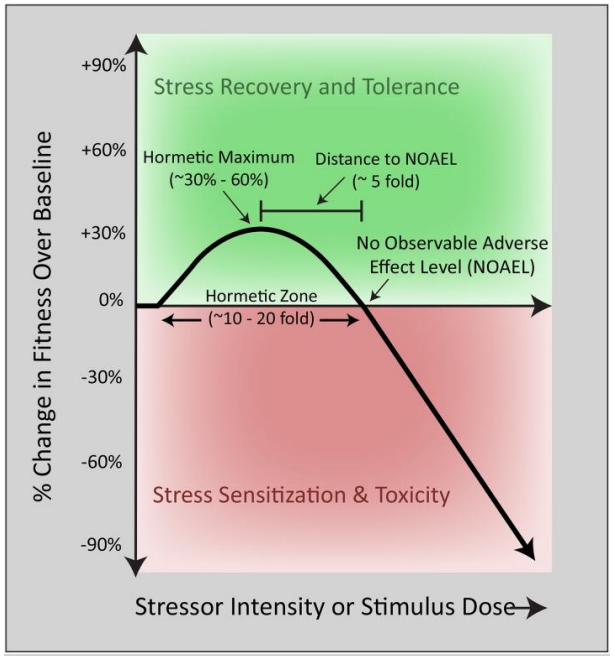


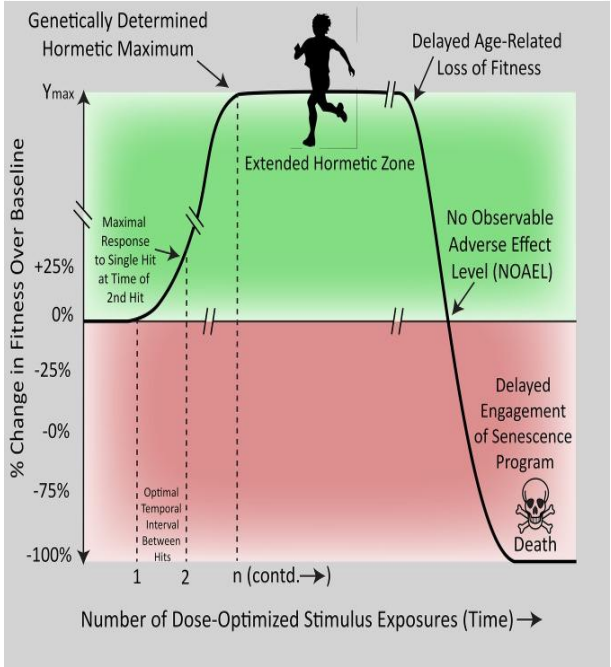


Enhancing and Extending Biological Performance and Resilience

Leak RK, Calabrese EJ, Kozumbo WJ, et al.. *Dose Response*. 2018;16(3):1559325818784501.

- Biological fitness as a function of repeated exposures to optimized hormetic stimuli applied at rhythmic intervals.
- A single hormetic stimulus exposure results in a modest amplitude effect and a time-limited response, but **repeated exposures build, in stepwise manner, the layers of a strong foundation for an extended, high-amplitude response.**
- **Environmental stimuli such as mind-body activity/dietary/lifestyle factors can be optimized so that the maximal epigenetic/genetic potential can be reached.**
- **Mind body approaches may be able to enhance and extend resilience through hormetic processes.**





The Neuroscience of Trauma, Yes

But Always In the Service of Attachment Solutions

Moriset: The Cradle and Feldes: The Doctor