The Impact of Emotional Health on Physical Well-being

Contributors constitute members of the https://liber8.health team.

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Introduction

Despite overall health progress, the World Health Organisation has recently stated that should current trends continue, chronic diseases – such as cardiovascular diseases, cancer, diabetes and respiratory illnesses – will account for 86 percent of the 90 million deaths each year by 2050. This would represent a 90 percent increase in absolute numbers since 2019.[1] Chronic diseases are the result of a combination of genetic, physiological, environmental and behavioral factors, which means that the individual has control over some aspects of the disease process.[2]

The origins of disease in the body are complex. Evidence points to a combination of a wide range of factors including genetics, pathogens, environmental exposures, diet, lifestyle, aging, mental health, childhood adverse experiences, and more. Despite this, our current medical treatment paradigm is almost entirely physical and largely focused on mitigating symptoms. This treatment approach does not adequately address or integrate important findings from academic studies covering such emerging sciences as psychoneuroimmunology, epigenetics, interoception, and trauma neurobiology. All emerging research strongly shows a bidirectional, causal relationship between our mental and emotional states, and the function of our physical bodies.[3]

The purpose of this white paper is to explore and establish the integral connection between emotional and physical health. With this knowledge, practitioners and patients alike are better able to regain control of the runaway train of chronic disease. Hope and autonomy is to be

[1] https://www.who.int/news-room/fact-sheets/detail/noncommunicable-diseases
[2] Ojo O. Nutrition and Chronic Conditions. Nutrients. 2019;11(2):459. Published 2019 Feb 22. doi:10.3390/nu11020459
[3] Yao C, Zhang Y, Lu P, et al. Exploring the bidirectional relationship between pain and mental disorders: a comprehensive Mendelian randomization study. J Headache Pain. 2023;24(1):82. Published 2023 Jul 7. doi:10.1186/s10194-023-01612-2

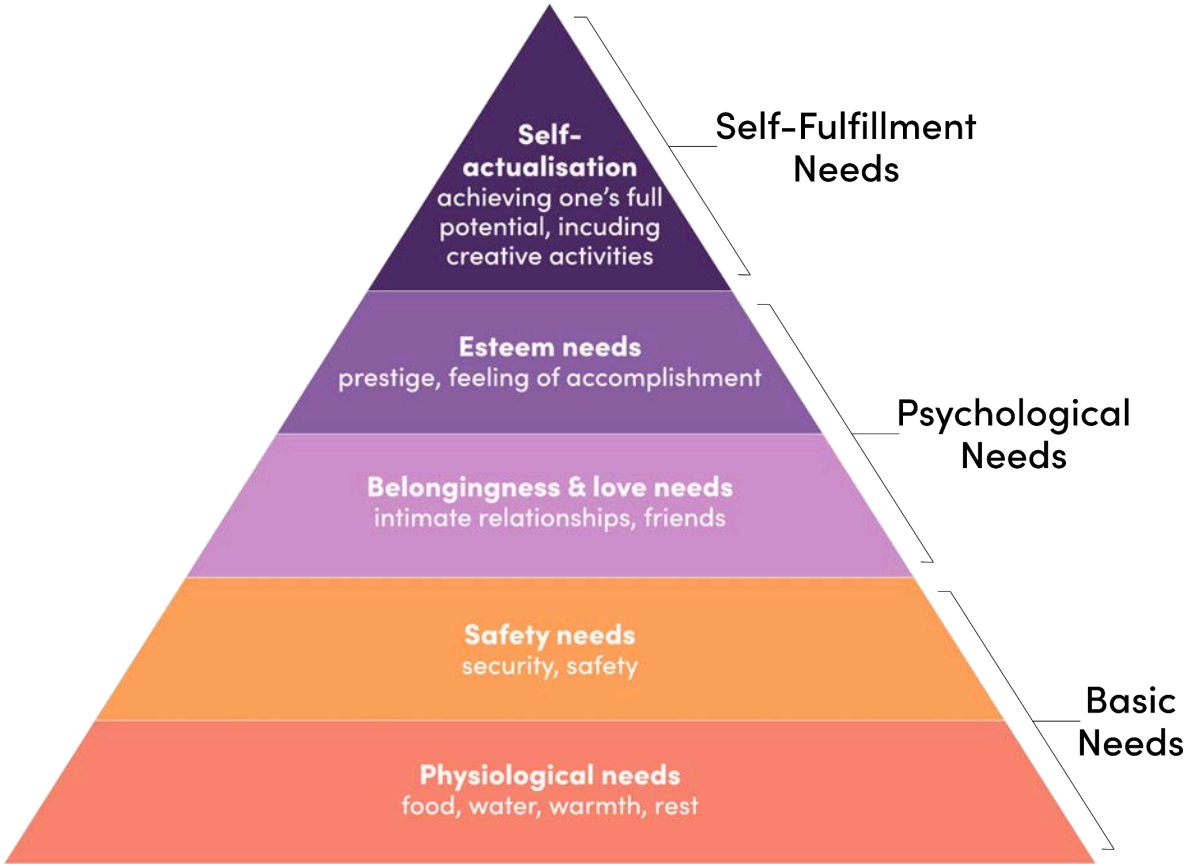
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found in the skillful manipulation of the various dominoes available to us. After all, if health is wealth, then why are we only focusing on physical health, sometimes at the expense of mental, and emotional health?[4] The perceived lack of quantifiability of these non-physical aspects of a patient's total health picture should not deter us from addressing them, especially when the literature has demonstrated that they are intertwined with patient outcomes[5]. At the very least, we know that approaching the patient as a whole person leads to their subjective experience of a better quality of life[6].

To meet these objectives, we have conducted a thorough review of existing research and literature on the correlation between emotional health and physiology, and ultimately, their bidirectionality. To highlight the correlations, the authors have chosen a number of frameworks to support this argument. These frameworks demonstrate how one perceives interpersonal, intrapersonal and person-environment interactions, and how humans adapt according to those interactions to improve future responses to said interactions. The innate driving goal of this process is long-term survival, rooted in Darwinism and captured by Maslow's Hierarchy of Needs.

[4] Turner J, Kelly B. Emotional dimensions of chronic disease. West J Med. 2000;172(2):124-128. doi:10.1136/ewjm.172.2.124
[5] de Brito Sena MA, Damiano RF, Lucchetti G, Peres MFP. Defining Spirituality in Healthcare: A Systematic Review and Conceptual Framework. Front Psychol. 2021;12:756080. Published 2021 Nov 18. doi:10.3389/fpsyg.2021.756080
[6] Shah R, Kulhara P, Grover S, Kumar S, Malhotra R, Tyagi S. Contribution of spirituality to quality of life in patients with residual schizophrenia. Psychiatry Res. 2011;190(2-3):200-205. doi:10.1016/j.psychres.2011.07.034

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This paper presents a novel therapeutic model of emotional healing to serve not only as an adjunct to maximize medical treatments but also as part of a preventative strategy for chronic disease. Its analysis includes a review of theoretical underpinnings of evolutionary adaptation and survival, human experience theories and their physiologic models, and psycho-physiological considerations. While it examines how some of these various theories may impact and/or synergistically affect one another, a high number of permutations and combinations exist which could not possibly be entirely covered within the limits of this paper.

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Understanding Emotions and their Role in the Human Being

Emotions are defined as mental reactions (such as anger, fear, or joy) experienced as feelings and typically accompanied by physiological and behavioral changes in the body[7], which leads to the emotional state being experienced somatically (in the body) as well. Emotions have long been classified as positive (i.e. joy, pleasure) or negative (i.e. fear, sadness, anger), but a better way to think of them might be to evaluate how they affect one's general outlook on life under a given set of circumstances. For instance, in some situations, anger or fear is a positive response, while in others, they are uncalled for and therefore negative. Emotional valence describes the extent to which an emotion is positive or negative, whereas arousal refers to its intensity, i.e., the strength of the associated emotional state.[8]

Gabor Maté is a pioneer in the field of psychoneuroimmunology and in his bestselling book “When the Body Says No: The Cost of Hidden Stress” he discusses emotional competence, which he defines as the capacity to feel our emotions and use it such to bring situational awareness to experiential stress. Emotional competence is “the ability to express our emotions effectively and thereby to assert our needs and to maintain the integrity of our emotional boundaries; the facility to distinguish between psychological reactions that are pertinent to the present situation and those that represent residue from the past.[9]” As psychologist Dr. Barbara Fredrickson of the University of North Carolina says, "All emotions - whether positive or negative

[7] Emotions definition & meaning. Merriam-Webster. Accessed February 14, 2024. https://www.merriam-webster.com/dictionary/emotions.
[8] Citron, F. M., Gray, M. A., Critchley, H. D., Weekes, B. S., & Ferstl, E. C. (2014). Emotional valence and arousal affect reading in an interactive way: neuroimaging evidence for an approach-withdrawal framework. Neuropsychologia, 56(100), 79–89. https://doi.org/10.1016/j.neuropsychologia.2014.01.002
[9] Maté, Gabor. When the Body Says No. Vermillion, 2019.

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- are adaptive in the right circumstances.[10]" This speaks to evolutionary adaptation which is discussed later on in this paper.

Emotional Response Coherence

For many theorists, a defining feature of emotion is response coherence[11,12,1314]. This refers to the coordination, or association, of a person's experiential, behavioral, and physiological responses as the emotion unfolds over time[15], rooted in a symphony of neurochemistry and the patterned activations of brain regions.

Natural science uses three measurable response classes to assess human emotions, namely (1) verbal reports of experience, (2) overt actions, and (3) associated physiological mobilization. They highlight previous theorists' suggestion that "primitive survival reflexes are the foundation for emotion's physiological mobilization and action."

Human beings, like other members of the animal kingdom, sustain life by meeting their most basic needs (i.e. water, food, sleep/"appetitive motivation") and engage fight and/or flight responses against threats to ensure survival ("defensive motivation"). Humans are complex sentient species with "higher order cortices, emerged enhanced capacity for inhibition, and evaluation of alternatives and outcomes," but while they have developed capacities for complex

[10] Positive emotions and your health (2024) National Institutes of Health. Available at: https://newsinhealth.nih.gov/2015/08/positive-emotions-your-health (Accessed: 30 June 2024).
[11] Ekman P. An argument for basic emotions. Cognition and emotion. 1992;6(3/4):169–200.
[12] Levenson RW. Human emotions: A functional view. In: Ekman P, Davidson RJ, editors. The nature of emotion: Fundamental questions. Oxford University Press; New York, NY: 1994. pp. 123–126.
[13] Panksepp J. The basics of basic emotion. In: Ekman P, Davidson RJ, editors. The nature of emotion: Fundamental questions. Oxford University Press; New York, NY: 1994. pp. 237–242.
[14] Mauss IB, Levenson RW, McCarter L, Wilhelm FH, Gross JJ. The tie that binds? Coherence among emotion experience, behavior, and physiology. Emotion. 2005;5(2):175-190. doi:10.1037/1528-3542.5.2.175
[15] Dan-Glauser ES, Gross JJ. Emotion regulation and emotion coherence: evidence for strategy-specific effects. Emotion. 2013;13(5):832-842. doi:10.1037/a0032672

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analysis and critical thought, ancient primitive reactance remains coded in muscles and glands, “supported by neural circuits deep within the brain and widely shared among species.[16]”

As a result, emotions are considered “action dispositions” or “physiological programs aimed at maintaining or restoring homeostasis by changing the body to more appropriately interact with the environment”[17], and are most evident in humans during overt passivity, yet can be mobilized “somatically and autonomically” for actions that may never be required[18].

Emotional Processing Model

“The ability to alter one's emotional responses is central to overall well-being and to effectively meeting the demands of life”[19]. Rachman[20] first introduced the concept of “emotional processing” in the context of anxiety disorders where he defined emotional processing as “a process whereby emotional disturbances are absorbed and decline to the extent that other experiences and behavior can proceed without disruption” (p. 51). He noted that while “most people successfully process the overwhelming majority of disturbing events that occur in their life” (p. 56), sometimes failures in emotional processing occur. He argued that if emotional experiences were incompletely absorbed or processed, then certain direct signs of this failure would appear (e.g., the return of fears, obsessions, and unpleasant intrusive thoughts).

According to the emotional processing model (EPM), acknowledging emotions and finding adaptive ways of expressing them are foundational to adaptive coping with stressful life

[16] McTeague LM, Lang PJ. The anxiety spectrum and the reflex physiology of defense: from circumscribed fear to broad distress. Depress Anxiety. 2012;29(4):264-281. doi:10.1002/da.21891
[17] Damasio A., Carvalho G. B. (2013). The nature of feelings: evolutionary and neurobiological origins. Nat. Rev. Neurosci. 14 143–152. 10.1038/nrn3403
[18] McTeague LM, Lang PJ. The anxiety spectrum and the reflex physiology of defense: from circumscribed fear to broad distress. Depress Anxiety. 2012;29(4):264-281. doi:10.1002/da.21891
[19] McCraty R, Zayas MA. Cardiac coherence, self-regulation, autonomic stability, and psychosocial well-being. Front Psychol. 2014;5:1090. Published 2014 Sep 29. doi:10.3389/fpsyg.2014.01090
[20] Rachman, S. Emotional processing. Behav Res Ther. 18(1), 51–60 (1980).

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events[21,22]. The EPM proposes that disruptions in coping can occur when people avoid or suppress their emotions, which will inhibit emotional processing and give rise to difficulties with unprocessed or uncontrolled emotions, which in turn may contribute to the development of psychiatric and somatic symptoms.

The concepts of emotional processing and the EPM are closely related to the concepts of emotional regulation[23] where situational avoidance may be used as a strategy to cope with upsetting events but where “emotional regulation” refers to the ability to modify the expression, experience, and physiology of emotion to meet situational demands. “Emotional processing” refers to what disrupts the overarching process of overcoming difficult or stressful life events more broadly[24,25]. Emotional regulation as a tool for healing and improving health is discussed later, although, interestingly, we wanted to also highlight evidence that adequate use of emotional regulation skills *with* social or peer support has been shown to remarkably decrease psychological distress[26].

In EPM, a negative event is regarded as “an input that needs to be registered (either consciously or unconsciously) by an individual as a prerequisite for emotional experience. A negative input could refer to a discrete major event (e.g., a car crash), a discrete minor event (e.g., an argument), or a continuous series of events (stressful work environment or deteriorating marital relationship). The cognitive appraisal of the meaning of the event shapes the nature of the emotion experienced and is often unconscious and rapid. Examples of

[21] ibid.
[22] Baker, R. et al. The emotional processing scale: Scale refinement and abridgement (EPS-25). J. Psychosom. Res. 68, 83–88 (2010).
[23] McRea, K. & Gross, J. Emotional regulation. Emotion 20, 1–9 (2020).
[24] ibid.
[25] Baker, R. Emotional Processing-Healing through Feeling. (Lion Hudson plc, 2007).
[26] Karam, JM., Fekih-Romdhane, F., Fawaz, M. et al. The moderating effect of emotion regulation in the association between social support and religiosity and psychological distress in adults. BMC Psychol 11, 120 (2023). https://doi.org/10.1186/s40359-023-01160-z

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problems that may occur at this stage include failure to register, misinterpretation, or active avoidance of an input event.[27]”

Internal Baseline Reference

According to McCraty et al., one of the chief symptoms of events such as trauma is a shift in our internal baseline reference such that there ensues a repetitive activation of the traumatic event. If the event had overwhelmed our capacities to successfully handle and adapt to the situation, the nervous system continues to generate iterations so as to decrease future surprise and increase reaction times and this rumination or repetitive emotional activation, can result in high vigilance and over-sensitivity to environmental signals[28], which can be demonstrated physiologically as decreased response coherence - desynchronized entrainment of respiration, heart rate variability, and blood pressure rhythms[29].

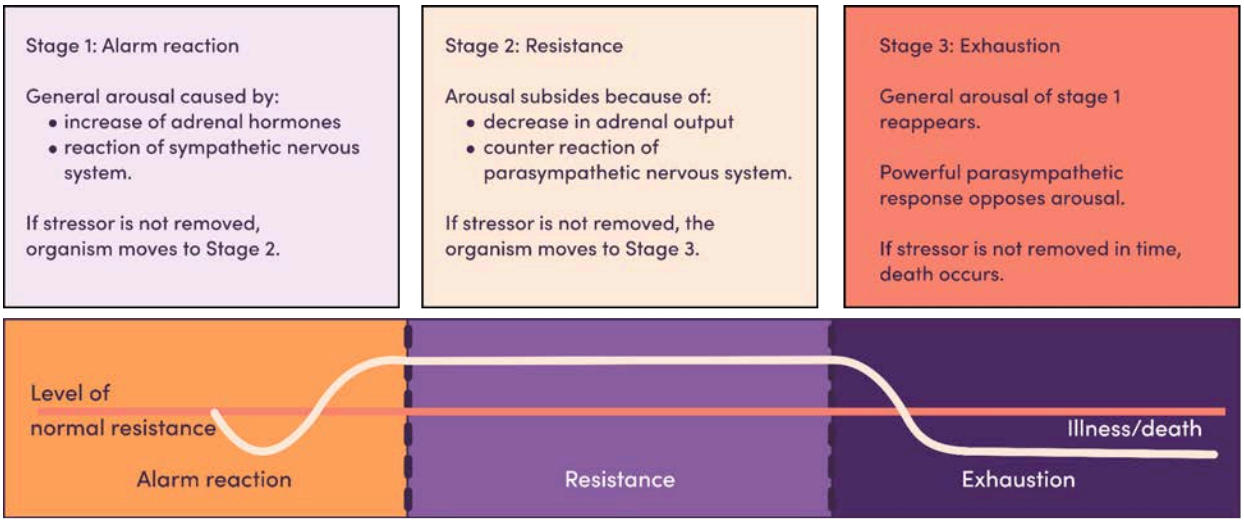
General Adaptation Syndrome

General Adaptation Syndrome (GAS), first introduced by Hans Selye in 1936, describes the body's nonspecific response to stressors, which can include emotional shock, trauma, infections, and other factors[30,31]. The GAS model outlines three stages: alarm, resistance, and exhaustion. During the alarm stage, the body recognizes the stressor and initiates a

[27] Maroti, D., Axelsson, E., Ljótsson, B. et al. Psychometric properties of the emotional processing scale in individuals with psychiatric symptoms and the development of a brief 15-item version. Sci Rep 12, 10456 (2022). https://doi.org/10.1038/s41598-022-14712-x
[28] McCraty R, Zayas MA. Cardiac coherence, self-regulation, autonomic stability, and psychosocial well-being. Front Psychol. 2014;5:1090. Published 2014 Sep 29. doi:10.3389/fpsyg.2014.01090
[29] Edwards SD, Edwards DJ, Honeycutt R. HeartMath as an Integrative, Personal, Social, and Global Healthcare System. Healthcare (Basel). 2022;10(2):376. Published 2022 Feb 15. doi:10.3390/healthcare10020376
[30] Chebyshev N, Berechikidze I, Philippova A, Lazareva Y, Gorozhanina E. [THE SIGNIFICANCE OF THE SYSTEM APPROACH IN THE STUDY OF THE GENERAL ADAPTATION SYNDROME' REACTIONS]. Georgian Med News. 2019 Jul-Aug;(292-293):102-108. Russian. PMID: 31560673.
[31] Fink G. Selye's general adaptation syndrome: stress-induced gastro-duodenal ulceration and inflammatory bowel disease. J Endocrinol. 2017 Mar;232(3):F1-F5. doi: 10.1530/JOE-16-0547.

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fight-or-flight response, releasing stress hormones like adrenaline and cortisol[32]. In the resistance stage, the body attempts to adapt to the stressor, maintaining a heightened state of alertness and physiological activity to cope with the stress. If the stressor persists, the body eventually enters the exhaustion stage, where its resources are depleted, leading to decreased stress resistance and potential development of stress-related pathologies such as coronary heart disease, hypertension, and peptic ulcers[33]. The GAS model is a valuable framework for conceptualizing how stress induces specific adaptations that enhance functional capabilities[34] and underscores the importance of negative feedback mechanisms that limit excessive stress responses to prevent organ damage[35].



[32] Gutsol L., Guzovskaiia E., Serebrennikova S., Seminsky I. Stress (general adaptation syndrome) Lecture. Baikal Medical Journal. 2022;1(1):70-80. doi:10.57256/2949-0715-2022-1-70-80
[33] Fink G. Selye's general adaptation syndrome: stress-induced gastro-duodenal ulceration and inflammatory bowel disease. J Endocrinol. 2017 Mar;232(3):F1-F5. doi: 10.1530/JOE-16-0547.
[34] Cunanan AJ, DeWeese BH, Wagle JP, Carroll KM, Sausaman R, Hornsby WG 3rd, Haff GG, Triplett NT, Pierce KC, Stone MH. The General Adaptation Syndrome: A Foundation for the Concept of Periodization. Sports Med. 2018 Apr;48(4):787-797. doi: 10.1007/s40279-017-0855-3. PMID: 29307100.
[35] Chebyshev N, Berechikidze I, Philippova A, Lazareva Y, Gorozhanina E. [THE SIGNIFICANCE OF THE SYSTEM APPROACH IN THE STUDY OF THE GENERAL ADAPTATION SYNDROME' REACTIONS]. Georgian Med News. 2019 Jul-Aug;(292-293):102-108. Russian. PMID: 31560673.

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Clinical Emotional and Psychological Interventions

There are many interventions developed over the decades to help patients deal with negative emotional and psychological stressors, in part, because the burden of these has long been recognised as deleterious for the well-being of the individual - whether because it was driving somatic disease or hindering global neuro processing by tying up “bandwidth”. We present the evidence for the benefits of emotional processing in this white paper, and are grateful that we stand on the shoulder of giants whose contributions to the field may not have been as wholeheartedly accepted by the medical and “hard” science communities because the assays and neuroimaging needed to support theorems had not yet been invented.

An example of an intervention which has enjoyed variable efficacy and good incorporation by the medical and psychological communities is Cognitive Behavioral Therapy (CBT). CBT is a “top-down” clinical approach to trauma treatment and our trigger-logging model (described later) is influenced by it. It trains people to rotely replace automatic reactions with more constructive ones until a negative thought loop is mitigated.

CBT is based on several core principles, including:

- Psychological problems are based, in part, on faulty or unhelpful ways of thinking.
- Psychological problems are based, in part, on learned patterns of unhelpful behavior.
- People suffering from psychological problems can learn better ways of coping with them, thereby relieving their symptoms and becoming more effective in their lives.

CBT treatment usually involves efforts to change thinking patterns. These strategies might include:

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- Learning to recognize one's distortions in thinking that are creating problems, and then to reevaluate them in light of reality.
- Gaining a better understanding of the behavior and motivation of others. Using problem-solving skills to cope with difficult situations.
- Learning to develop a greater sense of confidence in one's own abilities.

CBT treatment also usually involves efforts to change behavioral patterns. These strategies might include:

- Facing one's fears instead of avoiding them.
- Using role-playing to prepare for potentially problematic interactions with others.
- Learning to calm one's mind and relax one's body.

Bessel van der Kolk, psychiatrist and bestselling author of *The Body Keeps the Score*, takes particular issue with two of the most widely employed techniques in treating trauma: CBT and exposure therapy. Exposure therapy involves repeatedly confronting patients with what most haunts them until they become desensitized to it. Van der Kolk is cautious about both CBT and exposure therapy whilst recognising that they can be efficacious interventions. “Trauma has nothing whatsoever to do with cognition,” he says. “It has to do with your body being reset to interpret the world as a dangerous place.” That reset begins in the deep recesses of the brain with its most primitive structures, regions that, he says, no cognitive therapy can access. “It’s not something you can talk yourself out of.”[36].

[36] Interlandi, J. (2014) A revolutionary approach to treating PTSD, The New York Times. Available at: https://www.nytimes.com/2014/05/25/magazine/a-revolutionary-approach-to-treating-ptsd.html (Accessed: 12 April 2024).

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A randomized clinical trial published in June 2024[37] showed that despite the severity of chronic pain being associated with adverse childhood experiences, military combat, racism or discrimination, and psychiatric conditions, these are not directly addressed by CBT. Emotional awareness and expression therapy (EAET) was developed to target these critical drivers of chronic pain[38]. The goals of EAET are to learn that the brain's perception of pain is strongly influenced by evading trauma- or stress-related emotions (eg, emotional pain or grief, fear, rage, and guilt) and to face and resolve such emotions to reduce or eliminate chronic pain, and the RCT showed that EAET may be a preferred intervention for medically and psychiatrically complex patients with pain[39].

Hypnosis is another modality which has offered relief to patients who suffer from pain, depression, anxiety, emotional dysregulation and psychological anguish. Neuroimaging studies conducted with chronic pain patients showed a modulation of pain matrix activity during hypnosis with a specific involvement of the anterior cingulate cortex (related to emotional and cognitive processing of pain). Therefore, hypnosis seems to act upon regions underlying emotion and cognition, with an influence on pain perception and emotional regulation[40].

[37] Yarns BC, Jackson NJ, Alas A, Melrose RJ, Lumley MA, Sultzer DL. Emotional Awareness and Expression Therapy vs Cognitive Behavioral Therapy for Chronic Pain in Older Veterans: A Randomized Clinical Trial. JAMA Netw Open. 2024;7(6):e2415842. doi:10.1001/jamanetworkopen.2024.15842
[38] Lumley MA, Yamin JB, Pester BD, Krohner S, Urbanik CP. Trauma matters: psychological interventions for comorbid psychosocial trauma and chronic pain. Pain. 2022 Apr 1;163(4):599-603. doi: 10.1097/j.pain.0000000000002425.
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[40] Bicego A, Rousseaux F, Faymonville ME, Nyssen AS, Vanhaudenhuyse A. Neurophysiology of hypnosis in chronic pain: A review of recent literature. Am J Clin Hypn. 2022;64(1):62-80. doi:10.1080/00029157.2020.1869517

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Stress and Resilience

The National Comprehensive Cancer Network defines distress as “a multifactorial unpleasant emotional experience of a psychological (cognitive, behavioral, emotional) social, and/or spiritual nature that may interfere with the ability to cope effectively with cancer, its physical symptoms and its treatment. Distress extends along a continuum, ranging from common normal feelings of vulnerability, sadness, and fears to problems that can become disabling, such as depression, anxiety, panic, social isolation, and existential and spiritual crisis.”[41]

The significance of this is that heightened distress is associated with worse patient outcomes in terms of poorer health-related quality of life, lesser treatment adherence, lower satisfaction with care, and possibly lower survival[42]. Because of its significant impact, distress is now endorsed as the “6th vital sign” internationally. Accreditation Canada also includes assessment, evaluation, and monitoring of emotional distress in clients as an accreditation standard[43].

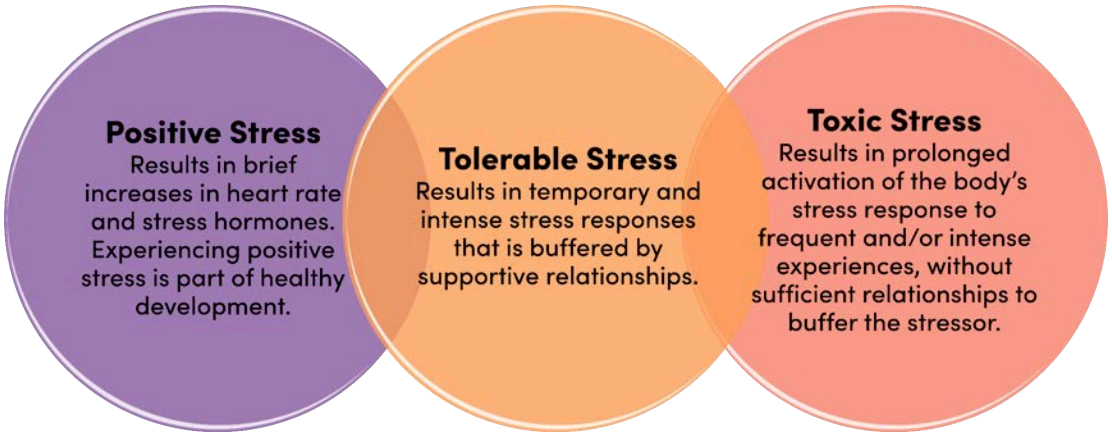
“Stress” as a word is commonly interpreted as negative, although there are forms of stress that are positive. McEwen defines stress as the bodily and emotional response to adverse stimuli/so-called “stressors” that can be classified into three subcategories.[44] Stress that is handled appropriately by the body (i.e. “good stress”) is referred to as “eustress” which is associated with appropriate sympathetic response and resolution. “Bad stress” incorporates both “tolerable stress” and “toxic stress”. “Tolerable stress” results from subjects’ bad/negative

[41] National Comprehensive Cancer Network (nccn) NCCN Clinical Practice Guidelines in Oncology: Distress Management. Fort Washington, PA: NCCN; 2010. Version 1.2011. [Available online at: http://www.nccn.org/professionals/physician_gls/pdf/distress.pdf (free registration required); cited May 30, 2024]
[42] Howell D, Olsen K. Distress-the 6th vital sign. Curr Oncol. 2011 Oct;18(5):208-10. doi: 10.3747/co.v18i5.790. PMID: 21980246; PMCID: PMC3185896.
[43] Accreditation Canada . Qmentum Program 2009 Standards: Cancer Care and Oncology Services. Ottawa, ON: Accreditation Canada; 2008. Ver. 2.
[44] McEwen BS. Neurobiological and Systemic Effects of Chronic Stress. Chronic Stress (Thousand Oaks). 2017;1:2470547017692328. doi:10.1177/2470547017692328

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experiences, but they are able to cope and recover, often with social support. “Toxic stress” occurs when the body cannot properly resolve stressors, resulting in negative emotional and physiological outcomes. This is subjective based on “innate (genetic and epigenetic), learned (determined by previous experiences) and external social factors (the available buffers and overall feeling of security and safety)” and associated with the usual negative emotions (i.e. frustration, anger, fear, shame, guilt).

Stressors can also be classified as acute and chronic. Acute stress responses are the result of immediate real or perceived threats, whereas chronic stress results from “repeated and unrelenting” stressors which can drive severe cumulative impacts over time despite being mild or low-threat in principle. Chronic stress becomes toxic when subjects’ adaptive responses become insufficient or maladaptive (such as increasing alcohol consumption as a coping mechanism). Positive and negative emotions differ largely in that positive emotions increase coherence of bodily rhythms, while negative emotions decrease coherence[45]. Throughout this paper, the discussion of “stress” is intended as synonymous with the negative emotions associated with toxic stress.

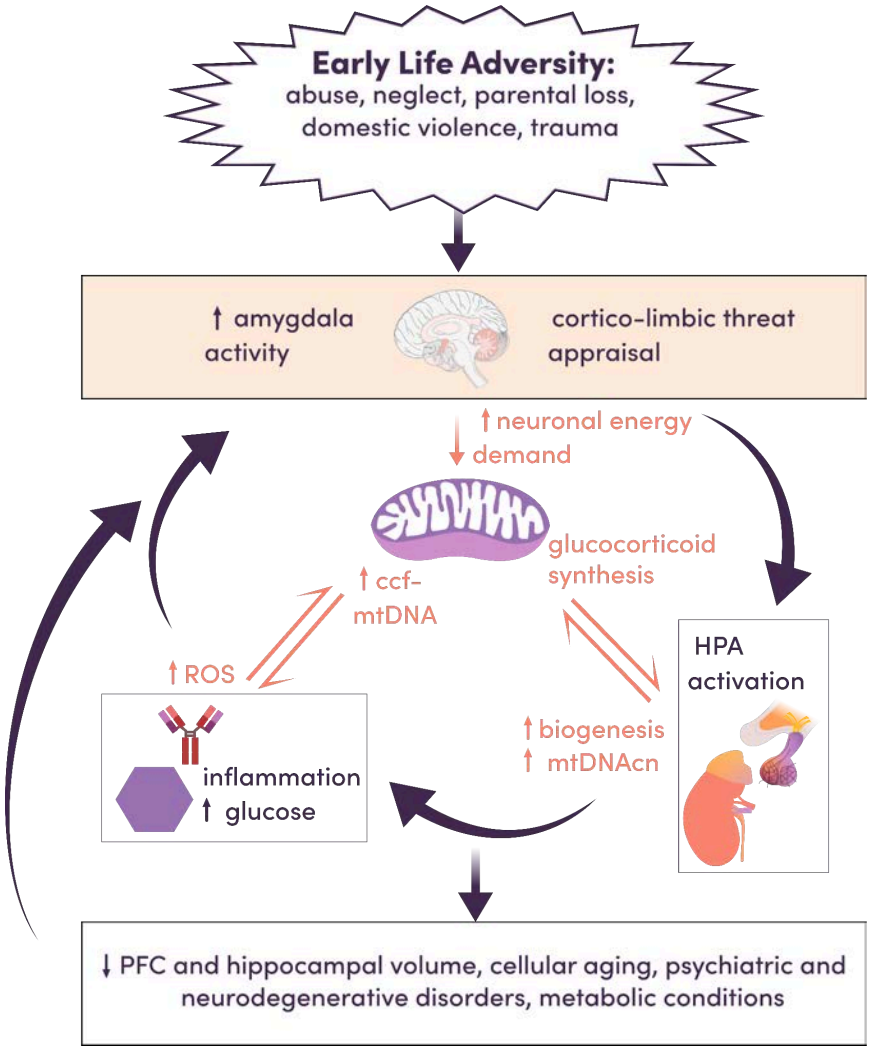


[45] McCraty R., Zayas M. A. (2014). Cardiac coherence, self-regulation, autonomic stability, and psychosocial well-being. Front. Psychol. 5:1090. 10.3389/fpsyg.2014.01090

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Mitochondria

Mitochondria are membrane-bound cell organelles (mitochondrion, singular) that generate most of the chemical energy needed to power the cell's biochemical reactions. They are often called the "powerhouse of the cell". Chemical energy produced by the mitochondria is stored in a small molecule called adenosine triphosphate (ATP). Mitochondria are capable of sensing and integrating social stress on a cellular level. A small number of human studies suggest that mitochondria interact dynamically with physiological stress responses coordinated by the central nervous, endocrine, and immune systems and in response to stress, undergo dynamic changes in their structure, leading to alterations in function[46]. Early clinical studies support that increased mitochondrial DNA content and altered



[46] Picard M, McEwen BS. Psychological Stress and Mitochondria: A Systematic Review. Psychosom Med. 2018 Feb/Mar;80(2):141-153. doi: 10.1097/PSY.0000000000000545. PMID: 29389736; PMCID: PMC5901654.

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cellular energy demands may be present in individuals with a history of early life adversity (graphic from same paper)[47].

For example, chronic stress due to caregiving for a family member with a chronic health condition was associated with lower mitochondrial respiratory capacity in blood cells among women[48]. Childhood maltreatment was found to be associated with changes in mitochondrial cellular respiration in blood cells related to ATP production[49]. New mothers who had a history of childhood maltreatment had alterations in ATP production, and women with a more severe history of maltreatment had a worse mitochondrial bioenergetic profile in blood cells[50].

The Mind and Emotions Can Affect the Body

The case for a mind-body connection in the etiology and healing of chronic disease, including cancer, is slowly growing as there is more acknowledgement that psychosocial factors affect disease development and progression[51]. However, the sporadic nature of spontaneous remission of cancers and other non-infectious chronic diseases, and lack of systematic approach to their study has marginalized these phenomena as largely “coincidental” or too difficult to qualify and quantify (and therefore the inquiry stops!). There are sound,

[47] Zitkovsky EK, Daniels TE, Tyrka AR. Mitochondria and early-life adversity. Mitochondrion. 2021 Mar;57:213-221. DOI: 10.1016/j.mito.2021.01.005. PMID: 33484871; PMCID: PMC8172448.
[48] Picard M, Prather AA, Puterman E, Cuillerier A, Coccia M, Aschbacher K, Burelle Y, Epel ES. A Mitochondrial Health Index Sensitive to Mood and Caregiving Stress. Biol Psychiatry. 2018 Jul 1;84(1):9-17. doi: 10.1016/j.biopsych.2018.01.012. Epub 2018 Feb 3. PMID: 29525040
[49] Boeck C, Koenig AM, Schury K, Geiger ML, Karabatsiakis A, Wilker S, Waller C, Gündel H, Fegert JM, Calzia E, Kolassa IT. Inflammation in adult women with a history of child maltreatment: The involvement of mitochondrial alterations and oxidative stress. Mitochondrion. 2016 Sep;30:197-207. doi: 10.1016/j.mito.2016.08.006. Epub 2016 Aug 13. PMID: 27530300.
[50] Gumpp AM, Boeck C, Behnke A, Bach AM, Ramo-Fernández L, Welz T, Gündel H, Kolassa IT, Karabatsiakis A. Childhood maltreatment is associated with changes in mitochondrial bioenergetics in maternal, but not in neonatal immune cells. Proc Natl Acad Sci U S A. 2020 Oct 6;117(40):24778-24784. doi: 10.1073/pnas.2005885117. Epub 2020 Oct 1. PMID: 33004627; PMCID: PMC7547248.
[51] Sood AK, Lutgendorf SK. Stress influences on anoikis. Cancer Prev Res (Phila). 2011;4(4):481-485. doi:10.1158/1940-6207.CAPR-10-0358

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research-supported mechanisms underlying remissions, but these are spread across many fields of research including psychology which has been historically given a large berth by the medical fraternity.

Launched in 1948, the Framingham Heart Study (FHS) was intended to identify common factors that contribute to cardiovascular disease. It has since become a successful, multigenerational study that analyzes family patterns of cardiovascular and other diseases[52]. Insights derived from studies of the original, and offspring, data in 2014, include “self-silencing”, which is a trait that has since been quantified and qualified as the tendency to silence one’s thoughts and feelings to maintain safe relationships, particularly intimate relationships[53], and has been found to correlate significantly with depressive symptoms in studies of various populations of women and men[54] and with irritable bowel syndrome in women[55]. This was after adjusting for age, systolic blood pressure, body mass index, cigarette smoking, diabetes, and total cholesterol/high density cholesterol. Women who "self-silenced" during conflict with their spouse, compared with women who did not, had four times the risk of dying. The conclusion was that marital communication, conflict, and strain were associated with adverse health outcomes[56].

Negative emotions such as fear, anger, frustration, sadness, helplessness, guilt and shame are well-documented as activating the sympathetic nervous system, causing a cascade of hormones including cortisol especially if the emotions are held in a continuous state. According

[52] Mahmood SS, Levy D, Vasan RS, Wang TJ. The Framingham Heart Study and the epidemiology of cardiovascular disease: a historical perspective. Lancet. 2014;383(9921):999-1008. doi:10.1016/S0140-6736(13)61752-3
[53] Jack DC, Dill D. The silencing the self scale: schemas of intimacy associated with depression in women. Psychology of Women Quarterly 1992;16:97–106.
[54] Thompson JM. Silencing the self: depressive symptomatology and close relationships. Psychology of Women Quarterly 1995;19:337–53
[55] Ali A, Toner BB, Stuckless N, et al. Emotional abuse, self-blame, and self-silencing in women with irritable bowel syndrome. Psychosom Med. 2000;62(1):76-82. doi:10.1097/00006842-200001000-00011
[56] Eaker ED, Sullivan LM, Kelly-Hayes M, D'Agostino RB Sr, Benjamin EJ. Marital status, marital strain, and risk of coronary heart disease or total mortality: the Framingham Offspring Study. Psychosom Med. 2007;69(6):509-513. doi:10.1097/PSY.0b013e3180f62357

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to the Polyvagal Theory by Stephen Porges, sustained activation of the sympathetic nervous system can act as a driver for chronic diseases. When a subject experiences fear or other equally activating negative emotions, the human brain drives production of chemicals in the body – primarily cortisol an immune suppressant, and adrenaline and noradrenaline (epinephrine and norepinephrine), both of which impact the cardiovascular and autonomic nervous systems – whether the cause is a modern stressor such as fear of losing one's job, or an ancient-conditioned stress response such as being hunted by a saber-toothed tiger. The production of the hormones is designed to keep you safe from whatever immediate "danger" you may be in and the strength of the response is determined, in part, by how much of the hormones you have produced.

Immune dysregulation as a result of psychological stressors (such as inappropriate and/or unhealthily sustained negative emotions) could be a base driver for aging, cardiovascular disease, Type 2 diabetes, cancers, arthritis, and even frailty, due to sustained production of inflammatory chemicals and immune-impacting hormones produced in response to said stressors[57]. Increases in rates of biological aging due to negative psychological stressors is further supported in a study by Galkin et al., who note that feeling unhappy or lonely can add up to 1.65 years to a subject's biological age, and "the aggregate effect exceeds the effects of biological sex, living area, marital status, and smoking status", concluding that the psychological component of subjects' health significantly impacts their biological age[58].

Important to note is that there is inquiry not just into negative emotions and psychological stressors as being drivers of ill health, but also failure to confront traumatic experiences. A

[57] McTeague, L.M. & Lang, P.J. "The Anxiety Spectrum and the Reflex Physiology of Defense: From Circumscribed Fear to Broad Distress," *Depress Anxiety* (2012 Apr); 29(4): 264-281.
[58] Galkin, F et al. Psychological factors substantially contribute to biological aging: evidence from the aging rate in Chinese older adults. Aging. 2022;14(18): 7206-7222.

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significant form of stress is associated with the work of inhibiting or holding back the disclosure of important traumas and actively ignoring triggers of negative emotions[59].

The human body not only drafts its response to the release of concentrations of stress chemicals, but it will do so in the context of previous experiences - how your system is "set up". In other words, if you have previously experienced traumas and negative life experiences which you have not "dealt with", your nervous system response will not only be swift but intense or even worse (e.g., violent rages, complete shut down). If you have dealt with those emotional issues in a way that they no longer "trigger" you and hold power over you, then your nervous system response will likely be far less explosive and reactive. An individual who has been previously assaulted, when faced with a threat to personal safety, will generate these chemicals more quickly and at higher concentrations than an individual who has not. This is in part due to Helmholtz's Unconscious Inference Theory where the mind makes a series of mental adjustments, "unconscious

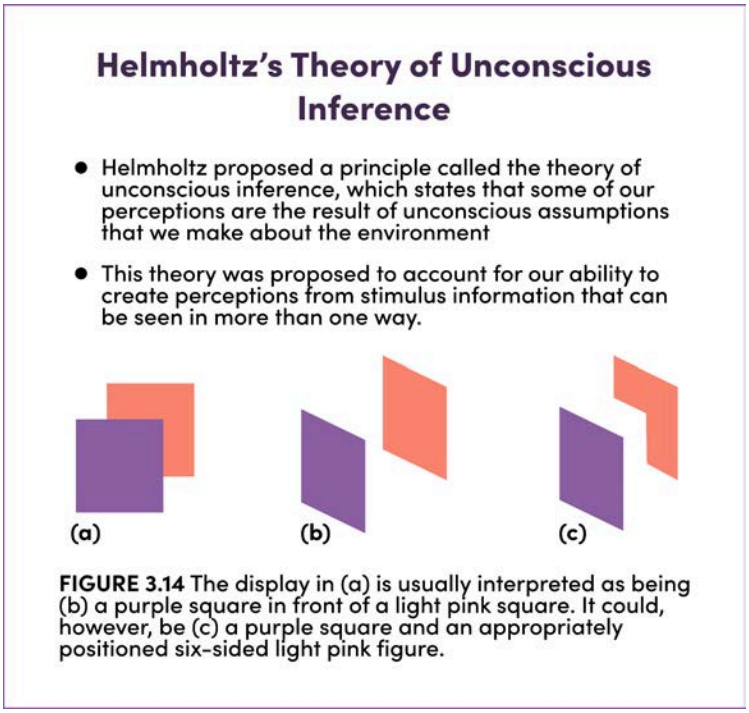


FIGURE 3.14 The display in (a) is usually interpreted as being (b) a purple square in front of a light pink square. It could, however, be (c) a purple square and an appropriately positioned six-sided light pink figure.

[59] Pennebaker JW, Kiecolt-Glaser JK, Glaser R. Disclosure of traumas and immune function: health implications for psychotherapy. J Consult Clin Psychol. 1988;56(2):239-245. doi:10.1037//0022-006x.56.2.239

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inferences," to construct a coherent picture of its experiences, where our perceptions are the result of unconscious assumptions that we make about the environment.

Subjects can also produce these chemicals in the body by merely thinking about a perceived threat, as supported by Karl Friston's Active Inference Theory[60]. Negative emotions sustained over long periods of time – conditions of which may be driven by factors such an inability to escape difficult circumstances (loss of agency), resolve or combat stressors, and/or feelings of helplessness/powerlessness – can drive a decrease in trigger thresholds, increases in the strength of the response, and compounded degradation of physiological systems[61]. This is all in keeping with evolutionary drivers of a subject's body attempting to protect them, but can lead to long-term physiological harm if agency is lost to the whims of unconscious reactivity.

Evolutionarily, we were used to pulses of sympathetic nervous system activation - stressors came intermittently and when they did, they were largely discrete definable events and came to absolute conclusions. The stressors we experience now in our modern world are constant and, many, frivolous, leading to an ancient system becoming quagmired in petty incidents it has little power to discern between, as the hormones produced are the same - cortisol, adrenaline and noradrenaline (epinephrine and norepinephrine). It is the prefrontal cortex that has the power to discern between the "triggers", thus negative emotions need to be actively dealt with to save the body from negative physiological processes.

McTeague et al.[62] posit that health issues may arise in the event that sustained negative emotions are because of "undue dwelling in the past or constant anxiety" rather than as a response to a subject's present scenario. They cite neuroticism – the "tendency to experience

[60] Friston K, FitzGerald T, Rigoli F, Schwartenbeck P, O Doherty J, Pezzulo G. Active inference and learning. Neurosci Biobehav Rev. 2016;68:862-879. doi:10.1016/j.neubiorev.2016.06.022
[61]McTeague, L.M. & Lang, P.J. "The Anxiety Spectrum and the Reflex Physiology of Defense: From Circumscribed Fear to Broad Distress," *Depress Anxiety* (2012 Apr); 29(4): 264-281.
[62] ibid.

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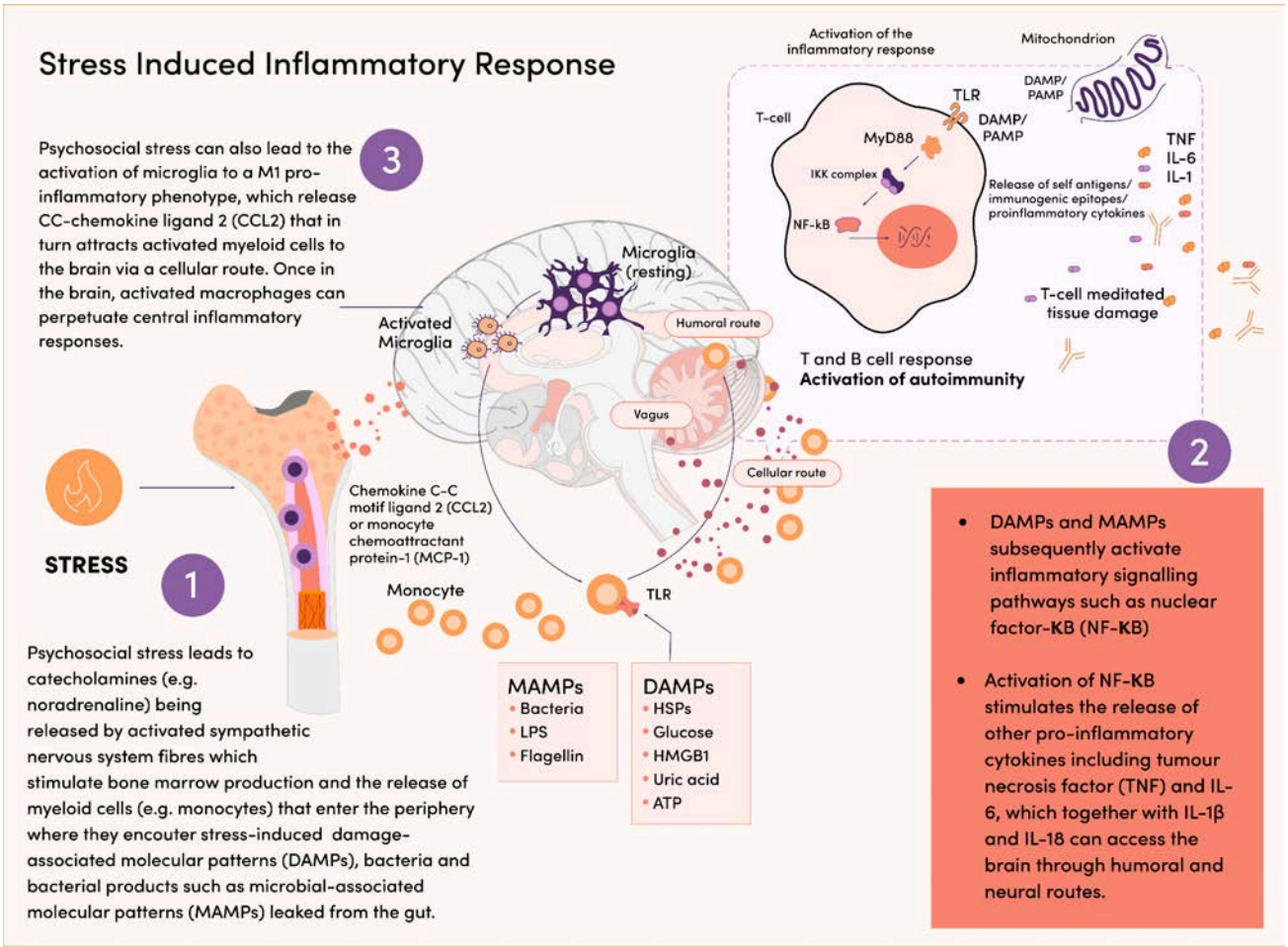
negative emotions and display aggressive, hostile, or angry behavioral patterns" – as a well-known risk factor in a range of chronic illnesses such as cardiovascular diseases, hypertension and asthma. They continue on to note depressive mood has been linked to "major changes in cellular immunity in a dose-dependent manner," including reduced lymphocyte response to antigens which normally incite their proliferation, and lowered levels of natural killer (NK) cell activity and white blood cell production. It seems the antidote to emotional distress is emotional resilience, where distress is the incapacity of the nervous system to deal with the burden it faces.

Negative impacts to the brain caused by toxic stress have also been qualified in numerous studies. Results presented by Knight et al suggest that perceived stress is linked to heightened systemic inflammation via diurnal cortisol in adults. "In particular, higher levels of perceived stress and traumatic life events were associated with flatter diurnal cortisol slopes, which in turn were associated with increased levels of inflammatory biomarkers. After adding covariates, this pattern was still observed for perceived stress but not for traumatic life events."[63]

[63] Knight, EL et al. Perceived Stress is Linked to Heightened Biomarkers of Inflammation via Diurnal Cortisol in a National Sample of Adults. Brain Behav Immun. 2021 Mar; 93: 206–213.

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Sickness Behavior



As discussed, stress is a state of threatened homeostasis provoked by a psychological, environmental, or physiological stressor, and the body responds by turning on inflammation, which is a protection mechanism[64]. Inflammation is the immune system's response to harmful stimuli, such as pathogens, damaged cells, toxic compounds, or irradiation[65], and acts by removing injurious stimuli and initiating the healing process[66]. Inflammation is therefore a

[64] Liu YZ, Wang YX, Jiang CL. Inflammation: The Common Pathway of Stress-Related Diseases. Front Hum Neurosci. 2017;11:316. Published 2017 Jun 20. doi:10.3389/fnhum.2017.00316
[65] Medzhitov R. Inflammation 2010: new adventures of an old flame. Cell. 2010;140:771–776.
[66] Ferrero-Miliani L, Nielsen O, Andersen P, Girardin S. Chronic inflammation: importance of NOD2 and NALP3 in interleukin-1β generation. Clin Exp Immunol. 2007;147:227–235.

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defense mechanism that is vital to the proper functioning of the body as it helps to mobilize the immune system when threats (real and perceived!) are detected and inflammation serves to flag the need for allocation of valuable metabolic resources to sites of injury. Usually, acute inflammatory responses lead to restoration of tissue homeostasis and resolution of the acute physiological issue. However, emerging research shows that persistent inflammation is a fundamental driver of many of today's chronic diseases, such as heart disease, cancer, type 2 diabetes, and irritable bowel syndrome[67].

Emotional stress may cause your body to have the same sickness response as infection or illness. The only difference is that it originates in the brain instead of being triggered by your immune cells. Your brain produces inflammatory molecules in response to stress exactly like it does in response to a message from your vagus nerve[68]. This is the premise of the Inflammatory Bias discussed previously.

It has been argued that sickness behavior evolved to reduce the probability of coming in contact with a predator, to minimize infection with conspecifics (a member of the same species aka someone else in the village!) or to reduce reproductive behavior at a time when the body's immune defenses are being actively mobilized.

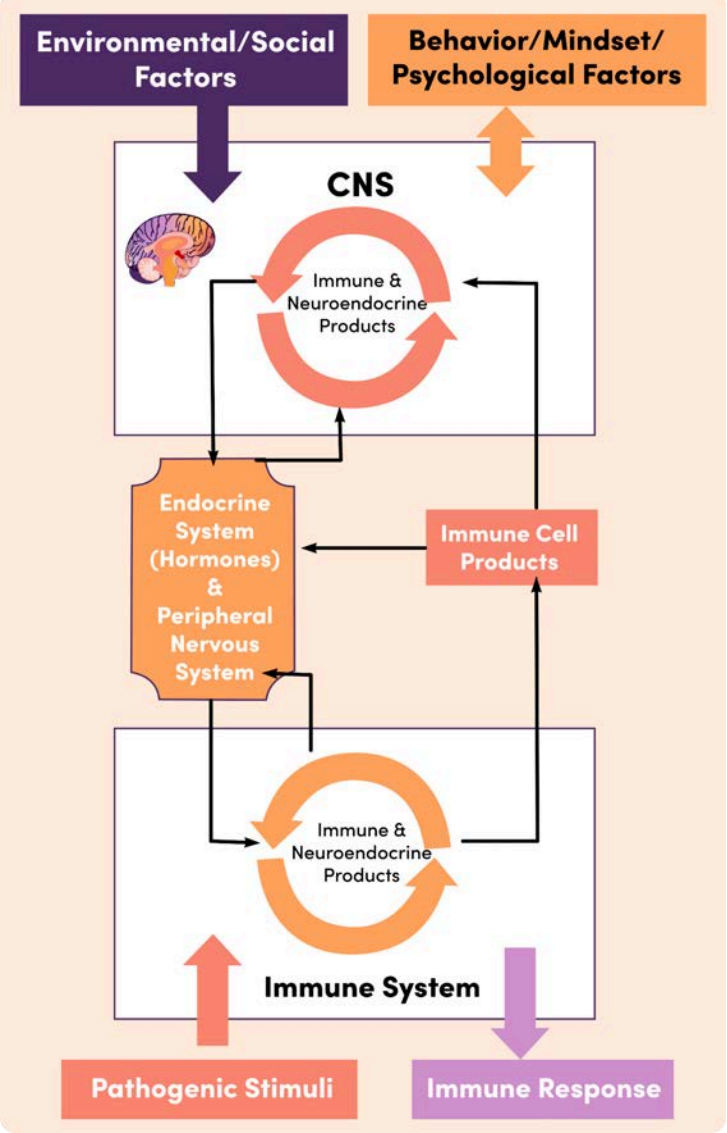
NeuroEndocrineImmune Circuit

It is too simplistic to view fever, pain, aversion to light, sound, and socializing, or sleepiness as the single specific physiological response that is solely responsible for imparting the survival-promoting property of sickness behavior. Instead, the mind and body is an integrated

[67] Chen L, Deng H, Cui H, et al. Inflammatory responses and inflammation-associated diseases in organs. Oncotarget. 2017;9(6):7204-7218. Published 2017 Dec 14. doi:10.18632/oncotarget.23208
[68] Lutgendorf SK, Costanzo ES. Psychoneuroimmunology and health psychology: an integrative model. Brain Behav Immun. 2003 Aug;17(4):225-32. doi: 10.1016/s0889-1591(03)00033-3. PMID: 12831823.

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unit that works together to promote survival and recovery during infectious episodes[69]. Behavioral changes are the same regardless of the infecting organism, and represent a critical component of the host *response* to infection[70].



Inflammatory molecules (cytokines) promote recruitment of immune cells locally, but also signal the brain and liver that infection (or injury) is occurring through neural and endocrine pathways. In response, the brain induces metabolic, hormonal, and behavior changes, such as fever, sickness behavior, activation of the HPA axis, and suppression of the HPG axis. Glucocorticoids released from the adrenals act as a brake on immune system activation to prevent the acute inflammatory phase from causing excessive damage to the body[71]. Besedovsky and del Ray

[69] Dantzer R, Kelley KW. Twenty years of research on cytokine-induced sickness behavior. Brain Behav Immun. 2007 Feb;21(2):153-60. doi: 10.1016/j.bbi.2006.09.006. Epub 2006 Nov 7. PMID: 17088043; PMCID: PMC1850954.
[70] Khandaker G, Colasanti A, Harrison N. Inflammation, Sickness Behaviour and Depression. In: Khandaker G, Harrison N, Bullmore E, Dantzer R, eds. Textbook of Immunopsychiatry. Cambridge University Press; 2021:109-138.
[71] Ashley NT, Demas GE. Neuroendocrine-immune circuits, phenotypes, and interactions. Horm Behav. 2017;87:25-34. doi:10.1016/j.yhbeh.2016.10.004

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were the first to discuss an integrated system in the body which they called the neuroendocrine-immune (NEI) circuit. The circuit represents a flow of signals and is defined by local (blue arrows) and long-loop (black arrows; multi-system) interactions that are altered according to extrinsic inputs (environment, social factors, pathogens). Primary outputs include immune responses, hormone secretions, activation of the peripheral nervous system, and behavioral alterations. Importantly, behavior can act as an input or output in the circuit. The white box encloses systems involved specifically with NEI interactions from the rest of the body[72].

Basic symptoms/behaviors observed in sickness behavior, are also observed in clinical depression, except for fever. Moreover, symptoms belonging to the three dimensions, for example, melancholia (a failure to react to pleasurable stimuli, and excessive psychomotor retardation and weight loss), anxiety, and somatic symptoms (malaise and hyperalgesia) also occur during sickness behavior[73].

PsychoDermatology

The skin not only senses stress but also responds to it - as the largest organ in the body, the skin plays crucial roles in protecting against outside threats and supporting the immune system, helping to keep the body balanced[74]. The skin is made up of two main layers: the epidermis and the dermis. The epidermis is a constantly renewing layer where new skin cells are produced, mature, and eventually shed. The outermost part of the epidermis, called the stratum corneum, is made of dead skin cells (corneocytes) embedded in a layer of fats. These corneocytes are

[72] Besedovsky HO, del Ray A. Immune-neuro-endocrine interactions: facts and hypothesis. Endocr Rev. 1996;17:64–102.
[73] Maes, M., Berk, M., Goehler, L. et al. Depression and sickness behavior are Janus-faced responses to shared inflammatory pathways. BMC Med 10, 66 (2012). https://doi.org/10.1186/1741-7015-10-66
[74] Chen Y, Lyga J. Brain-skin connection: stress, inflammation and skin aging. Inflamm Allergy Drug Targets. 2014;13(3):177-90. doi: 10.2174/1871528113666140522104422. PMID: 24853682

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tightly packed with keratin, a strong protein, and are connected to a protective outer layer. Lipids, or fats, in the skin flatten and form layers that spread out and join together, creating protective barriers. Beneath the epidermis, the dermis contains cells called fibroblasts and a network of proteins that give the skin its strength and flexibility.

The skin is the body's primary sensor for external stressors such as heat, cold, pain, and pressure. Three types of receptors—thermoreceptors (for temperature), nociceptors (for pain), and mechanoreceptors (for mechanical changes)—are responsible for transmitting signals from the environment to the spinal cord and then to the brain[75]. Additionally, the sensory fibers in the skin detect changes in temperature, pH, and the presence of inflammatory substances, relaying this information to the central nervous system. The nerve endings in the skin are often closely linked with these receptors, highlighting their strong interaction. The brain processes these signals and, in response, influences the skin's stress reactions. The skin and its associated structures are not only affected by key stress mediators but also produce these factors locally, which can trigger immune and inflammatory responses[76].

The detrimental effects of stress on wound healing were first clinically observed in humans when caregivers of relatives with dementia experienced a 20% longer healing time for dermal wounds[77]. Anxiety and depression have also been linked to slower healing in chronic wounds, with perceived stress and elevated cortisol levels identified as contributing factors[78].

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[75] Schmelz M. Neuronal sensitivity of the skin. Eur J Dermatol. 2011 May;21 Suppl 2:43-7. doi: 10.1684/ejd.2011.1265. PMID: 21628129.
[76] Slominski AT, Zmijewski MA, Skobowiat C, Zbytek B, Slominski RM, Steketee JD. Sensing the environment: regulation of local and global homeostasis by the skin's neuroendocrine system. Adv Anat Embryol Cell Biol. 2012;212:v, vii, 1-115. doi: 10.1007/978-3-642-19683-6_1. PMID: 22894052
[77] Kiecolt-Glaser JK, Marucha PT, Malarkey WB, Mercado AM, Glaser R. Slowing of wound healing by psychological stress. Lancet. 1995 Nov 4;346(8984):1194-6. doi: 10.1016/s0140-6736(95)92899-5.
[78] Ebrecht M, Hextall J, Kirtley LG, Taylor A, Dyson M, Weinman J. Perceived stress and cortisol levels predict speed of wound healing in healthy male adults. Psychoneuroendocrinology. 2004 Jul;29(6):798-809. doi: 10.1016/S0306-4530(03)00144-6. PMID: 15110929.

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Subsequent studies in both mice and humans have uncovered several key molecular mechanisms. The hypothalamic-pituitary-adrenal (HPA) axis is crucial, as treatments with glucocorticoid receptor antagonists have been shown to restore normal healing rates[79]. Stress disrupts the kinetics of inflammatory markers like IL1α and IL1β, and stressed patients exhibit significantly lower levels of the cytokines IL1α and IL8 at wound sites[80]. Additionally, MMP2 expression in blister wounds has been found to negatively correlate with plasma cortisol levels. In mice, stress can delay wound closure by slowing immune cell infiltration, reducing TNF-α levels at the wound site, and decreasing MMP activity[81]. Stress also compromises skin immune function, leading to more severe bacterial infections during the early stages of wound healing, partly due to reduced antimicrobial peptide expression[82]. Stress delays myofibroblast differentiation, which severely impairs wound contraction. TGF-β signaling is likely involved, as endogenous glucocorticoids influence wound healing by altering TGF-β expression, which in turn affects fibroblast proliferation, migration, and differentiation[83].

Emotional stressors have been shown to also exacerbate or cause a flare in atopic dermatitis and eczema[84], in part because psychological stress modulates various neuroendocrine

[79] Padgett DA, Marucha PT, Sheridan JF. Restraint stress slows cutaneous wound healing in mice. Brain Behav Immun. 1998 Mar;12(1):64-73. doi: 10.1006/brbi.1997.0512. PMID: 9570862.
[80] Glaser R, Kiecolt-Glaser JK, Marucha PT, MacCallum RC, Laskowski BF, Malarkey WB. Stress-related changes in proinflammatory cytokine production in wounds. Arch Gen Psychiatry. 1999 May;56(5):450-6. doi: 10.1001/archpsyc.56.5.450. PMID: 10232300.
[81] Romana-Souza B, Otranto M, Vieira AM, Filgueiras CC, Fierro IM, Monte-Alto-Costa A. Rotational stress-induced increase in epinephrine levels delays cutaneous wound healing in mice. Brain Behav Immun. 2010 Mar;24(3):427-37. doi: 10.1016/j.bbi.2009.11.012. Epub 2009 Nov 26. PMID: 19944145.
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[84] Lönndahl L, Abdelhadi S, Holst M, Lonne-Rahm SB, Nordlind K, Johansson B. Psychological Stress and Atopic Dermatitis: A Focus Group Study. Ann Dermatol. 2023 Oct;35(5):342-347. doi: 10.5021/ad.22.035. PMID: 37830415; PMCID: PMC10579569.

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mediators, which may in turn, activates local neurogenic inflammation and disrupt the skin barrier function[85].

Psycho-Oncology

Some studies have found that severe stress (e.g., death of a spouse or child) may increase cancer risk[86,87]; a 2008 meta-analysis did not find a significant effect for exposure to stressors on cancer incidence, but it suggested that certain personality and coping styles were associated with increased cancer risk[88]. More compelling and consistent is the evidence for the impact of psychosocial factors on clinical outcomes, particularly mortality, following a cancer diagnosis[89].

“About 50% of cancer patients have in fact been shown to have psychiatric disorders, including clinically significant emotional distress and/or unrecognized or untreated psychosocial conditions as a consequence of cancer at some point during the cancer trajectory. These problems are associated with the patient's reduction of quality of life, impairment in social relationships, longer rehabilitation time, poor adherence to treatment and abnormal illness behavior. Because of these reasons, the internationally recognised International Psycho-Oncology Society Standards of Quality Cancer Care underline that psychosocial cancer

[85] Arndt J, Smith N, Tausk F. Stress and atopic dermatitis. Curr Allergy Asthma Rep. 2008 Jul;8(4):312-7. doi: 10.1007/s11882-008-0050-6. PMID: 18606083.
[86] Duijts SF, Zeegers MP, Borne BV. The association between stressful life events and breast cancer risk: a meta-analysis. Int J Cancer. 2003;107:1023–9.
[87] Lillberg K, Verkasalo PK, Kaprio J, Teppo L, Helenius H, Koskenvuo M. Stressful life events and risk of breast cancer in 10,808 women: a cohort study. Am J Epidemiol. 2003;157:415–23.
[88] Chida Y, Hamer M, Wardle J, Steptoe A. Do stress-related psychosocial factors contribute to cancer incidence and survival? Nat Clin Pract Oncol. 2008;5:466–75.
[89] Sood AK, Lutgendorf SK. Stress influences on anoikis. Cancer Prev Res (Phila). 2011;4(4):481-485. doi:10.1158/1940-6207.CAPR-10-0358

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care should be recognised as a universal human right; that quality cancer care must integrate the psychosocial domain into routine care.[90]"

Early evaluation and screening for distress leads to early and timely management of psychological distress, which in turn has been proven to improve medical management[91]. Evidence from randomized trials shows that psychologically effective interventions may lead to a survival advantage in patients with cancer[92]. Overall, early detection and treatment of distress leads to better adherence to treatment, fewer calls and visits to the oncologist's office, and lower rates of severe anxiety or depression[93].

PsychoGynaecology

A 2023 cohort study[94] of over 138,000 women, acknowledged that psychological distress is considered a factor for cancer development and concluded that mood disorders were associated with an increased risk of cervical cancer development. In trying to theorize why this may be the case, the authors cited several possible physiological and psychological mechanisms: "... mental diseases may dysregulate several physiological functions leading to dysfunction of immune function, which in turn contributes to cancer development. For example, it has been suggested that stress and depression can foster tumor progression by inhibition of the expression of class-I and class-II major histocompatibility complex molecules and by reducing NK activity. Indeed, mental diseases are associated with decreased cytotoxic T cell

[90] Grassi L. Psychiatric and psychosocial implications in cancer care: the agenda of psycho-oncology. Epidemiol Psychiatr Sci. 2020 Jan 9;29:e89. doi: 10.1017/S2045796019000829. PMID: 31915101; PMCID: PMC7214699.
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[92] Spiegel D. Mind matters in cancer survival. JAMA. 2011 Feb 2;305(5):502-3. doi: 10.1001/jama.2011.69. PMID: 21285429.
[93] Holland JC, Andersen B, Breitbart WS, et al. Distress Management. J Natl Compr Canc Netw. 2013;11(2):190-209. doi:10.6004/jnccn.2013.0027
[94] Wu CT, Chiu LT. The Impact of Psychological Distress on Cervical Cancer. Cancers (Basel). 2023 Feb 9;15(4):1100. doi: 10.3390/cancers15041100. PMID: 36831443; PMCID: PMC9954541.

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and natural killer cell activities that are critical for the immune surveillance of tumors[95]. A previous study[96] reported that stressful negative life events were associated with a lower T cytotoxic/suppressor cell percentage and natural killer cell cytotoxicity in Black women and suggested that these events may lead to immune decrements, poor control over HPV infection, and increased vulnerability of developing cervical cancer. … (I)nnate psychological reasons for a link between mental diseases and cervical cancer may be due to negative emotional states, poor ego defense mechanisms, coping skills, a sad disposition following loss, and locus of control[97]."

Another paper[98] noted that a higher number of life stressors in the prior six months, the absence of social support, and personal coping styles employed influenced the progression of HPV infection[99]. In women, it has been shown that HPV infection and stress result in the disruption of IL-6 secretion and the progression of cervical lesions to cervical dysplasia. In chronically stressed caregivers who care for relatives suffering from dementia, a four-fold increase in IL-6 concentration was seen (by longitudinal observation). In women with cervical dysplasia, a connection between greater stress experiences and dysregulation of specific immune

[95] Reiche EM, Nunes SO, Morimoto HK. Stress, depression, the immune system, and cancer. Lancet Oncol. 2004 Oct;5(10):617-25. doi: 10.1016/S1470-2045(04)01597-9. PMID: 15465465.
[96] Byrnes DM, Antoni MH, Goodkin K, Efantis-Potter J, Asthana D, Simon T, Munajj J, Ironson G, Fletcher MA. Stressful events, pessimism, natural killer cell cytotoxicity, and cytotoxic/suppressor T cells in HIV+ black women at risk for cervical cancer. Psychosom Med. 1998 Nov-Dec;60(6):714-22. doi: 10.1097/00006842-199811000-00009. PMID: 9847030.
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responses has been observed. According to research by Cvitanović, a higher level of perceived stress means the probability of genital manifestations significantly increases (3.53 times)[100].

PsychoCardioangiology

A 1959 study of behavior patterns by Friedman and Rosenman suggested that a type A pattern of behavior, characterized by “an intense, sustained drive for achievement and as being continually involved in competition and deadlines, both at work and in their avocations” was a risk factor for cardiovascular disease. A very recent 2024 randomized control trial by Shimbo et al.[101] published in the Journal of the American Heart Association found that anger provocation adversely affects endothelial health by impairing endothelium-dependent vasodilation (there was impairment in RHI score from 0 to 40 minutes post induction of anger). Unlike anger, the emotions of anxiety and sadness did not show statistically significant adverse effects on endothelium-dependent vasodilation in this study.

Results from a 2021 study found that participants with cardiovascular diseases have experienced a higher number of early traumatic experiences compared to the control group, such as emotional neglect, emotional abuse, and physical abuse. Compared to the control group, women with cardiovascular diseases have experienced more traumatic events and seems to highlight an association between traumatic experiences in childhood and cardiovascular diseases in adulthood, particularly in women[102].

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[100] Cvitanović H, Milošević M, Bukvić-Bešlić I, Lugović-Mihić L. Determination of Psychological Stress, Serum Immune Parameters, and Cortisol Levels in Patients With Human Papilloma Virus. Clin Ther. 2020 May;42(5):783-799. doi: 10.1016/j.clinthera.2020.03.017. Epub 2020 Apr 25. PMID: 32340917.
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Another medical disease disproportionately affecting women is Takotsubo cardiomyopathy, also known as stress-induced cardiomyopathy or broken-heart syndrome. Takotsubo is a form of non-ischemic cardiomyopathy. In medical school, we are specifically taught this rare condition (it makes up for only around 1-2% of patients suspected of having acute coronary syndrome[103]) because the transient regional systolic dysfunction of the left ventricle is so overtly linked to an intense emotional or physical experience that it is presented as a curiosity to beguile the clinician-in-training. It is not usually studied as a unique insight into psychoneurohumoral pathways, or indeed any psychophysiological phenomenon.

The physiological expression of Takotsubo's is striking considering it is driven by psychological distress and as of 2023, the exact etiology is still not well understood! It is largely characterized by mimicking acute myocardial infarction with diffuse T-wave inversion and a prolonged QT interval, but with only minimal release of cardiac enzymes, and the regional wall motion abnormality extends beyond the territory perfused by a single epicardial coronary artery[104]. The negative emotional and stressful events that precede it are well documented and undoubtable, with 95% of sufferers being mostly post-menopausal women and the myopathy induced by acute intense stress[105] including: bereavement, divorce[106], bad financial news, legal problems, car accidents, natural disasters[107], exacerbation of chronic medical illness, new significant

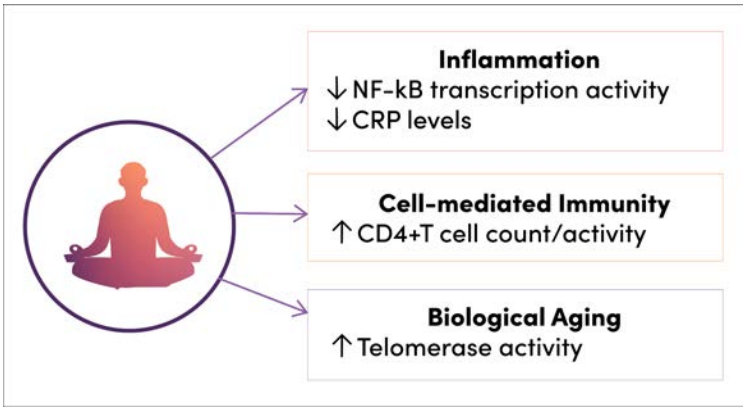
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[105] Merchant EE, Johnson SW, Nguyen P, Kang C, Mallon WK. Takotsubo cardiomyopathy: a case series and review of the literature. West J Emerg Med. 2008;9(2):104-111.
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medical diagnosis, surgery and other medical procedures, and staying in an intensive care unit[108].

Like many other clinical (medical) observations which are not purely within the spectrum of "physiological", those which partly sit within the realm of "psychological" are often ignored until they can no longer be. Takotsubo syndrome gained international awareness among researchers and physicians when Wittstein et al.[109] reported their findings in the New England Journal of Medicine in 2005. Case studies have actually been reported as far back as the early 1980s[110]. The Adverse Childhood Experiences (ACE) Study discussed later in this paper, is another such seminal study which changed the landscape of how psychophysiology was perceived by the medical community.

Biomarkers



A 2016 systematic review found that mindfulness meditation has at least a trend-level or dosage-dependent effect on immune parameters, specifically the following four parameters: reductions in the activity of the cellular transcription factor NF-kB,

[108] Park JH, Kang SJ, Song JK, et al. Left ventricular apical ballooning due to severe physical stress in patients admitted to the medical ICU. Chest. 2005;128:296–302.
[109] Wittstein IS, Thiemann DR, Lima JA, et al. Neurohumoral features of myocardial stunning due to sudden emotional stress. N Engl J Med. 2005;352(6):539-548. doi:10.1056/NEJMoa043046
[110] Y-Hassan S, Yamasaki K. History of takotsubo syndrome: is the syndrome really described as a disease entity first in 1990? Some inaccuracies. Int J Cardiol. 2013;166(3):736-737. doi:10.1016/j.ijcard.2012.09.183

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reductions in circulating levels of CRP, increases in CD4+ T cell count (in HIV-diagnosed individuals), and increases in telomerase activity[111].

A 2015 study of female breast cancer patients engaging in a 6-week mindful awareness practices course (compared to a waiting-list control group) showed a relative reduction in post-intervention circulating levels of interleukin 6 (IL-6 - an inflammatory cytokine) that was dependent on the frequency of practice dosage[112]. A 2009 study found that “women recently diagnosed with early stage breast cancer, enrolled in the mindfulness based stress reduction MBSR program had reduced cortisol levels, improved quality of life, and increased coping effectiveness compared to the Non-MBSR group.[113]”

Outside of cancer, Mindfulness-Based Interventions (MBIs) have showed significant improvements in the event-related potential amplitudes in attention-deficit hyperactivity disorder, the methylation of serotonin transporter genes in post-traumatic stress disorder, the salivary levels of IL-6 and tumor necrosis factor alpha (TNF-α) in depression, and the blood levels of adrenocorticotropic hormone (ACTH), IL-6, and TNF-α in generalized anxiety disorder. MBIs showed low but significant effects on health status related to biomarkers of low-grade inflammation with no heterogeneity[114]." A 2014 study showed a relative increase in IL-10 (anti-inflammatory cytokine and B-cell stimulator to make antibodies) in ulcerative colitis patients

[111] Black, D. S., & Slavich, G. M. (2016). Mindfulness meditation and the immune system: a systematic review of randomized controlled trials. Annals of the New York Academy of Sciences, 1373(1), 13–24. https://doi.org/10.1111/nyas.12998
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[114] Sanada K, Montero-Marin J, Barceló-Soler A, et al. Effects of Mindfulness-Based Interventions on Biomarkers and Low-Grade Inflammation in Patients with Psychiatric Disorders: A Meta-Analytic Review. Int J Mol Sci. 2020;21(7):2484. Published 2020 Apr 3. doi:10.3390/ijms21072484

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after mindfulness-based stress reduction (compared to a matched mind–body medicine program), specifically among patients who experienced a symptomatic flare up[115].

The Placebo and Nocebo Effects

The placebo effect is proof that healing can start in the mind. Placebo and nocebo are effects of the context surrounding medical treatment and are consistent across studies from different laboratories. These effects include reduced activity in brain areas associated with pain and negative emotion, and increased activity in the lateral and medial prefrontal cortex, ventral striatum and brainstem. Meaningfully, large placebo effects are likely to require a mixture of both conceptual belief in the placebo and prior experiences of treatment benefit, which engage brain learning processes[116]. Humans are endowed with uniquely powerful systems for representing context[117], which help to tailor our responses to the needs of a given situation[118].

The placebo effect can be orchestrated via the autonomic and neuroendocrine systems which are governed by the brain[119], and can be influenced by threatening psychological contexts[120] and verbal instructions[121]. Several studies have found that placebo analgesia is associated with

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[115] Jedel S, Hoffman A, Merriman P, et al. A randomized controlled trial of mindfulness-based stress reduction to prevent flare-up in patients with inactive ulcerative colitis. Digestion. 2014;89(2):142-155. doi:10.1159/000356316

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[119] Saper CB. The central autonomic nervous system: conscious visceral perception and autonomic pattern generation. Annu. Rev. Neurosci. 2002;25:433–469.

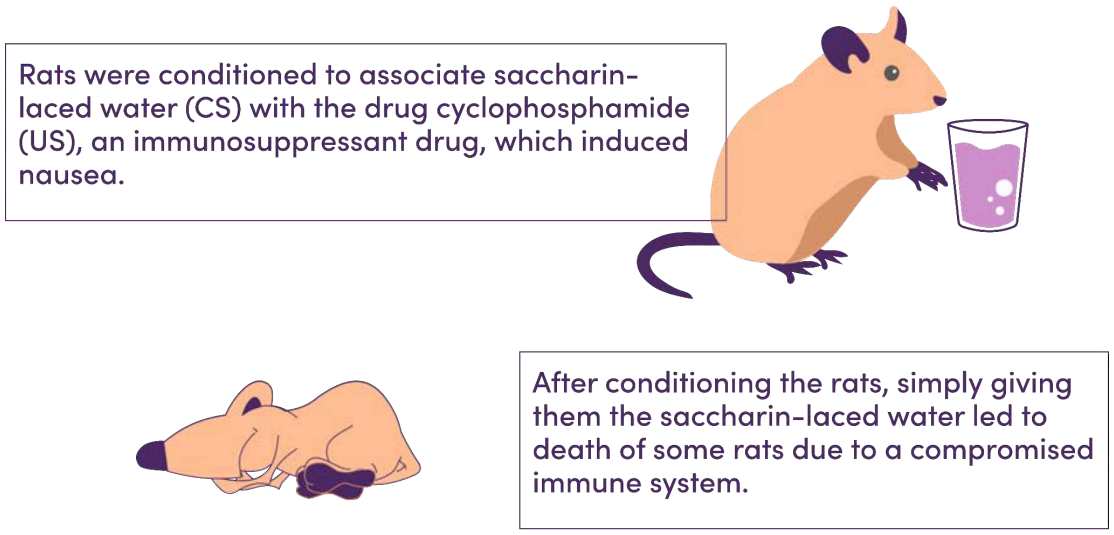
[120] Wager TD, et al. Brain mediators of cardiovascular responses to social threat, part II: prefrontal–subcortical pathways and relationship with anxiety. Neuroimage. 2009;47:836–851.

[121] Phelps EA, et al. Activation of the left amygdala to a cognitive representation of fear. Nat. Neurosci. 2001;4:437–441.

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changes in autonomic activity[122,123]. Placebo treatments can also affect hormonal responses that are mediated via forebrain control of hypothalamus–pituitary–hormone axes[124].

The autonomic and neuroendocrine systems interact with the immune system in multiple ways, providing a substrate for placebo effects on immune responses. The most compelling demonstrations of such interactions come from original psychoneuroimmunology work in the 1970s and 1980s which demonstrated that taste cues paired with immunosuppressive drugs in rats can induce immune responses just from subsequent exposure to the taste alone[125].



CS = conditioned stimulus; US= unconditioned stimulus.
Ader R, et al. Psychosom Med. 1975;37(4):333-340

[122]Geuter S, Büchel C. Facilitation of pain in the human spinal cord by nocebo treatment. J. Neurosci. 2013;33:13784–13790.
[123] Eippert F, et al. Activation of the opioidergic descending pain control system underlies placebo analgesia. Neuron. 2009;63:533–543. This study demonstrated, for the first time, that placebo-induced reductions in pain-related fMRI activity are reversible by naloxone.
[124] Benedetti F, et al. Conscious expectation and unconscious conditioning in analgesic, motor, and hormonal placebo/nocebo responses. J. Neurosci. 2003;23:4315–4323.
[125] Ader R, Cohen N. Behaviorally conditioned immunosuppression and murine systemic lupus erythematosus. Science. 1982;215:1534–1536.

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This psychoneuroimmune phenomena has been demonstrated in humans[126] which also showed that subsequent exposure to the taste cues that had been conditioned can suppress peripheral immune responses, particularly T lymphocyte proliferation and the release of interleukin-2 and interferon-γ from peripheral lymphocytes, with these effects likely mediated by norepinephrine sympathetic efferents[127]. This requires the insula and hypothalamus for their expression[128] and may be correlated with norepinephrine and anxious states[129], implicating forebrain control of the response.

Placebos might also affect other hormone systems, including those that regulate appetite. In one study, on 2 separate occasions, participants (n = 46) consumed a 380-calorie milkshake under the pretense that it was either a 620-calorie "indulgent" shake or a 140-calorie "sensible" shake. Ghrelin, a satiety hormone, was measured via intravenous blood samples at 3 time points: baseline (20 min), anticipatory (60 min), and post-consumption (90 min). During the first interval (between 20 and 60 min) participants were asked to view and rate the (misleading) label of the shake. During the second interval (between 60 and 90 min) participants were asked to drink and rate the milkshake. The mindset of indulgence produced a dramatically steeper decline in ghrelin after consuming the shake, whereas the mindset of sensibility produced a relatively flat ghrelin response. Participants' satiety was consistent with what they believed they were consuming rather than the actual nutritional value of what they consumed. Mindset meaningfully affects physiological responses to food[130].

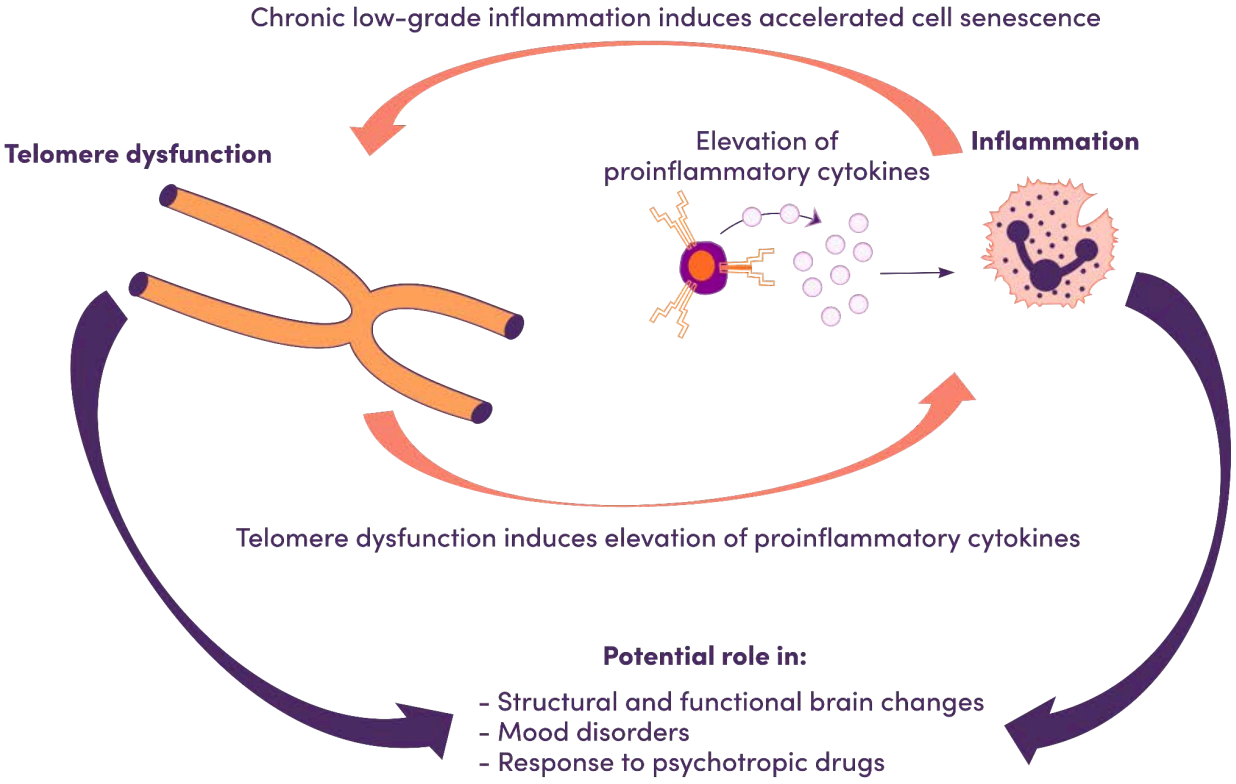
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[126] Goebel MU, et al. Behavioral conditioning of immunosuppression is possible in humans. FASEB J. 2002;16:1869–1873.
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Emotions and Telomere length

Telomeres are DNA–protein structures found at both ends of each chromosome that protect the genome from various issues including nucleolytic degradation, unnecessary recombination, and interchromosomal fusion. Progressive shortening of telomeres leads to senescence, apoptosis, or oncogenic transformation of somatic cells, affecting the health and lifespan of an individual. Shorter telomeres have been associated with increased incidence of diseases, including cancer, and poor survival[131].



[131] Shammas MA. Telomeres, lifestyle, cancer, and aging. Curr Opin Clin Nutr Metab Care. 2011;14(1):28-34. doi:10.1097/MCO.0b013e32834121b1

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The European Prospective Investigation into Cancer and Nutrition (EPIC) is an ongoing study located in 10 European countries, to track patients for cancer incidence and cause-specific mortality over several decades[132]. A 2011 study using EPIC data found evidence that adverse experiences during childhood may be associated with shorter telomere length with the findings remaining after covariate adjustment. There was evidence of a dose–response relationship with increasing number of reported childhood difficulties associated with decreasing relative mean telomere length[133].

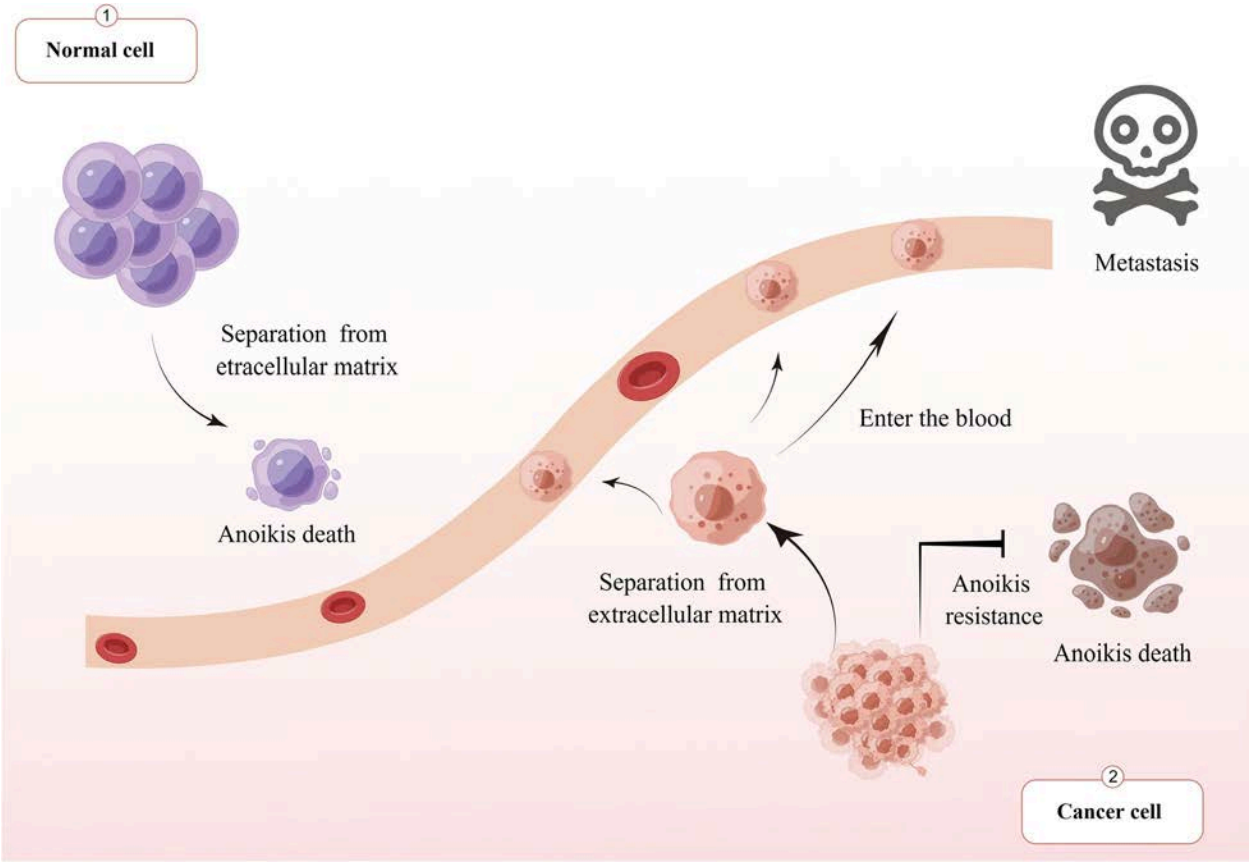
This is not the first study to show the correlation between life stressors, negative emotions, and shortened telomere length. The first study of this association, based upon a study of 58 healthy premenopausal women, found measures of perceived stress and enduring stress (through parenting a chronically ill child) to be associated with higher oxidative stress, lower telomerase activity, and shorter telomere length[134].

If emotional stress, an inability to recognise and/or deal with “triggers”, and impaired resilience is left untreated via an effective psychotherapeutic or psychosomatic intervention, their accompanying physiological changes can lead to a gradual degradation of the functioning of various bodily systems, including the immune system over time. This can eventually lead to epigenetic changes, DNA damage, cellular dysfunction and hence disease states like cancer, as the body/cells lose their ability to self-regulate properly due to the altered metabolic and physiological functioning from chronic stress. This is succinctly demonstrated by the fact that

[132] Riboli E, Hunt KJ, Slimani N, et al. European Prospective Investigation into Cancer and Nutrition (EPIC): study populations and data collection. Public Health Nutr. 2002;5(6B):1113-1124. doi:10.1079/PHN2002394
[133] Surtees PG, Wainwright NW, Pooley KA, et al. Life stress, emotional health, and mean telomere length in the European Prospective Investigation into Cancer (EPIC)-Norfolk population study. J Gerontol A Biol Sci Med Sci. 2011;66(11):1152-1162. doi:10.1093/gerona/glr112
[134] Epel ES, Blackburn EH, Lin J, et al. Accelerated telomere shortening in response to life stress, Proc Natl Acad Sci, 2004, vol. 101 (pg. 17312-17315)

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stress hormones can inhibit a process called anoikis, which kills diseased cells and prevents them from spreading[135].



Psychopathologies including Depression

Studies show psychopathologies, including rumination, anxiety and depression[136], involve dysfunction of cognitive and emotion regulation processes relying on distributed brain regions spanning multiple lobes[137]. Emotion regulation, as previously discussed in the Emotional

[135] Sood AK, Lutgendorf SK. Stress influences on anoikis. Cancer Prev Res (Phila). 2011;4(4):481-485. doi:10.1158/1940-6207.CAPR-10-0358
[136] Desrosiers A, Vine V, Klemanski DH, Nolen-Hoeksema S. Mindfulness and emotion regulation in depression and anxiety: common and distinct mechanisms of action. Depress Anxiety. 2013;30(7):654-661. doi:10.1002/da.22124
[137] Menon V. Large-scale brain networks and psychopathology: a unifying triple network model. Trends Cogn Sci. 2011;15(10):483-506. doi:10.1016/j.tics.2011.08.003

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Processing Model section, are primarily attempts at influencing emotions to reach adaptive goals (such as stable mental health) and impairment in any of these components leads to difficulties in emotion regulation and is a risk factor for psychopathologies[138]. In major depressive disorder, analyses of covariance and the repeated measures analysis of variance (ANOVA) show emotional regulation being impaired, persistent negative emotion and a decrease in positive affect, and deficits in cognitive control related to the use of maladaptive emotion regulation strategies[139].

Depression has been consistently associated with immune alterations and chronic low-grade inflammation, independent of risk factors such as poor diet, physical inactivity, obesity, smoking, atopy, dental caries, poor sleep and vitamin D deficiency,[140] as indicated by increased serum levels of the pro-inflammatory cytokines of CRP, IL-3, IL-6, IL-12, IL-18, sIL-2R and TNF α[141]. A 2020 meta-analysis concluded that "inflammatory marker elevations in depression are not due to an inflamed sub-group, but rather to a right shift of the immune marker distribution.[142]" Another study confirmed that "specific glycosylation traits are associated with depressive symptom severity and antidepressant response and may be of use as biomarkers.[143]"

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[138] Nolen-Hoeksema S, Aldao A. Gender and age differences in emotion regulation strategies and their relationship to depressive symptoms. Pers Individ Dif. 2011;51:704–8.
[139] Joormann J, Gotlib IH. Emotion regulation in depression: relation to cognitive inhibition. Cogn Emot. 2010;24(2):281-298. doi:10.1080/02699930903407948
[140] Berk M, Williams LJ, Jacka FN, O'Neil A, Pasco JA, Moylan S, Allen NB, Stuart AL, Hayley AC, Byrne ML, Maes M. So depression is an inflammatory disease, but where does the inflammation come from? BMC Med. 2013 Sep 12;11:200. doi: 10.1186/1741-7015-11-200. PMID: 24228900; PMCID: PMC3846682.
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[143] Park DI, Štambuk J, Razdorov G, Pučić-Baković M, Martins-de-Souza D, Lauc G, Turck CW. Blood plasma/IgG N-glycome biosignatures associated with major depressive disorder symptom severity and the antidepressant response. Sci Rep. 2018 Jan 9;8(1):179. doi: 10.1038/s41598-017-17500-0. PMID: 29317657; PMCID: PMC5760622.

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“Almost all molecular processes that are critical for physiological immune functioning (e.g., cell-cell communication, signal transduction, host-pathogen interactions) involve glycoproteins. The attachment of different glycans to the same protein (resulting in different glycoforms) influences its biological function, as it has an impact on the conformation, solubility, antigenicity, and the recognition of the associated glycoprotein. Alterations in the protein glycosylation pattern thereby allow the organism to quickly adapt its biological functions to changing environments.[144]” A 2018 study[145] was the first to demonstrate alterations in the serum glycation profile of women with major depressive disorder compared to controls which demonstrated a positive trend to the severity of depressive symptoms. The researchers also found that patients with a history of childhood sexual abuse showed the strongest alterations in the glycation profiles.

Adverse Maternal Emotional States Impacting Children’s Disease Risk

Lower fetal heart rate variability (fHRV) is associated with fetal distress and impaired development of the autonomic nervous system on both the sympathetic and parasympathetic branches[146]. The fetal autonomic nervous system adapts quickly to environmental changes, and maternal stress, chronic negative emotional states, poor lifestyle choices, pathologies and drug

[144] Boeck C, Pfister S, Bürkle A, Vanhooren V, Libert C, Salinas-Manrique J, Dietrich DE, Kolassa IT, Karabatsiakis A. Alterations of the serum N-glycan profile in female patients with Major Depressive Disorder. J Affect Disord. 2018 Jul;234:139-147. doi: 10.1016/j.jad.2018.02.082. Epub 2018 Feb 27. PMID: 29529546.
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[146] Schlatterer S.D., Du Plessis A.J. Exposures influencing the developing central autonomic nervous system. Birth defects res. 2021;113(11):845–863. doi: 10.1002/bdr2.1847.

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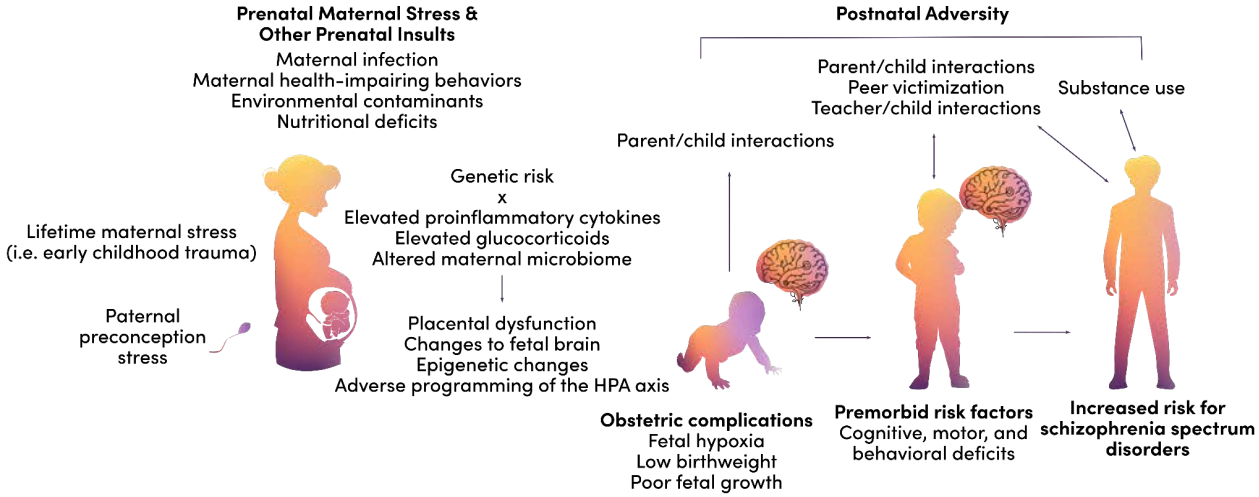
exposure[147] negatively influence fetal fHRV, especially in the second and third trimester of gestation[148], which is consistent with a delayed ANS maturation[149].

Psychological and emotional health, and chronic stress during pregnancy are also associated with many hormonal, inflammatory and metabolic changes. Maternal mood and emotional disorders have also been shown to activate the maternal HPA axis and is associated with a higher concentration of glucocorticoids hormones[150] and program the HPA axis and physiology of the fetus[151] which impacts fetal synaptogenesis and neurotransmitters' functions on receptor expression (see: Neuroplasticity), maturation of organs, birth weight[152]. The literature is full of examples of how the downstream effects of sustained and chronic negative emotions is negatively associated with fetal motor activity[153], infants' stress reactivity[154], and nervous system development[155] which leads to future impairments in cognitive functions[156], including poor attention regulation, fearful temperament, and negative reactivity to novelty in the first year of life; behavioral and emotional problems and decreased gray matter density in childhood; and

[147] Cerritelli F., et al. A review on the vagus nerve and autonomic nervous system during fetal development: searching for critical windows. Front. Neurosci. 2021;15 doi: 10.3389/fnins.2021.721605.
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poor emotion regulation[157], impulsivity, externalizing, and processing speed in adolescents; and major mental disorders in later life including schizophrenia[158,159,160].



As per the previous NeuroEndocrineImmune section, negative maternal emotional states affects the maternal inflammatory response, and there is a positive linear relationship between stress levels and IL-6 concentrations[161]. Whilst important for healthy and appropriate inflammatory responses, cytokines such as IL-6 can act as teratogens, leading to birth defects, pregnancy complications or premature birth[162,163].

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An important paper from 2021 demonstrated that negative affect/stress during pregnancy is reflected in functional network differences in the human brain in utero as the main criticism of the literature has been the confounding correlates of prenatal stress influencing the postnatal rearing environment. Importantly, Thomason et al. showed that emotional and stress management, and interpersonal and health behaviors could mitigate prenatal brain programming[164].

Pain and Central Sensitivity Syndromes

Studies exploring the impact of mood, mindset and emotions on the perception of pain, usually points to the priming of the defensive system by negative emotions which then facilitates pain perception, however, there is also a phenomena called “stress-induced analgesia”[165]. For the purposes of this document, I am going to focus on the fact that the majority of studies using mood induction on experimentally-induced pain found that positive emotions and mood reduces pain perception[166,167].

Findings from a psychophysical study by Rhudy et al. seem to confirm an interaction between emotion and arousal. The valence of stimuli presented for mood induction determined the direction of the modulation where there was decreased pain during positive emotion, and the magnitude of the modulation was determined by the level of arousal[168].

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[168] Rhudy JL, Williams AE, McCabe KM, Russell JL, Maynard LJ. Emotional control of nociceptive reactions (ECON): do affective valence and arousal play a role?. Pain. 2008;136(3):250-261. doi:10.1016/j.pain.2007.06.031

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There is a significant predisposing relationship between depression and headache, neck/shoulder pain, back pain, and stomach/abdominal pain. Baker et al. argued that emotions lie at the interface between physical and psychological processes and therefore, impaired emotional processing may be associated with both psychological factors and physical conditions such as chronic lower back pain[169].

A 2023 study stated that anxiety is a unidirectional high-risk factor for neck/shoulder pain and back pain. The somatic expression of psychic angst, apart from being due to neurohormones and immune aberrations, can also be traced to how the fascia and muscles respond to emotions. The study also highlighted a bidirectional predisposing relationship between the absence of pain and maintaining good mental health, further supporting the existence of causal relationships between localized pain and emotions[170].

Generalized sensory hypersensitivity has been associated with activation of a cortical network composed of the anterior cingulate, the insula, and the prefrontal cortex[171]. The function of these neural regions is not just correlated to pain but is also related to emotion perception and regulation. These regions are involved in the more general function of extracting salient sensory stimuli for subsequent higher-order neural processing[172]. More is discussed in the section on Neural Correlates of Emotion, and Neuroplasticity.

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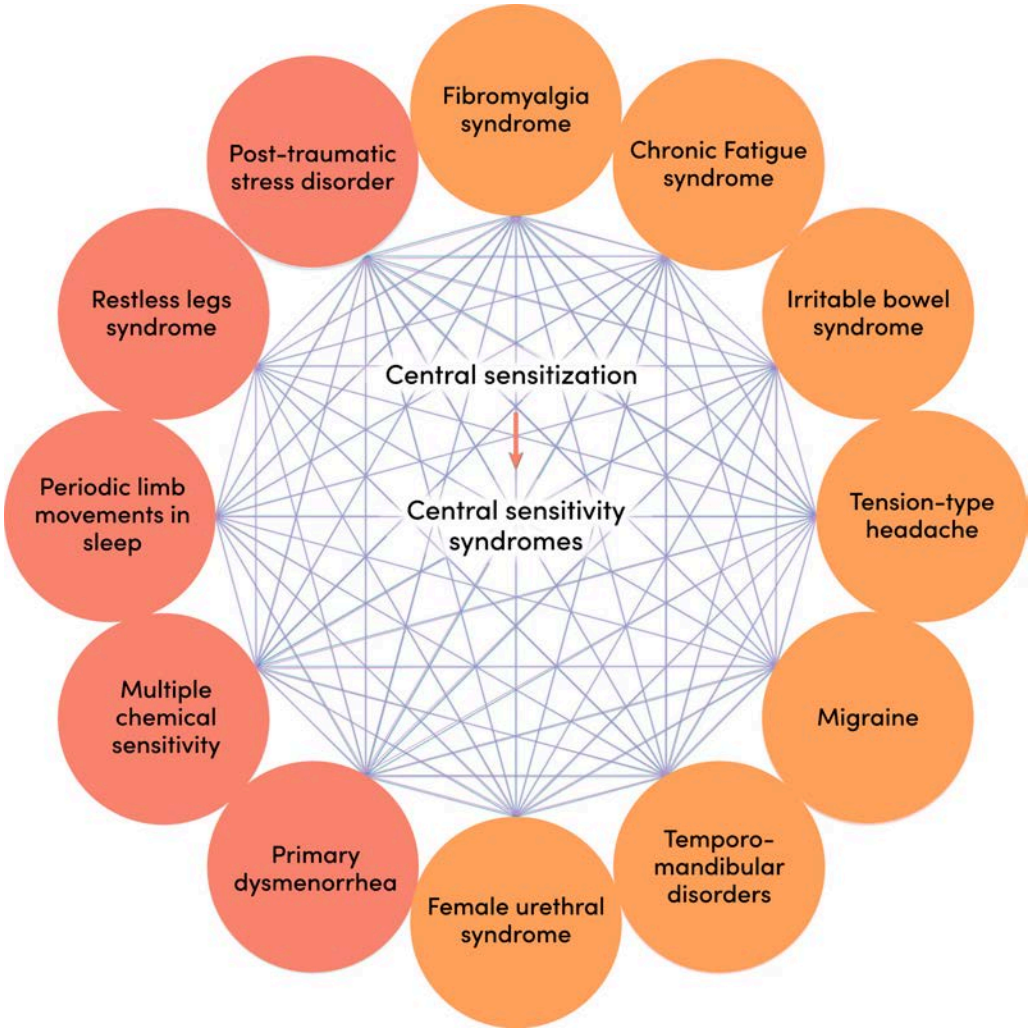
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There are many psychobehavioral interventions which have shown some efficacy on the bidirectional relationship of emotional regulation and pain. The Internal Family Systems (IFS) model is a rapidly emerging individual psychotherapeutic modality that teaches patients to attend to and interact with their internal experience mindfully. This non-pathologizing and non-judgmental noticing model actively recruits self-compassion to observe the “parts” that make up the person’s whole being, which (should) work harmoniously together, and which each has valuable qualities and roles. The parts are manifested by strong feelings, judgments, or physical sensations[173]. Through painful life experiences which exceed the capacity of the person to cope, these parts may be forced to adopt maladaptive and potentially unhealthy roles which phenotype as disease symptoms, but which are intended to help the person manage difficult emotions and buffer against future painful events. IFS is increasingly being used as adjunctive therapy for certain medical conditions, with anecdotal benefit reported in migraines and back pain[174].

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Myalgic Encephalomyelitis/Chronic Fatigue Syndrome ME/CFS

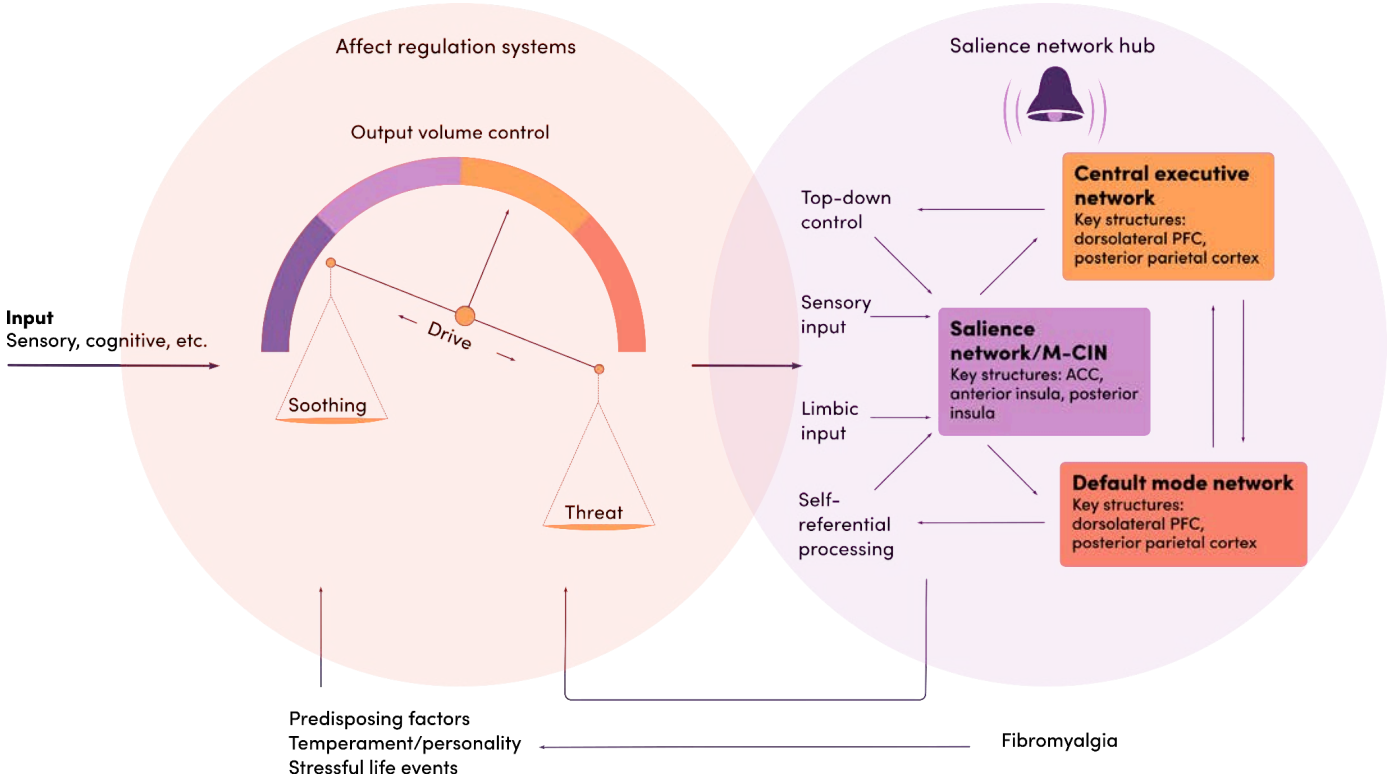
A study investigating emotional regulation in women with Myalgic Encephalomyelitis/Chronic Fatigue Syndrome and/or depression. ME/CFS participants, in general, were found to exhibit more impairment in representing emotions and in adaptive defenses compared to the depressive disorder and healthy control groups - within both the ME/CFS plus higher depression

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and the ME/CFS plus lower depression groups, weaknesses in representing emotions and in defensive functioning were associated with more severe physical symptoms[175].

Fibromyalgia

A 2022 paper published in Nature proposed a model of fibromyalgia that integrates current psychosocial and neurophysiological observations. In this integrative model, which Pinto et al. term “Fibromyalgia: Imbalance of Threat and Soothing Systems (FITSS)”, they propose that an imbalance in emotion regulation might keep the salience network in continuous alert mode, and this hyperactivation contributes to the syndrome known as fibromyalgia.



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Endometriosis

The Generalized Unsafety Theory of Stress suggests that people feel stressed until they see signs of safety. This idea helps understand why stress can last a long time even without immediate problems[176]. Endometriosis causes ongoing stress because it's unpredictable and hard to control, leading to constant worry about the disease getting worse without clear treatment.

Studies show that endometriosis can progress faster due to stress from feeling out of control. Lack of safety signals increases worry about symptoms, making people watch their symptoms more closely, also known as hypervigilance.

Research into the history of sexual or physical abuse and its subsequent diagnosis of endometriosis reveals a complex interplay of factors that contribute to the condition's development and diagnosis. A study by Johanna Netzl et al. found that 42.9% of participants with endometriosis reported childhood maltreatment, indicating a significant association between early life trauma and the later development of endometriosis[177]. Another study found a 79% higher risk of developing endometriosis for those who experienced both severe physical and sexual abuse during childhood[178]. We discuss later in this document how early trauma can affect how the body responds to stress, in fact, Reis et al.[179] concluded that childhood stress should be considered a risk factor for the development of endometriosis, since these events

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may cause persistent alterations in the neural and hormonal stress responses, chronic inflammation, dysregulation to the HPA axis and subsequent pain sensitivity and severity, and progression of disease.

Back Pain

John Sarno's work[180] on back pain emphasizes the significant role of emotions in the manifestation and persistence of pain. Sarno posited that repressed emotions, particularly anger and anxiety, could lead to tension myositis syndrome (TMS), a condition where psychological stress manifests as physical pain, particularly in the back. This perspective aligns with findings from various studies that highlight the intricate relationship between emotional states and pain perception.

A paper[181] that explored the brain maps of patients with acute pain vs chronic pain used meta-analytic probabilistic maps related to the terms pain, emotion, and reward (each map is based on >200 brain imaging studies, derived from neurosynth.org). They observed that “brain activity for back pain in the early, acute/subacute back pain group is limited to regions involved in acute pain, whereas in the chronic back pain group, activity is confined to emotion-related circuitry. In the recovered acute/subacute back pain group, brain activity diminished in time, whereas in the persistent acute/subacute back pain group, activity diminished in acute pain regions, increased in emotion-related circuitry, and remained unchanged in reward circuitry.”

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Positive Emotions as Drivers in Healing Processes

In contrast to negative emotions creating adverse physiological impacts, positive emotions have been associated with increases in health benefits and overall well-being, including lower blood pressure, reduced cardiovascular risk, better weight control, healthy blood sugar levels, and increased longevity. A key conceptual framework that describes the psychological benefits of positive emotions is Frederickson's Broaden and Build Model (BBM)[182] where an individual's attentional scope is broadened with more neural connections promoting more global information processing. Positive emotions are thought to build resilience[183] where resilience is seen as advantageous in decision-making and problem solving[184], self-regulation and coping[185] and social relationships[186].

McTeague's group of researchers note that neural functioning, cardiovascular health, immune function, and the hormone system are all involved with stress responses in the human body and their relationship could be bidirectional. Neuroimaging shows that positive emotions can drive healthful changes in the body by activating reward pathways in the brain[187]. This is discussed in more detail in the Neural Correlates of Emotion, and Neuroplasticity section.

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A cancer diagnosis and subsequent onerous treatment evoke existential concerns, especially ones related to meaning in life and meaning-making processes[188]. According to a 2018 paper in Frontiers in Pharmacology, “a growing body of evidence shows that existential and spiritual well-being in cancer patients is associated with better medical outcomes, improved quality of life, and serves as a buffer against depression, hopelessness, and desire for hastened death”[189]. Acceptance and Commitment Therapy (ACT) has an emphasis on accepting unwanted thoughts and emotions, and promoting actions in accordance with personal values. In cancer patients, ACT has been shown to help increase quality of life, promote positive emotional states, and improve psychological flexibility[190]. Regulation of emotions means that patients are able to appropriately and positively evaluate stressful situations, identify potential triggers, and resist reactivity whilst coping with more purpose, insight and proactivity[191]. These habits of thought and action help with the underlying neural structures associated with stress and response, including the amygdala. Structural changes in the amygdala associated with adverse childhood experiences, toxic stress and chronic negative emotions contribute to the later emergence of emotional pathologies by influencing the way that the brain responds to negative environments and provocation. A healthy amygdala is adept at modulating stress-induced activity of the HPA

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axis and protecting downstream bodily systems (i.e. cardiovascular, nervous, immune, endocrine) from the burden of overactivation[192].

In researching major institutions for their perspectives on the effects of emotions and psychology on physiology and disease manifestation, we came upon The Yale Program for Medicine, Spirituality & Religion under General Internal Medicine, which the university states is "founded upon the belief that healing concerns the wellness of both the body and the spirit".[193] The following is from the course material which can be freely found online:

> *"Mind, body, and spirit are closely interwoven, with each influencing the others. Some people believe that you cannot have healing on the level of the body without healing on the level of the mind and spirit. The word "spiritual" is often confused with religious. However, spirituality is not confined to religion or to one set of beliefs, or doctrines. Spirituality is an essential part of who and what we are and what we value. It is therefore profoundly personal, and means something different for every person."*[194]

Emotional Regulation as a Tool for Healing and Improving Health

Ontogenetic development can be conceptualized as the portion of physical, cognitive, emotional, and social development that can be attributed to experiences with the environment and the individuals within the environment. These developmental factors can positively or negatively influence a subject's emotional and physical well-being depending on the

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circumstances and the person's outlook. A subject's adeptness at emotional regulation and embracing a positive mindset can be helpful in adapting to their environment and enhancing their physical and emotional well-being. Subjects who promote and exhibit positive mindsets and emotions are better equipped to cope with difficult situations, demonstrating better resilience and ability to "bounce back". If positive emotional responses and regulation can be learned and/or employed by a subject, their control over their own bodily wellness improves.

Healing and Recovery

Comprehensive recovery from injury or disease involves two key components: recovery of the body and recovery of the self - a composite of one's roles, values, identities and beliefs. Recovery of the body included the functional outcomes commonly targeted by physical therapy and rehabilitation: the recovery of form, function, and ability. A 2020 paper on rehabilitation discussed the important component of "recovery of the self" where injury threatens one's self-concept, and the consequences of disability from injury or disease might be incongruent with an individual's understanding of themselves or their assumptions of how the world should operate. For example, an individual's form, function, and abilities could be a deeply integrated part of their identity and how they understood themselves (ie, through work, hobbies and social roles) and therefore, illness affecting one's ability to perform in a way that they self-identify could pose a threat to one's self-concept[195].

[195] Rosenberg G, Zion SR, Shearer E, et al. What constitutes a 'successful' recovery? Patient perceptions of the recovery process after a traumatic injury. Trauma Surg Acute Care Open. 2020;5(1):e000427. Published 2020 Feb 23. doi:10.1136/tsaco-2019-000427

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Internal Locus of Control and the Sense of Agency

Chronic disease burden can saddle patients with feelings of helplessness and loss of agency. Sense of agency refers to the feeling of control over actions and their consequences[196]. This is especially so in patients who have not been counseled about the potential benefits of their positive emotions and lifestyle choices to their disease trajectory. Reductions in a sense of agency is associated with poor health and a reduction in quality of life[197] and a key factor in this reduced feeling of control has been elucidated to be, in part, a reduction in the basic capacity for agency due physical impairment such as that which occurs in disease[198].

Psychological factors such as the locus of control and the sense of agency could influence an individual's ability to learn to control brain activity, and subsequently, physiological processes. Studies found that the locus of control was negatively correlated with the power of sensorimotor rhythm (SMR) self-regulation and this higher effort in turn may interfere with brain states of relaxation as reflected in the SMR. As a consequence, one way to improve control over brain signals in neurofeedback paradigms may be to explicitly instruct users not to force mastery but instead to aim at a state of effortless relaxation[199].

Sense of Agency has been discussed in the literature to recruit some of the same regions that have been described for intentional bodily actions, including the supplementary motor area, ventral premotor cortex, posterior parietal cortex, temporo-parietal junction, and cerebellum.

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Sense of Agency directly influences brain networks that affect physiology[200]. One study found that cognitive strategies activated the midbrain and that neurofeedback further enhanced midbrain activity, but self-regulation was not effective during the 'transfer' session when participants attempted to perform volitional control in the absence of feedback.[201]

In hospital settings, it is well-founded that interventions to improve patient knowledge have been directly linked to improved outcomes[202]. In a similar vein, we can demonstrate that people who have used the Liber8 app to help them deal with emotional struggles and triggers experience a heightened sense of well-being.

The Bidirectional Relationship Between Emotions and Behaviors

McTeague et al. note that psychologists have previously tried to explain how emotions and health relate to one another and that a transactional analysis model would consider health as determined by a subject's response to stressors, which is influenced by the subject's emotional regulation, incorporating choice and evaluation of both stressors and their coping responses. They cite another model as suggesting that emotional regulation affects adoption of both healthy and unhealthy behaviors which in turn influence physical health.

The self-perception theory is built on the natural science of behaviorism that explains how emotional feelings follow behavior, with variable individual expression[203]. The "somatic marker" of embodiment has been proposed as the reactivation of bodily and neural responses involved

[200] David N, Newen A, Vogeley K (2008) The "sense of agency" and its underlying cognitive and neural mechanisms. Conscious Cogn 17:523–534 10.1016/j.concog.2008.03.004
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in lower-level sensorimotor processes contributing to subjective awareness[204]. A comprehensive theoretical neuro model formulated by Seth et al. gave weight to emotion as an interoceptive inference and was based on interoceptive prediction error, and informed by "predictive models of agency, general models of hierarchical predictive coding and dopaminergic signaling in cortex, the role of the anterior insular cortex in interoception and emotion, and cognitive neuroscience evidence from studies of virtual reality and of psychiatric disorders of presence, specifically depersonalization/derealization disorder". Thus, subjective feelings can be seen as based on the active interpretation of changes in the physiological conditions of the body[205].

Bidirectional relationships in clinical phenotypes have been established between human emotions and exhibited behaviors, such as eating and breathing. Studies have shown that emotions can induce eating by controlling choice of foods or restricting food intake, emotions can switch off higher brain control of eating, and subjects will eat to reduce the intensity of their emotions.[206] Both overeating and undereating can harm a subject's physical health, but changes in their eating behaviors could result as a byproduct of their emotions/emotional regulation, hindering healthy eating patterns. Dubé et al. note that "comfort food" (i.e. high in fat and sugar) can temporarily alleviate negative emotions in humans, resulting in their use as a coping mechanism and that this temporary relief/stress response drives unhealthy food intake which can negatively impact the body later on.

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Breathwork

States of stress and negative emotions have correlating ANS sympathetic-dominant state activity, and low HRV are common in stress, and techniques like HRV biofeedback can be helpful[207], and similar efficacy is seen by pacing respiration slowly at approximately 5–6 breaths/minute[208]. Voluntary modification of breathing influences brain regions regulating behavior, thought and emotion[209], slower paced inspiration synchronizes brain waves[210], thus enabling more effective communication between neural networks[211].

Jerath et al. correlate waveforms of breathing activity with emotions, suggesting respiratory patterns are not only influenced by emotion but can themselves influence emotion in a “bi-directional relationship between the body and the mind."[212] Because the respiration-emotion relationship is reciprocal, people may voluntarily influence their emotional state by changing their respiration pattern. While emotions have such a reciprocal relationship with other bodily functions, respiration is special because it can be voluntarily altered. We want to highlight the fact that there is much agency and the person’s ability to change their physiology by emotional regulation and behavior.

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Neural Correlates of Emotion

The Human Connectome Project[213], the field of neuroscience, the study of neuroplasticity and advanced neuroimaging have been some of the biggest contributors to the understanding of how emotions can affect physiology, brain structure and brain function[214].

Brain imaging mapping of stimuli that trigger the mesolimbic (reward) system show longer activation by positive emotions as opposed to negative emotions, during which time, well-being is experienced by the individual[215]. All emotions, negative and positive engaged neural structures related to the representation and/or regulation of organism state, where the regions are all direct and indirect recipients of signals from the internal milieu, viscera and musculoskeletal frame, which would explain these structures also being involved in the perception and processing of pain. In addition, some of these regions, namely, some brainstem nuclei, the hypothalamus, and subsectors of the insula and cingulate, also generate regulatory signals necessary to maintain homeostasis[216], underpinning the close anatomical and physiological connection between emotion and homeostasis, and between emotion and mapping of the ongoing multidimensional state of the organism.

The maps in regions of the brain that receive regulatory signals from brainstem and hypothalamus in addition to direct sensory signals from the organism provide integrated perceptual maps of the organism state[217]. The feeling-state of emotions might be grounded in

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emotion-specific neural patterns in the anterior cingulate, insula, ventromedial prefrontal, and subcortical structures, such as the amygdala, ventral striatum, putamen, caudate nucleus, and ventral tegmental area[218]. The neural patterns provide distinctive ‘perceptual landscapes’ of the organism's internal state, and the differences among those landscapes constitute the critical reason why each emotion feels different[219].

Neuroplasticity and Epigenetics

Neuroplasticity is the brain's ability to change, reorganize, adapt and grow neural networks due to intrinsic and extrinsic stimuli e.g., thinking[220], emotions and their regulation[221], transcranial magnetic stimulation[222], experiences[223], and psychoactive drugs[224]. Our early neurological development has long-term impacts on our emotional, behavioral, and relational patterns. Developmental biologist Dr. Bruce Lipton suggests that as much of 95% of our life comes from the programs learned by our subconscious up to age seven[225]. As we age and cross the threshold into adolescence and then into adulthood, we default to the programs that were

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downloaded into our system as infants or young children, especially if we have not made conscious efforts to change habits of thought, emotions or movement via neuroplasticity[226].

Synaptogenesis is the process of new synapses forming between neurons within the nervous system. While this process happens throughout human life, it's particularly active within the first seven years of a child's life. Research shows that in addition to a child's genetics, this process is impacted by a child's environment[227]. The developing neural architecture is damaged when a child is subjected to an environment of toxic stress[228]. Despite the trauma that occurs when we are young, the human brain expresses a high degree of neuroplasticity throughout its lifespan and this capability makes it possible for us to address and modify our most self-limiting behaviors, beliefs, and mental loops[229].

Terasawa et al. argued effectively for their hypothesis that the anterior insular cortex (part of the salience network) represents the process of attending to interoceptive information, not only for bodily perception, but also the significance of interoceptive processing for the awareness of the subjective experience of emotion[230], and emotional and bodily awareness are both engaged during the suppression of emotional responses. In the first-of-its-kind study between emotions and neuroplasticity, Guiliani et al. (2011) showed that habitual engagement of expressive suppression (an emotion regulation strategy), but not negative affect and cognitive reappraisal relates meaningfully to anterior insula volume consistent with the idea that trait patterns of

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emotion processing are related to brain structure[231]. Encouraging social and peer support groups to their patients, is a strategy employed by the astute health practitioner which has been shown to positively affect cognitive reappraisal and negatively affect expressive suppression[232].

Davidson et al. demonstrated that for normal adults, training in mindfulness meditation (for 8 weeks) was associated with greater left-sided anterior brain activation which in turn has been linked with ‘‘more adaptive responding to negative and/or stressful events. Specifically, faster recovery after a negative provocation’’ (p. 569)[233].

The aberrant patterns, experiences, and rhythms of early-life inputs are, in part, experienced in the form of maternal (and paternal) care behaviors. This is discussed in more depth in the section on Erikson’s Psychosocial Stage Theory. These individual differences in emotion regulation usage have neural correlates that not only demonstrate the impact on neural processing, but also leads to internal working models, attachment styles, and influences cognitive and emotional outcomes by affecting the maturation and structure of the underlying brain networks[234,235].

Gratitude as a practice is a seeming institution in the halls of emotional wellness. Whilst it has been discussed in the literature as being a feeling/emotion[236] experienced when we are the

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“beneficiaries of good human conduct”, it is also a state of being that we can volitionally enter into - according to Fox et al., Seneca discussed gratitude as a “fundamental motivational drive”[237].

In 2015, Fox et al. conducted an experiment they found that ratings of gratitude correlated with brain activity in the anterior cingulate cortex (part of the salience network) and medial prefrontal cortex (the same part of the brain activated with the placebo effect, see section on the Placebo and Nocebo effects). The results provide a window into the brain circuitry for moral cognition and positive emotion that accompanies the experience of benefitting from the goodwill of others.

Both the anterior insula cortex and anterior cingulate cortex have been mentioned in this section and we wanted to briefly discuss the salience network in context of emotional processing. The salience network gauges the potential threat-value of any neural input, whatever its nature: painful, tactile, auditory, visual, olfactory, proprioceptive, biochemical, cognitive or emotional[238]. This network is sensitive to brain changes induced by real or imagined threats[239].

Sensorimotor Psychotherapy

Sensorimotor approaches to psychotherapy find their roots in experience-dependent neuroplasticity which seeks to repeatedly evoke an organizing response conducive to environmental and self-mastery. Interventions such as Sensorimotor Psychotherapy[240], Somatic

[237] Fox GR, Kaplan J, Damasio H, Damasio A. Neural correlates of gratitude. Front Psychol. 2015;6:1491. Published 2015 Sep 30. doi:10.3389/fpsyg.2015.01491
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Experiencing[241], and Sensory Motor Arousal Regulation Therapy[242] emphasize mindful attention to touch, postures, and movement. The neurophysiological rationale for Somatic Experiencing therapy involved, including a theory of trauma and chronic stress as a functional dysregulation of the complex dynamical system formed by the subcortical autonomic, limbic, motor and arousal systems.

Eye Movement Desensitization and Reprocessing therapy (EMDR)

EMDR is hypothesized to promote neuroplasticity in regulatory regions related to emotional processing[243], and the intervention facilitates heightened activity in motor regions involved in the cognitive–motor feedback loop. Areas of the frontal lobe, including the medial and dorsolateral prefrontal cortex[244,245] are stimulated during EMDR, which have been found to be responsible for fear inhibition, fear extinction learning, and emotional regulation[246].

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Theoretical Underpinnings

The major issues with “Mind-Body Medicine” being perceived as “woo” and “not scientific” are behind us, but the biases live on. Up until recently, we had seemingly not been able to qualify and quantify the science behind how stress, thoughts and feelings can change physiology and thus affect disease. The other aspect that has made this field difficult to embrace by the medical community, is that it is the perception of events and interactions that lead to thoughts, feelings and emotions, and perception changes vastly from person to person as it is massaged by epigenetics, personality, and previous experiences. *How* one *perceives* interactions is a difficult-to-quantify phenomenon, and this is why we needed Human Experience Theories to provide a framework.

Dr Gabor Maté and Dr Janet Dollin have collaborated academically and in an opinion piece in 2005, Dr Maté rejected Dr Dollin’s claim that there was a dearth in the ability to validate the science of psychoneuroimmunology, stating that “(t)he new science of psychoneuroimmunology has more than validated age-old human wisdom about the unity of mind and body, showing that the emotion-processing centers of the brain are inextricably linked with the nervous system, the immune system, and the hormonal apparatus.[247]” As Candace Pert, the legendary American neuroscientist and pharmacologist who discovered the opioid receptor, wrote, “the conceptual division between the sciences of immunology, endocrinology, and psychology/neuroscience is a historical artifact.[248]”

[247] Maté G. The science of psychoneuroimmunology. Can Fam Physician. 2005;51(4):489.
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Evolutionary Adaptability and Survival

The body physically and metabolically manifests what is experienced psychologically, in that it will institute ancient survival mechanisms - symptoms or responses which we may not understand in context of the modern world. As humans living in organized societies, we view our day-to-day lives through a modern lens but the body defaults back to ancient programming to increase survivability when it feels under threat. Some of these we experience but do not recognise the evolutionary reason for the physical feeling, for example: our heart rate increases when we lose our car key. Our heart rate increases because we activate our sympathetic nervous system and a primitive program kicks in to increase blood flow and oxygen to our muscles and brain in case we need to run or fight. To further explain this, essentially the human's brain, mind, and body start to run primitive programs if threat (even before it can be fully quantified or qualified) is perceived.

There are five major threat categories which our ancient evolutionary biology instinctively prioritizes, which I have termed the Five Ancient Survival Threats (FAST):

- Plague (disease and infection risk)
- Predator (threat to life determined by how you move and act, and correlated with stress hormones)
- Winter (extremes of temperature)
- Famine (lack of fuel and nutrients)
- Damage to the Eight Senses (sight, taste, touch, hearing, smell, vestibular, proprioception and interoception.

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- The three we're not so familiar with are vestibular [balance], proprioceptive [joint positions in relation to each other] and interoceptive [internal sense e.g., knowing when you get too hot or too cold, knowing when you are hungry]

These eight senses take in information from the internal and external environments and help our brain and body assess risk to decrease surprise and improve responses for increased survivability). These five categories describe threats that can induce stress responses that are deeply rooted in our evolutionary biology.



FAST is tightly related to neuroception (Polyvagal Theory) where “regulation of the ANS involves a built-in surveillance system involving higher brain structures that dynamically and continuously interpret information regarding risk that is being transmitted via sensors throughout the body. From this matrix of sensory information our nervous system is constantly discerning risk without involving the thinking parts of the brain. Our neuroception scans other people, our own body, and the environment for cues of safety and danger. As these cues come in, the nervous system reflexively and instantaneously shifts the

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ANS state to manage the situation and optimize survival. Neuroception and autonomic state are intertwined: although neuroception is a powerful mechanism capable of shifting autonomic state, it is dependent upon the individual's current autonomic state and historical flexibility to move back and forth among states (i.e., resilience). A more resilient individual will have a neuroception biased towards detecting cues of safety, while a less resilient individual will have a neuroception biased towards detecting threat." See the section on Human Experience Theories.

Megginson stated that according to Darwin's Origin of Species, "it is not the most intellectual of the species that survives; it is not the strongest that survives; but the species that survives is the one that is able best to adapt and adjust to the changing environment in which it finds itself.[249]"

The HPA-Axis

With negative emotional states, amygdala activation occurs. Interestingly, this part of the brain is involved in processing emotions and regulating stress responses mediated by the important hypothalamo-pituitary-adrenal (HPA) axis. It is, therefore, key to the experience of feeling fear and anxiety.

With slow amygdala recovery from activation, individuals may be at higher risk for disease than faster recovery. Similarly, a larger volume of gray matter in the amygdala is linked to better emotional regulation and thus a more positive emotional response, as well as to better health outcomes.

Interestingly, these differences in amygdala gray matter volume and activation were also linked to the release of cortisol over the course of the day (the circadian rhythm), as well as in

[249] 1963 June, Southwestern Social Science Quarterly, Volume 44, Number 1, Lessons from Europe for American Business by Leon C. Megginson, (Presidential address delivered at the Southwestern Social Science Association convention in San Antonio, Texas, April 12, 1963), Start Page 3, Quote Page 4, Published jointly by The Southwestern Social Science Association and the University of Texas Press.

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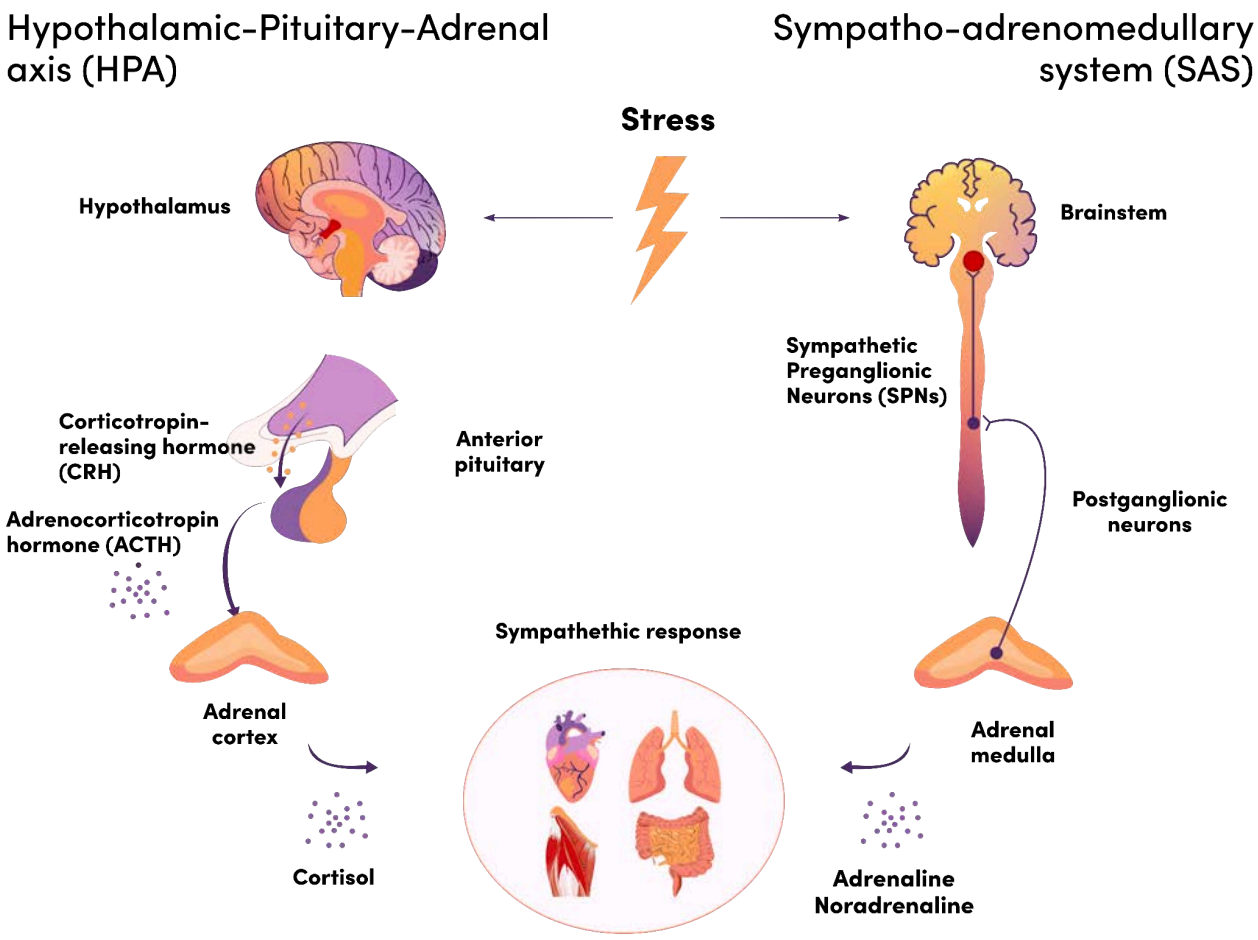
response to stressors, and with the stress responses of the individual, such as rising blood pressure and atherosclerotic changes.

Interoceptive stressors are real threats to homeostasis, the carefully maintained internal state of the body. Examples include blood loss, exposure to toxic substances and acute illness. Interoceptive stress responses originate outside the brain and are driven initially by the immune, endocrine and peripheral nervous systems, which act locally and relay signals of stress to the brain[250].

Psychogenic stressors, in contrast, are perceived (real or imagined) threats to the well-being of the organism. Examples include predator exposure and social rejection. In contrast to interoceptive stressors, psychogenic stressors originate externally and are processed initially by the brain. Although these starting points are distinct, both types of stressors engage partly overlapping neural circuits to achieve adaptive changes in physiology and behavior, namely an increase in sympathetic outflow, activation of the hypothalamic–pituitary–adrenal (HPA) axis and an increase in avoidance behaviors[251]. These rapid processes allow the body to prioritize defensive behaviors and mobilize glucose while also initiating slower endocrine feedback. This slower endocrine response driven by glucocorticoids limits the duration of the stress response to facilitate recovery and also serves to drive genetic and structural changes in the stress circuits of the brain[252].

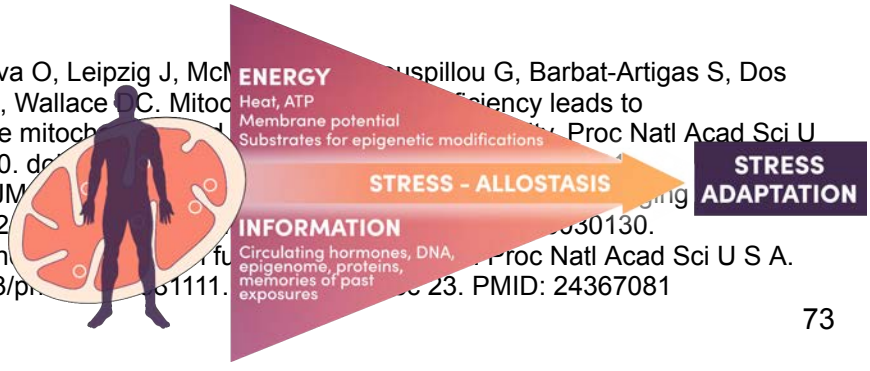
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[252] ibid.

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Mitokines

Research in animal models and a limited number of human studies over the past decade has confirmed that changes in mitochondria directly influence systemic metabolic regulation[253], brain function[254,255], immune



[253] Morrow RM, Picard M, Derbeneva O, Leipzig J, McM… uspillou G, Barbat-Artigas S, Dos Santos C, Hepple RT, Murdock DG, Wallace DC. Mitoc… iency leads to hyperproliferation of skeletal muscle mitoch… Proc Natl Acad Sci U S A. 2017 Mar 7;114(10):2705-2710. do…
[254] Bartman S, Coppotelli G, Ross JM… Diseases. Curr Issues Mol Biol. 202… 030130.
[255] Picard M, McEwen BS. Mitochon… fu… Proc Natl Acad Sci U S A. 2014 Jan 7;111(1):7-8. doi: 10.1073/pn… 1111… 23. PMID: 24367081

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function and activation[256], and even the rate of aging[257,258]. Refer to the section on mitochondria to see more about how psychology can affect physiology by way of the mitochondria. One potential pathway by which adverse childhood experiences may lead to mitochondrial dysfunction involves excessive glucocorticoid levels equating to undue oxidative stress because of an increase in calcium buffering capacity, mitochondrial membrane potential, and apoptotic signaling resistance[259].

The story of mitochondria involved in the stress axis and their production of mitokine (mitochondria-derived glucocorticoids) is well elucidated by Martin Picard et al.[260] (2018):

"It is enlightening to consider that evolution has routed the production of glucocorticoids and sex hormones within the mitochondria of specialized steroid-secreting cells (adrenal cortex, gonads). In turn, mitochondria in other tissues like the brain, muscles, and liver sense and functionally respond to glucocorticoids via the action of GR and other "nuclear" receptors on the mtDNA. Mitochondria are both mediators and targets of the main stress axes. … (mitokines mediate) mitochondria-to-mitochondria communication among distant sites throughout the organism. … Mitochondria play a vital role in sustaining basic life processes and those that specifically become activated during allostasis. An "energetic" scientific perspective of stress and the downstream (mal)adaptive consequences invites a focus on the communication systems and mechanisms that ensure and direct the flow of energy towards adaptive processes. Energy and mitochondria are primary drivers of these processes. Moving away from

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a predominantly anatomically-directed scientific framework, we must consider a model of stress focused on understanding how information and energy in their different forms are exchanged between the environment, the organism, organelles, and the plastic epigenome."

How the Ancient Hindbrain Emerges to Protect in Times of Stress

The brain is incredibly complicated but the structure can be divided into three layers - the hindbrain (brainstem and cerebellum), the subcortical region (memory and emotions), and the forebrain (most modern, executive functioning). Each of these is loosely associated with the different phases of human evolution, where the ancient hindbrain is reflective of the evolutionary stage of us learning how to control our movements more efficiently and learn how to express our needs. Around the ages of two to three years of age, we typically further learn to express our emotions and develop an understanding of our place in the world as our brains elaborate further into the limbic system. With time, neural growth reaches the cortex of the brain and we learn to control our feelings and emotions and not be controlled by them. Emotionally and socially, these are fleshed out in Erikson's Psychosocial Stage Theory.

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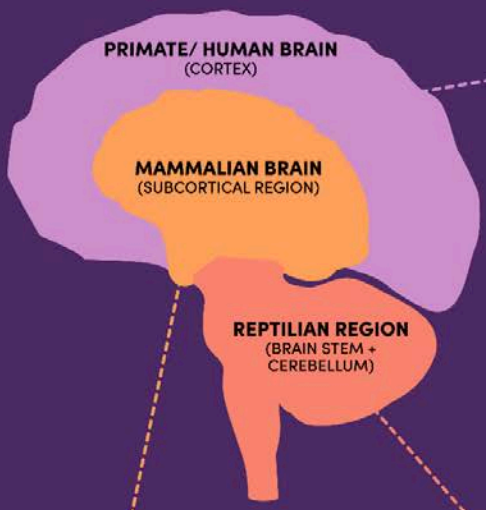
A Quick and Simple Way to Think About the Brain

Paul D. MacLean, MC. developed the concept of the triune brain in The Triune Brain in Evolution: Role in Paleocerebral Functions. Rick Hanson, PhD, author of Hardwiring Happiness: The New Brain Science of Contentment, Calm and Confidence built on this original concept.

In many ways, the brain is considered the most complex of human organs.
But complex doesn't have to mean complicated. Especially when we're trying to explain the brain's different but necessary functions.

Our brain structure can be divided into three layers - the brain stem, the subcortical region, and the cortex. And each layer can be loosely associated with the reptile, mammal, and primate/human phases of evolution, respectively.

So, if you think about it, it's almost as we're carrying a little lizard, a little mouse, and a little monkey inside our brains. And as the brain evolved, so did it's capacity to meet the three fundamental needs of any animal... Safety, satisfaction, and connection.



PRIMATE/ HUMAN BRAIN
(CORTEX)

The cortex is larger and more sophisticated than the other two layers - thus, we link this part of the brain to primate and human evolution. (In fact, the human cortex has roughly tripled in volume over the last three million years of evolution).

RESPONSIBLE FOR:	Higher mental functions
CORE FUNCTIONS:	Regulating attention, feelings, and desires, complex reasoning, abstract thoughts, imagination, language, empathy
BASIC "NEED":	Connection and attachment to others
WHEN NEED IS MET:	We feel LOVE
WHEN NEED IS *NOT* MET:	We experience HEARTACHE



MAMMALIAN BRAIN
(SUBCORTICAL REGION)

The subcortical region is associated with mammalian evolution - we might think of it as the little mouse part of the brain.

RESPONSIBLE FOR:	Feelings and memory formation
CORE FUNCTIONS:	Emotions, learning and memory, reward/motivation
BASIC "NEED":	Satisfaction and approaching rewards
WHEN NEED IS MET:	We feel CONTENTMENT
WHEN NEED IS *NOT* MET:	We experience FRUSTRATION



REPTILIAN REGION
(BRAIN STEM + CEREBELLUM)

The brain stem is the most ancient part of the brain. This brain structure shares a similar function to the brain found in simple creatures, like crabs or lizards.

RESPONSIBLE FOR:	Survival and maintenance
CORE FUNCTIONS:	Regulating heartbeat, breathing, and other vital organs
BASIC "NEED":	Safety and avoiding harm
WHEN NEED IS MET:	We feel PEACE
WHEN NEED IS *NOT* MET:	We experience FEAR

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Brainstem (Caudal) Nucleus of the Solitary Tract

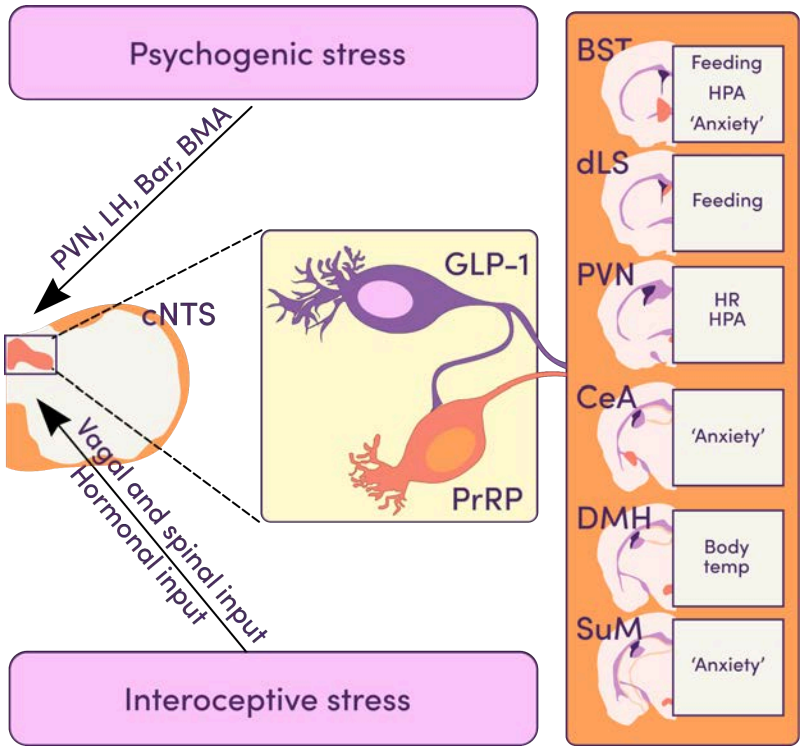
The behavioral and physiological responses to acute stress are modulated by distributed circuits within the brain. In addition to corticolimbic and subcortical hypothalamic structures, acute stressors engage regions in the lower brainstem, including the rostroventrolateral medulla, the raphe magnus and the caudal nucleus of the solitary tract (cNTS).

Stress responses are often thought to be driven mainly by forebrain areas; however, within the dorsal vagal complex, the caudal nucleus of the solitary tract (cNTS) is a major first stop for incoming information from the body to the brain carried by the vagus nerve[261]. The anatomy of this region makes it ideally positioned to respond to signals of change in both emotional and bodily states and integrate multimodal signals relating to the physiological and emotional state of the organism. Indeed, the cNTS is robustly activated after both interoceptive stressors - lithium chloride[262], lipopolysaccharide[263], hypoxia[264] and loss of blood volume[265] and psychogenic stressors - forced swimming[266], restraint[267] and predator odor[268]. Preclinical evidence demonstrates that the cNTS and its resident glucagon-like peptide-1

[261] Holt MK. The ins and outs of the caudal nucleus of the solitary tract: An overview of cellular populations and anatomical connections. J Neuroendocrinol. 2022;34(6):e13132. doi:10.1111/jne.13132
[262] Rinaman, L. (1999). Interoceptive stress activates glucagon-like peptide-1 neurons that project to the hypothalamus. The American Journal of Physiology, 277, R582–R590.
[263] ibid.
[264] Teppema, L. J., Veening, J. G., Kranenburg, A., Dahan, A., Berkenbosch, A., & Olievier, C. (1997). Expression of c-fos in the rat brainstem after exposure to hypoxia and to normoxic and hyperoxic hypercapnia. Journal of Comparative Neurology, 388, 169–190. https://doi.org/10.1002/(SICI)1096-9861(19971117)388:2
[265] Dun, N. J., Dun, S. L., & Chiaia, N. L. (1993). Hemorrhage induces Fos immunoreactivity in rat medullary catecholaminergic neurons. Brain Research, 608, 223–232. https://doi.org/10.1016/0006-8993(93)91462-2
[266] Cullinan, W. E., Herman, J. P., Battaglia, D. F., Akil, H., & Watson, S. J. (1995). Pattern and time course of immediate early gene expression in rat brain following acute stress. Neuroscience, 64, 477–505. https://doi.org/10.1016/0306-4522(94)00355-9
[267] ibid.
[268] Day, H. E. W., Masini, C. V., & Campeau, S. (2004). The pattern of brain c-fos mRNA induced by a component of fox odor, 2,5-dihydro-2,4,5-trimethylthiazoline (TMT), in rats, suggests both systemic and processive stress characteristics. Brain Research, 1025, 139–151. https://doi.org/10.1016/j.brainres.2004.07.079

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(GLP1)-expressing and prolactin-releasing peptide (PrRP) neurons play crucial roles in organizing neural responses to a broad range of stressors[269].



"Interoceptive and psychogenic stressors activate neurons in the caudal nucleus of the solitary tract (cNTS), including both GLP-1 and PrRP neurons. GLP-1 neurons then further drive activation of PrRP neurons and PrRP and GLP-1 signaling in distributed forebrain nuclei leads to suppression in feeding, HPA axis activation, increased heart rate (HR) and body temperature, and enhanced anxiety-like behaviors. Displayed are regions in which endogenous GLP-1 signaling has been demonstrated to contribute to the indicated stress-related responses (see text for references). The lack of a selective antagonist for the receptor for PrRP (GPR10) has precluded parallel pharmacological studies focused on the role of endogenous PrRP signaling. Bar: Barrington's nucleus; BMA: Basomedial amygdala; BST: Bed nucleus of the stria terminalis; CeA: Central nucleus of the amygdala; DMH:

[269] Holt MK, Rinaman L. The role of nucleus of the solitary tract glucagon-like peptide-1 and prolactin-releasing peptide neurons in stress: anatomy, physiology and cellular interactions. Br J Pharmacol. 2022;179(4):642-658. doi:10.1111/bph.15576

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Dorsomedial hypothalamus; dLS: Dorsal lateral septum; LH: Lateral hypothalamus; PVN: Paraventricular nucleus of the hypothalamus; SuM: Supramammillary nucleus[270]."

Signals of interoceptive threat originate within the body and are conveyed to the central nervous system largely through sensory pathways that converge onto cNTS neurons, which in turn modulate the activity of, among other things, parasympathetic neurons in the dorsal motor vagal nucleus[271] which ties in with Stephen Porges' Polyvagal theory.

Transient Receptor Potential Ion Channels

Transient receptor potential channels, also called TRP (pronounced "trip") channels, are a superfamily of ion channels occurring in cell membranes that are involved in various types of sensory reception, including thermoreception (heat), chemoreception (chemicals), mechanoreception (pressure and touch), and photoreception (light)[272]. These channels are *multifunctional signaling molecules*, which play various roles in sensory perception and also cell physiology health and disease conditions[273]. They are located in the outer membranes of many sensory cell types. Their responses to various stimuli are manifested through their functions as ion channels, regulating the flow of ions, such as potassium, calcium, and sodium, into or out of cells.

Chemosensation is determined primarily by the chemical activation of nociceptors and thermoreceptors and that activation by chemicals involves the direct activity of an ion channel

[270] Holt MK, Rinaman L. The role of nucleus of the solitary tract glucagon-like peptide-1 and prolactin-releasing peptide neurons in stress: anatomy, physiology and cellular interactions. Br J Pharmacol. 2022;179(4):642-658. doi:10.1111/bph.15576
[271] Travagli, R. A., Hermann, G. E., Browning, K. N., & Rogers, R. C. (2006). Brainstem circuits regulating gastric function. Annual Review of Physiology, 68, 279–305. https://doi.org/10.1146/annurev.physiol.68.040504.094635
[272] Rogers, K. (2018, November 15). transient receptor potential channel. Encyclopedia Britannica. https://www.britannica.com/science/transient-receptor-potential-channel
[273] Zhang, X., Hu, M., Yang, Y., and Xu, H. (2018). Organellar TRP Channels. Nat. Struct. Mol. Biol. 25 (11), 1009–1018. doi:10.1038/s41594-018-0148-z

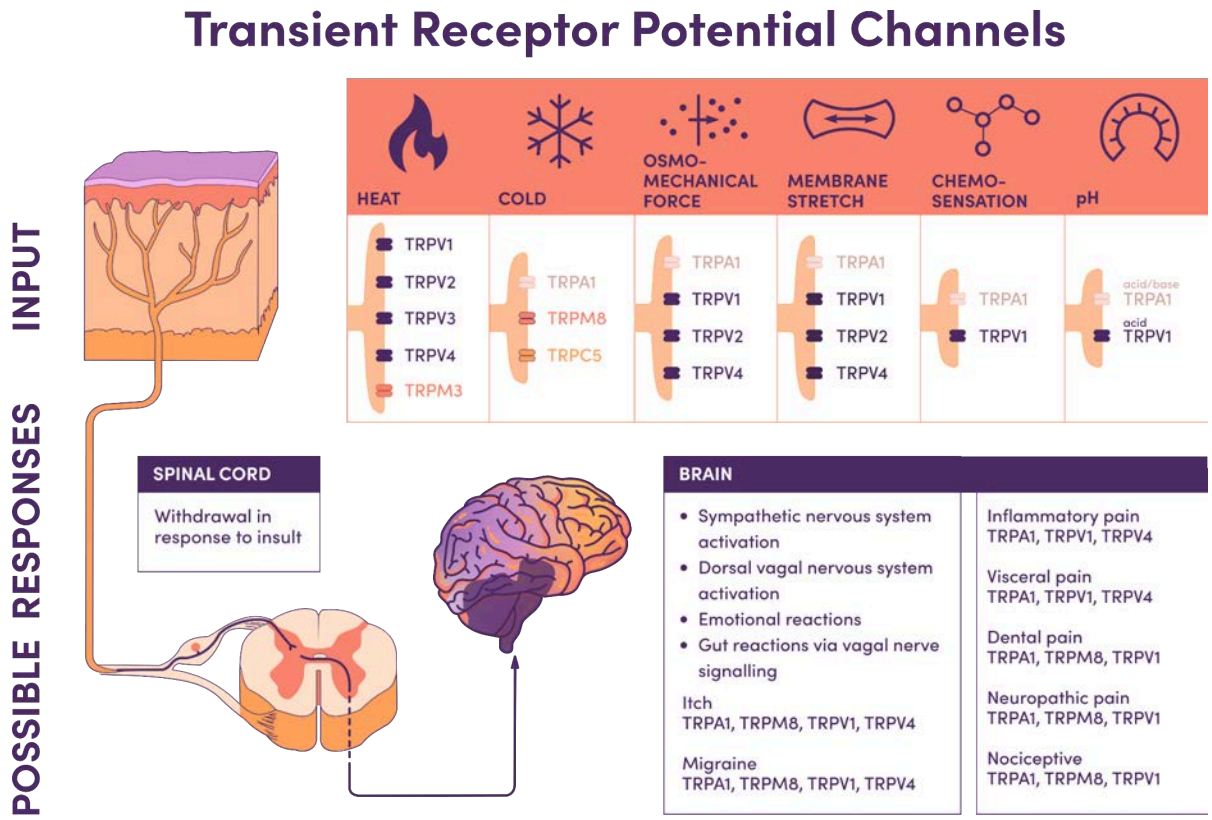
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by chemical stimuli: the so-called ionotropic transduction[274,275]. TRP channels play integral roles in transducing chemical stimuli, giving rise to sensations of taste, irritation, warmth, coolness, and pungency[276]. Ion flux can lead to cell membrane depolarization (less negative charge across the cell), which leads to an action potential - a brief electric polarization that results in a nerve impulse and physiological sensation or perception[277].

Originally, TRP channel physiology was focusing on its fundamental meaning in sensory neuronal function. Today, it is known that activation of several TRP ion channels in peptidergic neurons does not only result in neuropeptide release, but also consecutive neurogenic inflammation which will be variously discussed as part of the Inflammatory Bias. Although not necessarily “threat” receptors, the drivers of survival from an evolutionary perspective compels animals to use the information gleaned from TRPs to constantly calculate risk.

[274] Wood JN, Docherty R. Chemical activators of sensory neurons. Annual Review of Physiology. 1997;59:457-482
[275] Lee Y, Lee CH, Oh U. Painful channels in sensory neurons. Molecules and Cells. 2005;20:315-324
[276] Roper SD. TRPs in taste and chemesthesis. Handbook of Experimental Pharmacology. 2014;223:827-871
[277] Rogers, K. (2018, November 15). transient receptor potential channel. Encyclopedia Britannica. https://www.britannica.com/science/transient-receptor-potential-channel

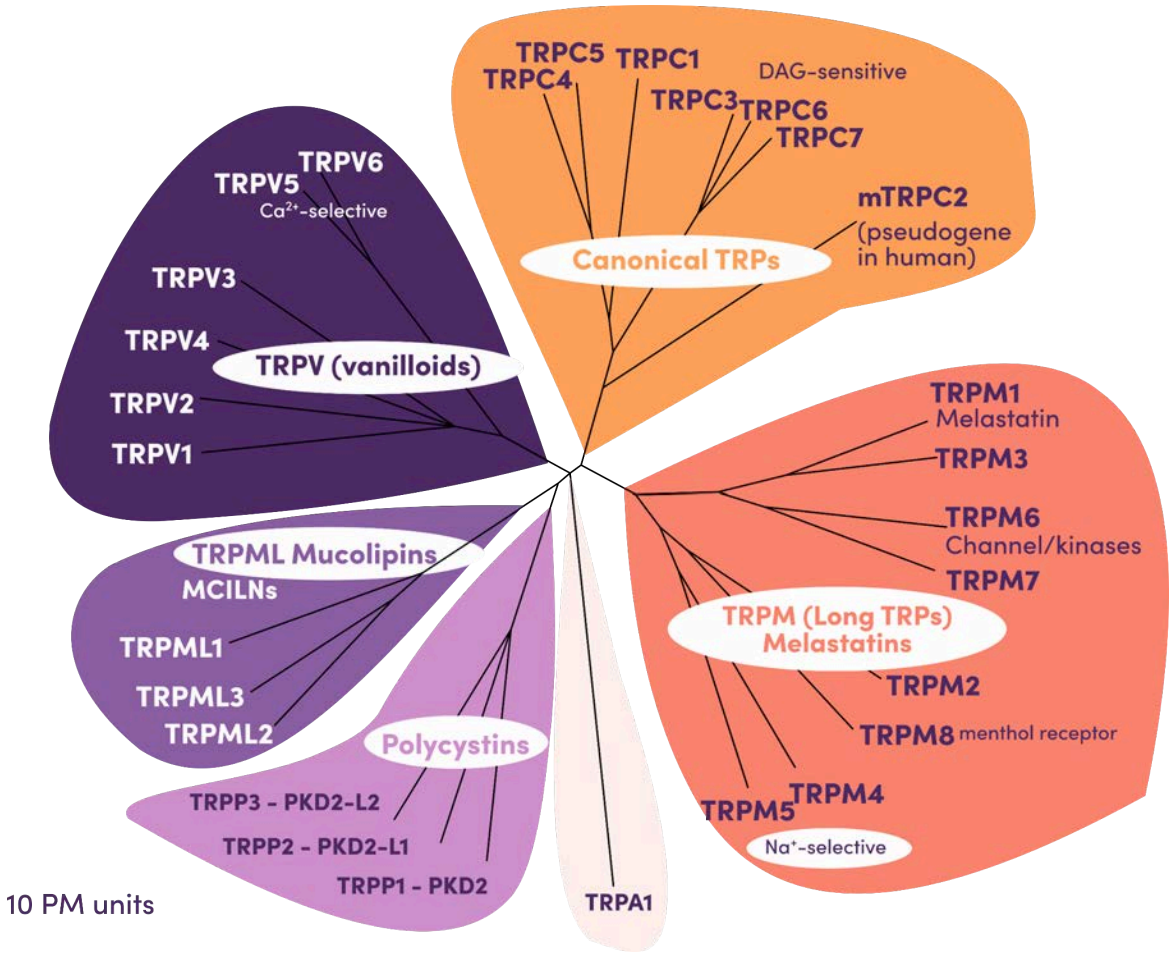
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In the animal TRP superfamily there are currently 9 proposed families split into two groups, each family containing a number of subfamilies. Group one consists of TRPC, TRPV, TRPVL, TRPA, TRPM, TRPS, and TRPN, while group two contains TRPP and TRPML. There is an additional family labeled TRPY that is not always included in either of these groups. All of these sub-families are similar in that they are molecular sensing, non-selective cation channels that have six transmembrane segments, however, each sub-family is very unique and shares little structural homology with one another. This uniqueness gives rise to the various sensory perception and regulation functions that TRP channels have throughout the body[278].

[278] Himmel NJ, Cox DN. Transient receptor potential channels: current perspectives on evolution, structure, function and nomenclature. Proc Biol Sci. 2020 Aug 26;287(1933):20201309. doi: 10.1098/rspb.2020.1309. Epub 2020 Aug 26. PMID: 32842926; PMCID: PMC7482286.

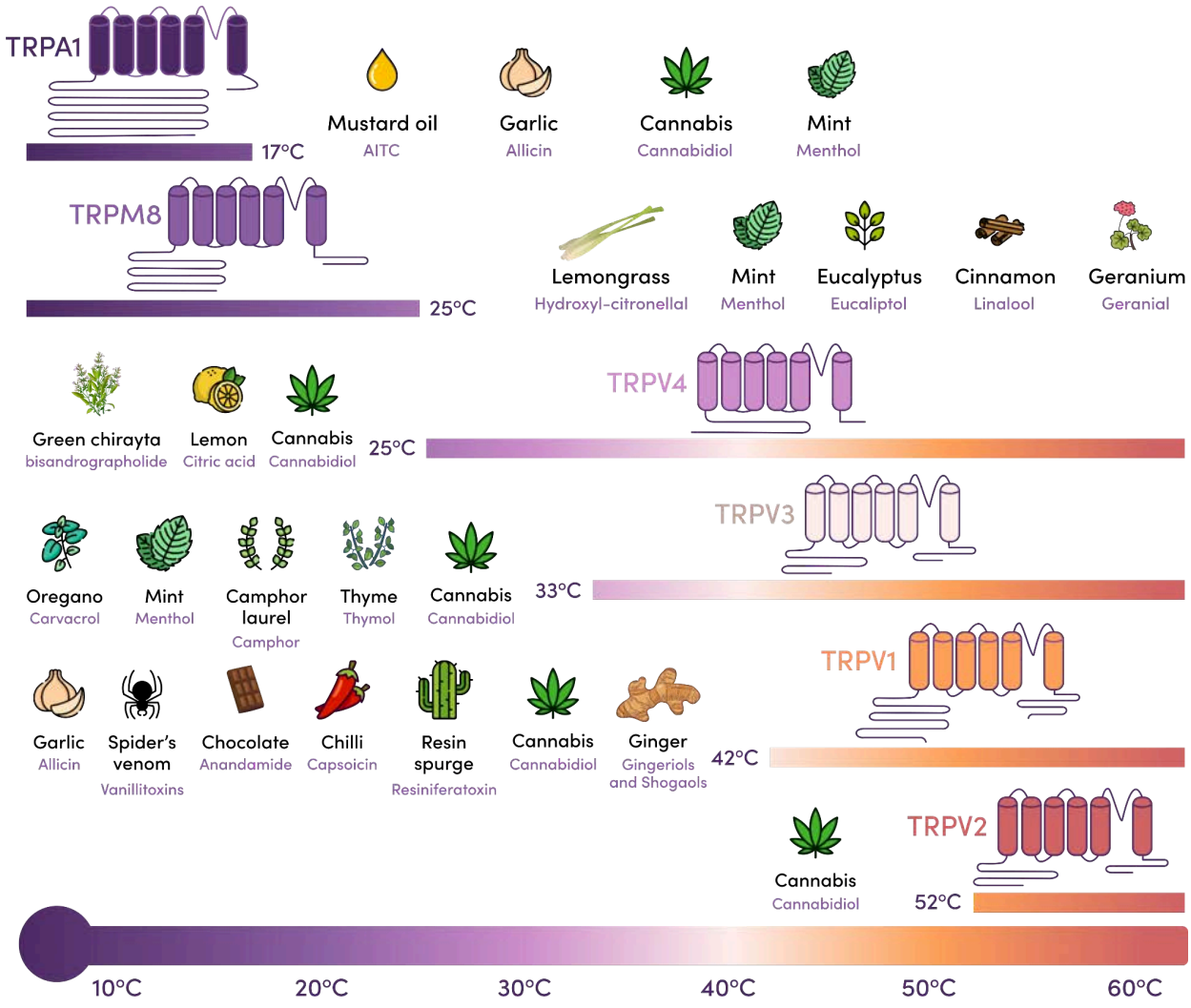
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Six members of this superfamily TRPA1 TRPM8 TRPV1 TRPV2 TRPV3 and TRPV4, seem to participate in temperature sensing and TRPV1, TRPV2, TRPV3, and TRPV4 have incompletely overlapping functions over a broad thermal range from warm to hot[279,280]. They are also able to be modulated and activated by various substances, including herbs, spices and foodstuffs[281].

[279] Voets T. Quantifying and modelling the temperature-dependent gating of TRP channels. Reviews of Physiology, Biochemistry and Pharmacology. 2012;162:91-119
[280] Wang H, Siemens J. TRP ion channels in thermosensation, thermoregulation and metabolism. Temperature (Austin). 2015;2:178-187
[281] Belvisi MG, Dubuis E, Birrell MA. Transient receptor potential A1 channels: insights into cough and airway inflammatory disease. Chest. 2011;140(4):1040-1047. doi:10.1378/chest.10-3327

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A systematic review from 2019 found that one mechanism through which whole body hyperthermia treatments might improve mood is by activating temperature-sensitive ion channels in the skin (including TRPV3 and TRPV4). Those have been shown to signal directly to brainstem serotonergic neurons when activated during warmer temperatures. Dysregulation

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of this thermosensitive population of serotonergic neurons plays an important role in stress-related neuropsychiatric disorders, including anxiety and affective disorders[282].

Growing evidence demonstrates functional extra-neuronal TRP channel expression in immune and epithelial cells with important implications for mucosal immunology. Crosstalk between neurons, epithelial cells, and immune cells induced by activation of TRP channels orchestrates the immunologic response[283].

Primitive Physical and Psychological Reflexes

Primitive reflexes are involuntary motor responses originating in the brainstem present after birth in early child development that facilitate survival. Primitive reflexes are highly stereotyped responses generated by certain sensory stimuli. The sucking, Moro, and Babinski reflexes are among the primitive reflexes that have been extensively studied in the literature due to their significance. The sucking reflex, which works in tandem with breathing and swallowing to provide nutrients for life and growth, is vital for oral feeding. The Moro reflex is a naturally occurring protective motor reaction to abrupt shifts in bodily balance or intense stimulations. The Babinski reflex is a pyramidal tract nociceptive motor response that affects the foot's extensor and flexor muscles[284].

These central nervous system motor responses are eventually inhibited by 4 to 6 months of age as the brain matures and replaces them with voluntary motor activities but may return with the

[282] Lowry CA, Lightman SL, Nutt DJ. That warm fuzzy feeling: brain serotonergic neurons and the regulation of emotion. J Psychopharmacol. 2009;23:392–400.
[283] Khalil M, Alliger K, Weidinger C, et. al. Functional Role of Transient Receptor Potential Channels in Immune Cells and Epithelia. Front Immunol. 2018 Feb 7;9:174. doi: 10.3389/fimmu.2018.00174.
[284] Modrell AK, Tadi P. Primitive Reflexes. [Updated 2023 Mar 6]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK554606/

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presence of neurological disease, traumatic brain injury, and indeed has been documented to also return with exposure to traumatic events[285].

Evolutionary psychology studies the ways in which the mind was shaped by pressures to survive and reproduce. According to evolutionary theory, different emotions evolved at different times. Romantic jealousy and mate-guarding are behaviors that can be explained by the fact that losing a romantic partner jeopardizes one's ability to reproduce and raise children. Primal emotions, such as love and fear, are associated with ancient parts of the psyche. Social emotions, such as guilt and pride, evolved among social primates. Primal emotions, being linked to the primal hindbrain, activates cTNS which affects physiology, especially ancient mechanisms of inflammation which will be explored later.

Human behavior, like physical traits, is shaped by natural selection. Our behavior is naturally selected just as our physical traits are. Through centuries of generations, evolution has helped us pass along adaptive behaviors that promote our reproduction[286].

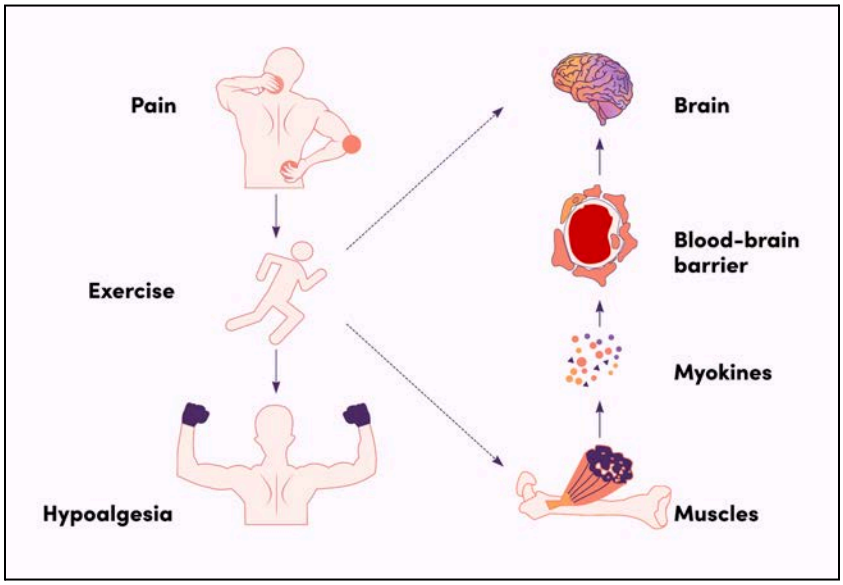
The theoretical model of emotion is supported by basic experiments from both animal and human research. The idea that emotions are products of Darwinian evolution is based on the concept that expressed emotions developed from primitive actions that facilitated the survival of species and individuals, that emotions are seen as evolved affects that are motivationally tuned states of readiness.

[285] McTeague LM, Lang PJ. The anxiety spectrum and the reflex physiology of defense: from circumscribed fear to broad distress. Depress Anxiety. 2012;29(4):264-281. doi:10.1002/da.21891
[286] https://www.psychologytoday.com/au/basics/evolutionary-psychology

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Muscles, Movement and Myokines

Myokines are inflammatory molecules synthesized and released by myocytes during muscular contractions. They are implicated in autocrine regulation of metabolism in the muscle as well as in the paracrine/endocrine regulation of other tissues and organs including adipose tissue, the liver, and the brain through their receptors[287]. They help recover individuals from stress and trauma because of their antidepressant effects on the brain. According to Kelly McGonigal, a noted Stanford psychologist, myokines can cross the blood-brain barrier and make the brain more resilient to stress, increase motivation, and help learn from experience. The only way to release myokines is through muscle contraction. Aerobic workouts (such as power walking or running) increase the secretory levels of these “hope molecules” and accelerate their transportation to the brain through the bloodstream with the help of an increase in circulation[288]. This is an important consideration with regards to the fact that the modern human does not move nearly as much as they used to and sedentary behavior has implications on our emotional health.

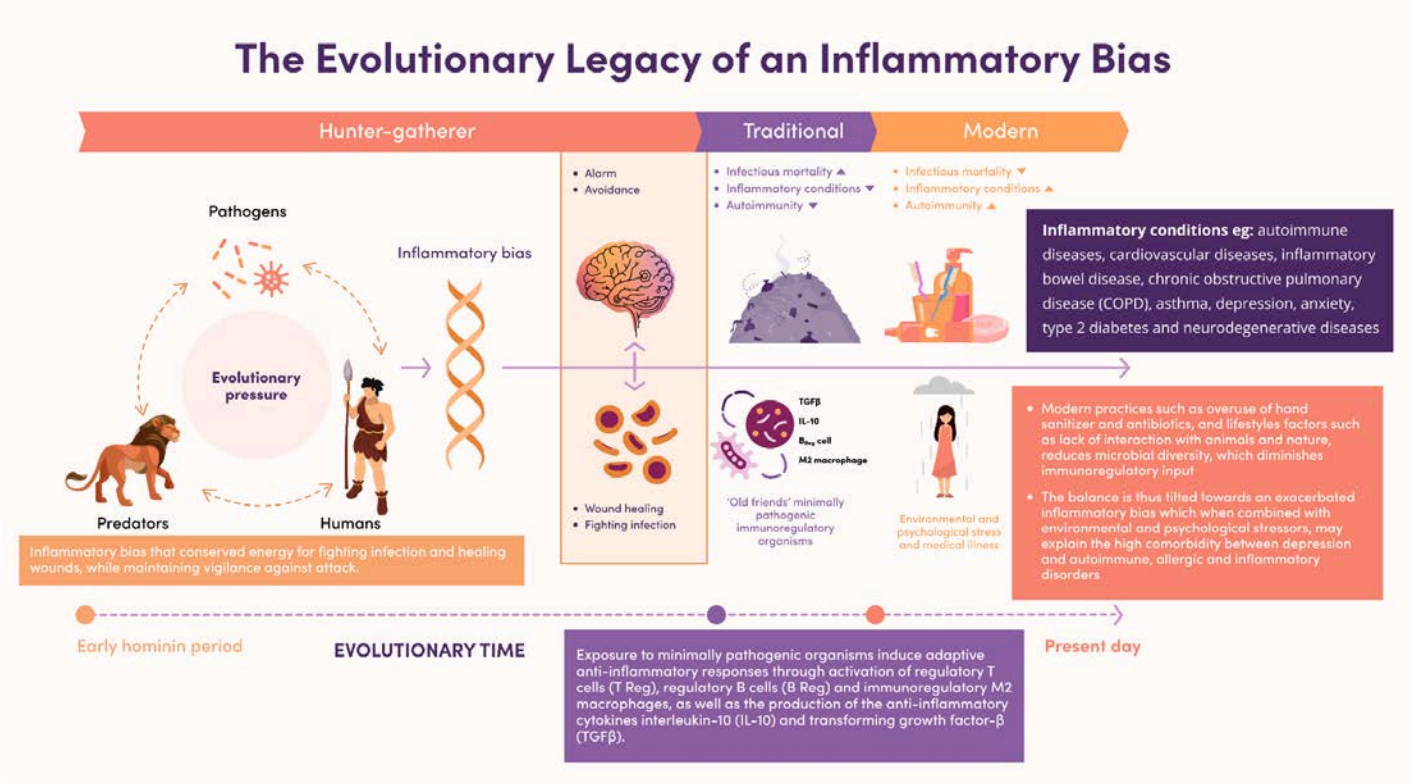


[287] Lee JH, Jun HS. Role of Myokines in Regulating Skeletal Muscle Mass and Function. Front Physiol. 2019;10:42. Published 2019 Jan 30. doi:10.3389/fphys.2019.00042
[288] Krishnan V. Muscle-bone crosstalk by organokines-the new "hope molecules". J World Fed Orthod. 2022;11(2):47-48. doi:10.1016/j.ejwf.2022.03.001

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The Inflammatory Bias (PATHOS-D Hypothesis)

The Inflammatory Bias is a theory rooted in depression research. Depression leads to changes in autonomic control of the body and changes the autonomic balance in favor of an increased sympathetic tone, which can be detected with fair accuracy with HRV analysis[289].



It was also found that depression risk alleles were found to be regularly associated with immune responses to infection that were likely to enhance survival in the ancestral environment. Moreover, data support the role of specific depressive symptoms in pathogen host defense including fever, anemia, conservation/ withdrawal behavior, hypervigilance and loss of appetite. By shifting the adaptive context of depression risk alleles from interpersonal relationships and

[289] Singla S, Jhamb S, Singh KD, Kumar A. Depression affects autonomic system of the body? Yes, it does! J Educ Health Promot. 2020 Aug 31;9:217. doi: 10.4103/jehp.jehp_627_19. PMID: 33062750; PMCID: PMC7530411.

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solely a maladaptation to life stressors, to relations with the microbial world, the Pathogen Host Defense (PATHOS-D) hypothesis by Professor Charles Raison provides a novel explanation for how depression can be nonadaptive in the social realm, whereas its risk alleles served an adaptive evolutionary function when pathogens were the primary reason for risk of death[290].

Human Experience Theories

Grof's COEX Theory

Resolving incomplete condensed emotional experiences (COEXes) is a way to describe the way the human brain organizes its experience. A COEX is basically a set of related experiences organized around a powerful emotional center which do not necessarily contain traumatic and painful experiences but the intensity of the experience and its emotional relevance is what determines whether a memory will be included into a COEX. The term was coined by Stanislav Grof, a Czech psychiatrist and long-time researcher of non-ordinary states of consciousness. As Grof defines them, COEXes include all experiences that overwhelm the nervous system, and, unable to process its experiences, stores information about them (the COEX event memory) in various parts of itself. These COEXes often span periods of time that go beyond a single traumatic event.

In this model, we aim to map current-state emotional triggers to COEXes that have accrued, or stacked, over time on top of a root COEX. We identify the learned limiting beliefs associated with each COEX and track how the stack has been built up over time from a root COEX occurring before approximately age seven. For example, a child's mother left them in the store

[290] Raison CL, Miller AH. The evolutionary significance of depression in Pathogen Host Defense (PATHOS-D). Mol Psychiatry. 2013;18(1):15-37. doi:10.1038/mp.2012.2

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by accident; the child had an emotional experience (COEX) and took on a core wound of abandonment and the belief that they are not enough. Over time, other intense emotional experiences (COEXes) mirror back this experience of abandonment and reinforce the belief that they are not enough. These COEXes can manifest as partners leaving, friends becoming distant, etc. Our model identifies how a current-state trigger relates to COEXes over time and tracks triggers back to the root COEX.

Erikson's Psychosocial Stage Theory

We build on Grof's approach by layering in Erikson's psychosocial stage theory to break up how we look at COEXes. Erik Erikson, a German psychoanalyst, built upon Freud's theory of psychosexual development by drawing parallels in childhood stages while expanding it to include the influence of social dynamics as well as the extension of psychosocial development into adulthood. Erikson's biopsychosocial theory considers the impact of external factors, parents, and society, on personality development from childhood to adulthood. According to Erikson's theory, every person must pass through a series of eight interrelated psychosocial stages of development, and that when trauma occurs at any of these stages, a person can become "stuck" at that stage. Healing can only occur after a stage is completed. Identifying and addressing the traumas that occurred at each stage can promote healing and wholeness.

In the practical application of the model, we track COEXes across all eight stages and identify, by going in reverse history from the present day to early childhood (birth to age seven), the root COEX and what the historical account of COEXes are across all eight frames. Following Erikson's stages, we identify a full picture of emotional moments that reinforce beliefs at key development stages.

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Attachment Theory

As proposed by psychiatrist John Bowlby in the attachment theory, an attachment is an emotional bond between a caretaker and a child. The attachment theory suggests that attachment is formed due to the infant's deep-rooted desire to remain close and connected to the attachment figure. Unlike many other species, human babies need prolonged care because they are born unable to feed or defend themselves. Developing attachment behaviors that can keep them close to their caregivers for protection can increase the likelihood of infant survival[291]. Child attachment styles can be categorized into four types[292]:

- Secure attachment style
- Avoidant attachment style (insecure)
- Ambivalent attachment style (insecure)
- Disorganized attachment style (insecure)

In the 1980s and 1990s, social psychologists Cindy Hazan and Phillip Shaver found parallel attachment styles in adult relationships[293,294] and proposed an extension to Bowlby's theory of attachment. They found that individual differences observed in infant attachment are manifested similarly to those in adult attachment. The four adult attachment styles are:

- Secure attachment style
- Avoidant attachment or dismissive-avoidant attachment style

[291] Mikulincer M, Shaver PR, Pereg D. Attachment Theory and Affect Regulation: The Dynamics, Development, and Cognitive Consequences of Attachment-Related Strategies. Motivation and Emotion. Motivation and Emotion. 2003;27:77-102. doi:10.1023/a:1024515519160
[292] Bretherton I. The origins of attachment theory: John Bowlby and Mary Ainsworth. Developmental Psychology. Published online 1992:759-775. doi:10.1037/0012-1649.28.5.759
[293] Shaver P, Hazan C. Being lonely, falling in love. Journal of Social Behavior and Personality. 1987;2(2):105.
[294] Hazan C, Shaver PR. Deeper Into Attachment Theory. Psychological Inquiry. Published online January 1994:68-79. doi:10.1207/s15327965pli0501_15

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- Anxious attachment, preoccupied attachment style, or anxious preoccupied attachment style
- Fearful attachment or fearful-avoidant attachment style

Although an adult's attachment style is partially associated with early attachment, its stability can change depending on other life experiences[295,296]. Long-term studies show that early attachment does not consistently predict adult attachment[297]. The main attachment styles are characterized by two dimensions – attachment anxiety and attachment avoidance[298]. The degrees of anxiety and avoidance predict one's attachment strategies in their relationships.

Internal Working Model

The representations created out of the infant-parent attachment form the internal working model. This model shapes the child's self-perception and understanding of the world, impacting their personality, emotion regulation, and interaction styles. For instance, children who view the world as supportive can trust and rely on others to help them cope with their own emotions, which often results in developing healthy emotional regulation. Conversely, those who perceive the world as unsupportive or unhelpful may feel abandoned to deal with their emotional struggles on their own, which may lead to maladaptive coping.

[295] Chris Fraley R. Attachment Stability From Infancy to Adulthood: Meta-Analysis and Dynamic Modeling of Developmental Mechanisms. Pers Soc Psychol Rev. Published online May 2002:123-151. doi:10.1207/s15327957pspr0602_03
[296] Crowell JA, Treboux D, Waters E. Stability of attachment representations: The transition to marriage. Developmental Psychology. Published online 2002:467-479. doi:10.1037/0012-1649.38.4.467
[297] Fraley RC, Roisman GI. The development of adult attachment styles: four lessons. Current Opinion in Psychology. Published online February 2019:26-30. doi:10.1016/j.copsyc.2018.02.008
[298] Brennan KA, Shaver PR. Attachment Styles and Personality Disorders: Their Connections to Each Other and to Parental Divorce, Parental Death, and Perceptions of Parental Caregiving. Journal of Personality. Published online October 1998:835-878. doi:10.1111/1467-6494.00034

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Internal working models are prone to intergenerational transmission. A parent's working model patterns, especially the insecure attachment system, tend to be passed on to their offspring. Adults with insecure attachments can still change and adapt, as our brains can rewire and evolve. An earned secure attachment can be developed through a close, long-term relationship with a surrogate attachment figure who provides a stable foundation.[299]

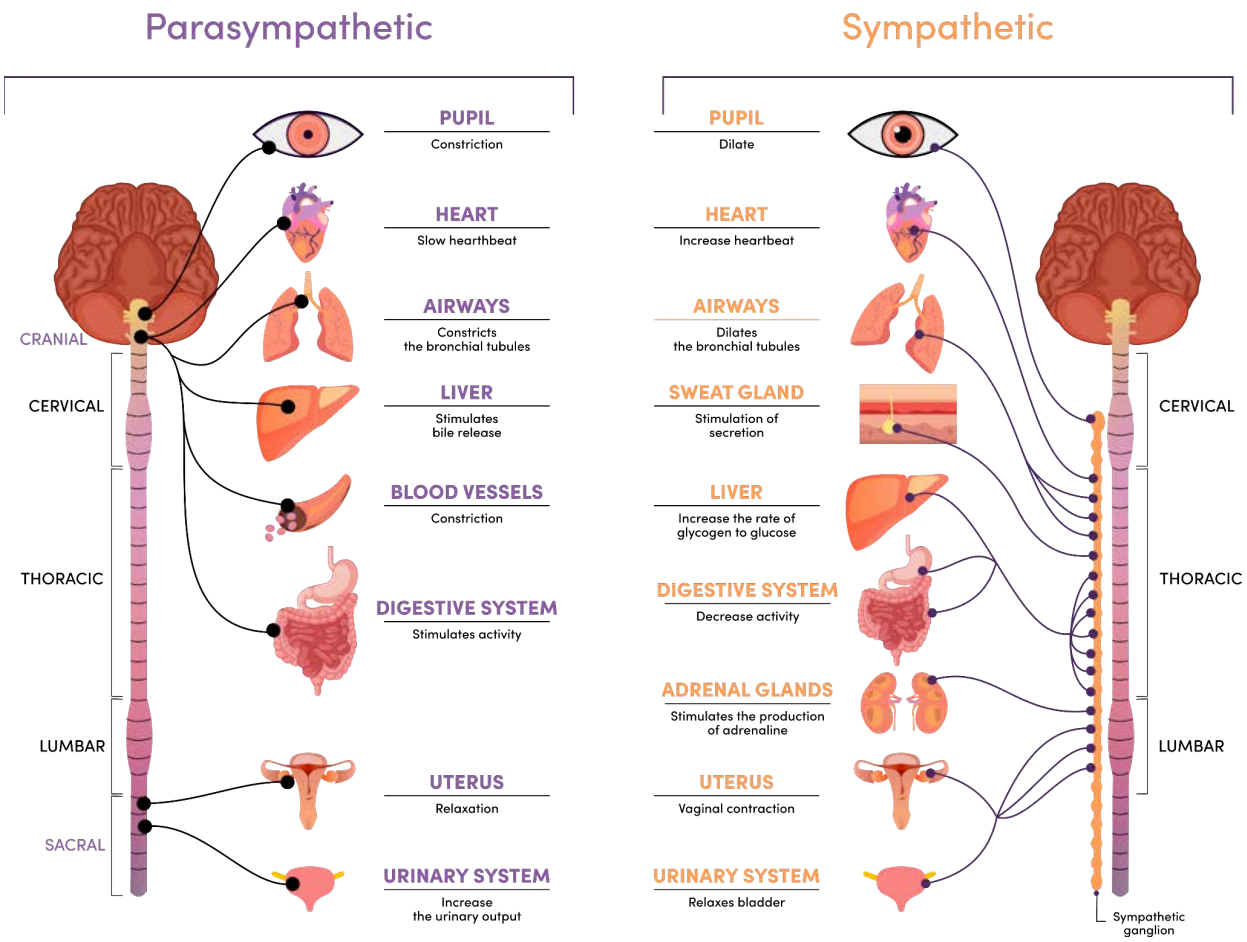
Internal Working Models are essentially downloaded behaviors and ideas of the world acquired before age 7. The vast majority of these subconscious programs acquired from other people, especially primary care-givers, are themes of limitation, disempowerment, and self-sabotage as these threats foster survival counter-skills by the brain. According to Bruce Lipton PhD, the cell biologist and best-selling author of The Biology of Belief, states that "(b)ecoming aware of the subconscious source of our behavior gives us an opportunity to change our lives by rewriting the programs of limitation or the things that interfere with us.[300]"

Polyvagal Theory

The vagus nerve is the longest cranial nerve. It runs from the brain stem to part of the colon. It represents the main component of the parasympathetic nervous system, which oversees a vast array of crucial bodily functions, including part control of mood, immune response, digestion, and heart rate. It establishes one of the connections between the brain and the gastrointestinal tract and sends information about the state of the inner organs to the brain.

[299] Saunders R, Jacobvitz D, Zaccagnino M, Beverung LM, Hazen N. Pathways to earned-security: The role of alternative support figures. Attachment & Human Development. Published online July 2011:403-420. doi:10.1080/14616734.2011.584405
[300] Gustafson C. Bruce Lipton, PhD: The Jump From Cell Culture to Consciousness. Integr Med (Encinitas). 2017;16(6):44-50.

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A healthy parasympathetic nervous system response, which is governed by the vagus nerve, is essential for our mental well-being and physical health. This is because when we are functioning from a parasympathetic position, we are able to digest our food and assimilate nutrients properly, and be in a state to repair and regenerate[301]. We have evolved to be in this state the majority of the time, however, due to the pressures of modern life and chronic stress, many of us are continuously in a sympathetic state, where we are constantly in a physiological 'fight or flight' mode. For some, as elucidated in the previous section, stress becomes toxic and the person is not able to initiate sympathetic reflexes of running or fighting, and defaults back to

[301] Breit S, Kupferberg A, Rogler G, Hasler G. Vagus Nerve as Modulator of the Brain-Gut Axis in Psychiatric and Inflammatory Disorders. Front Psychiatry. 2018;9:44. Published 2018 Mar 13. doi:10.3389/fpsyt.2018.00044

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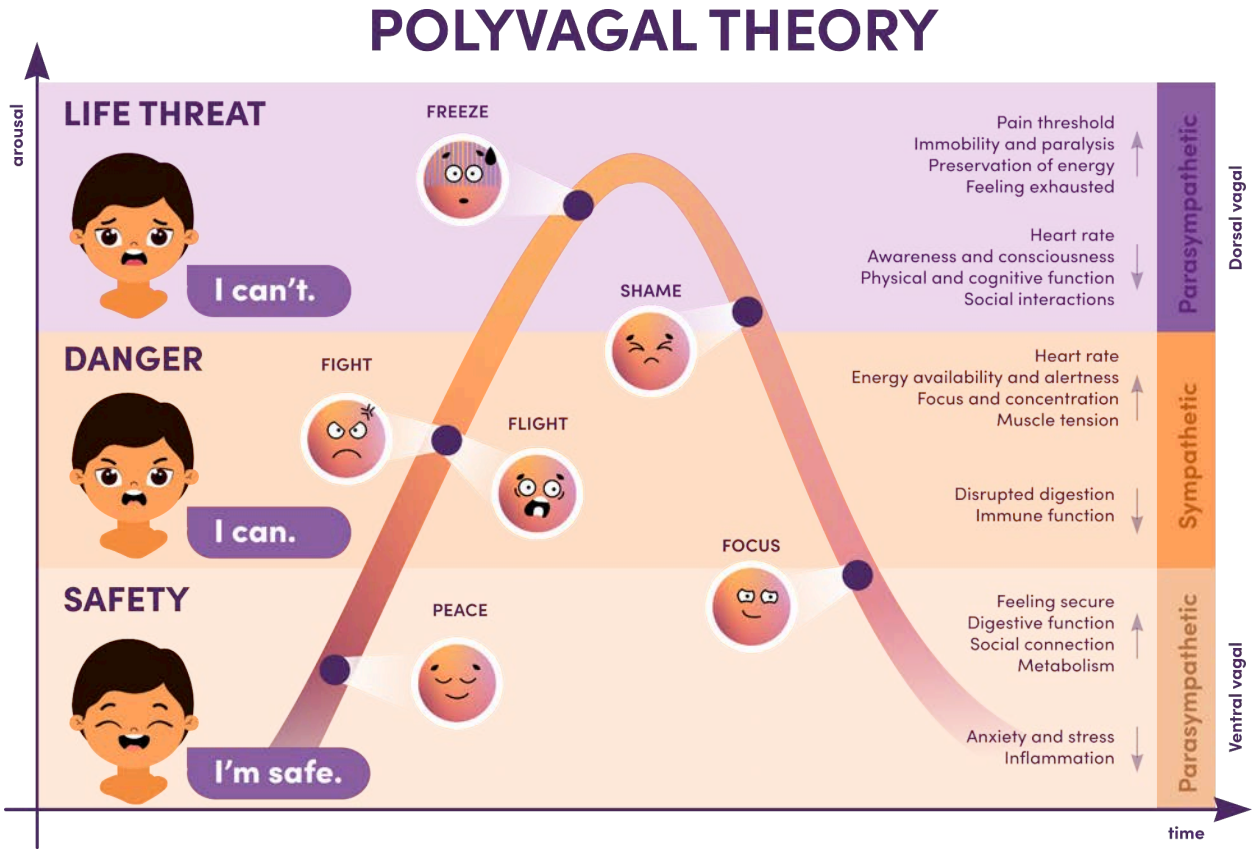
ancient mechanisms of self-preservation - an effective shutting down of the body presumably to force the animal into a safe space (cave) or to stop provoking the attack of a predator.

The polyvagal theory articulates how the development of the human autonomic nervous system is associated with a distinct autonomic subsystem that evolved from lower animals and how they respond to threats. These autonomic subsystems are phylogenetically ordered and behaviorally linked to social communication (eg, facial expression, vocalization, listening), mobilization (eg, fight–flight behaviors), and immobilization (eg, feigning death, vasovagal syncope, and behavioral shutdown)[302].

The social communication system involves the myelinated vagus, which serves to foster calm behavioral states by inhibiting sympathetic influences to the heart and dampening the hypothalamic-pituitary-adrenal (HPA) axis[303]. The mobilization system is dependent on the functioning of the sympathetic nervous system. The most phylo-genetically primitive component, the immobilization system, is dependent on the unmyelinated vagus which originates in the dorsal motor nucleus of the vagus[304].

[302] Porges SW. The polyvagal theory: new insights into adaptive reactions of the autonomic nervous system. Cleve Clin J Med. 2009;76 Suppl 2(Suppl 2):S86-S90. doi:10.3949/ccjm.76.s2.17
[303] Bueno L, Gue M, Fargeas MJ, Alvinerie M, Junien JL, Fioramonti J. Vagally mediated inhibition of acoustic stress-induced cortisol release by orally administered kappa-opioid substances in dogs. Endocrinology. 1989;124:1788–1793.
[304] Porges SW. The polyvagal theory: new insights into adaptive reactions of the autonomic nervous system. Cleve Clin J Med. 2009;76 Suppl 2(Suppl 2):S86-S90. doi:10.3949/ccjm.76.s2.17

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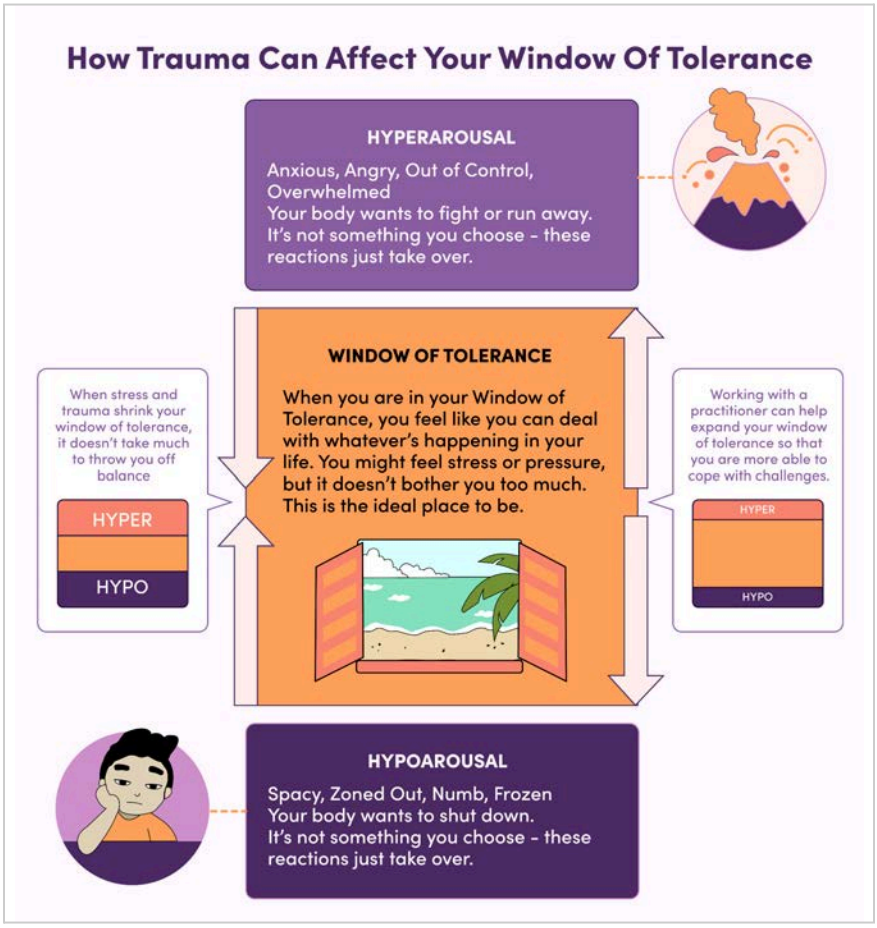


In the case of unresolved emotional traumas, for example, the deep and lasting psychophysiological feelings of unsafety perpetuate a continual state of hypervigilance, an attempt by the nervous system to avoid future circumstances that could re-trigger the original trauma or lead to new ones. Ongoing hyperarousal results in the release of a cascade of neurotransmitters and neuro-hormones that cause chronic activation of the sympathetic nervous system and can lead to both localized and widespread maladaptive changes in physiology. On the other hand, patients who are pushed past sympathetic activation would enter into the dorsal vagal state.

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Window of Tolerance

The “window of tolerance” is a concept originally developed by Dr. Dan Siegel, MD to describe the optimal zone of “arousal” for a person to function in everyday life. When a person is operating within this zone or window, they can effectively manage and cope with their emotions. When an experience overwhelms the nervous system’s capacity, it can be perceived as a trauma, and subsequently it may become difficult for the person to stay grounded in the present because the past is more vivid and intrusive. As discussed in the section on Evolutionary Adaptability and Survival, someone who has not effectively dealt with their past trauma or negative experiences, and who is under the burden of constant negative emotions and stress, is primed to detect threat and has a very narrow window of tolerance.



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Adverse Childhood Experiences ACE

Adverse Childhood Experiences are traumatic events that happen early in life (childbirth to 18 years of age) that affect children while growing up, such as suffering maltreatment or living in a household affected by domestic violence, substance misuse or mental illness. Unlike single incident traumas, ACEs are often likely to last longer (or they may be repeated) and this can cause a child's developing brain to become stuck in a physiological state of 'threat'. Bessel van der Kolk wrote about the neurobiology of childhood trauma and described trauma-induced alterations in threat perception being expressed in how children think, feel, behave, and regulate their biological systems[305].

The Adverse Childhood Experiences (ACE) Study (by the USA's Centre for Disease Control & Intervention & Kaiser Permanente) is one of the world's largest investigations of the effects of childhood abuse, neglect and household challenges on later-life health and well-being.

Completed in the late 1990s, 17,000 Kaiser patients completed a 10-question questionnaire regarding their childhood experiences, and their current health status and lifestyle behaviors. Their answers were compared against their medical histories, and researchers were able to calculate with a high degree of accuracy the relationship between ACEs and the likelihood of later medical issues.

Results from the study were shockingly clear: Early adversity can have lasting impacts, including having a strong association with risky behaviors, susceptibility to mental health and chronic health conditions. The more ACEs children experience, the more harm they can sustain over time. Adults who have experienced one or more ACEs are at a higher risk for depression,

[305] van der Kolk BA. The neurobiology of childhood trauma and abuse. Child Adolesc Psychiatr Clin N Am. 2003;12(2):293-ix. doi:10.1016/s1056-4993(03)00003-8

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diabetes, cancers, heart disease and other health conditions during their lifetime. For adults who have more than 4 ACEs and who have not received adequate therapy, this can negatively affect longevity through the role of unhelpful coping behaviors and negative lifestyle factors.

In addition to the hugely influential nature of the attachment relationship between a parent and a child, ongoing adverse experiences (such as those listed above) can cause toxic levels of stress that sadly can negatively impact on both brain structure (i.e., the development of neural networks) and brain function (i.e., can alter a developing brain's biochemistry and thus response to input).

Toxic stress happens when ACEs repeatedly trigger a child's fight-flight-freeze system (our innate stress response governed by our sympathetic nervous system). It also occurs when emotions associated with coping (like anger, fear, frustration, shame, humiliation, anxiety) continue to trigger a stress response in the body and mind. This is commonplace in families where children are either punished for their emotional experiences, or parents who may lack the skills / awareness to navigate certain emotions themselves miss opportunities (cues) to settle and soothe their children.

Unfortunately, parents who have experienced ACEs and who have not developed adaptive ways to resolve the complex and challenging impacts of these experiences, or who may have not have developed adaptive ways of coping with stress, are statistically more likely to create environments – or have lifestyles – that place their offspring at risk of experiencing ACEs themselves. Often, this is how the cycle of intergenerational trauma continues.[306]

With repeated exposure to high levels of stress (particularly in the absence of attachment safety), the accumulation of toxic stress can affect both skill and brain development. Living in a

[306] Daines, C.L., Hansen, D., Novilla, M.L.B. et al. Effects of positive and negative childhood experiences on adult family health. BMC Public Health 21, 651 (2021). https://doi.org/10.1186/s12889-021-10732-w

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heightened state characteristic of perpetual fear (or the need to ensure safety) can effectively narrow our Window of Tolerance making us susceptible to chronic health conditions.

Gabor Maté states that a survival strategy in the face of repeated or sustained adverse childhood experiences is the brain shutting down conscious awareness “when pain becomes so vast or unbearable that it threatens to overwhelm our capacity to function. The automatic repression of painful emotion is a helpless child’s prime defense mechanism and can enable the child to endure trauma that would otherwise be catastrophic.”

Kübler-Ross Model of Grief

We also leverage the Kübler-Ross model of grief, which explains how people get stuck in a stage of grief. When an individual is stuck in a cycle of limiting beliefs or undesirable patterns due to a COEX, our model utilizes the Kübler-Ross model to assess the stages of grief they may need to go through in order to heal that COEX. For example, if a person lost their parents at a young age and has never felt anger around the loss, they may be arrested at that particular grief stage in processing that COEX. Our model helps identify the need for healthy expression of anger and suggests tools that have been successful for other individuals in a similar stage of grieving.

From interviews with the dying, Dr. Kübler-Ross identified five stages that many people go through—denial, anger, bargaining, depression, and acceptance. Not all dying patients follow the same progression, but most experience two or more of the five stages:

- Denial — Often denial is the first stage. "I can't be dying. Not me."
- Anger — As the disease worsens and denial becomes less possible, there may be anger. "Why me?"

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- Bargaining — "If I do such and such, can I put off death for a while?"
- Depression — When the bargaining doesn't work, depression may set in. “Why bother? There is no meaning.”
- Acceptance — "I accept my fate and am ready to die."

The stages may not progress in this order. The dying person and those who love them may go back and forth among some or all of these and other emotions.

The goal of moving through these stages is to get to acceptance, which is achieved by learning what is necessary to open up and allow other emotions to come through. This process, when applied to healing a COEX, is about uncovering what the subconscious learned at a young age about what was acceptable or deemed worthy of love. When we allow that emotion to move through us, we arrive at acceptance, and then we can further address the original COEX. Getting “unstuck” from a COEX is first and foremost about moving to acceptance and recognizing the value of the experience in question.

Once we address the original COEX, the cells will be able to themselves get back on track with healing and disease can thus be mitigated or resolved.

Physiologic Models that Mirror the Human Experience

Theories

Naviaux’s Cell Danger Response

Robert K. Naviaux is the founder and co-director of the Mitochondrial and Metabolic Disease Center (MMDC) at UCSD and is a Professor of Genetics in the departments of Medicine,

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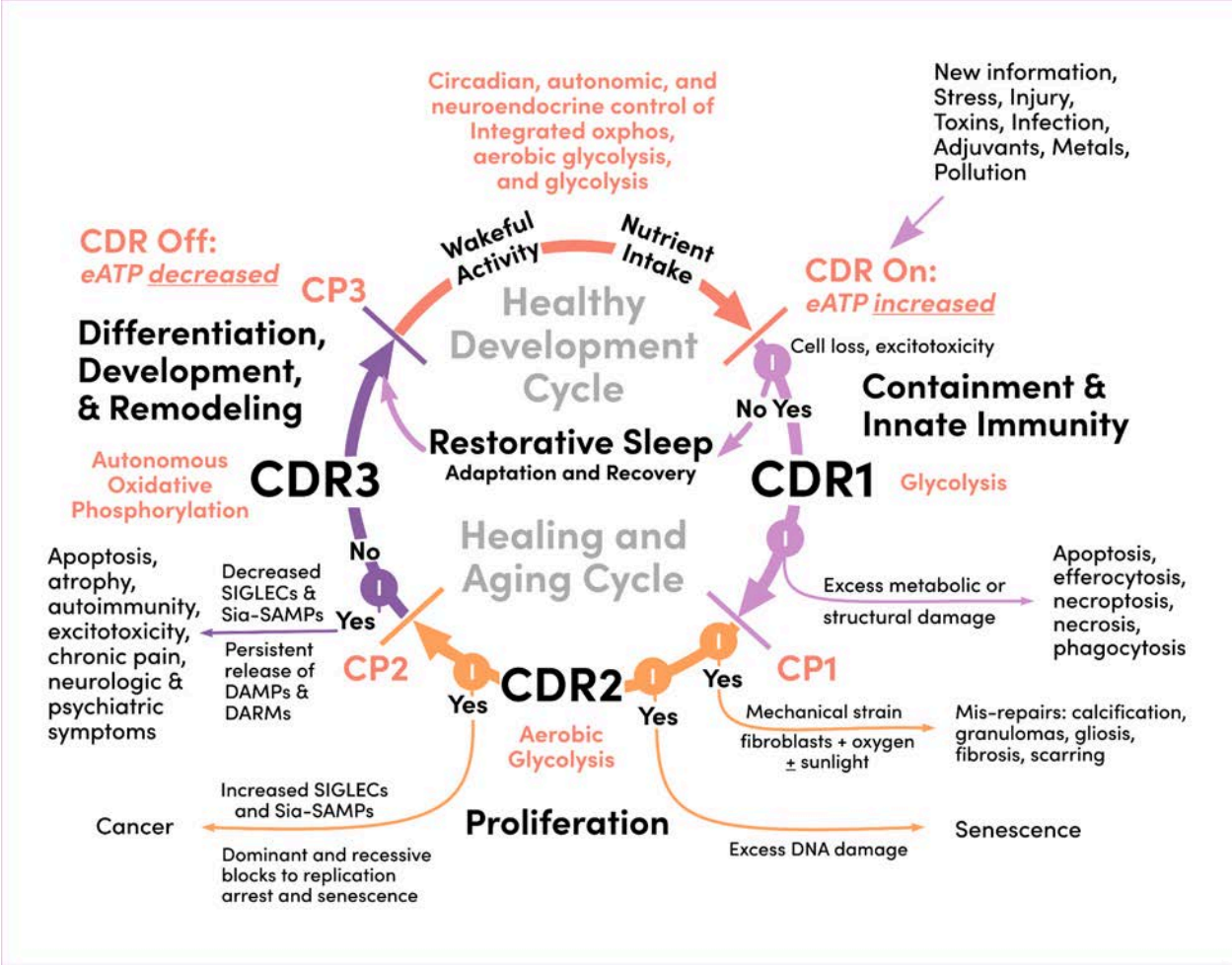
Pediatrics, and Pathology at the UCSD School of Medicine, who specializes in mitochondrial medicine and complex chronic disorders. Naviaux proposed the cell danger response (CDR) and hyperpurinergia hypothesis for complex disorders in 2014[307].

The CDR is the evolutionarily conserved metabolic response that protects cells and hosts from harm. Triggers are encounters (chemical, physical, or biological threats) that exceed the cellular capacity for homeostasis. After the danger has been eliminated or neutralized, a choreographed sequence of anti-inflammatory and regenerative pathways is activated to reverse the CDR and to heal.

When the CDR persists abnormally, whole body metabolism and the gut microbiome are disturbed, the collective performance of multiple organ systems is impaired, behavior is changed, and chronic disease results. Much like the parallel in our nervous systems, metabolic memory of past triggers alters physiology to increase functional reserve capacity. In this case, “mitocellular hormesis” changes mitochondrial and cellular macromolecule content[308]. The systemic form of the CDR is under direct control by ancient pathways in the brain that are ultimately coordinated by centers in the brainstem[309].

[307] Naviaux RK. Metabolic features of the cell danger response. Mitochondrion. 2014;16:7-17. doi:10.1016/j.mito.2013.08.006
[308] Manoli I, Sysol JR, Epping MW, et al. FGF21 underlies a hormetic response to metabolic stress in methylmalonic acidemia. JCI Insight. 2018;3(23):e124351. Published 2018 Dec 6. doi:10.1172/jci.insight.124351
[309] Naviaux RK. Metabolic features of the cell danger response. Mitochondrion. 2014;16:7-17. doi:10.1016/j.mito.2013.08.006

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To put this into context of illness and disease, Naviaux states that “most chronic illness is caused by the biological reaction to an injury, and not the initial injury, or the agent of injury itself. For example, melanoma can be caused by sun exposure that occurred decades earlier, and post-traumatic stress disorder (PTSD) can occur months or years after a bullet wound has healed. If healing is incomplete between injuries, more severe disease is produced. If a new head injury is sustained before complete healing of an earlier concussion, the clinical severity of the second injury is amplified, and recovery is prolonged. This occurs even when the energy of

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the second impact was less than the first. Progressive dysfunction with recurrent injury after incomplete healing occurs in all organ systems, not just the brain.[310]"

Bioinformational Theory and Psychoneuromuscular Theory

Bioinformational theory proposes that narrative imagery activates an associative memory network in the brain that includes stimulus (e.g., agents, contexts), semantic (e.g., facts and beliefs) and, most critically for emotion, response procedural information (e.g., autonomic and somatic) that represents relevant real-world coping actions and reactions. It is concerned with how emotions are elicited and displayed and with how they interact.

The link between emotions and physiology is demonstrated in this field of study, where psychophysiological studies reliably find measurable response output during aversive and appetitive narrative emotional imagery and "neuroimaging studies confirm that narrative imagery prompts mental simulation of events that critically includes the actions and reactions engaged in emotional contexts"[311].

This is a cousin field of study to Psychoneuromuscular Theory which states that, during the processing of imagery, not only do the parts of the brain involved in spatial navigation (retrosplenium) and movement (supplementary motor area, lateral cerebellum, and left inferior frontal gyrus[312]) light up in neuroimaging, but the brain actually sends electrical impulses to the muscles. Numerous studies have indicated that motor imagery may result in the same plastic changes in the motor system as actual physical practice.

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[310] Naviaux RK. Metabolic features and regulation of the healing cycle-A new model for chronic disease pathogenesis and treatment. Mitochondrion. 2019;46:278-297. doi:10.1016/j.mito.2018.08.001
[311] Bradley MM, Sambuco N, Lang PJ. Imagery, emotion, and bioinformational theory: From body to brain. Biol Psychol. 2023;183:108669. doi:10.1016/j.biopsycho.2023.108669
[312] Sabatinelli D, Lang PJ, Bradley MM, Flaisch T. The neural basis of narrative imagery: emotion and action. Prog Brain Res. 2006;156:93-103. doi:10.1016/S0079-6123(06)56005-4

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Motor imagery is the mental execution of a movement without any overt movement or without any peripheral (muscle) activation leading to the activation of the same brain areas as actual movement; the more vivid the imagery, the stronger the brain activation and the tighter the muscle correlates. These impulses are identical to those that cause muscle contraction with movement and despite being of of lower intensity, the neural pathways are activated (and thus strengthened), facilitating the learning and performance of motor skills[313].

Developmental Kinesiology

Human locomotion, unlike many animals, is immature at birth and muscle function matures in-step with anatomical maturation. Developmental kinesiology is the development of motor functions after birth and as the central nervous system matures, purposeful muscle function becomes increasingly activated and is driven in a genetically predetermined sequence. Human developmental motor patterns can be divided into three levels of sensorimotor control within the central nervous system.

As already alluded to in the section on Primitive Psychological and Primitive Reflexes, during the neonatal stage, general movements and primitive reflexes are controlled at the spinal and brain stem levels. Following the newborn period, the subcortical level of the central nervous system motor control emerges and matures mainly during the first year of life. This allows for basic trunk stabilization, a prerequisite for any phasic movement and for the locomotor function of the extremities. At the subcortical level, orofacial muscles and afferent information are automatically integrated within postural-locomotor patterns. Finally, the cortical (the highest) level of motor control increasingly becomes activated. Cortical control is important for the

[313] Mulder T. Motor imagery and action observation: cognitive tools for rehabilitation. J Neural Transm (Vienna). 2007;114(10):1265-1278. doi:10.1007/s00702-007-0763-z

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individual qualities and characteristics of movement. It also allows for isolated segmental movement and relaxation[314].

Human emotions include three measurable response classes: verbalisation, overt actions, and associated physiological changes[315]. Lang et al. posit that primitive survival reflexes are the foundation for emotion's physiological mobilization and action[316] where appetitive motivations drive animals to approach elements that benefit survival and defensive motivations instigate the sympathetic nervous system where threats to survival are perceived. However, humans are more complex than this and have developed higher order cortices with "enhanced capacity for inhibition and delay, and evaluation of alternatives and outcomes"[317].

Our primitive reflexes are imprinted in muscles and glands, supported by neural circuits. As a physiological model of the human experience, we see a general reemergence of primitive reflexes in negative emotional states. McTeague and Lang[318] found that in patients with anxiety and depression, there was exaggerated reactivity to emotional imagery meant to elicit a negative state - most pronounced in startle reflex responding. Interestingly but not surprisingly, disorders of long-enduring, pervasive apprehension and avoidance with broad anxiety and depression comorbidity (e.g., PTSD secondary to cumulative trauma, GAD), startle responses were paradoxically diminished to all aversive contents. The mind falls back on ancient

[314] Kobesova A, Kolar P. Developmental kinesiology: three levels of motor control in the assessment and treatment of the motor system. J Bodyw Mov Ther. 2014 Jan;18(1):23-33. doi: 10.1016/j.jbmt.2013.04.002. Epub 2013 May 14. PMID: 24411146.
[315] Lang PJ, Bradley MM, Cuthbert BN. Emotion, motivation, and anxiety: brain mechanisms and psychophysiology. Biol Psychiatry. 1998;44(12):1248–1263.
[316] Lang PJ, Bradley MM. Emotion and the motivational brain. Biol Psychol. 2010;84(3):437-450. doi:10.1016/j.biopsycho.2009.10.007
[317] McTeague LM, Lang PJ. The anxiety spectrum and the reflex physiology of defense: from circumscribed fear to broad distress. Depress Anxiety. 2012;29(4):264-281. doi:10.1002/da.21891
[318] McTeague LM, Lang PJ. The anxiety spectrum and the reflex physiology of defense: from circumscribed fear to broad distress. Depress Anxiety. 2012;29(4):264-281. doi:10.1002/da.21891

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programming in an attempt to protect the body, as previously discussed in How the Ancient Hindbrain Emerges to Protect in Times of Stress.

Weber-Fechner Law

Weber's Law, also known as the Weber-Fechner law, is a fundamental principle in psychology and psychophysics that describes the relationship between the intensity of a physical stimulus and the perceived magnitude of the sensation it produces. It states that the smallest detectable change in the intensity of a stimulus, is proportional to the initial intensity of the stimulus. As the intensity of a stimulus increases, the amount of change required for a person to notice the difference also increases. Weber's law underwent extensive testing throughout the 19th and much of the 20th century, primarily in the realm of sensory perceptions like light, taste, sound, pain, and heat. Essentially, this model states that the brain accumulates evidence and it makes a decision when there is enough evidence to make it. The more intense a stimulus is, the more its perception can vary, making it harder to differentiate between very intense stimuli than between stimuli of low intensity.

A 2023 study found that as emotions (induced by pictures) became more pleasant, the accuracy with which participants gauged their intensity decreased. This showed, for the first time, that in humans, pleasant emotional experiences follow Weber's classical psychophysical law - indicating that we become less accurate in estimating the intensity of our pleasant emotional experiences as the experience becomes more pleasant[319]. However, this pattern wasn't observed for unpleasant emotions, suggesting a survival-related need for accurately discerning high-intensity negative emotions.

[319] Berkovich R, Meiran N. Pleasant emotional feelings follow one of the most basic psychophysical laws (weber's law) as most sensations do. Emotion. 2023;23(5):1213-1223. doi:10.1037/emo0001161

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Stages of Change Model

Emotional healing is an endeavor of self-discovery, self-compassion, and self-improvement. As with all journeys of seeking insights into self for betterment, the individual must be ready for change. This is acknowledged by our team and we understand the stages of change as being:

- Precontemplation (Not yet acknowledging that there is a problem behavior that needs to be changed)
- Contemplation (Acknowledging that there is a problem but not yet ready, sure of wanting, or lacks confidence to make a change)
- Preparation/Determination (Getting ready to change)
- Action/Willpower (Changing behavior)
- Maintenance (Maintaining the behavior change)

Whilst we are ready and willing to assist clients who are at the contemplation or preparation stage, Liber8's Precision Emotional Healing System is most effective for those at the action stage - someone who understands the benefits of emotional healing, and is willing to do the work.

Apply The Concepts

The Precision Emotional Healing System

In order to apply the various theories and psychological models discussed, it is necessary to have a working model of how an individuals' perception, awareness and model of reality fit

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together, and the factors required for change. A root-cause engineering framework has been developed by Liber8 and the Humans Are Good Foundation to optimize this highly complex system of interaction.

The Precision Emotional Healing System uses this framework to help individuals track and shift root psychological patterns contributing to toxic stress. This framework is broken down into:

- Logging new emotional data
- Mapping logged data to previous experiences
- Analyzing the binding properties of mapped data
- Prescribing a tool or process
- Viewing the changes in new logged data and mapped data through the lens of understood healing phases
- Anchoring new insights and client created legacy statements into the psyche
- Allowing the organic process of life to test new truths

Shifting one's perception creates an opportunity to ascertain any and all aspects of one's life, condition or situation. Processing information provided by this new vantagepoint can give rise to new levels of cognizance, which enables individuals to permanently shift previously held beliefs and relative truths. This becomes a cyclical process of shifting perspective, incorporating new heights of awareness that create healing changes, and provide insight to the next healing tool.

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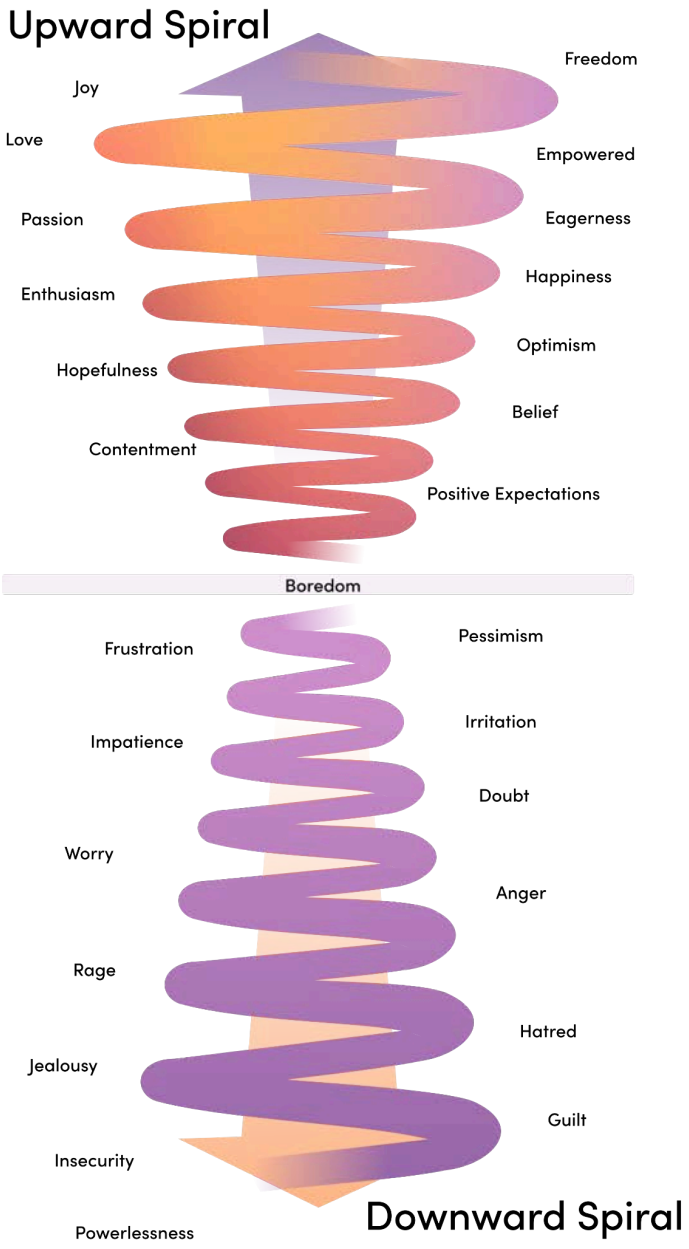


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The Physics of Awareness

Logging new emotional data

The opportunity to create efficient, effective, scalable change in emotional health begins by helping individuals capture and track their perspective changes brought on by emotional shifts. Through analysis of triggers (via negative emotions) and insights (via positive emotions) the most relevant [and present] data of one's nervous system can be used to build a personalized model of their psyche.



Mapping logged data to previous experiences

By following the emotional trail of beliefs using present day emotional triggers, charged condensed emotional experiences can be mapped within the nervous system. These experiences are relationship phenomena – in relation to oneself, another person, or another thing. This mapping process must be conducted in a psychologically safe container (from the individual's perspective) to harvest information properly

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and accurately. The collected data has various properties and parameters which can illustrate the current wound structure within the individual.

During mapping, an individual may recall a memory or experience associated with significant negative emotion. This indicates a requirement for healing and/or resolution. By healing or completing the incomplete emotional experience, one's mind and body can reach a place of acceptance where their nervous system is no longer carrying additional stress. By removing this unaddressed excess stress, the individual's body is able to heal itself more effectively.

Analyzing the binding properties of mapped data

Once the mapping process is complete, Liber8 software analyzes the binding properties of the mapped data to identify trends, patterns, and variations which occur at different stages of brain development. The resulting Emotional Lab Report is used to develop the most effective and efficient healing protocol for the individual.

Moving Through The Healing Phases

Wound structures are composed of multiple condensed emotional experiences across multiple stages of brain development, and encompass permutations of multiple learned limited beliefs which stack and synergistically build upon each other over time.

The processing and release of these wound structures is conducted through three core phases during the healing process, facilitated by an understanding of specific concepts, usage of tools to encourage neuroplasticity, and collective experiences within individual and group therapeutic processes. This process is rarely linear, often incorporating high and low points as an individual navigates to emotional resolution and healing.

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The healing phases are as follows.

1) Reaching a state of full emotional cognizance and acceptance in order to resolve negative emotional charges within the nervous system. For emotional information codified in the nervous system to be processed in full, it must be reviewed in full, within the context of the relationship layer in which it was originally bound by the individual. This binding originates from the phenomenon of being “unseen” or unable to attune one’s nervous system to the safety of another [primary caretaker][320]. As such, various psychologically safe “containers” must be created to enable a fully functional healing process. The primary relationship layers are: self, partner, family, tribe, community.

2) Leveraging gratitude as a by-product of whole mind-body emotional cognizance to transition emotional charges held in the nervous system from neutral to positive.

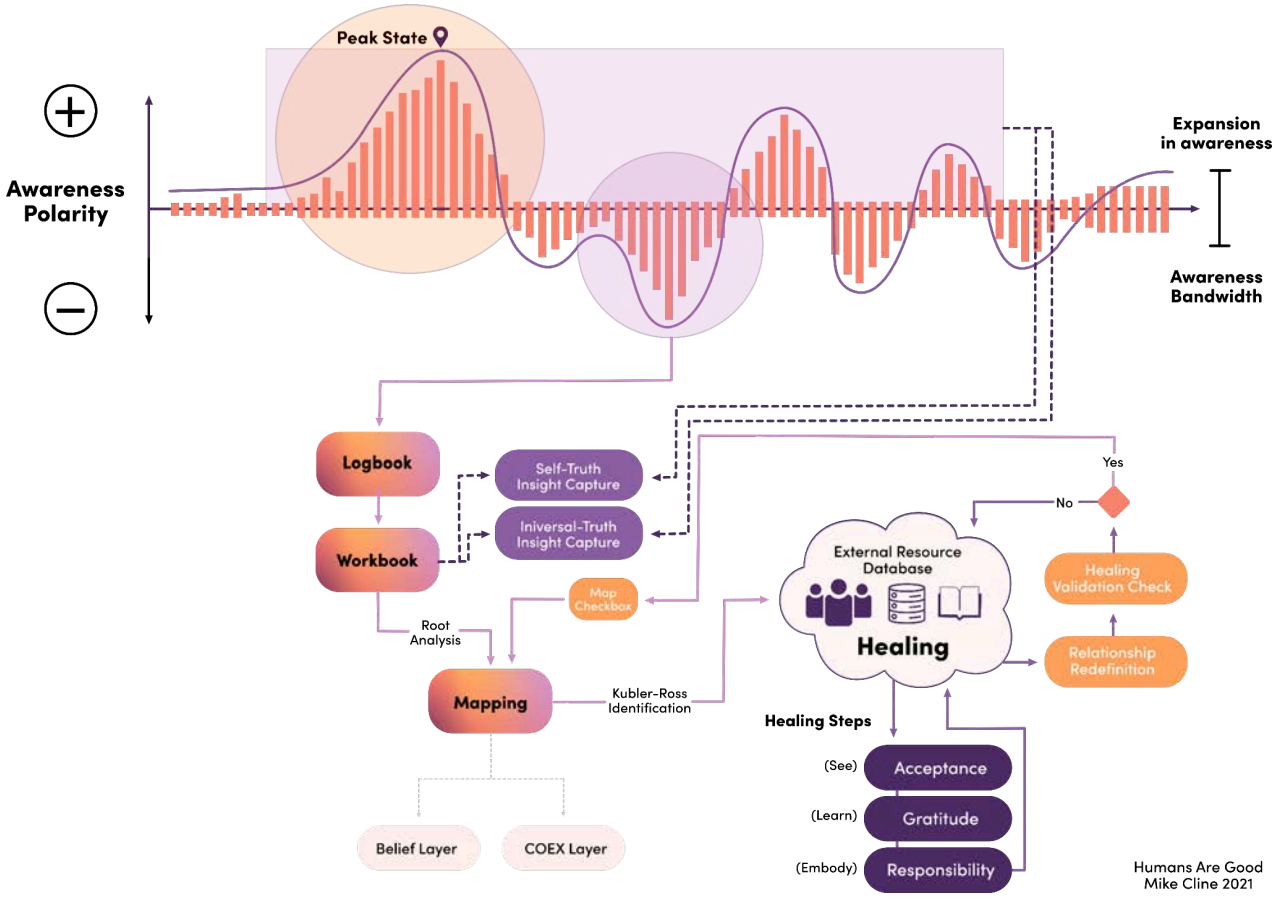
3) Establishing the embodiment of conscious responsibility to redefine relationships within the wound structure, in order to reclaim emotional sovereignty over the nervous system and establish intentional emotional cognition processes.

These three phases of healing are monitored by way of Liber8’s feedback loop, logging present-day emotional data. This data will shift and change as one advances through the healing and resolution process to address deeper elements within the psyche.

[320] Fiskum C, Andersen TG, Johns UT, Jacobsen K. Changes in Affect Integration and Internalizing Symptoms After Time-Limited Intersubjective Child Psychotherapy-A Pilot Study. Front Psychol. 2022;13:906416. Published 2022 Jul 8. doi:10.3389/fpsyg.2022.906416

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The illustration below provides a strategic-level model of this process.



It is important to note all data is treated as relative data. There are no absolutes in classifications by design, but instead data is treated as entirely personalized. This abstracted approach enables greater precision for personalized care. The relational data model created consists of several interrelated objects within multiple fields. Below is a partial list:

Trigger

- **Description**: Represents present day [negative] emotional data captured using the mobile app.
- **Key Fields**:

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- **Intensity** (Int): Perceived intensity of the event by the individual.
- **What Happened** (String): Perceived experience of what caused the trigger.
- **What Happened In Body** (String): Perceived physiological effects in the body.
- **Raw Emotions** (String): Perceived emotions occurring at the time of trigger.
- **Core Wound Category** (Picklist): Perceived categorization of what was true.
- **Manifestation** (Picklist): Perceived categorization of what was true as a response.
- **Force of Activation** (Picklist): Perceived movement of the event itself.
- **Type of Response** (Picklist): Perceived body response to the event.
- **Consumption Level** (Picklist): Perceived level of amygdala hijacking that occurred.
- **Relationship Category** (Picklist): Perceived relationship layer associated with the event.
- **Related** (Learned Limited Belief): Previously identified, associated Learned Limited Belief.

Insight

- **Description**: Represents present day [positive] emotional data captured using the mobile app as well as during a mapping session. Utilized in the process of shifting Learned Limited Beliefs.
- **Key Fields**:
  - **Insight Statement** (String): Present anchoring and understanding of a truth that embodies an emotional reality. Statements that are fundamentally true to one's being.

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- **Supporting Statement** (String): Statements that support reconnecting with the emotional truth of the insight statement.
- **Free Writing** (String): Additional information related to the insight.
- **Insight Type** (Picklist): Categorization of Insight (e.g., Self, Universal).
- **Insight Prompt** (Picklist): Prompt question that stimulated the insight.

COEX (Condensed Emotional Experience)

- **Description**: Represents historical emotional data captured during a mapping session.
- **Key Fields**:
  - **Age** (Int): Perceived age at which the charged condensed emotional experience event occurred
  - **Intensity** (Int): Perceived intensity of the event by the individual at recall
  - **What Happened** (String): Perceived experience of what happened in the past
  - **What Happened In Body** (String): Perceived present physiological effects in the body
  - **Raw Emotions** (String): Perceived emotions occurring in the present
  - **Core Wound Category** (Picklist): Perceived categorization of what was true.
  - **Manifestation** (Picklist): Perceived categorization of what was true as a response.
  - **Force of Activation** (Picklist): Perceived movement of the event itself.

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- **Type of Response** (Picklist): Perceived body response to the event.
- **Relationship Category** (Picklist): Perceived relationship layer associated with the event.
- **Related** (COEX): Previously identified, associated COEX part of linked stack.

Learned Limited Belief

- **Description**: Represents learned limited beliefs present in an individual's psyche. Captured during mapping sessions.
- **Key Fields**:
  - **Limiting Belief** (String): Perceived learned limited belief about one's reality.
  - **Example Statement** (String): Contextual statement supporting the way this belief was digested and understood.
  - **Core Belief Category** (Picklist): Perceived categorization of fundamental belief.
  - **Related** (COEX): COEX associated with this learned limited belief.

As these data elements are identified, their shared properties become evident. Liber8's recommendation engine analyzes these shared properties and formulates questions to further determine the best course of healing. Is the trauma more bound in the mind? Is it in the body? What types of relationship layer binding needs to be addressed?

The recommendation engine guides individuals through protocols aligned to healing phases designed to resolve their personal wound structure. Individuals might be recommended a series of books, a particular self-practice, or a list of practitioners who provide the most optimal somatic

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work or cognitive mental work. Fundamentally, the recommended healing tools and protocol must align within the individuals' personal parameters for psychological safety.

The data classification of healing tools within the model are as follows:

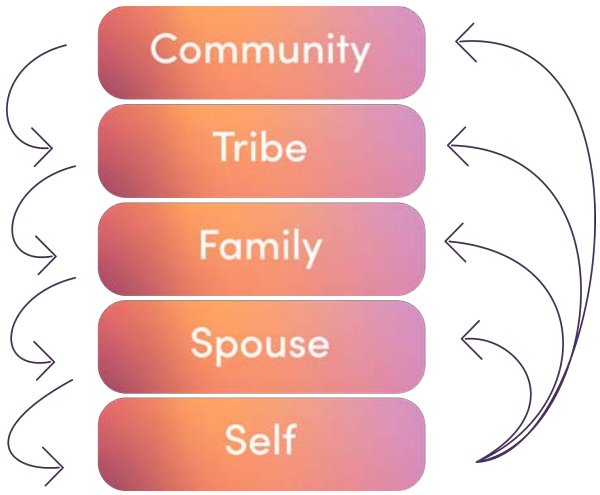
- **Healing Phases**
    - **Acceptance**: Tools focused on adding new perspective and awareness to the wound structure beginning to be uncovered.
    - **Gratitude**: Tools focused on enabling positive outcomes from lessons learned through the wound structure and leveraging those outcomes constructively.
    - **Responsibility**: Tools focused on helping embodiment of the lessons learned in one's own unique way and establishing a statement of self-legacy.
    - **Magic Keys**: Foundational philosophical concepts that are prerequisites for an individual to move through the various healing phases.
- **Binding Site Tools**
    - **Mind**: Tools focused on processing mind-based wound structures.
    - **Body**: Tools focused on processing body-based wound structures.
    - **Heart**: Tools focused on processing heart-based wound structures.
    - **Spirit**: Tools focused on general awareness and whole system expansion.
- **Relationship Layers**
    - **Self**: Tools focused on one's relationship to self.

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- **Partner**: Tools focused on the single-other and intimate wound structures.
- **Family**: Tools focused on the family-unit wound structures.
- **Tribe**: Tools focused on the connected tribe wound structures. Up to 150 people.
- **Community**: Tools focused on the unconnected tribe wound structures. Beyond 150 people.

Healing The Relationship Layers

The specifics of wound structures are important in understanding the correct tool for application to an individual relative to the phase of healing. Additionally, the environment provided – combined with psychological safety – plays a large role relative to the individual's emotional recognition (i.e. "being seen").



The optimized process of achieving emotional recognition first requires placing the individual into the perceived safest environment possible -- one with a certified "professional", or peer support specialist. From this perspective an individual begins to open up, allowing themselves

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emotional vulnerability and recognition, which in turn enables them to confront deeper traumas encoded within their own psyche.

Following this step, the protocol progressively transitions the individual through the aforementioned relationship binding layers. The “tribe” layer by way of peer support groups. At this layer, one is allowing themselves to be seen and to see others in a more loose and open manner. At this layer individuals hold space for each other in mapping sessions, with a certified peer support specialist present, creating deeper intimacy. At the completion of this level an education on “how to hold safe space” is needed in order to go further.

The final relationship layer to complete the fundamental understandings is at the “partner” layer. This is achieved through a pairing up of individuals in a high school chemistry lab like environment. Through mutual learning, and seeing each other, deeper forms of intimacy are possible. The lens is that of best friends. Helping individuals build best-friend type relationships from a place of grounded compassion, love, respect and honesty completes the necessary perspectives.

These three stages combined with the education and elements of the healing stages above represents an optimized approach to experientially teaching nervous system regulation.

What Is Our System Optimizing For?

Tracking progress is done by looking for the signs of neuroplasticity and increased emotional resilience, demonstrated as a change in the trigger data being logged. How consumed an individual is by a recurring trigger, and how that changes over time, is one example of this. Another is an individual’s relationship to their learned limited beliefs and the insights collected that help them morph into formal legacy statements. Additionally the process of reviewing and

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processing through insight cards helps give a clear understanding of what an individual is anchoring into their nervous system. Emotional self-regulation in the moment, comfort in being seen at the various relationship layers, the ability to reframe a situation and connect with gratitude all represent additional data points of positive change.

Our approach is based upon both what serves an individual efficiently and effectively as well as what enables the utilization of machine learning to continue to optimize the understanding of what works for what type of person and wound structure. The long term plan is the optimization of the recommendation engine to assess individuals early on in their journey and have the system identify enough information to point them in the right direction, while tracking progress. The goal is to continue to radically speed up the inner work healing process and make up for the lack of therapists in this mental health crisis.

Conclusion

Despite compelling evidence for the link between emotional well-being and physical health, significant challenges in effectively addressing the complex interconnections between emotions and disease remain within the $4.4 trillion global Mind-Body Wellness market.

Three key issues hinder progress:

1. A shortage of therapists specializing in mind-body-relational wellness, stemming from insufficient training and data on the intricacies of the human system as an interconnected whole.
2. Slow and costly healing processes that focus on symptom reduction rather than resolving the underlying neurological and emotional root causes that contribute to

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dysregulation and disease. Sophisticated data collection is needed to enable this deeper level of healing.

3. The absence of a clear, universal path to healing, given the highly individualized nature of people's emotional wound structures and the complex web of mind-body connections. One-size-fits-all solutions are wholly inadequate.

A more elegant and complete approach to addressing the problem is required.

Liber8's Precision Emotional Healing system allows us to collect and track the data needed to create the most efficient, effective, and scalable solutions for an individual to experience the perception and neurological shifts necessary to increase emotional resilience and reduce the toxic stress contributing to disease states.

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