A Systems Approach to Stress, Stressors and Resilience in Humans

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Abstract

The paper focuses on the biology of stress and resilience and their biomarkers in humans from the system science perspective. A stressor pushes the physiological system away from its baseline state towards a lower utility state. The physiological system may return towards the original state in one attractor basin but may be shifted to a state in another, lower utility attractor basin. While some physiological changes induced by stressors may benefit health, there is often a chronic wear and tear cost due to implementing changes to enable the return of the system to its baseline state and maintain itself in the high utility baseline attractor basin following repeated perturbations. This cost, also called *allostatic load,* is the utility reduction associated with both a change in state and with alterations in the attractor basin that affect system responses following future perturbations. This added cost can increase the time course of the return to baseline or the likelihood of moving into a different attractor basin following a perturbation. Opposite to this is the system's resilience which influences its ability to return to the high utility attractor basin following a perturbation by increasing the likelihood and/or speed of returning to the baseline state following a stressor. This review paper is a qualitative systematic review; it covers areas most relevant for moving the stress and resilience field forward from a more quantitative and neuroscientific perspective.

Keywords

psychological stress; systems science; allostatic load; resilience

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1. Introduction

Psychological stress is common in our society. A recent survey indicated that 25% of Americans reported high stress and 50% identified a major stressful event during the previous year [1]. Chronic psychological stress increases risk of health problems and contributes to cardiovascular problems [2, 3], neurologic and psychiatric diseases such as epilepsy [4], Parkinson's disease [5], multiple sclerosis [6], eating disorders, addictions [7], post-traumatic stress disorder (PTSD), and sleep difficulties. Therefore, it is important to develop evidence-based methods that minimize stress impact. A fuller understanding of stress physiology and psychology can be achieved by approaching this topic from different angles. This work offers a review of stress physiology and psychology from a systems science perspective.

Systems science is a methodology used to understand complex systems from organizational, structural, and dynamic perspectives [8]. From a systems science viewpoint, stress often corresponds to a state away from optimal in a dynamical system where the optimal location represents a high utility attractor. An attractor basin in a dynamical system corresponds to the conceptual space of locations in which the system resides over time. The state of stress results from a perturbation arising from the internal or external environment (stressor). This stressor could result in the system returning to the baseline optimal attractor or moving into a lower utility attractor basin. The attractor basin is the region of space that shares the same attractor and the whole space may have multiple attractors (Figure 1).

The attractor in the human system is not a fixed point attractor given the multidimensional nature and, almost inherent, within-subject temporal variability of the physiological measures of state. The noise present in the measurement of the many variables constituting the human system implies the observed human system is stochastic; thus, the attractors are very difficult to describe. In addition, given the varying time frames over which the components of the human physiological system change, the terms *state* and *variable* describing more immediate changes and the terms *trait* or *parameter* describing longer time frame changes represent an artificial separation of the various physiological measures that have different units and widely distributed half-lives. Whatever the attractor, even if the system returns to the baseline high utility attractor, there is often some underlying cost. This cost to the system is a change in the underlying physiology that may: 1) decrease the rate of return to the high utility attractor or 2) decrease the likelihood of returning to the optimal attractor following a future stressor perturbation because the size of the attractor basin is smaller or the attractor has moved closer to a boundary with a non-optimal attractor basin. The movement of the dynamical system into a different attractor basin could also be due to a single severe stressor potentially via a dynamical system catastrophe, for example, development of PTSD following a single event (Figure 2).

Besides negative effects, the stressor can also induce beneficial changes leaving the system more resilient to future perturbations, i.e., cause the opposite of 1) and 2) above. The term *resilience* includes several conceptual aspects. *Resilienc*e refers to how effectively and quickly the system returns to baseline [9]. This includes whether the human dynamical system avoids moving to a lower utility disease state following a stressor [10]. A related

term is *stability* which refers to how well the system can maintain its current high utility condition without being pushed away.

Although a stressor may cause a short-term decrease in some measure of utility, sometimes it results in longer-term utility increase. In the case of humans, this is related to learning as discussed below. The human dynamical system may experience some low-stress environmental perturbation that results in a relatively immediate gain in reward or utility, e.g., obtaining food when hungry or some longer-term gain in utility, e.g., the brain acquiring a better understanding of the environment. There is an apparent inverted u-shaped effect of stress on longer-term utility, such that occasional small amounts of stress may improve both short- and long-term utility but experiencing no stress or large amounts of stress may have negative long-term effects on the organism. Though the term "human" will be used, most of this discussion applies to other animals and to systems in general.

2. The human physiologic system: brain structure and network (Figure 3)

A human is a dynamical system composed of subsystems that help maximize utility of the organism. Utility may be defined: 1) from a purely biological perspective such as immediate reproductive success or obtaining food, or 2) from a more complex, perhaps hedonic or longer-term perspective such as longer-term reproductive success, obtaining more resources, gaining group support or enjoying an amusement park ride. Longer-term utility could extend beyond the lifespan, e.g., survival of the related social unit or the entire species (see section 9 for more information about utility). The organism is maintained by many critical systems and subsystems, such as cardiovascular and renal, but this paper focuses on the brain dynamical system and its communication links with the body via autonomic nervous system (ANS), hypothalamo-pituitary-adrenal (HPA) axis and neuroimmune system. The limbic system is involved in psychological aspects of stress, including neocortex activation by emotional states and memories of events associated with emotional valences. Older and more caudal brain parts including the brainstem and spinal cord are generally not critical for the following discussion with some exceptions including ANS components. The sympathetic portion of the ANS involving central catecholaminergic systems is particularly important for communicating the brain perception of stress to the whole body by causing changes such as increased blood pressure and heart rate. The hypothalamus is an important communication link secreting neurohormones, e.g., adrenocorticotrophic hormone (ACTH). Given this background, the most commonly discussed physiologic responses to a stressor involve the HPA axis, the locus coeruleus-norepinephrine-sympathetic nervous system pathway, the parasympathetic system, the immune system, and gene expression and alterations including epigenetic changes.

The two-way communication between the major effector systems (ANS, HPA, and immune) and the brain exist in part to ensure the stress-related systems provide feedback for learning and help avoid over-reactivity. The communication system between the immune system and the brain constitutes an entire field itself, psychoneuroimmunology [11]. The immune system - brain communication is significantly mediated by cytokines. All these two-way communication systems directly impact the brain via its receptors for norepinephrine, ACTH, cortisol, and cytokines, with prefrontal cortex, hippocampus, and amygdala being

most prominent [12]. Feedback is often inhibitory and is not perfect. Occasional errors in this two-way communication system may arise. For example, a major increase in heart rate in an exercising older adult with atherosclerosis might be accompanied by an attempt to decrease the heart rate, but this decrease may be insufficient to prevent a myocardial infarction and even a sudden death [13]. Additionally, the awareness of stress may itself be a stressor; however, this type of stress is distinct from experiencing external environmental stressors. Stress awareness may be commonly related to the "recall" or association of particular environmental inputs with prior stress.

3. Stressor

A stressor is an environmental event that significantly perturbs the entire human dynamical system away from the optimal attractor resulting in a state of lower utility. The stressor may move the physiological system to a different attractor basin, move the system state closer to the edge between its current attractor basin and another attractor basin of the physiological system ("precariousness"), or slow the rate at which the system returns to the optimal attractor. The movement of the system is not dependent solely on objective measures of the stressor but also on the individuals' traits of distress proneness and their perceptions of the stressor. If the perturbation is perceived to impact an organism negatively or associated with obvious threats (hunger/visualization of aggressor), there is an immediate effect to reduce the likelihood of a negative stressor impact. For example, seeing a bear with her cub while hiking will generate physiological changes important for action (elevated heart rate and blood pressure) and increased attention to environmental stimuli, thus improving encoding of the situation for future recollection. These perturbations increase likelihood of survival over the short-term but if maintained long-term may have deleterious effects. For example, a transient increase in blood pressure is tolerable and may be helpful, but a chronic increase in blood pressure is not high utility. Stress doses that are not high enough to cause significant health problems such as disease or death from a state change may produce higher average utility within the basin by altering the shape of the basin or by moving to a different, higher utility basin. In an athletics example, both short-term stress at an Olympic competition and longer-term stress from high effort athletic activity over a training period may improve athletic performance. However, excessive or repeated perturbations may have a cost to the underlying system that outweighs the benefit.

Stressors may include external environment perturbations such as extreme heat or icy roads while driving. Stressors may also include internal environment perturbations such as infections or elevated glucose. Stressors may be predominantly psychological and mediated by brain perception and future expectancy. Stressors are not necessarily physical changes in the environment but may involve loss of a significant relationship, financial stress, negative neighborhood characteristics, or social threats including discrimination [14-17].

For most of this discussion, the stressor referring to perturbations under tight physiological control will be omitted. Information signals from these perturbations such as alterations in serum sodium do not need to reach the brain level to be regulated. *Homeostasis* refers to the dynamic control of these state variables maintained within a narrow window for humans to successfully function. The dynamical system representing the whole person is regularly

exposed to more heterogeneous stressors than serum sodium changes, including potential stressors that are anticipated. *Allostasis* has been used to describe "actively maintaining homeostasis" [18], but the practicality of this distinction from *homeostasis* is uncertain [19].

Some stressors represent state perturbations to which the person may respond without any obvious long-term negative ramifications. Some stressors, in part related to their chronicity, may have negative long-term ramifications. The perturbation may induce changes in several systems. For example, as time passes from the previous meal, a human's stomach is growling and blood sugar is getting lower; the brain senses hunger and mobilizes to address the perturbation stressor. Part of the response to a stressor will be mediated directly by the internal environment without requiring any mediation by the brain, e.g., hunger causing the release of hormones to break down glycogen. Part of the response is directly mediated by the brain responsible for planning how to interact with the external environment, e.g., walking into the kitchen to get food. The perturbation may induce changes in physiological parameters, e.g., DNA transcription or epigenetic modifications to alter neurotransmitter receptor sensitivity. Responding to these stress perturbations may induce some cost to the system. This cost may involve the movement of the system into another basin of attraction or an increase in the probability that the system will move into another basin following future perturbations.

Though the stressor has some objective qualities, it can be difficult to quantify because physiological stress effects are highly dependent on the subjective perception. Quantifying an individual's stressors has been attempted [20]. Some examples of stressors include events that have **n**ovelty, **u**npredictability, (any information-rich input beyond the brain processing ability), **t**hreat to one's ego, or **s**ense of loss of control (NUTS) [21]. Short-term laboratory experimental stressors are related to these NUTS concepts including the Trier Social Stress Test, [22], the Montreal Imaging Stress Task [23], titrated Stroop color-word interference task [24], physical (e.g., putting a hand in ice water) [25], or perceptual stressors (e.g., the disturbing pictures of the International Affective Picture Scale [26]). Stress responses can also be conditioned [27] allowing for comparison between humans and other animals. It is more challenging to study long-term stressors experimentally but occasional misfortunes such as wars and other disasters have generated informative epidemiological data, e.g., the World Trade Center disaster. Stressors may involve awareness of a stressor, even if it is erroneous, e.g., misperception of an environmental change. Relevant examples include erroneous stress associations with ordinary loud sounds that have developed from explosion-related PTSD or a pheochromocytoma producing a surge of catecholamines perceived as a stress state because of diaphoresis and a fast heart rate.

In general, frequent perturbations into a stressed state away from the high utility attractor have a cost to the system. The cost of going to the refrigerator when feeling hungry is low. However, a related perturbation, the blood sugar increase and the need to secrete insulin due to overeating high-sugar items may eventually cause long-term negative effects. If repeated enough, it may diminish the human's ability to stay in a positive functional attractor, and the lack of responsiveness to insulin at the cellular level (i.e., insulin resistance) may cause adult type 2 diabetes. This common stress-related change has resulted in a common diabetes measure, glycosylated hemoglobin HgbA1c, frequently used as a chronic stress biomarker.

In humans, *allostatic load* is the cost to the system due to repeatedly returning to baseline, i.e., the costs of executing the physiological changes and the potential costs of making the changes in architecture of the basins of attraction (their size, depth, etc.) following a stressor as well as the eventual impacts of the architecture change. *Allostasis* has been used to describe the dynamical control over these variable perturbations for maintaining a functional state. Though there is some controversy over whether allostasis is truly different from homeostasis [19], the term *allostatic* load has been used as a conceptual measure of the physiological cost due to chronic stressors [28] and be will be used in this paper. Attempts to define a metric of allostatic load for experimental use are discussed below.

4. Measurement of stress

The term stress describes a state of physiologic and behavioral responses to a stressor with the brain being the critical interpreter of what is stressful. Though inconsistently used, the stressed state in humans for the purposes of this discussion is linked to dynamical physiological change. The stressed state also involves the conscious and unconscious stressor interpretation by the brain including the conscious perception of the stressors and the perception of the physiologic response generated by the stressor [29-31]. Stressors result in changes in state variables and parameters and have been measured using various biomarkers.

There are many objective ways to measure human stress responses other than commonly used self-rated scales. As previously noted, physiologic responses to stress include activation of the HPA axis, activation of the locus coeruleus-norepinephrine-sympathetic nervous system pathway, the parasympathetic system, immune system, and genes [29, 31-35]. Importantly, the timing of these changes is variable. When measured as state variables, they may or may not shed light on the dynamical nature of the physiologic system, resilience, or allostatic load. Dynamical aspects of stress and resilience may be estimated with repeated measurements over longer periods during daily routines or following a known experimental stressor.

4.1. Peripheral biomarkers

Each biological assessment has a sampling time window. For example, a peripheral blood draw to assess cortisol reflects cumulative changes over minutes, cortisol overnight urine collection measure reflects cumulative changes over hours, and a hair sample may reflect cumulative changes over months.

HPA axis activity biomarkers include glucocorticoids: free cortisol (or corticosterone in experimental animals), ACTH, and corticotropin releasing hormone [36, 37]. In addition to acute stressor-induced changes in these biomarkers, there are alterations in diurnal fluctuations with chronic stress, e.g., in cortisol awakening response [38, 39]. Dehydroepiandrosterone (DHEA) and its sulfate (DHEAS) act to counter-regulate cortisol [40]. DHEA is used as a stress marker by itself [41] or as a ratio to cortisol and has been affected by depression [42]. Mineralocorticoids may also be stress biomarkers [43].

Several autonomic activity measures are associated with acute or chronic stress including blood pressure, electrodermal response, skin temperature, respiratory rate, heart rate and heart rate variability (HRV) [44]. A variety of HRV measures in the time and frequency domains have been evaluated [45, 46]. While HRV may look at dynamical changes over long periods, e.g., 24 hours or more, longer-term HRV requires more sophisticated data processing to correct for exercise and unrelated to stress activities modifying the heart rate.

Many measures correlated with stress have been treated as relatively static measures. There are alterations in immunologic function including cytokines; gene and epigenetic modifications involving telomere changes; and metabolic activity fluctuations resulting in generation of reactive oxygen and nitrogen species damaging to cellular structures [29, 33, 35, 47-49] .

There are other biomarkers not directly related to the currently discussed physiological stress pathways. To assess stress responses researchers have used measures of muscle activity e.g., using electromyographic activity for biofeedback in treatment of muscle contraction and other types of headaches. Biofeedback has been used on many physiological measures with only few (peripheral temperature and electrodermal activity) being closely related to ANS activation [50]. Additionally, as many have casually observed, stress alters voice characteristics [51] and posture in a chair [52]. Other biomarkers are listed below under allostatic load.

4.2. Brain changes

4.2.1. Cognition—Cognitive function including memory is significantly altered by stress in humans and non-human animals [53-55]. Cognitive decline associated with stress (and the closely related construct depression) may affect speed, attention, and executive function [54, 56]. Prefrontal cortical dysfunction is particularly impacted by stress [57]. This pathological relationship becomes more evident with age [58], and highly stressed elders such as dementia caregivers may be particularly at risk [48].

4.2.2. Structural brain changes—Stress-related states such as PTSD and fear conditioning are linked to decreased hippocampal size, decline in prefrontal cortex, increased size of portions of the amygdala, and decreased inhibition of the amygdala and related brain regions by the frontal lobes [55, 57, 59, 60]. The brain changes are at least partially mediated by cortisol with increased cortisol related to smaller hippocampi [61]. The time course of structural change is much longer than the half-life of cortisol; cortisol elevation needs to be sustained to cause longer-lasting brain changes. Smaller hippocampi are common among people with PTSD or trauma exposure [62, 63] and they also are linked to increased risk for PTSD development [64] so the causative relationship is uncertain. Further, PTSD sufferers are at higher risk of dementia [65] and those with smaller hippocampi have increased the risk of dementia [66]. Therefore, defining the causative aspects of these relationships is critical and can affect other important health concerns. From the perspective of beneficial effects, research shows increased hippocampal volume and improved verbal declarative memory in PTSD patients after using a selective serotonin

reuptake inhibitor (SSRI) antidepressant for 9-12 months [67]. This is likely related to SSRI-related neurogenesis increase [68].

4.2.3. Physiological brain changes: *EEG, event-related potential, fMRI*—EEG stress-related changes, particularly frontal asymmetries [69, 70], and alterations in event-related potentials [71] have been noted, but these changes have not been consistent, in part due to lack of distinction between state and trait markers and limitations in signal processing [72]. Chronic psychological stress impairs sleep and the resultant sleep deprivation may impact EEG. PET and fMRI detect brain activation changes due to experimental stressors [73-75].

4.2.4. Genetic changes in brain—There are different functional gene classes that underlie the diverse effects of glucocorticoids on brain function, e.g., energy metabolism, signal transduction, neuronal structure, and neurotransmitter catabolism [32]. Stress effects on telomeres have been mentioned but assessments of human telomeres are generally performed on peripheral blood limiting their direct brain association.

4.3. Allostatic load

The underlying biological definition of allostatic load is very broad since the physiological system represents a highly multidimensional state space with many parameters. Potential examples of underlying load include the cost of gene transcription, metabolic activity, and alteration in cell receptor sensitivity. Frequent DNA processing may produce changes in telomere length.

Allostatic load was originally developed as a composite marker of chronic stress-related disequilibrium generated from a number of physiological measures. The originally described allostatic load score was a composite of 10 measures (systolic and diastolic blood pressure; waist-hip ratio; ratio of total cholesterol to high density lipoproteins; high density lipoprotein cholesterol; glycosylated hemoglobin; overnight 12-hour urinary cortisol, epinephrine and norepinephrine; and DHEA-S [76]. The score obtained by summing the ten measures (0 if normal, 1 if 75th percentile or worse) was associated with mortality. Related composite allostatic load measures have been correlated to childhood poverty [77] and measures of work exhaustion [78]. The latter study added several measures (tissue necrosis factor-alpha, C-reactive protein, fibrinogen, and D-dimer) and other measures have also been added, e.g., pro-coagulant activity. Despite the widespread interest in allostatic load, the optimum measure has not been defined; the measures currently used are based on non-experimental approaches (e.g., simple availability and a priori rationales). As a result there is much variety in the definition of a composite measure [79], but there needs to be improvement in its definition to advance the field of biomarkers for chronic psychological stress. This could potentially result from better analytic techniques.

Allostatic load measures have highly variable time frames. Some may change relatively quickly, e.g., fibrinogen, some are integrated over some time period (e.g., 12-hour urinary cortisol), and some change much more slowly or are integrated over longer time frames (e.g., waist-hip ratio or HgbA1c). Most physiological parameters are not only stress indicators but also change with other biorhythms, e.g., circadian or prandial.

Another rationale for allostatic load as a composite measure of stress effects is that different people likely have different subsystems affected by stress. Some people experiencing high stress develop headaches, while others develop gastrointestinal or other disorders. The particular organ systems affected by stress is an interaction between these systems and the brain. The individual reactions to stress are dependent on an individual's genes, learning and environment. Thus, it is likely that different people have different patterns of alteration in stress-related biomarkers or allostatic load component measures that may potentially be discerned by better analytic techniques, e.g., structural equation modeling or machine learning. It may ultimately be important to understand the individual relationships, but at this state of the research it may be helpful to have a combined measure.

4.4. Stress and disease

Acute stress may have some metabolic, immunologic and cognitive benefits. For example, alterations in system properties may produce a higher transient utility, decrease the likelihood that a stressor will move the state of the system away from an optimal attractor (robustness), or increase the size of an attractor basin (see hormesis below). A helpful example is the immune system which learns to react to foreign substances when exposed to non-virulent ones that do not result in death. If the immune system is not exposed to sufficient foreign substances, the result could be over-reactivity to foreign substances or allergies [80]. However, as stated in the introduction, more often impairments in health and a broad range of diseases are produced by chronic psychological stress.

Chronic stress may cause cognitive decline, adverse effects in the hippocampus, and contribute to neurodegenerative diseases either directly or through stress mediators including allostatic load [3, 18, 81-83]. The negative effect of psychological stress on cognitive function may be greater with aging [58, 84, 85]. Stressors including anesthesia, drugs, depression may be more likely to result in a state of impaired cognitive function with increased age. Cognitive reserve, a measure of how well the brain works [86], may be one aspect of resilience to the effects of stress on cognition.

5. Dynamics of stress system - time course of stress-induced physiological changes: state/trait and variables/parameters (Figure 4)

Stress can cause a perturbation of state but the associated changes to physiological measures occur at varying time scales. The time courses of marker changes in psychology are sometimes grouped into fairly mobile, shorter-term changes reflecting the person's current *state* and longer-term, more stable changes reflecting *traits*. Standard measures of psychological stress aspects, such as anxiety, are often measured by a widely used inventory, e.g. the State-Trait Anxiety Inventory [87]. However, even relatively stable traits, such as the personality trait neuroticism, often considered stable over a lifespan, can be malleable thus limiting the clear distinction between state and trait. Systems science uses terms analogous to state and trait: *variables* reflecting current state measures and *parameters* reflecting more stable attributes of the system. The change in parameters may decrease the likelihood of the system staying in the optimal attractor basin in the face of typical environmental fluctuations, but the distinction from variables is simply the time scale and

thus is somewhat artificial. This section is focused on the varying time courses of physiological makers which are only moderately correlated with commonly used self-rated markers. All biomarker measurements, including common physiological measurements (e.g., cortisol) and many anatomic and experimental physiological measurements (e.g., hippocampal size or neuronal receptor sensitivity) change over time, but the time courses differ.

The sympathetic branch of the ANS is the quickest to respond. Stress response can be measured by heart rate, blood pressure, electrodermal activity, or catecholamine release [88]. Epinephrine and norepinephrine release occur in seconds. The two-minute half-life of epinephrine highlights the generally short time course of this response. This ANS response is presumably geared to short-acting flight-or-fight changes such as metabolic needs, blood flow, and non-specific alerting of the brain [89], with norepinephrine projecting throughout the brain contributing to both phasic and tonic alertness [90, 91]. HPA activity has a slower time course and is activated by threats and negative consequences even when only anticipated. Cortisol has effects throughout the body and is impacted by many factors other than stress. Cortisol also directly affects the brain via cortisol receptors present in the pituitary, cerebellum, hypothalamus paraventricular nucleus and in neocortex. The cortisol peak onset occurs 15-30 minutes after a stressor [73, 92].

Stressor effects on the immune system have a long-time course, and effects on learning and DNA have even a longer-time frame and are important for sustained stress effects. Some personality traits have been linked to specific genotypes, e.g., single nucleotide polymorphisms. For example, a specific genotype (5HTTLPR) relevant for stress affects serotonin transport and has been related to stress reactivity [93] and the personality trait of neuroticism. Particularly relevant for our discussion involving time courses in human stress are the brain network changes altering perception of the stressfulness of an environmental stimulus; this may be related to sudden awareness (consciousness) of the stressor or of the induced physiological state change. A system that reacts differently if consciousness is achieved and responds based on conscious perceptions and concepts, such as the perception of causality, is inherently biased.

There are different approaches to measure stress and resilience dynamically. One can measure the magnitude of the change at some time point following a stressor, e.g., the cortisol increase from baseline to 15 minutes after an experimental stressor. One can incorporate a more sophisticated temporal measure estimating the area under the curve or half-life of a biomarker stress response if enough assessments are available. Another measure is the time it takes to return to baseline following an experimental stressor, e.g., fMRI changes 2 hours after a stressor [74]. In the event one does not use an experimental stressor, one can observe response following a significant environmental stressor, as in epidemiological studies related to war injuries or catastrophes. If enough measurements over sufficient number of days are available it is possible to calculate the variability of the physiological system. This variability of the system relates to stress responses but other variables (e.g. age) enter as well. For example, aging is associated with increased variability of measures of performance, and this variability can serve as a marker for insipient dementia among elders [94].

In general, the slowly changing traits or parameters are potentially harder if not impossible to measure empirically. Given the variable time frame of the biomarkers, assessment by many repeated measurements over a prolonged period may provide a better representation of the dynamical stress system response to psychological stress than single time-point assessments. This is especially true because each biomarker already captures the physiological system over some cumulative time window. The many physiological measurements needed over a prolonged time can be obtained over days or weeks using continuous recording in a lab or repeated assessments using ecological momentary assessment [95, 96]. Looking at reactivity to an experimental laboratory stressor may also provide good markers of the dynamic nature of the physiological system related to stress. Epidemiological studies can use data acquired following population exposure to a common stressor. Figure 4 offers a schematic representation of the conditions related to shorter- and longer-term stressors and physiological responses. There are many systems science methodologies that could be used to analyze the multidimensional nature of stress physiology including system dynamics modeling, agent-based modeling, network analysis, discrete event analysis, Markov modeling, and control systems engineering [8].

6. Resilience

As discussed in the introduction, the term *resilience* has been used in different ways. *Resilience* affects how effectively and quickly the system returns to a high utility attractor basin [9]. Despite the neuroscientific interest in resilience [10, 97], its definitions remain variable. *Resilience* or *robustness* is the capacity of the system to return to a high utility attractor following perturbation, the system's ability to avoid shifting to another attractor basin presented in this paper as a dysfunctional or diseased condition, or moving more quickly to its optimal location within its original attractor basin (Figure 1). Specific examples of resilience from a systems perspective include: 1) the distance of a location in one attractor basin to the boundary of an adjacent basin of inferior utility, i.e., greater resilience means the attractor is further away from boundaries with low utility neighboring regions; and 2) the strength of the vector field in the basin, where resilience might mean more rapid return to the attractor, so a repeat of a state perturbation before full return will make leaving the basin less likely. From a biological perspective, *resilience* may refer simply to the ability of a person to cope with a significant external stressor or insult. Related terms include: *stability* or *resistance,* indicating the difficulty moving a system away from its baseline "optimal' region; *precariousness* suggesting system proximity to some threshold of moving into another attractor basin, and *latitude* related to the maximum amount of change the system undergoes before losing its ability to remain within its high utility attractor basin. The resilience of a dynamical system to maintain itself within a functional high utility attractor basin is very important to the long-term health of the system. Resilience is not simply the opposite of allostatic load. Allostatic load is a measure of physiological system parameters that may impact resilience but it also has other effects on long-term health or disease risk.

It is known that many human stressors are best remediated by significant behavior change affecting stressor exposure (e.g., ingesting less glucose if pre-diabetic or decreasing work hours in a stressful job if hypertensive); some stressors in humans are related to the

perception of the stressor more than the stressor itself. For example, someone with PTSD is in a pathological lower utility attractor that could relate to the brain misperceiving the environment in a way harmful to the person's health (e.g., a truck backfire causing a veteran to engage in recollections and emotions associated with war).

Resilience to psychological stress is evident when some people avoid significant psychopathology, such as PTSD and depression when exposed to a stressor [10]. In the World Trade Center disaster resilience, measured by a likelihood of developing PTSD, was related to age (older did better), gender (males did better), social support (more did better), self-esteem (higher did better) and lifetime history of depression (worse with a positive history), but was not related to education [98].

Some amount of stress in the environment may be useful for maximizing the system's ability to respond to future stressors. Humans living with no stressors may lose the ability to respond to future stressors. From the brain perspective, some amount of stress is useful for maximizing learning and maintaining cognitive function. Systems that learn to cope with some amount of stress may be less affected by future stressors. *Hormesis* refers to a biphasic response to a stressor, "a process in which exposure to a low dose of … environmental factor that is damaging at higher doses induces an adaptive beneficial effect on the cell or organism" [99]. This adaptation could be to environmental stressors such as cold and exercise [100]. A stressor can cause the system to be non-optimal for a short time but still result in returning to baseline. While there may be some allostatic load cost, the stressor may induce changes in system physiological parameters that strengthen the future ability to return to its greater utility locations, i.e., increase resilience. This low level of stress exposure occurs in some clinical treatments, e.g., allergy therapy and exposure therapy in PTSD. In some sense such exposures to a low-level stressor is a way to exercise the resilience aspects of the system. In general, repeated external stimuli elicit less of a physiological response because of habituation that can be measured by fMRI, event-related potentials or electrodermal response [101, 102]. However, in some cases repeated external stressors result in the excessive response, as in PTSD (e.g., hyperarousal to loud noises) and become self-reinforced rather than extinguished.

This decreased efficiency and ability of the human dynamical physiological system to stay in or get back to a functionally positive attractor basin is the negative effect of chronic stress or allostatic load. Changing the parameters of the human system to bring the system back to the optimal state or high utility attractor often entails a cost to the basic human constituents but the changes can be used to simply indicate previous stress exposure. This could be DNA modification, receptor sensitivity changes, or changes to blood vessels from high blood pressure. Another example of changes to the underlying system is aging, which can make a person more likely to exist in a non-optimal state or attractor basin. It could be that the attractor basin becomes smaller or less steep. The change of the state space attractor basin that decreases the system's ability to stay in its higher utility states without moving to lower utility states in its current attractor basin or to a lower average utility attractor basin represents the chronic stress effect or allostatic load. These changes over time can be defined mathematically. The suboptimal attractor basins do not become necessarily larger; rather,

the high utility attractors become smaller with shallower sides. Thus, the time required for return to the baseline state tends to increase.

From a probabilistic perspective, the resilience of the system could be considered the probability that an environmental perturbation results in returning to the high utility attractor basin, as opposed to ending up in an attractor basin with lower utility. The capacity of a system to stay in a high utility attractor basin could be defined stochastically: the likelihood that following a particular perturbation the person returns to the high utility attractor basin. The capacity to stay in this high utility attractor basin is especially relevant when, following a stressor, the state may be closer to the basin boundary and be more likely to shift to a non-optimal attractor basin should another stressor manifest. Even without changing the specific attractor basin but simply the shape of the basin, resilience could be defined based on the probabilistically weighted average utility in a single attractor basin following expected stressors.

PTSD is a useful example of state space and attractors since some of the physiologic responses may initially have been an adaptive response during specific time and environment but when they persist in other environments, the result is moving to a lower utility attractor where the abnormal response is self-reinforcing. A high stress physiological state may be high utility during a war but if that state persists after returning home it can be lower utility. The transition to PTSD is not reversed immediately as soon as causes are reversed or disappear. Reversal might require going all the way back to an earlier state in a system which induces the possibility for a cusp catastrophe (Figure 2).

7. Environment and its perception

In addition to knowing the physiological state of the person, one should also know the state of their environment because certain physiological measures may be a reaction to the environment. It must be reiterated that although some environmental stressors have a direct effect on stress responses, e.g., extreme cold, stress responses are significantly related to the person's perception of the stressor. The perception of the environment (Figure 3) is affected by a person's prior experiences through attention and memory. Many environmental stressors are stressful because of the way they are perceived and processed. A person focused on an important phone call may not realize it's hailing outside because of their attention on call. As a result, one may not be worrying about whether the car was left outside the garage. Attention refers to systems in the brain that allow some information to be processed more than other information [103]. Memory is a broad term with many subsystems loosely divided into declarative and non-declarative memory [104]. Emotional memory has critical brain hubs not relevant for other types of memory. The amygdala rather than the hippocampus is critical for registering the emotional valence of an event [105]. Beta-blockers that block aspects of the ANS can have an impact on emotional memory without any impact on episodic memory [105, 106]. The memory-induced changes in neural connectivity that result from gene expression and protein synthesis require hours to days. A person with a memory of a previous environmental stressor will perceive the perturbation differently from the person with no prior associations to it. For example, a physically abused wife might associate the noise of her husband returning home with the physical abuse that

often follows. The sound of an opening door will have different neural associations to her than her non-abused neighbor.

High reactivity to negative events produces physiological changes [107]. In fact, negative reactions to events are more predictive of emotional well-being than the event itself [108]. Reactivity to stress can be examined though neuroticism, one of the five factors in the widely used five-factor personality inventory [109]. Neuroticism has genetic, neurobiological, and environmental contributions [85, 110, 111]. High neuroticism contributes to many health disorders [112] and relates to increased age-related cognitive change and clinical Alzheimer's disease in longitudinal studies [113-115]. The cognitive deficits related to distress proneness are not specific and most consistently included frontal-executive function and perceptual speed [113, 115], not dissimilar to cognitive changes associated with affective disorders such as PTSD and depression [116, 117]. Neuroticism with its negative effects on cognition is a modifiable risk factor [118] with a potentially large impact on population health [119].

The internal physical components of the human are part of the brain environment, considered the internal environment in contrast to the external environment located outside the physical body. The brain has partial awareness of the internal (interoception) and external (exteroception) environment. Interoception and exteroception may produce brain and other physiological changes without awareness, but humans can become aware of their internal states such as anxiety or stress. Interoception may be taught as awareness and control over internal organs (e.g., learning to modulate one's blood pressure through biofeedback or mind-body practices).

As previously mentioned, the effect of an environmental stressor on health may be modified by how the brain perceives the environment. This perception can be altered by higher level concepts beyond attention and memory as highlighted by the concept of hope. From a health perspective, optimists fare better than pessimists [120] and those with higher religious involvement and spirituality do better than those with lower involvement [121]. The beneficial placebo response, i.e., the improvements in physiological measures or perceptions of health following administration of a treatment without any direct biological affect, can be elicited by merely telling someone that a treatment may work (even if there is no directly active components in the treatment) [122, 123]. It is likely that some mechanisms of placebo or expectancy effects overlap with some of the mechanisms underlying perception of stress [124]. The major stress hormone cortisol can be altered by experimental manipulation of expectancy in placebo effect studies [125, 126].

8. Stress and resiliency biomarker changes with treatment

There are physiological and genetic markers associated with improved resilience to stress-induced physiological changes [117, 127, 128], and there are also psychological tools to increase resilience, or the ability to tolerate stress perturbations without decreasing utility. Exposure therapy has been used to reduce the person's reactivity to stressors, e.g., an allergen or an environmental stimulus precipitating PTSD symptoms. Mind-body techniques and biofeedback provide cognitive strategies to decrease emotionally-activated responses,

avoid unnecessary negative internal associations (i.e. sense of stress) to current events, and to maximize capacity to return to a positive state attractor following a stressor.

A key facet of many mind-body therapies is mindfulness, attending to the present moment in a non-judgmental way. With several ways to measure mindfulness, the judging and negative appraisal of thoughts, emotions, and behavior factor may be particularly important for stress management. The mindfulness-non-judgmental score, i.e., being aware of the environment without attaching an emotional tag [129], is diminished by the chronic stress in dementia caregivers and in veterans with post-traumatic stress disorder [85, 130].

Mind-body studies have suggested biomarker changes related to mindfulness or mindfulness training partially overlap with the allostatic load biomarkers but in the opposite direction. These include telomerase [131], immune function [132, 133], cognitive function [133, 134], catecholamines [135], HRV [136], cortisol [133, 137-139], EEG [140], structural MRI [141, 142] and fMRI [143]. Meditation alters physiological responses to an experimental stressor [144]. However, the preferred or composite biomarkers relating to benefits of mind-body medicine have not been identified.

9. Utility

Utility is essentially the same as success of the organism (e.g., life, procreation or, in the case of humans, earning money). Long-term health is an important focus of the utility definition concerning stress-related impact on human health. While utility is the benefit to the person (or genes), the benefit also depends on the environment, i.e., the specific calculation of utility varies with the environment and the time course over which it is calculated. During war, utility is more immediate, perhaps simply surviving to the next day with a very high discount for future situations. Therefore, utility of a response to a stressor depends on the environment and on a person's degree of discounting future events. Thus, the calculation of utility in different environments will be dependent on the rewards and penalties in the current environment and on the time duration and differential weighting used for calculating the utility.

10. Conclusions

This paper has described human stress physiology and psychology from the systems science perspective. Specifically we focused on environmental perturbation stressors that produce significant long-term changes in the human dynamical system. Acute stressors usually do not produce long-term negative effects although a significantly powerful acute stressor may push the brain dynamical system into a new, functional attractor basin with lower utility. In general, chronic psychological stress produces changes in the system, such as a slower response to a future stressor or a higher potential for moving to a new lower utility attractor basin. If a human is exposed to a "tolerable" dose of a stressor that results in return to the original high utility attractor basin, the outcome may be improved resilience. From a systems science perspective, behavioral and physiological measurements attempting to capture the degree of stress of a system should incorporate the dynamics of the physiological stress response system as well as some measures of the environmental stressors and their

perception. Understanding stress will require all of the interacting components from Figure 3 to be measured and described, at least partially. In general, the systems dynamics of stress physiology has much less temporal empirical data to inform the model than, for example, meteorological data because of the difficulty acquiring the human data. Nevertheless, analyzing dynamical data will be important to better understand stress physiology since the timing and strength of feedback loops likely contributes to disorders of stress and resilience to stress. In addition to measuring stress responses over time, it may be useful to repeat administration of experimental stressors to understand self-reinforcing loops. These systems science concepts and better measurement techniques will lead to better understanding of the stress system that ultimately can be used to improve the resilience of the human system and thereby improve long-term health.

Acknowledgements

Abbreviations

ACTH	adrenocorticotrophic hormone
ANS	autonomic nervous system
DHEA	dehydroepiandrosterone
DHEAS	dehydroepiandrosterone sulfate
EEG	electroencephalogram
fMRI	functional magnetic resonance imaging
HgbA1c	glycosylated hemoglobin A1c
HPA axis	hypothalamo-pituitary-adrenal axis
HRV	heart rate variability
PET	positron emission tomography
PTSD	post-traumatic stress disorder
SSRI	selective serotonin reuptake inhibitor

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Highlights

- Stress physiology was reviewed from a systems science perspective.

- Stressors push biological systems from baseline towards lower utility states.

- The system change is based on objective attributes and perceptions of the stressor.

- Allostatic load is utility reduction due to stress-related state changes.

- Resilience affects ability to return to high utility state following perturbations.

a) Higher Resilience Case
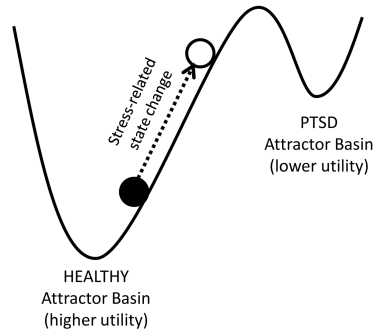
b) Lower Resilience Case
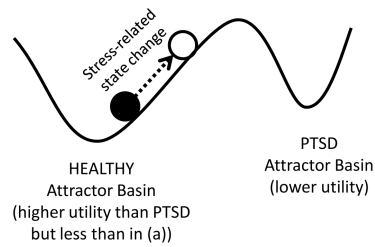

Figure 1. Attractor basins, utility, and resilience
Hypothetical example of space of possible human physiological states with two attractor basins, one being a healthy higher utility condition and one a lower utility condition state of PTSD (in this figure, higher utility is downward). The attractor basins can tolerate movement of the hypothetical person (solid circle) in the horizontal direction from an external stressor without leaving its basin of attraction. However, with sufficient movement from a stressor, one may go from a higher utility healthy condition basin to a lower utility PTSD basin. The healthy condition in b has lower resilience than in a, with less stress required to shift it to the lower utility basin.
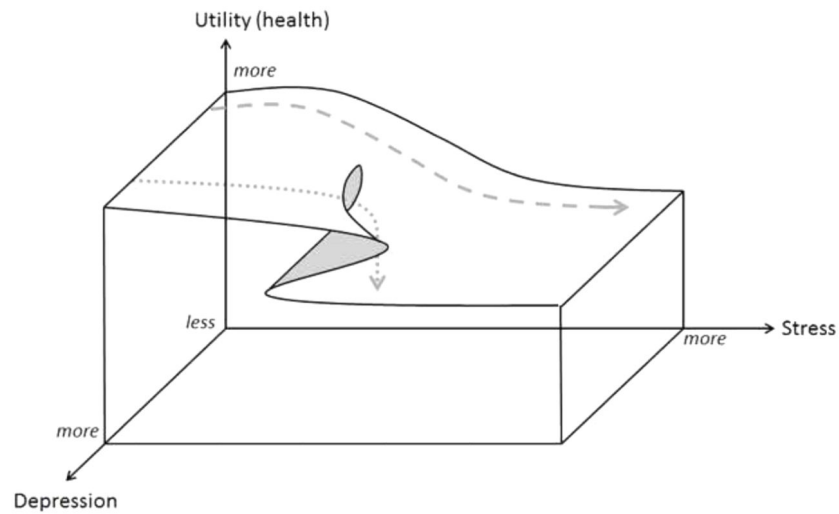
Figure 2. Cusp catastrophe

An example of a cusp catastrophe where the state space of human physiology has a complex 3-dimensional shape, with no pictorial representation of attractors, and there may be an abrupt state change. In this example, as stress increases at higher levels of depression there may be a sudden drop in location to a new state, PTSD (marked by a dotted line). Here, utility is up rather than down as in Figure 1.
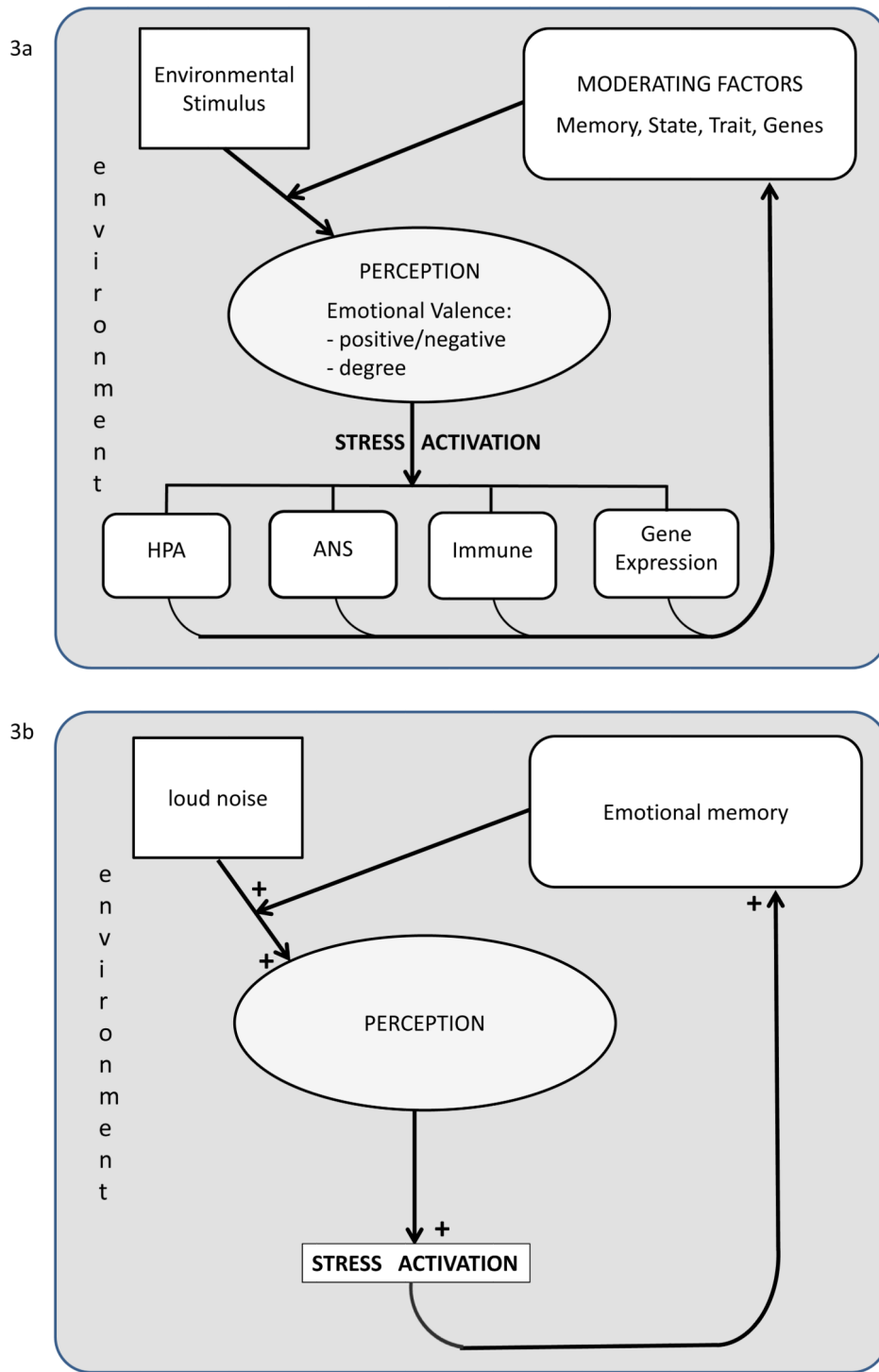
Figure 3. a). Interpretation of stressors: brain processing and communication
The brain's perception of the emotional valence of an external event as a stressor is
dependent on the current environment and modulated by previous experiences (memory),
current physiological state, traits (e.g., neuroticism), and genotype. The brain generates
outputs to the autonomic nervous systems (ANS), the hypothalamo-pituitary-adrenal (HPA)

axis, the immune system, gene expression and epigenetics (overall increasing time duration of stress activation components from left to right. These responses directly affect the body but also feedback to the brain. Learning includes assessment of risks and rewards and it can be clinical designed to reduce reactivity, e.g., allergy therapy or mindfulness meditation. b). Example of self-reinforcing stress response system that is pathological if in a non-threatening environment. Normally, while stress activation from a loud non-threatening noise may initially activate a stress response, response to repeated loud noise will be attenuated through negative feedback (e.g., habituation). In PTSD emotional memories and the stress activation itself may contribute to an auto-reinforcing positive feedback loop. As mentioned in the text and Figure 2, this PTSD attractor basin may be entered secondary to a single severe negative event via a catastrophic dynamical systems event. This pathological transition is more likely in those with predispositions, e.g., neurotransmitter alterations such as depression.
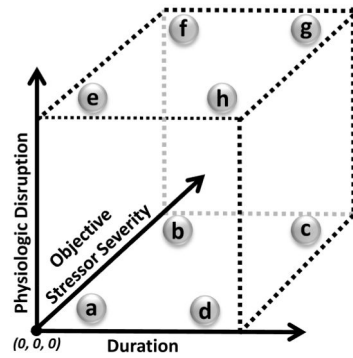
STATE EXAMPLES

a. Relaxation
b. Inappropriately low response due to inattention, trait, etc.
c. Diminished response to chronic stress
d. Boredom/lack of stimulation
e. Exaggerated transient response
f. Normal transient stress response
g. Hyperarousal/sensitization to chronic stressor
h. Exaggerated chronic response

Figure 4. A three-dimensional model of stress-related states

A rough schematic of three dimensions related to stress. Physiological activation can be low or high and sustained for a short or long period of time. The response can be to a stressor that is relatively low from an objective or population perspective or relatively high. Normal function usually goes from relaxation state (a) to short duration high physiological activation when exposed to a stressor (f). If the stressor response is too sustained or occurs too frequently, there is some cost to the system.