

Rewiring the stress response: A new paradigm for health care

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In describing the conceptual basis of a stress intervention method, Emotional Brain Training (EBT), a program which integrates advances in neuroscience and stress physiology, we propose a new paradigm for health care. Many health care treatments focus on managing symptoms of stress-related disorders. In modern society stress is primarily psychological in nature and in its chronic form, the result of allostatic (non-homeostatic) neural circuits that amplify and prolong stress. The result is cognitive, emotional, behavioral and physiologic dysregulation resulting in wear and tear (allostatic load). The effectiveness of treating any one stress symptom is likely decreased because of the persistent allostatic state. Emerging understanding of neuroplasticity suggests that this circuitry is capable of change. EBT is based on the repeated use of techniques that mirror secure attachment and optimal self-regulatory processing to alter allostatic circuits through the process of reconsolidation, therefore decreasing allostatic load. This results in an improved state of well-being. We hypothesize that decreased dominance of allostatic neuronal circuits leads to improved health outcomes, offering a new paradigm for health care.

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her ability to cope (1). Identifying and modifying the brain circuits that trigger maladaptive stress responses should result in overall health improvement and likely decrease reliance on medications, procedures and devices.

The hypothalamic-pituitary-adrenocortical axis (HPA) and the sympathetic-medullo-adrenal (SMA) system are activated in response to a stressor or fear. Their prolonged or repeated activation interferes with most physiological systems, resulting in increased risk for physical and psychiatric disorders (2-4). Links between stress and disease have been reported for depression (5-8), obesity (9-10) and cardiovascular disease (11-15). Each of the top ten causes of death in the United States is caused by or exacerbated by stress (16). Nationally, 75 % of adults report experiencing moderate to high levels of stress in the past month and 42 % report that their stress has increased in the past year (17). As much as 75-90 % of primary care office visits are due to symptoms that have stress related components (18).

In 1979, Laurel Mellin began developing a treatment program for obesity (19–20), aimed at decreasing the drive to overeat; the program has since evolved into a method of training adults and children in the skills of self-regulation (19-21) called Emotional Brain Training (EBT). Over time, the method was informed by emerging neuroscience research

Introduction

MANY DISEASES INCLUDING OBESITY, irritable bowel syndrome, gastroesophageal reflux disease, depression, anxiety, chronic pain and

headaches are symptoms of stress or exacerbated by stress. Stress occurs when an individual's perception or responses suggest that environmental demands tax or exceed his or

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in the areas of neuroplasticity, emotion research, stress biology and attachment theory. The neuroscience of rewiring self-regulation utilized by EBT is based on physiologic brain states of stress. The skills used to rewire the stress response are based on four core concepts enumerated below.

Concept 1: It's not us. It's our wiring.

The full-blown stress response evolved in reaction to an imminent threat to survival – it is triggered rapidly and nonspecifically (22). However, this kind of threat is rare in modern society leading to an often inappropriate triggering of the full-blown stress response. The wiring that triggers this unnecessary, amplified or prolonged stress response is stored in the unconscious implicit memory systems (23) via the HPA and SMA axes (24).

The self-regulatory processing is learned from parental interaction with his/her infant. In combination with genetic and environmental factors, the attachment between parent and child is encoded in the circuits of the infant's brain. This attachment is the result of the capacity of the parent to appraise the emotional state of the offspring and take necessary actions to change the child's physiology from stress to well-being, optimizing the chances for survival. Those early connections, especially before the age of three, or later in life during periods of trauma, form the

basis for the circuitry of resiliency and health (25-28).

These circuits may be effective or ineffective. Each new stress stimulus is compared with internal representations of past experiences stored in our memory. These representations are "archived" in neural circuits whose activation enables the brain to bring elements of past experience forward in time and to anticipate future stressors in order to respond effectively to the current milieu (22). Each circuit is the product of neurons being co-activated in response to a stressor, leaving behind a propensity to co-activate in the same pattern again. This increased likelihood of activation of synapses that have a history of strong previous activation - long-term potentiation - is the basis for long-term memory and learning (29-30). Simply, based on Hebb's Law (31) the circuits that fire together wire together and become stronger and more dominant; and those that do not fire together wire apart and become weaker (32-33).

We hypothesize that the self-regulatory circuitry that responds to stress and reflects potentiation involves three phases: 1) quick sub-cortical processing phase (responses of the HPA and SMA axes), which is nonspecific, evolutionarily based and primarily emotive (based in fear) (34); 2) cortical/cognitive processing of emotions into conscious feelings based on expectations and past experiences

- the second phase concludes with the identification of needs; 3) generation of thoughts and actions to marshal a corrective response to meet those perceived needs. The process, if adaptive, returns the person to a state of well-being.

Each episode of stress may arouse self-regulatory circuitry that is an effective (adaptive) or ineffective (maladaptive) response to the stressor. The effective response or homeostatic circuit is a self-correcting, negative feedback loop, leading to a state of well-being. It triggers an emotional response that is consistent with the actual stressor, a cortical processing phase that is effective in discerning the true need based on reasonable expectations, and finally, a corrective action that returns the organism to a state of well-being, quickly and easily. Ultimately, physical, emotional, psychological and behavioral homeostasis is restored. The ineffective response (activation of an allostatic circuit) is a positive feedback loop and not self-correcting. It arouses an emotional processing that under- or over-reacts to the actual stressor, a cortical processing phase that is based on unreasonable expectations and, thus, ineffective in identifying the actual need, and finally, a corrective action that does not return the person to a state of well-being. Ultimately, this prolongs and amplifies the stress response and becomes the source of stress in its own right (35). It all depends on the active wiring.

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Concept 2: Wiring triggers brain states.

To promote the survival of the species, the brain has evolved into an organized hierarchy, which includes the simple, quick, regulatory functioning of the reptilian brain, the emotional arousal and fear-generating limbic brain and the slower, complex and analytical neocortical brain (36-37). In response to the activation of self-regulatory circuitry, the brain establishes a state in which a specific brain area becomes dominant (38). The actual number of brain states is not known. However, based on observed phenomena in EBT (consistent with the work of Perry investigating the effects of trauma (39)) there are at least five distinct brain states (see Figure 1).

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As illustrated in Figure 1, as arousal and stress increase, dominance shifts to more primitive areas of the brain. The limbic and reptilian brains have limited functions focused primarily on survival. The stress-brain area dominance relationship impacts all domains of life, as the organization of the brain to facilitate survival draws upon all systems

(40). Which brain area is dominant does not determine the precise symptom but rather the extent of deviation from homeostatic states associated with health and well-being. For example, an individual in brain state 4 may have one of various symptoms of emotional stress such as hostility, mania, depression or anxiety.

Knowing which specific symptom is involved is important in prescribing the most effective pharmacologic treatment. However, since the allostatic circuitry is not modified, the onset of another maladaptive emotional stress symptom, different from the original, may occur. Identifying the problem as a brain state of stress as opposed to just an emotional symptom of stress, may reframe the treatment

plan from treating the symptoms to treating the underlying brain state, thus, reducing the risk of symptom substitution.

In regards to the above described brain states, there are brain state-related characteristics in the areas of cognition (39), emotion, relation and behavior. A summary of these characteristics can be found in Table 1.

Concept 3: Brain states become persistent.

An occasional, brief experience of brain state in fight or flight (brain state 5) is not concerning and it can be adaptive (depending on the circumstances). However, allostatic states tend to become persistent. They are positive feedback loops, with each triggering and

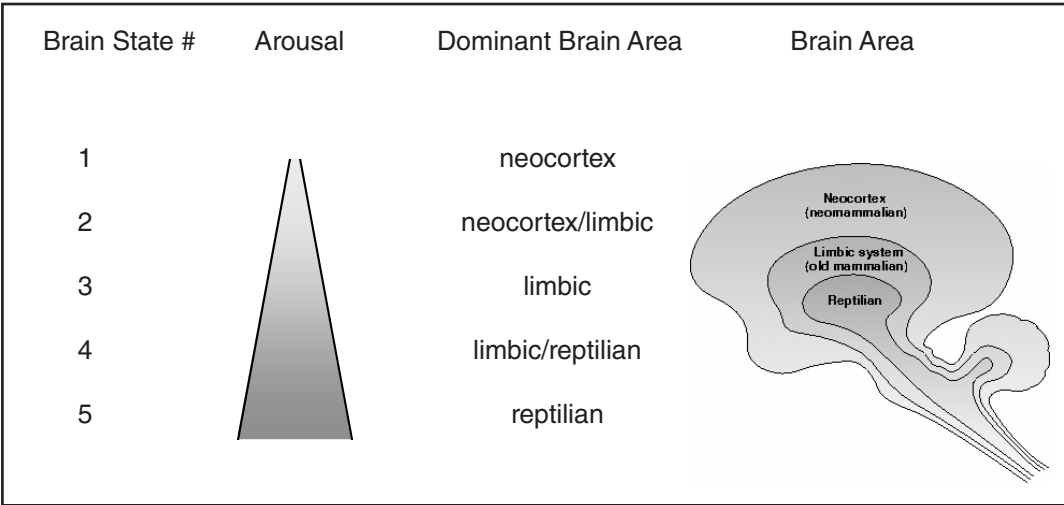


Figure 1 | Stress and Dominant Brain Areas. Representation of five brain states, their level of arousal and dominant brain area

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arousing other circuits as the brain stores memories in a state-specific way (35). This makes access to memories of similar circumstances more easily accessible in response to similar experiences (22).

The stress response is organized as a survival drive. Thus, to maximize self-preservation, the brain uses generalization; as new stressors are processed they are related to previous experiences, and the existing neuronal circuits are preferentially activated and strengthened (22, 32). If these self-regulatory circuits are ineffective (allostatic circuits) then wear and tear on the brain and body (allostatic load) increases. Stress can then cannibalize the very brain structures that process stress, causing a set point in stress (allostatic state) that is associated with the chronic elevation of stress hormones and the risk of negative sequelae observed in all domains of life (4, 40).

Once an allostatic state is established, the new set point is defended; the stress is preferred to well-being (homeostasis) and the allostatic brain state becomes persistent. The brain is not only stress-driven but also reward-driven. In chronic stress the eudonic rewards (41), obtained via meaning and purpose in life (i.e. happiness attained through pursuit of a virtuous life – intrinsic reward), are not accessible. Yet, reward circuits are activated to deal with the pain (both emotional

Table 1 | Brain State-related Characteristics. A summary of the cognitive, emotional, relational and behavioral characteristics for each of the 5 brain states.

State (#)	Cognitive	Emotional	Relational	Behavior
1	Abstract	Joyous	Intimate	Optimal
2	Concrete	Balanced	Companionable	Healthy
3	Rigid	Mixed	Social	Moderate
4	Reactive	Unbalanced	Needy/Distant	Unhealthy
5	Irration	Terrified	Merged/Disengaged	Destructive

and often, physical) associated with the allostatic state. Since the eudonic rewards aren't attainable, the brain defaults to accessing hedonic rewards (42-43), or pleasure for pleasure's sake (extrinsically evoked rewards). Hedonic rewards which are pleasurable (and, often, adaptive) in the short term have the potential to become repetitive, deleterious and maladaptive in the long term as the brain begins to rely on those rewards as the means for creating a pain-free life.

The associations between levels of stress and maladaptive behaviors are stored in the survival brain states of 4 and 5. As the brain tends to generalize, when that level of stress is encountered, the allostatic circuit for brain state 4 or 5 is triggered and the associated maladaptive response is induced. The pro-

cess is potentially repeated thousands of times over the course of a lifetime. This interpretation of maladaptive behavioral responses suggests an explanation for low adherence to behavioral recommendations seen in the current model for health care. In stress, it does not matter what the neocortex knows because the limbic and reptilian brains are dominant, set in a persistent allostatic brain state.

Concept 4: We can change our wiring.

Recent studies of neuroplasticity demonstrate presence/persistence of a high degree of plasticity in adult brain circuitry (44, 45) regulating motor behavior and cognition as well as emotions (46). EBT is based on positive emotional plasticity; repeated use of tools that mirror the evolutionarily-based secure at-

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tachment between parent and child, (which is critical to the survival of the species) (47–49). Adults can create their own secure attachment to return themselves to a state of well-being. Changing the allostatic state occurs in two steps: 1) activation (and identification) of the maladaptive circuit and 2) alteration of the circuit through intervention during the reconsolidation window (46, 50).

Hedonic rewards which are pleasurable (and, often, adaptive) in the short term have the potential to become repetitive, deleterious and maladaptive in the long term as the brain begins to rely on those rewards as the means for creating a pain-free life.

In EBT individuals learn skills to assess their brain state (1-5), and then use a specific state-based tool to elevate their brain state to a homeostatic state. Clinically, this appears to decrease the strength of allostatic circuitry, while increasing the strength of homeostatic circuitry promoting well-being. Similar forms of treatment that reconsolidate allostatic circuits have been published for obsessive compulsive disorder (43,51) and have been observed in a form of psychotherapy (51). Repeated use of the tools eventually results

in spontaneous conversion to a new set point in homeostasis. Thus, the individual changes his or her wiring to strengthen their state of well-being.

Conclusion

Applying the principles of positive emotional plasticity to rewiring the stress response is a novel intervention that merits further evaluation. Stress-processing circuitry is formed early in life or during periods of trauma, and stored in implicit memory systems. Excessive and, especially, inappropriate activation of the stress circuitry strengthens maladaptive circuits and can lead to persistent maladaptive (allostatic) brain states. We hypothesize that with the recognition that dominant neurocircuitry can lead to persistent brain states, a new approach can be utilized for health care treatment of stress-related symptoms and diseases. Potentially, providing an individual with the skills to reconsolidate those stress circuits, and thus decrease or reverse allostatic load, may improve health and well-being. Therefore, we propose a new paradigm for health care – focusing on rewiring the stress response in favor of adaptive neuroplasticity.^H

About the Authors

Dr. Igor Mitrovic is Jack D. and DeLoris Lange Endowed Chair in Systems Physiology I Professor of Physiology at UCSF School of Medicine. He is a medical educator and neuroscientist who has worked on

developing Emotional Brain Training and anchoring it in the current understanding of neuroplasticity and neurobiology of emotions and stress. Lindsey Fish de Pena is an Internal Medicine Physician employed by the Colorado Department of Corrections. Her work with EBT involves validating the method with scientific research. She is interested in bringing EBT to the medical community and underserved populations. Dr. Lynda Frassetto is a nephrologist, Professor of Medicine at UCSF and Director of the Adult Clinical Research Center at Moffitt hospital. She and her colleagues study physiologic adaptations (and advantages) of Paleolithic-type diets, and drug pharmacokinetics in kidney failure. Dr. Frassetto has also been involved in development of the EBT and studying the efficacy of the method. Laurel Mellin directs the Center for Emotional Brain Training research and is the founder of EBT. She is an Associate Professor of Family and Community Medicine and Pediatrics at UCSF and directs the institute that certifies health professionals in the clinical applications of the method.

Author Contributions

LM developed the intervention and the five brain state model and drafted the manuscript. IM developed the model of relationship between neuronal stress circuitry and brain states. IM, LM and LFP contributed to the theories described. LF, IM and LFP contributed to the manuscript. All authors read and approved the final manuscript.

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