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Stress today: From Basics to COVID-19

Summer School on Stress: From the Basics to the New 'Post-COVID Stress Disorder'

American University of Health Sciences

Signal Hill/Long Beach, CA

June 13-14, 2022

Monday, June 13, 2022

Visit and discussions at AUHS

Tueasday, June 14, 2022

	Session chairs*: Sandor Szabo, AUHS & Yvette Taché, UCLA*
9:00 – 9:15 am	Greetings and opening remarks
	Founders, President, Provost & *Deans of AUHS Schools of Nursing, Pharmacy & Medcine*
9:15 – 9:45 am	**What is stress and what is not: From the discoveries of Hans Selye to COVID-19**
	Sandor Szabo, AUHS
9:45 – 10:15 am	**Corticotropin releasing factor (CRF) signaling pathways and the stress response**
	Yvette Taché, UCLA
10:15 – 10:45 am	**The ulcerogenic and gastroprotective effects of glucocorticoids**
	Ludmila Filaretova, Pavlov Institute of Physiology, St. Petersburg, Russia
10:45 – 11:15 am	**Stress and functional GI disorders: Motility disorders, IBS (irritable bowel syndrome)**
	Bruno Bonaz, Grenoble, France
11:15 – 11:45 am	**Effect of stress on fat: What is the evidence?**
	Oksana Zayachkivska, Lviv, Ukraine

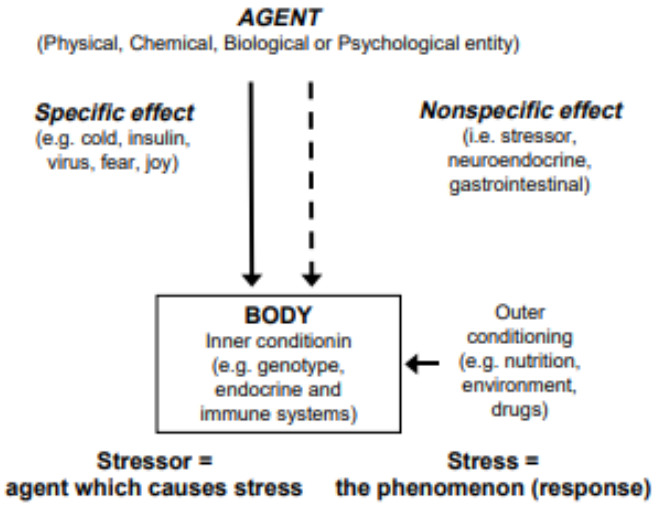
11:45 – 12 noon	General discussion
12 noon – 1:00 pm	Lunch
1:00 – 1:30 pm	**Stress and sex differences in IBS** *Muriel Larauche, UCLA*
1:30 – 2:00 pm	**Nutritional deficiencies in stress and COVID-19** *John Schloss, AUHS*
2:00 – 2:30 pm	**Stress and other endocrine changes in COVID-19** *Pantelina Zourna-Hargadean, AUHS*
2:30 – 3:00 pm	**Lack of professionalism: A distress for peers and coworkers** *Grant Lackey, AUHS*
3:00 – 3:30 pm	**Stress and mental health problems in post-COVID youth** *Gerald Maguire, AUHS*
3:30 – 4:00 pm	Round table discussion

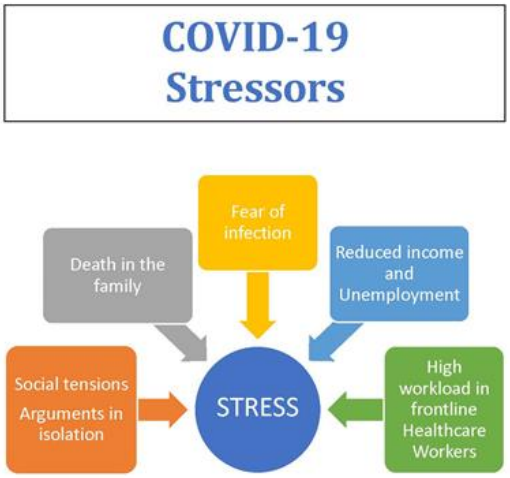
ABSTRACTS

What is stress and what is not: From the discoveries of Hans Selye to COVID-19

Sandor Szabo, MD, PhD, MPH, Schools of Medicine & Pharmacy, American University of Heath Sciences, Signal Hill/Long Beach, CA, USA

"Stress is the nonspecific response of the body to any demand on it." This definition originates from Hans Selye (1907, Vienna - 1982, Montreal) who first published his seminal papers in 1936 (*Nature*) and 1937 (*Science*) on the 3 stages of stress reaction (i.e., alarm reaction, resistance & exhaustion) in rats exposed to cold, immobilization or toxic agents. His basic definition of stress didn't much change over the decades; despite the initial criticism and objections he faced, eventually the stress concept was not only widely accepted and reproduced/identified not only in experimental animals but was also overused. Furthermore, he distinguished physical, chemical, biologic and psychologic stressors (agents which cause stress), and emphasized that only the nonspecific, common (neuroendocrine) manifestations and consequences should be called "stress." His favorite illustration was that in cold we shiver, in heat we sweat (physical stressors) and while insulin lowers blood sugar levels, but in large doses insulin also elicits enhanced adrenocortical secretion, with all the consequences of mostly glucocorticoids, — hence, insulin in large doses may also be a chemical stressor. Selye went out of his way to vehemently protest that by using one agent, the reaction and results can never be called stress! Even in our daily life, instead of just saying 'I am exhausted' or 'tired', we often say 'I am under stress' or 'stressed out'… This is a totally unnecessary over-use and over-implication of "stress"!





Fast forward to COVID-19: as the above illustration demonstrates, the complex, multifactorial issues associated with this disease surely meet the definition of COVID-19 being the first, new major human stressor in the 21st century. Although this illustration was prepared in mid-2020, subsequent clinical studies identified the underlying mechanisms and manifestations of a new 'post-COVID-19 stress disorder.' Thus, Hans Selye's original discoveries & observations in animal experiments have been proven, including the 3 stages of stress reaction, in humans during a worldwide pandemic.

Szabo S, Tache Y, Somogyi A. The legacy of Hans Selye and the origins of stress research: A retrospective 75 years after his landmark brief "Letter" to the Editor of Nature. *Stress*, 2012; 15: 472–478.
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Szabo S., Zourna -Hargaden P.: COVID-19: New disease and the largest new human stressor. *Integr. Physiol*., 2020; 1 (4): DOI: 10.33910/2687-1270-2020-1-4.

Corticotropin releasing factor (CRF) signaling pathways and the stress response

Yvette Taché, PhD, CURE: Digestive Diseases Research Center and Center for Neurovisceral Sciences & Women's Health, Digestive Diseases Division, David Geffen School of Medicine at UCLA and VA Greater Los Angeles Healthcare System, Los Angeles, CA, USA

Stress may cause behavioral and/or psychiatric manifestations such as anxiety and depression and also impact on the endocrine and autonomic nervous systems and visceral organ function namely the gastrointestinal and cardiovascular. During the past decades substantial progress have been made in the understanding of the underlying mechanisms recruited by stressors. Experimental studies point to the activation of the corticotropin-releasing factor (CRF) signaling system being implicated in a large number of stress-related behavioral and visceral disorders. This is supported by the distribution of the CRF system (ligands and receptors) expressed in specific brain nuclei and peripheral viscera. In addition, the exogenous injection of CRF agonists and selective antagonists to CRF receptors unraveled the importance of brain CRF signaling in the stress-related endocrine (activation of pituitary-adrenal axis), behavioral (anxiety/depression), autonomic nervous system (activation of sympathetic system and sacral parasympathetic, decreased vagal activity), and immune responses. In the gut, the administration of CRF agonists recapitulate stress-related alterations of gastrointestinal function including in the stomach, the inhibition of gastric transit, and in the colon, the induction of diarrhea, enhanced motility, mucus secretion, mucosal permeability to macromolecules, bacterial translocation, and mast cell activation which in turn promote visceral hypersensitivity. Moreover, CRF antagonists' pretreatment blocked all stress-related gastrointestinal alterations. Clinical studies indicate that CRF administration can induce irritable bowel syndrome (IBS)-like symptoms in healthy subjects and heighten colonic sensitivity to colorectal distention in IBS patients. However so far, there is still an unmet need for the use of CRF antagonists to treat stress-related disorders.

The ulcerogenic and gastroprotective effects of glucocorticoids

Ludmila Filaretova, PhD, DSc

Pavlov Institute of Physiology, Russian Academy of Sciences, World-Class Research Center “Pavlov Center Integrative Physiology,” St. Petersburg, Russia

The activation of hypothalamic-pituitary adrenocortical (HPA) axis is the key hormonal component of stress response. Glucocorticoids released during acute stress-induced activation of the HPA axis help the body overcome negative effects of stress stimuli thanks to a wide range of concerted physiological effects. These hormones are absolutely fundamental for human health. Synthetic analogues of endogenous human glucocorticoids are used in almost all medical specialties as anti-inflammatory and immunosuppressive drugs. However, from the early trials, clinicians were also well aware of the many adverse effects of the hormonal therapy. The adverse, pharmacological, effects of glucocorticoids have been repeatedly confirmed by extended clinical experiences over the past 60 years. Thus, in general glucocorticoid hormones may have dual actions: physiological and pathological. They may have dual actions on the gastric mucosa: gastroprotective and ulcerogenic ones.
Various manifestations of pathological changes induced by stress in the gastrointestinal tract (from functional changes to erosions and ulcer damage) are a serious medical problem, which can be solved with results gained from fundamental studies. The findings of fundamental studies suggest that gastric mucosal injury may occur when noxious factors overwhelm an intact mucosal defense or when the mucosal defensive mechanisms are impaired. Stress-related mucosal disease occurs in conditions in which gastric mucosal injury is directly related to impairment in mucosal defense.
Various stressful stimuli activate the HPA axis, and consequently, the production of glucocorticoids, and severe stress stimuli may also induce gastric erosion, called “stress ulcers.” From the very outset, researchers have focused on the idea that stress-induced glucocorticoids are causally related with gastric ulcerogenesis. To clarify the validity of this view, we examined the effect of glucocorticoid deficiency or the glucocorticoid receptor antagonist RU-38486 on stress-produced gastric erosion in rats. The data obtained show that the reduction in the stress-induced corticosterone release, or its actions, aggravates stress-caused gastric erosion. It is suggested that an acute increase in corticosterone during stress protects the stomach against stress-induced injury. The results obtained do not support the traditional paradigm and suggest that glucocorticoids released during acute activation of the HPA axis are naturally occurring gastroprotective factors.

Learning objectives

- Activation of hypothalamic-pituitary-adrenocortical (HPA) axis as main characteristic of stress.
- Physiologic actions of glucocorticoids
- Synthetic analogues of endogenous human glucocorticoids and their beneficial effects.
- Pharmacological actions of glucocorticoids (adverse effects of glucocorticoid therapy).
- Stress-related mucosal disease
- Gastric cytoprotection/Gastroprotection
- Glucocorticoids and gastric ulceration
- Stress-induced activation of the HPA axis as gastroprotective component of stress response & stress-produced glucocorticoids as gastroprotective hormones.

The study was supported by the Ministry of Education and Science of the Russian Federation (agreement No. 075-15-2020-921 for the creation and development of the World-Class Research Center "Pavlov Center "Integrative Physiology - to medicine, high-tech healthcare and technologies of stress resistance ").

Stress and functional GI disorders: Motility disorders and IBS (Irritable Bowel Syndrome)

Bruno Bonaz[1,2], MD, PhD

1. Division of Hepato-Gastroenterology, CHU Grenoble Alpes, Grenoble, France.
2. Grenoble Institute of Neurosciences (GIN), INSERM U1216, Grenoble Alpes University, Grenoble, France.

The effects of stress on digestive functions are associated with modifications of visceral sensitivity, local inflammatory response and motility[1,2,3]. IBS is a dysfunction of brain-gut interactions [4]. Psychosocial factors and concomitant psychopathologies (somatization, anxiety, and depression) are key components in IBS. Abdominal pain is the main symptom prompting the patient to refer to a gastroenterologist; altered bowel habits, bloating and discomfort are also associated to pain[5]. Heightened sensitivity to visceral distension, particularly when perceived as noxious, is described in these patients[6]. Visceral hypersensitivity has underlined the role of visceral (digestive) afferents of the sympathetic and parasympathetic systems, with the role of inflammation/infection, as well as the spinal (spinal hyperexcitability) and supra-spinal treatment of the nociceptive visceral message[7]. Perturbations of descending spinal inhibitory pathways are also involved in IBS pathophysiology[8]. Gastrointestinal sensory motor dysfunction in IBS is consistent with an up-regulation in neural processing between the gut and the brain and functional dysfunction of the sympatho-vagal balance is observed in IBS[9.] Many arguments argue for a conceptual model of an increase of the stress response to explain many of the symptoms of IBS patients. Major advances have been made in unraveling the biochemical coding of stress with the identification of 41 amino-acids, corticotropin releasing factor (CRF) and other CRF-related peptides Urocortins (Ucns) 1, 2, and 3 in the brain and the gut. CRF receptor 1 (CRF1) and CRF2 display distinct binding affinity with selectively for CRF and Ucn 1 (CRF1) or Ucn 2,3 (CRF2). The use of selective CRF receptor antagonists has enabled the unraveling of the role of CRF1 in the stress-related endocrine (activation of pituitary-adrenal axis), behavioral (anxiety/depression), autonomic nervous system (sympathetic system and sacral parasympathetic activation, vagal inhibition), and immune responses. IBS patients have an increase colonic motor response to CRF consistent with the occurrence of an increased gastrointestinal stress response. Experimental studies using CRF1 antagonists also support the involvement of CRF1 in the hyper-sensitivity to colorectal distension (CRD) and increase in colonic motility induced by intracerebroventricular CRF and in a variety of rodent IBS models namely acute or repeated exposure to water avoidance stress combined with neonatal maternal separation or sets of nociceptive CRD or repeated daily CRD six weeks after the development of colitis, intracolonic infusion of 0.5% acetic acid or a high-anxiety rat strain, the Kyoto. It is presently obvious that stress, i.e., the CRFergic system (either central or peripheral), is a major effector in the pathophysiology of many functional digestive disorders and particularly in IBS.[3] Recent studies identified the hippocampus and the central amygdala (CeA) as brain sites of action. CRF microinjected into the CeA induces a hyperalgesic response to CRD and enhances the noradrenaline levels at this site which are blocked by a CRF1 antagonist injected into the CeA[10]. Pharmacological interventions targeting the CRFergic system would be of interest in stress-related functional bowel disease. So far, non-pharmacologic therapies to reduce the stress component including cognitive behavioral therapy, relaxation therapy, and hypnotherapy, alone or in com-bination, are reportedly effective for IBS symptoms[11].

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Stress and sex differences in IBS

Muriel Larauche, PhD

Vatche and Tamar Manoukian Division of Digestive Diseases and UCLA DDRCC:SigCo, Department of Medicine, David Geffen School of Medicine, University of California Los Angeles, Los Angeles, CA, USA

Irritable bowel syndrome (IBS) is the most common bowel disorder of the gut-brain interaction (DGBI). The most important determinant of IBS severity, quality of life impairment and healthcare utilization is abdominal pain. Visceral hypersensitivity to rectosigmoid distension is an important hallmark feature of IBS, believed to underlie abdominal pain in patients. Epidemiologic studies have shown that stress (psychosocial and other stressors) is a trigger for the first onset or exacerbation of IBS symptoms and that presentation of IBS is more prevalent in women. The underlying reasons for this sex difference are not well understood yet, but include a role for sex hormones, interactions with microbiota (microsexome), and a differential response to stress. The participation of these different factors in the sex-dependent influence of stress on visceral pain will be discussed in the context of both clinical and preclinical studies.

Effect of stress on fat: What is the evidence?

Oleh Revenko, MD, PhD(c)**; Iryna Kovalchuk,** MD, PhD**; Maryana Savytska,** MD, PhD**; Oksana Zayachkivska**, MD, PhD, DSc

Physiology Department of Danylo Halytskyy Lviv National Medical University, Lviv, Ukraine.

The effects of stress on white and brown fat play a crucial role in metabolic homeostasis and metabolic disorders, including obesity, and the mechanisms involved in its changes are still being estimated. According to Barker's "fetal programming hypothesis," the importance of maternal lifestyle and conditions on early fetal development is undoubted when changes in an organism are caused by different environmental stimuli, including nutrition. Moreover, there was a demonstrated association between prenatal stress exposure and subsequent shorter telomere length, a predictor of ageing and mortality (Entringer S., 2011-2014). Thus, the elucidation of new triggers and biomarkers of early stages of alterations induced by adipocytes is urgently needed. The approaches to evaluating the role of the obesogenic environment during early-life exposure (*in utero)* or how visceral fat changes in humans are limited. Thus, to evaluate in animal models the impact of maternal stress and imbalanced nutrition on changes in brown and white adipocyte physiological activities, hepatocellular organization in offspring, and how changes in mesenteric white adipocytes' resistance to stress injury are urgently needed. Identification of changes in leptin/adiponectin indexes, proinflammatory ILs, new non-invasive alternative biomarkers to assess early fat tissue and liver changes will be useful for prognosis of ectopic and intrahepatic fat accumulation compared to the invasive "gold standard" methods of assessment of liver (biopsy) [1]. Thiosulfate Sulfurtransferase (TST) activity is an essential regulator of an adequate amount of hydrogen sulfide (H2S), which regulates several important physiological processes, including mitochondrial respiration and control of the redox status in cells in vivo. The present review, based on our results, demonstrates the potential role of TST in mesenteric cellular cytoprotection during aging, stress response, or hurtful diet based on chronic fructose intake [2, 3].

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Nutritional deficiencies in stress and COVID-19

John Schloss, PhD
Schools of Pharmacy and Medicine, American University of Health Sciences, Signal Hill, CA, USA

COVID-19 continues to be a significant source of stress. There is a long-standing relationship between stress and nutritional deficiencies. Recent studies report a clear relationship between stress and nutritional deficiencies, including magnesium, zinc, iron, calcium, and niacin [Lopresti A. L., *Adv Nutr* 2020;11:103–112]. Similarly, dietary deficiencies also can induce stress, with the notable example of vitamin B_{12} deficiency-induced stress in mothers and their offspring [Krishnaveni *et al., J Clin Endocrinol Metab* 2020; 105(7):e2591–e2599]. Although conventional nutritional science estimates less than 6% of Americans have multiple nutritional deficiencies, other estimates, based on lymphocyte proliferation assays (LPA), suggest that 83% of Americans have two or more and 25% have five-or-more nutritional deficiencies. Stress resulting from COVID-19 has combined with viral-induced nutritional deficiency to exacerbate the risks of morbidity, mortality, and long-term sequelae from infection (Long COVID). Both zinc and selenium deficiencies correlate with morbidity and mortality from COVID-19 disease. At least one symptom of Long COVID, the loss of smell (anosmia), has been linked to zinc deficiency, as zinc supplements dramatically reduce the duration of anosmia. Suboptimal zinc increases the risk of immune dysfunction (cytokine storm), cognitive impairment (brain fog), depression, retarded wound healing: various types of cancer, and heart failure.

Stress response to infection from SARS-Cov-2 and major endocrine disorders

Pantelina Zourna-Hargaden, MD, PhD, MPH

American University of Health Sciences, School of Medicine, Signal Hill, CA, USA

In light of recent research, the adrenal glands may be the direct target of severe SARS-CoV-2 infection with evidence of cellular damage (1). Whether this local damage is responsible alone, or in combination with other factors, for the adrenal dysfunction, whether short-term or long-term (as in long COVID), it is still unclear. The therapeutic interventions in managing adrenal dysfunction are constantly being updated as new evidence comes to light (2,4). A new entity 'newly diagnosed diabetes mellitus' (NDDM), is evident among admitted patients with COVID-19 disease. A recent study from MGH-Harvard Medical School examined the hypothesis that the inflammatory stress from COVID-19 disease is a contributor to new onset type II DMII in COVID-19 disease (3). ACE-2 receptors are also present on pancreatic islet cells, but the underlying mechanism is still unclear. Stress hyperglycemia is considered to be the result of both insulin resistance and insulin deficiency, secondary to islet cells destruction by the virus. (3,4). Infection-induced oxidative stress, hypothalamic–pituitary axis dysfunction due to acute severe infection and direct gonadal damage seem to be the prevalent mechanisms of testicular dysfunction with hormonal imbalances (5). Despite the abundance of ACE-2 receptors in the ovaries and oocytes, no solid evidence exists regarding possible ovarian dysfunction after COVID-19 infection or any long-term sequelae on female fertility.

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Lack of professionalism: A distress for peers and coworkers

Grant D. Lackey, PharmD

American University of Health Sciences, Schools of Medicine & Pharmacy, Signal Hill, CA, USA

The pandemic, as example, is approaching the second year. Healthcare professionals and patients are feeling the effects of the many changes the pandemic has caused. To serve ourselves and our patients, this seminar will reiterate practical tools for increasing our satisfaction with the practice of medicine and pharmacy. We all should focus on skills of self-reflection and improved understanding of ourselves and our relationship to others. I refer to this as a part of **PROFESSIONALISM: Service Above Self**. Stress is something that can take over your life; it affects your health and happiness. Beyond directly correlating to your health, did you know stress can cause your business to lose money? Unfortunately, US businesses lose up to $300 billion yearly because of workplace stress. Sadly, but not surprisingly 83% of US workers suffer from work-related stress. There are many kinds of stress, but **Professional Stress**, or **Lack of Professionalism Stress** is that stress that is related to your job or profession and is of a very special type. If professional stress is not managed, and allowed to remain to torment you, it easily deserves its name, "the silent killer." A lack of professionalism can cause stress on professional relationships, cause an increase in professional errors which can lead to confusion, and depression. Professional stress is the stress that occurs within the workplace, or while performing professional activity, and is nothing more than a person's physio-psychological response to various stimuli that sets off our inbred fight-or-flight reaction. In its basic form, stress and the fight-or-flight reaction is meant to protect us. This stress stimuli can be caused by one's superiors, co-workers, tasks, workplace environmental factors, and a host of other conditions. In its basic form, stress and the fight-or-flight reaction is meant to protect us. It causes physical reactions, such as the endocrine glands secreting hormones and enzymes to prepare our bodies for combat or a quick removal from the stress stimuli. Once resolved (either through a fight or flight), our bodies return to normal. More so in the professional workplace, where these stimuli are constant, our bodies are continually in a state of stress causing **a lack of professionalism, performance, and possibly life-threatening errors.** It is now a well-accepted fact that this kind of stress is one of the greatest causes of all illness. This stress can be responsible for both stroke and heart attack; it daily destroys the immune system, in lighter forms causes migraine headaches, eczema, complications in pregnancy, high blood pressure. heart disease, diabetes, obesity, depression or anxiety, and high susceptibility to any infectious disease. The good thing is people learn how to deal with stress every day. The importance of learning coping techniques will assist you in dealing with stress and will lead to a more fulfilling and rewarding professional life.

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Stress and mental health in post-COVID youth

Gerald A Maguire, MD

American University of Health Sciences, School of Medicine, Signal Hill, CA, USA

The vast majority of the focus of the COVID-19 pandemic was on the physical health of our community. However, with the world emerging from this devastation, our mental health community is facing major sequelae from the massive lockdown. In the USA, suicide is now the leading cause of death in adolescents and young adults. Since the beginning of the pandemic, deaths from overdoses have increased nearly 90%. In relation, our youth were exposed to even greater adverse childhood experiences (such as trauma and neglect) related to the pandemic response of social isolation and lockdown. Our youth that experience trauma and stress are at greater risk for psychiatric conditions such as depression, anxiety and eventual co-existing medical problems such as cardiovascular disease, endocrinologic disorders and cancer. Stress can directly exacerbate and/or cause psychiatric disorders through the flight, fight or freeze response with resulting hyperactivity of the amygdala and decreased activity of the medial prefrontal cortex. With the ever present and growing pandemic of youth depression, trauma, suicide and overdose, our healthcare community must pivot to address this growing pandemic. A strategy to address this would implement preventive screenings in less stigmatized locales such as education, community, and spiritual settings and by integrating psychiatric services with primary care. Effective psychiatric treatment utilizing pharmacotherapy and psychotherapy can effectively treat the psychiatric conditions related to trauma and stress and improve not only the mental health of the individual but the physical health as well.

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Notes

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