The Stressed Brain – A Clinician's Perspective Part 2

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Prenatal and Postnatal Early Life Experiences Alter Biology and Create Life-Long Vulnerability

Research has consistently shown that early life experiences promote a more vulnerable or hardy (i.e., resilient) human being. McEwen and Getz[7] reviewed animal research demonstrating that "early life experiences become biologically inscribed" (p.S22). They noted that factors before birth (e.g., prenatal stress) and those occurring postnatally (e.g., extended separation of the infant from mother) can impair normal brain development and function. By contrast, adequate maternal care and consistent caregiving benefited the offspring by creating durable patterns of reduced anxiety, more efficient stress reactivity, and better social and cognitive development. There are also transgenerational effects that have been shown to be behaviorally and genetically transmitted by mother rats to their offspring. For instance, environmental manipulations that alter maternal rat behavior will impart nongenomic differences in stress reactivity across generations of female offspring.[21] Similarly, environmental manipulations that increase maternal stress during pregnancy resulted in genetically transmitted alterations in hypothalamic-pituitary-adrenal (HPA) axis reactivity to stress and anxiety-like behaviors among second generation male rats.[22]

In humans, similar findings have shown that stress does become biologically inscribed in human fetuses and children and yields effects that endure well into adulthood. One of the more salient (and perhaps extreme) examples of this comes from an extensive systematic review done on the intergenerational (or transgenerational) effects of Holocaust survivors and the mental health of their offspring (a.k.a., ***Holocaust survivor offspring***; HSO).[23] The findings of this review yielded convincing evidence of intergenerational effects that showed associations between parental mental health, perceived parenting and attachment quality, and increased psychiatric symptoms among HSO, including high conflict and less cohesion within families of HSO. Having two survivor parents was associated with greater mental health problems among the HSO compared to having only one survivor parent. The HSO also exhibited a heightened vulnerability for stress, but this seemed to only happen when faced with genuine danger. Lastly, intergenerational effects on cortisol modulation (i.e., levels) was also evidenced among the HSO.

Heritable factors, such as genetics, also represent an avenue that exposes how stress becomes biologically inscribed. For instance, some human carriers of a particular allele – i.e., the methionine allele of the valine 66met ***brain-derived neurotrophic factor*** (BDNF) polymorphism or the Val66Met polymorphism in the BDNF gene – have inherited genetics that influence the expression of this important growth factor.[11] BDNF is a "major neurotrophic factor that plays an important role in the formation, guidance, and survival of neurons during development but also in synaptic plasticity and survival in the adult brain" (p.410).[24] Having this polymorphism can result in lower grey matter volume in the hippocampus and PFC due to alterations in the production and expression of BDNF, thus, undermining synaptic or cellular plasticity and neurogenesis in response to stress exposure.[11] This particular polymorphism is also linked to impaired episodic memory, as well as cognitive impairment in older adults more than 55 years of age.[25]

In keeping with our discussion about genetics, other alleles can impact stress regulation over the course of a person's life. Aggression from difficulties coping with stress, for example, can arise due to genetic variants that are associated with increased ***monoamine oxidase-A activity*** (i.e., results in an increased breakdown of monoamine neurotransmitters, such as dopamine, norepinephrine, and serotonin).[26,27] This speaks to the concept known as ***reactive alleles***, which refers to how some gene variants increase or decrease in response to environmental influences like stress.[7] The point is that all allelic variants are in a sense reactive, whether the heritable variants involve BDNF or those variants are associated with monoamine oxidase-A; when combined with environmental stressors, phenotypic expression changes, which may facilitate allostasis, or may result in

enduring patterns of allostatic load (AL) and/or allostatic overload (AO).

The length of ***telomeres*** is another example of how stress becomes biologically inscribed. A telomere is a region situated at each end of a chromosome, which protects the chromosome from deterioration while preserving vital genetic information.[28] Age-related health problems and diseases have been consistently associated with excessive or accelerated telomere shortening.[28] Stress, resulting in the release of glucocorticoids, has been shown to reduce the levels of antioxidant proteins, leading to increased oxidative damage to DNA, and quickened telomere shortening.[28] Cross-sectional human studies have demonstrated associations between compromised telomere integrity and high levels of psychosocial stress exposure.[29] Even factors that happen before birth, such as prenatal stress exposure, have been shown to be a significant predictor of subsequent shorter leukocyte telomere length in young adulthood. These findings are believed to represent an important biological pathway that broadly influences the "developmental origins of adult health and disease risk" (p.E513).[29]

Other, and perhaps more relevant research to the practicing clinician, involves associations between large cohorts (i.e., involving several thousand individuals or more) that experienced ***adverse childhood experiences*** (known as ACEs) and enduring problems in adulthood. ACEs have been described by the CDC as potentially traumatic experiences happening in childhood (i.e., between 0-17 years of age) that comprise a child's sense of safety, security, and bonding, and include all or some of the following: witnessing or experiencing violence in the home or community; experiencing neglect; having a family member attempt or die by suicide; and being in a household with substance misuse, mental health problems, or parental separation or members of the household being in jail or prison.[30] Increasing amounts of ACEs have been associated with adult health risk behaviors and diseases.[31] Compared to individuals without any ACEs, those exposed to four or more categories of ACEs experienced a 4- to 12-fold increase in alcoholism, drug abuse, depression, and suicide attempt. The same individuals had a 2- to 4-fold increase in smoking, poor self-rated health, 50 or more sexual intercourse partners, and sexually transmitted disease. There was also a 1.4- to 1.6-fold increase in physical inactivity and obesity. This data was sadly presumed to have underestimated the actual consequences of ACEs, and their relationship to adult risk behaviors and diseases.

Additional data has demonstrated that a graded relationship exists between ACEs and the risk of attempted suicide.[32] Merely having experienced an ACE was associated with a 2- to 5-fold increased risk of attempted suicide. Individuals without ACEs were shown to have a 1.1% prevalence of attempted suicide. Though the statistical marker known as odds ratio is somewhat different from prevalence, individuals with seven or more ACEs had an odds ratio of attempted suicide of 31.1%. Other studies evaluating the impact of ACEs demonstrated an association between elevated ACE exposures or scores and problems in adulthood that include childhood autobiographical memory disturbance,[33] alcoholism and depression,[34] depressive disorders,[35] and hallucinations.[36]

There are also consequential changes to brain structures and function, and overall physiology that result from ACEs. Several examples are provided here to demonstrate this association. A report that documented a 10-year history of children growing up with mothers having chronic depression, showed larger amygdala volumes in the childrens' brains.[37] Another report identified increased negative functional connectivity between the PFC and amygdala among adolescents exposed to physical, sexual, or emotional abuse compared to adolescents without a history of maltreatment.[38] These findings were more pronounced among adolescents that had more severe abuse, and were also associated with higher amounts of ***externalizing psychopathology*** (e.g., opposition/conduct and attention disorders) some 2 years later. Other data has shown that children raised without sufficient verbal stimulation, and in unstable home environments were more likely to develop impaired cognitive function, increased systemic inflammation, cardiovascular disease, substance abuse, anti-social behavior, and depression.[39,40]

Prenatal and postnatal stress become biologically inscribed, impacting vulnerable brain structures and altering physiology.

Above all, prenatal and postnatal stress does become biologically inscribed by adversely impacting vulnerable brain structures, altering physiology, and shaping adult development. Not surprisingly and almost in a rather banal way, a combination of these aforementioned factors disrupt allostatic mechanisms to such a great extent, practically guaranteeing AL and AO, psychopathology, physical disease, and a cascading path of enduring mental and physical problems lasting well into adulthood.

Chronic Stress and Social Isolation, Loneliness, and Socioeconomic Status

Similar to prenatal and postnatal stress, social isolation, loneliness, and socioeconomic status (SES) activate allostatic systems, and result in AL and AO due to detrimental life outcomes, pathophysiological changes, and consequential brain changes.

Social isolation and loneliness are common experiences that all of us have endured (or will endure) at certain times over the course of our lives. In a meta-analytic review on loneliness and social isolation, Holt-Lunstad et al defined these terms and then analyzed aggregated data to determine associated health outcomes.[41] ***Social isolation*** was defined as living alone, having infrequent social contacts, and having sparse social network connections. ***Loneliness*** represented the subjective experience of social isolation, resulting from disparities between one's desire

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for social relationships and one's actual social relationships. The results of the meta-analytic review showed social isolation and loneliness to yield weighted average effect sizes that increase the risk of mortality in a manner comparable to other health risk factors like obesity, substance abuse, physical inactivity, and mental health problems. Specifically, the odds ratio of increased mortality was 1.29 (29%) for social isolation, 1.26 (26%) for loneliness, and 1.32 (32%) for living alone.

In a review paper, Cacioppo and Hawkley described underlying mechanisms associated with social isolation.[42] Individuals that perceive themselves to be socially isolated often experience insecure adult attachments that beget physiological changes characterized by activation of the sympathetic nervous system (SNS), the sympathetic adrenomedullary (SAM) system, and the hypothalamic-pituitary-adrenal (HPA) axis. Additionally, perceived social isolation becomes its own stressor and produces negative emotions (e.g., depression and anxiety), negative reactivity (e.g., hostility, mistrust, and irritability), and reduced feelings of self-worth, happiness, and life satisfaction. The autonomic patterning of socially isolated individuals is also characterized by a higher total peripheral resistance, and lower cardiac output. These latter effects degrade both central and peripheral hemodynamics leading to increased vascular resistance and decreased vascular compliance, and the likely development of hypertension. Perceived social isolation also undermines repair and maintenance functions and weakens anabolic processes, such as wound healing time and restorative sleep (i.e., lower sleep efficiency and higher wake times after sleep onset).

Similar to social isolation and loneliness, SES is also a significant stressor since it imposes disadvantages and impediments that undermine a person's ability to succeed in life for countless reasons. McEwen and Getz cited several sources when documenting the deleterious effects of low SES and perceived SES.[7] They cited research demonstrating that individuals having low SES are at greater risk for "predisease" conditions, such as obesity, metabolic syndrome, substance abuse and psychiatric disorders (p.S23). Similarly, they noted other research that showed an association between perceived low SES and a poor sense of control and low self-esteem.

The brain is the primary organ that mediates how a person perceives and responds to chronic stressors.

With respect to brain changes, there is evidence of deleterious effects arising from social isolation, loneliness, and SES. For example, the chronic stress associated with individuals perceiving themselves to have a low social standing (i.e., a composite marker that includes standard measures of SES) was linked to reduced grey matter volume in the ***anterior cingulate*** cortex (ACC) located proximally to the prefrontal cortex (PFC).[43] This was deemed important because this particular neuroanatomical area plays a role in how people experience emotions and regulate their behavioral and physiological reactivity to psychosocial stress. Even low perceived parental standing – known to be a likely indicator of socioeconomic hardship during childhood and adolescence – was "associated with greater amygdala reactivity to threatening (angry) facial expressions" in "healthy individuals who had not yet reached their adult SES" (p.203).[44] This finding was believed to represent a neurobiological pathway by which early SES experiences become biologically embedded, impacting allostatic systems, and likely future health and disease vulnerability.[44]

Research on social isolation has reviewed brain changes among individuals that spent 14 months living in isolation in the Antarctic.[45] The results showed statistically significant reductions compared to controls in the hippocampal volume of the ***dentate gyrus*** from before to after the expedition. This particular part of the hippocampus contributes to the formation of episodic memories.[46] The results showed that other hippocampal regions and even several regions of the PFC had reduced volumes compared to controls but these changes did not reach statistical significance.[45] Serum BDNF levels were also measured before and after the expedition. Compared to serum measurements before, BDNF levels dropped during the expedition and did not recover to their pre-expedition levels when assessed 1.5 months after the expedition had ended. The decreased serum BDNF levels that happened during the expedition were also associated with reductions in the hippocampal volume of the dentate gyrus, and reduced cognitive performance (i.e., as shown by tests of spatial processing and selective attention). The results of this study demonstrated how vulnerable the dentate gyrus of the hippocampus is to environmental deprivation, and revealed similarities to animal studies in which "neurogenesis, stress-induced behavioral changes, and environmental deprivation" adversely impacted this particular hippocampal region as well (pp.2274-2275).[45] Even though the sample size was very small in this study (n=9) and other factors might have contributed to the observed brain changes from environmental deprivation, it is clinically plausible that similar brain changes and reductions in BDNF and cognitive performance will be found among people living socially isolated lives.

Chronic Stress and Personality

It would seem important to consider personality as a potential influencer of chronic stress, as it plays an essential role in facilitating and/or moderating how the brain and body respond to ongoing challenges. Canli extensively reviewed extraversion (E) and neuroticism (N) – both of which are heritable personality traits – and determined associated brain imaging mechanisms.[47] ***Neuroticism*** as a personality trait encompasses individuals that are more likely to be moody and to experience feelings such as worry, fear, anxiety, anger, frustration,

guilt, depressed mood, and loneliness. ***Extroversion*** as a personality trait refers to individuals that are sociable, talkative, assertive, excitable, have lots of energy, and tend to be full of life and energy. Canli's study showed that Individuals with dominant E traits experience more positive affect in their daily lives compared to individuals with dominant N traits that experience more negative affect in their daily lives. These personality orientations were enduring and noted to last "for periods of up to 10 years" (p.1106). The affective associations between individuals with E and N personality dispositions may also be mediated to some extent "by cognitive biases in the processing of emotional stimuli" (p.1107).[47]

When Canli evaluated subjects with brain imaging, he found differences between these two types of personality dispositions.[47] Individuals high in E showed greater activation of the amygdala when positive images or happy faces were shown. Individuals high in N exhibited greater activation of the amygdala when negative images were shown. Why does this seem important? The amygdalar activation was oriented towards positive and negative stimuli and was specific to these personality types. These brain differences in personality were also postulated to have some involvement in resilience and vulnerability factors for specific types of psychopathologies. Cited data pertaining to individuals high in N (or higher N relative to lower E) showed more vulnerability towards the development of eating disorders, low self-esteem, post-stroke depression, and more unfavorable outcomes when being treated for depression.

Interested readers may want to additionally review an important cohort study that documented increased all-cause mortality among individuals having a N personality disposition (i.e., based on a composite of pessimistic, anxious, and depressive personality traits).[48] These individuals were assessed early in life, and their N personality disposition had significant negative consequences on mortality when evaluated over four decades (i.e. a hazard ratio of 1.42 or 42% in the primary analysis). Other studies were also cited showing a relationship between N personality traits and increased mortality (see Table 5, p.498).[48] Some of the biological mechanisms believed to be responsible for the increased all-cause mortality among individuals with a dominant N personality disposition included the following: hippocampal atrophy and other brain lesions; stress and depression causing "increased heart rate, hypertension, increased plasma norepinephrine levels, or changes in blood coagulation that may increase the risk of cardiovascular disease"; and stress causing reduced immune system responsiveness and a greater risk of cancer (p.496). Other mechanisms attributed to individuals with the N personality disposition and the finding of increased all-cause mortality included poor self-care, unhealthy behaviors, and underutilizing healthcare resources and/or poor compliance with treatment.

There are certainly other personality types – i.e., other than N and E – that modulate chronic stress, impact the brain, and are also associated with diverse health outcomes. The N personality type was highlighted here because it seems to more commonly occur in my clinical practice and is perhaps more deleterious than other personality types in relation to chronic stress and adverse health outcomes.

Chronic Stress and Medical Disease

As mentioned near the beginning of this paper, there are four different types of allostatic responses, and for three of them the resulting biological adaptations would be required to manage alterations in cortisol[9] (as well as adaptations resulting from activation of the SAM system[49]) over prolonged periods of time. In this section, I will briefly review the links between chronic stress and medical (i.e., physical) disease, and highlight what happens when the body is unable to cope with stress resulting in a breakdown of bodily resources. For example, chronically elevated cortisol levels due to persistent or poorly managed psychosocial stress could promote insulin resistance leading to weight gain and obesity. In one such publication, the dichotomous roles of cortisol were described in relation to what it does in the short-term compared to its deleterious effects when there is persistent and poorly managed psychosocial stress over the long-term.[50] When the physiological stress response leads to the release of cortisol, there will be an abrupt impairment of insulin secretion and an increase in the production of hepatic glucose. However, should the stress response persist for a prolonged duration, it will inhibit insulin secretion, impair insulin-mediated glucose uptake, and disrupt insulin signaling within skeletal muscle. Individuals can compensate homeostatically by increasing pancreatic beta-cell function, or by increasing the release of insulin. However, when stress becomes prolonged, insulin resistance develops, or becomes worsened by established obesity, resulting in biological adaptations that cause hyperglycemia and adverse metabolic consequences.

In addition to weight gain, obesity, and metabolic consequences, there

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are other stress-related diseases that are presumed to result from prolonged biological adaptations to cortisol secretion, including biological adaptations resulting from activation of the SAM system. The list includes asthma, gastrointestinal diseases (e.g., ulcerative colitis), functional gastrointestinal diseases, coronary heart disease, rheumatoid arthritis, migraine headaches, being more susceptible to cold viruses, nonalcoholic liver disease, neurodegenerative disorders (e.g., Alzheimer's and Parkinson's disease), and even cancer.[51,52] The list of diseases that are stress-related, however, is likely to be much greater since prolonged (i.e., chronic) stress is considered a common risk factor in 75%-90% of all diseases.[52]

The implicating factor in all these diseases involves an inability to discharge or effectively manage perceived stress over time, which of course strongly implicates the brain because it is the primary organ that mediates how a person perceives and responds to chronic stressors. In fact, the continued ***uncertainty*** (i.e., when anticipated outcomes are unexpected) associated with chronic stress is believed to create a situation in which the brain cannot meet its demand for extra energy, and because of ***failed stress habituation*** (i.e., the inability to "attenuate autonomic, endocrine, and metabolic reactions when repeatedly exposed to the same hostile environment"), the resulting AL and subsequent AO yields both systemic pathology (as described above), as well as brain malfunction or pathology (will be described in the next section; p.167).[53]

Chronic Stress, Psychiatric Illness (Mental Disorders), Suicide, and Brain Mechanisms in General Terms

When faced with chronic stress, which seems to always be adjoined with the subjective experience of uncertainty, some individuals will be able to habituate (a.k.a., habituators) and attenuate their biological stress mechanisms. However, some individuals will be unable to habituate, and therefore their biological stress mechanisms will continue to disrupt the healthy functioning of their entire biological system (i.e., resulting in AL), which adversely impacts both the brain and body. As pointed out by Peters et al, when uncertainty cannot be resolved this leads to a "vicious cycle of altered brain architecture and systemic pathophysiology, which further damages the capability of the subject to cope with uncertainty" (p.168).[53] When this proceeds for too long or when resources to attenuate the chronic stress become depleted and damaged, AO ensues, and gives rise to brain malfunction or pathology.[53]

It is of no surprise then that life events, such as the unexpected COVID-19 pandemic, are major players in the difficult subjective experience of uncertainty. The brain must have sufficient energy to meet its high metabolic demands in the face of chronic stress and uncertainty. When there is failed habituation, which happens for some individuals, the levels of self-esteem and locus of control are significantly diminished, placing the individual at high risk of ***mental morbidity*** and mortality.[53] With respect to mental morbidity, there also exists a significant body of literature demonstrating a relationship between life events and the onset of psychiatric illness. Apparently, the strength of associations between stressful life events (i.e., also often mired in uncertainty) and psychiatric illness is stronger than similar associations and the development of medical disease.[51]

Though the names of psychiatric illnesses differ diagnostically, what is apparent is that the brain mechanisms implicated in chronic stress are more similar than dissimilar across a broad range of neuropsychiatric phenomena. For example, when an individual is faced with uncertainty arising from chronic stress and cannot habituate, specific areas of the PFC activate the ACC because it "assesses the degree of uncertainty about whether future outcomes are uncertain"(p.166).[53] This results in activation of the amygdala and an ensuing stress response - mediated by the release of norepinephrine - that leads to a hypervigilant state, and simultaneous activation of the SNS (increases glucose for energy utilization) and the HPA axis (increases cortisol) that plays a vital role in synaptic plasticity and learning after stress.[53] The released cortisol passes through the blood-brain-barrier and binds to glucocorticoid receptors in and on neurons of the amygdala, hippocampus, and PFC (i.e., three key brain structures mentioned earlier in this paper).[51] In simple terms, the net result leads to feelings of threat and loss of control, concomitant with damaging alterations to brain architecture within these three key brain areas, and greater bottom-up control via the ACC-amygdala complex that is not being properly attenuated by specific areas within the PFC.[53]

When looking at a broad range of psychiatric illnesses, it should come as no surprise that many of the same brain mechanisms are implicated. This strongly suggests that chronic stress is a significant or major underlying trigger for the majority of psychiatric illnesses. As Patriquin and Mathew pointed out, "Chronic stress may be one cross-cutting construct or dimension (i.e., that occurs across diagnostic categories defined by

Table 3. Mediators and outcomes of chronic stress

Mediators of AL and AO	Implicated brain structures	Possible health outcomes that further mediate AL and AO
Stress-vulnerability Prenatal and postnatal early life experiences Social isolation, loneliness, and SES Neuroticism personality type Uncertainty	Prefrontal cortex Amygdala Hippocampus	Atrophy and damage to these brain structures Low self-esteem Diminished locus of control Premature mortality Poor quality of life Medical disease Mental morbidity, psychiatric illness and/or suicide

the DSM-5) related to GAD, as well as other diagnoses (such as highly related MDD)" (p.2).[54] In the section below, I will review brain mechanisms in general terms that become triggered by chronic stress for several common psychiatric illnesses, such as generalized anxiety disorder (GAD), major depressive disorder (MDD), PTSD, and even borderline personality disorder (BPD).

In GAD, for example, the ACC-amygdala complex gets activated under situations of chronic stress, resulting in decreased connectivity between the amygdala and PFC, making it very difficult for such individuals to effectively regulate their emotions.[54] These brain circuit issues are implicated in symptoms, such as anxious arousal, attentional bias to threat, avoidance, and even helplessness behavior.[54] Similarly, in MDD, chronic stress leads to impairment in PFC function, an overactivated amygdala resulting in more fear-based or bottom-up control, and a concomitant downgrading of hippocampal functioning.[55] Some of the common features of MDD, such as neurocognitive impairment, withdrawing from aversive environments, and anhedonia are linked to these brain circuit issues.[55] In PTSD, there is impaired PFC function, elevated cortico-amygdala activity resulting in heightened vigilance and reactions to threatening stimuli, and reduced cortico-basal ganglia reward sensitivity.[56] In an older publication on PTSD, the amygdala was noted to exert an overarching influence upon the hippocampus causing reduced functionality and hypermnesia for stressful experiences, behavioral disinhibition, and impaired PFC function.[57] In BPD, affect dysregulation happens because certain areas within the PFC are known to be impaired (i.e., as evidenced by abnormal neuronal activity and prefrontal hypometabolism), and is also associated with top-down processing problems.[58] Disruptions in prefrontal-limbic circuitry have also been found among people with BPD due to functional disconnectivity between the amygdala and various regions of the PFC with associated volume reductions noted in the amygdala, hippocampus, and in several other subcortical brain regions.[58] The amygdala is also believed to be overactive or poorly controlled among BDP patients, such that it directs "their unfiltered attention to predominantly negative and threatening social stimuli" (p.842).[58]

Outside of psychiatric illnesses, suicide has not specifically been addressed though chronic stress and vulnerability have been proposed as the key triggers toward dying by suicide. Heeringen and Mann noted that "suicide is the result of an interaction between state-dependent (environmental) stressors and a trait-like diathesis or susceptibility to suicidal behaviour, independent of psychiatric disorders" (p.63).[59] For a brief review of additional theoretical models of suicide see the reference noted here.[60] Similar to our previous discussion on childhood adverse experiences, early life adversity appears to affect suicide risk because of alterations to brain architecture, dysregulation of the stress response, and likely cytotoxic effects from excessive concentrations of increased CRH and glucocorticoids.[59] In terms of neurobiological mechanisms, certain genetic variants (i.e., alleles for lower expression of the serotonin transporter gene 5HTTLPR) associated with suicide are linked to "impaired connectivity between the prefrontal cortex, amygdala, and anterior cingulate" (p.68).[59]

Though the clinical manifestations of the aforementioned psychiatric illnesses are both similar and different, they are also principally related to the same key brain areas. Suicide and certain genetic variants were also noted to involve the PFC, amygdala, as well as other brain areas. The genetics and epigenetics, however, of the noted psychiatric illnesses (as well as others) and suicide is very complex and plays an important role in how the brain mediates stress, and the ensuing biological responses. Interested readers should review the following references[(i.e., 54-59, 61)] to further understand this complex subject matter.

Conclusion

There ought to be no further dispute or controversy about the devastation that chronic stress imposes on both the body and brain. Chronic stress, as noted earlier, is pathological and happens when allostatic mechanisms fail to adapt because resources have been exhausted. The brain, the principal organ that perceives and determines how an individual responds to the world, is subject to multiple stressful and chronic insults that increase the risks of body and brain damage, disease, psychiatric illness, and other health outcomes (Table 3). Thus, understanding what stresses the brain is of paramount importance for any clinician whose aim is to provide treatment that regulates the brain and alters a patient's current and future morbidity and mortality. ◆

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