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PERSPECTIVES

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In Times of Adversity: A Neuroscience Perspective on Stress, Health, and Implications for Society Post-pandemic

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The relationship between chronic stress and chronic disease (including mental illness) is well established: HPA-axis hyperactivity leads to hormonal dysregulation of primary mediators (eg, glucocorticoids, cytokines, etc.), allostatic overload, and neurological degradation, followed by clinical manifestations of disease. Amid the largest public health crisis of the century lay a myriad of challenges pushing people beyond their limit. From experiencing loss of connection or dealing with loss of life to financial shocks of COVID-19 lockdowns or infection by the SARS-CoV-2 virus, stress is at an all-time high, threatening both brain and mental health at scale. Fortunately, there is a way forward: the neuroscience of resilience teaches us that it is possible to resist, recover, and redirect the brain from trauma to re-establish balance in the body and improve well-being. At the same time, health follows a social gradient: adverse and protective psychosocial factors are shaped by wider social and economic determinants of health. This paper argues the neurobiology of stress is not separate from health disparities linked to adverse factors (ie, stress) created by complex social and economic contexts. Therefore, the field of neuroscience is challenged to inform multi-context and multi-level approaches and engage with decision-makers to enact policies and interventions aimed at promoting the resilient element in a wider population health context. Undoubtedly, achieving such a goal for current and future generations to benefit and lead healthier lives requires a heroic effort from all key stakeholders. The cost of willful neglect to resolve these issues is too expensive.

INTRODUCTION

The neurohormonal stress response—a systemic response produced by activation of the Sympathetic-Adrenal-Medullary (SAM)-axis and Hypothalamus-Pituitary-Adrenal (HPA)-axis—is the human body's most distinctive attribute [1]. Considering this evolutionary systems' resolve for performance and protection (rather than sickness or death) under conditions of threat, it is unsurprising that the burgeoning field of the neuroscience of resilience has begun seeking meaningful advances in brain health and mental functioning through evidence-based interventions, integrating social work, and clinical research.

There is a tonic strength in stress—this is a key concept to allostatic load. But when there is an over-exposure to stressors, structural changes in the brain, including hormonal and immune system changes, can lead to chronic disease (including mental illness) and early mortality risk [2]—emotional stress is the largest contributor of the six

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Abbreviations: HPA-axis, Hypothalamus-Pituitary-Adrenal-axis; ACE2, Angiotensin Converting Enzyme 2; GC, glucocorticoids; PA, Psychological First Aid; SDOH, the social (and structural) determinants of health.

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leading causes of death [2]. Today's new life rhythms and demands, as a result of the social and economic fallout of the COVID-19 pandemic, are creating intense, long-lasting psychological and physiological problems in people, highlighting the boundaries of this inherent automatism at a scale unseen in decades [3]. While stress impacts all populations across the social gradient, disease burden falls disproportionately on groups on the lower end of the gradient. For instance, adults in households with job loss or lower incomes report higher rates of symptoms of mental illness than those without job or income loss [4]. Similarly, Taylor and colleagues found that racial and ethnic minority groups are more vulnerable to the newly discovered "COVID Stress Syndrome"—a disorder characterized by "unprecedented psychological distress"—compared to White people [5,6]. Psychosocial stress is not the only pathway through which disadvantage influences health disparities, although it can be pivotal in the goal of advancing population health equity.

The magnitude of today's mental health needs (exacerbated by COVID-19) has blurred the lines between neuroscience, clinical medicine, social work, and public policy more than ever before. Calls for integration of quality, and comprehensive, mental health and social care services prompts a deeper discussion on the broader factors at work, particularly the the ways in which the wider social and economic determinants of health promote HPA-axis hyperactivity, producing lasting and potentially crippling dysfunction in historically disadvantaged and marginalized populations. Indeed, the transition from early mortality to chronic adult illness in the course of human history, compounding COVID-19 morbidity and rising mental health issues are major concerns for the future of public health and society at large; the single most important risk factor is stress [7,8].

STRESS IS ALL ABOUT THE NEURON

Referred to as the "fundamental unit of the nervous system," neurons are cells responsible for receiving sensory input and relaying the message to other cells via neurotransmitters [9]. Interestingly, the word neuron did not exist before 1891 [10]. Mid nineteenth-century scientists had discovered that every living thing consisted of discrete units called "cells"—however, the nervous system was the only exception to cell theory [10]. Invention of the electron microscope in the 20th century later revealed that neurons communicate with each other through chemical and electrical synapses implicating the presence of voltage-gated ion channels on dendrites and propagation of action potential from the cell body [11] —a vital component of virtually all physiological processes in living systems.

Real or perceived, both acute and chronic stressors elicit neuroendocrine, autonomic, and behavioral responses that act directly upon neuronal function and cell structure to promote survival [12]. Disturbances at any level of the stress response can lead to an imbalance of physiology of the body, although acute stress (short-term stress) is typically viewed as "advantageous" to living organisms, as it has been found to enhance neuroprotection in mice via preconditioning [13], protects against spinal ischemia in piglets [14], and boosts alertness in humans [15]. Chronic stress (prolonged stress), however, leads to a causal sequence of primary effects (eg, dendritic remodeling in neurons, reduced neurogenesis, cell death, etc.) [16] that result in psychological, cardiovascular, and metabolic impairments. The implication here is that neurons are the pathway between life or death [16].

For example, Angiotensin Converting Enzyme 2 (ACE2) is a protein highly expressed on the surface of many cell types including lung, gut, nasal mucosa, and the brain [17]. The salutary function of ACE2 is the degradation of angiotensin-II (ang-II) to vasodilatory angiotensin-(1-7) [18]. Importantly, ACE2 is the entry receptor for SARS-CoV-2 to gain access to its hosts [18]. Clinical reports of several neurological manifestations in COVID-19 patients include headaches, anosmia, and nausea [19]. The human induced pluripotent stem cell-derived BrainSphere model has demonstrated SARS-CoV-2 infectivity of neuronal cells, suggesting direct neurotropism of several cell types through the presence of viral RNA [20]. Neuroinvasion of SARS-CoV-2 on hypothalamic circuits negatively impacts the central nervous system (CNS), the peripheral nervous system (PNS), and associated neuroendocrine signaling and pituitary function—essential for the regulation of the body's physiological processes [21]. Considering these effects, a disturbed neuron is the gateway to malady.

GLUCOCORTICOIDS AND STRESS RESILIENCE

Conversely, there are mechanisms in place to build stress resilience and prevent the development of maladaptive physiological and psychological responses and disease [1,22]. Defined as "the ability to achieve a successful outcome in the face of adversity" [23], resilience is derived from the interplay between internal disposition (eg, personality, genetic makeup, etc.) and external experience (eg, quality social support) [24]. The metabolic process behind this interplay is mediated by one of the most versatile molecules in the world: glucocorticoids (GC) [25].

When exposed to stressors, GCs are released from the adrenal cortex as a consequence of HPA-axis activation and interact with various mediators to regain homeostasis [25]. Glucocorticoids bind glucocorticoid

receptors (GR) and mineralocorticoid receptors (MR)–two corticotropic receptors profoundly expressed in the hippocampus, amygdala, prefrontal cortex (PFC), and other limbic and midbrain structures associated with cognition, memory consolidation, behavior, and negative emotion [26]. Thus, GCs are ideally placed to regulate a multitude of signaling pathways activated in response to traumatic stress, depression, and addiction [25,26]. After responding to stressors, the HPA-axis resets. However, over-reaction of the HPA-axis (resulting in increased GC hormone levels) has been implicated in underlying mechanisms contributing to organ damage (eg, intestinal barrier dysfunction) [27], metabolic syndromes, and the development of hepatic disorders [28]. Dehydroepiandrosterone (DHEA), a metabolic intermediate, may serve as a causative factor in positive coping and/or stress resilience: DHEA is secreted by the adrenal gland with cortisol (or corticosterone, in rodents) in response to stress. Though there are no receptors known in tissues for DHEA, studies show that it might counter the actions of GC hormones [25]. Furthermore, the capacity to block proinflammatory cytokine production is suppressed under stress: in severe COVID-19, coagulopathy can occur, resulting in cell inflammation and cytokine storms [28,29]. Inflammatory cytokines appear to be the most reliably elevated inflammatory markers in the peripheral blood of subjects with depression [30]. Just as GCs and DHEA influence one another, the ability of GCs to induce and/or enhance the expression of cytokines is widely reported [31]. Altogether, overproduction of GCs due to chronic stress-induced activation of the HPA-axis favors nervous tissue vulnerability, prognosis of clinical markers, and a host of mental health issues triggered by a physiological cascade that influences inflammatory responses.

To help build stress resilience and restore health in people, we have witnessed the combination of enriched rehabilitation and physiotherapy forge standard approaches to neurorehabilitation (eg, stroke recovery) [32,33]. Likewise, the combined efforts of social and developmental psychology have resulted in the validation of a range of interventions, such as drug therapy (eg, anti-glucocorticoid therapy), cognitive-behavioral therapy (CBT), and aerobic exercise [32]. Yet, allied to the development and implementation of these individual-level interventions are questions about quality, effectiveness, and impact at the population level. For example, depression has always been associated with chronic disease, and in spite of existing behavioral therapies, the prevalence continues to rise. As a result, newer theoretical models of behavioral medicine intervene at multiple levels of a patient's social ecology (eg, interpersonal factors, community influences, social policies or national laws) [34]. Similarly, Psychological First Aid (PA) has gained traction in the global conversation of "recovery plans" for life post-pandemic [35,36]. But until PA establishes connections among community resource centers and becomes a universal program that is accessible to all, its hyperfocus on the individual as the point of intervention is unlikely to reduce disparities in mental health at scale or with proper intensity. Prevention efforts are critical, particularly given that individual-level interventions do not take into consideration the wider social, economic, and environmental influences that impede the adoption of new behaviors to lead healthier lives and increase levels of allostatic load among individuals from lower socioeconomic status (SES) [37]. If we are to consider the double-fail of health behavior interventions (ie, exclusion of the social context in health and failure to reach priority groups) as potentially contributing disproportionately to allostatic overload in the form of stress-induced disorders (eg, hypertension, depression, etc.) among the disadvantaged, there remains one question confronting the field of neuroscience: is there not a duty to go beyond microlevel analyses of clinical populations and engage more with public health frameworks, particularly the social (and structural) determinants of health (SDOH), to consider resilience in the context of population health and point decision-makers to integrated approaches and multi-level interventions that support people to address determinants along the psychosocial pathway? [38]

THE SOCIAL DETERMINANTS, STRESS, AND SOCIETY

Despite ongoing debates about the extent to which individual behaviors contribute to health inequalities, the fact is that structural inequities limit the scope of opportunities disadvantaged people have for reaching their full health potential [38]. For example, the US Centers for Disease Control and Prevention (CDC) have estimated that Black individuals have died from COVID-19 at more than twice the rate as White individuals [39]. A variety of pathways have been hypothesized to contribute to racial disparities in COVID-19 cases and deaths, such as genetic susceptibility, medical bias in testing and treatments [40], and health disparities: Black populations disproportionately account for cardiovascular disease and asthma–two major risk factors for COVID-19 [40]. However, a massive body of literature points to inequalities across the SDOH as the largest contributing factor to the disproportionate impact of COVID-19 among communities of color [40-42].

According to the World Health Organization's report *Closing the Gap in a Generation: Health Equity through Action on the Social Determinants of Health*, "poor and unequal living conditions are the consequences of deeper structural conditions that together fashion the way societies are organized—poor social policies and programs,

unfair economic arrangements, and bad politics [43].” Precisely because disorders originate from stress, neuroscience forces us to think diligently about how upstream determinants of health impact downstream, psychosocial effects via stress pathways and consider what policy interventions and strategic actions are necessary to effectively support people in their particular social, economic and environmental situations to advance health equity [38]. For instance, when we consider how over exposure to macro-level psychosocial stressors such as structural racism, discrimination, police brutality, and segregation—which are not without their biological costs (eg, HPA-axis dysfunction, inflammation, and premature cellular aging)—ought to contribute to a disproportionately higher risk for poor mental health outcomes among Black people [40], what are the prospects for expanding access and availability of culturally competent mental healthcare, and are medical schools offering residents adequate cross-cultural training? How can there be mental health without housing when animal studies, spanning decades, have shown that an enriched environment promotes neurogenesis and dendritic branching, upregulation of growth factors (eg, BDNF) and synaptogenesis [44]? In a recent study looking to investigate the impact of income on the neurodevelopment of babies, the researchers found that cash-aid to low-income mothers increases brain activity in their babies [45]. What are the implications of this study on safety net policy reforms? How about the workforce?

In these two combined realities: risk of stress-related illness is higher for those on the lower end of the social gradient *and* resilience is a trait that arises from receiving quality support [32,38]–do we realize that significant change cannot come from within the healthcare system alone? Looking back to gross mishandling of the 2002 SARS outbreak in China and Canada, it is evident that public health infrastructure, capacity and dynamics of the State’s political structure, and its ability to address outbreaks play a significant role during an epidemic [46]. If through mass mobilization of government various countries were able to gain control of the outbreak [46], are populations that disproportionately face complex threats to brain and mental health unworthy of support from the State (in the same manner) to reach their highest health potential, or a society that implements health equity-enhancing public policies to create conditions where they can thrive–and not merely survive? This is not to ignore the critiques of policy and practice implementation related to the SDOH (eg, lack of rigorous design and evaluation of outcome, proliferation of theories, silo-thinking among stakeholders, etc.) [47]. As one of the most challenging issues facing our time, public mental health is in need of new outcome measures for knowledge implementation, systematic intervention development, and revision of procedures for accountability, as the road previously taken to address disparities in physical and mental health linked to adverse factors (ie, HPA-axis hyperactivity) that arise from one’s socioeconomic position has been one of increased individualism, downstream interventions, yielding minimal benefit for those in desperate need of services and nurturance [37,38]. Indeed, advancing population health equity is not only a shared responsibility, but also a moral imperative and ethical duty of public health to the principles of protection, prevention, and the promotion of health. In addition to the need for overt commitments and action to protect people’s lives and create equitable societies, coordination and alignment between research, policy, practice, and power is our best chance at achieving this goal.

CONCLUSION

As we have seen throughout the literature synthesized in this paper, preventing and managing long-term stress is critical to the quality and longevity of our lives. While the neuroscience of resilience has expanded our knowledge on the brain structure and mechanisms that underlie adaptability in the face of stress and adversity, gaps remain. Specific to lessons drawn from COVID-19, future studies could aim to address the connection between COVID-19 pathogenesis and brain health in populations across the social gradient to help with targeting future therapeutic treatments to populations in most need. Reports of SARS-CoV-2 entry into the brain due to blood brain barrier (BBB) vulnerability could also advance developments in clinical treatments for elderly populations living with a stress-related condition susceptible to BBB damage (eg, Alzheimer disease, etc.) [48]. As previously mentioned, an obstacle in prevention and treatment is focus on proximal factors, rather than fundamental causes which are often social, and thus, implicates the necessity for screening for social determinants of health in clinical practice to help identify patients who need more support in primary care [49,50]. Importantly, coping abilities (ie, resilience) and social support can buffer against the negative impact of psychological stressors, including COVID-19-related stressors. Alas, government investment into social prescribing (ie, the demedicalization of social needs), is a practical, effective, trackable, and measurable way for clinicians to address the social context of medical illnesses via nonmedical treatments may help with reducing psychosocial stress at the community level [50].

The single most important lesson here is that the active pursuit of reducing stress cannot be viewed simply as a matter of individual skill. Indeed, this global health crisis is a stark reminder that long-standing social and health inequities—not the sum of individual fail-

ures—are population health determinants for the disproportionate distribution of stress exposures and risk for chronic illness. Society, in general, cannot afford the cost of willful neglect by key decision-makers. Therefore, it is on the State and all other relevant actors to double down on investments in community partnered services, research, and resources for mental health, leverage wisdom in the neurosciences to advocate for and implement evidence-based interventions and policies best suited to protect the evolutionary-conserved circuits in the brain and foster a healthier future for all.

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