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Developing Comprehensive Models of the Effects of Stress and Trauma on Biology, Brain, Behavior, and Body

Erika J. Wolf, PhD^{1,2} and Paula P. Schnurr, PhD^{3,4}

¹National Center for PTSD at VA Boston Healthcare System

²Boston University School of Medicine, Department of Psychiatry

³National Center for PTSD, White River Junction, Vermont

⁴Geisel School of Medicine at Dartmouth

Nusslock and Miller (1) present an integrative model to explain the complex associations between early life adversity and subsequent development of psychopathology and physical health conditions. They suggest that neuroimmune processes take on a central bidirectional role in connecting early life adversity to later behavior, brain structure and function, and health and wellness. This is thought to occur through enhanced “crosstalk” between peripheral inflammation and cortico-amygdala, cortico-basal ganglia, and pre-frontal circuits that govern, respectively, exaggerated emotional and physiological responses to perceived threat, decreased reward sensitivity, and insufficient executive control. This model is impressive in its efforts to broadly conceptualize neuroimmune mediators of the association between early life adversity and a host of subsequent biological and psychological outcomes. Many studies have focused only on bivariate and unidirectional associations (e.g., adversity and inflammation) and/or have failed to consider the role of development and other lifespan processes in understanding how life experiences affect the brain, behavior, and the body. Yet the model also gives rise to questions about other variables and processes that may be as important, if not more, in explaining how negative life experiences “get under the skin.”

Nusslock and Miller (1) focus on the role of parental maltreatment, early deprivation, and low socioeconomic status in priming maladaptive neuroimmune responses. Some of these conditions, such as parental maltreatment and child neglect, may be severe enough to be considered a traumatic experience. This is an important distinction when considering the potential for stressor-related health effects. Only traumatic experiences are recognized as playing a causal role in the development of posttraumatic stress disorder (PTSD), a condition associated with a host of biological perturbations, including increased inflammation, autonomic reactivity, and dysregulated hypothalamic-pituitary-adrenal (HPA) axis functioning, that collectively increase risk for cardiovascular and other physical health problems through both biological and behavioral pathways (2). The fact that only a minority

Corresponding Author: Erika J. Wolf, PhD, National Center for PTSD, VA Boston Healthcare System (116B-2), 150 South Huntington Ave., Boston, MA 02130; erika.wolf@va.gov.

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of trauma-exposed individuals develop PTSD is consistent with the idea that it is the pathological response to trauma, as opposed to the trauma itself, that is most critical in understanding the pathway from adversity to poor health (2). PTSD (and potentially, other adverse psychological responses to trauma) may be a primary mediator of the association between early life trauma and subsequent health outcome (2), yet it is absent from Nusslock and Miller's (1) model.

Moreover, PTSD-related medical morbidities are not specific to those with early childhood trauma, but can be found among samples with adult trauma exposure as well (2). This raises doubt about the centrality of early life adversity in the development of later health problems. For example, in US military veterans of the wars in Iraq and Afghanistan, we recently found that combat-related PTSD was associated with metabolic syndrome, which in turn, was associated with substantial reductions in cortical thickness (3). In a distinct longitudinal study of veterans who deployed to Iraq and/or Afghanistan, we found evidence that PTSD predicted increased metabolic syndrome severity over time, and that the effects of trauma exposure on later metabolic syndrome were indirect, via PTSD (4). Thus it is possible that studies focused on the role of early life adversity in understanding negative health consequences have missed the role of adult trauma and of PTSD in promoting disease.

We prioritize the role of PTSD, over and above that of trauma and stressor exposure, because we view its symptoms as part of a stress-perpetuating intra-individual environment that exerts effects on peripheral and central biological processes and ultimately contributes to disease, especially when symptoms are chronic (5). Protracted experiences of exaggerated startle, emotional and physiological reactivity to trauma cues, anger and arousal, and poor sleep may directly promote neuroimmune, autonomic, metabolic, HPA-axis, oxidative stress, and other biological dysregulation (2,5). Over time, the cumulative burden of these symptoms and their associated physiological correlates may contribute to increased allostatic load, which broadly dysregulates homeostatic biological processes, thereby contributing to multiple types of medical morbidities (2,6). Alterations in neuroimmune functioning may be just one symptom of a more systemic process driven by increased allostatic load.

A related issue that is not addressed by the model (1) is the finding that trauma exposure and PTSD tend to be associated with premature onset of medical morbidities (4,5). Neuroimmune networks alone are not sufficient for understanding this phenomenon. PTSD-related premature physical health decline may be a reflection of an accelerated aging process wherein the chronic stress of PTSD symptoms actually influences the pace of cellular aging via epigenetic mechanisms (5,7). Specifically, recent research suggests that PTSD is associated with accelerated "DNA methylation age" (an epigenetic index of cellular age) relative to chronological age (7). Incorporation of the role of DNA methylation and other epigenetic processes into the model could also potentially address the important question of how adverse environments not only get "under the skin" but of how they cross the blood-brain barrier as well. To this end, rodent models of PTSD reveal overlap across the PTSD-associated genes that are expressed in both blood and brain tissue, with enrichment of biological pathways that are implicated in the integrity of the blood-brain barrier (8). Thus PTSD symptoms directly, or perhaps through their intermediate effects on allostatic load, could set in motion wide-spread and coordinated premature changes in age-dependent

peripheral and central biological processes via epigenetic mechanisms. As such, we think incorporating PTSD and epigenetic processes into a model of adversity and health is critical.

Life stressors, trauma, PTSD, and other adverse psychological reactions to stress and trauma, occur in the context of genetic variability. The effects of these external and intra-individual environments are likely to be moderated by individual differences in genetic susceptibility towards inflammation, sub-optimal neural structure and circuitry, poor health, and other processes that influence disease outcome, i.e., gene-environment interaction (G X E). There are many ways this could affect the hypothesized pathways in Nusslock and Miller's (1) model. For example, it could be that the association between stress and obesity is moderated by genetic risk for obesity such that, rather than being fully dependent on the adverse environment, only those with the greatest genetic loading show the association.

Genetic variation may also have pleiotropic effects that increase the risk of both psychopathology and dysregulated biological processes that would predispose individuals to poor health. In line with this, recent work suggests that a single nucleotide polymorphism (SNP) in *CRP* was associated with increased circulating levels of C-reactive protein (an inflammatory marker), and with greater risk for PTSD (9); the SNP showed the strongest association with hypervigilance (9), a fear-related PTSD symptom. Thus, the neuroimmune association with cortico-amygdala reactivity, as proposed by Nusslock and Miller (1), may have a basis in genetic variation rather than reflecting an adversity-related acquired pathway. As an additional example, we recently demonstrated that an oxidative stress gene, *ALOX12*, moderated the association between PTSD and cortical thickness in the right prefrontal cortex (10). This raises the possibility that the suboptimal performance of pre-frontal circuits that govern executive control, which in Nusslock and Miller's (1) model stems from early adversity, may instead arise from a complex interaction of biological predisposition and adverse intra-individual environmental experiences. Moreover, these genetic predispositions could be important not just for neurobiological systems gone awry but could also prime insufficient repair processes that lead to the organism's failure to return to homeostasis following an acute stressor. These are but a few of many examples from the genetics literature that collectively suggest that a model focused only on a causative role of adversity in neuroimmune mechanisms of poor health is incomplete and may risk misattributing genetic and G X E effects to the external environment.

No model can account for all of the potentially important pathways linking adversity to health outcome. The neuroimmune mediator theory put forth by Nusslock and Miller (1) represents a great step forward in developing a more comprehensive understanding of these associations. The model, with its focus on circuits, physiology, and behavior across the timeline of development, also has the potential to be studied using the National Institute of Mental Health's Research Domain Criteria (RDoC) Initiative and could thereby contribute to a bottom-up approach to understanding the adversity to health pathway. For example, the cortico-amygdala pathway in the model would lend itself well to the study of the RDoC Sustained Threat construct, the pre-frontal circuit to the cognitive control construct, and the cortico-basal ganglia circuit to the frustrative nonreward construct. However, neither RDoC nor traditional diagnostic approaches to studying this pathway are likely to prove fruitful if the role of genetic and epigenetic variation are not also incorporated into the model and if

the biological and behavioral *consequences* of psychiatric symptoms, like those of PTSD, are not considered. Inclusion of these factors is critical to understanding how adversity influences biology, brain, behavior, and body and of understanding the link between extreme stress and trauma and accelerated aging.

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