

Response to Jerome Kagan's Essay on Stress (2016)

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Abstract

To be useful, the concept of *stress* needs to be defined in biological terms linked to a broader framework of allostasis and its role in the adaptation of brain and body to positive and negative life experiences. A clear biological framework helps connect and organize animal and human research on stress. In particular, the concepts of “toxic stress” and “allostatic load and overload” highlight those experiences and situations that, as Kagan says, “compromise an organism’s health and capacity to cope with daily challenges” (p. 442). A deeper understanding is needed of the epigenetic influences throughout the life course that contribute both to these negative outcomes and to positive ones.

Keywords

epigenetics, allostasis, allostatic load/overload, life course

Addressing psychologists in particular, Jerome Kagan (2016, this issue) writes that the concepts of *stressor* and *stress* have limited theoretical and practical value when researchers use the terms both for events that produce changes in biology or behavior that do not impair “an organism’s health or capacity to cope with daily challenges” (p. 442), as well as for those that do. The excellent research review by Koolhaas and colleagues (Koolhaas et al., 2011), leaders in animal stress research, serves as an important reference point for Kagan as they propose narrowing the definition of “stressful” events to those that are unpredictable and/or uncontrollable. Whereas their review and much of Kagan’s commentary focus on animal research, we will focus largely on research with humans.

In response to the overuse of the general term *stress*, Kagan urges researchers to abandon it or limit its application “to select events that pose a serious threat to an organism’s well-being” (p. 442). He also urges psychologists to follow the example of biologists who he believes do much better at operationalizing concepts and imbedding them in context. We believe that the free-floating use of the stress concept that Kagan rightly critiques should not lead to its abandonment, but rather to its anchoring in well-specified biological and health-related behavioral responses.

To begin, we note that biologists use the concept of stress and define “the stress response” (or sometimes “the fight or flight response”) in introductory texts. This response involves acute activation of the secretion of adrenalin and cortisol in the aftermath of acute danger, as for a zebra chased by a lion. We also note that it has been the common but often undisciplined use of the stress concept that has allowed researchers in biology, neuroscience, psychology, and human development to connect their findings and begin to tease out the conditions under which stress responses occur that lead to impairment of an organism’s health or capacity to adapt.

The crucial distinctions among “good stress,” “tolerable stress,” and “toxic stress” (<http://developingchild.harvard.edu/activities/council/>) differentiate among the varied stress responses that are otherwise undifferentiated in the global use of the concept. “Good” stress involves the efficient, acute activation and efficient turning off of the normal physiological stress response when one faces a challenge, like giving a talk, that generally has a positive outcome. “Tolerable” stress involves the more chronic

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activation of the same physiological stress responses in the face of a major life event, like loss of a job, that is eventually turned off by an individual who has good internal stability and self-esteem and material and social support systems. “Toxic” stress also involves the chronic activation of the same physiological stress responses in the face of a major life events or the accumulation of many chronic stressors. In toxic stress, however, the stress response continues without being turned off. Thus, the physiological reaction to life events, from tolerable to toxic stress, falls on a gradient related to the individual’s ability or inability to cope, which is shaped by internal resources (e.g., self-esteem, self-regulation) and external social and material supports. An accumulation of adverse childhood experiences in the absence of strong adult supports, for example, increases the likelihood of experiencing toxic stress with resultant harm to early brain development, mental health, and adult health (Shonkoff, Boyce, & McEwen, 2009). Thus the concept of toxic stress emphasizes those experiences and situations that Kagan believes should be the focus of the stress concept.

The biological responses accompanying acute stress go away, as Kagan notes, and have no apparent long or short-term ill effects on the organism, at least on the surface. However, patterns of gene expression in the brain are continually changing as a result of acute as well as chronic stress (Gray, Rubin, Hunter, & McEwen, 2014; McEwen, Bowles, et al., 2015a). Indeed, these responses of cortisol and other mediators are needed to promote adaptation and survival since the mediators like cortisol are also important for coordinating sleep–waking–feeding cycles (McEwen, Sakai, & Spencer, 1993), facilitating synapse formation and turnover (Liston et al., 2013), and promoting adaptive immune function (Dhabhar, Malarkey, Neri, & McEwen, 2012). Without adrenal glands, animals do not survive very well!

The concepts of *allostasis* and *allostatic load* broaden the focus from “fight or flight” responses to a broader set of biological responses to continuing or extreme stressful conditions (McEwen & Lasley, 2002). Allostasis involves “maintaining stability through change”: It is a fundamental process through which an organism actively adjusts to both predictable and novel experiences. Allostatic load and overload refers to the cumulative cost to the body of allostasis, with allostatic overload being a state in which serious pathophysiology can occur in the brain as well as the body, as in toxic stress (McEwen & Wingfield, 2003).

These concepts, as Koolhaas et al. (2011) note, point to the importance of combining a series of biological measures to provide more reliable and consistent indicators of the harmful consequences of toxic stress for bodies and brains. The challenge is to operationalize “stress as allostatic load” effectively since we know, as Kagan reminds us, that single indicators such as cortisol release

do not capture the complex phenomena with which we should be most concerned. Cortisol and adrenalin are the most commonly recognized mediators of the stress response. Yet they do not work alone. Rather, they work with other mediators from the immune and metabolic system and neurotransmitters, as well as with neuromodulators of the nervous system. Efforts are underway to develop multidimensional measures of allostatic load (Seeman, Epel, Gruenewald, Karlamangla, & McEwen, 2010). These will go a long way toward specifying the biological indicators of toxic stress.

This nonlinear “network of allostasis” involving these interacting mediators promotes adaptation when it is turned on and off efficiently, as in “good” stress. Overactivity of the same mediators and imbalances within the network (e.g., too much or too little cortisol or inflammation) promotes allostatic load and overload with consequent wear and tear on the body. This wear and tear is consequential. For example, adverse childhood experiences such as sexual and physical abuse along with other events in the family and living environment increase the lifelong frequency of mental and physical health problems and allostatic load (Anda, Butchart, Felitti, & Brown, 2010). Such experiences also increase vulnerability to acute traumatic experiences that can cause posttraumatic stress disorder (De Bellis, Spratt, & Hooper, 2011) with changes in brain circuitry and physiology and increase in cardiovascular disease and diabetes (Jordan et al., 2013; Miller-Archie et al., 2014; O’Donovan et al., 2015; Schelling, Roozendaal, & De Quervain, 2004). Circadian disruption, as in shift work and jet lag, as well as chronic sleep deprivation, impair cognitive flexibility, and memory promotes metabolic syndrome and body weight gain and impairs resilience to experiences of daily life (Karatsoreos & McEwen, 2014). Sustained poverty in early childhood increases the likelihood of weak self-regulatory skills with important implications for school performance and measurable impairment of brain development (Farah et al., 2006; Hanson et al., 2013).

Animal model research has led to imaging studies of the human brain that show changes in stress-related conditions and their alleviation that are consistent with findings in the animal models (Sheline, 2003). For example, chronic anxiety and major depression are associated with overactivity of the amygdala and shrinkage of the hippocampus and prefrontal cortex (McEwen & Gianaros, 2011), whereas regular physical activity enlarges the hippocampus and improves memory and mood (Erickson et al., 2011). Furthermore, there is often comorbidity with systemic illnesses such as cardiovascular diseases and metabolic syndrome (Bizik et al., 2013; McEwen, Gray, & Nasca, 2015b).

Kagan and Koolhaas and colleagues call for greater precision in characterizing both “stressful events” and the

internal and social contexts that shape how they are experienced. Kagan turns our attention, for example, to lack of clarity about which individual stressors matter for harmful biological effects and which do not. This observation raises, in part, the question of duration of effect of stressors. It turns out that the appearance of temporariness and reversibility are misleading if temporary effects are assumed to have no lasting effect. As noted, experiences of all kinds continually change the brain and body from conception throughout the life course (Gray et al., 2014; Halfon, Larson, Lu, Tullis, & Russ, 2014) via epigenetic mechanisms operating through the multiple biological mediators of allostasis. These mediators also feed back on the brain to affect its architecture and function, but the changes are never truly reversible since gene expression continually changes (Gray et al., 2014) and apparent "recovery" of brain architecture involves changing the architecture of the recovered neurons (Goldwater et al., 2009), even though there is recovery of function. With modified gene expression, the brain is poised to respond in different ways, since it stores memories of life experiences (McEwen, Bowles, et al., 2015a). These alter how the individual responds to later events—sometimes adaptively and sometimes not. Thus, research looking only at short-term effects of stressors may miss the cumulative toll that they produce.

Indeed, we must also be particularly attentive to the cumulative character of stressors. Although single stressors may produce little clear effect, they can affect body and brain development when combined with others (Evans, Gonnella, Marcynyszyn, Gentile, & Salpekar, 2005; Kim et al., 2013). Thus, all potential stressors may matter if they accumulate in varying ways and impact brain and body development and produce still poorly understood epigenetic changes. Research about individual stressors may miss their impact when combined with others. Thus, Kagan is certainly right—it is important to specify clearly what those stressors are and how they accumulate as well as the contexts in which they do.

Nowhere is Kagan's emphasis on specifying conditions and context for examining stress more important than in research about early childhood adversity. The important Adverse Childhood Experiences (ACE) study identified 10 stressors (e.g., physical and psychological neglect, sexual and physical abuse) that, as they accumulate, have powerful and lasting influences, correlating with poor physical and mental health throughout the life course (Anda et al., 2010). Other research correlates extended early childhood poverty and living in high poverty neighborhoods with similar effects as a result of allostatic load that extend to brain structure and function (Gianaros, Marsland, Sheu, Erickson, & Verstynen, 2013; Hanson et al., 2013). Future research, ideally in collaboration with sociologists and social psychologists, can do much to map out the

conditions, relationships, and behaviors that produce toxic stress and protect against it. Biology matters too, of course, because we know that genetic variation and epigenetic influences make some children more and others less vulnerable to accumulating stressors (Obradovic, Bush, Stamperdahl, Adler, & Boyce, 2010).

Future research also has to take account of the internal states of individuals as well as their circumstances or context. Indeed, Kagan reminds us that humans think and that their response to stressors may be different from those of other organisms as a result. In the study of stress responses in humans, for example, increasing attention has focused on "resilience" as a "quality" that can prevent adversities from increasing allostatic load with varied negative consequences for brain, body health, and behavior. But what is resilience? It cannot be understood primarily as an internal state but rather must be viewed as resulting from "a dynamic interaction between internal predispositions and external experiences" and social support systems that help produce a positive outcome in the face of adversity (National Scientific Council on the Developing Child, 2014). For example, we know that strong and consistent support of a child by a caregiver or other adult protects against toxic stress and helps build internal skills such as self-regulation that allow the individual to achieve positive outcome in the face of significant adversities.

In summary, we believe that the concept of *stress*, when biologically specified in the broader framework of positive and negative life experiences and resulting health behaviors, and the concept of *allostasis* both serve as a useful way of organizing and connecting animal and human research. Moreover, the concepts of "toxic stress" and "allostatic load and overload" highlight those experiences and situations that, as Kagan says, "compromise an organism's health and capacity to cope with daily challenges" (p. 442). We need to deepen our understanding, however, of the interplay between social supports and internal psychological and biological states and their manifestations in brain and body—including epigenetic influences—as well as sharpen our examination of the social conditions and behaviors and their contexts that lead to allostatic load and its negative consequences.

Declaration of Conflicting Interests

The authors declared that they had no conflicts of interest with respect to their authorship or the publication of this article.

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