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Bringing a Neurobiological Perspective to Resilience

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Introduction

The concept of resilience has become remarkably popular in recent years, across a range of academic fields and within the media. This popularity stems, in part, from a culture shift toward wanting to focus on positive outcomes. Understanding within the psychological and social sciences has been based largely upon the rich conceptualization and articulation of leaders such as Ann Masten (2015; Masten & Barnes, 2018; Masten, Best, & Garmezy, 1990) and Michael Rutter (1987, 2012), and more recently, Michael Ungar (2006, 2015). In this chapter, we leverage those expert frameworks and describe their application to children's mental and physical health outcomes, with a predominant focus on describing the growing literature on *neurobiological* indicators of risk, protection, and resilience across early development.

Brief Introduction to Resilience

Our review of neurobiological resilience must be couched in the larger framework of resilience theory and research, briefly reviewed here. Although definitions vary, many social scientists agree that resilience can be defined as the capacity of a dynamic system to withstand or recover from significant disturbances that threaten its adaptive function, viability, or development (Masten, 2014). Key to this definition within our fields is that a challenging or threatening disturbance must occur, which can be an acute or chronic adversity or an accumulation of risk factors that becomes threatening. Others have emphasized that when explicitly considering a child's capacity to resist the effects of adverse exposures, one must evaluate the capacity of that child's formal and informal social ecological networks to facilitate

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positive development after stress; importantly, individuals and their environments interact to optimize development and individuals' capacity, within the constraints of opportunities and resources in their communities (Ungar, 2011). These definitions and conditions highlight the role of micro- and macrolevel factors in culture and society, in addition to individual agency, in different constellations that contribute to the chances for resilience (Ungar, 2013).

After an individual experiences adversity, a range of potential patterns of outcomes reflecting resilience can occur. First, one may experience a major adversity without any change in functioning, which would be considered "buffered" from the adversity. High-visibility studies of adverse childhood experiences (ACEs) have focused on how many individuals experience trauma and the negative outcomes that ensue (Hughes et al., 2017). However, a significant proportion (sometimes even the majority) of children who experienced trauma are without the poor outcomes examined, suggesting resilience to the experience of ACEs, at least in the measured domains. Second, one may have an initial decline in functioning or increase in problems, but a later return to pre-adversity levels; such a recovery response suggests the individual became resilient to the adversity after some time. Importantly, resilience may not just be the absence of a "bad" outcome in the context of adversity, but can also be reflected in the presence of "good" outcomes, such as positive health and well-being. Thus, third, one may also demonstrate increased positive outcomes or higher-than-previous functioning after an adversity either as an immediate response to the threat or after time, often referred to as "posttraumatic growth."

Resilience is not a trait—it is dynamic, arising from the interaction of many systems across many levels (Gottlieb & Halpern, 2002; Waddington, 1966) and the capacity for adaptation to adversity is distributed across systems. Within a system, main effects of factors that are risks, assets, and promoters can accumulate in a summative fashion to influence a child's developmental outcome. However, in the remarkable symphony of human social processes, interactions can matter more than main effects. Social or biological factors within a system can enhance vulnerability to the effects of adversity or confer protection, moderating the effects of exposure. In line with this chapter's focus on biological factors, we emphasize biological moderators. For example, biological sensitivity to context (BSC; Boyce, 2015; Bush & Boyce, 2016; Ellis, Boyce, Belsky, Bakermans-Kranenburg, & van Ijzendoorn, 2011) and differential susceptibility (DS; Belsky & Pluess, 2009, 2013; also see Popham, McEwen, & Pluess, 2020) theories articulate how individual differences in stress-relevant biology can make children more or less sensitive to both positive and negative influences in the environment, with "more sensitive" children demonstrating the worst outcomes in contexts of adversity but the best outcomes in advantaged environments. In contrast, "less sensitive" children are more likely to be buffered from adversity and demonstrate greater resilience, but they also do not demonstrate advantage in more optimal contexts. Empirical tests of BSC and DS have demonstrated that such sensitivity to context can be reflected in a variety of physiological systems and genomic markers. We provide highlights of this influential work later in the chapter. Importantly, even though this BSC or DS framework can imply a trait-like susceptibility to environment, each circumstance of sensitivity is system and environmentally dependent, will vary by outcome considered, and thus does not reflect a cross-situation or system trait of biological resilience.

How Resilience Can Be Understood Systemically

Advances in the study of childhood resilience are not the product of a single discipline. Rather, formative resilience research has spanned fields of genetics, biology, and neuroscience as well as psychology, sociology, and public health. Moreover, it is arguably not simply the additive products of various disciplines, but the *interdisciplinary* collaborations across fields that have yielded the greatest progress in understanding the factors that promote and sustain processes of resilience early in life.

The perspective of childhood resilience as a multisystemic construct has its theoretical roots in broader frameworks that have recognized the interactive influences of multiple contexts on human development. One of the most highly regarded and well-referenced of these frameworks is Bronfenbrenner's bioecological model of human development, which describes how systems ranging from the individual and the microsystem (e.g., family, peers, school) to the macrosystem (e.g., social attitudes and ideologies) guide human development (see Figure 2.1). Bronfenbrenner posited that human development occurs not through the independent activities within these subsystems, but through "complex reciprocal interactions between an active, evolving biopsychological human organisms and the persons, objects, and symbols in its immediate external environment" (Bronfenbrenner & Morris, 1998, p. 996; Masten & Monn, 2015). Guided by this framework, research has provided evidence of how such interactive effects may operate to promote children's resilience. In several empirical examinations of a diverse community sample of kindergarten children (the Peers and Wellness Study), multilevel variables have emerged as powerful protective factors for children reared under conditions of risk. For example, children were buffered from the negative physical health consequences of low family socioeconomic status (SES) by higher quality, more resourced neighborhoods (Roubinov, Hagan, Boyce, Adler, & Bush, 2018) and lower levels of negativity in the parent–child relationship (Hagan, Roubinov, Adler, Boyce, & Bush, 2016). Across the sample, offspring exposed to harsh parenting were more likely to exhibit hostile, aggressive behavior; however, risk was reduced if children had warmer, more positive relationships with their peers and teachers (Roubinov, Boyce, & Bush, 2018). In these examples, the poor physical or health outcomes that would be expected on the basis of early family adversity were significantly diminished by processes originating within another developmental context (e.g., neighborhood, school, peer).

As illustrated by the aforementioned examples, resilience research has mainly focused on the contribution of psychosocial and environmental factors, with limited attention to the potential role of intraindividual biological factors (Curtis & Cicchetti, 2003), perhaps owing to the once prevalent, but largely superficial distinction between biological and psychological domains (Cicchetti & Rogosch, 2009). An abundance of literature has documented for decades how varied biological factors interact with environmental exposures to elevate the risk for psychopathology (Shonkoff, Boyce, & McEwen, 2009); a logical extension of such work would suggest that the pathways to resilient functioning are similarly multiply influenced by the dynamic activity of biological and environmental systems across many levels of analysis. Yet, it is only in recent years that research has adopted a more integrative perspective in which physiological and neurobiological systems (and their interactions with each other

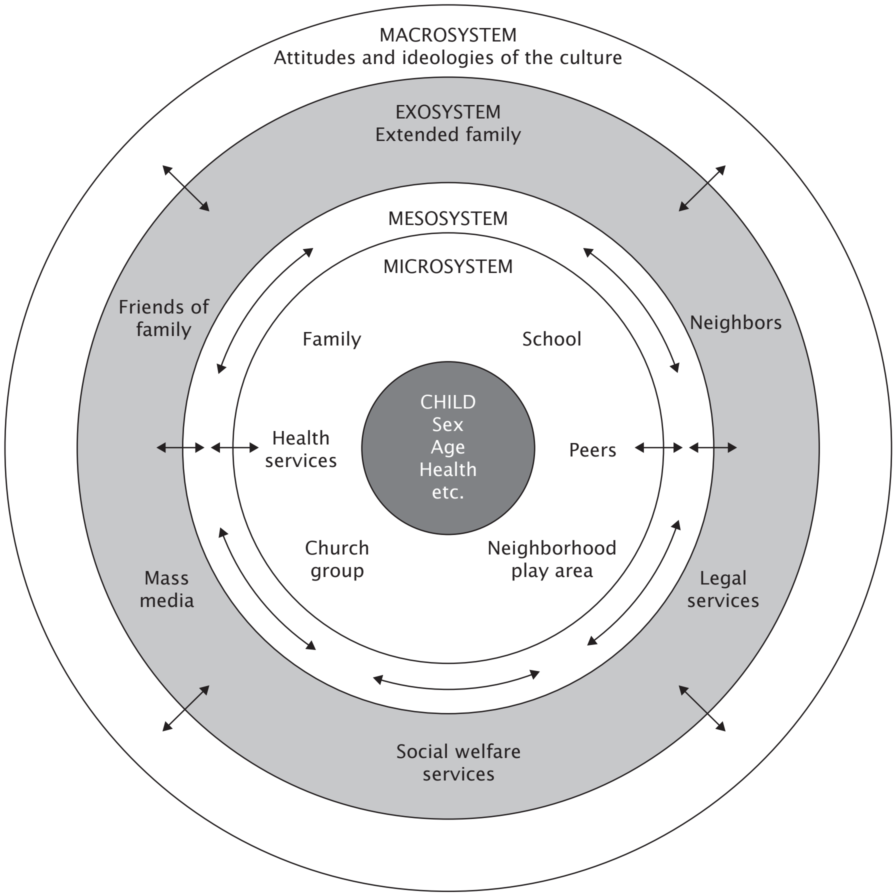

FIGURE 2.1 Bronfenbrenner's bioecological model. From sociocultural risk: Dangers to competence, by J. Garbarino. In C. B. Kopp & J. B. Krakow (Eds.), *The child: Development in a social context* (pp. 630–685). Copyright © 1982 by Addison-Wesley Longman Publishing Company, Inc. Reprinted with permission.

and the environment) are viewed as integral to processes of psychological resilience. Notably, indicators of biological functioning may be viewed as not only predictors or promoters of resilient processes, but reflections of resilient functioning.

There are several potential advantages of examining biological indicators of risk and resilience. Self- or proxy reports of symptoms and functioning are heavily influenced by the reporter's awareness, biases, and social desirability, whereas physiology is more precisely quantified in a standardized manner across individuals, regions, and cultures. Another advantage is that a focus on physiological changes and their recovery allows neutrality regarding whether resilience is achieved via automatic, unconscious processes or intentional, conscious efforts of the individual, which can provide opportunities for tracking markers of resilience that are agnostic to theoretical or political goals. Evidence of the biological impact of adversity can minimize perceptions of psychological weakness and victim blaming, and policymakers may be motivated to promote biological resilience for its potential to improve healthcare costs and economic opportunities at a population level. Certain biological outcomes may be considered intermediary variables that predict longer term physical and psychological health, thus it is possible to consider neural, physiological, and other biological factors as indicative of the degree to which resilient processes are occurring. In this manner, biomarkers of risk and resilience can be "canaries in the coalmine" or, more positively, migrating birds whose return predicts the coming spring, allowing communities to intervene early to prevent trajectories of decline and poor health and create the conditions for positive development as children age.

Brief Overview of Stress-Relevant Neurobiological Systems and their Indicators

Although a comprehensive review is outside the scope of the current chapter, we briefly describe the primary biological systems that are involved in stress responsivity (and by extension, resilience). The autonomic nervous system (ANS) is comprised of two branches: the parasympathetic nervous system (PNS), which is conventionally described in terms of its role in reducing arousal and promoting restoration ("rest and digest") and the sympathetic nervous system (SNS), which is known for its capacity to mobilize the body to respond to stress through physiological activation ("flight or fight"; Gunnar & Vazquez, 2006; Lovallo & Sollers, 2007). Individuals' reactivity (change from baseline) and recovery (time it takes to return to baseline levels) within their ANS can be assessed in response to standardized challenges by attaching noninvasive electrodes that measure indices of activation at rest, during the stressors, and after the stressor has ended (for video example, see Bush, Caron, Blackburn, & Alkon, 2016). Compared to the faster acting PNS and SNS, the hypothalamic–pituitary–adrenal (HPA) axis enacts a more delayed, longer-term response to stress through a cascade of hormonal processes that culminates in the release of cortisol (Del Giudice, Ellis, & Shirtcliff, 2011). Key functions of cortisol include mobilizing energy, enhancing alertness, facilitating memory formation, and deploying the physiological resources needed to adequately respond to stress (Sapolsky, Romero, & Munck, 2000). Cortisol can be assessed in circulating blood or, less invasively, in saliva samples collected before and after stressors (Gunnar, Talge, & Herrera, 2009). More recently, cortisol levels in hair have been used to reflect HPA axis activity over the three months prior to hair collection, allowing for indication of more chronic levels of activation or blunting/suppression (Gray et al., 2018).

In addition to well-studied effects of adversity and resilience with the PNS, SNS, and HPA axis, increasingly evidence is pointing to the utility of other biomarkers, including indicators of immune functioning (Dantzer, Cohen, Russo, & Dinan, 2018; Segerstrom & Miller, 2004), cellular aging (Shalev et al., 2013), epigenetic modifications to DNA that can alter gene activity (Boyce & Kobor, 2015; Choi, Stein, Dunn, Koenen, & Smoller, 2019; Provençal & Binder, 2015; Romens, McDonald, Svaren, & Pollak, 2015), and brain structure and activity (Bick & Nelson, 2016; Carnevali, Koenig, Sgoifo, & Ottaviani, 2018; Miller et al., 2018). Interested readers are referred to various reviews for a deeper discussion on the myriad of biological systems involved in the neurobiology of resilience to stress (e.g., Charney, 2004; Osório, Probert, Jones, Young, & Robbins, 2017) and to more lay-accessible reviews such as those in social work (Hunter, Gray, & McEwen, 2018). A recent review in the adult psychiatry literature (Walker, Pfingst, Carnevali, Sgoifo, & Nalivaiko, 2017) suggests that immune system responses to laboratory challenges (e.g., cytokines) and lab-based in vitro immune cell assay are some of the most promising resilience biomarker candidates, yet both require blood draws and complex laboratory efforts, which may inhibit their realistic use in samples of young children, low-income communities, or developing countries. However, this is shifting as the science advances, alternative collection methods are developed, and cultural uptake around the value of biology increases. One example of this is reflected by the increasing use of biomarkers by anthropologists, such as using dried blood spots for population-based research, even in remote, undeveloped regions (McDade, Williams, & Snodgrass, 2007).

Although stress response systems are often studied in isolation of each other, the well-supported concept of *allostasis* describes how multiple biological systems work together in a complex, integrated manner to promote the body's adaptation to threat or challenge (McEwen, 2007). Allostasis functions to achieve stability through change and is an essential, life-supporting process that underlies physiological homeostasis. Allostasis can be achieved quickly, via automatic processes, or more slowly through intentional adaptations, such as cognitive reappraisal or meditation after a stressor—both types of responses promote resilience in the face of challenge to achieve allostasis. However, exposure to repeated or chronic stressors may lead to a state of dysregulated physiological responses termed *allostatic load* that is associated with elevated risk for disease and poor health across the lifespan (McEwen, 2017; McEwen & Wingfield, 2010).

Evidence for the Role of Neurobiology in Resilience Processes

A limited, but growing body of research has incorporated biological measures into multilevel analyses of resilience. We highlight exemplars of such research in the following section, although we recognize that several may fall short of the most optimal representations of resilience, given the scarcity of research in this area.

Family

Attachment relationships are likely the most primary source of neurobiological resilience for young children, as development regulatory systems are dependent on the primary caregiver (Bowlby, 1988; Thompson, Kiff, & McLaughlin, 2018) and stress-buffering social influences reside most proximally within the family and childcare context (Hostinar & Gunnar, 2015). A large body of animal research has established the remarkable causal effects of higher quality parenting practices on offspring biological, behavioral, and emotional outcomes (Meaney, 2001) and the manner in which postnatal care can buffer offspring from risk (Fish et al., 2004). Although ethics prohibit experimental manipulation of parenting and care provision, well-designed observational studies in humans also demonstrate that parenting behaviors can promote child resilience. For example, more sensitive and responsive parenting buffers infants from the effects of prenatal stress (Conradt & Ablow, 2010), with effects that may persist to ameliorate the effects of childhood adversity on a range of adult health outcomes (Farrell, Simpson, Carlson, Englund, & Sung, 2017). Parent–child attachment has also been found to associate with epigenetic profiles of late adolescents within genes related to stress reactivity (Jones-Mason, Allen, Bush, & Hamilton, 2016). As another example, kindergarten children with better parental relationships were protected from the negative effects of socioeconomic adversity on their physical health (Hagan et al., 2016). Although research of the potential protective effects of high-quality parental relationships predominantly focuses on mothers, emerging work highlights the importance of studying the father role. In a sample of low-income, Mexican origin families, infants with higher PNS activity at rest exhibited more behavior problems at two years of age in the context of lower father engagement. However, behavior problems did not vary by infant resting PNS levels among those exposed to higher levels of father engagement (Luecken, Somers, & Roubinov, 2020). Current societal shifts toward increasing paternal time in childcare activities (Hofferth & Lee, 2015) obligate future research to explore dynamic interactions between fathering and children's biological functioning in the prediction of developmental outcomes.

Temperament/Personality

Individual differences in temperament, biologically based behavioral, and emotional differences in reactivity and regulation that are present at birth but shaped over time (Rothbart, Ahadi, & Evans, 2000), have been shown to meaningfully alter trajectories of risk and resilience for child outcomes. For example, children higher in self-regulation are less likely to demonstrate disruptive behaviors and emotional dysregulation in the context of family adversity (Lengua, Bush, Long, Kovacs, & Trancik, 2008) and less likely to report symptoms of depression and anxiety in the presence of negative parenting (Kiff, Lengua, & Bush, 2011). Children high in negative emotionality (e.g., fearfulness, difficult temperament) are prone to depression or anxiety and demonstrate elevated biological risk factors (Goldsmith & Lemery, 2000); however, as a striking example of the need to consider all individual differences in context and system, such children are also less likely to engage in antisocial activities and display conduct disorder (Nigg, 2006), even when raised in families/neighborhoods with many risk factors. This contrasting pattern of findings reveals how one individual factor might be considered a "resilience trait" but is highly situation-dependent.

Physiology

Physiological reactivity demonstrates risk and protective effects that parallel temperament. For example, children who show lower ANS or HPA axis reactivity to standardized stress-evoking challenges are often buffered from risk and show protection from the effects of family adversity or low SES on physical health, socioemotional behavior, and school readiness, whereas their more reactive counterparts demonstrate worse outcomes in those adverse contexts (Conradt, Measelle, & Ablow, 2013; Hagan et al., 2016; Obradovic, Bush, Stamperdahl, Adler, & Boyce, 2010; Rudolph, Troop-Gordon, & Granger, 2011). Although physiology may interact with environmental contexts to exacerbate or buffer risk, it may also be the case that physiological factors are the product of dynamic factors across multiple resilience-related systems. As an example of such cross-system resilience, research has observed that "risky child temperaments" in kindergarten (high negative affect, overcontrolled) were associated with elevated levels of children's daily cortisol, but children within classrooms where teachers provided high levels of motivational support were buffered from this potentially harmful association between temperament and stress physiology (Roubinov, Hagan, Boyce, Essex, & Bush, 2017).

Brain Structure and Function

As brain imaging techniques become more accessible and understanding of brain structure and function relevant to the study of resilience advances, evidence points to the growing value of examining resilience within the brain. The capacity for social support to buffer children from the effects of adversity increasingly appears to operate through neural substrates associated with effective self-regulation (Hostinar & Gunnar, 2015). Miller et al. (2018) recently found that urban adolescents who displayed greater brain connectivity (assessed by functional magnetic resonance imaging) within an area of the brain that facilitates self-control, reinterpretation of threatening events, and suppression of unwanted emotional imagery were protected from the harmful cardiometabolic effects of living in high-violence neighborhoods. These findings suggest functional connectivity in specific brain regions may be a neurobiological contributor to resilience. In a compelling study of high-neglect conditions within Romanian orphanages, children were randomized to either high-quality foster care or continued care in the institution. At age eight, children in the early intervention condition demonstrated more normative brain development (white matter microstructure), showing resilience to the effects of early deprivation on their brains' structural development (Bick et al., 2015).

Genetics

Individual differences in genetic make-up have also been shown to promote resilience for children. One of the most robust associations in the health disparities literature is that children of low SES are at increased risk, in a linear fashion, for being overweight or obese. Among children with a specific genotype related to oxytocin hormone regulation however, there was no relation between SES and body mass index, revealing likely metabolic and behavioral-emotional genomic pathways for protection from that risk (Bush, Adler, & Boyce, 2011). Genetic differences have also been shown to buffer adolescents from the effects of unsupportive parenting on their self-regulatory abilities (Belsky & Beaver, 2011). An increasing wealth of evidence shows that children's variation in specific genes, such as those regulating dopamine and serotonin, can enhance their sensitivity to intervention and promote resilient outcomes (Belsky & van Ijzendoorn, 2015). For example, behavioral benefit for Romanian orphans who were randomized to the foster care condition described earlier appears to differ depending upon children's genetic sensitivity, promoting greater resilience in some children (Drury et al., 2012). In another example, adolescents' cumulative counts of specific "sensitivity" genetic variants (polygenic scores) predicted who would benefit most from a smoking prevention and cessative intervention (Musci et al., 2015). The lure of genomics for explanations about who may be buffered most from adversity or benefit most from interventions is strong, yet issues around placing emphasis on this immutable individual difference factor are controversial (Belsky & van Ijzendoorn, 2015), and this work should be considered with caution as genetics are one of myriad factors influencing systemic resilience.

Across all these systems, or layers of context or process, it is important to note that none can be considered in isolation. A child lacking protective factors in her HPA axis functioning may have resilience-promoting differences in her ANS response to stress, nutritional advantages that influence the expression of her genes related to stress regulation, or an exceptionally supportive classroom environment that offsets her risk for neurobiological deficits and subsequent mental and physical health risks related to chronic adversity. We have attempted to highlight various layers of a child's internal biology that might be affected by adversity or protective/promotive against risk, yet it is typically only examined at one cross-section of the complex system within and external to the child. Emerging multisystem physiology models hold promise for advancing understanding in this realm (see, e.g., Roubinov, Boyce, Lee, & Bush, 2020).

Issues of Developmental Timing and Domain

Beyond the examination of various layers and systems, it is critical to consider the additional influence of time. First, timing in development affects a child's sensitivity to the influence of adversity or factors promoting neurobiological resilience (Hunter et al., 2018; Masten & Barnes, 2018). Data from the intervention with Romanian orphans highlight how critical earlier timing of adoption placement was for children to demonstrate beneficial effects on their biology and behavioral and cognitive functioning (Almas et al., 2012; Bick et al., 2015; Nelson et al., 2007). A second key factor is that development involves the progressive changing and growth of systems, with processes at one time point having cascading effects and influences on trajectories of later functioning and well-being. There has been a tendency in the resilience literature to overinterpret findings at one period of development (and in one system). Given the considerable variation in trajectories of development, and the ever-changing social/environmental exposures with which a child interacts as he or she matures, it is critical to consider development and timing as co-dependent dimensions of resilience. Factors might promote resilience in the short term, but have long-term trade-offs that are maladaptive for other, later outcomes—for example, the body's physiological adaptation to stress in the short term that leads to allostatic load later is one version of this (McEwen, 2007). Another example comes from work showing children with high cortisol and blood pressure exhibited lower concurrent internalizing symptoms than peers; however, the same physiological pattern was associated with greater symptomatology two years later (Hastings et al., 2011). In a third manner, there are specific windows of risk or opportunity across development, or sensitive periods when plasticity is surging, when conditions converge for change, and when systems are in flux or unstable (Shonkoff et al., 2009). In light of these issues, the understanding and promotion of biological resilience requires addressing unique needs by developmental period. A small body of evidence informs this area. For example, prenatal stress effects on offspring physiology may be best mitigated by social support for mothers (Racine et al., 2018; also see Chapter 3 of this volume on perinatal mental health) or early postnatal sensitive parenting (Conradt & Ablow, 2010; Ham & Tronick, 2006). Concerns during early to middle childhood may benefit from a focus on peer support (Roubinov, Boyce, et al., 2018) and promotive classroom environments (Roubinov et al., 2017), whereas promotion of resilience to trauma in adolescence requires developmentally-sensitive approaches that incorporate adolescents needs for confidentiality and emerging independence (Soleimanpour, Geierstanger, & Brindis, 2017). More longitudinal research is needed for a richer understanding of the role of developmental timing in biological resilience.

It is also critical for readers to understand that factors promoting resilience in one domain (e.g., psychological) may not promote resilience in another/all other domain/s (e.g., physiological). This is one reason to carefully consider biomarkers of resilience. A key illustration of this is the idea of "skin-deep resilience." Brody et al. (2013) found that rural Black youth from high-cumulative-risk backgrounds who showed positive psychosocial functioning at 19 also displayed higher "allostatic load," the multisystem biological "wear and tear" described earlier. This group later found that, although certain Black individuals from disadvantaged backgrounds showed successful psychosocial functioning in terms of educational attainment, symptoms of depression, and quality of relationships, they were more likely to contract infectious illness in an experimental exposure paradigm, revealing a "double-edged sword" to their apparent resilience (Miller, Cohen, Janicki-Deverts, Brody, & Chen, 2016). They also found that Black and White high-striving adolescents were more likely to report positive psychosocial outcomes at age 29 than their lower-striving counterparts; however, among those identified as high-strivers, Black adolescents from disadvantaged backgrounds had greater risk for physical health problems in adulthood than Black adolescents from lower-risk backgrounds (Brody, Yu, Miller, & Chen, 2016). This is in line with the long-standing weathering hypothesis (Geronimus, 1992), which argues that Black Americans exposed to high rates of chronic stress, such as that related to racism, must engage in sustained high-effort coping, which although protective in the short run, increases wear and tear on physiological systems. A key examination from this perspective demonstrated that in the American context, the health biomarker profile of accomplished Blacks was worse than for Whites or less-accomplished Blacks, particularly for females, providing evidence for disparities in chronic disease risk that were dependent upon outcome and which biological system was examined (Geronimus, Hicken, Keene, & Bound, 2006). Evidence that resilience in psychosocial outcomes does not necessarily extend to skin-deep resilience is a core finding supporting the value of examining biology in those who have experienced significant adversity, particularly early in life.

Biological Resilience in a Culturally Sensitive Framework

Social and cultural values assume a key role in Bronfenbrenner's bioecological model and are represented by the most encompassing layer of nested environmental influences on child development. More recently, Ungar's work has articulated the manner in which culture is core to defining and promoting resilience (e.g., Ungar, 2013). Others provide a comprehensive introduction to the newly emerging field of "cultural neurobiology," with a specific focus on psychophysiological stress systems (Doane, Sladek, & Adam, 2018). Here, we introduce select examples of culturally salient resilience processes in biological markers.

Empirical studies have identified values unique to particular communities that may operate to promote resilience processes. For example, familism is conceptualized as one of the defining Latino cultural values, representing a strong identification with and attachment to immediate and extended family (Sabogal et al., 1987). Familism values may operate in a protective fashion by espousing the provision of economic and emotional support to family members and a sense of loyalty and respect within family relations (Germán, Gonzales, & Dumka, 2008). Illustratively, bicultural adolescents who endorse high orientation to both Anglo and Mexican orientation have been shown to exhibit a stronger, more adaptive cortisol response to a laboratory stressor compared to adolescents who endorsed high levels of Anglo orientation only (Gonzales et al., 2018). Similar values emphasize the primacy of family/social ties that exist in other cultural contexts (e.g., communalism among African Americans and filial piety among Asian Americans) and may also operate to buffer minority individuals from the negative consequences of physiological stress response systems that are chronically activated by discriminatory practices, racism, neighborhood violence, and other daily stressors disproportionally experienced by individuals of nonmajority culture groups (Doane et al., 2018).

In addition to defining unique factors that promote resilience within a particular community, social and cultural values may *redefine* a particular construct as contributing to resilience in a given environment when it may otherwise operate in a risk-promoting fashion. For example, greater levels of restrictive, controlling parenting have been positively associated with early behavior problems among White offspring; however, this relation has been negative or nonsignificant among African American children (Deater-Decker & Dodge, 1997). More restrictive parenting has also been associated with fewer upper respiratory and febrile illnesses among minority, but not White children (Roubinov, Bush, Adler, & Boyce, 2018). Differences in children's appraisal of such parental behaviors and what is considered normative or functional within varied sociocultural contexts may help explain the mechanisms underlying these cultural differences (Soenens, Vansteenkiste, & Van Petegem, 2015).

Finally, the long reach of the cultural context may extend to influence the very way in which purported resilience-promoting factors relate to health outcomes within different communities. As previously discussed, a growing body of research finds evidence of skin-deep resilience among at-risk African American youth who were followed longitudinally from childhood through adulthood (Brody et al., 2016; Miller, Yu, Chen, & Brody, 2015). These studies observed that factors traditionally conceptualized as promoting resilience (e.g., high educational aspirations, persistence, optimism) were associated with poorer physiological and physical health despite more adaptive psychosocial health, perhaps due to the unique features of the cultural context. More specifically, it was hypothesized that maintaining positive *outward* functioning amid the systematic adversities associated with poverty and racial inequities may have exacted an *internal* toll on physiological functioning, possibly via excessive activation of stress response systems (Brody et al., 2013). This interpretive framework is also informed by John Henryism, a construct named for an African

American railroad worker of that name who exerted remarkable physical strength to beat a mechanical drill, only to die soon after from mental and physical exhaustion (James, Hartnett, & Kalsbeek, 1983).

Intervention/Reversibility

The dynamic and rapidly changing nature of early developmental periods may make it difficult to use sharply defined diagnostic classifications of psychopathology to assess and identify children in need of intervention (Boyce et al., 1995), and stress-related diseases do not typically manifest in childhood, although their initial roots may be laid during this period. For this reason, elucidating intermediate, presyndromal neurobiological risk factors offers utility for predicting the onset—and intervening in the development—of adversity-induced physical and mental health problems. Moreover, although it is preferable to prevent harm from occurring, it is critical that resilience science focuses on how we might reverse biological or psychosocial risk trajectories/harms through intervention (resilience after the fact). Understanding the biological processes that influence pathology and moderate intervention effects can contribute to tailored programs, answering questions of *for whom* and *which treatment* enhances or promotes resilience (Cicchetti & Curtis, 2007). However, intervention research has predominantly focused upon bolstering the supportive factors that are *external* to the child. Early Head Start and Head Start are some of the largest and most highly researched examples of such programming, which have been shown to improve developmental outcomes for infants, toddlers, and preschool children from economically disadvantaged backgrounds through home visits, parent education, case management, and other supportive services (Anderson et al., 2003; Love et al., 2005). There is some good evidence for the "reversibility" of harm in biological systems, although much more research is needed. An early harbinger is the work of Phil Fisher and colleagues who found that maltreated children who were in a randomized foster care intervention, compared to foster care as usual, were protected from expected cortisol dysregulation after placement in a new home (Fisher, Van Ryzin, & Gunnar, 2011). Their intervention trial also produced evidence that it is possible to impact many areas that have been negatively affected by early stress beyond the child's HPA axis activity, including child problem behavior, attachment to caregivers, and caregiver stress, all of which affect multiple systems/levels.

Informed by theoretical and empirical research on early neurobiological functioning and attachment relationships, Mary Dozier and colleagues developed the Attachment and Biobehavioral Catch-Up (ABC) program for infants and toddlers in high-risk family environments. The intervention focuses on improving parental sensitivity, responsivity, and other environmental inputs to children's developing stress physiology. In a series of randomized controlled trials, children who received ABC were shown to demonstrate more adaptive regulatory activity within the ANS (Tabachnick, Raby, Goldstein, Zajac, & Dozier, 2019) and HPA axis (Bernard, Dozier, Bick, & Gordon, 2015; Bernard, Hostinar, & Dozier, 2015), as well as more normative patterns of neural functioning (Bick, Palmwood, Zajac, Simons, & Dozier, 2019) compared to children in a control condition.

Another notable illustration of how an intervention can affect multiple systems/levels comes from the MAMAS study, a longitudinal trial examining the effects of a mindfulness-based stress reduction intervention during pregnancy on maternal well-being and health. Compared to a matched comparison group of low-income pregnant women, women in the intervention group showed decreases in stress and depression during pregnancy that were sustained through 18-months postpartum (Epel et al., 2019; Felder et al., 2018). This finding showed highly stressed women could fare better, in terms of mental health, in response to an intervention. Impressively, resilience for maternal mental health was also associated with a women's level of healthcare utilization for her infant in its first year of life (Roubinov, Felder, et al., 2018).

Importantly, the aformentioned intervention examples all focused on dyadic or family factors even though that their impacts ranged across multiple levels of outcomes and systems. Investigation of intervention programs to promote reversibility of biological vulnerabilities for health problems later in life is a remarkably promising current area of research (Bush & Aschbacher, 2019).

Challenges and Tension in Understandings of Resilience Processes Moving Ahead

One challenge for the field is the inconsistent use of the term *resilience* and confusion about related constructs. Social scientists have used the term to refer to an individual's "ability" to succeed, a style or way of being in the world (a "resilient personality"), and a process (our definition). As previously noted, we emphasize that resilience is not a trait and differs markedly from trait constructs such as "grit" (Duckworth & Gross, 2014), which is defined as the tendency to sustain interest and effort toward long-term goals and defer short-term gratification. Trait definitions are least systemic in their thinking because labels of *resilient type* or *high in a resilience-factor* do not consider the myriad outcomes across development and contexts with potential divergent functioning, the manner in which a child reaches a successful outcome at the cost of burdening a parent in its system, or ignoring the time-course issue that may bring resilience now but put the child at risk for later health problems.

Another core challenge for the field involves measurement. In social sciences, some have used a single questionnaire item (Bethell, Newacheck, Hawes, & Halfon, 2014), whereas others have developed cross-cultural questionnaires to assess resilience processes (Liebenberg, Ungar, & LeBlanc, 2013; Ungar & Liebenberg, 2011). Others have developed models outlining steps necessary to determine resilience (Masten, 2011; Masten & Obradovic, 2006; Rutter, 2012). Just as has been done with ACEs where children receive a score for each adversity type they have experienced, researchers have created counts of "resilience assets" using a cumulative exposure-type count. For example, one group quantified cumulative counts of community assets, including being treated fairly, supportive childhood friends, being given opportunities to use your abilities, and access to a trusted adult and having someone to look up to, and found that children with higher counts demonstrated better outcomes vs. children with assets in a single domain (Bellis et al., 2018). Paralleling efforts in the questionnaire domain, researchers have begun to move beyond single-system, single biomarker indicators and are attempting to create biological indices of neurobiological resilience. Although the previously reviewed data points to promising biological indicators, there are currently no established robust biomarkers of resilience, as all proposed biomarkers currently lack evidence for consistent discriminative power (Walker et al., 2017). For these reasons, we need more research that explores relations between these potential indicators of biological resilience and psychosocial/psychological resilience. Even more so, there are not multisystem indices of resilience that would reflect the complexity of the myriad of layers and systems required to understand vulnerability and recovery or biological thriving. Of course, substantial economic and public health advantages would come from identifying individuals susceptible to risk or intervention prospectively to target resilience-enhancing interventions, however such identifying neurobiological profiles are yet to be determined (Bush & Aschbacher, in press).

Another major deficit in the field is the typical lack of measurement of positive factors to ascertain what multi-level conditions promote resilience, as well as resilience reflected by greater levels of positive outcomes (rather than the absence of risky ones), such as social competence, although this is shifting (Bush & Bibbins-Domingo, 2019). A comprehensive view of multisystem resilience requires knowing that although an adversity-exposed child may show a risky profile of stress biomarkers and behavioral outcomes, she may exhibit resilience in other systems, such as better expression of anti-inflammatory markers, greater circulating oxytocin (bonding hormone) and better academic competence.

Confronting the origins of disparities in neurobiology or physical and mental health problems early in life is more likely to produce desired positive outcomes than attempting to modify health-related behaviors or improve access to healthcare in adulthood (Shonkoff et al., 2009). Policymakers can play a major role in advancing neurobiological resilience early in life at the population level. For example, the American Academy of Pediatrics has recently emphasized the need to screen children for early social determinants of health during primary care visits (American Academy of Pediatrics, 2016), and subsequently their organization and others have provided recommendations for pediatric practitioners to leverage modifiable factors that can promote resilience (American Academy of Pediatrics, 2019; Traub & Boynton-Jarrett, 2017).

Principles to Guide Future Research

Our goal for the current chapter was to review and provide evidence for the inclusion of biology as part of a comprehensive, systemic understanding of resilience. The extant evidence is promising, but very limited, and future resilience research is tasked to integrate the complexities of biological functioning in a sophisticated manner that will advance the field. With this in mind, we offer the following guidelines for ongoing studies of biological resilience:

1. In recognition of rapid developmental change that occurs in the early years of life, biological functioning should be measured at multiple timepoints, particularly before, during,

and after periods of transition. It is important to remember that the implications of a biomarker may shift over time such that short-term adaptive functioning or purported biological resilience at any given stage may be associated with longer-term poor outcomes.

2. Consider the ways in which biological functioning may be operating to predict resilience in the context of adversity (direct relation), shape the nature of relations between another environmental/biological system and an outcome (moderated relation), and/or serve as an indicator of resilient functioning in and of itself.
3. Unlike established medical biological indicators such as blood pressure or hemoglobin A1C, to date, there are not established cut points or "thresholds" within the biomarkers described here that indicate a particular child is suffering, adapting, or thriving; a value that is atypically high for one child may be normative or reflect health for a different child. When research includes samples across the early life course developmental stages and represents children of all races, ethnicities, and SES, clarity on optimal values may be achieved. Until then, major changes within children will be helpful to indicate impact, and values relative to other same aged children in their communities may be useful.
4. Interpretation of any single measure of biological functioning requires careful consideration of context—environmental, social, cultural, and the interactions therein. Even a biological value conventionally be interpreted as dysregulated may reflect an adaptive response within a given context.
5. There is no single measure of biological functioning that can serve as an indicator or predictor of resilient functioning. In addition to the need to consider context, biological systems are optimally studied in terms of their relations to and interactions with other biological systems (i.e., allostasis, multisystem resilience).
6. The absence of adaptive or resilience-promoting biological functioning is neither the fault of the individual nor is it immutable. Biological systems that promote adaptive responses to stress do not arise solely from internal factors and can develop through social environmental contexts related to families, schools, and neighborhoods. They can also be responsive to well-researched, theoretically and empirically sound interventions.

Conclusion

In sum, we suggest that a holistic approach to resilience science must include a neurobiological perspective. The considerable complexity this adds to the field is offset by wide-reaching benefits. Beyond simply understanding resilience on a much more comprehensive level, the incorporation of neurobiological factors offers the opportunity to identify early markers of risk prior to the development of detectable behavioral, emotional, or physical health disorders and provide targets of prevention/intervention previously believed to be immutable. Resilience cannot be determined by a single process, indicator, or outcome—biological or otherwise. Rather, resilience emerges through complex interactions of factors both internal and external to the individual. Thus, we may be most optimally positioned to promote successful adaptation with efforts that integrate factors across the many micro- and macrosystems in which human development unfolds.

Key Messages

1. A comprehensive understanding of resilience science requires interdisciplinary collaboration across multiple fields, including (but not limited to) psychology, sociology, and public health, genetics, biology, and neuroscience.
2. In the context of risk and resilience, biological factors may be considered intermediary variables that predict longer term physical and psychological health. Biological factors may also interact with factors across multiple other systems (e.g., environmental, social, familial) to predict adjustment to adversity.
3. There is no single measure of biological functioning that can serve as an indicator or predictor of resilient functioning. Interpretation of any single measure of biological functioning also requires careful consideration of context—environmental, social, cultural, and the interactions therein.
4. Biological factors are not immutable. Emerging research suggests such indicators may be targeted in novel prevention and intervention programs to promote resilience under conditions of risk.

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