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Lifetime Stress Exposure and Health: A Review of Contemporary Assessment Methods and Biological Mechanisms

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Abstract

Life stress is a central construct in health research because it is associated with increased risk for a variety of serious mental and physical health problems, including anxiety disorders, depression, cardiovascular disease, autoimmune disorders, Alzheimer's disease, certain cancers, and other diseases of aging. In this review, we examine how lifetime stress exposure contributes to elevated disease risk, and explore ongoing measurement and scientific issues related to this topic. To accomplish these goals, we first review existing instruments that have been developed for assessing perceived stress, self-reported life events, interviewer-assessed life stressors, and lifetime stress exposure. Next, we describe laboratory-based tasks that have been used for characterizing individual differences in psychological and biological stress reactivity. These methods have yielded an enormous amount of data showing how life stress influences the activity of the hypothalamic-pituitary-adrenal axis, hypothalamic-pituitary-gonadal axis, sympathetic-adrenal-medullary axis, and immune system, and how such processes can in turn cause allostatic load and biological embedding of the stress effect at the level of the human brain and genome. At the same time, many critical measurement and scientific issues remain unresolved, and we discuss these topics last while describing some pressing issues and opportunities for future research on stress and health.

Keywords

life stress; health; disease; risk; resilience; mechanisms; measurement; STRAIN

The concept of "stress" is ubiquitous in daily life, which is both a blessing and a curse for stress researchers. On the one hand, stress has long been readily understood as something that negatively affects health (e.g., Rosengren, Orth-Gomér, Wedel, & Wilhelmsen, 1993). On the other hand, the term "stress" has been associated with many different processes—including both life stress *exposure* and the psychological and biological *consequences* of such exposures—making the literature on stress imprecise and complicated. Improving how scientists conceptualize and assess stress exposure and reactivity has the potential to refine

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thinking and research on this important topic, but critical definitional and measurement issues are often overlooked, thus impeding progress.

The goal of this review is to provide an overview of conceptual and measurement issues in contemporary life stress research, and a summary of the present-day understanding of how stress exposure occurring over the life course affects health. First, we define stress and its various forms. Second, we describe self-report and interview-based instruments for assessing stress, with an eye toward newer technologies that have enabled investigators to assess lifetime stress exposure in a more low-cost, nuanced manner. Third, we describe experimental paradigms that have been developed for characterizing individual differences in acute stress reactivity in the laboratory. Fourth, we survey the present literature linking stress to poor health outcomes. Finally, we highlight some pressing measurement and scientific issues, and suggest possible avenues for future research.

Stress, its Definition, and Relevance for Health

Researchers have proposed that there are several different forms of life stress exposure, with each form having potentially different consequences for health. In this context, a *stressor* has been defined as any situation, or set of external demands, that requires an organism to expend resources to adapt or cope with its circumstances (Monroe, 2008). Situations that are most likely to be categorized as "stressful," in turn, are those that threaten the self and violate personal expectations, coupled with a perceived lack of coping ability (Lebois, Hertzog, Slavich, Barrett, & Barsalou, 2016; Slavich & Cole, 2013). Stressors can either be *acute life events* that occur and cease relatively quickly, such as a life-threatening accident or learning of impending company-wide layoffs, or they can occur as *chronic difficulties* that persist over time, such as caretaking for a terminally ill spouse or lacking a stable place to live (Brown & Harris, 1978; Slavich, 2016). Although conceptually separate, these forms of stress are often related. For example, an acute life event, such as the termination of employment, can sometimes (but not always) initiate a chronic difficulty, such as persistent unemployment or an ensuing financial difficulty; likewise, a chronic difficulty, such as living in a low-income neighborhood, can sometimes (but not always) give rise to specific acute life events, such as witnessing a major crime. Finally, *lifetime stress exposure* refers to the total sum of the acute life events and chronic difficulties that a person has experienced over his or her lifespan.

Intuition tells us that greater lifetime stress exposure is associated with poorer health, and research generally supports this idea. For example, greater stress exposure has been found to predict the onset or exacerbation of several mental health problems, such as depression, schizophrenia, and bipolar disorder, as well as several physical health conditions including cardiovascular disease, autoimmune disorders, and Alzheimer's disease (Bangasser & Valentino, 2014; Juster, McEwen, & Lupien, 2010; G. E. Miller, Chen, & Parker, 2011; Myin-Germeys, Krabbendam, Delespaul, & Van Os, 2003; Silverman & Sternberg, 2012; Slavich & Irwin, 2014). Greater stress exposure can also impair cognitive function (Shields, Sazma, & Yonelinas, 2016; Shields, Trainor, Lam, & Yonelinas, 2016), presumably degrading quality of life (Diamond, 2013), and is a strong predictor of earlier mortality (Rosengren et al., 1993). Multiple models have been proposed to account for these findings,

and these models have been discussed in several excellent reviews (e.g., Doom & Gunnar, 2013; Heim & Binder, 2012; Hostinar & Gunnar, 2013; Koenig, Walker, Romeo, & Lupien, 2011; McEwen, 1998; Nederhof & Schmidt, 2012). At the same time, not all individuals are at equal risk for poor health following stress (e.g., due to individual differences in stress responsivity), making it important to assess both lifetime stress exposure and stress reactivity (Boyce & Ellis, 2005; Slavich, 2015).

Assessing Life Stress Exposure

Exposure to life stress has been measured in numerous ways over the years and has included assessing individuals' overall perceived stress burden, as well as their experience of specific life stressors. Commonly used methods have included self-report perceived stress scales (e.g., Cohen, Kamarck, & Mermelstein, 1983; Levenstein et al., 1993), self-report life event checklists (e.g., Brugha & Cragg, 1990; Gray, Litz, Hsu, & Lombardo, 2004; Holmes & Rahe, 1967), and investigator-based life stress interviews (e.g., Brown & Harris, 1978; Hammen et al., 1987). The advantages and disadvantages of these approaches have been extensively reviewed elsewhere (Cohen, Kessler, & Gordon, 1997; Dohrenwend, 2006; Monroe, 2008). Therefore, we provide only a summary of the main issues here and in Table 1, followed by a discussion of the newest methods for assessing lifetime stress exposure.

Self-Report Measures of Perceived Stress

Questionnaires assessing perceived life stress, such as the Perceived Stress Scale (Cohen et al., 1983), are among the most frequently used instruments in stress research because they are very inexpensive and easy to administer. These questionnaires ask participants a number of different questions that assess perceived stress levels over a given period of time, such as "Over the last month, how often have you felt difficulties were piling up so high that you could not overcome them?", and the results can be automatically scored if the questionnaire is completed on a computer. Because of their low cost and ease of use, these scales have been extensively validated against many different health-related outcomes, including physical and mental health complaints, brain structure and function, and biological aging (Cohen et al., 1983; Epel et al., 2004; Gianaros et al., 2007).

Ironically, the main purpose of these measures (i.e., to assess *perceived* stress) is also frequently described as one of their main limitations (Monroe, 2008). The primary concern here is that if peoples' perceptions of stress are entirely self-generated, then these perceptions may lack objectivity or be only weakly related to the actual stressors that occur in peoples' lives. Consistent with this critique is the finding that certain personality traits, such as neuroticism and self-efficacy, are strongly correlated with perceived stress levels (Ebstrup, Eplov, Pisinger, & Jørgensen, 2011), meaning that these scores may reflect aspects of personality as much as stress levels. A second limitation of these measures is that they assess stress over only a relatively short timeframe (e.g., preceding month), even though many contemporary models of stress and health hypothesize that stressors occurring across the entire life course are relevant for health (Graham, Christian, & Kiecolt-Glaser, 2006; Lupien, McEwen, Gunnar, & Heim, 2009; Malat, Jacquez, & Slavich, in press; McEwen, 1998).

Self-Report Life Event Checklist Measures

Researchers who aim to catalogue the specific life stressors that individuals have experienced, rather than their overall perceived stress levels, have most often used self-report life event checklist measures of stress (Brugha, Bebbington, Tennant, & Hurry, 1985; Crandall, Preisler, & Aussprung, 1992; Gray et al., 2004; Holmes & Rahe, 1967), given that these instruments are also inexpensive, easy to administer, and can be automatically scored. Self-report measures of this type ask each participant if a variety of different life events have happened during a given timeframe (e.g., within the preceding year). Given their ability to detect such life events, these instruments have been found to predict a wide variety of health-related outcomes, including mental health problems and psychiatric diagnoses, immune system function, diagnosis of autoimmune disorders such as psoriasis, and early mortality (Naldi et al., 2005; Peng et al., 2012; Risch et al., 2009; Rosengren et al., 1993; Schlesinger & Yodfat, 1991).

As summarized in Table 1, however, self-report checklist measures also have several limitations. First, similar to perceived stress scales, self-report checklist measures of stress typically assess life stress exposure over only a short timeframe, such as during early childhood or over the previous week or year (cf. Gray et al., 2004). Second, although individuals are arguably "experts" on the types of life events they have experienced, individuals differ greatly in how they interpret life event questions. When asked if someone close to the participant has recently died, for example, some participants may consider an estranged but once close high school friend as "someone close," whereas other participants may not consider anyone except an immediate family member as "close." This issue, which has been called the *intracategory variability* problem (Dohrenwend, 2006), can cause substantial measurement error and lead to poor concurrent validity of these instruments with more probing, investigator-based measures of life stress exposure (Monroe, 2008).

Investigator-Based Life Stress Interviews

To address these limitations, some researchers have utilized a third method for assessing life stress—namely, investigator-based life stress interviews, such as the Life Events and Difficulties Schedule (LEDS; Brown & Harris, 1978) and UCLA Life Stress Interview (LSI; Hammen et al., 1987). These systems employ a life stress interviewer, who is trained to focus on the unique biographical details of the respondent and the objective characteristics of each life stressor that is reported. In addition, these systems typically employ an independent team of life stress raters, who are trained in the expert assessment of stress and who consult elaborate rating manuals when categorizing different life stressors and judging their "objective severity."

Because of these features, investigator-based life stress interviewing systems are presently heralded as the "gold standard" method for assessing stress exposure (Monroe, Slavich, & Georgiades, 2014; Monroe & Slavich, 2016). Nevertheless, these systems also have some limitations that are not frequently discussed. First, they require highly trained interviewers and raters, who must follow relatively complicated rules for obtaining and rating life stressor information. Investigator-based systems are thus very costly in terms of both money and time. Administering the LEDS, for example, can take up to six hours per participant (i.e., 2

hours to complete the interview, 1 hour to create the summary report, 2 hours to rate the case, and 1 hour to enter and cross-check the data), meaning that these systems are only used by the few investigators worldwide who have the time and resources that are needed to employ such an elaborate instrument. Second, although these systems yield very high-resolution stress data, the timeframe covered is extremely short (i.e., 1–2 years maximum). Therefore, the life stressors captured may be relevant for understanding the development of some specific health outcomes, such as onset of a major depressive episode, but these data are generally not useful for predicting the development of disease states that evolve more slowly over the life course, such as the metabolic syndrome, cardiovascular disease, cancer, and Alzheimer's disease.

Automated Systems for Assessing Lifetime Stress Exposure

Most recently, the limitations associated with each of the methods described above has provided the impetus for developing new methods for assessing life stress exposure that combine the depth and sophistication of a life stress interview with the simplicity of a self-report instrument. These automated life stress interviews are internet- or computer-based instruments that utilize branching logic to prompt the same types of follow-up questions that an expert life stress interviewer would typically ask in order to ascertain exactly what happened to the respondent (e.g., When did the stressor occur? How many times did you experience that stressor? How long did the stressor last? How much did the stressor interfere with your goals, plans, or aspirations for the future?). Similar to investigator-based systems, therefore, these automated systems provide information that is critical for fully characterizing an individual's lifetime stress exposure, but they do so in a much more cost effective and scalable manner. Likewise, these systems have the benefit of being easy to administer and score, just like self-report checklist measures of life stress, but they yield information that is much more nuanced and informative than what self-report checklists can produce.

To date, the only automated system that easily assesses stress exposure occurring across the entire life course is the **Str**ess and **A**dversity **In**ventory (STRAIN). The current version of the STRAIN enquires about 55 different stressors, including 26 acute life events and 29 chronic difficulties, that are known to impact health (see http://www.STRAINsetup.com). These stressors cover all of the major life domains that are important for functioning, including health, intimate relationships, friendships, education, work, finances, housing, living conditions, and crime. They also cover several core social-psychological characteristics that may have differential effects on lifespan health—specifically, interpersonal loss, physical danger, humiliation, entrapment, and role change/disruption. The STRAIN is available in English, Spanish, Italian, German, High German, and Brazilian Portuguese, and investigators can choose between two different interviewing platforms depending on whether they need to assess lifetime stress exposure in adolescents (i.e., Adolescent STRAIN) or adults (i.e., Adult STRAIN).

One important feature of the STRAIN is its ability to predict not just self-reported health outcomes that could be influenced by reporting biases, such as self-reported anxiety or depressive symptoms, but a wide variety of psychological, biological, and clinical outcomes.

To date, these outcomes include memory (Goldfarb, Shields, Daw, Slavich, & Phelps, 2017), diurnal cortisol levels (Cuneo et al., in press), biological reactivity to acute stress (Lam, Shields, Trainor, Slavich, & Yonelinas, 2017), metabolic function (Kurtzman et al., 2012), cancer-related depression and fatigue (Bower, Crosswell, & Slavich, 2014; Dooley, Slavich, Moreno, & Bower, 2017), physical and mental health problems (Shields, Moons, & Slavich, 2017; Toussaint, Shields, Dorn, & Slavich, 2016), and likelihood of being diagnosed with a stress-related illness or autoimmune disorder (Slavich & Shields, in press; see also Slavich & Toussaint, 2014). Moreover, when compared to other stress assessment instruments that are commonly used, such as self-report measures of perceived stress and stressful life events, the STRAIN has emerged as a relatively stronger predictor of respondent health (Slavich & Shields, in press).

As these technologies continue to improve and investigators come to appreciate the power of automated interviewing platforms, we believe that use of simple paper-and-pencil self-report measures of life stress and more time-consuming investigator-based systems will give way to sophisticated online interviewing platforms like the STRAIN, which enable investigators to acquire lifetime stress exposure information in a more cost efficient, reliable, and scalable manner. Ultimately, these platforms are not a substitute for intensive investigator-based systems like the LEDS, but they do cover the entire life course, which is something that even the prevailing gold standard systems cannot accomplish. Looking forward, then, the adoption of such systems will be important for conducting empirical tests of existing theoretical models that aim to explain how stressors occurring across the entire life course accumulate to impact human health and wellbeing.

Characterizing Stress Reactivity in the Laboratory

The foregoing review summarizes methods that have been employed for assessing life stress exposure as a means of better understanding who is at risk for poor health. It is well known, however, that stress does not impact everyone equally (Boyce & Ellis, 2005; Monroe et al., 2014; Slavich & Cole, 2013), which means that it is also important to characterize individual differences in stress reactivity that could explain why some individuals become ill following stress while others do not. To accomplish this, investigators have utilized different methods for inducing acute stress in the laboratory, where environmental conditions can be carefully controlled and psychological and biological outcomes can be closely measured. The characteristics of the three most commonly used methods for inducing stress in the laboratory (Shields, Sazma, McCullough, & Yonelinas, 2017) are summarized in Table 2.

Trier Social Stress Test

The gold-standard task for inducing acute stress in the laboratory is the Trier Social Stress Test (TSST), which was developed in the early 1990s (Kirschbaum, Pirke, & Hellhammer, 1993). In the stress portion of this task, a participant is taken to a laboratory room and told that he or she will give an upcoming speech in front of a panel of evaluators and a video camera. He or she is then given a brief period of time (usually 5–10 minutes) to prepare a speech on his or her qualifications for an important job (e.g., administrative assistant at his/her school). The participant is further told that the evaluators are trained in monitoring

nonverbal behavior and that a video analysis of their speech will be conducted after the session. In reality, the evaluators are research assistants who are trained to say only scripted lines and give no verbal or nonverbal signs of approval.

After the brief preparation phase, the participant is brought into the testing room for the speech task. The speech task lasts five minutes, and if a participant stops talking prior to the end of the five minutes, the evaluators prompt the participant to continue. After this task is finished, participants are given a difficult mental arithmetic task in front of the evaluators. In the arithmetic task, participants are told to verbally subtract 13 from 1,022 as quickly and accurately as possible. The evaluators are further instructed to tell the participant to restart at 1,022 every time he or she makes a mistake. After five minutes, the arithmetic task is finished and the participant is brought back to the preparation room.

This version of the TSST has been used in numerous studies and produces a relatively reliable and robust psychological and biological response that varies in magnitude across people (Allen, Kennedy, Cryan, Dinan, & Clarke, 2014; Dickerson & Kemeny, 2004; Kirschbaum et al., 1993; Shields, Sazma et al., 2017). In addition, a group version of the TSST has also been developed (von Dawans, Kirschbaum, & Heinrichs, 2011). The reliably strong effect that the TSST has on markers of stress reactivity is arguably its biggest advantage. Its biggest limitation, in contrast, involves the fact that the TSST is very resource intensive. For example, it requires three trained evaluators and an experimenter to be present for every participant, which either means that data collection proceeds slowly or that several people in the lab must be devoted to running multiple TSST sessions every day or week.

Cold-Pressor Test

Another very common acute stress manipulation is the Cold-Pressor Test (CPT), which has been used in laboratory settings for nearly 100 years (Hines & Brown, 1932). However, only recently has it gained traction as a way to induce acute stress (e.g., Cahill, Gorski, & Le, 2003; Felmingham, Tran, Fong, & Bryant, 2012; Gluck, Geliebter, Hung, & Yahav, 2004). In this task, a participant is told to submerse his or her nondominant hand up to the wrist joint in either nearly freezing water (usually 0°–3°C) for the stress condition or in lukewarm water for the control condition, both for up to 1–3 minutes. Afterward, the participant is instructed to withdraw his or her arm from the water and is then given a towel to dry off.

The CPT has been validated in numerous stress studies and is the task of choice in certain areas of stress research, such as examining post-encoding stress effects on memory (Shields, Sazma et al., 2017). The CPT thus has the advantage of being relatively quick, well validated, and easy on resources (e.g., it requires only one experimenter, a bucket of cold or lukewarm water, and less than 5 minutes to complete). However, the CPT induces a weaker cortisol response than the TSST (Shields, Sazma et al., 2017), and this reduced stress response is a limitation compared to other tasks like the TSST. Another limitation of the CPT is that it does not include a socio-evaluative component, which has been found to be an important feature of laboratory stressors that reliably induce strong cortisol and inflammatory reactivity (Dickerson & Kemeny, 2004; Slavich, Way, Eisenberger, & Taylor, 2010).

Socially Evaluated Cold Pressor Test

To address these limitations of the CPT, some researchers have developed hybrid stressor tasks that incorporate elements of both the TSST and CPT. One such task, the Socially Evaluated Cold Pressor Test, incorporates a stern evaluator and video camera (similar to the TSST), and thus produces a larger biological stress response than the classic CPT (Schwabe, Haddad, & Schachinger, 2008). Another task called the Maastricht Acute Stress Test requires participants to alternate between immersing their hand in ice water and performing a TSST-like arithmetic task while they are being watched by an evaluator and filmed by a video camera (Smeets et al., 2012). This task thus evokes a greater stress response than the CPT and one that is on par with the TSST. Considered together, these hybrid tasks are slightly more resource intensive than the CPT, but they have the advantage of being able to induce a relatively greater stress response, making them worth the additional resources. In terms of limitations, hybrid stressors are regarded as less ecologically valid than the TSST because they combine physical and social challenges that are not encountered in everyday life (e.g., immersing your hand in ice water while being socially evaluated).

Biological Mechanisms Linking Lifetime Stress Exposure and Health

Together, methods like those described above for assessing life stress exposure and reactivity have yielded a tremendous amount of data on biological processes linking stress and health. These pathways have been described in great detail elsewhere (e.g., Graham et al., 2006; Irwin & Cole, 2011; Lupien et al., 2009; McEwen, 1998; G. Miller, Chen, & Cole, 2009; Slavich & Cole, 2013; Slavich & Irwin, 2014). In this section, therefore, we summarize only the most important details presently known about how stress gets represented by the brain and how the brain in turn regulates peripheral physiologic and immune system processes that affect health.

Neural and Peripheral Mechanisms of the Stress Response

In response to a stressor, the brain is thought to initiate a complex cascade of events that culminate in what is generally referred to as the *biological stress response*. As described below, at least four major systems are typically involved: the hypothalamic-pituitary-adrenal (HPA) axis, hypothalamic-pituitary-gonadal (HPG) axis, sympathetic-adrenal-medullary (SAM) axis, and immune system (Allen et al., 2014; Lennartsson, Kushnir, Bergquist, Billig, & Jonsdottir, 2012; Segerstrom & Miller, 2004).

The HPA axis regulates secretion of hormones, such as the glucocorticoid cortisol (Dedovic, Duchesne, Andrews, Engert, & Pruessner, 2009; Sapolsky, Rivier, Yamamoto, Plotsky, & Vale, 1987; Sapolsky, Romero, & Munck, 2000). Under stress, activity within parts of the brain that are involved in processing social-environmental experiences, such as the dorsal anterior cingulate cortex and amygdala, signal to the hypothalamus (Dedovic et al., 2009), and activity in the paraventricular nucleus of the hypothalamus in turn results in the secretion of corticotropin-releasing hormone (Lovallo & Thomas, 2000; Sawchenko, Li, & Ericsson, 2000). Corticotropin-releasing hormone then stimulates the pituitary to release adrenocorticotropic hormone (Lovallo & Thomas, 2000; Sawchenko et al., 2000). Once released, adrenocorticotropic hormone enters the bloodstream and travels to the adrenal

glands, where it stimulates the adrenals to produce and release cortisol into the bloodstream (Sapolsky et al., 2000).

Activation of the HPG axis is similar to that of the HPA axis in that it starts with the hypothalamus, which secretes gonadotropin-releasing hormone (Millar et al., 2004). Gonadotropin-releasing hormone then triggers the pituitary gland to produce luteinizing hormone and follicle-stimulating hormone (Meethal & Atwood, 2005; Millar et al., 2004). These hormones then act on the gonads to upregulate production of sex hormones such as testosterone and estrogen, which are released into the bloodstream (Meethal & Atwood, 2005).

Activation of the SAM axis, in turn, begins with neural activity in the locus coeruleus and other regions of the brainstem stimulating the sympathetic nervous system, which innervates the adrenal medulla (Allen et al., 2014; Sabban & Kvetňanský, 2001). The adrenal medulla then upregulates production of norepinephrine and epinephrine, and releases them into the bloodstream.

Finally, the immune system is believed to be activated during stress largely by the SAM axis. An end product of SAM axis activation, norepinephrine, circulates in the body and acts on immune cell receptors to upregulate the activity of transcription factor nuclear factor-κB (NF-κB; Bierhaus et al., 2003). Through a complex series of intracellular events, NF-κB activation in turn promotes the synthesis of proinflammatory cytokines, which are then released into circulation. This is not the only way that stress influences the immune system (Silverman & Sternberg, 2012), since cortisol is also a strong regulator of inflammatory activity (Slavich & Irwin, 2014), but it represents a primary pathway through which stress affects immunity and health.

The systems described above are not the only ones affected by stress. For example, stress also influences, and may be modulated by, the opioid system, and may impair some cognitive functions through these effects (Laredo et al., 2015; Slavich, Tartter, Brennan, & Hammen, 2014). Glucocorticoids, sex hormones, sympathetic nervous system activation, and the immune system all have well-documented implications for health, though, which is why we focused on them here.

Allostatic Load

These stress-responsive systems are intended to promote biological stability during environmental change. For example, upregulation of norepinephrine and cortisol prime the body to “fight or flee” from a stressor (McEwen & Sapolsky, 1995), while activation of the immune system facilitates healing should an injury or infection occur as a result of the stressor or associated threat (Dhabhar, 2002). This process of “stability through change” has been labeled *allostasis* (McEwen, 1998; Sterling & Eyer, 1988), and it is a well-established mechanism through which the body deals with an everchanging, and sometimes threatening, environment.

Over time and with repeated activation, however, the functionality of these stress responsive systems can change and produce biological “wear and tear,” or *allostatic load*, that affects

health (Juster et al., 2010; McEwen, 1998, 2005, 2007). For example, greater life stress exposure has been associated with reduced HPA axis responses to acute stress (Carpenter et al., 2007), chronic low-grade inflammatory activity (Slavich & Irwin, 2014), and an inability for cortisol to properly regulate inflammatory activity (Cohen et al., 2012; Silverman & Sternberg, 2012). Moreover, these changes have been directly implicated in the development of disease (Cohen et al., 2012; Silverman & Sternberg, 2012; Slavich & Irwin, 2014).

One interpretation of the above data suggests that these physiological changes are adaptive for dealing with a chronically unstable environment. This interpretation is similar to the match/mismatch hypothesis, which argues that stress leads to negative health outcomes when an early environment is either more or less stressful than a later environment (Nederhof & Schmidt, 2012; Santarelli et al., 2014; Zalosnik, Pollano, Trujillo, Suárez, & Durando, 2014). Consistent with this formulation, both the brain and the immune system calibrate to the environment and are predictive systems that attempt to anticipate future challenges and threats (Chiel & Beer, 1997; Dhabhar, 2002; Schultz, Dayan, & Montague, 1997). As a result of these dynamics, the immune system can respond to bodily damage or infection relatively quickly, and sometimes before actual physical or biological damage has occurred (Dhabhar, 2002).

Consequences of Lifetime Stress Exposure and Allostatic Load

Adapting to conditions of environmental uncertainty is biologically beneficial, but also has physiological costs that can degrade health over the long term. In particular, by adapting to repeated elevations of glucocorticoids, certain cells in the body, such as immune system cells, become insensitive to glucocorticoids, which has been called *glucocorticoid resistance* (Cohen et al., 2012; A. H. Miller, Pariante, & Pearce, 1999; Pariante, 1999; Silverman & Sternberg, 2012; Wang, Wu, & Miller, 2004). Because glucocorticoids are primary regulators of inflammatory activity (Auphan, DiDonato, Rosette, Helmberg, & Karin, 1995; Silverman & Sternberg, 2012), glucocorticoid resistance disinhibits the release of inflammatory proteins from immune cells, leading to chronic, low-grade inflammation (Cohen et al., 2012; A. H. Miller et al., 1999; Silverman & Sternberg, 2012; Slavich & Irwin, 2014). This chronic, low-grade inflammatory state is in turn believed to promote the development or exacerbation of multiple diseases, including autoimmune disorders, rheumatoid arthritis, Alzheimer's disease, cardiovascular disease, and depression (Akiyama et al., 2000; Couzin-Frankel, 2010; Feigenson, Kusnecov, & Silverstein, 2014; Libby, 2002; Ridker, Cushman, Stampfer, Tracy, & Hennekens, 1997; Silverman & Sternberg, 2012; Slavich & Irwin, 2014).

Biological Embedding of Life Stress

The above consequences of greater lifetime stress exposure and allostatic load are due in part to the fact that lifetime stress exposure can become embedded on a neural and genomic level. For example, stress can induce lasting changes in catecholaminergic and cholinergic function in the brain (Sabban & Kvetňanský, 2001; Soreq, Kaufer, Friedman, & Seidman, 1998). Stress occurring over the lifespan can also promote lasting structural changes in the brain, especially in regions such as the prefrontal cortex (Dias-Ferreira et al., 2009; Hinwood et al., 2013; Hinwood, Morandini, Day, & Walker, 2012) and hippocampus (McEwen &

Sapolsky, 1995; McEwen, 2007; Zalosnik et al., 2014), which underpin cognitive processes that are important for everyday life. Together, these stress-related neural changes can alter the functioning of the physiologic stress systems described above, as well as how subsequent life stressors are perceived and managed.

Lifetime stress exposure can also have sustained effects on health by becoming embedded at the level of the human genome (Slavich & Cole, 2013). For example, stress is known to upregulate the expression of genes that code for proinflammatory cytokines and downregulate the expression of genes that code for antiviral cytokines. These alterations can promote a state of persistently elevated inflammation coupled with an inability to properly fight viral infections, thus increasing a person's risk for both inflammation-related disease and viral infection (Slavich & Cole, 2013). Chronic or repeated stress exposure can also lead to persistent alterations in glucocorticoid receptor gene expression in the brain, including reductions in the expression of hippocampal and cerebellar glucocorticoid receptors (Kitraki, Karandrea, & Kittas, 1999; Liu et al., 1997). These changes reduce the ability of glucocorticoids to initiate the negative feedback loop in the hippocampus that reduces the production of glucocorticoids, ultimately leading to a less controlled glucocorticoid response to stress that can promote inflammation and cause disease (Liu et al., 1997).

Pressing Problems and Future Directions

Despite the abundance of studies that have been conducted on stress and health, and the continued importance and public health relevance of this work, a majority of stress studies still employ assessment methods that have critical limitations. As a result, many important questions remain unanswered. We highlight some of these issues below, focusing first on existing measurement challenges and then on lingering scientific questions.

Measurement Issues

One of the greatest ongoing challenges in stress measurement involves the lack of tools for assessing life stress exposure that are inexpensive, easily scalable, and valid. Most instruments that presently exist for assessing life stress have inherent tradeoffs between cost and validity. For example, although paper-and-pencil measures are cheap, their validity is limited; in contrast, investigator-based interviewing systems are well-validated, but very expensive. Online systems like the STRAIN have made substantial progress in combining the sophistication of investigator-based interviewing systems with the ease of self-report instruments, but more methodological advancement is needed along these lines to improve how researchers assess stress.

Second, stress can occur on several different timescales, from moment-to-moment stress, to daily, to weekly, to lifetime stress exposure. However, no measurement system presently exists for assessing stress across multiple timescales. As a result, studies frequently assess stress at one timescale (e.g., daily hassles or major life events), but do not combine this information with other timescales, making an individual's stress profile arguably incomplete. This need could be addressed by developing tools that assess stress reactivity or exposure on an ongoing basis, but the challenge here is to create instruments that individuals are willing to use and find non-invasive.

Third, assessing both life stress exposure and stress reactivity are important for characterizing resilience to stress and for identifying persons at highest risk for poor health. However, current research and measurement strategies do not typically take both aspects of the stress process into account. Incorporating this measurement goal into future studies would be an important development methodologically, but this advancement could also yield important new discoveries on stress, coping, and resilience.

Finally, there is a need to further validate existing computer-based instruments for assessing life stress and to develop new applications for helping individuals manage stress. With respect to the first goal, it is possible that automated systems will eclipse paper-and-pencil based systems for assessing stress, but to be useful, these systems need to be validated across all major levels of analysis (e.g., psychological, neural, physiologic, molecular, genomic) and across different population groups and cultures. With respect to the second goal, automated systems are presently being developed to help individuals cope with stress – such as the acceptance and commitment-based smartphone app (Ly, Asplund, & Andersson, 2014) and BeWell smartphone app (Lane et al., 2014) – but development of these tools is still in its infancy, and additional research is needed to examine which tools provide the greatest stress-reducing benefit.

Scientific Issues

Partly because of these ongoing measurement issues, stress research has yet to address many important scientific questions that are relevant for public health. For example, why does major life stress precipitate illness in some individuals and not others? Moreover, what factors determine the type of stress-related disorder that develops? These questions have been answered in part (e.g., Elliott, Ezra-Nevo, Regev, Neufeld-Cohen, & Chen, 2010; Santarelli et al., 2014; Shansky, 2015; Slavich & Irwin, 2014). Unfortunately, however, this work has not yet produced translational models that would enable health care providers to make predictions in the clinic, which is what would be most useful for preventing and mitigating stress-related disease burden.

In addition, there is a pressing need to better understand mechanisms that underlie specific mental and physical disorders, as well as the co-occurrence of such disorders. Some biological processes, such as inflammation, have recently been described that may underlie the development of certain diseases and also represent a *common mechanism* that increases risk for poor health in general (Couzin-Frankel, 2010; Slavich, 2015). However, inflammation itself does not sufficiently explain why individuals develop certain inflammation-related health problems (e.g., cardiovascular disease) versus others (e.g., cancer).

Several other scientific issues are also ripe for investigation. For example, it has been proposed that humans have *sensitive periods* during which time stress is particularly impactful (Andersen & Teicher, 2008). However, it remains unclear when those sensitive periods are and what exact processes would be responsible for enhancing the effects of stress on health. Second, resilience to stress has been the subject of a great deal of research (Baratta, Rozeske, & Maier, 2013; Charney, 2004; Dooley et al., 2017; Elliott et al., 2010; Shansky, 2015; van der Werff, van den Berg, Pannekoek, Elzinga, & van der Wee, 2013), but

a complete understanding of the psychological and biological factors that confer resilience to stress is still unavailable. Finally, psychological and psychopharmacological interventions have been heralded as having great potential for reducing stress and enhancing human health, but we still do not have interventions that are cost-effective and scalable, and that have been shown to reduce the negative effects that stress has on health-relevant psychological, biological, and clinical outcomes.

Summary and Conclusions

In summary, lifetime stress exposure refers to the total sum of the acute stressful life events and chronic difficulties that a person has experienced over his or her lifespan. Theorists have proposed that lifetime stress exposure increases risk for a variety of mental and physical health problems, including depression, cancer, schizophrenia, Alzheimer's disease, and autoimmune disorders (Juster et al., 2010; McEwen, 1998; G. E. Miller et al., 2011; Silverman & Sternberg, 2012; Slavich & Cole, 2013; Slavich & Irwin, 2014; Slavich, O'Donovan, Epel, & Kemeny, 2010; Slavich, 2015). To date, however, only a few studies have actually measured lifetime stress exposure. Indeed, the rest of the vast literature on stress and health has assessed stress exposure using self-report checklist measures or investigator-based interviewing methods that assess stress over only short periods of time (e.g., past week or year), which is not sufficient for testing existing theories of lifetime stress exposure and health.

Looking forward, new online systems for assessing stress exposure have been developed that combine the thoroughness of a life stress interview with the ease of administration of a self-report checklist measure. The only online system that presently assesses *lifetime* stress exposure, though, is the STRAIN, and although this system performs well, it needs to be tested in additional populations and in relation to other psychological, biological and clinical outcomes. These methodological advancements will ultimately combine with innovative new tools for reducing stress to have a substantial impact on human health. However, much more research is needed to develop these instruments to address the enormous disease burden that is caused by stress-related health problems worldwide.

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Table 1

Comparison of Existing Instruments for Assessing Life Stress

Instrument	Advantages	Disadvantages
Self-Report Perceived Stress Scales	– Inexpensive – Quick and easy to use – Scalable	– Only moderate correspondence with actual stress exposure – Correlate strongly with personality – One main outcome variable – Very limited stress assessment timeframe (e.g., past month)
Self-Report Life Event Checklist Measures	– Inexpensive – Quick and easy to use – Scalable	– Suffer from intracategory variability problem – Only 1–2 outcome variables – Very limited stress assessment timeframe (e.g., past month)
Investigator-Based Interviewing Systems	– Extensively validated; considered the gold standard of stress assessment instruments – Thorough stress assessment with numerous outcome variables – Independent, investigator-based stress exposure ratings – Ability to examine stress exposure by different life domains and stressor characteristics	– Very expensive – Extremely resource intensive – Require extensive training for interviewer(s) and rater(s) – Not scalable – Limited stress assessment timeframe (e.g., past 1–2 years)
Automated Lifetime Stress Assessment Systems	– Inexpensive – Quick and easy to use – Scalable – Thorough stress assessment with numerous outcome variables – Ability to examine stress exposure by different life domains and stressor characteristics – Assesses stress exposure across the entire life course	– Limited validation data to date – Current absence of independent stress exposure ratings

Table 2

Comparison of Existing Laboratory-Based Psychosocial Stress Tasks

	Construct Validity	Ease of Use	Ecological Validity
Trier Social Stress Test	High	Low	High
Cold Pressor Test	High	High	Low
Socially Evaluated Cold Pressor Test	High	Moderate	Moderate