

Stress Measurement Toolbox

Purpose of the Toolbox

The Stress Measurement Toolbox provides a resource of informal recommendations of stress measures that researchers – primarily those involved in large-scale research – can use as an information source when deciding which psychological stress measures to include in their study. We asked contributing authors to select measures based on their expertise in studying the relationship between stress and health, describe what aspects of the construct each measure captures, and highlight unique or important features of each measure. By creating the Toolbox in this fashion, we hope other scholars interested in stress and health outcomes will learn about the various domains and aspects of stress, and ultimately advance the science of stress.

Methods for Toolbox Measure Selection

Based on theory and expert consensus, the Network developed a list of psychological stressors known to be important for health. **These are major life events, traumatic events, perceived stress, early life stress, caregiver stress, social isolation, loneliness, stigma/ discrimination, work stress, burnout, relationship conflict, financial strain, neighborhood safety and cohesion, and daily stress.** The impact of stress on health depends in part on one's appraisal of the stressor and trait level factors that make one more or less vulnerable to the impacts of stress, thus we also include measures that capture **acute stress appraisals**, measures of **threat sensitivity**, and psychological **resilience measures**. We also include descriptions of the following stress-related biomarkers: **hair cortisol, salivary cortisol, inflammatory cytokines, RNA profiling/gene expression, and telomeres & telomerase.**

Network members and affiliates were asked to write a brief summary of key measures within each domain given their expertise, and to have it reviewed by experts in that stress domain. Members chose measures based on their face validity, psychometric qualities, evidence linking them to physical and health outcomes, and length of time it takes to complete them. There were not formal literature reviews or meta-analyses conducted in each domain area. Instead, we relied on the experience of area experts to give us their opinion based on years of work in this area. Because our goal is to help improve stress measurement in epidemiologic studies in particular, we asked Network experts to select short measure in their evaluation. Note that for self-report measures, we discourage choosing specific items from the scale. In order to compare effect sizes or results across studies, it is important to have the full scale so scores can be calculated accurately and consistently.

Stress measures can be self-report questionnaires, interviews, physiological measurements, or task-based measures. We have not included full information on task-based measures. Other resources have been created that take more comprehensive and empirical approaches to psychosocial measure recommendations such as those found here: [ADOPT](#), [NIH Toolbox](#), [PROMIS](#), and [PhenX Toolkit](#). The Stress Measurement Toolbox is a living document so we welcome any input and suggested edits.

About the Stress Measurement Network

This Toolbox was developed as part of the Stress Measurement Network aims. Our Network's mission is to better understand the relationship between stress and health by improving the measurement of psychological stress in research studies. The Network is made up of experts from around the world who have come together to debate, improve, and develop measures of psychosocial stress. Our Network is funded by the National Institute of Aging (R24AG048024).

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Perceived Stress

Stress is a multi-dimensional construct that comprises of exposure to stressors (events), perceptions of psychological stress, and biobehavioral responses to stress. A more nuanced understanding of stress-health linkages requires assessment of each of these components. Here, we suggest measures that have been specifically developed to assess *perceptions* of stress – each with their own strengths and limitations.

Perceived Stress Scale

The **Perceived Stress Scale (PSS)** is one of the most common measures for assessing *global* stress perceptions. It measures the degree to which an individual perceives his/her life as uncontrollable, unpredictable, and overloading within the past month (Cohen et al., 1983). The PSS is closely linked with measures of psychological stress and self-reported health (depressive and physical symptomatology; Cohen et al., 1988); it is also correlated with biological markers of stress and disease (reviewed in Cohen, & Janicki-Deverts, 2012). The PSS (4-, 10-, and 14-item versions), its psychometric properties, and its translations into different languages can be found here: <http://www.psy.cmu.edu/~scohen/>

Stress Overload Scale

The **Stress Overload Scale (SOS)** is comprised of 30 items and is designed to measure “stress overload”, a state described in stress theories as occurring when demands overwhelm resources. The respondent uses a 5-point Likert scale (1= not at all, 5= a lot) to indicate subjective feelings and thoughts experienced over the prior week. There are two factors underlying overload: Personal Vulnerability (PV) and Event Load (EL), which are measured by two distinct but correlated subscales. Even numbered items on the SOS comprise the Event Load, and the odd numbered items (item 5 is reversed scored) comprise the Personal Vulnerability scale; there are also 6 filler items used to discourage negative response sets that are not scored. The scales can be summed to obtain a continuous total score, with higher scores indicating higher levels of stress overload. Or, the subscales can be split at their means to form a four-category diagnostic matrix; those scoring in the High EL-High PV category have been shown to be at the greatest risk for subsequent pathology. The SOS was constructed through a sequenced series of factor analytic and psychometric studies, all using community samples matched to US Census demographic proportions. It differs from other measures of stress in that it is (1) psychometrically strong; (2) appropriate to community research, due to its brevity and fit to a broad demographic spectrum; (3) unique in its ability to cross-section individuals into risk categories. The internal consistency of the SOS is excellent (with Cronbach’s alphas > .94 for both subscales and the measure as a whole). Test-retest reliability is good (with coefficients averaging .75 over one week). Construct validity has been demonstrated in significant correlations with other measures of stress and illness (Amirkhan, 2012; Amirkhan et al., 2015); Criterion validity has been shown in the SOS’ ability to predict illness and abnormal cortisol responses following a stressful event (Amirkhan et al., 2015). A 10-item scale (SOS-S) has recently been developed (Amirkhan, 2016). See cited articles for the full scale items.

Stress in Context (SIC) Questionnaire

Global stress measures, such as the Perceived Stress Scale, are relative measures, which is a strength, in that this measure can be used in any population and context. However, it also presents a limitation for assessing how stress perceptions may be linked to specific contexts that are typically creating demand.

For example, individuals facing *chronic* social adversity like living in a low socioeconomic neighborhood rife with danger, do not have as elevated stress scores as one might predict, suggesting there is habituation or social comparison that leads to normalizing the environment and thus lower stress scores. This may obscure links with health outcomes in chronic stress exposed populations. The Stress in Context (SIC) questionnaire has been developed to address this limitation. The SIC assesses stress perceptions in specific contexts, such as at home, neighborhood, in social relationships, at work, and during childhood. Weighting stress perceptions to each of these contexts may help remind people of the many potential sources of perceived stress from their environment, and thus get a more accurate summative measure. The SIC may be more relevant for lower income populations or samples exposed to chronic adversity. Currently, the SIC is being validated by the Stress Measurement Network, led by Wendy Berry Mendes. So far, it is equivalent to the PSS in self-report measures of psychological distress, well-being, and self-reported health, but shows a unique relationship to resting sympathetic state. To obtain the most current version, please contact us (Stefanie.Mayer@ucsf.edu).

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Early Life Stress (retrospective measures)

Stress in childhood is associated with vulnerability to psychological and physical illness in adulthood, including lung disease, heart disease, diabetes, cancer, depression, and premature mortality (e.g., Anda et al., 2009; Danese et al., 2000; Felitti et al., 1998). Much of the research in this area has focused on the long-term impact of severe forms of early life stress, such as physical or sexual abuse, and physical neglect. However, less severe and more common forms of early adversity such as growing up in poverty, and in a chaotic and conflictual home environment, are also associated with worse mental and physical health in adulthood (Evans & Kim, 2007; Repetti, Taylor, Seeman, 2002).

Measures to capture stressful experiences in childhood have largely focused on the individual's retrospective account of their experiences of threatening events or perceptions of threat in childhood. These measures tend to capture the severity of the adversity (via ratings from either the interviewer or the respondent), type of adversity, and number of adversities experienced. Severity as well as number of adverse experiences likely both have negative effects. Different forms of adversity may differentially impact health in adulthood although these distinctions have not been thoroughly tested.

The validity of retrospective reporting of childhood experiences is debated. Some researchers argue that retrospective reports are valid and participants may under report stressful experiences rather than over report them (Brewin, Andrews, & Gotlib, 1993; Henry, Moffitt, Caspi, Langley, & Silva, 1994), while other data suggests moderate associations between retrospective and prospective reports. For example, in the longitudinal birth cohort Dunedin Study, Reuben et al. (2016) reported that adverse childhood experiences captured by study staff throughout childhood was only moderately associated with retrospective reports of adverse childhood experiences reported by the participants at age 38 ($r=.47$; weighted Kappa=.31). Both retrospective and prospective measures of adverse childhood experiences were associated with health outcomes at mid-life. For the full article, [click here](#).

For retrospective measures of childhood trauma, a frequently used measure is the **Child Trauma Questionnaire (CTQ)**; Bernstein et al., 1994). The CTQ is a 28-item self-report questionnaire that captures experiences of maltreatment from ages 0-17, with five subscales: sexual, emotional, and physical abuse, and emotional and physical neglect. This measure captures perceptions of treatment primarily from family members (Example item: People in your family called you things like stupid, lazy, or ugly) and whether necessities were provided (Example item: You didn't have enough to wear). The measure does not capture stressful life events (e.g. divorce, death of parent) or stressful environmental contexts (e.g. socioeconomic adversity, unsafe neighborhood, overcrowded home). In large population-based studies, higher CTQ scores are associated with worse mental and physical health across the life span.

The Adverse Childhood Events Scale (ACES); Felitti et al., 1998) ask participants if prior to age 18 they experienced negative life events such as emotional, sexual, or physical abuse, or instability of the caregiver or close other (e.g. caregivers drank too much or did drugs, or someone in the household went to prison or had a mental illness). This scale assesses exposure (yes/no) and frequency (never to very often) of these stressors, though does not capture subjective severity like the CTQ does. The original scale was 28-items though has since been shortened to 10 items. The total score is used to indicate the cumulative number of adverse experiences in childhood. The primary focus is on the family or close-other network, and does not ask about traumas outside of those relationships (e.g. political turmoil, community violence), or take in to account the context of those experiences (e.g. socioeconomic status).

Greater number of ACEs is associated with worse mental and physical health in adulthood (e.g. Edwards, Holden, Felitti, Anda, 2003). The original scale and a shortened 10-item version can be found here: <http://www.acestudy.org/uploads/3/4/9/6/34961588/10-qacecalc.pdf>. The World Health Organization published an international version that can be found here: http://www.who.int/violence_injury_prevention/violence/activities/adverse_childhood_experiences/questionnaire.pdf?ua=1. There has also been an effort to create a two-item ACE screener that can be read about here: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5596508/>

Childhood Socioeconomic Status. Other experiences that often fall into the category of ‘early childhood adversity’ are common environmental and social aspects related to poverty and low socioeconomic conditions. These maybe more chronic and less severe than psychologically traumatic events, but are also important to capture given the association between low socioeconomic status (SES) and worse health. Childhood SES is often measured by asking participants about their parents level of education and whether their parents owned the home in which they lived. Specific wording for these measures can be found here: <https://www.cmu.edu/common-cold-project/measures-by-study/psychological-and-social-constructs/childhood-measures/childhood-ses.html>

Risky Family Environment. Less severe and more common forms of early adversity such as disrupted parent-child relationships have also been associated with worse mental and physical health in adulthood (e.g., Russek & Schwartz, 1997). Repetti, Taylor, and Seeman (2002) identified a cluster of family characteristics that are associated with behavioral problems in childhood, and worse health throughout life. Specifically, families that are characterized by high levels of conflict and aggression, relationships that are cold, unsupportive, and neglectful, and chaotic daily lives, are termed “risky families” because they leave children at risk for worse health. Children that grow up in risky families have higher rates of mental health problems throughout their lives, and accumulating evidence suggests that they also have worse physical health in adulthood (Carroll et al., 2013; Luecken & Lemery, 2004; Repetti, Robles, & Reynolds, 2011; Repetti et al., 2002; Taylor, Lehman, Kiefe, & Seeman, 2006; Taylor, Lerner, Sage, Lehman, & Seeman, 2004). Thus, **the Risky Families Scale** was developed to capture 13-item the extent to which the participant lived in a home characterized by high conflict, low parental warmth, and a chaotic or unpredictable daily life from ages 5 – 15 (Taylor et al., 2004).

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Social Isolation & Loneliness

Social relationships are central to human well-being and are critical to the maintenance of mental and physical health (Baumeister & Leary, 1995). There are different aspects of one's social relationships that can be assessed, including objective measures of how connected one is to others and the more subjective measure of perceived loneliness. A meta-analysis found that across studies and controlling for relevant confounds, social isolation, loneliness, and living alone were each independently associated with a greater than 25% increased likelihood of mortality (Holt-Lunstad, Smith, Baker, Harris, Stephenson, 2015). In analyses of the Health and Retirement Study data, Hughes et al. (2004) found that social isolation and loneliness were related, but the relationship was relatively modest, suggesting these are independent constructs and should both be measured.

Social Isolation

Social isolation is an objective and quantifiable reflection of reduced social network size and lack of social contact. Socially isolated individuals are at increased risk for cardiovascular disease (Barth, Schneider, & von Känel, 2010), cognitive decline (Bassuck, Glass, & Berkman, 1999), and mortality (Kaplan et al., 1998). Social isolation is also associated with precursors to disease such as heightened blood pressure and peripheral inflammation (Hawkey, Thisted, Masi, Cacioppo, 2010; Louks, Berkman, Gruenewald, Seeman, 2006; Shankar, McMunn, Banks, & Steptoe, 2011).

Social isolation is often measured with **Cohen's Social Network Index** measure. In a classic study linking social ties to the common cold, Cohen et al. (1997) assessed participation in 12 types of social relationships. These include relationships with a spouse, parents, parents-in-law, children, other close family members, close neighbors, friends, workmates, school-mates, fellow volunteers, members of groups with religious affiliations, and members of religious groups. One point was assigned for each type of relationship the participant indicates having, as defined by speaking to someone in that category at least once every two weeks. Number of total contacts is also captured. Results showed that people who participate in more *types of* social relationships have less susceptibility to the common cold. This relationship remained significant after controlling for *number of contacts*, indicating there is something health-protective about having a diversity of types of social relationships, not just a linear relationship between number of contacts and health. This scale can be found here:

<http://www.psy.cmu.edu/~scohen/SNI.html>

The **Berkman-Syme Social Network Index** (Berkman & Syme, 1979) is a similar measure that includes subjective experiences of connection to contacts. It asks participants both frequency of contact (e.g. how many close friends do you see at least once a week) and perceived closeness (e.g. how many close friends do you have that you feel at ease with, can talk to about private matters?) This is a composite measure of four types of social connections: marital status (married vs. not); sociability (number and frequency of contacts with children, close relatives, and close friends); church group membership (yes vs. no); and membership in other community organizations (yes vs. no). This measure allows researchers to categorize individuals into four levels of social connection: from socially integrated, moderately socially integrated, or socially isolated, the latter being characterized by being unmarried, having fewer than six friends or relatives, and no membership in either church or community groups. This measure can be found here:

<https://www.phenxtoolkit.org/index.php?pageLink=browse.protocols&filter=1&id=211100>

Loneliness

Loneliness can be defined as the perceived lack of social companionship. It can be conceptualized as the subjective psychological component of social isolation, or the individual's distress caused by infrequent contact or connection with their social contacts. To study loneliness, Russell, Peplau, & Ferguson (1978) developed the **UCLA Loneliness Scale**. The original version of this scale had 20 items and had strong validity and reliability. Hughes et al. (2004) shortened this scale to three items for epidemiological studies. These items are: How often do you feel that you lack companionship? How often do you feel left out? How often do you feeling isolated from others? Loneliness is associated with several indices of self reported and measured physical health, with higher self-reported loneliness positively associated with health outcomes such as mortality, functional limitations, and depressive symptoms (Holt-Lunstad et al., 2015; Luo, Hawkey, Waite, & Cacioppo, 2012; Shankar et al., 2017). The complete UCLA Loneliness Scale – Version 3 (Russell, 1996) can be found here: http://fetzer.org/sites/default/files/images/stories/pdf/selfmeasures/Self_Measures_for_Loneliness_and_Interpersonal_Problems_VERSION_3_UCLA_LONELINESS.pdf

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Major Life Events

Life events are time-limited and episodic in nature, such as getting into an accident, being laid off, being broken up with, or receiving a life-threatening diagnosis. Life events can be events that seem positive on the surface but are in fact quite demanding such as getting promoted at work or getting married. These circumstances occur in a specific moment in time, with an identifiable onset. Although the actual event can be relatively brief, events can have varying long-term consequences, depending on the nature of the event and its sequelae, especially in relation to initiating chronic stressors.

Major life events are typically captured by presenting respondents with a checklist of potential events and asking them to select the ones that occurred in a specific time frame (e.g., lifetime or past year). Various major life events measures exist, each with their own limitations. Wheaton & Turner's (1995) have reviewed major life events measures and provide a detailed discussion on various issues. There is no measure of major life events that is considered the gold standard. Below we outline several measures that are frequently used:

The **Life Events List** (LEL; Cohen, Tyrrell, & Smith, 1991) assesses the number and types of stressful life events experienced during the past year, as well as the degree of stress experienced in each. Respondents indicate if one of 21 life events or 3 optional events occurred during the past 12 months. More information is available here: <https://www.cmu.edu/common-cold-project/measures-by-study/psychological-and-social-constructs/stress-measures/major-stressful-life-events-questionnaire.html>

The **Psychiatric Epidemiology Research Interview life events scale** (Dohrenwend et al., 1982) lists 102 events, and is often used in large general population surveys.

Wheaton's stress measure is a 51-item inventory of subjectively reported chronic stressors has been developed by Wheaton (1991, 1994), available in Turner & Wheaton (1995, see appendix).

There are also more in-depth interview-based measures that capture major life events such as the **Life Events and Difficulties Schedule (LEDS)**, the **Standardized Event Rating System (SEPRATE)**, the **UCLA Life Stress Interview** (Hammen 1989; 2003; 2004), and the **Stress and Adversity Inventory (STRAIN)**.

The LEDS and SEPRATE are reviewed in detail here: <http://www.macses.ucsf.edu/research/psychosocial/stress.php#interview>

The UCLA Life Stress Interview assesses chronic, ongoing stressful conditions in major role domains, as well as episodic stressful life events. It takes 30-45 minutes to administer. More information is available here: <http://hammenlab.psych.ucla.edu/interview.html>

Major limitations of person interviews are that the process is time consuming and requires intensive interviewer and rater training. However, an automated online, based on the LEDS, is now available, the STRAIN. The STRAIN is the first online system for a comprehensive and systematic measurement of cumulative lifespan stress. For a detailed summary see our section on measures under development. Read more about this measure here: <http://stresscenter.ucsf.edu/measures/stress-and-adversity-inventory-strain>

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Traumatic Life Events

Traumatic events are life events that are particularly severe in that they clearly threaten the physical and/or psychological safety of the person or those close to them such as witnessing or experiencing violence, death of a loved one, experiencing abuse, or natural disasters. Experiencing a greater number of traumatic events across the lifespan is associated with worse self-reported health, greater health care utilization, functional disability, arthritis, greater number of acute and chronic illnesses, and mortality (Gawronski, Kim, & Miller, 2014; Keyes et al., 2013; Krause, Shaw, & Cairney, 2004; Rosengren, Wilhelmsen, & Orth-Gomér, 2004). Experiencing trauma in childhood is particularly deleterious for health; there is strong evidence that early childhood adversity is associated with higher rates of illness in adulthood including cancer, depression, cognitive decline, and premature mortality (Brown, Harris, & Hepworth, 1995; Kelly-Irving et al., 2013; Barnes et al., 2012; Montez & Hayward, 2014).

The Trauma History Questionnaire (THQ) assesses lifetime exposure to traumatic stressors (Green, 1996). Designed primarily as a method for assessing PTSD-related events, the instrument consists of 24 yes or no questions that address different traumatic events of three primary types: (a) crime-related events (e.g., robbery, mugging), (b) general disaster and trauma (e.g., injury, disaster, witnessing death), and (c) unwanted physical and sexual experiences. For each item that is endorsed, participants indicate whether they have experienced the stressor and, if so, the number of times it was experienced and the age of the exposure(s). For the six sexual and physical trauma questions, participants are asked whether the experience was repeated and, if so, approximately how often and at what age. Consequently, the THQ is best used to assess lifetime exposure to situations specifically involving threat to life, such as those involving assaults to physical integrity, tragic accidental loss of loved ones, and witnessing death or violence (Green, 1993).

The THQ can be self-administered (approximately 10-15 minutes) or interviewer-administered (15-20 minutes), with administration times varying based on the number of stressors experienced. Based on the information collected, investigators can in turn obtain a total score representing the frequency and types of stressors endorsed, as well as subscale scores that are calculated by summing items associated with crime-related events (4 items), general disaster and traumatic experiences (13 items), and physical and sexual experiences (6 items). The system has acceptable reliability, with stability coefficients for specific life events ranging from .51 - .91 (Hooper, Stockton, Krupnick, & Green, 2011). In addition, the instrument's validity has been examined in several different contexts and in relation to different mental and physical health problems (Hooper et al., 2011). More information, and the scale itself, are available here: <https://www.ptsd.va.gov/professional/assessment/te-measures/thq.asp>

Another self-report measure that assesses lifetime exposure to traumatic events is the **13-item Stressful Life Events Screening Questionnaire (SLESQ)** (Goodman, Corcoran, Turner, Yuan, & Green, 1998). It assesses life-threatening accidents, physical and sexual abuse, and witness to another person being killed or assaulted. Respondents indicate whether the event happened, their age at the time of the event, and other questions about the event (e.g., duration). It is recommended for research and general screening purposes in non-clinical samples. More information and the scale itself are available here: <https://www.ptsd.va.gov/professional/assessment/te-measures/stress-life-events.asp>

The **Life Events Checklist** (Blake, Weathers, Nagy, Kaloupek, Charney, & Keane, 1995) is another measure that captures 17 types of potentially traumatic events. This scale was developed at the National Center for Posttraumatic Stress Disorder (PTSD) concurrently with the Clinician Administered PTSD Scale (CAPS) to facilitate the diagnosis of PTSD. The response scale for this measure is unique because it lists the event, then asks what the relationship between the respondent and the event is. The response scale options are: happened to me, witnessed it, learned about it, not sure, doesn't apply.

Other common trauma exposure measures are also listed and described here:<https://www.ptsd.va.gov/professional/assessment/te-measures/index.asp>

Of note, these measures assess both stress exposure as well as subjective responses. At this point it is not clear how important subjective response are, but they may be more accurate and meaningful for recent events than assessing perceptions from events from years earlier.

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Stigma, Discrimination, and Vigilance for Bias

Stigma is defined in multiple ways from the classic definition by Goffman (1961) as a “mark that deeply discredits someone from a whole and usual person to a tainted and discounted one” to more contemporary definitions as a “negative social identity” (Crocker, Major, & Steele, 2001). The mental and physical health consequences of perceiving and experiencing discrimination or bias due to some aspect of the self that can be negatively judged appears to be persistent and pervasive. For example, in the U.S. individuals stigmatized based on racial categories, such as African Americans, are more likely than individuals not stigmatized by race, such as European Americans, to develop hypertension, cardiovascular disease, and lung cancer, have more years of morbidity, and higher mortality rates (Borrell et al., 2013; Krieger, 2014; Paradies, 2006; see also Dovidio et al., Priest & Williams, 2017; Richman, Pascoe, & Latteanner, 2017). Thus, stigmatized identities are viewed as possible *chronic stressors*.

Measuring perceptions and feelings related to stigma and bias has been approached from multiple perspectives including affective responses, cognitive perceptions, and implicit reactions.

Perceived Discrimination (Contrada, et al., 2001)

Similar to many stress measures, discrimination measures often focus on *perceptions, experience, and reaction* to actual/perceived events. The PEDQ (Perceived Ethnic Discrimination Measure) examines the extent to which people experience verbal rejection, perception of people avoiding them, denial of equal treatment, exclusion, threat of violence, peoples’ negative expectations—dishonest, violent, dirty, lazy—and experiencing aggression. The PEDQ limits the time to the last three months.

Contrada, R. J., Ashmore, R. D., Gary, M. L., Coups, E., Egeth, J. D., Sewell, A., . . . Chasse, V. (2001). Measures of ethnicity-related stress: Psychometric properties, ethnic group differences, and associations with well-being. *Journal of Applied Social Psychology, 31*(9), 1775-1820. Retrieved from <http://search.proquest.com/docview/619611719?accountid=14525>

Race-based Rejection Sensitivity (Mendoza-Denton, Downey, et al., 2002)

The race-based rejection sensitivity measure examines the extent to which individuals expect and are anxious about being rejected for reasons related to their racial identity. Each item in the scale consists of a context specific, ambiguous event – e.g., a teacher fails to call on you – and then participants are asked about the extent to which they expect this treatment to be due to their race and how anxious they would be if they experienced this.

Mendoza-Denton, R., Downey, G., Purdie, V. J., Davis, A., & Pietrzak, J. (2002). Sensitivity to status-based rejection: Implications for african american students' college experience. *Journal of Personality and Social Psychology, 83*(4), 896-918. Retrieved from <http://search.proquest.com/docview/619958380?accountid=14525>

Rejection sensitivity measures have also been developed for Asian Americans and socio-economic class differences:

Chan, W., & Mendoza-Denton, R. (2008). Status-based rejection sensitivity among asian americans: Implications for psychological distress. *Journal of Personality*, 76(5), 1317-1346. Retrieved from <http://search.proquest.com/docview/621848335?accountid=14525>

Rheinschmidt, M. L., & Mendoza-Denton, R. (2014). Social class and academic achievement in college: The interplay of rejection sensitivity and entity beliefs. *Journal of Personality and Social Psychology*, 107(1), 101-121. Retrieved from <http://search.proquest.com/docview/1539478943?accountid=14525>

Intergroup Contact (Islam & Hewstone)

Lack of quality and quantity intergroup contact is implicated in sustained anxiety during inter-racial/intergroup interactions. Assessing amount and quality of intergroup contact can provide an indicator of negative emotional responses associated with anticipated and actual interaction with outgroup members. In contrast, greater levels of past intergroup interaction has been associated with more positive/beneficial neurobiological responses such as decreased cardiovascular threat responses during intergroup interactions, lower levels of outgroup fear conditioning, and less amygdala responses upon viewing outgroup faces. Several intergroup contact measures exist but the advantage of the Islam and Hewstone measure is it provides both quality and quantity assessments of intergroup contact and is easily modified to change the target racial ethnic group.

Islam, M. R., & Hewstone, M. (1993). Dimensions of contact as predictors of intergroup anxiety, perceived out-group variability, and out-group attitude: An integrative model. *Personality and Social Psychology Bulletin*, 19(6), 700-710.

Implicit Association Test (Greenwald, Banaji, and Nosek, 2003)

While self-report measures are the most commonly used psychological assessment measures, there are limitations to self-report responses and this is particularly true when studying factors related to discrimination, bias, and racism. Either due to unwillingness or inability to accurately report on one's thoughts and feelings associated with these potentially complicated and politically charged issues, individuals may alter their explicit responses in ways that do not reflect their genuine thoughts or beliefs. One way to circumvent distortions in explicit self-reports is to use *implicit* measures that rely on reaction time responses as a way to understand deep-rooted cognitive associations with racial categories. The most commonly used implicit measure is the *Implicit Association Test*. This reaction time measure estimates biased responding by calculating difference scores between associations of two different comparison categories: for example White and Black persons, with valenced categories of good and bad. To the extent that individuals associate one racial category faster with positive words compared to the other category provides an estimate of bias that has been related to neurobiological responses, behavior such as doctor diagnosis and treatment, hiring decisions, and quick judgments of guilt or innocence of hypothetical individuals. The implicit association test can be found here at <https://implicit.harvard.edu/implicit/>

Greenwald, A. G., Nosek, B. A., & Banaji, M. R. (2003). Understanding and using the implicit association test: I. An improved scoring algorithm. *Journal of personality and social psychology*, 85(2), 197.

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Work Stress

Epidemiological studies and meta-analyses over the past several decades have clearly shown associations between high psychosocial work stress and worse physical health, including cardiovascular disease outcomes and mortality (e.g. Kivimäki et al., 2012; Nyberg et al., 2013). A meta-analysis of prospective cohort studies in 2013 found that an age- and sex-adjusted summary estimate of the relative risk for job strain on coronary heart disease is 1.35 (95% CI 1.2 to 1.5; Steptoe & Kivimäki, 2013).

Work stress in a psychosocial context is generally conceptualized in one of two ways: job strain and effort-reward imbalance. Job strain is defined as having a very demanding job coupled with little control over those demands. This definition comes from Karasek's job demand-control model (1979), which follows the Lazarus & Folkman (1984) argument that psychosocial stress is experienced when situational demands on the person outweighs perceived available resources. Job strain is most frequently measured with the Job Content Questionnaire (Karasek et al., 1998). The second conceptualization of work stress comes from the effort-reward imbalance model in which stress arises when people put a lot of effort into their jobs for little reward (in the form of money, career growth, or recognition). The basis for this theory comes from the premise that a fair balance between the costs invested in cooperative activities and the gains received from those behaviors is a fundamental component to cooperative social exchanges, and in cases when there is failed reciprocity, negative emotions and other detrimental outcome will occur (Siegrist, 1996; Siegrist et al., 2004; Siegrist & Wahrendorf, 2016). Although many measures of work stress exist, the two most commonly used ones come from these prevailing theories of work stress and health.

Job Content Questionnaire

The job demand-control model proposes that there are two areas of work that contribute to work stress: job demands and job control, with heavy job demands and low decision latitude leading to higher job strain (Karasek, 1979). Demands involves work load, time pressure and role conflict. Control is decision latitude, skill discretion, and decision authority. A job with both high demand and high control leads to active learning, motivation and skill development.

The original **Job Content Questionnaire (Karasek et al., 1998)** was 79 items that asks participants to self-report on experiences in their current job. The scale has since been used in considerably shorter iterations, including a 6-item version that is included in the Health and Retirement Study (along with several of the international HRS-family of studies). Example items for job strain are: My job requires working very fast; I am not asked to do an excessive amount of work; I have enough time to get the job done. Example item for job control is: I have very little freedom to decide how I do my work. For access to the scale visit <http://www.jcqcenter.org/>. For psychometric information see Kopp et al. (2010).

Effort-Reward Imbalance Scale

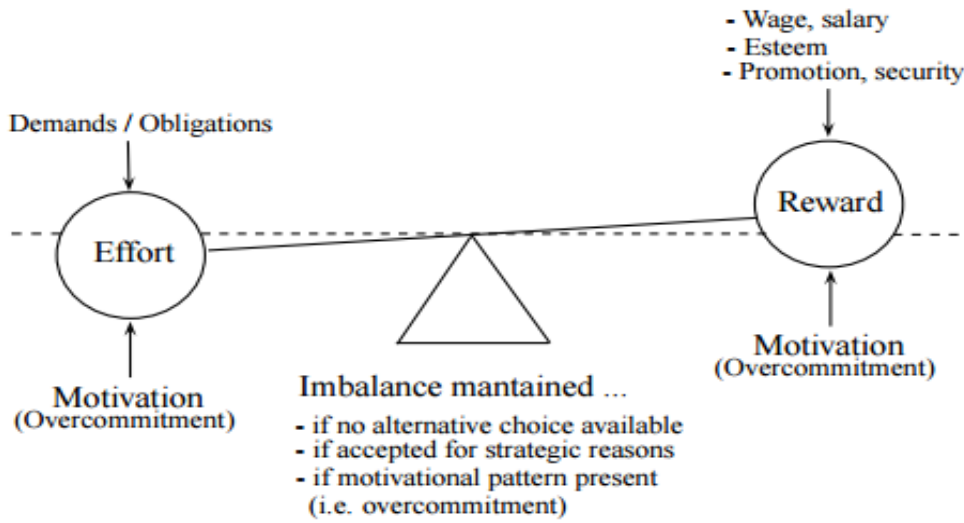
The effort-reward imbalance model (Siegrist, 1996; Figure 1) states that inadequate reciprocity for expended effort results in negative emotionality and is stress-related physiological dysregulation. It suggests that people characterized by a motivational pattern of excessive work-related commitment and a high need for approval, are at a high risk for distress from effort-reward imbalance. As a result of either exposing themselves to more demands at work or expending more effort than required, their expectations for rewards is higher (and often not met). Rewards include money, appreciation, and career or growth opportunities including job security. The model also states that the work role is vital to fulfill an individual's self-regulatory needs because work provides the opportunity to gain self-efficacy, self-esteem, and self-integration.

The theory that high effort-reward imbalance leads to physiological dysregulation associated with disease states is supported by empirical studies showing a link between effort-reward imbalance and objective measures of health like lower heart rate variability (Jarczok et al., 2013), coronary heart disease events (Dragano et al., 2017), type II diabetes incidence (Kumari, Head & Marmot, 2004), higher ambulatory blood pressure (Gilbert-Ouimet, Trudel, Brisson, Milot, & Vézina, 2014), depressive disorders (Rugulies, Aust, & Madsen, 2017), and sleep disturbances (Rugulies, Norborg, Sørensen, Knudsen, & Burr, 2009).

The **Effort-Reward Imbalance Questionnaire (Siegrist et al., 2004)** is a measure that captures three key components of the model – effort, reward, and tendency to ‘overcommit’. The scale was originally 22 items though a shorter 16-item version was developed and validated (Leineweber et al., 2010). Example items that capture effort component: I have constant time pressure due to a heavy workload; I have many interruptions and disturbances in my job. Example items that capture reward component: I receive the respect I deserve from my superiors; I experience adequate support in difficult situations. Example items that capture over-commitment: I get easily overwhelmed by time pressures at work; People close to me say I sacrifice too much for my job. In addition to the three components a ratio is then computed from the two scales to quantify the imbalance of effort and reward at individual level. For further scoring details and psychometric information see Montano et al. (2016) and Siegrist, Li, Montano (2014). For scale items see https://www.uniklinik-duesseldorf.de/fileadmin/Datenpool/einrichtungen/institut_fuer_medizinische_soziologie_id54/ERI/PsychometricProperties.pdf.

An important note here is that these work stress models were developed in the industrial era of the 1960s-1980s, when people worked in relatively secure jobs in factories and offices. In the current economic environment work cultures are different – people often work outside the office, industrial jobs are rarer, job security is a big issue, people move from one job to another, work is not confined to an 8 hour day for many people, work-life balance is a problem, to name a few changes. New models of work stress and new measures may need to be developed to capture these changes to modern life.

Figure 1: The effort-reward imbalance paradigm, and aspects that maintain imbalance



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Burnout

Burnout has been defined as a “prolonged response to chronic interpersonal stressors on the job” that is characterized by exhaustion, cynicism and detachment, and lack of accomplishment/ ineffectiveness from work (Maslach and Leiter, 2016). It is not simply the stress response of exhaustion, but includes a deterioration in the quality of one's work with others, and a subsequent negative evaluation of oneself. Burnout is reflected by negative scores on all three dimensions (Leiter and Maslach, 2016). For people working in health care and human services, burnout has long been recognized as a potential risk. But now burnout has been reported as a problem in many other occupations. Burnout is related to an increased risk for mental health problems (Leiter and Maslach, 2000) and physical health outcomes, including risk of cardiovascular disease and cardiovascular-related events (Melamed et al., 2006) as well as biological markers of neuroendocrine, immune, metabolic, and cardiovascular health (Juster et al., 2011).

Several research measures of burnout exist, and they vary in terms of what dimensions are assessed (all three or only exhaustion), and the number and response format of scale items. No clinical research has been done to establish a "cut-off score" (or "diagnosis") for dysfunctional levels of burnout. The measure of choice for new studies likely depends on the population of interest, the size of the population (shorter measures are only valid for very large samples), study hypotheses, financial limitations (e.g., licensing fees for propriety measures), study design considerations (e.g., repeated measures), and participants` time constraints.

The original research measure of burnout, and the one most commonly used, is the **Maslach Burnout Inventory (MBI; Maslach et al., 2017)**. The MBI assesses the three dimensions of the burnout experience -- exhaustion, cynicism/detachment, and professional inefficacy -- and contains either 22 items or 16 (for the General Surveys). Several MBI versions exist for different study populations -- the MBI-General Survey (which can be used for any population), the MBI-Human Services Survey, the MBI-Human Services Survey for Medical Personnel, MBI-Educators Survey, and MBI-General Survey for Students. The MBI has been translated into many languages and has been validated widely, including health care providers (Poghosyan et al., 2009; Rafferty et al., 1986). The MBI is copyrighted, and permission to reproduce it or translate it must be obtained from the publisher, Mind Garden: <http://www.mindgarden.com/117-maslach-burnout-inventory>

Additional multidimensional non-proprietary burnout measures exist, differing in occupational focus and measured dimensions of burnout (reviewed in Maslach and Leiter, 2016):

- **The Bergen Burnout Inventory, 9 items** (BBI; Feldt et al., 2014) measures burnout in the work context (in all occupations), assessing (1) exhaustion at work (emotional component), (2) cynicism toward the meaning of work (cognitive component), and (3) the sense of inadequacy at work (behavioral component). The 9-item BBI can be found in the paper by Salmelo-Aro and colleagues (2011).
- **The Oldenburg Burnout Inventory, 16 items** (OLBI; Halbesleben and Demerouti, 2005) assesses (physical, affective, and cognitive) exhaustion and disengagement in both work and academic contexts, whereas personal accomplishment is excluded. The English version of the original OLBI can be found here: (Demerouti et al., 2010). The OLBI has been adapted to capture academic burnout (OLBI-S). The OLBI-S English, German and Greek version can be found in the paper by Reis and colleagues (2015).

- **The Professional Quality of Life Compassion Satisfaction and Fatigue Version 5, 30 items** (ProQOL; Figley and Stamm, 1996; Stamm, 2010) scale assesses both positive and negative aspects of professional care; it is one of the most commonly used scales for frontline providers who work with stress- and trauma-exposed populations (Stamm, 2010). The ProQOL has subscales for burnout, compassion satisfaction and compassion fatigue/secondary traumatic stress. The ProQOL is freely available here, as long as author is credited, no changes are made, and it is not sold: http://www.proqol.org/ProQol_Test.html

Other burnout measures focus on exhaustion alone:

- **The 14 item Shirom-Melamed Burnout Measure** (SMBM; Shirom, 1989) conceptualizes burnout as the depletion of energetic resources, distinguishing between physical fatigue, emotional exhaustion, and cognitive weariness. The SMBM can be downloaded here: <http://www.shirom.org/arie/index.html>
- **The Copenhagen Burnout Inventory** (CBI; Kristensen et al., 2005) assesses personal burnout (6 items), work-related burnout (7 items), and client-related burnout (6 items). In the CBI, the core of burnout is physical and psychological exhaustion. The measure can be downloaded here: <http://www.arbejdsmiljoforskning.dk/upload/CBI-scales.pdf>
- **The Burnout Measure** (BM; Pines and Aronson, 1988) includes 21 items, designed to measure physical, emotional, and mental exhaustion. A shorter 10-item version is also available (see appendix in Malach-Pines, 2005).
- A **single-item measure** served as a reliable substitute for the MBI exhaustion dimension across occupations (Dolan et al., 2015).

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Financial Strain

This summary focuses on measures that capture the psychosocial distress related to insufficient financial resources (aka financial strain). Readers interested in measurement of socioeconomic status more broadly are directed to this existing resource: <http://www.macses.ucsf.edu/default.php>.

Measures of financial strain have been incorporated into several large-scale population health studies, including the Americans' Changing Lives Study, Coronary Artery Risk Development in Young Adults (CARDIA), Study of Women Across the Nation (SWAN), and the Whitehall II study, among many others. Overall, greater reports of financial strain are associated with poorer health, including increased mortality risk, poor mental health, and alterations in physiological processes implicated in the development of chronic diseases, such as cardiovascular disease and diabetes, as well as premature mortality (Georgiades et al., 2009; Matthews et al., 2002; Puterman et al., 2012; Szanton et al., 2008).

Several measures have been developed to assess financial strain. Recently the National Academy of Medicine convened a panel of experts to identify which social and behavioral measures should be captured as part of electronic health records (NAM, 2014). A measure of financial resource strain was recommended. Derived from (Kahn and Pearlin, 2006), the specific measure is as follows:

- In the past month, how hard has it been for you to pay for the very basics like food, housing, medical care, and heating? Would you say... 1 = very hard, 2 = hard, 3 = somewhat hard, or 4 = not very hard

Benefits of this measure is that it is a single item, face valid, and covers multiple life domains. However, this item may not be appropriate for researchers interested in the differential effects financial strain from specific sources. It is notable that versions of this measure have been used to assess financial strain at different stages of the life course. For instance, if interested in childhood financial strain, Kahn & Pearlin asked "Thinking back to your years up to age 18, how difficult was it for your family to meet expenses for basic needs like food, clothing, and housing?"

Additional measures of financial strain include:

Economic Strain Model measure (Pearlin et al., 1981)

At the present time:

1. Are you able to afford a home suitable for (yourself/your family)?
2. Are you able to afford furniture or household equipment that needs to be replaced?
3. Are you able to afford the kind of car you need?
4. Do you have enough money for the kind of food (you/your family) should have?
5. Do you have enough money for the kind of medical care (you/your family) should have?
6. Do you have enough money for the kind of clothing (you/your family) should have?
7. Do you have enough money for the leisure activities (you/your family) want(s)?
8. Do you have a great deal, some, a little, or no difficulty in paying your bills?
9. At the end of the month do you end up with some money left over, just enough to make ends meet, or not enough money to make ends meet?

These sets of questions were originally administered by interview. While scoring is not provided in the article, several large-scale studies have used item 9 as a stand-alone item. A cumulative score could also be created.

Financial strain items by McLoyd et al., (1994)

1. How often in the past 2 years, in order to make ends meet, you had to borrow money from friends or family to help pay bills? (1 = not at all, 4 = a lot).
2. How often you decided not to buy something you really needed for yourself or your children because you couldn't afford it (1 = not at all, 4 = a lot).
3. How difficult it has it been to pay the family bills lately? (1 = not difficult at all, 4 = very difficult).

Single item of financial strain (Pearlin et al., 1981; Okechukwu et al., 2012)

This single item is derived from Pearlin et al., 1981 and included in the Work, Family, and Health Network Study (Okechukwu et al., 2012).

- How would you describe the money situation in your household right now? Response options: “comfortable with extra,” “enough but no extra,” “have to cut back,” and “cannot make ends meet”

Financial Chronic Stress Scale (Lantz et al., 2005)

1. How satisfied are you with your/your family's present financial situation? (5-point response scale with 1 = completely satisfied and 5 = not satisfied at all)
2. How difficult is it for you/your family to meet monthly payments on your bills? (5-point response scale with 1 = extremely difficult and 5 = not difficult at all)
3. In general, how do your (family's) finances usually work out at the end of the month? (1 = some money left over, 2 = just enough money, and 3 = not enough money)

Responses to each item are standardized (with a mean of zero and standard deviation of one) and then averaged to create a scale with all items given equal weight.

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Neighborhood Safety and Cohesion

Perceptions of one's neighborhood, such as feeling unsafe in one's neighborhood or lack of neighborhood cohesion, have been linked to poorer physical health (Robinette, Charles, & Gruenewald, 2016; Murayama, Fujiwara, & Kawachi, 2012; Robinette, Charles, Mogle, & Almeida, 2013). Objective aspects of neighborhoods, such as crime statistics and income, are also often assessed and associated with health (Weden, Carpiano, & Robert, 2008). However, here we focus on measures to assess subjective reports of neighborhood qualities, given evidence that neighborhood perceptions may show particularly strong links with health outcomes compared to objective assessments (Weden, Carpiano, & Robert, 2008).

Several aspects of neighborhood environment have been proposed as relevant for health outcomes. For example, lack of **neighborhood social cohesion** has been associated with self-rated physical health and physical symptoms (Murayama, Fujiwara, & Kawachi, 2012; Robinette, Charles, Mogle, & Almeida, 2013). However, reliable and valid measures have been scarce. The most frequently used measure, developed by Sampson, Raudenbush, and Earls (1997), consists of 5 items rated on a five-point scale ("people around here are willing to help their neighbors," "this is a close-knit neighborhood," "people in this neighborhood can be trusted," "people in this neighborhood generally don't get along with each other," and "people in this neighborhood do not share the same values"). Variations of a subset of these items have also been used in some large-scale samples (e.g., the Midlife in the United States (MIDUS) study: "I could call on a neighbor for help if I needed it; People in my neighborhood trust each other").

Another important feature of neighborhood environment is perceived **neighborhood safety**. Feeling unsafe in one's neighborhood has been associated with later chronic health conditions (Robinette, Charles, & Gruenewald, 2016). No state-of-the-art measures exist, but previously tested items assessed global perceptions of neighborhood safety, such as "...how safe do you feel walking alone in your neighborhood?", which is rated by participants for both daytime and night-time (De Jesus, Puleo, Shelton, & Emmons, 2010). Slight variations have also been used in some large-scale studies. For example, the Midlife in the United States (MIDUS) study assessed participants' ratings of "I feel safe being out alone in my neighborhood during the daytime" and "I feel safe being out alone in my neighborhood at night" (based on Keyes, 1998).

A closely related concept is perceived **neighborhood disorder** – the degree to which there is a lack of safety, peace, social control, and observance of the law in the neighborhood. Ross and Mirowsky (1999) developed the 15-item Neighborhood Disorder Scale, which assesses aspects of physical order/disorder (e.g., graffiti, vandalism, cleanliness) as well as social order/disorder (e.g., drug use in neighborhood, police protection), which includes perceptions of safety (e.g., "My neighborhood is safe"). Perceived neighborhood safety and neighborhood disorder have been associated with physiological risk factors such as flatter diurnal cortisol slopes (Do et al., 2011; Karb, Elliott, Dowd, & Morenoff, 2012) and telomere shortness, even after adjusting for demographic and socioeconomic characteristics (Park, Verhoeven, Cuijpers, Reynolds Iii, & Penninx, 2015).

Other self reported neighborhood characteristics have also been examined. For example, Mujahid and colleagues (2007) have developed psychometrically and ecometrically valid subscales for social cohesion (4 items) and safety (3 items), aspects of aesthetic quality (6 items), walking environment (10 items),

availability of healthy foods (4 items), violence (4 items), and activities with neighbors (5 items), and similar scales have been developed for other countries, as well as for urban vs rural regions.

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Daily Stressors

Daily Stressors are defined as routine challenges of day-to-day living, such as the everyday concerns of work, caring for other people, and commuting between work and home. They may also refer to more unexpected small occurrences such as arguments with children, unexpected work deadlines, and malfunctioning computers that disrupt daily life. Daily stressors are often assessed via self-reports of specific events over multiple days. These events represent tangible, albeit minor interruptions that may have a more proximal effect on well-being than major life events such as job loss and divorce. In terms of their physiological and psychological effects, reports of major life events may be associated with prolonged arousal whereas reports of daily stressors may be associated with spikes in arousal or psychological distress that day. In addition, minor daily stressors exert their influence not only by having separate and immediate direct effects on emotional and physical functioning, but also by piling up over a series of days to create persistent irritations, frustrations, and overloads that may result in more serious stress reactions.

The Daily Inventory of Stressful Events (DISE), a semi-structured instrument that combines stem questions about specific stressors followed by open-ended probes (Almeida et al., 2002, Almeida et al., 2011). For each daily stressor, the DISE provides six categories of information. Expert coders rate the first four categories: (a) content classification of the stressor (e.g., work overload, argument over housework, traffic problem); (b) who was the focus of the event; (c) dimensions of threat (i.e., loss, danger, disappointment, frustration, opportunity); and (d) severity of the stressor. Inter-rater reliability ranges from .74 to .90 across all of the codes. The last two categories include respondents' reports of the (a) degree of subjective severity and (b) primary appraisal (i.e., areas of life that were at risk because of the stressor). Validation studies have shown a modest degree of independence between the severity ratings, threat dimensions, and appraisal domains (Almeida et al., 2002). A recent series of analyses shows that emotional reactivity to DISE assessed daily stressors (upticks in negative affect on stressor days) predicts long-term psychological and physical health. Using longitudinal data from the Midlife in the United States Study, individuals who reported greater stressor reactivity at baseline were 46 percent more likely to experience affective disorders and 33 percent more likely to have increased chronic health conditions 10 years later (Charles et al, 2013, Piazza et al., 2013a). Greater stressor reactivity was also associated with higher inflammation, lower heart rate variability and greater mortality (Chaing et al, 2018; Mroczek et al., 2015; Sin et al., 2015, Sin et al., 2016)

The DISE is an outgrowth of previous checklist approaches to the assessment of daily stress. **The Daily Life Experiences (DLE)** checklist comprises a list of 78 events that represent various domains in daily life, and scales for obtaining subjective ratings of the desirability and meaningfulness of each experienced event (Stone & Neale, 1982). Brantley and Jones (1989) developed a similar measure, the **Daily Stress Inventory**, which assesses 58 minor events as well as a subjective rating of how stressful each event was. Similarly, DeLongis and colleagues (DeLongis et al., 1992) **Hassles Scale** includes 53 items, assessing domains similar to those mentioned above. Zautra and colleagues (Zautra et al., 1986) have also shown that a shorter 18-item checklist, the **Inventory of Small Life Events (ISLE)**, can be effectively adapted for use in a daily diary design. The approach of administering event checklists on a daily basis has important implications for the assessment of daily stressors. The repeated daily assessment of individuals using checklists allows for improved precision in characterizing the typical days of individuals as the day is the unit of analysis. Checklists such as the DLE and ISLE also include subjective ratings about each event that provide more information than whether an event simply occurred, adding multidimensional data about events, days, and individuals. A potential limitation of the daily checklist approach is that the experience of a broad range of events is obtained at the expense that the experience of a broad range of events is

obtained at the expense of obtaining intimate, and potentially useful, in-depth knowledge that is captured in the DISE.

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Appraisals of Acute Stress

Acute stress is a relatively short-term response (minutes to hours as opposed to days and months) to an environmental, personal, or interpersonal situation, during which the body mobilizes metabolic resources and the individual's cognitive and affective resources are directed at the stimulus/event. Biological and physiologic responses are often used to quantify the body's response to acute stress using a variety of end outcome states such as cortisol, immune changes, blood pressure, cardiac responses (heart rate, cardiac output, pre-ejection period), and other peripheral measures like skin conductance, skin temperature, muscle contraction, pupil changes, and pulse related responses.

While common language labels have been used in measures to quantify the amount of stress one is experiencing (e.g., "how much stress do you feel?"), these questions don't align well with the varied responses that occur during acute stress episodes. That is, not all stress responses are created equal. Some stress profiles are believed to be detrimental to physical health and performance, whereas others are believed to benefit health and performance (Blascovich & Mendes, 2010; Dientsbier, 1989; Epel, McEwen, & Ickovics, 1998; Lazarus & Folkman, 1987; McEwen, 1998; Selye, 1982). Using self-report measures that attempt to capture the varied nature of stress reactions may provide a more useful metric to quantify and differentiate stress and provide more predictive utility.

Lazarus and Folkman's identified two distinct and independent elements of stress: 1) perceived situational and personal demands, and 2) personal resources. To the extent that perceived demands outweigh resources then individuals are anticipated to be in a "threat" state, whereas when resources outweigh demands individuals are expected to be in a "challenge" state. Lazarus and Folkman's theory was adopted to examine differences in cardiovascular (and, later, neuroendocrine) responses during acute stress episodes. Blascovich and Tomaka (1996) first identified cardiovascular (CV) patterns that differentiated self-reported appraisals of demands and resources such that a more adaptive/benign pattern of CV reactivity occurred when resources exceeded demands (i.e., challenge) and a more maladaptive pattern (i.e., threat) when demands exceeded resources. Using this foundation, Mendes and colleagues (Mendes, et al., 2007) developed a scale using the components of demands and resources. Specifically, demands are made up of perceived uncertainty, required effort, and how demanding the task seems, whereas resources comprise perceived knowledge and abilities, controllability, social support, and expectations. Two questionnaires were developed; one is a pre-task version that captures appraisals of the stressor after knowledge of the task demands is obtained but prior to the action/performance of the task (e.g., once a public speaking task is described, but before the speech is delivered). There is also a post-task questionnaire that assesses individuals' perceptions of the demands and resources after the task. Importantly, published and unpublished analyses support the conclusion that *pre-task* appraisals are more predictive of physiological responses during the task than *post-task* appraisals (Quigley, Barrett, Weinstein, 2002).

When citing the measure*, use: Mendes, W. B., Gray, H., Mendoza-Denton, R., Major, B. & Epel, E. (2007). Why egalitarianism might be good for your health: Physiological thriving during stressful intergroup encounters. *Psychological Science*, 18, 991-998.

*Note, this article is not a scale development article, but rather the first published article that used this scale. Many published papers have followed using this scale (see references).

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Trait Resilience

The concept of resilience describes a highly complex and multi-level construct. A person is thought to be resilient if they “bounce back” to their baseline level of functioning in the face of significant stress, trauma, adversity, or threat (Southwick et al., 2014). Resilience can further include going beyond baseline capacities and developing stronger resources or achieving benefits as a result of stress exposure (Bonanno, 2004). This has been given various labels such as “benefit finding,” (Tomich & Helgeson, 2004) and “post-traumatic growth,” (Tedeschi & Calhoun, 1996) each of which can be assessed with scales that measure aspects of growth (e.g. Post-Traumatic Growth Inventory; Tedeschi & Calhoun, 1996; and Benefit Finding Scale; Tomich & Helgeson, 2004.). For a helpful overview on benefit finding and post-traumatic growth, see Lechner, Tennen, and Affleck (2009). Here, we describe measurement options for the concept of trait resilience.

Certain traits confer resilient responses to stressors. There are also dynamic processes over time that can promote resilient responses. Given the multidimensional complexity of the construct of psychological resilience, and multiple ways to measure resilient responses over time, we focus narrowly on the former: trait-like protective factors, which can include individual traits (e.g. optimism, adaptive coping, personal competence, self-efficacy, and self-enhancement) and individual resources (e.g., family cohesion, social support, and cultural influences) (Ahern et al., 2006; Windle, Bennett, & Noyes, 2011). While there is no identified “gold standard” measure of resilience, we present four of the most commonly used self-report scales that assess personal characteristics and trait-like variables shown to predict outcomes of recovery or return to baseline in both clinical and non-clinical adult populations. These scales are considered one-dimensional in that each generates a total score that identifies resilience as a personal modifiable characteristic (Prince-Embury, Saklofske, & Vesely, 2015).

The Resilience Scale (RS) is a widely used 25-item scale that measures resilience as an accumulation of personal strengths and positive adaptation to stressful events (Wagnild & Young, 1993). The RS was designed to measure what the authors regarded as “the Resilience Core”, five core characteristics of resilience: Purpose, Equanimity, Self-Reliance, Perseverance, and Existential Aloneness. Rated on a 7-point response scale (1 = *disagree*; 7 = *agree*), the RS was originally validated with older adults and has since been used with a variety of ages including teens and young adults (Santos et al., 2013). The RS has demonstrated a significant inverse relationship with indices of psychological distress (e.g. depression, anxiety, and post-traumatic stress) and positive correlations with measures of well-being (e.g. self-esteem and self-efficacy). The scale has been extensively evaluated in clinical populations with cancer (Cohen, Baziliansky, & Beny, 2014), menopausal symptoms (Pérez-López et al., 2014), and mental illness (Aiena et al., 2015), to name a few. Sample items include “*I can get through difficult times,*” “*I am determined,*” and “*I take things in stride.*” The scale has shown high construct validity with α ranging from .87 to .95. Shorter versions of the scale, RS-14 and RS-10 (for children), also have solid psychometric properties with strong correlations to the original 25-item scale ($r = .97$) and internal consistency reliability of $\alpha = .93$ (Pritzker & Minter, 2014). Overall, the RS has proven useful in a variety of purposes including psychosocial intervention evaluation and clinical assessment.

Permission and location: For permission to use the Resilience Scale (RS) go to: www.resiliencescale.com

The Connor-Davidson Resilience Scale (CD-RISC) is a 25-item scale that has been commonly used to assess resilience in non-clinical trauma survivors and clinical populations suffering from post-traumatic stress and other psychiatric disorders (Connor & Davidson, 2003), with responses rated on a 5-point scale (0 = *not true at all*; 4 = *true nearly all of the time*). The CD-RISC demonstrates strong internal

consistency reliability, $\alpha = .89$ and has shown significant negative correlations with the Perceived Stress Scale and positive associations with measures of social functioning suggesting that greater resilience is related to lower levels of stress and greater social support. The CD-RISC has been used to evaluate resilience training interventions (Mealer et al., 2014), where improvements are typically found suggesting that it is a malleable trait. In clinical populations, the CD-RISC has been useful as an outcome measure and predictor of treatment effect in pharmacological trials (Vaishnavi, Connor, & Davidson, 2007) and psychosocial interventions such as cognitive behavior therapy (Davidson et al., 2005). Sample items include, *"I am not easily discouraged by failure,"* and *"I take pride in my achievements."* From a trait perspective, it is posited that the CD-RISC could function as a tool to assess resilience characteristics (e.g. hardiness) as a protective factor in clinical populations (Connor & Davidson, 2003). In general, the CD-RISC has utility in measuring resilience as a quantifiable outcome predictive of global health status and trait-like resistance to trauma exposure.

Permission and location: *For permission to use the Connor-Davidson Resilience Scale (CD-RISC) go to: www.connordavidson-resiliencescale.com*

The Brief Resilience Scale (BRS) is a 6-item scale developed to provide a brief assessment of recovery from illness or psychological pathology in non-clinical populations (Smith et al., 2008). The scale has been tested with a wide range of participants including healthy college students and adults, patients experiencing chronic health-related stressors (e.g. cardiac rehabilitation), and non-clinical populations facing life adversities (e.g. job-related stress) (Prince-Embury, Saklofske, & Vesely, 2015). The authors purport that the BRS is the only scale that measures the most basic definition of resilience, an individual's capacity to "bounce back" from stress-related adversity (Smith et al., 2013). Not to be confused with the 25-item RS (Wagnild & Young, 1993), this scale, rated on a 5-point scale (1 = *strongly disagree*; 5 = *strongly agree*), specifically assesses the ability to recover from rather than resist illness. With strong internal consistency reliability, $\alpha = .95$, convergent validity of the BRS is demonstrated by positive correlations with personal and social resources (resilience resources) typically associated with resilience as a process outcome (e.g. active coping, mindfulness, optimism, and social support). Sample items include, *"I tend to bounce back quickly after hard times,"* *"I tend to take a long time to get over set-backs in my life (reverse scored),"* and *"It does not take me long to recover from a stressful event."* Studies might find the BRS useful as a predictor of treatment effect in longitudinal interventions targeting "resilience resources." The scale provides a summary score that predicts health outcomes and specifically measures (1) psychological recovery during illness and (2) change in psychological pathology (anxiety, depression, negative affect).

Permission and location: *Contact the author for permission to use the Brief Resilience Scale (BRS).*

The Resilience Scale for Adults (RSA) (Friborg et al., 2003) is a 37-item scale that measures resilience as healthy adaptation and personal competence during exposure to significant adversity, trauma, or stress. Similar to Wagnild and Young's Resilience Scale (RS), the RSA assesses resilience as a construct of interpersonal protective factors (e.g. personal competence, social competence, family coherence, social support, and personal structure) with a total score calculated as a combination of each factor. Examples of factor content include trait measures of self-efficacy and self-confidence, positive affect, ability to organize and plan, and the availability of stable social support both given and received (Friborg et al., 2005). Sample items include, *"I believe in my own abilities,"* *"At hard times, I know that better times will come,"* and *"I have some close friends/family members who really care about me."* Each factor individually demonstrated strong internal consistency reliability with a Cronbach's alpha ranging from .90 to .67. Convergent validity was demonstrated with positive correlations with the Sense of Coherence Scale (Antonovsky, 1993) a self-report measure designed to assess the interaction between stressors, coping, and health leading to a global perspective of the stressor as comprehensible, manageable, and

meaningful. The RSA has been useful as a cross-cultural assessment of protective factors in both clinical and non-clinical populations with higher scores indicating higher levels of protective resilience.

Permission and location: *Contact the author for permission to use the RSA scale.*

Corresponding Author. This summary was prepared by Nikko Da Paz, PhD and a review is currently underway. This document will be updated when the review are received. If you have any comments on these measures, email Nikko.DaPaz@ucsf.edu. Version date: January 2018.

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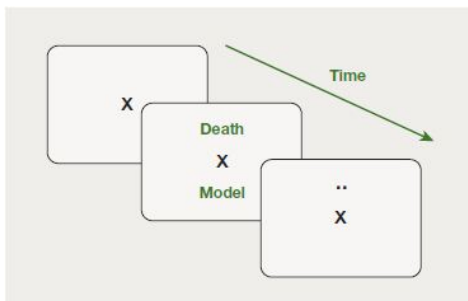
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Threat Sensitivity Measures

Some individuals may be more vulnerable to acute or chronic stress due to past experiences (trauma, early adversity), current environment (poverty, stigmatization), and/or personality/dispositions. Individual moderators of stress may illuminate who is more or less likely to experience physical or mental health problems. There are a variety of measures that attempt to capture individual vulnerability. Here we review a class of measures that fall under the larger category of “Threat Sensitivity Measures.” All of these measures offer a non-self-report approach to measuring threat sensitivity, which reduces concerns related to social desirability and dispositional positive/negative responding. Below we review seven of the most commonly used threat sensitivity measures.

Dot Probe Task

Description. The Dot Probe Task for assessment of attentional bias for threat displays two stimuli (e.g., words/images) on a screen with one at the top and the other at the bottom (or one on the left and one on the right). Following a brief presentation of the stimuli (e.g., 500ms), both stimuli disappear and a probe appears in the place of one of the stimuli. The participant must either identify the probe or indicate where it appeared as quickly as possible. Outcomes are based on response times to probes replacing threatening versus neutral stimuli.



Mather, M. & Carstensen, L. (2005). Aging and motivated cognition: the positivity effect in attention and memory, *Trends in Cognitive Sciences*, 9, 496-502.
doi.org/10.1016/j.tics.2005.08.005.

MacLeod, C, Mathews, A., & Tata, P. (1986). Attentional Bias in emotional disorders. *Journal of Abnormal Psychology*, 95, 15-20. <http://dx.doi.org/10.1037/0021-843X.95.1.15>

Wald, G. Lubin, Y. Holoshitz, D. Muller, E. Fruchter, D.S. Pine, D.S. Charney, Y. Bar-Haim (2011). Battlefield-like stress following simulated combat and suppression of attention bias to threat, *Psychological Medicine*, 41, 699-707, DOI 10.1017/S0033291710002308

Reliability. Both the test-retest reliability and internal consistency are “very low” for dot probe difference scores (i.e., bias scores). However, the test-retest reliability of individual emotional and neutral response times may be higher.

State or trait. Attentional bias for threat using dot probe associated with trait anxiety in a meta-analysis.

Older adults with high trait anxiety scores show a “vigilant-avoidant” reaction to sad faces (i.e., initially orient towards sad faces and then away from threat) and an “avoidant-vigilant” reaction to negative words (i.e., initially orient away from negative words but then towards them).

Lee, L.O., Knight, B.G. (2009). Attentional Bias for Threat in Older Adults: Moderation of the Positivity Bias by Trait Anxiety and Stimulus Modality. *Psychology and Aging, 24*(3). 741-747

Associations with chronic stress and depression. In a meta-analysis of 29 studies, there was a moderate and significant difference in attentional bias between groups, with depressed subjects showing significantly greater bias towards negative stimuli than healthy individuals.

Peckham, A. D., McHugh, R. K. and Otto, M. W. (2010), A meta-analysis of the magnitude of biased attention in depression. *Depress. Anxiety, 27*: 1135–1142. doi: 10.1002/da.20755

Stroop Task

Description. The Modified Stroop Task for assessment of cognitive interference by threat includes different types of words (either neutral or threatening) in varying colors. The participant is asked to report the color of the text while ignoring the semantic content of the word. One variation includes emotional and neutral pictures tinted a certain color. Longer response times to report the color of threat words indicates greater cognitive interference by threatening information.

HATE	CHAMPION
DEPRESSED	EXAM
CRYING	SKY
BULLY	CARWASH
SUICIDE	WIKIPEDIA

MacLeod, C. (1991) Half a century of research on the Stroop effect: An integrative review. *Psychological Bulletin, 109*1, 163-203. <http://dx.doi.org/10.1037/0033-2909.109.2.163>

Michael P., Milham, K., Erickson, M., Banich, AF., Kramer, AW, Wszalek, T., & Cohen, N.J. (2002). Attentional Control in the Aging Brain: Insights from an fMRI Study of the Stroop Task, *Brain and Cognition, 49*, 277-296, <http://dx.doi.org/10.1006/brcg.2001.1501>.

Reliability. Test-retest reliability and internal consistency appear low for difference scores between neutral and threatening conditions, but higher for scores for either neutral or threatening conditions considered separately.

Strauss, G.P., Allen, D.N., Jorgensen, M.L., Cramer, S.L., (2005). Test-Retest Reliability of Standard and Emotional Stroop Tasks: An Investigation of Color-Word and Picture-Word Versions. *Assessment, 12*(3). 330-337

Cisler, J.M., Bacon, A.K., Williams, N.L. (2009). Phenomenological Characteristics of Attentional Biases Towards Threat: A Critical Review. *Cognit Ther Res, 33*(2). 221-234

Kindt M, Bierman D, Brosschot JF. Stroop versus Stroop: comparison of a card format and a singletrial format of the standard color-word Stroop task and emotional Stroop task. *Personality and Individual Differences 1996*;21:653–661.

Schmukle SC. Unreliability of the dot probe task. *European Journal of Personality* 2005;19:595–605.

Siegrist M. Test-retest reliability of different versions of the Stroop test. *The Journal of Psychology* 1997;131:299–306.

State or trait. Researchers found a significant relationship between state anxiety and emotional Stroop reaction times.

Dresler, T., Meriau, K., Heekeren, H.R., van der Meer, E. (2009). Emotional Stroop task: effect of word arousal and subject anxiety on emotional interference. *Psychology Research*, 73(3). 364-71

The combination of low trait anxiety and high social desirability was associated with less interference in naming threat compared to neutral words, whereas the combination of high trait anxiety and low social desirability was associated with increased interference due to threat words.

Mogg, K., Bradley, B., Dixon, C., Fisher, S., Twelftree, H., McWilliams, A. (2000). Trait anxiety, defensiveness and selective processing of threat: an investigation using two measures of attentional bias

Associations with chronic stress and depression. In a meta-analysis of 29 studies, there was a marginally significant difference in Stroop scores between depressed and non-depression groups. Lim and Kim reported depressed patients showed slower response times to negative words on the Stroop compared to healthy controls. A study by Broomfield et al reported a similar finding in elderly depressed patients.

Conversely, Hill and Knowles reported that depressed subjects did not show selective attention to threat and instead displayed slower response to all verbal stimuli, including threatening, negative and positive nouns. Kerr et al reported similar findings, with MDD patients demonstrating slower response times on neutral, positive and negative conditions compared to healthy subjects.

Broomfield NM, Davies R, MacMahon K, *et al.* Further evidence of attentional bias for negative information in late life depression. *Int J Geriatr Psych* 2007;22:175–180.

Hill AB, Knowles TH. Depression and the “emotional” Stroop effect. *Pers Individ Differ* 1991;12:481–485.

Kerr N, Scott J, Phillips ML. Patterns of attentional deficits and emotional bias in bipolar and major depressive disorder. *Br J Clin Psychol* 2005;44:343–356.

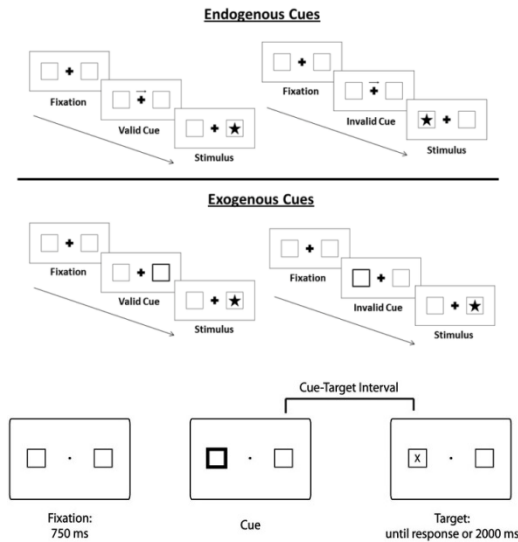
Lim SL, Kim JH. Cognitive processing of emotional information in depression, panic, and somatoform disorder. *J Abnorm Psychol* 2005;114:50–61.

Peckham, A. D., McHugh, R. K. and Otto, M. W. (2010), A meta-analysis of the magnitude of biased attention in depression. *Depress. Anxiety*, 27: 1135–1142. doi: 10.1002/da.20755

Posner Cueing Task/Posner Paradigm

Description. Participants are asked to focus on a fixation point between two rectangles. A cue is presented in one of the rectangles (e.g. a threatening stimulus), which is followed by an asterisk appearing in one of the two rectangles. The participants press a key to indicate which rectangle the asterisk is in. The paradigm consists of “valid cues” (i.e. the cue brings attention to the rectangle the

asterisk then appears in), “invalid cues” (i.e. the cue brings attention to the opposite rectangle that the asterisk then appears in), and “uncued” trials (no cue is presented). If a participant can detect the probe faster on validity cued trials with a threatening cue, it suggests “facilitated attention to threatening cues” as the threatening stimulus brings attention to the probe faster than a neutral cue. If a participant is slower in detecting the probe during invalid cues with a threatening cue, it suggests “difficulty in disengaging” from the threatening cue.



Cisler, J.M., Bacon, A.K., Williams, N.L. (2009). Phenomenological Characteristics of Attentional Biases Towards Threat: A Critical Review. *Cogn Ther Res*, 33(2). 221-234

Reliability. Attention bias scores from the Posner task have low reliability.

Enock, P.M., Hofmann, S.G., McNally, R.J. (2014). Attention Bias Modification Training Via Smartphone to Reduce Social Anxiety: A Randomized, Controlled Multi-Session Experiment. *Cogn Ther Res*, 38. 200-216

State or trait. Differences in attentional engagement and disengagement between high and low trait anxious individuals.

Sagliano, L., Trojano, L., Amoriello, K., Migliozzi, M., D’Olimpio, F. (2014). Attentional biases toward threat: the concomitant presence of difficulty of disengagement and attentional avoidance in low trait anxious individuals. *Frontiers in Psychology*, 5(685).

High compared to low trait anxious individuals showed slower reaction times on trials with invalid threat cues than invalid neutral cues, indicating difficulty in disengagement from threat cues. However, threat cues led to slowing of reaction times in high but not low anxious individuals. When adjusting for this threat cue-related slowing, high anxious individuals showed greater engagement with threat cues, but no evidence of a bias in disengagement processes.

Mogg, K., Holmes, A., Garner, M., Bradley, B.P. (2008). Effects of threat cues on attentional shifting, disengagement and response slowing in anxious individuals. *Behav Res Ther*, 46(5). 656-667.

Associations with chronic stress and depression. Unknown

Fear Potentiated Startle

Description. Startle responses to an acoustic stimulus are examined in varying threat conditions. Threat can be manipulated using dark/light, threat of shock and threat of airpuff etc. Outcomes can include changes in electromyography (EMG; eye blink, heart rate, skin conductance etc.). One startle paradigm consists of a visual threat cue (a monitor displaying the condition) as well as devices to deliver audio and shock and three threat conditions: low threat (participants perform the procedure without a finger shock device and are told they would not be shocked); ambiguous threat (participants wear a finger electrode during the procedure but are indicated by the monitor that they would not be shocked); and high shock (participants wear the finger shock device and the monitor indicated that shocks are possible). During the high threat condition, all shocks are delivered after the auditory cues.

Pole, N, Neylan, T. C., Otte, C., Metzler, t. J., Best, s. R., Henn-Haase, C., & Marmar, C. R. (2007). Associations between childhood trauma and emotion-modulated psychophysiological responses to startling sounds: A study of police cadets. *Journal of Abnormal Psychology* 116, 352.

Reliability. Multiple studies have claimed that the fear-potentiated startle response is a reliable measure that produces a reliable startle response in non-humans. However, reliability is less clear in humans.

Falls, W.A., Miserendino, M.J., Davis, M. (1992). Extinction of Fear-potentiated Startle: Blockade by Infusion of an NMDA Antagonist into the Amygdala. *The Journal of Neuroscience*, 12, 854-863

Campeau, S., Liang, K.C., Davis, M. (1990). Long-term retention of fear-potentiated startle following a short training session. *Animal Learning & Behavior*, 18, 462-468

Davis, M. (1993). Pharmacological analysis of fear-potentiated startle. *Brazilian Journal of Medical and Biological Research*, 26, 235-60

State or trait. The measure has been correlated more with state anxiety (as measured by the STAI). Grillon, C., et al. found that high-fear subjected (based on state anxiety score) had larger startle amplitudes at time of shock expectation compared to low-fear. Further, the high fear subjects showed no difference in startle amplitude during the transition between No-Threat and Treat conditions. Trait anxiety was not associated with fear-potentiated startle.

Grillon, C., Ameli, R., Foot, M., Davis, M. (1993). Fear-potentiated startle: relationship to the level of state/trait anxiety in healthy subjects. *Biological Psychiatry*, 33(8-9). 566-74

Morgan, C., Grillon, C., Southwick, S., Davis, M., Charney, D. (1995). Fear-Potentiated Startle in Posttraumatic Stress Disorder

Associations with chronic stress and depression. In a study of individuals with MDD, a lifetime history of suicide attempt was associated with increased fear-potentiated startle to predictable shock. Further, the retrospective subjective anxiety ratings were higher for subjects with a suicide attempt history during the unpredictable condition than for subjects without a history.

Ballard, E.D., Ionescu, D.F., Vande Voort, J.L., Slonena, E.E., Franco-Chaves, J.A., Zarate, C.A., Grillon, C. (2014). Increased Fear-Potentiated Startle in Major Depressive Disorder Patients with Lifetime History of Suicide Attempt. *Journal of Affective Disorders*, 162. 34-38

The study investigated whether children and grandchildren of individuals with MDD would exhibit increased startle reactivity. Results of the fear-potentiated startle task revealed a significantly greater overall magnitude of startle for the high-risk group compared to the low-risk group.

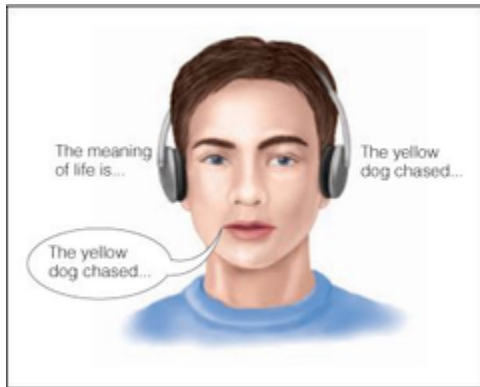
Grillon, C., Warner, V., Hille, J., Merikangas, K. R., Bruder, G. E., Tenke, C. E., ... & Weissman, M. M. (2005). Families at high and low risk for depression: a three-generation startle study. *Biological psychiatry*, 57(9), 953-960.

Childhood trauma associated with greater skin conductance responses to startle across all threat conditions.

Pole, N., Neylan, T. C., Otte, C., Metzler, t. J., Best, s. R., Henn-Haase, C., & Marmar, C. R. (2007). Associations between childhood trauma and emotion-modulated psychophysiological responses to startling sounds: A study of police cadets. *Journal of Abnormal Psychology* 116, 352.

Dichotic Listening Task

Description. This task is used to study selective attention. In this task, the participant is presented with two different stimuli simultaneously, each on one side of the headphones. The participant is directed to repeat aloud the words they heard in one ear while a different message is presented in the other year. As a result of focusing to repeat the words, participants do not notice the message in the other year, suggesting a selective consciousness to specific information. Attention bias in this task can be measured through 4 ways: **1)** Asking the participants questions about the two different auditory stimuli, **2)** Questions about the patterns of the words they were told to attend to, **3)** both parts 1) and 2), or **4)** Detect target words in the list of words.



Drachman, D. A., Noffsinger, D. Sahakian, B. J., Kurdziel, S., & Fleming, P. (1980). Aging, memory, and the cholinergic system: A study of dichotic listening. *Neurobiology of Aging*, 1, 39-43, ISSN 0197-4580, [http://dx.doi.org/10.1016/0197-4580\(80\)90022-6](http://dx.doi.org/10.1016/0197-4580(80)90022-6).

Arciuli, J., & Slowiaczek, L. M. (2006). What does Dichotic Listening reveal about the Processing of Stress Typically? <http://www.assta.org/sst/2006/sst2006-9.pdf>

Moray, N. (1959). Attention in dichotic listening: Affective cues and the influence of instructions. *Quarterly journal of experimental psychology* 11, 56-60.

Reliability. Unknown

State or trait. Anxious subjects complaining of generalized anxiety were slower in performing a simultaneous reaction time task when unattended words were threatening in content, although neither anxious nor non-anxious subjects could report on or recognize the words to which they had been exposed.

Mathews, Andrew, and Colin MacLeod. 1986. "Discrimination of threat cues without awareness in anxiety states." *Journal of Abnormal Psychology* 95, 131-138.

Associations with chronic stress and depression. Researchers found that patients with anxious depression have a greater propensity to activate right than left-hemisphere regions during auditory tasks. Those with a non-anxious depression have the opposite hemispheric asymmetry. There was no group difference in the sensitivity to emotional words.

Bruder, G.E., Wexler, B.E., Stewart, J.W., Price, L.H., Quitkin, F.M. (1999). Perceptual asymmetry differences between major depression with or without a comorbid anxiety disorder: A dichotic listening study. *Journal of Abnormal Psychology*, 108(2). 233-239

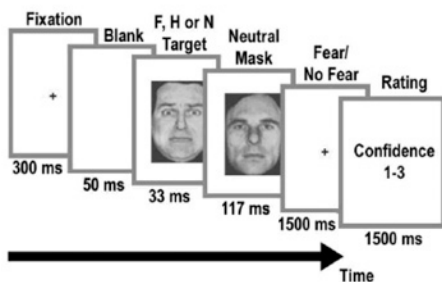
Researchers did not find a significant difference in cognitive functioning between the depressed patients and the control group. Both groups showed a right ear advantage during the not-forced and forced-right conditions and a left ear advantage during the forced left condition.

Hugdahl, K., Rund, B.R., Lund, A., Asbjornsen, A., Egeland, J., Landro, N.I., Roness, A., Stordal, K.I., Sundet, K. (2003). Attentional and executive dysfunctions in schizophrenia and depression: evidence from dichotic listening performance. *Biological Psychiatry*, 53(7), 609-616

Facial Recognition Task

Description. In relation to threat sensitivity, this task is also known as the Fearful Face Detection Task. This task asks participants to focus on a central point on a screen to orient themselves to the task, which is then followed by a blank screen. Next, a pair of faces appears on the screen consecutively. The first of the two faces, the target, is either fearful, happy, or neutral. The second face is neutral. Participants are asked to press a button to denote when they perceive fear, and press another button when they *do not* perceive fear. Threat sensitivity is measured by response time to each pair of faces, contrasting a pairing of neutral-neutral faces and fearful-neutral faces.

A



Doty, T.J., Japee, S., Ingvar, M., Ungerleider, L.G. (2013). Fearful Face Detection Sensitivity in Healthy Adults Correlates with Anxiety-Related Traits. *Emotion*, 13(2). 183-188

Pessoa, L., Japee, S., Sturman, D., Ungerleider, L.G. (2006). Target Visibility and Visual Awareness Modulate Amygdala Responses to Fearful Faces. *Cerebral Cortex*, 16(3). 366-375

Reliability. Unknown

State or trait. Higher trait anxiety scores correlate with detection sensitivity for fearful faces. Subjects who were faster to correctly identify faces as fearful also had higher levels of state anxiety.

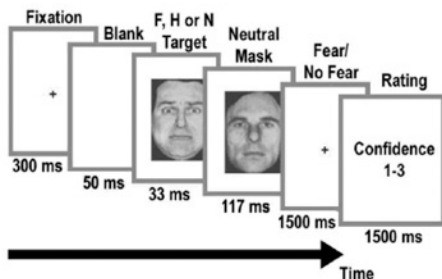
Doty, T.J., Japee, S., Ingvar, M., Ungerleider, L.G. (2013). Fearful Face Detection Sensitivity in Healthy Adults Correlates with Anxiety-Related Traits. *Emotion*, 13(2). 183-188

Associations with chronic stress and depression. Unknown

Visual Search Task

Description. In relation to threat sensitivity, this task is also known as the Fearful Face Detection Task. This task asks participants to focus on a central point on a screen to orient themselves to the task, which is then followed by a blank screen. Next, a pair of faces appears on the screen consecutively. The first of the two faces, the target, is either fearful, happy, or neutral. The second face is neutral. Participants are asked to press a button to denote when they perceive fear, and press another button when they *do not* perceive fear. Threat sensitivity is measured by response time to each pair of faces, contrasting a pairing of neutral-neutral faces and fearful-neutral faces.

A



Doty, T.J., Japee, S., Ingvar, M., Ungerleider, L.G. (2013). Fearful Face Detection Sensitivity in Healthy Adults Correlates with Anxiety-Related Traits. *Emotion*, 13, 183-188

Pessoa, L., Japee, S., Sturman, D., Ungerleider, L.G. (2006). Target Visibility and Visual Awareness Modulate Amygdala Responses to Fearful Faces. *Cerebral Cortex*, 16(3). 366-375

Reliability. Overall high test-retest reliability.

Van Wert, M., Nova, N., Horowitz, T., Wolfe, J. (2008). What does performance on one visual search task tell you about performance on another? *Journal of Vision*, 8(312)

State or trait. High trait anxiety associated with faster detection of angry faces, but that the time to disengage from angry faces was not associated with anxiety level.

Matsumoto, E. (2010). Bias in Attending to Emotional Facial Expressions: Anxiety and Visual Search Efficiency. *Applied Cognitive Psychology*, 24. 414-424

Associations with chronic stress and depression. Unknown

Corresponding Author. This summary was prepared by Aoife O'Donovan and edited and reviewed by Wend Berry Mendes. If you have any comments on these measures, email Wendy.Mendes@ucsf.edu.
Version date: January 2018.

Hair Cortisol

Overview: The stress hormone cortisol, secreted mainly from the adrenal gland, can be measured in various matrices, including blood, saliva, urine, and more recently hair. The method of choice depends on the time window of interest and the research question. Plasma and salivary cortisol samples reflect “snapshots” of recent hypothalamic pituitary adrenal (HPA) axis activity, reflecting cortisol activity over seconds to minutes prior to collection. Urinary cortisol samples provide insight into the time window of collection ranging from overnight to 24-hour periods. In contrast, hair cortisol provides a window on longer-term (months) cortisol exposure levels. Here we focus on hair cortisol, as a measure of long-term HPA activity that is relatively easy to implement in field and population-based studies of aging.

Background: Assessment of cortisol in hair is a recent method that quantifies cumulative cortisol production over extended periods of time (up to 6 months), suggesting that hair cortisol may be a unique biomarker of long-term HPA axis activity. Cortisol is incorporated into the hair as it grows (Pragst & Balíková, 2006) and measurement of cortisol levels within a specific hair segment reflects integrated, cumulative cortisol secretion within that hair growth period. Scalp hair growth is variable, but an average rate of 1 cm per month has been generally accepted (Harkey, 1993; Pragst & Balíková, 2006; Wennig, 2000). Thus, a proximal (scalp-close) 1–cm hair segment reflects total cortisol secretion in the last month, the second proximal 1–cm segment represents the cortisol production in the month before that and so on. Several studies have validated hair cortisol measurement, linking hair cortisol concentrations to repeated measures in saliva and urine, and studying hair cortisol concentrations in patients with endocrine disorders, such as hyper- or hypocortisolism (for reviews see Gow, Thomson, Rieder, Van Uum, & Koren, 2010; Russell, Koren, Rieder, & Van Uum, 2012). Hair cortisol has also been linked to chronic stress exposures and mental health conditions (Stalder et al., 2017; Staufienbiel, Penninx, Spijker, Elzinga, & van Rossum, 2013). It is higher in pregnancy, as expected (Kirschbaum, Tietze, Skoluda, & Dettenborn, 2009). It can be measured in newborns, and may be lower in newborns with preterm birth (Hoffman, D'Anna-Hernandez, Benitez, Ross, & Laudenslager, 2017).

Collection and Measurement: Hair collection is described in detail here:

<http://gero.usc.edu/CBPH/network/resources/hair.html>

Unfortunately, the link only describes hair collection for participants with long hair and does not give instructions for individuals with shorter hair. However, researchers with expertise in hair cortisol collection are often willing to share their knowledge with investigators

For more information on collecting hair samples for hair cortisol analysis in African Americans see (Wright et al., 2018): <https://www.jove.com/video/57288/collecting-hair-samples-for-hair-cortisol-analysis-african>

Strengths: Hair cortisol analysis advances neuroendocrine research for several reasons.

- 1) It provides a cumulative and retrospective measure of systemic cortisol secretion for periods up to 6 months (after which cortisol tends to decrease in hair), a time period previously difficult or impossible to capture (Kirschbaum et al., 2009). This makes it an ideal biomarker when studying allostatic load, including the effects of chronic psychological stress.
- 2) It is a non-invasive, painless method that allows easy and field-friendly sample collection by non-professionals.
- 3) Hair samples do not decompose like body fluids, which makes longer-term storage at room temperature feasible.

4) Hair cortisol likely reflects free, unbound cortisol, and is thus less susceptible to typical confounds such as oral contraceptive usage, as in salivary/serum cortisol research (Dettenborn, Tietze, Kirschbaum, & Stalder, 2012).

Limitations:

1) Interpretation of hair cortisol levels is complex, because cumulative cortisol secretions are a function of multiple, potentially interacting factors, including chronic stress experiences, genetic dispositions, developmental experiences, and altered receptor sensitivities in brain structures that shape its release. To meaningfully interpret hair cortisol levels, information on chronic stress is needed, ideally in combination with genetic and early developmental information.

2) Cumulative cortisol levels are crude averages across time and thus do not inform about regulation of the HPA axis diurnal rhythms (cortisol awakening response, nadir at night) or peak stress reactivity.

3) A major limitation in hair cortisol research is the use of different analysis methodologies across different laboratories. Most labs tend to use traditional immunoassay methods (vs. liquid chromatography/mass spectrograph), which are relatively easy to conduct. But intra assay variability is generally 9-12% but can be addressed by processing samples in a manner that balances for conditions or maintains all a participant's samples on the same assay plate. Different assay method such as ELISA, RIA, and HPLC/MS make comparison of levels of steroid difficult. Currently, there is no gold standard technique for cortisol extraction and analysis. Reference values of hair cortisol of typical groups have not yet been determined (Staufenbiel et al., 2013; Russell, et al., 2015).

3) To date, there is little available information on fundamental aspects that can influence hair cortisol concentrations. Therefore, acceptable co-variables are not well understood (e.g., frequency of hair washing, coloring, type of shampoo use, insufficient hair growth; age, ethnicity, sex). Effects of hair washing may be responsible for the decline in cortisol concentrations from scalp-near hair segments to more distal hair segments, which have been reported by some (e.g., Gao et al., 2010; Kirschbaum et al., 2009) but not all studies (e.g., Dowlati et al., 2010; Thomson et al., 2010). Additionally, it is unknown exactly how cortisol is incorporated into the hair. Four models have been proposed (Pragst & Balíková, 2006) a) Active or passive diffusion from blood into cells of the hair follicle, b) Diffusion from body secretion (e.g., sweat) during formation of the hair shaft, c) Incorporation from deep skin compartments during hair shaft formation, d) External environmental sources after hair shaft formation, but further experimental research is needed. Importantly the impact of stress of hair growth is not clear by could influence levels measured. Additionally, the medical use of topical, oral, injected, eye drops, and intranasal administration or medication containing cortisol, or an allied steroid will affect levels assessed in hair. Growth rates are also affected by racial origin and need to be considered in large mixed population studies. The impact of age is largely unknown.

Author and Reviewer(s)

This summary was prepared by Drs. Stefanie Mayer and Rachel Radin. Reviewed by Drs. Clemens Kirschbaum and. Mark Laudenslager. Please direct suggestions and feedback to stefanie.mayer@ucsf.edu. Version date: February 2, 2018.

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Salivary Cortisol

The hypothalamic-pituitary adrenal (HPA) axis has been proposed to play a key role in stress-health linkages (McEwen, 1998). Thus, interest in the HPA axis has been strong for decades, with a recent uptake in publications in the past decade in part due to the ability to measure cortisol in saliva at a relatively low cost. This allowed cortisol assessment in population-based and epidemiological research, providing valuable evidence of associations between salivary cortisol and job stress, trauma exposure, depression, socioeconomic and demographic status, and physical health outcomes including metabolic disease and cancer mortality (Adam & Kumari, 2009).

In addition to the HPA axis' critical role in the physiological stress response, it also is essential to many daily physiological functions, and thus the secretion of cortisol follows a diurnal pattern, with a sharp rise following awakening and a subsequent decline throughout the day. In response to a stressor, the paraventricular cells of the hypothalamus secrete corticotropin-releasing hormone (CRH) and vasopressin (AVP), which stimulate release of adrenocorticotropin hormone (ACTH) in the pituitary gland. ACTH reaches the adrenal glands through the blood stream and initiates the release of cortisol into the blood (Tsigos & Chrousos, 2002). Most secreted cortisol is bound to proteins in the blood, but a small fraction is unbound. Unbound cortisol can enter cells by passive diffusion, which allows measurement in bodily fluids, such as saliva. Assessment of salivary cortisol levels thus reflect momentary snapshots of HPA axis activity, capturing acute or short-term cortisol production over the past 15-20 minutes.

Strengths. Measuring cortisol in saliva has several advantages. First, it is easy to capture as it can be done using a cotton swab (called a salivette) that is placed in to the mouth to soak up saliva, or through drooling saliva into a tube. These processes are painless, do not require medical personnel, are non-invasive, require little training for appropriate collection, and the assays are low cost. Because of all these factors, saliva samples can and have been captured in a wide variety of study contexts. Salivary cortisol measurement has become extremely popular in field-based research (Adam & Kumari, 2009), studies with children (Jessop & Turner-Cobb, 2008), and laboratory studies examining psychological stress reactivity (Kirschbaum & Hellhammer, 1994).

There are several limitations about relying on salivary cortisol for stress-related biomarker measurement. First, salivary cortisol only captures momentary increases in HPA axis activity. Salivary cortisol concentrations are thought to indicate secretion of cortisol within the previous 20 minutes. This narrow time window makes it best suited for studies that are capturing trajectories of cortisol secretion such as acute stress studies or studies examining diurnal cortisol patterns. A single salivary cortisol measurement will inform little about levels of HPA activation or stress within a sample, this is especially true because the timing of the day matters a great deal for cortisol concentration. Hair cortisol on the other hand, captures longer term exposure to cortisol and thus is better suited as a measure of chronic cortisol exposure. A second limitation is that salivary cortisol is prone to a host of confounding variables. In addition to circadian variation (Kirschbaum & Hellhammer, 1994; Posener, Schildkraut, Samson, & Schatzberg, 1996), situational factors (e.g., novelty; Davis, Gass, & Bassett, 1981), food intake (Gibson et al., 1999), and intra-individual day-to-day variability (Hellhammer et al., 2007) also influence cortisol secretion levels. Thus, it is important to repeatedly sample salivary cortisol over time and to assess potentially confounding of psychosocial and biological factors. Adam & Kumari (2009) list psychosocial, biological, and methodological variables to consider in salivary cortisol measurement in laboratory and

field studies, and summarize aspects of the diurnal curve that can be assessed in epidemiological studies (Adam & Kumari, 2009).

Collection and Measurement: Cortisol collection in saliva using Salivettes is described in detail here: <http://gero.usc.edu/CBPH/network/resources/saliva.html>

Saliva Collection Material: http://gero.usc.edu/CBPH/network/resources/saliva_collection.html

A frequently asked questions guide by Dr. Kirschbaum's lab can be found here:

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This was written by Stefanie Mayer and reviewed by members of the Stress Network leadership team. Further review is pending. To make suggestions or comment email Stefanie.Mayer@ucsf.edu. Version date: March 6, 2018.

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Inflammatory Cytokines

Overview: Inflammation is a fundamental immune process for maintaining survival in that it serves as the body's natural response to insult or injury. Take, for instance, a cut on the skin. Such a puncture to barrier to the outside world increases the chances that antigens, such as bacteria, can get into tissues and the blood stream. As a defense mechanism, the inflammatory system, in part through the release of proinflammatory cytokines from the innate arm of the immune system, alerts the rest of the immune system, namely white blood cells, to migrate to the area of injury, resulting in swelling and redness. Inflammation also aids in recovery and wound healing.

Such acute inflammation, as described above, serves a critical function. In contrast, chronic inflammation, i.e., elevated concentrations of proinflammatory proteins in peripheral circulation, has been linked to a whole host of chronic health conditions, including cardiovascular disease, metabolic conditions like type 2 diabetes, and neurodegenerative diseases. Given the associations between stress and chronic health conditions, inflammation has been posited as a key biological pathway through which psychological factors, including stress, contribute to disease risk.

Proinflammatory cytokines play an important role in cell to cell communication, both within the immune system, but also in other systems such as the endocrine system (Medzhitov, 2008). There are a growing number of mediators that are considered proinflammatory. Here, the focus will be on a couple of key proinflammatory cytokines, interleukin (IL)-6, IL-1, tumor necrosis factor (TNF)-alpha, and the acute phase protein, C-reactive protein (CRP). Proinflammatory cytokines are derived from various biological sources, including immune cells (e.g., T cells, activated macrophages), adipocytes, myocytes, among others. In contrast, CRP is released by the liver in response to increasing levels of IL-6.

Links between stress and inflammation: There is fairly consistent evidence that stress, both acute and chronic, is related to elevated levels of inflammatory activity. Meta-analytic reviews of the acute laboratory stress literature demonstrate a significant stress-related increase in the concentrations of IL-6, TNF-alpha, and IL-1beta, but not CRP (Marsland et al., 2017; Steptoe et al., 2007). Chronic stress has also been linked to elevation in inflammatory markers (Miller et al., 2009; Segerstrom and Miller, 2004); this appears to be particularly consistent in models of caregiving (e.g. Kiecolt-Glaser et al., 2003).

Collection and measurement

Circulating levels of proinflammatory cytokines and CRP are typically measured in blood and, if possible, a fasting blood draw is recommended. Once the blood is drawn, it should be centrifuged, and the serum/plasma frozen at -80C until assay.

Use of saliva: Because blood is often hard to obtain in certain populations, e.g., children, investigators have turned to measuring proinflammatory cytokines in saliva. To date, the correlations between circulating levels of proinflammatory mediators in blood and saliva have been only modest (correlations around 0.5), and it is likely that levels of inflammation in saliva reflect that oral environment more than what is happening systemically (Fernandez-Botran et al., 2011; Out et al., 2012).

Typically, proinflammatory proteins are quantified using enzyme-linked immunosorbent assay (ELISA), multiplex arrays (e.g., Luminex, Meso Scale Discovery), or flow cytometry. There is growing interest in the use of multiplex assays, which provide concentration information for a multitude of analytes using a

small amount of sample. While cost effective, such assays may add additional error and in populations where concentrations are expected to be close to below the level of detection, use of a traditional ELISA may be advised.

Strengths and weaknesses: Measures of circulating levels of proinflammatory cytokines are commonly associated with sociodemographic, behavioral, and psychological measures of interest to social and clinical scientists. They are fairly easily obtained and when paired with other risk factors potentially provide a meaningful index of biological risk. In healthy individuals, changes in these measures may signal response to environmental demands, while in medically compromised participants may indicate change in disease status. Evidence that inflammation is the causal mechanism in disease is less clear and thus should be viewed as more of a biomarker than a causal pathway. The primary limitation for measuring circulating levels of proinflammatory mediators is that the biological source is typically unknown. Proinflammatory cytokines are derived from various biological sources, including immune cells (e.g., T cells, activated macrophages), adipocytes, myocytes, among others. Another limitation is that proinflammatory mediators, with the exception of CRP, show marked diurnal variation (Meier-Ewert et al., 2001). As such, researchers interested in measuring systemic levels of proinflammatory cytokines must account for this variation, often by collecting these blood measures within a predetermined window (e.g., between 9-11AM).

Stimulated cytokine production is an alternative way to measure levels of proinflammatory activity. Unlike measuring cytokine activity in circulation, this provides an estimate of the functional capacity for cells to produce inflammatory mediators is stimulate cells by a pathogen. Like circulating levels of inflammatory mediators, cytokine production is also sensitive to acute laboratory stress (Marsland et al., 2017). The procedures for carrying out this assay vary from laboratory to laboratory but for initiating proinflammatory cytokine production, investigators typically treat the sample with lipopolysaccharide (LPS) for a period ranging from 3 hours to 24 hours of incubation. This can be done in whole blood, isolated peripheral blood mononuclear cells (PBMCs) or isolated monocytes. After incubation, medium in which the cells were incubating is stored and frozen for assay. Proinflammatory cytokines are assayed in the same ways as described above.

Consideration for covariates: Like all other biological processes, markers of inflammation are influenced by a variety of factors in addition to stress. O'Connor et al., 2009 provides an overview of variables known to be associated with circulating measures of inflammation, in some cases, stimulated cytokine production. Unless relevant to the study question, researchers should consider requiring that participants refrain from acute exercise, caffeine use, tobacco use, alcohol use and sleep loss for 10-12 hours prior to a fasting blood draw. In addition, the following variables should be assessed and potentially treated as covariates in statistical models: age, sex, socioeconomic status, race/ethnicity, body mass index, alcohol use, sleep behavior, medication use (particularly aspirin, statins, and anti-hypertensives, and antidepressants), and menopausal status (O'Connor et al., 2009).

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This summary was prepared by Dr. Aric Prather. Reviews are pending. Please direct suggestions and feedback to Aric.Prather@ucsf.edu. Version date: March 3, 2018.

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RNA profiling

Overview: Our genes are comprised of DNA, but those DNA genes only influence cellular function, health, and behavior if they are transcribed into RNA, or “expressed.” Only a subset of our ~20,000 genes are actively transcribed in any given cell, and which genes are “on” and “off” determines not only the identity of the cell but its functional capacities and behavior. As such, RNA “transcriptome profiling” has become the dominant method for analyzing the molecular underpinnings of healthy physiology, development, aging, and disease¹. Research has also found that social and psychological processes can influence RNA profiles²⁻⁴. RNA profiling thus provides a useful method for mapping the molecular interface between social and behavioral processes and the biology of health and aging.

Background: Stress hormones and neurotransmitters exert their effects in part by altering the transcription of genes in cells and tissues throughout the body. These effects are mediated by cellular receptor systems that activate transcription factors within the cell which ultimately change the rate at which specific genes’ DNA is transcribed into RNA and subsequently translated into the proteins that mediate cell function. One major target of these effects are the immune cells (leukocytes) present in circulating blood.

RNA profiling can be used to assess general stress effects in various ways. For example, one could examine a specific gene of interest, assess an a priori-specified set of genes known to be involved in a common biological process (e.g., inflammation), or assess the shared biological characteristics of an arbitrary set of genes that empirically tracks a specific risk factor or outcome (e.g., common regulation by the pro-inflammatory transcription factor NF-kappaB, or shared expression in a subset of leukocytes called monocytes). Chronic stress can impact RNA profiles at each of these levels, and such effects can be detected by analyzing genome-wide surveys of RNA expression using specialized bioinformatics software. For example, leukocytes from people exposed to chronic stress often show up-regulated expression of genes involved in inflammation, and down-regulated expression of genes involved in antiviral responses (Type I interferons) and antibody production^{2,3}. This “Conserved Transcriptional Response to Adversity” (CTRA) pattern is seen across a diverse range of adverse environments and a diverse array of species including monkeys, mice, and fish. Transcriptome profiles such as the CTRA are directly relevant to health because immune cell-mediated inflammation and antimicrobial responses contribute to many of the disease processes that dominate contemporary epidemiology, including heart disease, cancer, neurodegeneration, and viral infections. A set of 53 genes involved in inflammation, antiviral responses, and antibody production has been used to assess the CTRA in several studies^{5,6}. CTRA biology can also be assessed by TELiS bioinformatics analyses to detect increased activity of the pro-inflammatory transcription factor NF-kappaB and decreased activity of Interferon Response Factors^{5,7}, or by Transcript Origin analyses to detect up-regulation of a specific type of leukocyte known as a CD16- Classical Monocyte⁸.

Blood cell RNA profiles reflect a combination of recent effects on RNA transcription in existing cells (occurring over hours) as well as longer-term effects in changing cell population composition (occurring over days to weeks)^{8,9}. Acute stress can also rapidly alter blood cell composition (over minutes)^{10,11}, although these effects are transient and their health significance remains uncertain. RNA is a useful level at which to assess the molecular impact of stress because, unlike DNA, it is quantitatively responsive to environmental conditions and can show large effect sizes (e.g., 20-100-fold change over hours), and unlike protein, it can be measured with high sensitivity and specificity. These measurement advantages allow for efficient assessment of all ~20,000 human genes simultaneously (“transcriptome profiling”). RNA profiling can also be applied to other tissues such as cancers (to understand the ultimate impact of stress on diseased tissue)^{12,13} or placentas (to understand effects on fetal

development)¹⁴. Here we focus on blood RNA profiling as a measure that is both health-relevant and easy to implement in field and population studies of aging.

Collection and Measurement: RNA profiling is most often performed on venipuncture blood samples (i.e., blood drawn into tubes with a needle by a phlebotomist), but dried blood spot (DBS) samples can also be used in field settings where phlebotomy is infeasible^{15,16}. Regardless of the sampling method or tissue analyzed, similar biochemical protocols are used to isolate RNA from other cellular components and quantify the abundance of RNA molecules derived from each gene¹⁷. These methods usually involve the “reverse transcription” of sample RNA into “complementary DNA” which can then be assayed by polymerase chain reaction (RT-PCR; if only a few genes are of interest) or by high-throughput DNA sequencing systems that survey all of the RNA species present (RNA sequencing, or RNAseq). The biggest challenge in transcriptome profiling studies involves analyzing the copious data that result, which often involves many more outcomes (~20,000 genes) than study subjects; large numbers of genes that are expressed weakly, inconsistently, or not at all; and >10-fold heteroscedasticity across genes. Different analytic strategies are appropriate for different study objectives, and the dominant approach among geneticists (searching for individual genes that show statistically significant association with an environmental risk factor) may not be optimal for most social or behavioral studies, which typically use genomic data to identify correlates of cellular and molecular signaling pathways already implicated in health and disease (i.e., focusing on sets of biologically-related genes rather than individual genes in isolation)^{17,18}. Such gene set or “pathway” analyses can be used to assess the activity of specific hormones/neurotransmitters, receptors, and transcription factors that mediate environmental influences on gene expression⁷; the specific cell types that respond to a given stimulus^{8,19,20}; a priori-defined transcriptome patterns such as the CTRA^{5,6}; and the role of genetic polymorphisms or epigenetic marks in modifying individual molecular responses to environmental stimuli²¹⁻²³. Gene set discovery analyses can also be used to identify novel groups of genes that track an environmental factor or health outcome^{24,25}. A recent integrative review provides more background on transcriptome profiling data collection and analysis¹⁷.

Many major research institutions have the ability to perform transcriptome profiling. To help social and behavioral scientists integrate transcriptome profiling into their studies, the National Institute of Aging-funded USC-UCLA Biodemography Center operates a Social Genomics Core Laboratory to provide strategic consulting in study design; sample processing and assay services; and assistance in data analysis, bioinformatics (including the free software for TELiS), and substantive interpretation (contact steve.cole@ucla.edu).

Strengths:

- 1) Provides a system-wide comprehensive portrait of genomic response to environmental stimuli
- 2) Direct significance for health and aging
- 3) Well-validated, sensitive, specific, and comprehensive assay platforms (RT-PCR, RNAseq)
- 4) Some biological pathways have already been identified to mediate causal effects of psychological/social processes on gene expression
- 5) Large open-access databases of accumulated gene expression data (NCBI Gene Expression Omnibus; EMBL ArrayExpress) help facilitate interpretation of new data by empirical relationship to previous findings

Limitations:

- 1) Complexity, both substantive and technical
- 2) Expense (per-sample costs currently \$150-\$500 depending on approach)
- 3) A moving target; genomics is a large field, much remains unknown, and technological and substantive state-of-the-art advance continually
- 4) Change in RNA abundance does not guarantee change in protein abundance or biological function (though they are generally well correlated)
- 5) Requires tissue capture, with varying invasiveness depending on tissue

Given the key role of RNA profiling in basic biology, transcriptome analyses will continue to be an essential tool for understanding how social, psychological, and environmental conditions interact with the human genome to shape individual health, development, and aging.

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Telomere length and telomerase activity*

*note that this version is currently in draft form as it has not been reviewed by all reviewers.

Overview: Immune cell **telomere length** has become a common biomarker in health studies because it reliably predicts later onset of several diseases such as cardiovascular disease, it's mechanisms of disease are understood, and it is easy to measure with blood. It is also associated with the wide range of exposome factors—chemicals, pollution, neighborhood safety, stressor exposures, and lifestyle. **Telomerase** is the intra-cellular enzyme that protects and lengthens telomeres. The GWAS determined **genetic index for telomere length** is another way to study contribution of telomere length directly, although this accounts for only around 1% of actual telomere length (Codd et al, 2013).

Background: Telomeres are made of non-coding sequences of DNA base pairs (TTAGGG), and wrap the tips of chromosomes. They protect the genes from damage, and they also shorten when there is cell division (since they cannot be fully replicated) or when there are biochemical stressors (oxidative stress) in the cell that can damage them or impair the telomerase enzyme, making them shorten prematurely with each division.

Telomere length is a marker of **healthspan**—in that shorter telomere length (TL) predicts earlier onset of many diseases of aging (such as cardiovascular disease, diabetes, and dementia), as shown by meta-analyses (D’Mello et al, 2015; Willeit et al, 2014; Forero et al, 2016), as well as worse functional immune outcomes in some studies (Cohen et al, 2013). However, telomere effects are complex when it comes to cancer. Short genotypically-estimated telomeres can be protective of certain types of cancer such as melanoma and glioma.

Short telomere length indicates that the cell is closer to ‘replicative senescence’ or the end state of a cell when it can no longer divide. Senescent cells become proinflammatory, and lose their ability to divide and proliferate.

Mechanism linking telomeres to psychological stress:

Telomere length appears to shorten after exposure to multiple childhood traumas or deprivation, in a dose response fashion, and these effects are observed prospectively in childhood as well as cross sectionally (using retrospective measures) in adults (Epel & Prather, 2018). It is shorter in most psychiatric disorders (Darrow et al, 2016) and in elderly caregivers (Damjanovic et al, 2007).

The mechanisms are likely different for exposure to in utero stress, childhood stress, and adulthood stress, although these are difficult to study in humans. The mechanisms likely involve over exposure to the biochemical changes induced by stress, such as over-exposure to cortisol, insulin resistance, pro-inflammatory cytokines, and possibly changes to stem cells, the source of all hematopoietic cells, that replace them through life (Epel & Prather, 2018).

Timescale:

Telomere length measurement is helpful when we want a stable and static measure of the status of one’s immune system. Telomeres reflect one’s genetic inheritance (at least 50%, Broer et al, 2013), and are influenced by long term exposures rather than acute exposures. We know that telomere length at midlife can predict earlier onset of disease. Telomere length can predict how vulnerable people are to

the common cold in young healthy people (Cohen et al, 2012), and a robust response to vaccination (Najarro et al, 2015).

Telomere length shortens rapidly during early childhood, during pruning of the immune system, and then more slowly throughout adulthood (Frenck et al, 1998). It is thought that telomere length at birth (initial setting) may be the most important predictor of health risks, although no studies have examined whether telomere length at birth or early childhood also tracks throughout life and predicts early disease. If so, prenatal stress exposures (Send et al, 2017) and possible epigenetic transmission of telomere length (Collopy et al, 2015) may be particularly critical for understanding late life health.

Telomerase activity can change acutely, within minutes. Acute psychological stress appears to boost PBMC telomerase by around 90 minutes, particularly in healthy people (Epel et al, 2010), whereas in vivo studies on lymphocytes have shown that cortisol exposure can dampen telomerase over days (Choi et al, 2008).

Collection and measurement

Telomere length can be measured in any type of somatic cells, but is most commonly measured in immune cells, using whole blood (**leukocyte telomere length or LTL**), and in more experimental studies, with peripheral blood mononuclear cells (PBMCs). Telomerase activity can be measured by labs very experienced in the specific method.

There are several methods for assaying telomere length that vary greatly in ease, cost, and information provided. The qPCR method is the least expensive but has the relatively high inter-assay coefficient of variation (ranging from 2% to 15% depending on the lab). The Southern blot requires more DNA, is more expensive, but has higher precision with lower assay coefficient of variation (1 to 2% CV). The Q-FISH flow method is typically used for clinical studies of telomere disorders, requires fresh blood, and can yield telomere length data in a various cell types. These methods have been compared in various studies. Researchers should carefully consider the pros and cons of each of the method, for their each specific studies (Aubert and Lansdorp 2012, *Mutat Res.* 2012 Feb 1;730(1-2):59-67. doi: 10.1016/j.mrfmmm.2011.04.003. Epub 2011 Jun 12.). Further work developing a low cost high accuracy assay is a critical goal for the field.

Collection of blood for telomere length may depend on the type of assay done and the lab. An example of the collection of blood for telomere length using the qPCR method, as done in the Blackburn lab, can be sent by Dr. Jue Lin, jue.lin@ucsf.edu.

Saliva is often used, but this includes both immune cell and epithelial cells, and is not as strongly correlated with venous blood draw telomere length. In a small study of 24 adults, saliva and venous blood telomeres were correlated $r = .56$, whereas blood spots and venous blood were more highly correlated, $r = .84$ (Stout et al, 2018).

Strengths:

Telomere length is appropriate when one wants an overall measure of the robustness of the immune system. It is relatively stable over time, and with one measure, it is often a weak but reliable predictor of health outcomes. It will likely serve best as one indicator among many, such as when used in an algorithm (Belsky et al, 2015).

Limitations:

Telomere length is not thought to be a sensitive measure to short term interventions. One study did find changes in telomere length after 3 weeks of an intensive residential retreat intervention, compared to a control group. However, it is not possible, when using leukocytes or PBMCs (mixed cell types) to know how much of the change was due to a redistribution of cell types (pseudo-lengthening, Epel, 2012), rather than a per cell lengthening. Use of single cell types, either through sorting cells, or collecting buccal cells, eliminates the confound of cell redistribution.

It seems that given the error from noise, and the variance in long term adherence to interventions, telomere length is likely a crude outcome for documenting long term intervention effects on health. However, when the intervention is strong and maintained, it will be more likely to be impacted. For example, immediate weight loss was not related to telomere length change at six months, but weight loss maintenance at one year was. These effects were significant but weak for 5% weight loss, and larger for the group who maintained a 10% weight loss, which was an infrequent outcome (Mason et al, 2018).

Telomere length is a weak predictor of outcomes. In humans, it will be difficult to get a granular understanding of telomere biology in vivo, during aging, without sampling from birth to older age, multiple tissue types rather than relying on blood, including post-mitotic tissue. It is important to refine assay methods, and develop better assays.

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