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Stress and inflammation – The need to address the gap in the transition between acute and chronic stress effects

Nicolas Rohleder

Chair of Health Psychology, Institute of Psychology, Friedrich-Alexander-Universität Erlangen-Nürnberg, Nägelsbachstr. 49a, 91052, Erlangen, Germany

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ABSTRACT

Stress responses help us navigate our environment and respond appropriately to threats. Stress systems communicate threats to the entire organism, and as such, also stimulate inflammatory mechanisms. This modulation might serve protective functions in the short term, but sustained low-grade inflammation has severe long-term health consequences. While we have reached a reasonable level of understanding of acute, as well as chronic stress effects on inflammatory mechanisms, there is a significant gap in our understanding of the transitional phase between acute and chronic stress. The purpose of this review is to first summarize current knowledge of our understanding of acute stress effects on inflammation, as well as of chronic stress effects on inflammation, and to then analyze the state of knowledge about the transitional phase between acute and chronic stress. Research discussed here shows that we are beginning to understand the early phase of repeated acute stress, but lack information on longer term exposure to repeated acute stress experiences. More research is needed to bridge this important gap und our conceptualization and understanding of the stress and health relationship.

1. Introduction

Navigating our environment, including complex societies comprised of human beings with potentially competing interests and demands, requires constant adaptation to changing conditions. Throughout our lives, we are therefore required to be able to react to situations that can be positive or negative, and in the worst case, threaten our health and survival. To respond to threats and challenges, as interpreted by the brain, we are equipped with stress systems that communicate the need to alter homeostatic states in order to adapt or survive. While necessary for survival, stress response systems have the potential to damage the organism, as described in the allostatic load model (McEwen, 1998; McEwen and Stellar, 1993).

There is now a substantial literature describing how stress response systems work to activate and change the states of dependent systems, which more or less all seem to provide short-term adaptation to threats, such as increases in blood glucose, blood pressure, heart rate, but also stimulation of the inflammatory response with increases of inflammatory cytokines in blood, all mainly mediated by the sympathetic branch of the Autonomic Nervous System (ANS; fight-or-flight response; (Sapolsky et al., 2000). There is further substantial evidence for adjustments of this initial response, which are mediated by the hypothalamus pituitary adrenal (HPA) axis and its main end hormone cortisol. Such adjustments include positive or negative modulation of those systems activated by the SNS, for example prolonging increases in blood pressure, but also shutting down activation of some immune mechanisms (Sapolsky et al., 2000). Such adaptations have been described with the term allostasis (McEwen, 1998; McEwen and Stellar, 1993) to account for the fact that these are transient alterations of systems that otherwise strive for homeostasis.

Furthermore, there is equally substantial evidence showing that chronic stress experience is associated with a large range of diseases, including life-threatening disease such as cardiovascular disease, insulin insensitivity, and cancer (Cohen et al., 2007). Further, several review articles have summarized that inflammatory processes play a central role in the link between exposure to chronic life stress and such diseases (e.g. Rohleder, 2014; Segerstrom and Miller, 2004; Slavich, 2015; Slavich and Irwin, 2014; Wirtz and von Känel, 2017), leaving no doubt that long-term exposure to psychosocial stress will lead to adverse long-term health outcomes in most people, and that biological mechanisms, in particular those related with regulation of the inflammatory cascade, play a central role.

Although there is considerable evidence of acute stress effects on biology, as well as of chronic stress effects on biology, these two issues are not studied together as often as they should be. Implicit theory is that a human being is at some point in life exposed to a potentially stressful situation for a first time, and will respond to that, likely in a way that we understand reasonably well, as will be outlined here. It is

E-mail address: nicolas.rohleder@fau.de.

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certainly possible that this person will not experience that situation ever again, but it is much more likely that a similar situation will be experienced again. Many situations can be thought of that have the potential to be experienced over and over again, maybe several times per day, as for example workplace stressors, or interpersonal stressors such as in marital distress, disputes with children, parents, siblings, or having to provide care duties to a family member. One could also be subject to bullying, to discrimination, or to threatening encounters when living in neighborhoods with high crime rates. Many more examples could be generated that have the potential to become repeated stressors. At first exposure, these would most likely elicit acute stress responses, which will help survive or cope with the situation more or less adequately. If the situation repeats itself, it will at some point become a chronic stressor, and categorized and studied as such. Certainly, work stress, caregiving, or living in neighborhood with high crime rates, and discrimination, are investigated in terms of what changes when individuals are experiencing these stressors longer time periods of months, years, or even decades.

A key question is, at which time do we change conceptualizing such repeated stressors as chronic stress? Related to that, a significant knowledge gap exists with regard to research focusing on the phase in which an initial, acute stressor and stress response transitions into becoming chronic stress. The goal of this review is to first provide an overview of the current state of the human stress literature with regard to inflammatory responses to initial acute stress, and second, with regard to stimulation of systemic low-grade inflammation in chronic stress, and to finally move to discussing the transitional phase, in which acute stress becomes chronic. Before doing so, the central role of inflammatory processes in the stress-disease link will be explained in the next section.

2. Inflammation as pathophysiological pathway linking stress and disease

In order to understand how stress *"gets under the skin"* and ultimately affects people's health and longevity, research has initially focused on the obvious candidates, which are the main stress responsive systems, i.e. the HPA axis and the sympathetic nervous system (SNS). Over the years, these systems' responses to acute stress have become very well understood, leading to the conclusion that such acute response are in most cases beneficial for immediate survival (McEwen, 1998; McEwen and Stellar, 1993; Sapolsky et al., 2000). HPA axis alterations in individuals under chronic stress have also been well-described, and are on average, associated with altered basal activity, characterized by loss of circadian rhythm and lower overall cortisol output throughout the day (Miller et al., 2007). Literature on SNS alterations is still less clear, as a recent review on caregiver stress demonstrates. Allen et al. (2017) summarize that the cardiovascular system shows signs of an overactive SNS, for example through findings of higher heart rate and blood pressure in chronic caregiving stress, but conclude that findings are inconclusive and in need of replication. With regard to neuroendocrine measures of SNS activity, findings in caregivers were similarly mixed, with only half of the studies finding higher epinephrine and norepinephrine concentrations (Allen et al., 2017).

While there is, overall, good knowledge of how stress systems respond to acute and chronic stress, the field has had much less success demonstrating prospective associations of changes in HPA axis and SNS with disease development. Disruption of diurnal cortisol rhythms has been found predictive of shorter survival in breast and lung cancer patients (Sephton et al., 2013, 2000), but these are findings from individuals with a specific disease, and are not easily generalizable to for example still-healthy but chronically stressed individuals.

One reason for the failure to predict disease development by looking at the HPA axis and/or SNS alone might be that, although necessary for survival, none of the end hormones of these stress systems has strong pathophysiological effects per se, but rather regulates further dependent systems, and does so in complex ways, i.e. with constantly changing efficiency, interacting with each other and other systems, and with differential effects on different downstream pathophysiological processes (e.g. Cohen et al., 2012; Miller et al., 2002; Rohleder, 2012).

One solution to this problem might be to assess and understand the entire signaling cascade from the central nervous system, via all stress-sensitive systems, to all potentially pathophysiologically relevant systems in the periphery of body. While this might become feasible with further development of laboratory techniques in the future, in the meantime the most promising approach likely is to study systems in the body that are found to be responsive to stress or stress system signals, and that have a demonstrated major role in the development of ideally several diseases. One such system is the inflammatory response within the innate immune system, in particular the phenomenon of systemic, low-grade inflammation. Low-grade inflammation has to be carefully distinguished from responses to infection or injury. This type of inflammation is systemic, and not limited to for example a local site of injury or infection. It is much lower in magnitude than what we would see during acute infection or even in sepsis. It is also usually a longer-term phenomenon, although transient changes do occur after acute stress. Most importantly, there is usually no apparent stimulus, such as infection and injury (Black, 2002). However, low-grade inflammation is powerful in predicting morbidity and mortality, and has been identified as key player in cardiovascular disease, cancer, diabetes, and age-related diseases such as Alzheimer's disease or frailty (e.g. Couzin-Frankel, 2010). In humans, systemic inflammatory activity or reactivity is typically assessed by measuring plasma concentrations of pro-inflammatory cytokines, such as interleukin-6 (IL-6), IL-1beta, tumor necrosis factor-alpha (TNF-alpha), or by measuring the acute phase protein C-reactive protein (CRP; see for example McInnis et al., 2014; Rohleder et al., 2009). Other pathophysiologically relevant processes that are gaining momentum in stress research, such as mitochondrial health (Picard and McEwen, 2018), and telomere shortening (Epel et al., 2004), as well as behavioral pathways between stress and health are not in the focus of this review, but should be taken into account for a complete picture.

3. Stimulation of systemic inflammatory responses by acute stress

The focus on this section will be to review current evidence on – usually temporary – activation of the inflammatory response by acute, i.e. short term stress, usually observed in the laboratory setting, using standardized acute stress paradigms. As already posited by Black (2002), stress has a strong effect on the inflammatory response, and the inflammatory response could be seen as the "ultimate stress response", activated by both, threats from the physical environment, such as infection and injury, and threats from the social environment (Black, 2002).

Several reviews and meta-analyses have summarized the effects of acute stress, usually in the form of public speaking paradigms or other laboratory tasks, on the immune system, in particular the inflammatory response, in the past. Marsland et al.'s (2002) analysis of a number of own studies (Marsland et al., 2002), as well as the seminal meta-analysis by Segerstrom and Miller (Segerstrom and Miller, 2004), revealed that acute stress has profound, rapid, short-term, and differential effects on several components of the immune system, including number and composition of circulating leukocytes, functional parameters assessed by in-vitro stimulation of various immune functions, as well as in-vitro stimulated production of different cytokines. While these meta-analyses included only a few very small studies testing acute stress effects on plasma concentrations of unstimulated cytokines, and did not find a significant stress effect on those, the overall pattern of results was interpreted as an upregulation of innate immune mechanisms by acute stress (Segerstrom and Miller, 2004).

A later review and meta-analyses by Steptoe et al. (2007), focused specifically on inflammatory cytokines, and separately analyzed in-

vitro stimulated versus unstimulated plasma cytokines. Results summarized over 13 studies revealed a significant increase of in-vitro stimulated IL-1beta, but not IL-6 or TNF-alpha. Analyses of studies reporting measurements of plasma inflammatory markers found significant stress-induced increases of IL-6, IL-1beta, but not CRP and TNF-alpha (Steptoe et al., 2007).

Results were updated recently in a further meta-analysis by (Marsland et al., 2017), which included 34 studies that measured circulating inflammatory markers, and 15 studies that measured in-vitro stimulated production of inflammatory markers. Results confirmed the previously reported increase of circulating IL-6, found smaller increase of IL-1beta, IL-10 and TNF-alpha, and did not find stress-induced increases of CRP. In the subset of studies reporting in-vitro stimulated cytokines, increases were found for IL-1beta, TNF-alpha, a marginally significant increase of IL-6, but no increase of IL-10. This most recent meta-analysis further revealed that age and sex are no significant moderators of stress-induced inflammatory activation.

In addition to clearly showing that there is no doubt that acute stress activates inflammatory responses, recent work has significantly increased our knowledge on factors moderating this acute inflammatory response since last summarized (Rohleder, 2014). Also, in addition to plasma and stimulated inflammatory cytokines, there is now increasing research on other ways to assess inflammation, such as via gene expression of pro- and anti-inflammatory factors (e.g. McInnis et al., 2015; Kuebler et al., 2015), and salivary cytokine measures (Slavish et al., 2015).

3.1. Associations with depressive symptoms

Stress responses of inflammatory markers have been found to be higher in individuals with different forms of depressive symptomatology. For example, Pace et al. (2006) found higher IL-6 responses in patients with a combination of early adversity and Major Depression (Pace et al., 2006). Higher IL-6, TNF-alpha, and CRP increases were also found in patients with clinical depression relative to controls by (Weinstein et al., 2010). Subclinical depressive symptoms measured by self-report have been found related with higher IL-6 responses in one study using the CES-D (Fagundes et al., 2013), but the reverse was found in an earlier study using the BDI (Benson et al., 2011), which might be explained by the different gender composition, or questionnaires used. Early life adversity without depression was also related with higher plasma IL-6 responses to stress (Carpenter et al., 2010).

3.2. Associations with stable psychological characteristics

Relationships have also been found between inflammatory stress responses and other stable characteristics, such as traits or anthropometric measures. Low self-esteem (O'Donnell et al., 2008), high hostility (Brydon et al., 2010), and increased loneliness in women, but not men, were found to be associated with higher stress responses of inflammatory mediators (Hackett et al., 2012). Higher inflammatory responses to stress have also been reported in individuals with lower socioeconomic status (SES; Brydon et al., 2004; Steptoe et al., 2002), and lower subjective social status (SSS; Derry et al., 2013), as well as in those with higher work stress (effort-reward imbalance; ERI; Hamer et al., 2006)). Higher inflammatory stress responses were also related with lower self compassion (Breines et al., 2014), lower trait reflection (Woody et al., 2016), and with less time spent meditating (in a meditation group of a randomized controlled meditation trial) (Pace et al., 2009). IL-6 responses were also higher in older adults reporting poorer sleep (Heffner et al., 2012), in African-American women compared to Caucasian women (Christian et al., 2013), and in young men who grew up in urban environments without animal contact (as compared to rural with animal contact; Böbel et al., 2018). Biomedical parameters including physical fitness (Hamer and Steptoe, 2007) and lower body fat (McInnis et al., 2014), were further related with lower IL-6 stress responses. IL-6 responses to acute stress were further related with basal HPA axis activity (Chen et al., 2017).

3.3. Associations with altered psychological states

Inflammatory responses to acute stress were also found to covary with state psychological stress responses. They were for example higher in individuals showing higher state anger and anxiety in response to stress (Carroll et al., 2011). IL-1beta, but not IL-6 responses were lower in people who were able to maintain a positive outlook during stress exposure (Aschbacher et al., 2012). Higher IL-6 responses were found in people with higher anger responses to the stressor, in combination with less social support (Puterman et al., 2014). Finally, IL-1beta stress response was positively related with higher overall stress ratings (Yamakawa et al., 2009).

3.4. Inflammatory biomarkers in saliva

Inflammatory cytokines have recently also been measured in saliva, despite the fact that as proteins, they do not easily cross cellular membranes into salivary glands. As summarized by Slavish et al. (2015), cytokines can be measured in saliva, but do not correlate with plasma correlations. Regardless, they show increases to acute laboratory stress (Slavish et al., 2015). Several recent studies have found associations with psychosocial factors. Perceived discrimination in women between 50 and 75 years of age was significantly associated with the salivary, but not plasma, IL-6 response to stress (Saban et al., 2018). Similarly, adolescents with greater peer victimization showed higher increases in salivary IL-6 and IL1-beta in response to stress (Giletta et al., 2018). Further, another study revealed that indirect exposure to neighborhood violence interacted with early adversity to predict higher salivary IL-6 responses (Janusek et al., 2017). Finally, salivary inflammatory cytokines showed lesser increases after an emotional video in participants with better cognitive control (Shields et al., 2016). Taken together, although salivary cytokines certainly do not reflect plasma concentrations, they can be measured, and they appear to be stress-responsive.

3.5. Summary of acute stress and inflammation

In summary, there is now a convincing body of evidence showing that acute stress stimulates a plasma inflammatory response, and to a limited extent, also an inflammatory response that is measurable in saliva. Of importance, responses covary with a large array of stable personal characteristics, ranging from biomedical factors to psychosocial traits such as self-compassion, and responses are further associated with state experiences, such as increases in anger, or anxiety.

4. Systemic low-grade inflammation in chronic stress

Exposure to adverse psychosocial conditions over longer time periods, summarized as chronic life stress, or chronic stress, can take many different forms, and is often characterized by inter-individual variability in time course and intensity (Segerstrom and Miller, 2004). While difficult to study experimentally in humans, there is evidence of chronic stress being associated with and predictive of disease (Cohen et al., 2007). Examples of diseases associated with chronic stress cover the entire range of diseases that plague modern societies, including depression (Slavich and Irwin, 2014) and cardiovascular disease (Kivimäki et al., 2006). As discussed above, systemic low-grade inflammation has been suggested as a key mechanism in a number of excellent reviews (Glaser and Kiecolt-Glaser, 2005; Segerstrom and Miller, 2004; Gouin et al., 2012, 2008; Wirtz and von Känel, 2017; Hänsel et al., 2010; Bauer, 2008; Slavich and Irwin, 2014). These reviews include studies focusing on job stress, burnout, socioeconomic status, childhood adversity and major life events (Hänsel et al., 2010).

In addition, including psychiatric diseases such as depression and posttraumatic-stress disorder (PTSD) can provide useful insights, because both are related to the experience of stress, and show marked alterations in stress system activity (Rohleder et al., 2010).

4.1. Caregiving stress

The most-studied variant of chronic stress is probably caregiver stress, in which frequently, but not always, older adults caring for their spouse with Alzheimer's Disease or other chronic condition, are studied cross-sectionally or longitudinally, and compared with non-caregivers (see Pinquart and Sörensen, 2003) for a summary of psychological effects). Caregivers who experience more stress have a higher risk of cardiovascular disease (Haley et al., 2010) and higher mortality (Schulz and Beach, 1999). Cross-sectional caregiving studies available to date provide evidence for a role of low-grade inflammation, which appears to be more prevalent in plasma levels of IL-6 (Lutgendorf et al., 1999; von Känel et al., 2006a; Gouin et al., 2012; Mausbach et al., 2011), while CRP was only found increased in some studies (Gouin et al., 2012; Lovell et al., 2012), and unchanged in others (von Känel et al., 2006a). One study revealed that caregivers had higher IL-6 levels four weeks after vaccination than controls (Segerstrom et al., 2008). Further, it was found that daily stressor experiences partially mediated higher CRP, but not IL-6 concentrations in caregivers (Gouin et al., 2012), and that self-efficacy buffered associations of caregiving with IL-6 (Mausbach et al., 2011). In partners of veterans with traumatic brain injury, higher self-reported blame and anger, as sub components of grief, were associated with higher salivary TNF-alpha concentrations (Saban et al., 2016). Miller et al. (2014) reported higher inflammatory transcriptional activity in monocytes of cancer caregivers compared to controls, but no changes in serum CRP concentrations. This finding suggests that pathophysiological changes might at some earlier stage only be detectable in intracellular analyses, before becoming manifest in circulating concentrations of inflammatory mediators (Miller et al., 2014).

In the first longitudinal study testing low-grade inflammation in caregivers, Kiecolt-Glaser and colleagues reported that IL-6 concentrations increased more over a six-year period in elderly caregivers of Alzheimer's Disease patients compared with controls (Kiecolt-Glaser et al., 2003). This was recently confirmed in another longitudinal study of Alzheimer caregivers by von Känel et al. (2012), who further found that duration of caregiving was related with higher CRP levels, and that, in contrast to the earlier findings, inflammation levels dropped significantly three months after the spouse's death. In a study on younger caregivers of brain cancer patients, we found linear increases of CRP, but not IL-6, during a 44-week period of diagnosis, treatment, and in many cases, death of the patient (Rohleder et al., 2009). Sherwood et al. (2016) found that longitudinal development of inflammatory cytokines in caregivers to cancer patients was associated with health status factors, i.e. BMI and psychological distress, i.e. perceived burden (Sherwood et al., 2016). In another longitudinal study, von Känel et al. (2014) reported that increased inflammatory cytokines of dementia caregivers were related with decreased satisfaction with leisure satisfaction, adding to our understanding of what drives increases in inflammation in caregiving stress (von Känel et al., 2014). A small sample of caregivers showed decreases in activity of two pro-inflammatory transcription control pathways after an eight-session stress management intervention (Laudenslager et al., 2016). Similar results were published by Black et al. (2013) who showed that meditation practice reversed increased inflammatory gene transcripts in dementia caregivers (Black et al., 2013).

Taken together, there is compelling evidence supporting the presence of chronic systemic low-grade inflammation in caregivers. Although a recent review came to the conclusion that the link between caregiver status and inflammation was only weakly supported (Potier et al., 2018), the data summarized above support the notion that there is variability in inflammation in caregivers, which might be explained by how caregiving is experienced, and that increases in inflammation are found predominantly in caregivers who experience more stress, or less life satisfaction during caregiving.

4.2. Occupational stress and unemployment

Others have addressed chronic inflammation in unemployment and work stress. In one study, unemployed middle-aged men and women were contrasted with employed individuals. While average concentrations of IL-6 and CRP did not differ, the rate of individuals with high IL-6 and CRP was higher in the unemployed (Hintikka et al., 2009). More evidence is available on burnout, which is frequently discussed as a consequence of work overload. Higher levels of inflammation were found in teachers (von Känel et al., 2008) and in women from the general population as a function of burnout (Grossi et al., 2003; Toker et al., 2005). While one study did not find associations of inflammation with burnout (Mommersteeg et al., 2006), the Dresden Burnout Study (Penz et al., 2018) revealed increases in neutrophils, which might be indicative of inflammatory activation, in individuals with stressful life events and burnout over a one-year observation period.

4.3. Early life stress

Early adversity might be considered a form of chronic stress as well, as there is now compelling evidence that experiences in early childhood leave a psychological, and biological mark for the entire human life span. Early adversity has been investigated in terms of low socioeconomic status when growing up, and has also been investigated by specifically assessing milder, and stronger forms of childhood adversity, up to asking for specific traumatic experiences, such as abuse or neglect. There is now strong evidence linking low childhood SES with higher systemic inflammatory activity in adolescence and adulthood. Miller and Chen have repeatedly reported that indicators of low childhood SES such as (lack of) home ownership, or low parental education, were strong predictors of current inflammatory status, as evidenced by increased expression of inflammatory genes in circulating immune cells (Miller et al., 2009) (Miller et al., 2009). Similar relationships were also found for plasma concentrations of IL-6 and CRP in adults with low childhood SES (Packard et al., 2011).

While the previous studies show that even milder adversity such as low childhood socioeconomic status contributes to later-life inflammation, even stronger relationships are further found when childhood maltreatment or trauma is investigated. In a recent meta-analyses, that included 25 studies with more than 15,000 participants, Baumeister et al. (2016) compiled strong evidence for associations of levels of three of the most important inflammatory mediators, i.e. IL-6, TNF-alpha, and CRP in relation with self-reported childhood adversity assessed by questionnaires such as the Childhood Trauma Questionnaire (Bernstein et al., 1994). Importantly, this strong association appears to remain present into older adulthood, as indicated by the finding that a history of childhood abuse magnifies the relationship of caregiving with IL-6 and TNF concentrations (Kiecolt-Glaser et al., 2011).

4.4. Associations of self-rated stress with inflammation

Finally, in studies of healthy individuals from the general population, associations between self-rated recent or current stress with inflammatory markers are frequently reported, and confirm associations of self-rated chronic stress with inflammatory activity (McDade et al., 2006; Ranjit et al., 2007). Extending this, self-reported social isolation or loneliness has also repeatedly found to be associated with plasma IL-6 and CRP, although relationships are stronger in, or sometimes restricted to older men, while not significant in younger adults, or younger women (43–46). (Häfner et al., 2011; Loucks et al., 2006; Ford et al., 2006; Loucks et al., 2005). Plasma inflammatory activity has also

been found to be positively related with self-rated depression, anger, and hostility (Suarez, 2004).

4.5. Summary of chronic stress and inflammation

As reviewed here and elsewhere (e.g. Hänsel et al., 2010; Slavich and Irwin, 2014), chronic life stress is consistently found to be associated with, and in some studies, predictive of increased inflammatory activity, as measured mainly by plasma inflammatory markers such as IL-6, TNF-alpha, and CRP. Research also revealed insights into the underlying mechanism, in particular when studying regulation of gene transcription (e.g. Slavich and Cole, 2013). Chronic life stress can take many different forms, can start in early childhood, with effects on the entire human lifespan, but it can also start late, in form of caregiving to a spouse with dementia. Effects on inflammatory activity are well-documented, and some studies point to an interaction of early and late adversity, in that early adversity enhances the inflammatory increase in late-life caregiving (Kiecolt-Glaser et al., 2011). Recent studies have further shown that increases in inflammatory activity are not uniformly observable in conditions of chronic life stress, but seem to be stronger when people experience stronger distress, and weaker when people are less affected by the experience.

5. What is the role of acute stress stimulation of systemic inflammation with regard to chronic systemic low grade inflammation?

As mentioned above, a key question is, at which time do we transition from conceptualizing repeated experience of acute stressors as chronic stress, or when are acute stressors experienced often enough to become chronic?

There are certainly some stressors that are per se chronic, and not just repetitions of stressful events, but many chronic stressors might indeed be conceptualized as a series of repeated acute stressors, to which an individual can adapt more or less effectively. In a way, the taxonomy of stressors by Elliot and Eisdorfer (1982), as adopted by Segerstrom and Miller (2004) in their meta-analysis, helps with this question (Segerstrom and Miller, 2004). Elliot and Eisdorfer distinguish stressors on two dimensions, course and duration, and doing so, describe two types of acute stressors, and three types of chronic stressors.

Acute stressors are differentiated into *acute time-limited stressors*, i.e. the kind that most researchers use to study stress responses, and *brief naturalistic stressors*, that are short and acute, but are experienced in the real world (Elliot and Eisdorfer, 1982). This is an important distinction, because although laboratory stressors are extremely useful for controlled experiments, they tend to lack external validity, and responses are not necessarily generalizable to real life exposure. We have, for example, in a study of competitive ballroom dancers, found that HPA axis responses were more than twice as high as those typically observed in the laboratory (Rohleder et al., 2007).

Categories of stressors that are considered as more chronic are *stressful event sequences*, in which an initial event leads to a series of repeated stressful events. *Chronic stressors*, in this taxonomy, are considered stronger, more pervasive, and excellent examples would probably be being a caregiver, as reviewed above. A final category, *distant stressors*, describes stressors such as traumata that typically have occurred in the past, are not a current threat at the time of observation, but still affect an individual's psychological health (Elliot and Eisdorfer, 1982; Segerstrom and Miller, 2004).

The category *stressful event sequences* best describes the key issue introduced above, i.e. a time period or phase between acute and chronic stress. Although this interpretation might not necessarily be exactly in line with the original intention of Elliot and Eisdorfer (1982), it comes closest to conceptualizing a transitional phase between one initial exposure to a new stress situation, and the subsequent development, by repeated exposure, into something that could be described as chronic stress. In a related, but different way, this is also addressed within the allostatic load model, were two of the four proposed allostatic load conditions clearly state that repeated exposure to stress (*"repeated hits"*) or failure to habituate to repeated exposures (*"non habituation"*) (McEwen, 1998; McEwen and Stellar, 1993). However, a significant knowledge gap exists with regard to research focusing on the phase in which an initial, acute stressor and stress response transitions into becoming chronic stress.

Several ways are conceivable to address this gap. One option might be to recruit individuals who are in life situations that fit the stressful event sequences description. While there are likely a good number of studies in which such situations are investigated, it is difficult at present to identify in which phase of such a sequence people are, and how that relates to specific biological changes.

Another way to address this gap is to test the effect of repeated stress in the laboratory. A number of studies have used the Trier Social Stress Test (TSST) to operationalize repeated stress exposure in the laboratory. Early studies using this paradigm have revealed patterns of habituation or non-habituation that differ between stress systems, and are related with psychological states and traits, as well as with anthropometric measures. The HPA axis has been shown to reliably habituate in response to already a second exposure to the TSST in about 70% of research participants (e.g. Kirschbaum et al., 1995; Petrowski et al., 2012; Schommer et al., 2003; Wüst et al., 2005); Habituation, although to a lesser degree, has also been found for salivary alpha-amylase, a marker of SNS activity (Petrowski et al., 2016), but plasma catecholamines, another measure of SNS reactivity, do not show habituation during repeated stress (Schommer et al., 2003). Of particular interest in this context is the recent observation that plasma inflammatory cytokine responses to stress do not show any sign of habituation, up to a third repeated stress exposure (McInnis et al., 2014; von Känel et al., 2006b). We have further reported that IL-6 responses to stress show stronger sensitization (or less habituation) in participants with lesser HPA axis habituation (Thoma et al., 2017), and that sensitization is stronger in individuals with higher measures of adiposity, i.e. BMI, body fat percentage, and waist-hip ratio (WHR; McInnis et al., 2014).

None of these studies have explicitly been designed to test trajectories of stressful event sequences, and it should be noted, that due to the fact that only two to three repeated instances of the TSST were performed, these studies would be targeting the very early phase of stressful event sequences, i.e. when going from initial to repeated exposure. In consequence, the conclusions that can be drawn from these studies at this point are limited.

Nevertheless, these studies using repeated stress paradigms have revealed a number of factors that are cross-sectionally related with individuals' mental or physical function, e.g. lower sensitization / stronger habituation of IL-6 responses with lower body fat, a more adaptive basal HPA axis activity, as well as higher subjective social status, and fewer self-reported traumatic events in their childhood. This also fits with studies showing that inflammatory responses to stress have prospective associations with adverse health outcomes. Brydon and Steptoe (2005) for example showed that the magnitude of interleukin-6 (IL-6) response to acute laboratory stress predicted ambulatory blood pressure after a 3-year follow-up (Brydon and Steptoe, 2005). Similarly, acute stress-evoked increases in fibrinogen and tumor necrosis factor alpha (TNF-a) predicted increasing carotid artery stiffness over time (Ellins et al., 2008), and more recent evidence shows that larger inflammatory stress responses are also associated with higher basal systemic inflammation (Lockwood et al., 2018). Finally, Aschbacher et al. (2012) found that inflammatory stress responses predicted depressive symptoms one year later (Aschbacher et al., 2012).

6. Summary and future directions

These initial results show that inflammatory responses in acute

stress do have value in predicting the development of long-term changes, while the few available repeated stress studies further hint to variability in how repeated acute stress is translated into long-term changes. Future studies will need to continue to fill this gap, by (a) better understanding cross-sectional predictors of habituation versus sensitization of stress responses, in particular of the inflammatory system; by (b) better understanding the long-term trajectories of habituation versus sensitization of stress responses. The latter could be achieved by bringing people into the laboratory that have already experienced a particular stressor, and recreating that specific stress experience in the laboratory, at specific phases during the stressful event sequence. Of course, there might be issues mixing naturalistic with laboratory stress tests. An additional approach and potential first step could be to apply repeated acute stress paradigms to individuals already experiencing chronic stress. Ultimately, only prospective studies will allow us to fully understand long-term effects of stress. In conclusion, we currently are at the very beginning of the task to understand the transitional phase between acute stress, repeated acute stress, and chronification. Laboratory research on repeated acute stress, as well as well as ambulatory assessment studies will have to fill this gap in the future.

Conflict of interest

None of the authors has any conflicts to report.

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